Randomised Trials in Child and Adolescent Health in Developing Countries

21st Edition
July 2023-June 2024

Please send suggestions about this booklet to:

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Introduction

Each year this booklet is compiled to summarize the evidence on child and adolescent health derived from randomized or controlled trials in low- and middle-income countries over the previous year. The aim is to make this information widely available to paediatricians, nurses, other health workers and administrators in resource poor settings where up-to-date information is hard to find. I hope that this information will be helpful in reviewing treatment policies, clinical practice and public health strategies.

The method of searching for studies uses PubMed, a search engine that is freely available and widely used throughout the world. The search strategy has been chosen to capture as many relevant studies as possible, although it is possible that I have missed some. If you know of a relevant RCT or meta-analysis that has not been included in this year's review, please let me know. The search strategy (see below) is reproducible by anyone with access to the Internet, through **http://www.ncbi.nlm.nih.gov/sites/entrez**

Randomized controlled trials (RCTs) are not the only valuable scientific evidence, and some RCTs, because of problems with design or implementation have limited value. However, the method of the Randomized Trial is the Gold Standard for determining attributable benefit or harm from clinical and public health interventions. When done properly they eliminate bias and confounding. Their results should not be accepted uncritically, but they should be evaluated for quality and validity. Before the result of an RCT can be generalized to another setting there must be consideration of wider applicability or reproducibility, feasibility and potential for sustainability.

This year 540 trial publications were identified. These were conducted in countries from all regions of the world. Several trials from 2023-24 will lead to significant changes in child health recommendations, and some already have. Where there were no trials this year under a certain sub-heading I have left the heading in the book. Many trials could be listed under several sub-headings, so there may be fewer gaps than is first apparent.

Most of the papers this year have free on-line access, which you can link to through the hyperlink in the title. Through HINARI, the Health Inter-Network Access to Research Initiative (http://www.who.int/hinari/en/) a program set up by WHO in collaboration with publishers, the full-text versions of over 8500 journal titles and 30,000 e-books in 30 languages are available to health institutions in over 100 countries. If your health institution (medical school, teaching hospital, nursing school, government office) has not registered with HINARI, you can check your eligibility and register online.

Please feel free to distribute this booklet to your colleagues. The previous editions (2002-2023) are available at: https://pngpaediatricsociety.org/research-2/

A summary of some of the important results from July 2023 to June 2024

- In urban Bangladesh, a community based early child development (ECD) social safety-net program using home visitation improved the development of children of

young mothers, including improved cognitive and motor skills, reduced experience of violence by mothers, and more engagement by fathers. Similar positive results for community ECD was found in rural India.

- In Rwanda, Bandebereho, a program that worked with parents to build couple relationship and parenting skills and included reflection on gender norms had lasting effects on reduced family violence and physical punishment of children, plus multiple health and relationship outcomes.
- In India, among 27,000 households where water sanitation and hygiene (WASH) training was conducted, households that engaged in a combination of four WASH characteristics: safe source of water for daily use, safe source of drinking water, private or shared flush toilet use, and always handwashing with soap after defecation had a 30% lower risk of cholera than those that did not have these 4 characteristics.
- In Bangladesh, several studies explored the effects of improved water, sanitation on hygiene (WASH) on childhood diarrhoea, including a large cluster RCT involving 360 clusters and 4941 children which showed improved WASH substantially reduces diarrhea risk with largest benefits among children with lowest socio-economic households and during the monsoon season, preventing an estimated 734 (95% CI 385, 1085) cases per 1000 children per month during the seasonal monsoon. A sub-study showed improved WASH may improve epigenetics including reduced methylation of cortisol genes, and enhanced adaptive responses of the physiological stress system in early childhood.
- Among 225 Ugandan school children with hookworm, dual-dose albendazole (400mg per day for 2 days) improved the cure rate of hookworm compared to a single-dose of 400mg albendazole (96 vs 84%). And in Gabon, a childhood hookworm vaccine underwent a phase II trial with prosing serological responses.
- In a large cluster RCT in Bangladesh, certain entero-pathogens were more prevalent in the hot rainy season, including Cryptosporidium, E. coli, Shigella, Campylobacter, Aeromonas, and Adenovirus.
- Three trials (in Niger, Mali and Kenya) showed the benefits of involving community health workers and decentralised care in the management of children with acute malnutrition, with equivalent or greater recovery rates, shorter length of hospital stay and reduced costs.
- In a large community based RCT in the Punjab, India involving over 70,000 households and 15,000 births, a maternal and newborn health package, plus training for community- and facility-based health care workers, and community counselling and education sessions improved neonatal mortality rate (39.2/1000 live births vs 52.2/1000 live births in control clusters, improved clean delivery practices, and use of chlorhexidine for cord care.
- In Zambia and Burkina Faso, breast fed infants without HIV, whose mothers had HIV and a viral load >1000 copies per ml, lamivudine prophylaxis in the first 12 months of life in addition to maternal antiretroviral therapy reduced the risk of post-natal mother-to-child HIV transmission.

- In Lesotho, an integrated parenting and HIV testing intervention held in 34 community clusters showed improvements in child language development, and child HIV testing.
- In Africa there were many studies further exploring aspects of azithromycin mass drug administration, including effect on mortality, pneumococcal and diarrhoeal pathogen resistance and delivery issues. In Burkina Faso, twice-yearly azithromycin resulted in a non-significant reduction in mortality in children in the presence of seasonal malaria chemoprevention. And among preschool children in Niger, mass azithromycin distribution aiming to reduce mortality, increased macrolide resistance determinants in the gut, but no study showed a clear sign that MDA substantially increased resistance.
- The malaria vaccine R21/Matrix-M was well tolerated and offered high efficacy against clinical malaria in over 3000 children in 4 African countries. And in implementation trials of the RTS,S/AS01E malaria vaccine (RTS,S), introduced by national immunisation programmes in Ghana, Kenya, and Malawi, over 650,000 children had received at least one dose, and RTS,S vaccine introduction was associated with a 32% reduction (95% CI 5-51%) in hospital admission with severe malaria, and a 9% reduction (95% CI 0-18%) in all-cause (non-injury) mortality.
- In Tanzania, in a study of over 4500 people, chlorfenapyr-pyrethroid impregnated bed nets reduced the incidence of malaria infection compared to standard pyrethroid insecticide treated bed nets over the 3-year bed-net lifespan. In a parallel study in Benin, the beneficial effect on malaria transmission of chlorfenapyr-pyrethroid impregnated bed nets waned by the third year, likely related to reduced bed-net usage.
- In a systematic review of trials in malaria-endemic countries in Africa, post-discharge malaria chemoprevention with sulfadoxine-pyrimethamine or artemether-lumefantrine monthly for 2 or 3 months or until the end of the malaria season, reduced mortality (77% reduction: RR 0·23 [95% CI 0·08-0·70], p<0·001) and readmissions in recently discharged children recovering from severe anaemia.
- A systematic review showed a significant impact of wMel-Wolbachia-carrying Ae aegypti mosquitoes in preventing dengue infection in an endemic setting, mostly based on study of over 6000 participants in Yogyakarta in Indonesia. The odds of contracting virologically confirmed dengue were reduced by 77% (OR 0.23, 95% CI 0.15 to 0.35).
- The Butantan-Dengue Vaccine, a single-dose, live, attenuated, tetravalent vaccine against dengue disease provided high protective efficacy through 2 years of follow-up in a study in Brazil involving over 10,000 vaccine recipients.
- In Malawi, as shown elsewhere, a single dose of typhoid conjugate vaccine (Vi-TT) is highly efficacious for at least 4 years among children aged 9 months to 12 years and showed efficacy in all age groups, including children younger than 2 years.
- In a large RCT of 680 patients (including adolescents) with rifampicin resistant pulmonary tuberculosis in Uzbekistan, Belarus, and South Africa, oral bedaquiline, pretomanid, linezolid plus moxifloxacin (BPaLM) for 24 weeks had lower adverse

outcome (composite of treatment failure, death, treatment discontinuation, disease recurrence, or loss to follow-up) than 36 months of standard care (12% vs 41%).

- In children in Bangladesh with persistent diarrhoea, green banana mixed rice suji (semolina) was more effective than rice alone as an option for managing persistent diarrhoea in young children.
- Among children with acute diarrhea and severe dehydration with severe non-anion gap metabolic acidemia, Hartmann's solution rehydration with additional bicarbonate deficit correction led to earlier resolution of metabolic acidemia, less utilization of critical care facilities, and fewer adverse outcome in children than Hartmann's solution rehydration only.
- In 100 mechanically ventilated children in a paediatric ICU in India, restricting fluids to 40%, compared to 70-80% of maintenance fluids resulted in lower fluid overload at 7 days, more ventilator free days, and a lower mortality rate, all of which were non-significant trends.
- In a stepped-wedge cluster randomised controlled trial in 20 hospitals in Uganda involving over 2000 children with pneumonia, there was a mortality benefit of improving oxygen access with solar-powered oxygen: relative risk reduction 48·7% (95% CI 8·5-71·5).
- In Ethiopian general hospitals, introduction of locally made bubble-continuous positive airway pressure (CPAP), supervised by general practitioners and paediatricians, was associated with a reduced risk of treatment failure in children with severe pneumonia and hypoxaemia compared with use of standard low-flow oxygen therapy. And bubble-CPAP was associated with a sustained lower mortality over 9 years in a tertiary hospital in Dhaka, Bangladesh.
- In a meta-analysis, children with asthma treated with fluticasone and salmeterol compared to fluticasone alone was associated with a greater proportion of time asthma-symptom free and without the use of short acting beta-2 agonists compared to fluticasone alone after 12 weeks of treatment.
- In China, a meta-analysis of 24 RCTs, involving over 2000 patients with mycoplasma pneumonia, the combination of budesonide with azithromycin showed improved lung function, reduced inflammatory markers and reduced the duration of symptoms.
- Among 60 Indian children with new-onset type 1 diabetes, in a blinded RCT, supplementation for 6 months with probiotics that included lactobacillus and bifidobacterium, improved glycaemic control, with a greater lowering of haemoglobin A1C levels, and improved immunoregulatory markers of islet cell function, compared with placebo. Other studies on type 1 diabetes in India this year explored the role of milk and calcium supplementation to improve bone health among children living in under-privileged communities, and the adjunctive use of metformin to improve glycaemic control in adolescents.
- Among 767 children in Indonesia with congenital heart disease undergoing cardiac surgery, tri-iodothyronine supplementation was associated with reduced duration of ventilation, and hospital length of stay (but had no effect in a parallel study in the US,

where malnutrition rates were lower, and baseline TSH and T3 were normal, whereas they were lower in Indonesia).

- In 160 Indian children with frequently relapsing nephrotic syndrome, levamisole 2-2.5 mg/kg/alternate days reduced the risk of relapse 40% to 23%, was steroid-sparing and reduced the risk of steroid toxicity. And daily dosing of levamisole may reduce use of steroids more than second daily dosing, in frequently relapsing nephrotic syndrome.
- In Uganda, among children with Nodding syndrome, a neurological disorder in Africa that carries a high mortality rate, treatment with doxycycline reduced acute seizure-related hospitalisations (rate ratio [RR] 0·43 [95% CI 0·20-0·94], p=0·028) and deaths (RR 0·46 [0·24-0·89], p=0·028). This was based on the hypothesis that nodding syndrome is a neuroinflammatory disorder, induced by antibodies to Onchocerca volvulus.
- In 2 RCTs in India and China, among mothers and their newborns, increasing the duration of early skin-to-skin contact from 60 to 90 minutes increased the likelihood of exclusive breastfeeding rates in the first 14 weeks of life.
- In a systematic review of 20 studies involving 3260 infants, deferred cord clamping, compared with immediate cord clamping, reduced death before discharge (odds ratio [OR] 0·68 [95% CI 0·51-0·91].
- In a systematic review of 24 studies and 1100 newborns, use of common salt for umbilical granulomas the treatment success rate was nearly 94%.
- In 286 preterm infants (gestational age 23-30 weeks) in China, breast milk enema reduced the time to achieve meconium evacuation and full enteral feeding compared to saline enema.
- Two systematic reviews studied whether shorter duration of antibiotic therapy (7-10 days) compared to a traditional longer duration of therapy (10-14 days) in culture proven and culture negative neonatal sepsis, is equivalent in terms of treatment failure or mortality. In culture proven sepsis the numbers are too small to detect a difference in mortality, and no apparent difference in treatment failure, and in culture negative sepsis short course antibiotic therapy was equally effective in all measures of morbidity, and significantly shortened hospitalisation.
- In a meta-analysis of RCTs involving 26 studies and 132,000 very low birthweight babies, the prevalence of chronic lung disease as defined by bronchopulmonary dysplasia or oxygen requirement at one month of age was 35% (95% CI, 28-42%).
- In a meta-analysis of 71 RCTs of cooling in neonatal hypoxic ischaemic encephalopathy, involving 5821 surviving infants who were assessed for hearing impairment, the prevalence rate of hearing loss in low and middle income countries was 7-8%.
- In a meta-analysis of 106 RCTs involving nearly 24,000 participants of preterm infants undergoing screening for retinopathy of prematurity, vitamin A supplementation markedly reduced the incidence of ROP in comparison with placebo (odds ratio 0.59, 95% credible interval 0.33, 0.85). Also effective were probiotics (OR = 0.48, 95% CrI

0.32, 0.97), human milk (OR = 0.50, 95% CrI 0.21, 0.78) fish oil-based lipid emulsion (OR = 0.57, 95% CrI 0.24, 0.90), and early erythropoietin (OR = 0.51, 95% CrI 0.34, 0.98).

- In exclusively breastfed Gambian infants, iron supplementation from 6 weeks of age was associated with a significant improvement in markers of iron status at around 6 months of age.
- Among Kenyan infants, adding prebiotics to iron-fortified infant cereal increases iron absorption and reduces the adverse effects of iron on the gut microbiome and inflammation.
- In an RCT involving year 8 students in 12 public schools in north India, a health-promotion intervention aimed at reducing the behavioural risk factors of chronic diseases reduced salt intake, and proportion of current alcohol users by 5%, and increased fruit consumption by 18 g/d and increased physical activity. No effect on smoking rates.
- Among 232 children living in rural India, a program of daily protein supplementation, yoga and physical exercise improved muscle function.
- Among 750 Ugandan children aged 1-5 years with stunting, lipid-based nutritional supplementation containing milk or soy protein and whey or maltodextrin for 12 weeks substantially increased Hb, and improved iron, cobalamin, and folate status, but had no effect on vitamin A, compared to children who received no supplementation.
- Positive results from peer support groups for adolescents with chronic illnesses, including HIV in South Africa, and for school health programs in Tanzania that included school meals, nutrition education, school gardens, and community workshops.
- Among 224 sexually active adolescent girls in South Ethiopia, an RCT of school-based peer education intervention effectively improved contraceptive use and unmet needs.
- In rural India, in a controlled trial involving 235 adolescent school students high dose vitamin D supplementation (2250 U per day for 9 weeks) reduced depression scores, compared to a group who received a lower dose of vitamin D (250 U per day for 9 weeks) and calcium supplementation.
- In 2024, there were four trials involving refugee populations: addressing interventions to improve the psychosocial health of mothers and infants among Syrian refugee populations in Egypt, and adolescent refugees in Lebanon; to improve hand-washing in a refugee settlement in Sudan; and to increase the very low rates of vaccine coverage in Lebanon.

I have been liberal in what is included as an RCT. Some papers are the reports of sub-studies within an RCT, they may be cohort or background studies rather than the primary results of the completed RCT.

Randomised trials often report the “average effect”, that is, the effect on the overall population. However, depending on how specifically that population is defined, within that

population may be children who will benefit from the therapy or intervention, children for whom the therapy will have no effect, and some children for whom it may be harmful. The "average" of these effects may be "no overall effect", but it is increasingly important that researchers try to understand the effects for individuals or sub-groups within trials, and the context in which benefit or not occurs.

Some of the context differences that influence the results of a trial include individual or population characteristics, comorbidities, the health care environment and health care providers, geographical factors, other interventions, the delivery mechanism for the drug, vaccine or other intervention, the disease stage and specific aetiology, economic, social and cultural characteristics of the population and individuals within it. This can be even more complex in understanding systematic reviews of randomised trials, where heterogeneity is often incompletely reported, and where there will be heterogeneity *within and between* studies.

Incorporating an understanding of the observed effect in context requires a nuanced approach, and the randomised trial design is not always the best method to trial all interventions. This can be the case for complex interventions (i.e. a complex clinical therapy or a health system improvement program) where other methods of evaluation may be more useful.

Since 2002 there have been **over 4200 trial publications** highlighted in the 21 editions of this publication. There has been a marked evolution of the content and nature of the RCTs. This reflects many things: the changing epidemiology of child health; the amazing application of new technology in vaccines and drugs against ever-changing pathogens; the "grand convergence" of health and medicine between the "developing" and "developed" countries of last century, manifest partly by far more trials in India and China; global targets such as the Millennium and Sustainable Development Goals (SDGs) and approaches such as the WHO "life-course" and "Survive and Thrive"; and the influences (and distortions) on the research agenda by global funding agencies and social and political trends.

Encouragingly, there are now more trials in the broader context of those global SDG targets: including field trials of interventions to provide better water, sanitation, hygiene, and to reduce pollution in the poorest communities, trials that address the local effects of climate change, more of a focus on the development, psychological, and mental health of children and adolescents, trials to reduce violence against children, holistic approaches to improve the health and education of adolescent girls and boys often co-designed by them, and trials to improve maternal health and parent-child interactions. RCT are being conducted not just in hospitals and health care settings, but in schools, villages, and communities.

Trevor Duke
August 2024

Search strategy

("Developing Countries"[Mesh] OR (austere OR limited resource* OR "resource limited" OR low resource* OR transitioning econom* OR lami countr* OR transitional countr* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less-developed) OR deprived OR poor) AND (countr* OR nation* OR econom* OR population OR world)) OR "third world" OR LMIC OR LMICs) OR "Africa"[Mesh] OR "caribbean region"[Mesh] OR "central america"[Mesh] OR "latin america"[Mesh] OR "mexico"[Mesh] OR "south america"[Mesh] OR "europe, eastern"[Mesh] OR "indian ocean islands"[Mesh] OR "pacific islands"[Mesh] OR "New Guinea"[Mesh] OR India OR Africa OR Asia OR South-America OR Papua-New-Guinea OR Pacific) AND (newborn* OR new-born* OR baby OR babies OR neonat* OR neo-nat* OR infan* OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric* OR paediatric* OR adolescen* OR youth OR youths OR teen OR teens OR teenage*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized-controlled-trial*[tiab] OR randomised-controlled-trial*[tiab] OR randomized-trial*[tiab] OR randomised-trial*[tiab] NOT (animals[mh] NOT humans[mh]))

Acute respiratory infection

(See also: Zinc; Vaccines - Pneumococcal vaccine; Hygiene and environmental health)

Treatment of pneumonia

EClinicalMedicine. 2024 May 14:72:102640.
doi: 10.1016/j.eclinm.2024.102640. eCollection 2024 Jun.

Nutritional supplementation in children with severe pneumonia in Uganda and Kenya (COAST-Nutrition): a phase 2 randomised controlled trial

Sarah Kiguli[1], Peter Olupot-Olupot[2,3], Mainga Hamaluba[4], Elisa Giallongo[5], Karen Thomas[5], Florence Alaroker[6], Robert O Opoka[1,7], Abner Tagoola[7], Shela Oyella[8], Damalie Nalwanga[1], Eva Nabawanuka[1,9], William Okiror[2,3], Margaret Nakuya[6], Denis Amorut[6], Rita Muhindo[3], Ayub Mpoya[4], Hellen Mnjalla[4], Emmanuel Oguda[4], Thomas N Williams[4,10], David A Harrison[5], Kathy Rowan[5], Andre Briend[11,12], Kathryn Maitland[4,10]

Abstract

Background: Severe pneumonia in African children results in poor long-term outcomes (deaths/readmissions) with undernutrition as a key risk factor. We hypothesised additional energy/protein-rich Ready-to-Use Therapeutic Foods (RUTF) would meet additional nutritional requirements and improve outcomes.

Methods: COAST-Nutrition was an open-label Phase 2 randomised controlled trial in children (aged 6 months-12 years) hospitalised with severe pneumonia (and hypoxaemia, SpO_2 <92%) in Mbale, Soroti, Jinja, Masaka Regional Referral Hospitals, Uganda and Kilifi County Hospital, Kenya (ISRCTN10829073 (registered 6th June 2018) PACTR202106635355751 (registered 2nd June 2021)). Children were randomised (ratio 1:1) to enhanced nutritional supplementation with RUTF (plus usual diet) for 56 days vs usual diet (control). The primary outcome was change in mid-upper arm circumference (MUAC) at 90 days as a composite with mortality. Secondary outcomes include anthropometric status, mortality, and readmissions at Days 28, 90 and 180.

Findings: Between 12 August 2018 and 22 April 2022, 846 eligible children were randomised, 424 to RUTF and 422 to usual diet, and followed for 180-days [12 (1%) lost-to-follow-up]. RUTF supplement was initiated in 417/419 (>99%). By Day 90, there was no significant difference in the composite endpoint (probabilistic index 0.49, 95% CI 0.45-0.53, p = 0.74). Respective 90-day mortality (13/420 3.1% vs 14/421 3.3%) and MUAC increment (0.54 (SD 0.85) vs 0.55 (SD 0.81)) were similar between arms. There was no difference in any anthropometric secondary endpoints to Day 28, 90 or 180 except skinfold thickness at Day 28 and Day 90 was greater in the RUTF arm. Serious adverse events were higher in the RUTF arm (n = 164 vs 108), mainly due to hospital readmission for acute illness (54/387 (14%) vs 37/375 (10%).

Interpretation: Our study suggested that nutritional supplementation with RUTF did not improve outcomes to 180 days in children with severe pneumonia.

Medicine (Baltimore). 2024 Jun 14;103(24):e38332.
doi: 10.1097/MD.0000000000038332.

Meta-analysis of combined azithromycin and inhaled budesonide treatment for Chinese pediatric patients with mycoplasma pneumonia

Jing Zhao[1], Xiaojing Pan, Peng Shao

Abstract

Background: Budesonide, capable of reducing vascular permeability, suppressing mucus secretion, and alleviating edema and spasms, is widely used in China for combined infectious disease treatment. This study assesses budesonide's efficacy and safety as an adjunct to azithromycin in pediatric Mycoplasma pneumonia management in China, aiming to establish a strong theoretical foundation for its clinical application.

Methods: We conducted a comprehensive search for qualifying studies across 5 English databases and 4 Chinese databases, covering publications until October 31, 2023. Endpoint analyses were performed using standard software (Stata Corporation, College Station, TX). This study was conducted in compliance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results: A total of 24 randomized controlled trials were involved in the current study, including 2034 patients. Our findings indicate that the combination of budesonide with azithromycin for the treatment of pediatric Mycoplasma pneumonia delivers superior therapeutic efficacy (Intravenous: odds ratio [OR], 0.156, P < .001; Sequential: OR, 0.163, P = .001; Oral: OR, 0.139, P < .001), improved pulmonary function (Forced expiratory volume in 1 second: weighted mean differences [WMD], -0.28, P = .001; Peak expiratory flow: WMD, -0.554, P = .002; Forced vital capacity: WMD, -0.321, P < .001), diminished lung inflammation (IL-6: WMD, 4.760, P = .002; c-reactive protein: WMD, 5.520, P < .001; TNF-α: WMD, 9.124, P < .001), reduced duration of fever, faster resolution of cough and rales, all without increasing the occurrence of adverse events.

Conclusion: The combination of budesonide and azithromycin demonstrates enhanced therapeutic effectiveness, promotes improved pulmonary function, shortens the duration of symptoms, and effectively mitigates the overexpression of inflammatory factors like c-reactive protein, TNF-α, and IL-6, all without an associated increase in adverse reactions in pediatric mycoplasma pneumonia.

Curr Opin Pediatr. 2024 Apr 1;36(2):144-149.
doi: 10.1097/MOP.0000000000001325. Epub 2024 Jan 3.

Community-acquired bacterial pneumonia in children: an update on antibiotic duration and immunization strategies

Edward Lyon[1], Liset Olarte[2]

Abstract

Purpose of review: This review is structured to update clinicians on the epidemiology, antibiotic treatment, and prevention of pediatric bacterial pneumonia. The review provides information regarding the current research on antibiotic management for bacterial pneumonia and the newest immunization recommendations to prevent pneumococcal pneumonia and other respiratory infections.

Recent findings: The recommended length of antibiotic therapy for bacterial pneumonia has been discrepant between low-income and high-income countries. Recently, randomized controlled trials conducted in high-income countries provided evidence to support a short antibiotic course (3-5 days) for uncomplicated bacterial pneumonia in otherwise healthy children. The negative impact of inaccurate penicillin allergy labels in children with

pneumonia has emphasized the importance of prompt allergy de-labeling. Newer pneumococcal vaccines are recommended for children and are expected to have a significant impact on bacterial pneumonia rates.

Summary: Pediatric bacterial pneumonia is an important contributor to childhood morbidity and mortality. A short antibiotic course seems to be sufficient for the outpatient management of uncomplicated bacterial pneumonia; however, more studies are required in the inpatient setting. Future studies will inform the impact of recently introduced pneumococcal and respiratory syncytial virus vaccines on the epidemiology of bacterial pneumonia.

Prevention of pneumonia

N Engl J Med. 2024 Jan 4;390(1):32-43.
doi: 10.1056/NEJMoa2305681.

Liquefied Petroleum Gas or Biomass Cooking and Severe Infant Pneumonia

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Abstract

Background: Exposure to household air pollution is a risk factor for severe pneumonia. The effect of replacing biomass cookstoves with liquefied petroleum gas (LPG) cookstoves on the incidence of severe infant pneumonia is uncertain.

Methods: We conducted a randomized, controlled trial involving pregnant women 18 to 34 years of age and between 9 to less than 20 weeks' gestation in India, Guatemala, Peru, and Rwanda from May 2018 through September 2021. The women were assigned to cook with unvented LPG stoves and fuel (intervention group) or to continue cooking with biomass fuel (control group). In each trial group, we monitored adherence to the use of the assigned cookstove and measured 24-hour personal exposure to fine particulate matter (particles with an aerodynamic diameter of ≤2.5 μm [$PM_{2.5}$]) in the women and their offspring. The trial had four primary outcomes; the primary outcome for which data are presented in the current report was severe pneumonia in the first year of life, as identified through facility surveillance or on verbal autopsy.

Results: Among 3200 pregnant women who had undergone randomization, 3195 remained eligible and gave birth to 3061 infants (1536 in the intervention group and 1525 in the control group). High uptake of the intervention led to a reduction in personal exposure to $PM_{2.5}$ among the children, with a median exposure of 24.2 μg per cubic meter (interquartile range, 17.8 to 36.4) in the intervention group and 66.0 μg per cubic meter (interquartile

range, 35.2 to 132.0) in the control group. A total of 175 episodes of severe pneumonia were identified during the first year of life, with an incidence of 5.67 cases per 100 child-years (95% confidence interval [CI], 4.55 to 7.07) in the intervention group and 6.06 cases per 100 child-years (95% CI, 4.81 to 7.62) in the control group (incidence rate ratio, 0.96; 98.75% CI, 0.64 to 1.44; P = 0.81). No severe adverse events were reported to be associated with the intervention, as determined by the trial investigators.
Conclusions: The incidence of severe pneumonia among infants did not differ significantly between those whose mothers were assigned to cook with LPG stoves and fuel and those whose mothers were assigned to continue cooking with biomass stoves.

Influenza Other Respir Viruses. 2024 Apr;18(4):e13285.
doi: 10.1111/irv.13285.

Predictors of Respiratory Syncytial Virus, Influenza Virus, and Human Metapneumovirus Carriage in Children Under 5 Years With WHO-Defined Fast-Breathing Pneumonia in Pakistan

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Abstract
Background: Pneumonia is a leading cause of morbidity and mortality in children < 5 years. We describe nasopharyngeal carriage of respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and influenza virus among children with fast-breathing pneumonia in Karachi, Pakistan.
Methods: We performed a cross-sectional analysis of nasopharyngeal swabs from children aged 2-59 months with fast-breathing pneumonia, enrolled in the randomized trial of amoxicillin versus placebo for fast-breathing pneumonia (RETAPP) (NCT02372461) from 2014 to 2016. Swabs were collected using WHO standardized methods, processed at the Aga Khan University, Pakistan. Viral detection was performed using LUMINEX xTAG respiratory viral panel assay and logistic regression identified clinical and sociodemographic predictors.
Findings: Of the 1000 children tested, 92.2% (n = 922) were positive for viral carriage. RSV, hMPV, and influenza virus were detected in 59 (6.4%), 56 (6.1%), and 58 (6.3%) children and co-infections in three samples (two RSV-hMPV and one influenza-hMPV). RSV carriage was common in infants (56%), we observed a higher occurrence of fever in children with hMPV and influenza virus (80% and 88%, respectively) and fast breathing in RSV (80%) carriage. RSV carriage was positively associated with a history of fast/difficulty breathing (aOR: 1.96, 95% CI 1.02-3.76) and low oxygen saturation (aOR: 2.52, 95% CI 1.32-4.82), hMPV carriage was positively associated with a complete vaccination status (aOR: 2.22, 95% CI 1.23-4.00) and body temperature ≥ 37.5°C (aOR: 2.34, 95% CI 1.35-4.04) whereas influenza viral carriage was associated with body temperature ≥ 37.5°C (aOR: 4.48, 95% CI 2.53-7.93).
Conclusion: We observed a high nasopharyngeal viral carriage among children with WHO-defined fast-breathing pneumonia in Pakistan. Fever, difficulty in breathing, hypoxia and vaccination status are important clinical predictors for viral nonsevere community-acquired pneumonia.

Oxygen therapy

Lancet. 2024 Feb 24;403(10428):756-765.
doi: 10.1016/S0140-6736(23)02502-3. Epub 2024 Feb 14.

Solar-powered O_2 delivery for the treatment of children with hypoxaemia in Uganda: a stepped-wedge, cluster randomised controlled trial

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Abstract

Background: Supplemental O_2 is not always available at health facilities in low-income and middle-income countries (LMICs). Solar-powered O_2 delivery can overcome gaps in O_2 access, generating O_2 independent of grid electricity. We hypothesized that installation of solar-powered O_2 systems on the paediatrics ward of rural Ugandan hospitals would lead to a reduction in mortality among hypoxaemic children.

Methods: In this pragmatic, country-wide, stepped-wedge, cluster randomised controlled trial, solar-powered O_2 systems (ie, photovoltaic cells, battery bank, and O_2 concentrator) were sequentially installed at 20 rural health facilities in Uganda. Sites were selected for inclusion based on the following criteria: District Hospital or Health Centre IV with paediatric inpatient services; supplemental O_2 on the paediatric ward was not available or was unreliable; and adequate space to install solar panels, a battery bank, and electrical wiring. Allocation concealment was achieved for sites up to 2 weeks before installation, but the study was not masked overall. Children younger than 5 years admitted to hospital with hypoxaemia and respiratory signs were included. The primary outcome was mortality within 48 h of detection of hypoxaemia. The statistical analysis used a linear mixed effects logistic regression model accounting for cluster as random effect and calendar time as fixed effect. The trial is registered at ClinicalTrials.gov, NCT03851783.

Findings: Between June 28, 2019, and Nov 30, 2021, 2409 children were enrolled across 20 hospitals and, after exclusions, 2405 children were analysed. 964 children were enrolled before site randomisation and 1441 children were enrolled after site randomisation (intention to treat). There were 104 deaths, 91 of which occurred within 48 h of detection of hypoxaemia. The 48 h mortality was 49 (5·1%) of 964 children before randomisation and 42 (2·9%) of 1440 (one individual did not have vital status documented at 48 h) after randomisation (adjusted odds ratio 0·50, 95% CI 0·27-0·91, p=0·023). Results were sensitive to alternative parameterisations of the secular trend. There was a relative risk reduction of 48·7% (95% CI 8·5-71·5), and a number needed to treat with solar-powered O_2 of 45 (95% CI 28-230) to save one life. Use of O_2 increased from 484 (50·2%) of 964 children before randomisation to 1424 (98·8%) of 1441 children after randomisation (p<0·0001). Adverse events were similar before and after randomisation and were not considered to be related to the intervention. The estimated cost-effectiveness was US$25 (6-505) per disability-adjusted life-year saved.

Interpretation: This stepped-wedge, cluster randomised controlled trial shows the mortality benefit of improving O_2 access with solar-powered O_2. This study could serve as a model for scale-up of solar-powered O_2 as one solution to O_2 insecurity in LMICs.

Lancet Glob Health. 2024 May;12(5):e804-e814.
doi: 10.1016/S2214-109X(24)00032-9. Epub 2024 Mar 21.

Effectiveness of bubble continuous positive airway pressure for treatment of children aged 1-59 months with severe pneumonia and hypoxaemia in Ethiopia: a pragmatic cluster-randomised controlled trial

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Abstract

Background: The safety and efficacy of bubble continuous positive airway pressure (bCPAP) for treatment of childhood severe pneumonia outside tertiary care hospitals is uncertain. We did a cluster-randomised effectiveness trial of locally made bCPAP compared with WHO-recommended low-flow oxygen therapy in children with severe pneumonia and hypoxaemia in general hospitals in Ethiopia.

Methods: This open, cluster-randomised trial was done in 12 general (secondary) hospitals in Ethiopia. We randomly assigned six hospitals to bCPAP as first-line respiratory support for children aged 1-59 months who presented with severe pneumonia and hypoxaemia and six hospitals to standard low-flow oxygen therapy. Cluster (hospital) randomisation was stratified by availability of mechanical ventilation. All children received treatment in paediatric wards (in a dedicated corner in front of a nursing station) with a similar level of facilities (equipment for oxygen therapy and medications) and staffing (overall, one nurse per six patients and one general practitioner per 18 patients) in all hospitals. All children received additional care according to WHO guidelines, supervised by paediatricians and general practitioners. The primary outcome was treatment failure (defined as any of the following: peripheral oxygen saturation <85% at any time after at least 1 h of intervention plus signs of respiratory distress; indication for mechanical ventilation; death during hospital stay or within 72 h of leaving hospital against medical advice; or leaving hospital against medical advice during intervention). The analysis included all children enrolled in the trial. We performed both unadjusted and adjusted analyses of the primary outcome, with the latter adjusted for the stratification variable and for the design effect of cluster randomisation, as well as selected potentially confounding variables, including age. We calculated effectiveness as the relative risk (RR) of the outcomes in the bCPAP group versus low-flow oxygen group. This trial is registered with ClinicalTrial.gov, NCT03870243, and is completed.

Findings: From June 8, 2021, to July 27, 2022, 1240 children were enrolled (620 in hospitals allocated to bCPAP and 620 in hospitals allocated to low-flow oxygen). Cluster sizes ranged from 103 to 104 children. Five (0·8%) of 620 children in the bCPAP group had treatment failure compared with 21 (3·4%) of 620 children in the low-flow oxygen group (unadjusted RR 0·24, 95% CI 0·09-0·63, p=0·0015; adjusted RR 0·24, 0·07-0·87, p=0·030). Six children died during hospital stay, all of whom were in the low-flow oxygen group (p=0·031). No serious adverse events were attributable to bCPAP.

Interpretation: In Ethiopian general hospitals, introduction of locally made bCPAP, supervised by general practitioners and paediatricians, was associated with reduced risk of treatment failure and in-hospital mortality in children with severe pneumonia and

hypoxaemia compared with use of standard low-flow oxygen therapy. Implementation research is required in higher mortality settings to consolidate our findings.

Pediatr Pulmonol. 2024 Jan 24.
doi: 10.1002/ppul.26881. Online ahead of print.

Implementation of bubble continuous positive airway pressure for children with severe pneumonia and hypoxemia in intensive care unit of Dhaka Hospital, Bangladesh-Effect on pneumonia mortality

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Abstract

Background: After the completion of a randomized trial at Dhaka Hospital in 2013, bubble continuous positive airway pressure (BCPAP) oxygen therapy was incorporated as the part of the standard treatment for children with severe pneumonia with hypoxemia in an intensive care unit at Dhaka Hospital in August 2013 instead of World Health Organization (WHO) standard low flow oxygen therapy.

Objective: To understand the long-term effectiveness of the introduction of bCPAP oxygen therapy by comparing pneumonia mortality in the post-trial period (August 2013 to December 2017) with the pre-trial (February 2009 to July 2011) and trial periods (August 2011 to July 2013).

Methods: It was a retrospective analysis of prospectively collected hospital data of all admissions. Mortality rates of all children with WHO-defined pneumonia, and the subset of children with severe pneumonia and hypoxemia (oxygen saturation <90%) were evaluated.

Results: The analysis covered 10,107 children with pneumonia: 2523 in the pre-trial (414 with severe pneumonia and hypoxemia; none of them received bCPAP), 2959 during the trial (376 with severe pneumonia and hypoxemia; 79 received bCPAP), and 4625 in the post-trial period (1208 with severe pneumonia and hypoxemia; 1125 had bCPAP). The risk of death from pneumonia in the post-trial period was lower than in pre-trial (adjusted risk ratio [RR] = 0.73, 95% confidence interval [CI] = 0.58-0.92; p = 0.007), among children with severe pneumonia and hypoxemia, the risk of death was lower in the post-trial period than in the pre-trial (adjusted RR = 0.46, 95% CI = 0.37-0.58, p < 0.001), and the trial period (adjusted RR = 0.70, 95% CI = 0.51-0.95; p = 0.023).

Conclusion: After the introduction of bCPAP oxygen therapy as part of the routine management of severe pneumonia and hypoxemia in the ICU of the Dhaka hospital, we observed significantly lower mortality, even after accounting for measurable confounding.

* not a randomised methodology, but analysis including the era of a randomised trial.

Pediatr Crit Care Med. 2024 Apr 19.
doi: 10.1097/PCC.0000000000003521. Online ahead of print.

High-Flow Nasal Cannula Versus Nasal Prong Bubble Continuous Positive Airway Pressure in Children With Moderate to Severe Acute Bronchiolitis: A Randomized Controlled Trial

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Abstract

Objectives: To compare high-flow nasal cannula (HFNC) versus nasal prong bubble continuous positive airway pressure (b-CPAP) in children with moderate to severe acute bronchiolitis.

Design: A randomized controlled trial was carried out from August 2019 to February 2022. (Clinical Trials Registry of India number CTRI/2019/07/020402).

Setting: Pediatric emergency ward and ICU within a tertiary care center in India.

Patients: Children 1-23 months old with moderate to severe acute bronchiolitis.

Intervention: Comparison of HFNC with b-CPAP, using a primary outcome of treatment failure within 24 hours of randomization, as defined by any of: 1) a 1-point increase in modified Wood's clinical asthma score (m-WCAS) above baseline, 2) a rise in respiratory rate (RR) greater than 10 per minute from baseline, and 3) escalation in respiratory support. The secondary outcomes were success rate after crossover, if any, need for mechanical ventilation (invasive/noninvasive), local skin lesions, length of hospital stay, and complications.

Results: In 118 children analyzed by intention-to-treat, HFNC (n = 59) versus b-CPAP (n = 59) was associated with a lower failure rate (23.7% vs. 42.4%; relative risk [95% CI], RR 0.56 [95% CI, 0.32-0.97], p = 0.031). The Cox proportion model confirmed a lower hazard of treatment failure in the HFNC group (adjusted hazard ratio 0.48 [95% CI, 0.25-0.94], p = 0.032). No crossover was noted. A lower proportion escalated to noninvasive ventilation in the HFNC group (15.3%) versus the b-CPAP group (15.3% vs. 39% [RR 0.39 (95% CI, 0.20-0.77)], p = 0.004). The HFNC group had a longer median (interquartile range) duration of oxygen therapy (4 [3-6] vs. 3 [3-5] d; p = 0.012) and hospital stay (6 [5-8.5] vs. 5 [4-7] d, p = 0.021). No significant difference was noted in other secondary outcomes.

Conclusion: In children aged one to 23 months with moderate to severe acute bronchiolitis, the use of HFNC therapy as opposed to b-CPAP for early respiratory support is associated with a lower failure rate and, secondarily, a lower risk of escalation to mechanical ventilation.

Asthma

Thorax. 2024 Feb 22:thorax-2023-220877.
doi: 10.1136/thorax-2023-220877. Online ahead of print.

Improved childhood asthma control after exposure reduction interventions for desert dust and anthropogenic air pollution: the MEDEA randomised controlled trial

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Abstract

Introduction: Elevated particulate matter (PM) concentrations of anthropogenic and/or desert dust origin are associated with increased morbidity among children with asthma.
Objective: The Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches randomised controlled trial assessed the impact of exposure reduction recommendations, including indoor air filtration, on childhood asthma control during high desert dust storms (DDS) season in Cyprus and Greece.
Design, participants, interventions and setting: Primary school children with asthma were randomised into three parallel groups: (a) no intervention (controls); (b) outdoor intervention (early alerts notifications, recommendations to stay indoors and limit outdoor physical activity during DDS) and (c) combined intervention (same as (b) combined with indoor air purification with high efficiency particulate air filters in children's homes and school classrooms. Asthma symptom control was assessed using the childhood Asthma Control Test (c-ACT), spirometry (forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC)) and fractional exhaled nitric oxide (FeNO).
Results: In total, 182 children with asthma (age; mean=9.5, SD=1.63) were evaluated during 2019 and 2021. After three follow-up months, the combined intervention group demonstrated a significant improvement in c-ACT in comparison to controls (β=2.63, 95% CI 0.72 to 4.54, p=0.007), which was more profound among atopic children (β=3.56, 95% CI 0.04 to 7.07, p=0.047). Similarly, FEV1% predicted (β=4.26, 95% CI 0.54 to 7.99, p=0.025), the need for any asthma medication and unscheduled clinician visits, but not FVC% and FeNO, were significantly improved in the combined intervention compared with controls.
Conclusion: Recommendations to reduce exposure and use of indoor air filtration in areas with high PM pollution may improve symptom control and lung function in children with asthma.

Heart Lung. 2023 Sep 21:63:23-34.
doi: 10.1016/j.hrtlng.2023.09.004. Online ahead of print.

Efficacy and safety of fluticasone propionate/salmeterol and fluticasone propionate monotherapy in step-up treatment of childhood asthma: A systematic review and meta-analysis

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Abstract
Background: Asthma is a chronic respiratory disease that affects millions of children worldwide and can impair their quality of life and development. Inhaled glucocorticoids are the mainstay of asthma treatment, but some children require step-up therapy with additional drugs to achieve symptom control. Fluticasone propionate and salmeterol (FSC) has been shown to reduce asthma exacerbations and improve lung function in adults. However, the evidence for its efficacy and safety in children is limited.
Objective: This study aims to provide a comprehensive basis for treatment selection by summarizing existing clinical randomized controlled trials (RCTs) on the efficacy of FSC compared to fluticasone propionate (FP) monotherapy in children with asthma who require step-up treatment.
Methods: Five online databases and three clinical trial registration platforms were systematically searched. The effect size and corresponding 95% confidence interval (CI) were calculated based on the heterogeneity among the included studies.

Results: Twelve RCTs were identified and a total of 9, 859 patients were involved. The results of the meta-analysis revealed that the use of FSC was associated with a greater reduction in the incidence of asthma exacerbations than FP alone when the dose of FP was the same or when the duration of treatment exceeded 12 weeks. In addition, FSC resulted in a greater proportion of time with asthma-free and without the use of albuterol compared to FP alone when the duration of treatment exceeded 12 weeks. No significant differences were observed between FSC and FP alone in the incidence of drug-related adverse events and other adverse events.
Conclusion: Both FSC and FP alone are viable options for the initial selection of step-up treatment in asthmatic children. While, FSC treatment demonstrates a greater likelihood of reducing asthma exacerbations which is particularly important for reducing the personnel, social and economic burden in children requiring step-up asthma treatment.

Respir Med. 2024 Apr 1:107611.
doi: 10.1016/j.rmed.2024.107611. Online ahead of print.

Benralizumab efficacy and safety in severe asthma: A randomized trial in Asia

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Abstract

Background: Benralizumab is indicated as add-on therapy in patients with uncontrolled, severe eosinophilic asthma; it has not yet been evaluated in a large Asian population with asthma in a clinical trial.
Objective: To evaluate the efficacy and safety of benralizumab in patients with severe asthma in Asia.
Methods: MIRACLE (NCT03186209) was a randomized, Phase 3 study in China, South Korea, and the Philippines. Patients aged 12-75 years with severe asthma receiving medium-to-high-dose inhaled corticosteroid/long-acting β_2-agonists, stratified (2:1) by baseline blood eosinophil count (bEOS) (≥300/μL; <300/μL), were randomized (1:1) to benralizumab 30 mg or placebo. Endpoints included annual asthma exacerbation rate (AAER; primary endpoint),

change from baseline at Week 48 in pre-bronchodilator (BD) forced expiratory volume in 1 second (pre-BD FEV_1) and total asthma symptom score (TASS). Safety was evaluated ≤ Week 56.
Results: Of 695 patients randomized, 473 had baseline bEOS ≥300/µL (benralizumab n = 236; placebo n = 237). In this population, benralizumab significantly reduced AAER by 74% (rate ratio 0.26 [95% CI 0.19, 0.36], p < 0.0001) and significantly improved pre-BD FEV_1 (least squares difference [LSD] 0.25 L [95% CI 0.17, 0.34], p < 0.0001) and TASS (LSD -0.25 [-0.45, -0.05], p = 0.0126) versus placebo. In patients with baseline bEOS <300/µL, there were numerical improvements in AAER, pre-BD FEV_1, and TASS with benralizumab versus placebo. The frequency of adverse events was similar for benralizumab (76%) and placebo (80%) in the overall population.
Conclusions: MIRACLE data reinforces the efficacy and safety of benralizumab for severe eosinophilic asthma in an Asian population, consistent with the global Phase 3 results.

J Asthma. 2024 Jun;61(6):574-583.
doi: 10.1080/02770903.2023.2294909. Epub 2023 Dec 28.
Doxofylline as a steroid-sparing treatment in Mexican children with asthma
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Abstract
Objective: The aim of this pilot study was to assess the efficacy of doxofylline as an ICS-sparing agent in the treatment of Mexican children with asthma.
Methods: 10-week, open-label, crossover, pilot study, we examined the steroid-sparing effect of doxofylline in Mexican children with asthma. Patients aged 6-16 years treated with inhaled corticosteroids (ICS) for at least 8 wk before enrollment were divided randomly into two groups at the baseline visit. Group A (*n* = 31) received doxofylline (18 mg/kg/day) plus standard-dose budesonide (D + SDB) for the first 4-week period followed by doxofylline plus reduced-dose budesonide (D + RDB) for the second 4-week period. Group B (*n* = 30) received D + RDB followed by D + SDB. Clinical outcomes assessed included lung function (forced expiratory volume; in 1 s, FEV1), fractional exhaled nitric oxide (FeNO), asthma control, number of exacerbations and use of rescue medication (salbutamol).
Results: It was shown that combined use of doxofylline and ICS may allow children with asthma to reduce their daily dose of ICS while maintaining lung function and improving asthma control (*p* = 0.008). There were few asthma exacerbations and only one patient required treatment with systemic corticosteroids. Rescue medication use decreased significantly in patients receiving D + SDB during the first 4-week period.
Conclusions: Our results suggest that doxofylline may be a steroid-sparing treatment in asthma, but longer-term, controlled studies are needed to confirm these observations.

J Asthma. 2023 Oct 3:1-11.
doi: 10.1080/02770903.2023.2267113. Online ahead of print.
Efficacy of Bhramari pranayama and Om chanting on asthma control, quality of life, and airway inflammation in asthmatic children: an open-label randomized controlled trial

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Abstract

Objectives: To explore the efficacy of combination of *Bhramari pranayama* and *om* chanting as an adjunct to standard pharmacological treatment on asthma control, quality of life, pulmonary function, and airway inflammation in asthmatic children.

Methods: Children (n = 110; 8-15 years) with uncontrolled or partly controlled asthma were recruited from the Pediatric Chest Clinic of All India Institute of Medical Sciences, New Delhi. Eligible participants were randomized to either home-based online *Bhramari pranayama* and *om* chanting plus standard treatment (YI + ST) group, or standard treatment (ST) alone group. Primary outcome measures were 12-week change in level of asthma symptom control; asthma control questionnaire (ACQ) score, spirometry indices, impulse oscillometry parameters, and pediatric asthma quality of life questionnaire (PAQLQ) score. Secondary outcome was a change in fractional exhaled nitric oxide (FeNO) levels at 12 weeks. Beginning from the enrollment, every participant was evaluated at 0, 2, 6, and 12 weeks.

Results: After 12 weeks of intervention, higher proportion (68.2%) of children were found to have controlled asthma symptoms in the YI + ST group as compared to ST group (38.5%) according to per protocol analysis (p = 0.03). When compared to ST group, children in YI + ST group showed significantly lower ACQ score, higher PAQLQ score and reduced FeNO levels. No significant changes were observed for the lung function parameters.

Conclusion: Children practicing *Bhramari pranayama* and o*m chanting* for 12 weeks have better asthma symptom control, quality of life, and reduced airway inflammation than those taking standard pharmacotherapy alone.

J Ethnopharmacol. 2024 Jan 10;318(Pt A):116862.
doi: 10.1016/j.jep.2023.116862. Epub 2023 Jul 10.

The hydroalcoholic extract of Nasturtium officinale reduces oxidative stress markers and increases total antioxidant capacity in patients with asthma

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Abstract

Ethnopharmacological relevance: Asthma is a common chronic disease characterized by inflammation of the airways. One of the most devastating consequences of this inflammatory process is the production of reactive oxygen species responsible for oxidative stress. Nasturtium officinale commonly known as watercress has traditionally been applied in Iranian folk medicine to treat respiratory disorders and diseases mainly bronchitis and asthma. In accordance with these ethnopharmacological reports, through our previous in vivo experiment, we have confirmed significant effect of its hydroalcoholic extract in reducing lung inflammation and oxidative stress in an ovalbumin-induced asthmatic rat model.

Aim of the study: The aim of the present study was to investigate the anti-inflammatory and antioxidant effects of N. officinale hydroalcoholic extract (NOE) in patients with asthma, in order to confirm our findings of the previous performed in vivo study.

Material and methods: The NOE capsules (500 mg) were treated twice daily for 4 weeks as a supplementary treatment in a randomized, double-blind, and placebo-controlled trial in asthmatics. The primary outcome was Asthma Control Test score. The blood samples were taken at the beginning and end of the study. Then, the level of inflammatory markers, oxidative stress markers and antioxidant enzyme activity were measured.
Results: Treatment with NOE for one month caused a reduction in the levels of MDA, PCO and NO metabolite markers compared to the placebo group. In addition, FRAP levels as an indicator of total antioxidant capacity in the intervention group was significantly increased at the end of the treatment period compared to pre-treatment values.
Conclusion: Findings demonstrated that NOE may have a therapeutic effect on asthma by improving oxidative stress. However, more studies are required to support these results. Moreover, bio-assay guided fractionation and isolation approach can be conducted to identify major bioactive compound/s.

Adolescent health

Overall health and well-being

J Adolesc Health. 2024 Apr 8:S1054-139X(24)00124-1.
doi: 10.1016/j.jadohealth.2024.02.032. Online ahead of print.

Meals, Education, and Gardens for In-School Adolescents: A Cluster Randomized Trial of an Adolescent Nutrition Intervention Package in Tanzania

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Abstract
Purpose: This study aimed to implement and evaluate integrated, school-based nutrition intervention packages for adolescents in Dodoma, Tanzania.
Methods: A cluster randomized controlled trial was conducted among six secondary schools in Dodoma, Tanzania. Two schools received the full-intervention package of school meals, nutrition education, school gardens, and community workshops. Two schools received the partial-intervention package without the school meals component. Two schools served as the controls and did not receive any intervention. The intervention was implemented over one academic year. The analytical sample included 534 adolescents aged 14 to 17 at baseline and 286 parents. Outcomes included nutrition knowledge, food preferences, diet quality, food insecurity, physical activity, growth, and anemia. Linear models were used to estimate mean differences, and logistic regression models were used to estimate odds ratios (ORs).
Results: Compared to the control, both the partial (OR: 0.59; 95% confidence interval [CI]: 0.35, 1.00) and full (OR: 0.49; 95% CI: 0.40, 0.59) interventions were associated with lower odds of poor diet quality among adolescents. Among the parents, both the partial (OR: 0.28; 95% CI: 0.20, 0.40) and full (OR: 0.28; 95% CI: 0.13, 0.58) interventions were associated with lower odds of poor diet quality. The partial (OR: 0.29; 95% CI: 0.18, 0.47) and full (OR: 0.47; 95% CI: 0.30, 0.72) interventions were associated with lower odds of adolescent overweight or obesity.

Discussion: School-based nutritional intervention packages incorporating multiple actions may improve the diet quality of adolescents and their household members and reduce the double burden of adolescent malnutrition.

J Int AIDS Soc. 2023 Oct;26 Suppl 4(Suppl 4):e26148.
doi: 10.1002/jia2.26148.

Better Together: acceptability, feasibility and preliminary impact of chronic illness peer support groups for South African adolescents and young adults

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Abstract

Introduction: Peer support can help navigate the isolation and psychological strain frequently experienced by youth living with chronic illness. Yet, data are lacking on the impact of providing support for youth living with mixed chronic conditions. We assessed the acceptability, feasibility and preliminary mental health impacts of a clinic-based peer support group for South African youth living with chronic illnesses, including HIV.

Methods: This mixed-methods pilot study (September 2021-June 2022) enrolled 58 young patients, ages 13-24, at an urban hospital in Cape Town, South Africa. In-depth interviews elicited the perspectives of 20 young people in relation to their participation in the Better Together programme, a recurring clinic-based peer support group for patients with mixed chronic illnesses. Self-reported resilience, attitudes towards illness, stigma and mental health were captured via established measures. T-tests and multivariate analysis of variance compared psychosocial outcomes for 20 group participants and 38 control patients, controlling for socio-demographic characteristics at enrolment. Logistic regression analyses estimated the predicted probability of a positive depression or anxiety screening given peer group participation.

Results: All interviewees valued being able to compare treatment regimens and disease management habits with peers living with different conditions. Adolescents living with HIV stated that understanding the hardships faced by those with other conditions helped them accept their own illness and lessened feelings of isolation. Compared to patients who did not participate in Better Together, those who attended ≥5 groups had statistically significantly higher individual-level resilience, a more positive attitude towards their illness(es), lower internalised stigma and a more positive self-concept. The probability of being screened positive for depression was 23.4 percentage points lower (95% CI: 1.5, 45.3) for Better Together participants compared to controls; the probability of a positive anxiety screening was 45.8 percentage points lower (95% CI: 18.1, 73.6).

Conclusions: Recurring, clinic-based peer support groups that integrate youth living with HIV and other chronic diseases are novel. Group sustainability will depend on the commitment of experienced peer leaders and providers, routine scheduling and transportation support. A fully powered randomised trial is needed to test the optimal implementation and causal mental health effects of the Better Together model.

PLoS One. 2023 Nov 3;18(11):e0293941.
doi: 10.1371/journal.pone.0293941. eCollection 2023.

Delivering PACE++ curriculum in community settings: Impact of TARA intervention on gender attitudes and dietary practices among adolescent girls in Bihar, India

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Abstract

Adolescence phase has high intrinsic and instrumental relevance. The Transformative Action for Rural Adolescents intervention delivered PACE++ curriculum with innovations to introduce a) health and nutrition sessions and b) delivery of the content in community settings of rural Bihar. This paper examines impact of the intervention showcasing establishment of intergenerational community connect for empowering and invigorating adolescent girls on gender attitude, empowerment and adolescent health and nutrition. The impact evaluation is based on a two-arm (intervention and comparison groups) cluster randomized controlled design with two rounds of representative cross-sectional surveys. The baseline and endline sample comprised of 2327 and 2033 adolescent girls (15-19 years), respectively. Descriptive statistical, difference-in-differences and propensity score matching methods are used to confirm the program impact. The DID and PSM analyses confirm high significance of impact on gender equity norms, diets and nutritional knowledge and understanding of employee related rights and responsibilities. School-going adolescent girls performed better than those who have discontinued formal education. The intervention showcases the importance of delivering the modified PACE curriculum in rural settings through leveraging community platforms. The findings call for greater policy attention on scaling up of similar initiatives for empowerment and social capital development of adolescent girls.

J Prev (2022). 2024 Feb;45(1):87-105.
doi: 10.1007/s10935-023-00751-1. Epub 2023 Oct 31.

Effectiveness of an e-Health Quasi-Randomized Controlled Universal Prevention Program for Eating Disorders in Spanish Adolescents

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Abstract

Eating disorders (EDs) and sub-threshold conditions are prevalent in the adolescent population. Unfortunately, most preventive interventions have been targeted at emerging adults and the effectiveness of online prevention programs has yet to be determined in adolescents. This study sought to examine the short-term effectiveness of a universal e-Health psychoeducational prevention program for EDs compared to a control (non-intervention) group in Spanish adolescents. Using a quasi-randomized trial design, a total of 161 [% girls: 45.96; Mage(SD) = 12.43 (0.43)] adolescents from 5 participating schools were allocated to two intervention arms: (1) psychoeducational intervention (n = 79) and (2) wait-list control (n = 82). The intervention was delivered over 3 months through 3 modules that were accessible 24/7 and 3 school sessions guided by the students´ tutors focusing on nutrition, promoting a healthy lifestyle, mitigating body concerns, and social pressures. Participants completed an online assessment battery including the Eating Attitudes Test (EAT-26) and measures of self-esteem, family disruption, compliance with the Mediterranean diet, and lifestyle. Correlational analysis showed small to moderate relationships between self-esteem and family function (rho = 0.413, p = 0.001), BMI (body mass index) and the EAT-26 dieting subscale (rho = 0.417, p = 0.001), physical activity and the bulimia subscale (rho = -

0.237, p = 0.003), and self-esteem and the dieting subscale (rho = - 0.223, p = 0.004). At the post-intervention assessment, the intervention group showed a statistically significant reduction in ED risk (EAT-26) (d = - 0.323, p = 0.040) and the oral control subscale (d = 0.327, p = 0.038). The e-health intervention including tutor-led digital components was effective for reducing ED risk in children. Results must be interpreted with caution due to the low statistical power and the limited sample size. Large scale randomized controlled trials with longer follow-ups will be needed to bolster the evidence.

Adolescent mental health

Compr Psychiatry. 2023 Nov:127:152424.
doi: 10.1016/j.comppsych.2023.152424. Epub 2023 Sep 16.

Evaluation of the Early Adolescent Skills for Emotions (EASE) intervention in Lebanon: A randomized controlled trial

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Abstract

Background: There is a need for scalable evidence-based psychological interventions for young adolescents experiencing high levels of psychological distress in humanitarian settings and low- and middle-income countries. Poor mental health during adolescence presents a serious public health concern as it is a known predictor of persistent mental disorders in adulthood. This study evaluates the effectiveness of a new group-based intervention developed by the World Health Organization (Early Adolescent Skills for Emotions; EASE), implemented by non-specialists, to reduce young adolescents' psychological distress among mostly Syrian refugees in Lebanon.

Methods: We conducted a two-arm, single-blind, individually randomized group treatment trial. Adolescents aged 10 to 14 years who screened positive for psychological distress using the Pediatric Symptom Checklist (PSC) were randomly allocated to EASE or enhanced treatment as usual (ETAU) (1:1.6). ETAU consisted of a single scripted psycho-education home-visit session with the adolescent and their caregivers. EASE consists of seven group sessions with adolescents and three sessions with caregivers. The primary outcome was adolescent-reported psychological distress as measured with the PSC (internalizing, externalizing, and attentional symptoms). Secondary outcomes included depression, posttraumatic stress, well-being, functioning, and caregivers' parenting and distress. All outcomes were assessed at baseline, endline, and 3 months (primary time point) and 12 months follow-up.

Results: Due to the COVID-19 pandemic and other adversities in Lebanon at the time of this research, the study was prematurely terminated, resulting in an under-powered trial sample (n = 198 enrolled compared to n = 445 targeted). We screened 604 children for eligibility. The 198 enrolled adolescents were assigned to EASE (n = 80) and ETAU (n = 118), with retention rates between 76.1 and 88.4% across all timepoints. Intent-to-treat analyses demonstrated

no between-group differences on any of the outcome measures between the EASE and ETAU. We did observe a significant improvement on the primary outcome equally in the EASE and ETAU groups (-0.90, 95% CI: -3.6, 1.8; p = .52), - a trend that was sustained at three months follow-up. Sub-group analyses, for those with higher depression symptoms at baseline, showed ETAU outperformed EASE on reducing depression symptoms (difference in mean change = 2.7, 95% CI: 0.1, 5.3; p = .04; d = 0.59) and internalizing problems (difference in mean change 1.0, 95% CI: 0.08, 1.9; p = .03; d = 0.56) .
Conclusion: No conclusions can be drawn about the comparative effectiveness of the intervention given that the sample was underpowered as a result of early termination. Both EASE and single session psycho-education home visits resulted in meaningful improvements in reducing psychological distress. We did not identify any indications in the data suggesting that EASE was more effective than a single session family intervention in the context of the COVID-19 pandemic and other crises in Lebanon. Fully powered research is needed to evaluate the effectiveness of EASE.

Body Image. 2023 Dec 5:48:101654.
doi: 10.1016/j.bodyim.2023.101654. Online ahead of print.

Evaluating a school-based body image lesson in Indonesia: A randomised controlled trial

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Abstract
Negative body image is a common public health concern among adolescents, globally. The aim of the current study was to evaluate the effectiveness, implementation fidelity, and acceptability of a single session, school-based universal body image intervention in Indonesia. A total of 1926 adolescents (59.4 % girls) and 12 school guidance counsellors (lesson facilitators) from nine state junior secondary schools in Surabaya, East Java took part in a two-arm open parallel cluster randomised controlled trial. In response to the changing circumstances due to the COVID-19 pandemic, half of the lessons were conducted in person and half were delivered online. Results showed that the lesson did not significantly improve adolescent body image or secondary outcomes relative to the control, though there was no evidence of harm. There were no substantive findings regarding intervention effectiveness by gender. The mode of intervention delivery (online vs. in-person) did not significantly influence the main findings. Implementation fidelity varied widely, and the lesson content and pedagogy were largely acceptable, though there was a strong preference for in-person lesson delivery. Findings have implications for researchers aiming to improve adolescent body image in low- and middle-income countries. Lessons learned can inform future school-based efforts to support adolescent body image.

Integr Med Res. 2023 Sep;12(3):100979.
doi: 10.1016/j.imr.2023.100979. Epub 2023 Jul 28.

The impact of yoga on stress, metabolic parameters, and cognition of Indian adolescents: Cluster randomized controlled trial

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Abstract

Background: This project aimed to assess the impact of yoga on stress, metabolic parameters and cognition (attention & concentration) in adolescents, aged 13-15 years from public and private schools in two cities (Chennai and New Delhi) in India.

Methods: The study recruited 2000 adolescents from 24 schools in a cluster randomized controlled trial design. The yoga group participants underwent 17 yoga sessions, which included: pranayama, basic asanas, meditation and relaxation exercises. Yoga sessions, were held in the school premises once a week. A total of five awareness talks on healthy lifestyle were delivered once a month to the education group. ADOlescence Stress Scale (ADOSS), salivary cortisol, metabolic and clinical parameters and Letter Cancellation Test (LCT) score were measured at baseline and post-intervention (5-6 months).

Results: The yoga group showed statistically significant differences in the mean ADOSS score, metabolic parameters, salivary cortisol, and LCT scores compared to the education group. In the intention- to- treat analysis, a significant reduction [5.11, 95% CI (4.78, 5.36), p = 0.001] in ADOSS score was seen in the yoga group compared to education.

Conclusion: Implementation of a 17-week standardized yoga program at the school level significantly decreased stress, improved attention and concentration, metabolic and clinical parameters in Indian adolescents.

BMC Health Serv Res. 2023 Aug 4;23(1):827.
doi: 10.1186/s12913-023-09856-z.

Costs and cost-effectiveness of Shamiri, a brief, layperson-delivered intervention for Kenyan adolescents: a randomized controlled trial

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Abstract

Background: Low- and middle-income countries (LMICs) have the highest socio-economic burden of mental health disorders, yet the fewest resources for treatment. Recently, many intervention strategies, including the use of brief, scalable interventions, have emerged as ways of reducing the mental health treatment gap in LMICs. But how do decision makers prioritize and optimize the allocation of limited resources? One approach is through the evaluation of delivery costs alongside intervention effectiveness of various types of interventions. Here, we evaluate the cost-effectiveness of Shamiri, a group- and school-based intervention for adolescent depression and anxiety that is delivered by lay providers and that teaches growth mindset, gratitude, and value affirmation.

Methods: We estimated the cost-effectiveness of Shamiri using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for economic evaluations. Changes in depression and anxiety were estimated using the Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder questionnaire (GAD-7) at treatment termination

and 7-month follow-up using two definitions of treatment benefit. Cost-effectiveness metrics included effectiveness-cost ratios and cost per number needed to treat.
Results: Base case cost assumptions estimated that delivering Shamiri cost $15.17 (in 2021 U.S. dollars) per student. A sensitivity analysis, which varied cost and clinical change definitions, estimated it cost between $48.28 and $172.72 to help 1 student in Shamiri, relative to the control, achieve reliable and clinically significant change in depression and anxiety by 7-month follow-up.
Conclusions: Shamiri appears to be a low-cost intervention that can produce clinically meaningful reductions in depression and anxiety. Lay providers can deliver effective treatment for a fraction of the training time that is required to become a licensed mental health provider (10 days vs. multiple years), which is a strength from an economic perspective. Additionally, Shamiri produced reliable and clinically significant reductions in depression and anxiety after only four weekly sessions instead of the traditional 12-16 weekly sessions necessary for gold-standard cognitive behavioral therapy. The school setting, group format, and economic context of a LMIC influenced the cost per student; however, broader conclusions about the cost-effectiveness of Shamiri have yet to be determined due to limited economic evaluations of mental health programs in LMICs.

J Adolesc Health. 2024 Jan;74(1):78-88.
doi: 10.1016/j.jadohealth.2023.08.012. Epub 2023 Sep 16.

Combining Asset Accumulation and Multifamily Group Intervention to Improve Mental Health for Adolescent Girls: A Cluster-Randomized Trial in Uganda

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Abstract
Purpose: The aim of this study is to expand the current knowledge on the relationship between poverty, family functioning, and the mental health of adolescent girls in families affected by poverty and HIV/AIDS in southern Uganda. The study investigates the association between family functioning and mental health and examines whether family functioning moderates the intervention effect on adolescent mental health.
Methods: Longitudinal data were collected over the course of 24 months in a cluster randomized controlled trial conducted among N=1,260 girls aged 14-17 years in Uganda. Participants were randomized into control group (n=408 girls from n=16 schools), matched youth development accounts treatment, YDA (n=471 girls from n=16 schools), and integrated intervention combining YDA with multiple family group component (n=381 girls from n=15 schools).
Results: We found a significant positive association between family functioning and mental health of adolescent girls in our sample. Moderator analyses suggests that effect of the intervention on Beck Hopelessness Scale was significantly moderated by family cohesion (χ^2 (4) =21.43; p = .000), frequency of family communication (χ^2 (4) =9.65; p = .047), and quality of child-caregiver relationship (χ^2 (4) =11.12; p = .025). Additionally, the intervention effect on depression was moderated by the comfort of family communication (χ^2 (4) =10.2; p = .037).
Discussion: The study findings highlight the importance of family functioning when examining the link from poverty to adolescent mental health. The study contributes to the scarce evidence suggesting that asset-accumulation opportunities combined with a family strengthening component may improve parenting practices and adolescent mental health in poor households.

PLoS One. 2023 Nov 20;18(11):e0293988.
doi: 10.1371/journal.pone.0293988. eCollection 2023.

Effectiveness of school-based psychological interventions for the treatment of depression, anxiety and post-traumatic stress disorder among adolescents in sub-Saharan Africa: A systematic review of randomized controlled trials

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Abstract

Background: Mental disorders among adolescents represent a high burden and early onset. They compromise their physical health, survival, and future potential. On the other hand, young people have inadequate access to essential health services in sub-Saharan Africa. We aimed to review school-based psychological interventions, contents, delivery, and evidence of effectiveness designed to treat depression, anxiety, or posttraumatic stress symptoms among adolescents and young adults aged 10-24.

Method: We searched articles on the following databases: PubMed, Scopus, Embase, and Science Direct from 17/10/2022 to 30/12/2022. Furthermore, relevant studies were searched from advanced google scholar, google and identified reference lists. We used MeSH browser for key words: psychological interventions, depression, anxiety, posttraumatic stress disorder and lists of Sub-Saharan Africa countries. We combined words using standard Boolean operators (OR, AND). The quality of studies was evaluated using the Cochrane Collaboration's risk of bias tool and the results were presented as a narrative synthesis since the interventions were very heterogenous.

Results: Fourteen randomized controlled trials were included for systematic review and more than half (57.14%) were from Kenya and Nigeria. Common school-based psychological interventions were cognitive behavioral therapy and Shamiri interventions (an intervention that focuses on youths to cultivate a growth mindset, practice gratitude and take the value). More than half (57.14%) of the interventions were delivered by non-specialists like teachers, lay providers and community health workers. Nearly one-fifth of the interventions were used individual modality. School-based psychological interventions provided by non-specialists also produced a greater reduction in adolescents' depressive, anxiety, and post-traumatic stress symptoms compared to the control groups.

Conclusion: Cognitive behavioral therapy and Shamiri interventions were the common treatment delivered in school settings. The range of interventions could be effectively delivered by non- professionals that promote task-shifting of psychological interventions from very scarce mental health specialists in these countries.

Rural Remote Health. 2023 Jul;23(3):7553.
doi: 10.22605/RRH7553. Epub 2023 Jul 10.

Effects of psychosocial support-based psychoeducation for Turkish pregnant adolescents on anxiety, depression and perceived social support: a randomized controlled study

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Abstract

Introduction: In this study, a psychosocial support-based (PSSB) psychoeducation program was provided to pregnant adolescents for improving their mental health and providing them with knowledge and skills to make positive behavioral changes. This study aimed to determine the effect of PSSB psychoeducation on anxiety, depression and perceived social support.

Methods: This study was conducted using a pre-test-post-test randomized controlled design. The population of the study included pregnant adolescents presenting to the obstetrics and gynecology outpatient clinic of a state hospital located in eastern Turkey. The sample size, determined using power analysis, included 105 pregnant adolescents (experimental group n=50, control group n=55). The participants in the experimental group were given PSSB psychoeducation. The control group did not receive any intervention. The data were collected using an introductory characteristics form, the Beck Anxiety Inventory, the Edinburgh Postpartum Depression Scale and the Multidimensional Scale of Perceived Social Support. SPSS v24.0 was used to analyze the data, and p-values less than 0.05 were accepted as statistically significant.

Results: It was established that there was a significant decrease in the anxiety and depression levels and a significant increase in the perceived social support levels in the experimental group in comparison to the control group after the PSSB psychoeducation intervention ($p<0.05$). In the intragroup comparisons, the difference between the pre-test and post-test scores for anxiety, depression and perceived social support was statistically significant in the experimental group ($p<0.05$), whereas this difference was insignificant in the control group ($p>0.05$).

Conclusion: The PSSB psychoeducation program reduced anxiety and depression and increased perceived social support levels of the pregnant adolescents. The PSSB psychoeducation program is a useful practical intervention for the mental health of pregnant adolescents. Thus, we recommend that psychiatric nurses take an active role in planning and implementing psychosocial interventions for pregnant adolescents and develop culture-specific interventions.

BMJ Open. 2023 Oct 3;13(10):e066586.
doi: 10.1136/bmjopen-2022-066586.

Effect of multi-level interventions on mental health outcomes among adolescents in sub-Saharan Africa: a systematic review

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Abstract

Objective: In sub-Saharan Africa (SSA), multiple factors contribute to the considerable burden of mental health disorders among adolescents, highlighting the need for interventions that address underlying risks at multiple levels. We reviewed evidence of the effectiveness of community or family-level interventions, with and without individual level interventions, on mental health disorders among adolescents in SSA.

Design: Systematic review using the Grades of Recommendation, Assessment, Development and Evaluation approach.

Data sources: A systematic search was conducted on Cochrane Library, MEDLINE, EMBASE, PSYCINFO and Web of Science up to 31 March 2021.

Eligibility criteria: Studies were eligible for inclusion in the review if they were randomised controlled trials (RCTs) or controlled quasi-experimental studies conducted in sub-Saharan African countries and measured the effect of an intervention on common mental disorders in adolescents aged 10-24 years.
Data extraction and synthesis: We included studies that assessed the effect of interventions on depression, anxiety, post-traumatic stress disorder and substance abuse. Substance abuse was only considered if it was measured alongside mental health disorders. The findings were summarised using synthesis without meta-analysis, where studies were grouped according to the type of intervention (multi-level, community-level) and participants.
Results: Of 1197 studies that were identified, 30 studies (17 RCTs and 3 quasi-experimental studies) were included in the review of which 10 delivered multi-level interventions and 20 delivered community-level interventions. Synthesised findings suggest that multi-level interventions comprise economic empowerment, peer-support, cognitive behavioural therapy were effective in improving mental health among vulnerable adolescents. Majority of studies that delivered interventions to community groups reported significant positive changes in mental health outcomes.
Conclusions: The evidence from this review suggests that multi-level interventions can reduce mental health disorders in adolescents. Further research is needed to understand the reliability and sustainability of these promising interventions in different African contexts.

Adolescent sexual and reproductive health

J Adolesc Health. 2023 Aug;73(2):244-251.
doi: 10.1016/j.jadohealth.2023.02.034. Epub 2023 Apr 17.
Using Hierarchical Regression to Examine the Predictors of Sexual Risk-Taking Attitudes among Adolescents Living with Human Immunodeficiency Virus in Uganda
Samuel Kizito[1], Flavia Namuwonge[2], Josephine Nabayinda[1], Proscovia Nabunya[1], Jennifer Nattabi[1], Ozge Sensoy Bahar[1], Joshua Kiyingi[1], Natasja Magorokosho[1], Fred M Ssewamala[3]
Abstract
Purpose: We explored the factors influencing sexual risk-taking attitudes-defined as beliefs and values regarding sexual activity-among adolescents living with human immunodeficiency virus (ALHIV) in Uganda.
Methods: The study used baseline data from a five-year cluster-randomized control trial (2012-2018) among 702 ALHIV in Uganda. Participants were aged 10-16 years, HIV-positive, taking antiretroviral therapy, and living within a family. We fitted hierarchical regression models to assess the demographic, economic, psychological, and social predictors of sexual risk-taking attitudes. Using R^2, the final model explained 11.4% of the total variance.
Results: Under economic factors, caregiver being formally employed (β = -0.08, 95% confidence interval [CI]: -0.10-0.06, p < .001), and the ALHIV working for pay (β = 1.78, 95% CI: 0.28-3.29, p = .022), were associated with sexual risk-taking attitudes. Among the psychological factors, more depressive symptoms (β = 0.22, 95% CI: 0.11-0.32, p < .001) were associated with more approving attitudes toward sexual risk-taking. Family and social

factors including communicating with the caregiver about HIV (β = 1.32, 95% CI: 0.56-2.08, p = .001), sex (β = 1.09, 95% CI: 0.20-1.97, p = .017), and experiencing peer pressure (β = 3.37, 95% CI: 1.85-4.89, p < .001) were also associated with more approving attitudes toward sexual risk-taking. The final model explained 11.54% of the total variance.
Discussion: Economic, psychological, and social factors influence sexual risk-taking attitudes among ALHIV. There is a need for more research to understand why discussing sex with caregivers improves adolescents' positive attitudes toward sexual risk-taking. These findings have significant ramifications in preventing sexual transmission of HIV among adolescents in low-income settings.

Reprod Health. 2023 Jul 19;20(1):105.
doi: 10.1186/s12978-023-01643-7.

Effectiveness of school-based sexual and reproductive health education among adolescent girls in Urban areas of Odisha, India: a cluster randomized trial

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Abstract
Background: Various studies revealed that adolescent girls have limited knowledge pertaining to sexual and reproductive health (SRH). The current study assessed the effectiveness of SRH education among adolescent girls in urban areas of Odisha, India.
Methods: The study design was a cluster randomized trial, where the clusters composed of eight Odia (regional language) medium government girls' high schools in Bhubaneswar, the capital city of the state of Odisha, India. For the selection of study participants, adolescent girls who were studying in the ninth and tenth standards were recruited from each school. Eight schools were randomized through restrictive randomization at a 1:1 ratio, with four schools each in the intervention and control arm. Baseline and end-line assessments were done using a pre-tested, semi-structured questionnaire. Following baseline assessment, an intervention was given with the help of handbooks developed by the study authors to the schools in the intervention arm. Outcomes included change in knowledge, attitude and practices pertaining to SRH.
Results: In our study at baseline, there were a total of 790 students, where 469 (59.4%) students were in the intervention arm, and 321 (40.6%) students were in the control arm. At baseline, only 282 (60.1%) in the intervention arm and 171 (53.3%) in the control arm were aware that physical bodily changes due to puberty were normal. After the intervention, there was a statistically significant increase in knowledge in intervention group 367 (94.8%) (p-value < 0.001). Most students used sanitary pads as absorbent, 97.2% in the intervention group and 98.4% in the control group. However, after the intervention, the use of other absorbents reduced to zero in the intervention group with a statistically significant difference (p < 0.05). The number of students having awareness on different methods of contraception increased from 51 (10.9%) to 337 (87.1%) in the intervention arm (p < 0.001), and of those having awareness on STIs/RTIs increased from 177 (38.2%) to 371 (96.1%) in the intervention group (p < 0.001).
Conclusion: From our study, there is a significant proportional change in knowledge, attitude, and practices pertaining to SRH. Our study recommends policymakers and program managers for the implementation of comprehensive SRH in the regular school curriculum.

Glob Health Action. 2023 Dec 31;16(1):2160543.
doi: 10.1080/16549716.2022.2160543.

Effectiveness of peer-led education interventions on contraceptive use, unmet need, and demand among adolescent girls in Gedeo Zone, South Ethiopia. A cluster randomized controlled trial

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Abstract

Background: Peer-led education interventions are assumed to be an effective means of increasing contraceptive utilization and demand in adolescents. However evidence is lacking on whether peer-led education is effective in promoting the demand for and use of contraceptives in adolescent girls, especially in resource-limited settings.

Objective: The present study evaluated the effectiveness of peer-led education interventions in improving contraceptive use, unmet needs, and demand among sexually active secondary school adolescent girls in Gedeo Zone, South Ethiopia.

Methods: A single-blinded cluster randomised controlled trial study was performed in six randomly selected secondary schools in the Gedeo Zone, southern Ethiopia. A total of 224 participants were recruited and randomly assigned to the intervention and control groups. The intervention group received peer-led education intervention for six months. A pre-tested and validated questionnaire was used to measure contraceptive use, unmet need, and contraceptive demand. A generalised estimating equation (GEE) model was used to examine the effectiveness of the intervention.

Result: After six months of intervention, the Differences-in-difference in contraceptive use, unmet need, and contraceptive demand between the intervention and control groups were 25.1%, 7.4%, and 17.7%, respectively. There was a statistically significant difference in contraceptive use [AOR = 8.7, 95% CI: (3.66, 20.83), unmet need for contraceptives [AOR = 6.2, 95% CI: (1.61, 24.36)] and contraceptive demand [AOR = 6.1, 95% CI: (2.43, 15.11)] between the intervention and control groups.

Conclusions: School-based peer education intervention effectively improved contraceptive use and unmet needs in a low-resource setting and created demand in sexually active adolescent girls. These results support the potential utility of this approach in similar settings for the promotion of contraception use and demand.

Front Public Health. 2023 Oct 23:11:1203376.
doi: 10.3389/fpubh.2023.1203376. eCollection 2023.

Effect of a school-linked life skills intervention on adolescents' sexual and reproductive health skills in Guji zone, Ethiopia (CRT)-A generalized linear model

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Abstract

Background: Although appropriate life skills are recognized as a fundamental right for adolescents and a critical component of health policy, they are often overlooked and rarely researched in pastoral communities. Life skills encompass the ability to adopt positive behaviors, which enable individuals to effectively deal with the demands and challenges of everyday life. This study aimed to evaluate the effectiveness of a school-linked life skills

intervention program on adolescents' sexual and reproductive health skills in the pastoral community of Guji zone.
Methods: A two-arm cluster randomized control trial with a pretest-posttest experimental design was conducted, involving the intervention group ($N = 375$) and the control group ($N = 384$). This study assessed the effect of a school-linked adolescent-friendly life skills intervention in comparison to the usual RH curriculum, used as a control arm. Pretest-posttest and posttest-posttest scores of the control group and trial groups were compared, and the data were collected using 27 self-administered questions. The collected data were analyzed using paired-sample independent *t*-tests and a generalized linear model to examine the relationship between the dependent and independent variables.
Results: Data were collected from 759 adolescents in 15 intervention and 15 control clusters. The findings have shown that the proportion of mean life skills score was significantly higher in the intervention clusters than controls [(375) 70.49% vs. (384) 62.25%, $P < 0.001$ 95% CI (0.06 and 0.1)]. Adolescents who were trained in school-linked life skills (β = 1.915, 95% CI: 1.411-2.418), were confident to make safe and informed decisions (β = 1.999, 95% CI: 1.562-2.436), and had life skills to deal with SRH issues (β = 1.66, 95% CI: 1.233-2.087) were significantly correlated with predicting the relevant life skills. The proportion of adolescents with SRH life skills increased from 384 (52%) at baseline to 375 (70%) at end line in the intervention group compared to 384 (60.31%) at baseline to 384 (62.31%) in control arms, respectively.
Conclusions: The implementation of a school-linked life skills intervention program proved to have a significant effect on SRH life skills development. Furthermore, individual-level and behavioral-level variables were significant in explaining variability in life skills development within the pastoral community. Therefore, we recommend scaling up this intervention in all high schools.

Health Educ Res. 2023 Sep 20;38(5):375-391.
doi: 10.1093/her/cyad025.

Goals for girls: a cluster-randomized trial to investigate a school-based sexual health programme amongst female learners in South Africa

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Abstract

The delivery of comprehensive sexuality education to adolescents at school is recognized as a long-term strategy to support adolescent health. Suboptimal sexual and reproductive health (SRH) outcomes among South African adolescents necessitate the ongoing development and optimization of SRH education and promotion models. We conducted a cluster-randomized controlled trial amongst secondary schools (n = 38) in Cape Town, South Africa, to evaluate a sport-based, near-peer-led SRH curriculum, SKILLZ, amongst female learners (n = 2791). Biomedical (sexually transmitted infections [STIs], human immunodeficiency virus [HIV] and pregnancy) and socio-behavioural (social support, gender norms and self-concept) outcomes were assessed pre and post intervention. Attendance at SKILLZ was low and intervention participants did not show an improvement in SRH outcomes, with HIV and pregnancy incidence remaining stable and STI prevalence remaining high and increasing in both control and intervention arms. Although evidence of positive socio-behavioural measures was present at baseline, participants with high attendance

showed further improvement in positive gender norms. SKILLZ did not demonstrate the capacity to significantly impact clinical SRH outcomes. Modest improvements in outcomes amongst high attenders suggest that the impact may be possible with improved attendance; however, in the absence of optimal attendance, alternative intervention strategies may be required to improve SRH outcomes amongst adolescents.

Int J Community Based Nurs Midwifery. 2023 Oct;11(4):237-246.
doi: 10.30476/IJCBNM.2023.99040.2276.

The Effect of Cognitive-behavioral Counseling on the Resilience of Female Adolescents with Premenstrual Syndrome: A Randomized Controlled Trial

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Abstract

Background: Premenstrual syndrome (PMS) is one of the causes of poor performance in women, with direct and indirect adverse effects on their marital, family, and social life. This study aimed to examine the effect of cognitive-behavioral counseling on resilience in adolescent girls with PMS.

Methods: This randomized clinical trial was conducted from February to May 2018 on 15-17-year-old girl adolescents in Hamadan high schools. Using the block randomization method and the block size of 10, we randomly assigned 120 participants with moderate to severe PMS into intervention (N=60) and control groups (N=60). Participants in the intervention group received eight 60-minute cognitive-behavioral counseling sessions for 8 weeks, and the control group received no intervention. Data were gathered using demographic questionnaire, Premenstrual Symptoms Screening Tool, and the Connor-Davidson resilience scale. Statistical analysis was performed using SPSS version 16. The Chi-square, independent-samples t-test, and paired t-tests were used to analyze the data. P values <0.05 were considered significant.

Results: The mean total resilience score and all its dimensions increased in the intervention group 3 months after the intervention (P<0.05). Mean scores of total resilience and all subscales except spiritual influences showed statistically significant differences between the intervention and control groups 3 months after the intervention (P<0.05).

Conclusion: Cognitive-behavioral counseling can improve resilience in female adolescents with moderate to severe PMS. It is recommended that school counselors can use cognitive-behavioral counseling to improve the resilience of girls with moderate to severe PMS

EClinicalMedicine. 2023 Oct 10:65:102261.
doi: 10.1016/j.eclinm.2023.102261. eCollection 2023 Nov.

Menstrual cups and cash transfer to reduce sexual and reproductive harm and school dropout in adolescent schoolgirls in western Kenya: a cluster randomised controlled trial

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Mwaki[3], Alie Eleveld[3], Isaac Ngere[4], Eunice Fwaya[5], Feiko O Ter Kuile[1], Daniel Kwaro[2], Penelope A Phillips-Howard[1]

Abstract

Background: High rates of sexual and reproductive health (SRH) harms and interrupted schooling are global challenges for adolescent girls, requiring effective interventions. We assessed the impact of menstrual cups (MCs) or cash transfers conditioned on school attendance (CCTs), or both, on SRH and schooling outcomes in western Kenya.

Methods: In this cluster-randomised Cups or Cash for Girls (CCG) trial, adolescent girls in Forms two and three at 96 secondary schools in Siaya County (western Kenya) were randomised to receive either CCT, MC, combined CCT and MC, or control (1:1:1:1) for an average of 30 months. The CCT intervention comprised 1500KES (US$15 in 2016) via a cash card each school trimester. All four treatment groups received puberty and hygiene training. Assenting girls with parent or guardian consent who were post-menarche, not pregnant, area residents, not boarding, and had no disabilities precluding participation were eligible. Socio-behavioural risk factors and incidence of HIV and herpes simplex virus type 2 (HSV-2) were measured annually. School retainment and adverse events were monitored throughout. The primary outcome comprised a composite of incident HIV, HSV-2 and/or all-cause school dropout by school exit examination. The primary analysis was by intention-to-treat (ITT) using generalised linear mixed models, controlling for *a priori* selected baseline covariates. The trial is registered with ClinicalTrials.gov, NCT03051789.

Findings: Between February 28, 2017 and June 30, 2021, 4137 girls (median age 17.1 [interquartile range (IQR): 16.3-18.0]) were enrolled and followed annually until completion of secondary school (median 2.5 years [IQR: 2.4-2.7]); 4106 (99.3%) contributed to the ITT analysis. No differences in the primary composite outcome between intervention and control groups were seen (MC: 18.2%, CCT: 22.1%, combined: 22.1%, control: 19.6%; adjusted risk ratio [aRR]: 0.97, 95% confidence interval 0.76-1.24; 1.14, 0.90-1.45; and 1.13, 0.90-1.43, respectively). Incident HSV-2 occurred in 8.6%, 13.3%, 14.8%, and 12% of the MC, CCT, combined and control groups, respectively (MC: RR: 0.67, 0.47-0.95, p = 0.027; aRR: 0.71, 0.50-1.01, p = 0.057; CCT: aRR: 1.02, 0.73-1.41, p = 0.92; combined aRR: 1.16, 0.85-2.58, p = 0.36). Incident HIV was low (MC: 1.2%, CCT: 1.5%, combined: 1.0%, and control: 1.4%; aRR: 0.88, 0.38-2.05, p = 0.77, aRR: 1.16, 0.51-2.62, p = 0.72, aRR: 0.80, 0.33-1.94, p = 0.62, respectively). No intervention decreased school dropout (MC: 11.2%, CCT: 12.4%, combined: 10.9%, control: 10.5%; aRR: 1.16, 0.86-1.57; 1.23, 0.91-1.65; and 1.06, 0.78-1.44, respectively). No related serious adverse events were seen.

Interpretation: MCs, CCTs, or both, did not protect schoolgirls against a composite of deleterious harms. MCs appear protective against HSV-2. Studies of longer follow-up duration with objective measures of health impact are needed in this population.

Reprod Health. 2024 Jan 13;21(1):6.
doi: 10.1186/s12978-023-01735-4.

The effectiveness of an m-Health intervention on the sexual and reproductive health of in-school adolescents: a cluster randomized controlled trial in Nigeria

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Abstract

Background: The implementation of the country-wide comprehensive sexuality education (CSE) curriculum among in-school adolescents remains abysmally low and mHealth-based interventions are promising. We assessed the effect of a mHealth-based CSE on the sexual and reproductive health (SRH) knowledge, attitude and behaviour of in-school adolescents in Ilorin, northcentral Nigeria.

Methods: Using schools as clusters, 1280 in-school adolescents were randomised into intervention and control groups. Data was collected at baseline (T_0), immediately after the intervention (T_1) and 3 months afterwards (T_2) on SRH knowledge, attitude and practice of risky sexual behaviour (RSB). Data analysis included test of associations using Chi-square, independent t-test and repeated measures ANOVA. Predictors were identified using binary logistic regression.

Results: In the intervention group, there was a statistically significant main effect on mean knowledge score ($F = 2117.252$, $p = < 0.001$) and mean attitude score ($F = 148.493$, $p = < 0.001$) from T_0 to T_2 compared to the control group which showed no statistically significant main effects in knowledge ($p = 0.073$), attitude ($p = 0.142$) and RSB ($p = 0.142$). Though the mean RSB score declined from T_0 to T_2, this effect was not statistically significant ($F = 0.558$, $p = 0.572$). Post-intervention, being female was a positive predictor of good SRH knowledge; being male was a positive predictor of RSB while being in a higher-class level was a negative predictor of RSB.

Conclusion: The mHealth-based CSE was effective in improving SRH knowledge and attitude among in-school adolescents. This strategy should be strengthened to bridge the SRH knowledge and attitude gap among in-school adolescents.

SSM Popul Health. 2024 Feb 15:25:101617.
doi: 10.1016/j.ssmph.2024.101617. eCollection 2024 Mar.

Age-disparate relationships at first sex and reproductive autonomy, empowerment, and sexual violence among adolescent girls and young women in Rwanda

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Abstract

Background: Age-disparate relationships (ADR) place adolescent girls and young women (AGYW) at higher risk of unprotected sex and HIV infection; few studies have investigated ADR at first sex in sub-Saharan Africa. This study investigates ADR at first sex and its association with reproductive autonomy, reproductive empowerment, contraception coercion, and consent at first sex among female Rwandan youth.

Methods: Cross-sectional data from a randomized trial ($n = 5768$) of in-school youth ages 12-19 at enrollment were analyzed with focus on those who reported sexual activity ($n = 1319$). General estimating equation linear models and Poisson models were used to estimate linear coefficients and prevalence ratios (PR), with 95% confidence intervals (CIs) estimated using robust standard errors.

Results: Females reported a significantly higher average partner age gap than males by 2.43 years (2.90 years vs. 0.46 years, 95% CI: 2.01, 2.86). Overall, 23.4% ($n = 102$) of sexually active AGYW engaged in an ADR at first sex. The prevalence of non-consensual first sex was 60% higher among AGYW reporting ADR at first sex compared to AGYW reporting similar-aged

partners (adjusted PR = 1.59, 95% CI: 1.25, 2.02). No association was found between ADR at first sex and reproductive autonomy, reproductive empowerment, or contraception coercion.
Conclusions: Our results suggest a high prevalence of sexual violence among AGYW engaging in first sex with an age-disparate partner. However, we did not find evidence that ADR at first sex affects reproductive autonomy or empowerment within the first few years of sexual initiation. Further research is needed to explore the impact of ADR at first sex and longer-term trajectories of sexual behaviour, empowerment and autonomy.

PLoS Med. 2023 Jul 25;20(7):e1004258.
doi: 10.1371/journal.pmed.1004258. eCollection 2023 Jul.

Analysis of bacterial vaginosis, the vaginal microbiome, and sexually transmitted infections following the provision of menstrual cups in Kenyan schools: Results of a nested study within a cluster randomized controlled trial

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Abstract
Background: Nonhygienic products for managing menstruation are reported to cause reproductive tract infections. Menstrual cups are a potential solution. We assessed whether menstrual cups would reduce bacterial vaginosis (BV), vaginal microbiome (VMB), and sexually transmitted infections (STIs) as studies have not evaluated this.
Methods and findings: A cluster randomized controlled trial was performed in 96 Kenyan secondary schools, randomized (1:1:1:1) to control, menstrual cup, cash transfer, or menstrual cup plus cash transfer. This substudy assessing the impact of menstrual cups on BV, VMB, and STIs, included 6 schools from the control (3) and menstrual cup only (3) groups, both receiving BV and STI testing and treatment at each visit. Self-collected vaginal swabs were used to measure VMB (16S rRNA gene amplicon sequencing), BV (Nugent score), and STIs. STIs were a composite of Chlamydia trachomatis and Neisseria gonorrhoeae (nucleic acid amplification test) and Trichomonas vaginalis (rapid immunochromatographic assay). Participants were not masked and were followed for 30 months. The primary outcome was diagnosis of BV; secondary outcomes were VMB and STIs. Intention-to-treat blinded analyses used mixed effects generalized linear regressions, with random effects term for school. The study was conducted between May 2, 2018, and February 7, 2021. A total of 436 participants were included: 213 cup, 223 control. There were 289 BV diagnoses: 162 among control participants and 127 among intervention participants (odds ratio 0.76 [95% CI 0.59 to 0.98]; p = 0.038). The occurrence of Lactobacillus crispatus-dominated VMB was higher among cup group participants (odds ratio 1.37 [95% CI 1.06 to 1.75]), as was the mean relative abundance of L. crispatus (3.95% [95% CI 1.92 to 5.99]). There was no effect of intervention on STIs (relative risk 0.82 [95% CI 0.50 to 1.35]). The primary limitations of this study were insufficient power for subgroup analyses, and generalizability of findings to nonschool and other global settings.
Conclusions: Menstrual cups with BV and STI testing and treatment benefitted adolescent schoolgirls through lower occurrence of BV and higher L. crispatus compared with only BV

and STI testing and treatment during the 30 months of a cluster randomized menstrual cup intervention.

SAHARA J. 2024 Dec;21(1):2320188.
doi: 10.1080/17290376.2024.2320188. Epub 2024 Feb 22.

Sexual behaviour among Kenyan adolescents enrolled in an efficacy trial of a smartphone game to prevent HIV: a cross-sectional analysis of baseline data

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Abstract

Sexual behaviour of adolescents is contextual, with various determinants affecting sexual activity and age of sexual debut. Insight into sexual activity among young adolescents has the potential to influence appropriate sexual and reproductive health interventions. For this analysis, adolescents were recruited as part of the *Tumaini* smartphone game efficacy trial. Data collection included a self-administered behavioural survey and blood test for HIV and HSV-2. Descriptive statistics were calculated for demographics and measures of sexual behaviour and behavioural intent based on gender and sexual experience, with associations assessed using chi-square tests, *t*-tests and Wilcoxon rank sum tests as appropriate. We enrolled 996 adolescents, mean age 14 years and 2.2% HSV-2 positivity. Overall, 15% of the adolescents were sexually experienced, this being associated with lower socio-economic status ($p = 0.01$), household food insecurity ($p = 0.008$), a living situation without both parents ($p < 0.01$), substance use ($p = 0.02$), no adult conversation about future goals ($p = 0.003$), conversations about condoms ($p = 0.01$), with some gender disparity within these factors. Among those sexually experienced, 21.7% reported unwilling sex; 17.5% had engaged in transactional sex; 57.8% had willing first sex, of whom 60.9% reported no condom use. Among those abstaining, female adolescents were less likely to contemplate condom use at first sex ($p = 0.006$). Our findings determine that young sexually active adolescents are likely engaging in unprotected sex and having unwilling sexual experiences. Socio-economic status, living situation and parental monitoring remain significant factors associated with sexual experience among young adolescents. In this context, early adolescence is an opportunity to provide age- and developmentally appropriate education about safer sex practices.

Reprod Health. 2024 Apr 22;21(1):56.
doi: 10.1186/s12978-024-01789-y.

High uptake of menstrual health information, products and analgesics within an integrated sexual reproductive health service for young people in Zimbabwe

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Abstract

Background: Despite being integral to women's well-being, achieving good menstrual health (MH) remains a challenge. This study examined MH services uptake (including information, analgesics, and a choice of MH products - the menstrual cup and reusable pads) and sustained use of MH products within an integrated sexual and reproductive health intervention for young people in Zimbabwe.
Methods: This mixed-methods study was nested within a cluster randomised trial of integrated sexual and reproductive health services (CHIEDZA) for youth in three provinces (Harare, Mashonaland East, and Bulawayo). The study collected qualitative and quantitative data from 27,725 female clients aged 16-24 years, who accessed CHIEDZA from April 2019 - March 2022. Using a biometric (fingerprint recognition) identification system, known as SIMPRINTS, uptake of MH information, products, and analgesics and other services was tracked for each client. Descriptive statistics and logistic regression were used to investigate MH service uptake and product choice and use over time, and the factors associated with these outcomes. Thematic analysis of focus group discussions and interviews were used to further explore providers' and participants' experiences of the MH service and CHIEDZA intervention.
Results: Overall, 36,991 clients accessed CHIEDZA of whom 27,725 (75%) were female. Almost all (n = 26,448; 95.4%) took up the MH service at least once: 25433 took up an MH product with the majority (23,346; 92.8%) choosing reusable pads. The uptake of cups varied across province with Bulawayo province having the highest uptake (13.4%). Clients aged 20-24 years old were more likely to choose cups than reusable pads compared with those aged 16-19 years (9.4% vs 6.0%; $p < 0.001$). Over the implementation period, 300/1819 (16.5%) of clients swapped from the menstrual cup to reusable pads and 83/23346 (0.4%) swapped from reusable pads to the menstrual cup. Provision of the MH service encouraged uptake of other important SRH services. Qualitative findings highlighted the provision of free integrated SRH and MH services that included a choice of MH products and analgesics in a youth-friendly environment were key to high uptake and overall female engagement with SRH services.
Conclusions: High uptake demonstrates how the MH service provided much needed access to MH products and information. Integration of MH within an SRH intervention proved central to young women accessing other SRH services.

BMC Public Health. 2024 May 28;24(1):1424.
doi: 10.1186/s12889-024-18894-z.

The impact of an innovative community-based peer-led intervention on uptake and coverage of sexual and reproductive health services among adolescents and young people 15-24 years old: results from the Yathu Yathu cluster randomised trial

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Abstract
Background: The Yathu Yathu ("For Us, By Us") cluster-randomized trial (CRT) evaluated a peer-led community-based sexual and reproductive health(SRH) intervention implemented to address persistent barriers to SRH service use among adolescents and young people (AYP). We report the impact of the intervention on coverage of key SRH services among AYP.

Methods: The trial was conducted from Jul 2019-Oct 2021 in two urban communities in Lusaka, Zambia, divided into 20 zones (~ 2350 AYP/zone). Zones were randomly allocated to intervention (N = 10) or control (N = 10) arm. In all zones, a census was conducted and all AYP aged 15-24-years offered participation. The intervention consisted of peer-led community-based hubs providing SRH services; a prevention points card (PPC) system to incentivize and track SRH service use and community engagement. This paper reports on the outcome of coverage (accessing at least one key SRH service), comparing intervention and control arms using PPC data and standard methods of analysis for CRTs.
Results: Among enumerated AYP, 93.6% (14,872/15,894) consented to participate from intervention zones and 95.1% (14,500/15,255) from control zones. Among those who accepted a PPC, 63.8% (9,493/14,872) accessed at least one key SRH service during the study period in the intervention arm, compared to 5.4% (776/14,500) in the control arm (adjPR 12.3 95%CI 9.3-16.2, p < 0.001).
Conclusions: The Yathu Yathu intervention increased coverage of key SRH services among AYP and reached two-thirds of AYP. These findings demonstrate the potential of providing peer-led community-based SRH services.

Adolescent pregnancy and child marriage

J Glob Health. 2024 Feb 23:14:04020.
doi: 10.7189/jogh.14.04020.

Effectiveness of combined interventions to empower girls and address social norms in reducing child marriage in a rural sub-district of Bangladesh: A Cluster Randomised Controlled Trial of the Tipping Point Initiative

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Abstract
Background: Elimination of girl child marriage (CM) globally at the current pace is projected to take about 300 years. Thus, innovative and effective solutions are urgently warranted. Bangladesh reports one of the highest rates of CM in the world. We present the impact of Tipping Point Initiative (TPI), a combined intervention to empower girls and to address social norms on CM in Bangladesh.
Methods: A three-arm non-blinded Cluster Randomised Controlled Trial was conducted in 51 villages/clusters in a sub-district of Bangladesh. Clusters were randomly assigned to the arms: Tipping Point Program (TPP), Tipping Point Program Plus (TPP+), and Pure Control. TPP conducted 40 weekly single-gender group sessions with never-married adolescent girls and boys recruited at 12 -<16 years; and 18-monthly gender-segregated group sessions with the parents. On top of TPP, TPP+ included cross-gender and -generation dialogues, girls' movement building and girl-led community sensitisation. Intention-to-treat analysis was performed to assess the impact of TPI on the hazard of CM, the primary outcome. The impact of girls' session attendance on CM was also assessed. At baseline 1275 girls (TPP = 412; TPP+ = 420; Control = 443) were interviewed between February-April 2019. At endline 1123 girls (TPP = 363; TPP + = 366; Control = 394) were interviewed and included in the analyses.

Results: No intervention impact was detected on the full sample (TPP vs. Control: adjusted hazard ratio (aHR) = 1.14; 95% CI = 0.79-1.63, P = 0.47), (TPP + vs. Control: aHR = 1.24; 95% CI = 0.89-1.71, P = 0.19, (TPP vs. TPP+: aHR = 1.03; 95% CI = 0.72-1.47, P = 0.87). However, in the TPP arm, the hazard of CM was reduced by 54% (aHR = 0.46; 95% CI = 0.23-0.92, P = 0.03) among the girls in the highest tertile of session attendance, compared to the lowest. In the TPP+ arm, this hazard was reduced by 49% (aHR = 0.51; 95% CI = 0.23-0.92, P = 0.03) among girls in the highest tertile, compared to the lowest tertile.
Conclusions: Although TPI did not show an effect on CM in any of the intervention arms, within each intervention arm, a positive effect was detected in reducing CM among girls in the highest tertile of session attendance despite implementation challenges due to COVID-19.

Sci Rep. 2024 Mar 1;14(1):5070.
doi: 10.1038/s41598-024-55709-y.

Effect of nutrition counseling on nutritional status and gestational weight gain of pregnant adolescents in West Arsi, Central Ethiopia: a cluster randomized controlled trial

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Abstract
When pregnancy occurs in adolescence, the growth and development of the mother and fetus may be impaired due to strong competition for nutrients between the still-growing adolescent and the fetus. Pregnant adolescents constitute an underserved population; they lack adequate nutritional knowledge. Therefore, this study investigated the effect of nutritional behavior change communication (NBCC) through alliance for development (AFD) on the nutritional status and gestational weight gain (GWG) of pregnant adolescents. A two-arm parallel cluster randomized controlled community trial was conducted in the West Arsi Zone, central Ethiopia, from August 2022 to July 2023. The nutritional status of the pregnant adolescent was assessed using mid-upper arm circumference. Weight was measured at baseline and at the end of the intervention. A total of 207 and 219 pregnant adolescents participated in the intervention and control clusters, respectively. The intervention started before 16 weeks of gestation, and the intervention group attended four NBCC sessions. The NBCC was based on the health belief model (HBM) and was given at the participants' homes with their husbands. The NBCC intervention was delivered by AFDs and community-level health actors. Pregnant adolescents in the control group received routine nutrition education from the health care system. A linear mixed-effects model and difference in difference (DID) were used to measure the intervention effect after adjusting for potential confounders. After the implementation of the trial, the mean mid-upper arm circumference (MUAC) in the intervention arm significantly increased from baseline ($p \leq 0.001$), 23.19 ± 2.1 to 25.06 ± 2.9 among intervention group and 23.49 ± 2.1 to 23.56 ± 2.0 among control group and the mean difference in the MUAC (DID) was 1.89 ± 2 cm ($p \leq 0.001$); the mean GWG in the intervention arm significantly increased from baseline; 51.54 ± 4.7 to 60.98 ± 4.6 among intervention group and 52.86 ± 5.27 to 58 ± 5.3 among control group; the mean GWG in the intervention group was 9.4 kg, and that in the control group was 5.14 kg, and the difference in difference was 4.23 kg and this was statically significant $p \leq 0.001$). This study demonstrated that the use of the HBM for NBCC delivered through the AFD was effective at

improving the nutritional status and GWG of pregnant adolescents. These results imply the need for the design of model-based nutritional counseling guidelines.

Adolescents and HIV prevention and treatment

Lancet HIV. 2023 Aug;10(8):e518-e527.
doi: 10.1016/S2352-3018(23)00118-2.

A multilevel health system intervention for virological suppression in adolescents and young adults living with HIV in rural Kenya and Uganda (SEARCH-Youth): a cluster randomised trial

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Abstract

Background: Social and cognitive developmental events can disrupt care and medication adherence among adolescents and young adults living with HIV in sub-Saharan Africa. We hypothesised that a dynamic multilevel health system intervention helping adolescents and young adults and their providers navigate life-stage related events would increase virological suppression compared with standard care.

Methods: We did a cluster randomised, open-label trial of young individuals aged 15-24 years with HIV and receiving care in eligible clinics (operated by the government and with ≥25 young people receiving care) in rural Kenya and Uganda. After clinic randomisation stratified by region, patient population, and previous participation in the SEARCH trial, participants in intervention clinics received life-stage-based assessment at routine visits, flexible clinic access, and rapid viral load feedback. Providers had a secure mobile platform for interprovider consultation. The control clinics followed standard practice. The primary, prespecified endpoint was virological suppression (HIV RNA <400 copies per mL) at 2 years of follow-up among participants who enrolled before Dec 1, 2019, and received care at the study clinics. This trial is registered with ClinicalTrials.gov, NCT03848728, and is closed to recruitment.

Findings: 28 clinics were enrolled and randomly assigned (14 control, 14 intervention) in January, 2019. Between March 14, 2019, and Nov 26, 2020, we recruited 1988 participants at the clinics, of whom 1549 were included in the analysis (785 at intervention clinics and 764 at control clinics). The median participant age was 21 years (IQR 19-23) and 1248 (80·6%) of 1549 participants were female. The mean proportion of participants with virological suppression at 2 years was 88% (95% CI 85-92) for participants in intervention clinics and 80% (77-84) for participants in control clinics, equivalent to a 10% beneficial effect of the intervention (risk ratio [RR] 1·10, 95% CI 1·03-1·16; p=0·0019). The intervention resulted in increased virological suppression within all subgroups of sex, age, and care status at baseline, with greatest improvement among those re-engaging in care (RR 1·60, 95% CI 1·00-2·55; p=0·025).

Interpretation: Routine and systematic life-stage-based assessment, prompt adherence support with rapid viral load testing, and patient-centred, flexible clinic access could help bring adolescents and young adults living with HIV closer towards a goal of universal virological suppression.

PLoS One. 2023 Oct 13;18(10):e0292719.
doi: 10.1371/journal.pone.0292719. eCollection 2023.

"Project YES! has given me a task to reach undetectable": Qualitative findings from a peer mentoring program for youth living with HIV in Zambia

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Abstract

The Project YES! clinic-based peer mentoring program was a randomized controlled trial (RCT) conducted among 276 youth from four HIV clinics to test the impact of the program on promoting HIV self-management and reducing internalized stigma among youth living with HIV (ages 15-24 years) in Ndola, Zambia. We conducted a qualitative sub-study involving in-depth interviews with 40 intervention youth participants (21 female, 19 male) to explore their experiences with Project YES! which included: an orientation meeting led by a healthcare provider, monthly individual and group counseling sessions over six months, and three optional caregiver group sessions. Using baseline RCT data, we used maximum variation sampling to purposively select youth by sex, age, change in virologic results between baseline and midline, and study clinic. A four-person team conducted thematic coding. Youth described their increased motivation to take their HIV care seriously due to Project YES!, citing examples of improvements in ART adherence and for some, virologic results. Many cited changes in behavior in the context of greater feelings of self-worth and acceptance of their HIV status, resulting in less shame and fear associated with living with HIV. Youth also attributed Project YES! with reducing their sense of isolation and described Project YES! youth peer mentors and peers as their community and "family." Findings highlight that self-worth and personal connections play a critical role in improving youths' HIV outcomes. Peer-led programs can help foster these gains through a combination of individual and group counseling sessions. Greater attention to the context in which youth manage their HIV, beyond medication intake, is needed to reach global HIV targets.

PLoS One. 2024 Feb 8;19(2):e0296734.
doi: 10.1371/journal.pone.0296734. eCollection 2024.

Estimating the costs of adolescent HIV care visits and an intervention to facilitate transition to adult care in Kenya

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Abstract

Introduction: Adolescents with HIV in sub-Saharan Africa face challenges transitioning to adult HIV care, which can affect long-term HIV care adherence and retention. An adolescent transition package (ATP) focused on transition tools can improve post-transition clinical outcomes, but its implementation costs are unknown.

Methods: We estimated the average cost per patient of an HIV care visit and ATP provision to adolescents. Data was collected from 13 HIV clinics involved in a randomized clinical trial evaluating ATP in western Kenya. We conducted a micro-costing and activity-driven time estimation to assess costs from the provider perspective. We developed a flow-map, conducted staff interviews, and completed time and motion observation. ATP costs were estimated as the difference in average cost for an HIV care transition visit in the intervention compared to control facilities. We assessed uncertainty in costing estimates via Monte Carlo simulations.
Results: The average cost of an adolescent HIV care visit was 29.8USD (95%CI 27.5, 33.4) in the standard of care arm and 32.9USD (95%CI 30.5, 36.8) in the ATP intervention arm, yielding an incremental cost of 3.1USD (95%CI 3.0, 3.4) for the ATP intervention. The majority of the intervention cost (2.8USD) was due ATP booklet discussion with the adolescent.
Conclusion: The ATP can be feasibly implemented in HIV care clinics at a modest increase in overall clinic visit cost. Our cost estimates can be used to inform economic evaluations or budgetary planning of adolescent HIV care interventions in Kenya.

J Int AIDS Soc. 2023 Oct;26(10):e26185.
doi: 10.1002/jia2.26185.

Findings from the Tushirikiane mobile health (mHealth) HIV self-testing pragmatic trial with refugee adolescents and youth living in informal settlements in Kampala, Uganda

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Abstract
Introduction: Urban refugee youth remain underserved by current HIV prevention strategies, including HIV self-testing (HIVST). Examining HIVST feasibility with refugees can inform tailored HIV testing strategies. We examined if HIVST and mobile health (mHealth) delivery approaches could increase HIV testing uptake and HIV status knowledge among refugee youth in Kampala, Uganda.
Methods: We conducted a three-arm pragmatic controlled trial across five informal settlements grouped into three sites in Kampala from 2020 to 2021 with peer-recruited refugee youth aged 16-24 years. The intervention was HIVST and HIVST + mHealth (HIVST with bidirectional SMS), compared with standard of care (SOC). Primary outcomes were self-reported HIV testing uptake and correct status knowledge verified by point-of-care testing. Some secondary outcomes included: depression, HIV-related stigma, and adolescent sexual and reproductive health (SRH) stigma at three time points (baseline [T0], 8 months [T1] and 12 months [T2]). We used generalized estimating equation regression models to estimate crude and adjusted odds ratios comparing arms over time, adjusting for age, gender and baseline imbalances. We assessed study pragmatism across PRECIS-2 dimensions.
Results: We enrolled 450 participants (50.7% cisgender men, 48.7% cisgender women, 0.7% transgender women; mean age: 20.0, standard deviation: 2.4) across three sites. Self-reported HIV testing uptake increased significantly from T0 to T1 in intervention arms: HIVST arm: (27.6% [n = 43] at T0 vs. 91.2% [n = 135] at T1; HIVST + mHealth: 30.9% [n = 47] at T0 vs. 94.2% [n = 113] at T1]) compared with SOC (35.5% [n = 50] at T0 vs. 24.8% [= 27] at T1) and

remained significantly higher than SOC at T2 (p<0.001). HIV status knowledge in intervention arms (HIVST arm: 100% [n = 121], HIVST + mHealth arm: 97.9% [n = 95]) was significantly higher than SOC (61.5% [n = 59]) at T2. There were modest changes in secondary outcomes in intervention arms, including decreased depression alongside increased HIV-related stigma and adolescent SRH stigma. The trial employed both pragmatic (eligibility criteria, setting, organization, outcome, analysis) and explanatory approaches (recruitment path, flexibility of delivery flexibility, adherence flexibility, follow-up).
Conclusions: Offering HIVST is a promising approach to increase HIV testing uptake among urban refugee youth in Kampala. We share lessons learned to inform future youth-focused HIVST trials in urban humanitarian settings.

J Pediatr Psychol. 2023 Nov 16;48(11):907-913.
doi: 10.1093/jpepsy/jsad081.

Enhancing Adherence to Antiretroviral Therapy Among Adolescents Living With HIV Through Group-Based Therapeutic Approaches in Uganda: Findings From a Pilot Cluster-Randomized Controlled Trial

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Abstract
Objective: We examine the preliminary impact of group-cognitive behavioral therapy (G-CBT) versus a family-strengthening intervention delivered via multiple family group (MFG) in improving ART adherence among adolescents living with HIV (ALHIV) in Uganda.
Methods: We analyzed data from a pilot cluster-randomized trial (2020-2022) conducted in 9 clinics in Uganda among 89 participants, who were eligible out of the 147 ALHIV screened. Participants were eligible if they were aged 10-14 years, HIV positive, taking ART, and living with a family. Adolescents were randomized, at the clinic level, to receive the usual care (n = 29), MFG (n = 34), or G-CBT (n = 26). The interventions were delivered over 3 months. Overall, the mean percentage attendance for the 10 G-CBT and MFG sessions was 87.7% and 90.2%, respectively. Three ALHIV were lost to follow-up, while 1 child died. Adherence was assessed using pharmacy records collected at baseline and 4 additional pharmacy visits. We used mixed-effects logistic regression analysis to examine the effect of the interventions on ART adherence.
Results: We found statistically significant main effects for the intervention, $\chi2(2) = 7.76$, $p = .021$, time, $\chi2(2) = 39.67$, $p < .001$, and intervention-time interaction effect $\chi2(6)= 27.65$, $p < .001$. Pairwise comparisons showed increasing adherence in the MFG group compared to usual care at visit 3 (odds ratio [OR] = 4.52 [1.01-20.11], p = .047) and visit 5 (OR = 3.56 [1.42-8.91], p = .007). Also, compared to usual care, participants who received G-CBT showed higher adherence at visit 4 (OR = 2.69 [1.32-5.50], p = .007).
Conclusions: Our study showed preliminary evidence that G-CBT and MFG might have contributed to improved ART adherence among ALHIV. Moreover, G-CBT is a low-cost alternative to expensive individual therapy, especially in low-resource settings. The results warrant the need for more extensive studies to better understand the role of these interventions in the routine care of ALHIV

J Pediatr. 2024 Jun:269:113983.

doi: 10.1016/j.jpeds.2024.113983. Epub 2024 Feb 23.

Preliminary Impact of Group-Based Interventions on Stigma, Mental Health, and Treatment Adherence Among Adolescents Living with Human Immunodeficiency Virus in Uganda

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Abstract

Objective: To examine the preliminary impact of group cognitive behavioral therapy and multiple family group-based family strengthening to address HIV stigma and improve the mental health functioning of adolescents living with HIV in Uganda.

Study design: We analyzed data from the Suubi4Stigma study, a 2-year pilot randomized clinical trial that recruited adolescents living with HIV (10-14 years) and their caregivers (n = 89 dyads), from 9 health clinics. We fitted separate three-level mixed-effects linear regression models to test the effect of the interventions on adolescent outcomes at 3 and 6 months post intervention initiation.

Results: The average age was 12.2 years and 56% of participants were females. Participants in the multiple family group-based family strengthening intervention reported lower levels of internalized stigma (mean difference = -0.008, 95% CI = -0.015, -0.001, P = .025) and depressive symptoms at 3 months (mean difference = -0.34, 95% CI = -0.53, -0.14, P < .001), compared with usual care. On the other hand, participants in the group cognitive behavioral therapy intervention reported lower levels of anticipated stigma at 3 months (mean difference = -0.039, 95% CI = -0.072, -0.006), P = .013) and improved self-concept at 6 months follow-up (mean difference = 0.04, 95% CI = 0.01, 0.01, P = .025).

Conclusion: Outcome trends from this pilot study provide compelling evidence to support testing the efficacy of these group-based interventions on a larger scale.

Indian J Pediatr. 2024 Jun;91(6):578-583.
doi: 10.1007/s12098-022-04195-z. Epub 2022 Jun 30.

Effect of Nutritional Supplementation on Illness Outcome in Adolescents with HIV on HAART: A Randomized, Double-Blind Clinical Trial

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Abstract

Objective: To assess the effect of macronutrient and micronutrient supplementation on body mass index (BMI), hemoglobin (Hb), CD4 count, triglyceride levels, and morbidity among adolescents with human immunodeficiency virus (HIV) living in India.

Methods: A prospective, randomized, double-blinded, placebo-controlled trial was conducted among 80 adolescents (10-19 y) with HIV on highly active antiretroviral therapy (HAART) for a minimum of 6 mo using simple randomization. Participants in the intervention arm received 400 kcal and 15 g protein as a powder daily and multivitamin tablets thrice weekly for 3 mo. Those in the placebo arm received a similar-appearing sachet containing 100 kcal and 2 g protein daily and a placebo tablet thrice weekly. Weight, height, BMI, Hb, CD4 count, triglycerides, and number of intercurrent illnesses were measured at 3 and 6 mo.

Results: At 6 mo, the intervention group showed an increase in weight from 36.4 ± 10.9 kg to 39.7 ± 8.5 kg and a significant increase in BMI from 16.6 ± 2.3 kg/m^2 to 17.5 ± 2.3 kg/m^2. Increase in CD4 count in the placebo arm was more than that in the intervention arm, but the difference between the arms was not statistically significant. Intervention group showed a pronounced rise in Hb from 9.7 ± 2.3 g/dL to 11.4 ± 1.6 g/dL, significant reduction in triglyceride levels from 99.2 ± 92.7 mg/dL to 81.0 ± 12.8 mg/dL and reduction in intercurrent illnesses from 32.5% to none.
Conclusions: Nutritional supplementation of adolescents with HIV on HAART improves BMI, hemoglobin, and reduces triglyceride levels and intercurrent illnesses.

PLOS Glob Public Health. 2024 Feb 21;4(2):e0002553.
doi: 10.1371/journal.pgph.0002553. eCollection 2024.

Differentiated care for youth in Zimbabwe: Outcomes across the HIV care cascade

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Abstract

Youth living with HIV are at higher risk than adults of disengaging from HIV care. Differentiated models of care such as community delivery of antiretroviral therapy (ART) may improve treatment outcomes. We investigated outcomes across the HIV cascade among youth accessing HIV services in a community-based setting. This study was nested in a cluster-randomised controlled trial (CHIEDZA: Clinicaltrials.gov, Registration Number: NCT03719521) conducted in three provinces in Zimbabwe and aimed to investigate the impact of a youth-friendly community-based package of HIV services, integrated with sexual and reproductive health services for youth (16-24 years), on population-level HIV viral load (VL). HIV services included HIV testing, ART initiation and continuous care, VL testing, and adherence support. Overall 377 clients were newly diagnosed with HIV at CHIEDZA, and linkage to HIV care was confirmed for 265 (70.7%, 234 accessed care at CHIEDZA and 31 with other providers); of these 250 (94.3%) started ART. Among those starting ART at CHIEDZA who did not transfer out and had enough follow up time (>6 months), 38% (68/177) were lost-to-follow-up within six months. Viral suppression (HIV Viral Load <1000 copies/ml) among those who had a test at 6 months was 90% (96/107). In addition 1162 clients previously diagnosed with HIV accessed CHIEDZA; 714 (61.4%) had a VL test, of whom 565 (79.1%) were virally suppressed. This study shows that provision of differentiated services for youth in the community is feasible. Linkage to care and retention during the initial months of ART was the main challenge and needs concerted attention to achieve the ambitious 95-95-95 UNAIDS targets.

BMC Public Health. 2023 Nov 2;23(1):2143.
doi: 10.1186/s12889-023-16955-3.

"It's already in your body and it's preventing": a qualitative study of African female adolescent's acceptability and preferences for proxy HIV prevention methods in Cape Town, South Africa

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Abstract

Background: Advances in biomedical HIV prevention will soon offer young women a choice of HIV prevention methods, including various pre-exposure prophylaxis (PrEP) modalities such as daily oral pills, dapivirine vaginal ring, and long-acting injectable agents. By understanding preferences for contraceptive methods, we may draw analogies for the HIV prevention needs of young women. The UChoose Study was an open-label randomised cross-over study designed to evaluate the acceptability and preference for several contraceptive options as a proxy for HIV prevention methods that use similar types of administration. The study enrolled healthy HIV uninfected young women aged 15 to 19 years. At enrolment, participants were randomly assigned to a contraceptive method for a period of 16 weeks in the form of monthly Nuvaring® (vaginal ring), daily combined oral contraceptive (daily pills), or bi-monthly injectable contraceptive (injectable). After 16 weeks, participants crossed over to another contraceptive method, and those who had received the injectable and the daily pills received the vaginal ring for another 16 weeks, whereas those who had received the vaginal ring were able to choose between the injectable and daily pills, to ensure that all participants tried the vaginal ring-the least familiar option to the study population.

Results: Thirty-three participants were purposively recruited to participate in seven focus group discussions (FGD) and completed a pre-survey for their assigned group. Our sample comprised 14 participants randomised to use of the vaginal ring and daily pills and 19 participants randomised to use of the vaginal ring and injectable. For most participants, their preferences for a prevention method were based primarily on their desire to avoid negative aspects of one method rather than their positive user experience with another method. Most participants expressed initial hesitancy for trying new contraception method products; however, a lack of familiarity was moderated by a strong interest in diverse user-controlled prevention methods. Participants valued methods that had infrequent dosing and simplified use requirements. The injection and vaginal ring were preferred over daily pills as a potential HIV prevention method.

Conclusion: Expanding the availability of diverse products could provide adolescents with multiple choices in HIV prevention for the uninitiated.

J Adolesc Health. 2023 Oct;73(4):632-639.
doi: 10.1016/j.jadohealth.2023.02.031. Epub 2023 Apr 17.

Access to Oral Fluid-Based Human Immunodeficiency Virus Self-Tests Increases Testing Among Male Partners of Adolescent Girls in Kenya: A Randomized Controlled Trial

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Abstract

Purpose: The risk of human immunodeficiency virus (HIV) among adolescent girls (AGs) may be reduced if they know the HIV status of their male partners. We assessed the ability of AGs

in Siaya County, Kenya, to offer HIV self-tests to their partners to promote partner and couples testing.
Methods: Eligible AGs were 15-19 years old, self-tested HIV-negative, and had a male partner not tested in the past 6 months. Participants were randomly assigned to receive two oral fluid-based self-tests (intervention arm) or a referral coupon for facility-based testing (comparison arm). The intervention included counseling on ways to safely introduce self-tests to partners. Follow-up surveys were conducted within 3 months.
Results: Among 349 AGs enrolled, median age was 17 years (interquartile range 16-18), 88.3% of primary partners were noncohabiting boyfriends, and 37.5% were unaware if their partner had ever tested. At 3 months, 93.9% of the intervention arm and 73.9% of the comparison arm reported that partner testing occurred. Compared to the comparison arm, partner testing was more likely in the intervention arm (risk ratio = 1.27; 95% confidence interval 1.15-1.40; $p < .001$). Among participants whose partners got tested, 94.1% and 81.5% in the intervention and comparison arms, respectively, reported that couples testing occurred; couples testing was more likely in the intervention than comparison arm (risk ratio = 1.15; 95% confidence interval 1.15-1.27; $p = .003$). Five participants reported partner violence, one study-related.
Discussion: Provision of multiple self-tests to AGs for the purpose of promoting partner and couples testing should be considered in Kenya and other settings where AGs face a high risk of HIV acquisition.

Adolescent substance use

J Adolesc Health. 2023 Sep;73(3):412-420.
doi: 10.1016/j.jadohealth.2023.05.009. Epub 2023 Jul 7.
Keepin' It REAL-Mantente REAL in Mexico: Longitudinal Examination of Youth Drug Resistance Strategies and Substance Use Among Early Adolescents
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Abstract
Purpose: This study examined if culturally and linguistically adapted versions of a US-developed adolescent substance use prevention intervention, keepin' it REAL (kiREAL), for Mexico increases the use of drug resistance strategies and if increased use of resistance strategies subsequently leads to a reduction in the frequency of substance use (i.e., alcohol, cigarette, marijuana, and inhalants).
Methods: Students (N = 5,522, 49% female, age range = 11-17) in 36 middle schools across three cities in Mexico were randomized into three conditions: (1) Mantente REAL (MREAL), the culturally adapted version, (2) kiREAL-S, the linguistically adapted version, and (3) Control. Using survey data collected at four time points, random intercept cross-lagged path analyses tested the direct and indirect effects of MREAL and kiREAL-S compared to Control.
Results: At time 2, the number of drug resistance strategies used by students increased in both MREAL ($\beta = 0.103$, $p = .001$) and kiREAL-S ($\beta = 0.064$, $p = .002$) compared to Control. However, only MREAL lead to less frequent use of alcohol ($\beta = -0.001$, $p = .038$), cigarettes ($\beta = -0.001$, $p = .019$), marijuana ($\beta = -0.002$, $p = .030$), and inhalants ($\beta = -0.001$, $p = .021$) at time 4, mediated through increased use of drug resistance strategies.

Discussion: This study provides evidence that MREAL and kiREAL-S are successful in spurring use of the drug resistance strategies that are the core component of the intervention. Only MREAL achieved long-term effects on substance use behaviors, the ultimate objective of these interventions. These findings provide support for the value and importance of rigorous cultural adaptation of efficacious prevention programs as a necessary condition for enhancing prevention benefits for participating youth.

Adolescent prevention of violence

J Adolesc Health. 2023 Jul;73(1):102-109.
doi: 10.1016/j.jadohealth.2023.02.027. Epub 2023 Apr 20.

Pre-post Mixed Methods Study of a Parent and Teen Support Intervention to Prevent Violence Against Adolescents in the Philippines

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Abstract

Purpose: This study examines the feasibility of a culturally adapted parenting intervention (MaPa Teens) within the national cash transfer system to reduce violence against adolescents, the first such program in the Philippines.

Methods: Thirty caregiver-adolescent dyads who were beneficiaries of a government conditional cash transfer program participated in a pilot of a locally adapted version of the Parenting for Lifelong Health for Parents and Teens program. Primary outcomes of reducing child maltreatment and associated risk factors were evaluated using a single-group, pre-post design. Focus group discussions explored the perceptions of participants and facilitators regarding program acceptability and feasibility.

Results: Significant and moderate reductions were reported in overall child maltreatment and physical abuse (caregiver and adolescent reports) and in emotional abuse (adolescent report). There were significant reductions in neglect, attitudes supporting punishment, parenting stress, parental and adolescent depressive symptoms, parent-child relationship problems, and significant improvement in parental efficacy in managing child behavior. Adolescents reported reduced behavior problems, risk behavior, and witnessing of family violence. Participants valued learning skills using a collaborative approach, sustained their engagement between sessions through text messages and phone calls, and appreciated the close interaction with caring and skilled facilitators. Program areas of improvement included addressing barriers to attendance, increasing adolescent engagement, and revising the sexual health module.

Discussion: The study provides preliminary support for the effectiveness and feasibility of the program in reducing violence against Filipino adolescents. Findings suggest potential adaptations of the program, and that investment in more rigorous testing using a randomized controlled trial would be worthwhile.

Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

Bull World Health Organ. 2024 Mar 1;102(3):176-186.
doi: 10.2471/BLT.23.289942. Epub 2024 Jan 29.

Early iron supplementation in exclusively breastfed Gambian infants: a randomized controlled trial

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Abstract

in English, French, Spanish, Arabic, Chinese, Russian

Objective: To investigate the effect of daily iron supplementation for 14 weeks on the serum iron concentration and other markers of iron status in exclusively breastfed infants in Gambia.

Methods: A placebo-controlled, randomized, double-blind trial was performed in rural Gambia between 3 August 2021 and 9 March 2022. Overall, 101 healthy, exclusively breastfed infants aged 6 to 10 weeks were recruited at vaccination clinics and through community health workers. Infants were randomized to receive iron supplementation (7.5 mg/day as ferrous sulfate in sorbitol solution) or placebo for 98 days. Venous blood samples were collected at baseline and on day 99 to assess the serum iron concentration and other markers of iron and haematological status.

Findings: At day 99, the serum iron concentration was significantly higher in the iron supplementation group than the placebo group (crude difference in means: 2.5 µmol/L; 95% confidence interval: 0.6 to 4.3) and there were significant improvements in other iron and haematological markers. There were 10 serious adverse events (five in each group), 106 non-serious adverse events (54 with iron supplementation; 52 with placebo) and no deaths. There was no marked difference between the groups in maternally reported episodes of diarrhoea, fever, cough, skin infection, eye infection or nasal discharge.

Conclusion: In exclusively breastfed Gambian infants, iron supplementation from 6 weeks of age was associated with a significant improvement in markers of iron status at around 6 months of age. There was no indication of adverse effects on growth or infections.

Arch Argent Pediatr. 2023 Aug 1;121(4):e202202815.
doi: 10.5546/aap.2022-02815.eng. Epub 2023 Mar 2.

Effectiveness of weekly and daily iron administration for the prevention of iron deficiency anemia in infants

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Abstract

Introduction. Iron deficiency (ID) is the most prevalent nutritional deficiency and the main cause of anemia in infants. There is consensus on daily iron supplementation as a preventive strategy; and weekly iron supplementation has also been shown to be effective, but evidence in infants is scarce. The objective of this study was to compare the effectiveness of daily versus weekly iron administration for the prevention of ID anemia (IDA) in infants. Population

and methods. Randomized, controlled clinical trial. Infants seen at a public health center, without anemia at 3 months of age, were randomized into 3 groups: daily supplementation (1 mg/kg/day), weekly supplementation (4 mg/kg/week), or no supplementation (control group with exclusive breastfeeding [EB]). Anemia and ID were assessed at 3 and 6 months old. Adherence and adverse events were recorded. Data were analyzed using the R software, version 4.0.3. Results. A total of 227 infants participated. At 6 months, the group of infants with EB without supplementation (control) had a higher prevalence of ID and IDA than the intervention groups (daily and weekly). ID: 40.5% versus 13.5% and 16.7% ($p = 0.002$); IDA: 33.3% versus 7.8% and 10% ($p < 0.001$). There were no differences between the daily and weekly supplementation groups. There were also no differences in the percentage of high adherence to supplementation (50.6% daily versus 57.1% weekly) or adverse events. Conclusions. No significant differences in effectiveness were observed between daily and weekly administration for the prevention of infant IDA.

BMC Public Health. 2023 Sep 18;23(1):1814.
doi: 10.1186/s12889-023-16611-w.

Factors associated with anemia among school-going adolescents aged 10-17 years in Zanzibar, Tanzania: a cross sectional study

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Abstract

Background: Anemia among adolescents (ages 10-19 years) is a leading cause of morbidity and mortality in low- and middle-income countries and carries long-term health and economic consequences. To address the issue, policymakers and programmers require evidence of the burden of anemia among adolescents in specific contexts, as well as an understanding of the factors associated with anemia in this population.

Methods: We conducted a cross-sectional survey as a baseline assessment to determine the prevalence and factors associated with anemia in secondary school students, as part of a cluster-randomized effectiveness trial testing different micronutrient supplementation strategies in addressing anemia among adolescents in Zanzibar. Between March 7th to 25th, 2022 the survey was conducted on 2,479 school-going adolescents aged 10-17 years from 42 schools on the island of Zanzibar, Tanzania. Hemoglobin concentration was measured along with the collection of socio-demographics, health, food frequency, and water, sanitation and hygiene data.

Results: Based on the World Health Organization cutoffs for anemia, 53.3% of the sample had anemia (mild, moderate, or severe). Using chi-square tests and logistic regressions, we determined that females had higher odds of anemia than males (Adjusted OR = 1.47; 95% CI: 1.24, 1.74), those in the highest wealth quintile had lower odds of anemia than those in the lowest wealth quintile (Adjusted OR = 0.7; CI: 0.54, 0.91), stunted adolescents had higher odds of anemia than non-stunted students (Adjusted OR = 1.38; 95% CI: 1.06,1.81), and those who used shared toilets had higher odds of moderate or severe anemia than those with private toilet access (Adjusted OR = 1.68; CI: 1.07, 2.64).

Conclusions: The high prevalence of anemia in this sample indicates an urgent need to address anemia among adolescents in Zanzibar, and the factors associated with anemia

point to the importance of water, sanitation, and hygiene interventions in addition to dietary and nutritional support.

BMJ Open. 2024 Jun 11;14(6):e084033.
doi: 10.1136/bmjopen-2024-084033.

Weekly iron-folic acid supplementation and its impact on children and adolescents iron status, mental health and school performance: a systematic review and meta-analysis in sub-Saharan Africa

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Abstract

Objective: This systematic review and meta-analysis aimed to comprehensively assess the impact of weekly iron-folic acid supplementation (WIFAS) on the nutrition, health and educational outcomes of children and adolescents in sub-Saharan Africa.

Design: A systematic review and meta-analysis was used.

Data sources: Five databases, namely, MEDLINE, Scopus, Web of Science, Cochrane Library and Google Scholar, were systematically searched for relevant articles up to 23 August 2023.

Eligibility criteria: It was focused on randomised controlled trials involving children and adolescents in sub-Saharan Africa, exploring the effects of iron supplementation on various outcomes, such as serum ferritin and haemoglobin levels, anaemia, mental health and school performance.

Data extraction and synthesis: The Joanna Briggs Institute Critical Appraisal tools were used for quality assessment, with two independent reviewers thoroughly evaluating each paper. Using the Cochrane risk of bias tool, we evaluated the certainty of evidence such as the risk of bias, inconsistency, indirectness, imprecision and publication bias.

Results: A systematic review of 10 articles revealed that WIFAS significantly increased serum ferritin levels in adolescent girls (Hedge's g=0.53, 95% CI 0.28 to 0.78; heterogeneity I^2=41.21%, p<0.001) and haemoglobin levels in school-aged children (Hedge's g=0.37, 95% CI 0.01 to 0.73; heterogeneity I^2=91.62%, p<0.001). The analysis further demonstrated a substantial reduction in the risk of anaemia by 20% (risk ratio=0.8, 95% CI 0.69 to 0.93; heterogeneity I^2=28.12%, p<0.001).

Conclusion: WIFAS proved effective in enhancing serum ferritin and haemoglobin concentrations and lowering the risk of anaemia in school-aged children and adolescents compared with a placebo. Similarly, there are not enough studies to examine the effects of WIFAS on school performance. However, information regarding mental health problems, mortality and potential side effects remains insufficient.

Indian Pediatr. 2023 Sep 15;60(9):752-758.
Epub 2023 May 19.

Iron Preparations in the Management of Iron Deficiency Anemia in Infants and Children: A Systematic Review and Meta-Analysis

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Abstract

Background: Various therapeutic iron preparations are available in the market, which differ in their pharmacokinetic and safety profiles. There is insufficient evidence regarding the superior safety or efficacy of one over the other.
Objectives: To study the effects of iron preparations on various parameters like hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and serum ferritin.
Study design: A systematic review and meta-analysis of randomized controlled trials (RCT) was conducted from inception till 3 June, 2022.
Data sources and selection criteria: Databases like MEDLINE and COCHRANE were searched for RCTs evaluating the effects and safety profile of various iron salts in the management of iron deficiency anemia in children and adolescents.
Main results: Eight studies with a total of 495 children were included the review. Pooled analysis showed ferrous sulphate to cause a significant increase in hemoglobin compared with other iron compounds [mean difference (95% CI) 0.53 (0.22 to 0.83; P <0.001]. Also ferrous sulphate is superior to iron polymaltose complex (IPC) (P<0.001). However, there was a significant increase in gastrointestinal adverse effects with ferrous sulphate compared to IPC (P=0.03). Other iron compounds were more efficacious than IPC in raising hemoglobin levels (P<0.001). Among the few studies evaluating iron indices like MCV, MCH, and serum ferritin, there was no significant difference between the iron preparations (P>0.05).
Conclusion: A low quality evidence suggests that ferrous sulphate is more efficacious than other compounds (P<0.001); though, there is an increase in gastrointestinal side effects with ferrous sulphate.

Am J Clin Nutr. 2023 Sep 15:S0002-9165(23)66129-5.
doi: 10.1016/j.ajcnut.2023.09.004. Online ahead of print.

School-based supplementation with iron-folic acid or multiple micronutrient tablets to address anemia among adolescents in Burkina Faso: a cluster-randomized trial

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Abstract
Background: Iron-deficiency anemia is a leading cause of morbidity among adolescents (aged 10-19 y), especially in low- and middle-income settings. Few policies and programs have targeted adolescent health.
Objectives: This study aimed to evaluate the effectiveness of school-based supplementation with iron-folic acid (IFA) or multiple micronutrient supplements (MMSs) in addressing anemia among adolescents in Burkina Faso.
Methods: In this cluster-randomized trial, 3123 secondary school students aged 10 to 18 y in Burkina Faso were either supplemented with weekly IFA, daily MMSs, or received standard nutrition education as controls. Supplementation occurred between April 2021 and April 2022 over 2 supplementation periods (10 wk, then 16 wk) separated by a gap of 20 wk without supplementation. Hemoglobin was evaluated 4 times: at baseline prior to each supplementation period and at the end of each period. Anemia was categorized by the World Health Organization hemoglobin level cutoffs as none, mild, moderate, or severe. Associations between treatment arm and anemia or continuous hemoglobin (g/dL) were assessed using multilevel mixed effects generalized linear models with schools as a random effect, controlling for baseline hemoglobin or anemia status.

Results: Baseline anemia prevalence was similar across study arms, with 32.7% in IFA, 31.2% in MMS, and 29.5% in the control arm. Over the full study period, adolescents provided IFA had hemoglobin levels higher than those in the control arm (adjusted β: 0.32; 95% CI: 0.02, 0.62). No significant associations were observed for MMS or for anemia outcomes; however, the direction and magnitude of nonsignificant associations indicate potential protective effects of IFA and MMSs on anemia.
Conclusions: The results do not provide strong evidence that weekly IFA or daily MMS alone is effective, but supplementation may play a role in addressing adolescent anemia if combined with cointerventions. Additional research is required to determine the best strategy to address anemia. This trial was registered at clinicaltrials.gov as NCT04657640.

Am J Clin Nutr. 2024 Feb;119(2):456-469.
doi: 10.1016/j.ajcnut.2023.11.018. Epub 2023 Nov 30.

Prebiotics increase iron absorption and reduce the adverse effects of iron on the gut microbiome and inflammation: a randomized controlled trial using iron stable isotopes in Kenyan infants

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Abstract
Background: Iron fortificants tend to be poorly absorbed and may adversely affect the gut, especially in African children.
Objective: We assessed the effects of prebiotic galacto-oligosaccharides/fructo-oligosaccharides (GOS/FOS) on iron absorption and gut health when added to iron-fortified infant cereal.
Methods: We randomly assigned Kenyan infants (n = 191) to receive daily for 3 wk a cereal containing iron and 7.5 g GOS/FOS (7.5 g+iron group), 3 g (3-g+iron group) GOS/FOS, or no prebiotics (iron group). A subset of infants in the 2 prebiotic+iron groups (n = 66) consumed 4 stable iron isotope-labeled test meals without and with prebiotics, both before and after the intervention. Primary outcome was fractional iron absorption (FIA) from the cereal with or without prebiotics regardless of dose, before and after 3 wk of consumption. Secondary outcomes included fecal gut microbiota, iron and inflammation status, and effects of prebiotic dose.
Results: Median (25th-75th percentiles) FIAs from meals before intervention were as follows: 16.3% (8.0%-27.6%) without prebiotics compared with 20.5% (10.4%-33.4%) with prebiotics (Cohen d = 0.53; P < 0.001). FIA from the meal consumed without prebiotics after intervention was 22.9% (8.5%-32.4%), 41% higher than from the meal without prebiotics before intervention (Cohen d = 0.36; P = 0.002). FIA from the meal consumed with prebiotics after intervention was 26.0% (12.2%-36.1%), 60% higher than from the meal without prebiotics before intervention (Cohen d = 0.45; P = 0.007). After 3 wk, compared with the iron group, the following results were observed: 1) Lactobacillus sp. abundances were higher in both prebiotic+iron groups (P < 0.05); 2) Enterobacteriaceae sp. abundances (P = 0.022) and the sum of pathogens (P < 0.001) were lower in the 7.5-g+iron group; 3) the abundance of bacterial toxin-encoding genes was lower in the 3-g+iron group (false discovery rate < 0.05); 4) fecal pH (P < 0.001) and calprotectin (P = 0.033) were lower in the 7.5-g+iron group.

Conclusions: Adding prebiotics to iron-fortified infant cereal increases iron absorption and reduces the adverse effects of iron on the gut microbiome and inflammation in Kenyan infants. This trial was registered at clinicaltrials.gov as NCT03894358.

Anaesthesia and intensive care

(see also Asthma)

Anaesthesiol Intensive Ther. 2023 Jul 6;51037.
doi: 10.5114/ait.2023.129276. Online ahead of print.

Comparison of intranasal dexmedetomidine-midazolam, dexmedetomidine-ketamine, and midazolam-ketamine for premedication in paediatric patients: a double-blinded randomized trial

Vaishnavi Bd[1], Shilpa Goyal[1], Ankur Sharma[1], Nikhil Kothari[1], Narendra Kaloria[2], Priyanka Sethi[1], Pradeep Bhatia[1]

Abstract

Background: Paediatric patients are a population with a high level of anxiety. The prevention of perioperative stress in a frightened child is important to render the child calm and cooperative for smoother induction. Intranasal premedication is easy and safe, and the drug is rapidly absorbed into the systemic circulation, ensuring early onset of sedation in children and good effectiveness.

Methods: 150 patients in the age group 2-4 years, ASA class I, undergoing elective surgical procedures were enrolled. The patients were randomly divided into 3 groups: a DM group (receiving intranasal dexmedetomidine 1 µg kg -1 and midazolam 0.12 mg kg -1), a DK group (receiving intranasal dexmedetomidine 1 µg kg -1 and keta-mine 2 mg kg -1), and an MK group (receiving intranasal midazolam 0.12 mg kg -1 and ketamine 2 mg kg -1). After 30 minutes of administration of the drugs, the patients were assessed for parent separation anxiety, sedation, ease of IV cannulation, and mask acceptance.

Results: The comparison among the 3 groups showed a statistically significant difference for ease of IV cannulation and mask acceptance at 30 minutes, with a P -value of 0.010 with CI of 0.0-0.02, and P -value 0.007 with CI 0.0-0.02, respectively. The parent separation anxiety and sedation score at 30 minutes was statistically insignificant with a P -value of 0.82 with CI of 0.03-0.14 and P -value 0.631 with CI of 0.38-0.58, respectively.

Conclusions: The combination of midazolam and ketamine had a better clinical profile for premedication as compared to other combination drugs used in our study in terms of IV cannulation and acceptance of masks with a comparable decrease in separation anxiety from parents and adequate sedation.

Paediatr Anaesth. 2023 Aug;33(8):636-646.
doi: 10.1111/pan.14689. Epub 2023 May 1.

The effect of intranasal dexmedetomidine administration on emergence agitation or delirium in pediatric patients after general anesthesia: A meta-analysis of randomized controlled trials

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Abstract

Background: Emergence agitation or delirium can occur in pediatric patients after anesthesia. Dexmedetomidine is known to reduce the impairment of postoperative cognitive function.

Aims: This study aimed to identify the role of intranasal administration of dexmedetomidine in lowering the development of emergence agitation or emergence delirium in pediatric patients after general anesthesia.

Methods: Electronic databases, including PubMed, EMBASE, CENTRAL, Scopus, and Web of Science, were searched to identify studies. The primary outcome was the proportion of patients who underwent emergence agitation or emergence delirium after the surgery. Secondary outcomes included emergence time and incidence of postoperative nausea and/or vomiting. We estimated the odds ratio and mean difference with 95% confidence intervals for the determination of effect size using a random-effects model.

Results: In total, 2103 pediatric patients from 20 randomized controlled trials were included in the final analysis. The incidence of emergence agitation or emergence delirium was 13.6% in the dexmedetomidine group and 33.2% in the control group. The pooled effect size revealed that intranasal dexmedetomidine administration significantly reduced the incidence of postoperative emergence agitation or emergence delirium in pediatric patients undergoing surgery under general anesthesia (odds ratio 0.25, 95% confidence interval 0.18-0.34; p = .0000; I^2 = 37.74%). Additionally, significant difference was observed in emergence time between the two groups (mean difference 2.42, 95% confidence interval 0.37-4.46; p = .021; I^2 = 98.40%). Children in the dexmedetomidine group had a significantly lower incidence of postoperative nausea and/or vomiting than those in the control group (odds ratio 0.39, 95% confidence interval 0.24-0.64; p = .0002; I^2 = 0.00%).

Conclusions: Intranasal dexmedetomidine reduced the incidence of emergence agitation or emergence delirium in pediatric patients after general anesthesia.

Curr Drug Saf. 2024;19(1):33-43.
doi: 10.2174/1574886318666230302124634.

Sugammadex *versus* Neostigmine for Reversal of Neuromuscular Blockade in Adults and Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Ridhi Chhabra[1], Rachna Gupta[2], Lalit K Gupta[1]

Abstract

Background: Cholinesterase inhibitors, such as neostigmine and edrophonium, commonly used to reverse the residual effects of nondepolarizing neuromuscular blocking drugs at the end of surgery are associated with a high rate of residual neuromuscular blockade (NMB). Due to its direct mechanism of action, sugammadex is associated with rapid and predictable reversal of deep NMB. The current analysis compares the clinical efficacy and risk of postoperative nausea and vomiting (PONV) on using sugammadex or neostigmine for routine NMB reversal in adult and pediatric populations.

Methods: PubMed and ScienceDirect were searched as the primary databases. Randomized controlled trials comparing sugammadex with neostigmine for routine NMB reversal in adult and pediatric patients have been included. The primary efficacy endpoint was the time from

initiation of sugammadex or neostigmine to the recovery of a time-of-four ratio (TOF) ≥ 0.9. PONV events have been reported as secondary outcomes.
Results: A total of 26 studies have been included in this meta-analysis, 19 for adults with 1574 patients and 7 for children with 410 patients. Sugammadex, when compared to neostigmine, has been reported to take a shorter time to reverse NMB in adults (mean difference = -14.16 min; 95% CI [-16.88, -11.43], $P < 0.01$), as well as in children (mean difference = -26.36 min; 95% CI [- 40.16, -12.57], $P < 0.01$). Events of PONV have been found to be similar in both the groups in adults, but significantly lower in children treated with sugammadex, *i.e.*, 7 out of 145 with sugammadex versus 35 out of 145 with neostigmine (odds ratio = 0.17; 95% CI [0.07, 0.40]).
Conclusion: Sugammadex is associated with a significantly shorter period of reversal from NMB in comparison to neostigmine in adult and pediatric patients. Regarding PONV, the use of sugammadex for NMB antagonism may offer a better option for pediatric patients.

J Anesth. 2023 Aug;37(4):582-588.
doi: 10.1007/s00540-023-03207-2. Epub 2023 Jun 13.
Efficacy of McGRATH®MAC videolaryngoscope blade 1 for tracheal intubation in small children: a randomized controlled clinical study
Katsuhide Masui [1], Takashi Asai [2], Tomoyuki Saito [2], Yasuhisa Okuda [2]
Abstract
Background: Videolaryngoscopes may not be as effective in small children as they are in older children and in adults. The size 1 blade is commercially available for the McGRATH®MAC videolaryngoscope (Covidien, Medtronic, Tokyo, Japan), but its efficacy in comparison with a Macintosh laryngoscope blade 1 is not known.
Aim: The main aim of this study was to assess the efficacy of McGrath®MAC blade 1 in comparison with a conventional Macintosh laryngoscope blade 1, in children aged less than 24 months.
Methods: Thirty-eight children aged less than 24 months were randomly allocated to one of two groups, and tracheal intubation was attempted using either a direct laryngoscope with a Macintosh blade 1 or a videolaryngoscope with a McGRATH®MAC blade 1. In another 12 children aged 2-4 years, the same comparisons were made with blade 2. The primary outcome measure was time to tracheal intubation using a size 1 blade.
Results: Tracheal intubation took significantly longer with a McGRATH®MAC blade 1 (median (interquartile range): 38.0 (31.8-43.5) s) than with the Macintosh blade 1(27.4 (25.9-29.2) s) ($p < 0.0001$; median difference (95% CI for the median difference): 10.6 (6.4-14.0) s), mainly due to difficulty in advancing a tube into the trachea. No significant difference was observed for the size 2.
Conclusions: In small children without predicted difficult airways, time to intubate the trachea was significantly longer for a McGRATH®MAC blade 1 than a Macintosh blade 1.

Paediatr Anaesth. 2023 Nov;33(11):905-912.
doi: 10.1111/pan.14725. Epub 2023 Jun 29.
Supraglottic airway device versus tracheal tube for pediatric laparoscopic surgery-A systematic review and meta-analysis

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Abstract

Background: Conventionally, tracheal tubes have been used for general anesthesia in pediatric laparoscopic surgeries. Recently, supraglottic devices are being used for the same. The performance of supraglottic devices versus tracheal tubes in children undergoing laparoscopic surgery is uncertain.

Methods: A systematic review and meta-analysis of randomized controlled trials that compared supraglottic devices versus tracheal tubes in patients ≤18 years undergoing laparoscopic surgery under general anesthesia was conducted. The outcomes were peak airway pressures (cm H_2O), end-tidal carbon dioxide during pneumoperitoneum (mm Hg), recovery time (min), postoperative sore throat and adverse events. Mean difference and odds ratio, with 95% confidence intervals were reported using a random effect model.

Results: Eight trials (n = 591) were included in the final meta-analysis. There was no statistically significant difference in the peak airway pressures (MD 0.58, 95% CI: -0.65 to 1.8; p = .36) and end-tidal carbon dioxide (MD -0.60, 95% CI: -2.00 to 0.80; p = .40) during pneumoperitoneum in the supraglottic device and the tracheal tube group. The tracheal tube group had higher odds of sore throat (OR 3.30, 95% CI: 1.69-6.45; p = .0005) and the supraglottic airway group had faster recovery time (MD 4.21, 95% CI: 3.12-5.31; p < .0001), which were statistically significant. The certainty of evidence is graded low.

Conclusion: There is low quality evidence to suggest that for pediatric laparoscopic surgeries of short duration, supraglottic devices could provide comparable intraoperative ventilation in terms of peak airway pressures and end tidal carbon dioxide, with lower odds of postoperative sore throat and faster recovery time when compared to tracheal tubes.

Pediatr Investig. 2023 Sep 26;7(4):233-238.
doi: 10.1002/ped4.12401. eCollection 2023 Dec.

Safety of removal of ProSeal laryngeal mask airway in children in the supine versus lateral position in a deep plane of anesthesia: A randomized controlled trial

Shweta Dhiman [1], Anju R Bhalotra [1], Kavita R Sharma [2]

Abstract

Importance: When a ProSeal laryngeal mask airway (PLMA) is removed with the child in a deep plane of anesthesia, the upper airway muscle tone and protective upper airway reflexes may be obtunded.

Objective: To determine whether the supine or lateral position is safer for the removal of a PLMA in deeply anesthetized children by comparing the incidence of upper airway complications.

Methods: This randomized single-blind comparative trial was conducted at a tertiary care hospital between January 2020 and September 2020. Forty children of the American Society of Anesthesiologists class I/II of ages 1-12 years age undergoing surgery under general anesthesia with PLMA used as the definitive airway device were recruited. Patients were randomly allocated to lateral group or supine group for PLMA removal in a deep plane of anesthesia in the lateral or supine position. The primary outcome was the number of patients experiencing one or more upper airway complications and the secondary outcomes were incidence of individual respiratory adverse effects and of severe airway complications.

Results: The incidence of airway complications was 30% in the supine group and 20% in the lateral group ($P = 0.6641$). Incidence of laryngospasm, immediate stridor, and excessive

secretions were similar. Early stridor and oxygen desaturation were higher in the supine group ($P = 0.0374$, $P = 0.0183$ respectively).
Interpretation: The overall incidence of upper airway complications was similar with the removal of a PLMA in the supine or lateral position in deeply anesthetized children. The incidence of oxygen desaturation and stridor were higher with PLMA removal in the supine as compared to the lateral position.

Paediatr Anaesth. 2024 Jan 8.
doi: 10.1111/pan.14837. Online ahead of print.
Comparison of preformed microcuff and preformed uncuffed endotracheal tubes in pediatric cleft palate surgery-A randomized controlled trial
Rithu Krishna Kamaladevi [1], Sandeep Kumar Mishra [2], Priya Rudingwa [2], Devi Prasad Mohapatra [3], Ashok Shankar Badhe [2], Muthapillai Senthilnathan [2]
Abstract
Background and aims: Airway management in children with oral cleft surgery carries unique challenges, concerning the proximity of the surgical site and the tracheal tube. We hypothesized that using a Microcuff oral RAE tube would reduce tube exchange and migration rate. We aimed to compare the performance of Microsoft and uncuffed oral performed tracheal tubes in children undergoing cleft palate surgeries regarding the rate of tracheal tube exchange, endobronchial intubation, and ventilatory parameters.
Methods: One hundred children scheduled for cleft palate surgery were randomized into two groups. In the uncuffed group (n = 50), the tracheal tube was selected using the Modified Coles formula, and in the Microcuff (n = 50) group, the manufacturer's recommendations were followed. Intraoperatively, we compared the primary outcome of tube exchange using the chi-square test. The leak pressure and ventilatory parameters after head extension and mouth gag application were measured in both groups.
Results: The tracheal tube exchange rate was significantly lower in the Microcuff group (0/50) than in uncuffed (19/50) preformed tubes (0 vs. 38% respectively; p <.001). The uncuffed and Microcuff tracheal tube were comparable concerning ventilation parameters and leak pressure of finally placed tubes (17.78 ± 3.95 vs. 19.26 ± 3.81 cm H_2O respectively, with a mean difference (95% CI) of -1.48 (-0.01-2.98); p-value =0.059. Cuff pressure did not vary significantly during the initial hour, and the incidence of postoperative airway morbidity between uncuffed and Microcuff tube was comparable, 5/50 (10%) versus 7/50 (14%) with risk ratio (95% CI) of 0.71(0.24-2.1), p value .49.
Conclusion: Microcuff oral preformed tubes performed better than uncuffed tubes regarding tube exchange during cleft palate surgery.

Intensive care

Indian J Pediatr. 2023 Sep;90(9):899-906.
doi: 10.1007/s12098-023-04532-w. Epub 2023 May 25.
Hypertonic Saline vs. Mannitol in Management of Elevated Intracranial Pressure in Children: A Meta-Analysis

Nihar Ranjan Mishra [1], Amit Agrawal [2], Rashmi Ranjan Das [3]

Abstract

Objective: To compare the efficacy and safety of two hyperosmolar agents (hypertonic saline vs. mannitol) used for the reduction of elevated intracranial pressure (ICP) in children.

Methods: A meta-analysis of randomized controlled trials (RCTs) was conducted and GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) of evidence was applied. Relevant databases were searched till 31st May 2022. Primary outcome was mortality rate.

Results: Of 720 citations retrieved, 4 RCTs were included in the meta-analysis (n = 365, male = 61%). Traumatic and non-traumatic cases of elevated ICP were included. There was no significant difference in the mortality rate between the two groups [relative risk (RR), 1.09; (95% confidence interval (CI), 0.74 to 1.6)]. No significant difference was found for any of the secondary outcomes, except serum osmolality (being significantly higher in mannitol group). Adverse events like shock and dehydration were significantly higher in the mannitol group, and hypernatremia in the hypertonic saline group. The evidence generated for primary outcome was of "low certainty", and for secondary outcomes, it varied from "very-low to moderate certainty".

Conclusions: There is no significant difference between hypertonic saline and mannitol used for the reduction of elevated ICP in children. The evidence generated for primary outcome (mortality rate) was of "low certainty", and for secondary outcomes, it varied from "very-low to moderate certainty". More data from high-quality RCTs are needed to guide any recommendation.

Indian J Pediatr. 2023 Dec 7.
doi: 10.1007/s12098-023-04959-1. Online ahead of print.

Protocolized Sedation Utilizing COMFORT-B Scale versus Non-protocol-directed Sedation in Mechanically Ventilated Children - An Open-label, Randomized Controlled Trial

Pujitha Vallabhaneni [1], Daisy Khera [2], Bharat Choudhary [3], Surjit Singh [4], Kuldeep Singh [1], Siyaram Didel [1], Suman Saurabh [5], Nisha Toteja [6]

Abstract

This study aimed to determine the effect of protocolized sedation using the COMFORT-B scale on the duration of mechanical ventilation (DMV). Eighty children with anticipated Duration of mechanical ventilation (DMV) >24 h admitted to the Pediatric intensive care unit (PICU) were randomized into one group that received protocolized sedation (PS) using the COMFORT behavioural (COMFORT-B) scale, and another group that received non-protocolized sedation (NPS). The primary outcome was the impact on the DMV. The DMV was significantly lower in PS (PS: 3.5 [3-7] vs. NPS group: 8.5 [4.25-13.75] d; p = 0.008). The cumulative dose and duration of fentanyl in the PS group was significantly lower (median [IQR]; 120 [62.88-279.12] vs. 320.4 [110.88-851.52] µg/kg; p = 0.007 and 4 [2.25-7.75] vs. 8 [4-17.5] d; p = 0.009, respectively). The authors found a decrease in DMV and sedation related adverse events (SRAE) like ventilator associated pneumonia (VAP), accidental extubation, post-extubation stridor and dose and duration of sedative agents with PS.

Indian J Pediatr. 2023 Dec 8.
doi: 10.1007/s12098-023-04941-x. Online ahead of print.

Comparison of Protocol-Based Continuous and Intermittent Tube Feeding in Mechanically Ventilated Critically Ill Children - An Open Label Randomized Controlled Trial

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Abstract

Objectives: To compare the time taken to reach the target calories and proteins by protocol based "continuous tube feeding (CTF)" and "intermittent tube feeding (ITF)" in critically ill children.

Methods: This trial was conducted in the Pediatric Intensive Care Unit (PICU) of a tertiary care institute. Eligible children were randomized to receive CTF or ITF. Target calories were defined as 70% of calorie amount as per the WHO formula and target protein was defined as 1.5 g/kg as per the American Society of Parenteral and Enteral Nutrition (ASPEN) criteria. The primary outcome was time taken to reach target calories, the secondary outcomes were time taken to reach target protein, incidence of feed intolerance, PICU mortality, duration of ventilation, and outcome on 28th day.

Results: Fifty-eight children were randomized; 29 in each group. The baseline characters were comparable. The median (IQR) times for reaching target calories were 1.7 (1.4, 2.5) d and 1.8 (1.4, 4.4) d in the CTF and ITF groups, respectively [Hazards ratio (HR) 0.89 (95% CI 0.5, 1.5); p = 0.69]. For the target protein intake, the median times were comparable in the 2 groups [HR 0.82 (95% CI 0.4-1.5); p = 0.55]. The other outcomes were not significantly different between the groups.

Conclusions: The authors did not observe any difference in the time taken to reach target calories and protein between the two different modes of delivery of enteral nutrition.

Indian Pediatr. 2024 Feb 15;61(2):132-138.
Epub 2024 Jan 9.

Heparin vs Saline Infusion to Maintain Patency of Arterial Catheters in Children: A Randomized, Double-Blind, Noninferiority Trial

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Abstract

Objective: To determine whether normal saline flush solution is noninferior to heparinised saline for maintaining the patency of arterial intravascular catheters in children.

Methods: A single centre, double blind, parallel group, noninferiority, randomized control study was conducted in the Pediatric Intensive Care Unit of Kanchi Kamakoti CHILDS Trust hospital, a tertiary children's hospital, Chennai, India. 92 children requiring arterial catheters for more than 12 hours were randomized to receive either normal saline or heparinized saline (1 U/ml) flush solution. Primary outcome was a noninferiority comparison between normal saline and heparinised saline in maintaining the patency of arterial catheters using the proportion of occlusion of arterial catheters as primary endpoint. Secondary outcome was mean duration of patency of arterial catheters in each treatment group.

Results: Ninety-two children with a median (interquartile range, age of 84 (33.5-132) months and 52% males were enrolled. 15.2% of catheters in the heparin group and 17.4% of

catheters in the normal saline group were occluded (P = 0.77). The 95% upper confidence interval for the difference in proportion was 0.148 (+14.8%), establishing noninferiority (< 15%). The median (IQR) duration of a patent arterial catheter was 47 (27.75 - 94.5) hours in the heparin group and 35.50 (24.50 - 62) hours in the normal saline group (P = 0.10). Comparison of duration of patency using Kaplan Meier survival analysis and log rank test showed no statistically significant difference. There were no serious adverse events noted in either group.
Conclusions: Our data suggests that normal saline is noninferior to heparinized saline infusion in maintaining the patency of arterial lines in children. This may benefit clinicians worldwide as normal saline would be a safer and cost-effective option.

Antibiotics

Antibiotic prophylaxis

Int J Infect Dis. 2023 Aug;133:31-35.
doi: 10.1016/j.ijid.2023.04.409. Epub 2023 Apr 27.
Effect of prophylactic amoxicillin on tonsillar bacterial pathogens after (adeno)tonsillectomy in children
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Abstract
Objectives: Unnecessary and inappropriate antibiotic use is an increasing global health challenge. In limited resource settings, prophylactic antibiotics are still often used in (adeno)tonsillectomy (AT), despite evidence against their effectiveness. This study aimed to investigate the effect of prophylactic amoxicillin, given after AT in children.
Methods: This is a secondary analysis from a two-center, double-blinded, randomized controlled, non-inferiority trial to study the effect of prophylactic amoxicillin on post-AT morbidity. Children aged 2-14 years with recurrent chronic tonsillitis and/or obstructive sleep apnea were randomly assigned to receive either placebo or amoxicillin for 5 days after the operation. Pre- and postoperative samples were collected for polymerase chain reaction (PCR) analyses to detect the five most important pathogens known to be common causes of tonsillitis. PCR results were compared before and after surgery as well as between placebo and amoxicillin.
Results: PCR results were obtained, 109 in the amoxicillin group and 115 in the placebo group. In the amoxicillin group, 91% of patients had at least one positive PCR test before surgery and 87% after surgery. In the placebo group, the respective percentages were 92% and 90%. In both groups, a decrease in the total number of pathogens was found after surgery.
Conclusion: Prophylactic amoxicillin given after AT in children did not show a clinically relevant effect with respect to the number of oropharyngeal microorganisms as compared to placebo.

Antibiotics – mass drug administration with Azithromycin

JAMA. 2024 Feb 13;331(6):482-490.
doi: 10.1001/jama.2023.27393.

Mass Azithromycin Distribution to Prevent Child Mortality in Burkina Faso: The CHAT Randomized Clinical Trial

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Abstract

Importance: Repeated mass distribution of azithromycin has been shown to reduce childhood mortality by 14% in sub-Saharan Africa. However, the estimated effect varied by location, suggesting that the intervention may not be effective in different geographical areas, time periods, or conditions.

Objective: To evaluate the efficacy of twice-yearly azithromycin to reduce mortality in children in the presence of seasonal malaria chemoprevention.

Design, setting, and participants: This cluster randomized placebo-controlled trial evaluating the efficacy of single-dose azithromycin for prevention of all-cause childhood mortality included 341 communities in the Nouna district in rural northwestern Burkina Faso. Participants were children aged 1 to 59 months living in the study communities.

Interventions: Communities were randomized in a 1:1 ratio to receive oral azithromycin or placebo distribution. Children aged 1 to 59 months were offered single-dose treatment twice yearly for 3 years (6 distributions) from August 2019 to February 2023.

Main outcomes and measures: The primary outcome was all-cause childhood mortality, measured during a twice-yearly enumerative census.

Results: A total of 34 399 children (mean [SD] age, 25.2 [18] months) in the azithromycin group and 33 847 children (mean [SD] age, 25.6 [18] months) in the placebo group were included. A mean (SD) of 90.1% (16.0%) of the censused children received the scheduled study drug in the azithromycin group and 89.8% (17.1%) received the scheduled study drug in the placebo group. In the azithromycin group, 498 deaths were recorded over 60 592 person-years (8.2 deaths/1000 person-years). In the placebo group, 588 deaths were recorded over 58 547 person-years (10.0 deaths/1000 person-years). The incidence rate ratio for mortality was 0.82 (95% CI, 0.67-1.02; P = .07) in the azithromycin group compared with the placebo group. The incidence rate ratio was 0.99 (95% CI, 0.72-1.36) in those aged 1 to 11 months, 0.92 (95% CI, 0.67-1.27) in those aged 12 to 23 months, and 0.73 (95% CI, 0.57-0.94) in those aged 24 to 59 months.

Conclusions and relevance: Mortality in children (aged 1-59 months) was lower with biannual mass azithromycin distribution in a setting in which seasonal malaria chemoprevention was also being distributed, but the difference was not statistically significant. The study may have been underpowered to detect a clinically relevant difference.

PLoS Med. 2024 May 6;21(5):e1004386.
doi: 10.1371/journal.pmed.1004386. eCollection 2024 May.

Prolonged mass azithromycin distributions and macrolide resistance determinants among preschool children in Niger: A sub-study of a cluster-randomized trial (MORDOR)

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Abstract

Background: Randomized controlled trials found that twice-yearly mass azithromycin administration (MDA) reduces childhood mortality, presumably by reducing infection burden. World Health Organization (WHO) issued conditional guidelines for mass azithromycin administration in high-mortality settings in sub-Saharan Africa given concerns for antibiotic resistance. While prolonged twice-yearly MDA has been shown to increase antibiotic resistance in small randomized controlled trials, the objective of this study was to determine if macrolide and non-macrolide resistance in the gut increases with the duration of azithromycin MDA in a larger setting.

Methods and findings: The Macrolide Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) study was conducted in Niger from December 2014 to June 2020. It was a cluster-randomized trial of azithromycin (A) versus placebo (P) aimed at evaluating childhood mortality. This is a sub-study in the MORDOR trial to track changes in antibiotic resistance after prolonged azithromycin MDA. A total of 594 communities were eligible. Children 1 to 59 months in 163 randomly chosen communities were eligible to receive treatment and included in resistance monitoring. Participants, staff, and investigators were masked to treatment allocation. At the conclusion of MORDOR Phase I, by design, all communities received an additional year of twice-yearly azithromycin treatments (Phase II). Thus, at the conclusion of Phase II, the treatment history (1 letter per 6-month period) for the participating communities was either (PP-PP-AA) or (AA-AA-AA). In Phase III, participating communities were then re-randomized to receive either another 3 rounds of azithromycin or placebo, thus resulting in 4 treatment histories: Group 1 (AA-AA-AA-AA-A, N = 51), Group 2 (PP-PP-AA-AA-A, N = 40), Group 3 (AA-AA-AA-PP-P, N = 27), and Group 4 (PP-PP-AA-PP-P, N = 32). Rectal swabs from each child (N = 5,340) were obtained 6 months after the last treatment. Each child contributed 1 rectal swab and these were pooled at the community level, processed for DNA-seq, and analyzed for genetic resistance determinants. The primary prespecified outcome was macrolide resistance determinants in the gut. Secondary outcomes were resistance to beta-lactams and other antibiotic classes. Communities recently randomized to azithromycin (groups 1 and 2) had significantly more macrolide resistance determinants than those recently randomized to placebo (groups 3 and 4) (fold change 2.18, 95% CI 1.5 to 3.51, Punadj < 0.001). However, there was no significant increase in macrolide resistance in communities treated 4.5 years (group 1) compared to just the most recent 2.5 years (group 2) (fold change 0.80, 95% CI 0.50 to 1.00, Padj = 0.010), or between communities that had been treated for 3 years in the past (group 3) versus just 1 year in the past (group 4) (fold change 1.00, 95% CI 0.78 to 2.35, Padj = 0.52). We also found no significant differences for beta-lactams or other antibiotic classes. The main limitations of our study were the absence of phenotypic characterization of resistance, no complete placebo arm, and no monitoring outside of Niger limiting generalizability.

Conclusions: In this study, we observed that mass azithromycin distribution for childhood mortality among preschool children in Niger increased macrolide resistance determinants in

the gut but that resistance may plateau after 2 to 3 years of treatment. Co-selection to other classes needs to be monitored.

PLOS Glob Public Health. 2023 Nov 15;3(11):e0002559.
doi: 10.1371/journal.pgph.0002559. eCollection 2023.

Comparison of door-to-door and fixed-point delivery of azithromycin distribution for child survival in Niger: A cluster-randomized trial

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Abstract

Recent evidence indicates mass azithromycin distribution reduces under-5 mortality. This intervention is being considered for child survival programs in high mortality sub-Saharan African settings. The delivery approach used in prior studies required a full-time census and distribution team, which is not feasible for most programs. To determine the optimal programmatic approach to delivery, this study aimed to compare treatment coverage, costs, and acceptability of different delivery approaches with existing community health workers (CHWs). This cluster-randomized trial included rural and peri-urban communities in Dosso, Niger (clinicaltrials.gov, NCT04774991). A random sample of 80 eligible communities was randomized 1:1 to biannual door-to-door or fixed-point delivery of oral azithromycin to children 1-59 months old over 1 year. Data analysts alone were masked given the nature of the intervention. The primary outcome was community-level treatment coverage defined as the number of children treated recorded by CHWs divided by the number of eligible children determined using a post-distribution census. Costs were monitored through routine administrative data collection and micro-costing. The census included survey questions on intervention acceptability among caregivers, community leaders, and CHWs. After randomization, 1 community was excluded due to inaccuracies in available administrative data, resulting in 39 communities receiving door-to-door delivery. At the second distribution, community-level mean treatment coverage was 105% (SD 44%) in the door-to-door arm and 92% (SD 20%) in the fixed-point arm (Mean difference 13%, 95% CI -2% to 28%, P-value = 0.08). The total cost per dose delivered was $1.91 in the door-to-door arm and $2.51 in the fixed-point arm. Indicators of acceptability were similar across stakeholder groups in both arms, with most respondents in each group indicating a preference for door-to-door. Overall, door-to-door delivery is the preferred approach to azithromycin distribution in this setting and might reach more children at a lower cost per dose delivered than fixed-point.

PLoS Med. 2024 Jan 23;21(1):e1004345.
doi: 10.1371/journal.pmed.1004345. eCollection 2024 Jan.

Single-dose azithromycin for infant growth in Burkina Faso: Prespecified secondary anthropometric outcomes from a randomized controlled trial

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Abstract

Background: Antibiotic use during early infancy has been linked to childhood obesity in high-income countries. We evaluated whether a single oral dose of azithromycin administered during infant-well visits led to changes in infant growth outcomes at 6 months of age in a setting with a high prevalence of undernutrition in rural Burkina Faso.

Methods and findings: Infants were enrolled from September 25, 2019, until October 22, 2022, in a randomized controlled trial designed to evaluate the efficacy of a single oral dose of azithromycin (20 mg/kg) compared to placebo when administered during well-child visits for prevention of infant mortality. The trial found no evidence of a difference in the primary endpoint. This paper presents prespecified secondary anthropometric endpoints including weight gain (g/day), height change (mm/day), weight-for-age Z-score (WAZ), weight-for-length Z-score (WLZ), length-for-age Z-score (LAZ), and mid-upper arm circumference (MUAC). Infants were eligible for the trial if they were between 5 and 12 weeks of age, able to orally feed, and their families were planning to remain in the study area for the duration of the study. Anthropometric measurements were collected at enrollment (5 to 12 weeks of age) and 6 months of age. Among 32,877 infants enrolled in the trial, 27,298 (83%) were followed and had valid anthropometric measurements at 6 months of age. We found no evidence of a difference in weight gain (mean difference 0.03 g/day, 95% confidence interval (CI) -0.12 to 0.18), height change (mean difference 0.004 mm/day, 95% CI -0.05 to 0.06), WAZ (mean difference -0.004 SD, 95% CI -0.03 to 0.02), WLZ (mean difference 0.001 SD, 95% CI -0.03 to 0.03), LAZ (mean difference -0.005 SD, 95% CI -0.03 to 0.02), or MUAC (mean difference 0.01 cm, 95% CI -0.01 to 0.04). The primary limitation of the trial was that measurements were only collected at enrollment and 6 months of age, precluding assessment of shorter-term or long-term changes in growth.

Conclusions: Single-dose azithromycin does not appear to affect weight and height outcomes when administered during early infancy.

Am J Trop Med Hyg. 2023 Oct 2;109(5):1107-1112.
doi: 10.4269/ajtmh.23-0431. Print 2023 Nov 1.

Temporal Trends in Phenotypic Macrolide and Nonmacrolide Resistance for Streptococcus pneumoniae Nasopharyngeal Samples Up to 36 Months after Mass Azithromycin Administration in a Cluster-Randomized Trial in Niger

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Abstract

Azithromycin mass drug administration decreases child mortality but also selects for antibiotic resistance. Herein, we evaluate macrolide resistance of nasopharyngeal Streptococcus pneumoniae after azithromycin MDA. In a cluster-randomized trial, children 1-59 months received azithromycin or placebo biannually. Fifteen villages from each arm were randomly selected for antimicrobial resistance testing, and 10-15 randomly selected swabs from enrolled children at each village were processed for S. pneumoniae isolation and resistance testing. The primary prespecified outcome was macrolide resistance fraction for azithromycin versus placebo villages at 36 months. Secondary non-prespecified outcomes were comparisons of azithromycin and placebo for: 1) macrolide resistance at 12, 24, and 36 months; 2) nonmacrolide resistance at 36 months; and 3) suspected-erm mutation. At 36

months, 423 swabs were obtained and 322 grew S. pneumoniae, (azithromycin: 146/202, placebo: 176/221). Mean resistance prevalence was non-significantly higher in treatment than placebo (mixed-effects model: 14.6% vs. 8.9%; OR = 2.0, 95% CI: 0.99-3.97). However, when all time points were evaluated, macrolide resistance prevalence was significantly higher in the azithromycin group (β = 0.102, 95% CI: 0.04-0.167). For all nonmacrolides, resistance prevalence at 36 months was not different between the two groups. Azithromycin and placebo were not different for suspected-erm mutation prevalence. Macrolide resistance was higher in the azithromycin group over all time points, but not at 36 months. Although this suggests resistance may not continue to increase after biannual MDA, more studies are needed to clarify when MDA can safely decrease mortality and morbidity in lower- and middle-income countries.

J Infect Dis. 2024 Jan 31:jiae049.
doi: 10.1093/infdis/jiae049. Online ahead of print.

Minimal impact on the resistome of children in Botswana after azithromycin treatment for acute severe diarrhoeal disease

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Abstract

Background: Macrolide antibiotics, including azithromycin, can reduce under-five mortality rates and treat various infections in children in sub-Saharan Africa. These exposures, however, can select for antibiotic-resistant bacteria in the gut microbiota.

Methods: Our previous randomized controlled trial (RCT) of a rapid-test-and-treat strategy for severe acute diarrhoeal disease in children in Botswana included an intervention (three-day azithromycin dose) group and a control group that received supportive treatment. In this prospective matched cohort study using stools collected at baseline and 60 days after treatment from RCT participants, the collection of antibiotic resistance genes or resistome was compared between groups.

Results: Certain macrolide resistance genes increased in prevalence by 13% to 55% at 60 days, without differences in gene presence between the intervention and control groups. These genes were linked to tetracycline resistance genes and mobile genetic elements.

Conclusions: Azithromycin treatment for bacterial diarrhoea for young children in Botswana resulted in similar effects on the gut resistome as the supportive treatment and did not provide additional selective pressure for macrolide resistance gene maintenance. The gut microbiota of these children contains diverse macrolide resistance genes that may be transferred within the gut upon repeated exposures to azithromycin or co-selected by other antibiotics.

Arthritis

Cochrane Database Syst Rev. 2024 Feb 9;2(2):CD003129.
doi: 10.1002/14651858.CD003129.pub2.

Methotrexate for juvenile idiopathic arthritis

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. Methotrexate has broad immunomodulatory properties and is the most commonly used disease-modifying antirheumatic drug (DMARD). This is an update of a 2001 Cochrane review. It supports a living guideline for children and young people with JIA.

Objectives: To assess the benefits and harms of methotrexate for children and young people with juvenile idiopathic arthritis.

Search methods: The Australian JIA Living Guideline Working Group created a registry of all randomised controlled trials (RCTs) of JIA by searching CENTRAL, MEDLINE, Embase, and trials registries. The date of the most recent search of online databases was 1 February 2023.

Selection criteria: We searched for RCTs that compared methotrexate with placebo, no treatment, or another DMARD (with or without concomitant therapies) in children and young people (aged up to 18 years) with JIA.

Data collection and analysis: We used standard Cochrane methods. The main comparison was methotrexate versus placebo. Our outcomes were treatment response, sustained clinically inactive disease, function, pain, participant global assessment of well-being, serious adverse events, and withdrawals due to adverse events. We used GRADE to assess the certainty of evidence for each outcome.

Main results: We identified three new trials in this update, bringing the total number of included RCTs to five (575 participants). Three trials evaluated oral methotrexate versus placebo, one evaluated methotrexate plus intra-articular glucocorticoid (IAGC) therapy versus IAGC therapy alone, and one evaluated methotrexate versus leflunomide. Doses of methotrexate ranged from 5 mg/m^2/week to 15 mg/m^2/week in four trials, and participants in the methotrexate group of the remaining trial received 0.5 mg/kg/week. Trial size varied from 31 to 226 participants. The average age of participants ranged from four to 10 years. Most participants were females and most had nonsystemic JIA. The study that evaluated methotrexate plus IAGC therapy versus IAGC therapy alone recruited children and young people with the oligoarticular disease subtype of JIA. Two placebo-controlled trials and the trial of methotrexate versus leflunomide were adequately randomised and blinded, and likely not susceptible to important biases. One placebo-controlled trial may have been susceptible to selection bias due to lack of adequate reporting of randomisation methods. The trial investigating the addition of methotrexate to IAGC therapy was susceptible to performance and detection biases. Methotrexate versus placebo Methotrexate compared with placebo may increase the number of children and young people who achieve treatment response up to six months (absolute difference of 163 more per 1000 people; risk ratio (RR) 1.67, 95% confidence interval (CI) 1.21 to 2.31; I^2 = 0%; 3 trials, 328 participants; low-certainty evidence). However, methotrexate compared with placebo may have little or no effect on pain as measured on an increasing scale of 0 to 100 (mean difference (MD) -1.10 points, 95% CI -9.09 to 6.88; 1 trial, 114 participants), improvement in participant global assessment of well-being (absolute difference of 92 more per 1000 people; RR 1.23, 95% CI 0.88 to 1.72; 1 trial, 176 participants), occurrence of serious adverse events (absolute difference of 5 fewer per 1000 people; RR 0.63, 95% CI 0.04 to 8.97; 3 trials, 328 participants), and withdrawals due to adverse events (RR 3.46, 95% CI 0.60 to 19.79; 3 trials, 328 participants) up to six months. We could not estimate the absolute difference for withdrawals due to adverse events because there were no withdrawals in the placebo group. All outcomes were reported within

six months of randomisation. We downgraded the certainty of the evidence to low for all outcomes due to indirectness (suboptimal dosing of methotrexate and diverse outcome measures) and imprecision (few participants and low event rates). No trials reported function or the number of participants with sustained clinically inactive disease. Serious adverse events included liver derangement, abdominal pain, and inadvertent overdose. Methotrexate plus intra-articular corticosteroid therapy versus intra-articular corticosteroid therapy alone Methotrexate plus IAGC therapy compared with IAGC therapy alone may have little or no effect on the probability of sustained clinically inactive disease or the rate of withdrawals due to adverse events up to 12 months in children and young people with the oligoarticular subtype of JIA (low-certainty evidence). We could not calculate the absolute difference in withdrawals due to adverse events because there were no withdrawals in the control group. We are uncertain if there is any difference between the interventions in the risk of severe adverse events, because none were reported. The study did not report treatment response, function, pain, or participant global assessment of well-being. Methotrexate versus an alternative disease-modifying antirheumatic drug Methotrexate compared with leflunomide may have little or no effect on the probability of treatment response or on function, participant global assessment of well-being, risk of serious adverse events, and rate of withdrawals due to adverse events up to four months. We downgraded the certainty of the evidence for all outcomes to low due to imprecision. The study did not report pain or sustained clinically inactive disease.
Authors' conclusions: Oral methotrexate (5 mg/m^2/week to 15 mg/m^2/week) compared with placebo may increase the number of children and young people achieving treatment response but may have little or no effect on pain or participant global assessment of well-being. Oral methotrexate plus IAGC injections compared to IAGC injections alone may have little or no effect on the likelihood of sustained clinically inactive disease among children and young people with oligoarticular JIA. Similarly, methotrexate compared with leflunomide may have little or no effect on treatment response, function, and participant global assessment of well-being. Serious adverse events due to methotrexate appear to be rare. We will update this review as new evidence becomes available to inform the living guideline.

* although not written by authors from a low or middle income country, the results are relevant to practitioners treating JIA in all countries.

Cash transfers and family economic support

Soc Sci Med. 2023 Sep;332:116102.
doi: 10.1016/j.socscimed.2023.116102. Epub 2023 Jul 20.
The impact of poverty-reduction intervention on child mental health mediated by family relations: Findings from a cluster-randomized trial in Uganda
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Abstract
Reviews that synthesize global evidence on the impact of poverty reduction interventions on child and adolescent mental health (CAMH) report inconclusive results and highlight the need to unpack the mechanisms that connect poverty-reduction to CAMH. To address this gap, we examine the proposition that family relations is an important relational factor

transmitting effect of poverty on CAMH, and test whether family relations mediate the effect of poverty-reduction intervention on depression, hopelessness, and self-concept among AIDS orphans in Uganda. We use longitudinal data collected over the course of 48 months in a cluster-randomized controlled trial conducted among N = 1410 AIDS orphans from n = 48 schools in Uganda. To examine the relationship between intervention, latent mediator (family relations and support) and CAMH outcomes (Beck Hopelessness Scale (BHS), Tennessee Self-Concept Scale (TSCS), and Depression), we ran structural equation models adjusting for clustering of individuals within schools. Relative to the control group, participants in both treatment arms reported lower levels of hopelessness and depression, and significantly higher levels of self-concept. They also report significantly higher levels of latent family relationship in all three models. In both treatment arms, the direct effect of the intervention on all three outcomes is still significant when the latent family relations mediator is included in the analyses. This suggests partial mediation. In other words, in both treatment arms, the significant positive effect of the intervention on children's depression, hopelessness, and self-concept is partially mediated by their family relationship quality. Our findings support the argument put forward by the Family Stress Model showing that the poverty-reduction program improves children's mental health functioning by improving family relationships. The implications of our study extend beyond the narrow focus of poverty reduction, suggesting that asset-building interventions have broader impacts on family dynamics and child mental health.

Econ Educ Rev. 2023 Aug;95:102429.
doi: 10.1016/j.econedurev.2023.102429. Epub 2023 Jun 14.

Effects of a single cash transfer on school re-enrollment during COVID-19 among vulnerable adolescent girls in Kenya: Randomized controlled trial

John A Maluccio[1], Erica Soler-Hampejsek[2], Beth Kangwana[3], Eva Muluve[3], Faith Mbushi[3], Karen Austrian[3]

Abstract

COVID-19 related school closures in Kenya were among the longest in Africa, putting older adolescent girls nearing the end of secondary school at risk of permanent dropout. Using a randomized-controlled trial we evaluated a logistically simple cash transfer intervention in urban areas designed to promote their return to school. There were no required conditions for receiving the transfer and the intervention is interpreted as a labeled cash transfer. It had substantial significant effects on re-enrollment of adolescent girls, with greater effectiveness for older girls and even for some not enrolled earlier in the school year. The program effectiveness demonstrates feasibility of the approach and underscores the potential importance of additional resources for schooling during the pandemic, when a large majority of households had suffered income losses.

Community child health

Glob Health Action. 2023 Dec 31;16(1):2203541.
doi: 10.1080/16549716.2023.2203541.

Trial-based economic evaluation of the system-integrated activation of community health volunteers in rural Ghana

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Abstract

Background: Globally, steps to revitalise programmes deploying community health workers (CHWs) on a national scale have been growing, but few economic evaluations have been done on system-integrated CHW programmes. Ghana has dual cadres of CHWs: community health officers (CHOs) and community health volunteers (CHVs). CHO plays a major role in primary health services but has suffered from chronic staff shortages. We activated CHVs in communities to mitigate the negative impact due to CHO shortages. The CHVs conducted home visits and provided health education to prevent childhood diseases.

Objective: We evaluated the cost-effectiveness and cost-benefit of activating CHVs.

Methods: In a cluster-randomised trial with 40 communities in rural Ghana, the changes in disease incidence were inferred from a statistical model using a Bayesian generalised linear multilevel model. We evaluated the total incremental cost, benefit, and effectiveness for the intervention from an economic model. In cost-effectiveness analysis, disability-adjusted life years (DALYs) were estimated using a decision tree model. In the cost-benefit analysis, the cost-benefit ratio and net present value of benefit were estimated using a decision tree model, and a standardised sensitivity analysis was conducted. The decision tree model was a one-year cycle and run over 10-years. Costs, benefits, and effectiveness were discounted at a rate of 3% per year.

Results: According to the cost-effectiveness analysis, the programme was highly likely to exceed the WHO-CHOICE threshold (1-3 times GDP per capita), but it was unlikely to exceed the conservative threshold (10-50% of GDP per capita). In the cost-benefit analysis, the mean and median cost-benefit ratios were 6.4 and 4.8, respectively.

Conclusion: We found the potential economic strengths in the cost-benefit analysis. To integrate CHW programmes with national health systems, we need more research to find the most effective scope of work for CHWs.

Trop Med Health. 2024 Jan 8;52(1):7.
doi: 10.1186/s41182-023-00572-2.

The impact of home-based management of malaria on clinical outcomes in sub-Saharan African populations: a systematic review and meta-analysis

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Abstract

Background: Malaria remains a significant cause of morbidity and mortality globally and continues to disproportionately afflict the African population. We aimed to evaluate the effect of home management of malaria intervention on health outcomes.

Methods: In our systematic review and meta-analysis, six databases (Pubmed, Cochrane CENTRAL, EMBASE, CAB Abstracts and Global Health, CINAHL Complete, and BIOSIS) were searched for studies of home management of malaria from inception until November 15, 2023. We included before-after studies, observational studies, and randomised controlled trials of home management intervention delivered in community settings. The primary outcomes were malaria mortality and all-cause mortality. The risk of bias in individual observational studies was assessed using the ROBINS-I tool, whilst randomised controlled trials were judged using a revised Cochrane risk of bias tool and cluster-randomised

controlled trials were evaluated using an adapted Cochrane risk of bias tool for cluster-randomised trials. We computed risk ratios with accompanying 95% confidence intervals for health-related outcomes reported in the studies and subsequently pooled the results by using a random-effects model (DerSimonian-Laird method).
Results: We identified 1203 citations through database and hand searches, from which 56 articles from 47 studies encompassing 234,002 participants were included in the systematic review. All studies were conducted in people living in sub-Saharan Africa and were rated to have a low or moderate risk of bias. Pooled analyses showed that mortality rates due to malaria (RR = 0.40, 95% CI = 0.29-0.54, P = 0.00001, I^2 = 0%) and all-cause mortality rates (RR = 0.62, 95% CI = 0.53-0.72, P = 0.00001, I^2 = 0%) were significantly lower among participants receiving home management intervention compared to the control group. However, in children under 5 years of age, there was no significant difference in mortality rates before and after implementation of home management of malaria. In terms of secondary outcomes, home management of malaria was associated with a reduction in the risk of febrile episodes (RR = 1.27, 95% CI = 1.09-1.47, P = 0.002, I^2 = 97%) and higher effective rates of antimalarial treatments (RR = 2.72, 95% CI = 1.90-3.88, P < 0.00001, I^2 = 96%) compared to standard care. Home malaria management combined with intermittent preventive treatment showed a significantly lower incidence risk of malaria than home management intervention that exclusively provided treatment to individuals with febrile illness suggestive of malaria. The risks for adverse events were found to be similar for home management intervention using different antimalarial drugs. Cost-effectiveness findings depicted that home malaria management merited special preferential scale-up.
Conclusions: Home management of malaria intervention was associated with significant reductions in malaria mortality and all-cause mortality. The intervention could help decrease health and economic burden attributable to malaria. Further clinical studies are warranted to enable more meaningful interpretations with regard to wide-scale implementation of the intervention, settings of differing transmission intensity, and new antimalarial drugs.

Child development and parenting programs

Compr Psychiatry. 2023 Nov 4:128:152436.
doi: 10.1016/j.comppsych.2023.152436. Online ahead of print.
Efficacy of a dialogic book-sharing intervention in a South African birth cohort: A randomized controlled trial
Sheri-Michelle Koopowitz[1], Karen Thea Maré[2], Marilyn Lake[3], Christopher du Plooy[3], Nadia Hoffman[4], Kirsten A Donald[3], Susan Malcolm-Smith[5], Lynne Murray[6], Heather J Zar[3], Peter Cooper[6], Dan J Stein[2]
Abstract
Objective: Evidence shows that dialogic book-sharing improves language development in young children in low-middle income countries (LMICs), particularly receptive and expressive language. It is unclear whether this intervention also boosts development of other neurocognitive and socio-emotional domains in children. Using a randomized controlled trial (RCT) nested in the Drakenstein Child Health Study (DCHS), a book-sharing intervention

was implemented in caregivers of 3.5-year-old preschool children living in low-income South African communities.
Methods: 122 Caregivers and their children (mean age 3.5 years) were randomly assigned to an intervention group (n = 61) or waitlist control group (n = 61). A neurocognitive battery determined baseline receptive and expressive language, executive function, theory of mind, and behavior scores.
Results: No differences were observed between intervention and control groups on receptive and expressive language, or any of the neurocognitive or socio-emotional measures from baseline (3.5 years) to 4 months post-intervention administration (4 years).
Conclusion: The benefits noted in prior literature of book-sharing in infants did not appear to be demonstrated at 4 months post-intervention, in children from 3.5 to 4 years of age. This suggests the importance of early intervention and emphasizes the need for further research on adaptation of book-sharing for older participants in a South African context.

Lancet Reg Health Southeast Asia. 2024 Mar 19:25:100388.
doi: 10.1016/j.lansea.2024.100388. eCollection 2024 Jun.

Effect of a parenting and nutrition education programme on development and growth of children using a social safety-net platform in urban Bangladesh: a cluster randomized controlled trial

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Abstract
Background: Although sustainable development goals mandate for quality early childhood development (ECD) interventions for children <8 years, little occurs for children <3 years, especially in urban settings in low-and-middle-income countries (LMICs). Our primary objective was to measure the effect of an ECD-focused parenting and nutrition education on children's development through home visits using a social safety net platform of urban Bangladesh.
Methods: A cluster randomized controlled trial was conducted with mothers of children aged 6-16 months in 20 clusters across the Rangpur city, Bangladesh. The intervention group received fortnightly ECD-focused parenting and nutrition education at homes by local Community Health Workers (CHWs) for one year. Bayley-III was used to measure children's cognitive, language and motor development. Data were analyzed using intention to treat. ClinicalTrials.gov Identifier: NCT03753646.
Findings: Out of 599 mother-child dyads, 56.6% mothers were aged ≤≤ 25 years old. After one year, the intervened children had higher cognitive [Effect size Cohen's d; 0.42 SD (95% CI: 0.58-0.25)], language (0.38 SD, 95% CI: 0.55-0.22) and motor (0.17 SD, 95% CI: 0.01-0.34) development. In the intervention group, mothers experienced less violence [Odds ratio; 0.6 (95% CI: 0.4-1.0)] and fathers engaged more (0.23 SD, CI: 0.39-0.06) in ECD activities with their children compared to the comparison group. Total home stimulation and mothers' knowledge on child care were also improved in the intervention. But the children's growth was not improved.
Interpretation: This ECD programme improves the development of children of young mothers in urban settings using a social safety-net platform. The evidence may help in increasing ECD coverage in urban areas in LMICs.

Front Public Health. 2023 Nov 14:11:1165728.
doi: 10.3389/fpubh.2023.1165728. eCollection 2023.

Design-redesign, implementation, and evaluation of effectiveness of maternal nutrition and responsive parenting program on child development at 2 years of age from rural India: a cluster RCT

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Abstract

Background: To promote early childhood development (ECD), we require information not only on what needs to be addressed and on what effects can be achieved but also on effective delivery methods that can be adapted to local context. We describe design, implementation, and evaluation of a complex intervention to strengthen nurturing environment for young children.

Methods: Study participants were pregnant women and their children from birth to 2 years. We used design and redesign, implementation, and evaluation approaches for the study. We co-created curriculum and delivery plan with stakeholders, based on the theoretical framework, findings from formative research, and our preliminary work. We recruited 656 pregnant women and newborns, 326 (49.69%) from intervention and 330 (50.30%) from the control group. We conducted a cluster randomized controlled trial to evaluate the program's effectiveness. The outcomes of children were assessed at 12 and 24 months.

Findings: At recruitment, study participants from both the study arms were similar in sociodemographic characteristics. We conducted 6,665 home visits, 25 toy-making workshops, and 65 caregiver-meetings. The initial examination of program data revealed gaps in quality and coverage of interventions. The intervention was redesigned based on feedback from stakeholders in community meetings. At recruitment, participants in both study groups had similar socio-demographics. We conducted 6,665 home visits, 25 toy workshops, and 65 caregiver meetings. Initial program data showed intervention quality and coverage gaps, leading to a redesign program based on community and stakeholder feedback. Post-re-designing, session quality improved, with program coverage rising from 32 to 98%. Male participation in home visits increased from 4.3 to 32.65%, and data errors reduced from 270 to 140 per month on average. At 24 months, program showed moderate-mild impact on ECD - cognitive (0.31, 95%CI: 0.13-0.48), language (0.2, 95%CI: 0.01-0.39), and socioemotional-development (0.19, 95%CI: 0.01-0.37), moderate effect on home-environment and mother-child interaction. 96% of women initiated breastfeed within one-hour of delivery, and exclusive-breastfeeding rate of 89.80%.

Interpretations: The study provides an evidence-based community centered ECD curriculum and implementation strategies to enhance service providers, and caregivers' knowledge and skills for promoting ECD in low-resource settings with the potential to scale within existing Government Program.

J Nutr. 2024 Feb;154(2):755-764.
doi: 10.1016/j.tjnut.2023.12.008. Epub 2023 Dec 9.

Effect of a Center-Based Early Childhood Care and Education Program on Child Nutritional Status: A Secondary Analysis of a Stepped-Wedge Cluster Randomized Controlled Trial in Rural Sindh, Pakistan

Nazia Binte Ali [1], Aisha K Yousafzai [2], Saima Siyal [3], Shelina Bhamani [4], Christopher R Sudfeld [5]

Abstract

Background: High-quality early childhood care and education (ECCE) programs can positively impact children's development. However, as an unintended consequence, ECCE attendance may also affect children's nutritional status.

Objective: We evaluated the effect of a center-based ECCE intervention on child nutritional outcomes in rural Pakistan.

Methods: This study utilized data from a stepped-wedge cluster randomized controlled trial of a center-based ECCE program that trained female youth to run high-quality preschools for children aged 3.5-5.5 y (Youth Leaders for Early Childhood Assuring Children are Prepared for School (LEAPS) program) in rural Sindh, Pakistan. The program did not include any school meals. A total of 99 village clusters were randomized to receive the LEAPS intervention in 3 steps, and repeated cross-sectional surveys were conducted to assess the impact on children (age: 4.5-5.5 y) at 4- time points. ITT analyses with multilevel mixed-effect models were used to estimate the effect of the intervention on child anthropometric outcomes.

Results: The analysis included 3858 children with anthropometric data from 4 cross-sectional survey rounds. The LEAPS intervention was found to have a positive effect on child height-for-age z score (mean difference: 0.13 z-scores; 95% confidence interval [CI]: 0.02, 0.24). However, there was a negative effect on weight-based anthropometric indicators, -0.29 weight-for-height z score (WHZ) (95% CI: -0.42, -0.15), -0.13 BMI z score (BMIZ) (95% CI: -0.23, -0.03), and -0.16 mid-upper arm circumference-for-age z score MUACZ (95% CI: -0.25, -0.05). An exploratory analysis suggested that the magnitude of the negative effect of LEAPS on WHZ, BMIZ, and weight-for-age z score (WAZ) was greater in the survey round during the COVID-19 lockdown.

Discussion: The LEAPS intervention positively affected child linear growth but had negative effects on multiple weight-based anthropometric measures. ECCE programs in low- and middle-income country settings should evaluate the integration of nutrition-specific interventions (eg school lunch, counseling on healthy diets) and infection control strategies to promote children's healthy growth and development.

J Child Psychol Psychiatry. 2024 May;65(5):694-709.
doi: 10.1111/jcpp.13897. Epub 2023 Oct 6.

Effects of engaging fathers and bundling parenting and nutrition interventions on early child development and maternal and paternal parenting in Mara, Tanzania: a factorial cluster-randomized controlled trial

Joshua Jeong [1 2], Marilyn N Ahun [2], Nilupa S Gunaratna [3], Ramya Ambikapathi [3 4], Frank Mapendo [5], Lauren Galvin [6], Mary Pat Kieffer [6], Mary Mwanyika-Sando [5], Dominic Mosha [5], Savannah Froese O'Malley [3 7], Cristiana K Verissimo [7], George PrayGod [8], Aisha K Yousafzai [2]

Abstract

Background: Multicomponent interventions are needed to address the various co-occurring risks that compromise early child nutrition and development. We compared the independent

and combined effects of engaging fathers and bundling parenting components into a nutrition intervention on early child development (ECD) and parenting outcomes.
Methods: We conducted a 2×2 factorial cluster-randomized controlled trial across 80 villages in Mara Region, Tanzania, also known as EFFECTS (Engaging Fathers for Effective Child Nutrition and Development in Tanzania; ClinicalTrials.gov, NCT03759821). Households with children under 18 months of age residing with their mother and father were enrolled. Villages were randomly assigned to one of five groups: a nutrition intervention for mothers, a nutrition intervention for couples, a bundled nutrition and parenting intervention for mothers, a bundled intervention for couples, and a standard-of-care control. Interventions were delivered by trained community health workers through peer groups and home visits over 12 months. Mothers, fathers, and children were assessed at baseline, midline, and endline or postintervention. We used a difference-in-difference approach with intention-to-treat analysis to estimate intervention effects on ECD (Bayley Scales of Infant and Toddler Development, third edition) and maternal and paternal parenting and psychosocial well-being.
Results: Between October 29, 2018, and May 24, 2019, 960 households were enrolled (n = 192 per arm). Compared to nutrition interventions, bundled interventions improved children's cognitive (β = .18 [95% CI: 0.01, 0.36]) and receptive language development (β = .23 [0.04, 0.41]). There were no differences between interventions for other ECD domains. Compared to nutrition interventions, bundled interventions achieved additional benefits on maternal stimulation (β = .21 [0.04, 0.38]) and availability of home learning materials (β = .25 [0.07-0.43]) and reduced paternal parenting distress (β = -.34 [-0.55, -0.12]). Compared to interventions with mothers only, interventions that engaged fathers improved paternal stimulation (β = .45 [0.27, 0.63]).
Conclusions: Jointly bundling parenting components into nutrition interventions while also engaging both mothers and fathers is most effective for improving maternal and paternal parenting and ECD outcomes.

Glob Health Sci Pract. 2023 Oct 30;11(5):e2300037.
doi: 10.9745/GHSP-D-23-00037. Print 2023 Oct 30.

Is Early Childhood Development Care at Public Health Facilities in Pakistan Effective? A Cluster Randomized Controlled Trial

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Abstract
Background: Significant brain development in children occurs from birth to 2 years, with environment playing an important role. Stimulation interventions are widely known to be effective in enhancing early childhood development (ECD). This study aims to assess the feasibility and effectiveness of integrating ECD care delivered by lady health visitors (LHVs) at public health facilities in rural Pakistan.
Method: A cluster randomized controlled trial was conducted through public health facilities in 2 districts of Punjab, Pakistan. A total of 22 clusters (rural health centers and subdistrict hospitals) were randomly allocated to receive routine care (control: n=11 clusters, 406 mother-child pairs) or counseling (intervention: n=11 clusters, 398 mother-child pairs). All

children aged 11-12 months without any congenital abnormality were eligible for enrollment. The intervention was delivered by the LHVs to mothers with children aged 12-24 months in 3 quarterly sessions.
Results: The primary outcome was the prevention of ECD delays in children aged 24 months (assessed with the Ages and Stages Questionnaire-3). Analysis was done on an intention-to-treat basis. A total of 804 mother-child pairs were registered in the study, of which 26 (3.3%) pairs were lost to follow-up at the endpoint. The proportion of children with 2 or more developmental delays was significantly less in the intervention arm (13%) as compared to the control arm (41%) at an endpoint (odds ratio=0.21; 95% confidence interval=0.11, 0.42). Children in the intervention arm also had significantly better anthropometric measurements when aged 24 months than the children in the control arm.
Conclusion: The integrated ECD care intervention for children aged 12-24 months at public health facilities was found to be effective in enhancing ECD and reducing the proportion of children with global development delays.

J Child Psychol Psychiatry. 2023 Oct 6.
doi: 10.1111/jcpp.13897. Online ahead of print.

Effects of engaging fathers and bundling parenting and nutrition interventions on early child development and maternal and paternal parenting in Mara, Tanzania: a factorial cluster-randomized controlled trial

Joshua Jeong [1,2], Marilyn N Ahun [2], Nilupa S Gunaratna [3], Ramya Ambikapathi [3,4], Frank Mapendo [5], Lauren Galvin [6], Mary Pat Kieffer [6], Mary Mwanyika-Sando [5], Dominic Mosha [5], Savannah Froese O'Malley [3,7], Cristiana K Verissimo [7], George PrayGod [8], Aisha K Yousafzai [2]

Abstract
Background: Multicomponent interventions are needed to address the various co-occurring risks that compromise early child nutrition and development. We compared the independent and combined effects of engaging fathers and bundling parenting components into a nutrition intervention on early child development (ECD) and parenting outcomes.
Methods: We conducted a 2×2 factorial cluster-randomized controlled trial across 80 villages in Mara Region, Tanzania, also known as EFFECTS (Engaging Fathers for Effective Child Nutrition and Development in Tanzania; ClinicalTrials.gov, NCT03759821). Households with children under 18 months of age residing with their mother and father were enrolled. Villages were randomly assigned to one of five groups: a nutrition intervention for mothers, a nutrition intervention for couples, a bundled nutrition and parenting intervention for mothers, a bundled intervention for couples, and a standard-of-care control. Interventions were delivered by trained community health workers through peer groups and home visits over 12 months. Mothers, fathers, and children were assessed at baseline, midline, and endline or postintervention. We used a difference-in-difference approach with intention-to-treat analysis to estimate intervention effects on ECD (Bayley Scales of Infant and Toddler Development, third edition) and maternal and paternal parenting and psychosocial well-being.
Results: Between October 29, 2018, and May 24, 2019, 960 households were enrolled (n = 192 per arm). Compared to nutrition interventions, bundled interventions improved children's cognitive (β = .18 [95% CI: 0.01, 0.36]) and receptive language development (β = .23 [0.04,

0.41]). There were no differences between interventions for other ECD domains. Compared to nutrition interventions, bundled interventions achieved additional benefits on maternal stimulation (β = .21 [0.04, 0.38]) and availability of home learning materials (β = .25 [0.07-0.43]) and reduced paternal parenting distress (β = -.34 [-0.55, -0.12]). Compared to interventions with mothers only, interventions that engaged fathers improved paternal stimulation (β = .45 [0.27, 0.63]).
Conclusions: Jointly bundling parenting components into nutrition interventions while also engaging both mothers and fathers is most effective for improving maternal and paternal parenting and ECD outcomes.

J Med Internet Res. 2023 Oct 13:25:e47266.
doi: 10.2196/47266.
Effect of Short, Animated Video Storytelling on Maternal Knowledge and Satisfaction in the Perinatal Period in South Africa: Randomized Controlled Trial
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Abstract
Background: Innovative mobile health (mHealth) interventions can improve maternal knowledge, thereby supporting national efforts to reduce preventable maternal and child mortality in South Africa. Studies have documented a potential role for mobile video content to support perinatal health messaging, enhance maternal satisfaction, and overcome literacy barriers. Short, animated storytelling (SAS) is an innovative, emerging approach to mHealth messaging.
Objective: We aimed to measure the effect of SAS videos on maternal knowledge and user satisfaction for mothers enrolled in antenatal care programs at 2 public health facilities in the Tshwane District of South Africa.
Methods: We used a randomized controlled trial with a nested evaluation of user satisfaction. Participants were randomized 1:1 into Standard-of-Care (SOC) Control, and SAS Intervention groups. The intervention videos were delivered through WhatsApp, and 1 month later, participants responded to telephone surveys assessing their knowledge. The intervention group then participated in a nested evaluation of user satisfaction.
Results: We surveyed 204 participants. Of them, 49.5% (101/204) were aged between 25 and 34 years. Almost all participants self-identified as Black, with the majority (190/204, 93.2%) having completed secondary school. The mean overall knowledge score was 21.92/28. We observed a slight increase of 0.28 (95% uncertainty interval [UI] -0.58 to 1.16) in the overall knowledge score in the intervention arm. We found that those with secondary education or above scored higher than those with only primary education by 2.24 (95% UI 0.76-4.01). Participants aged 35 years or older also scored higher than the youngest age group (18-24 years) by 1.83 (95% CI 0.39-3.33). Finally, the nested user satisfaction evaluation revealed high maternal satisfaction (4.71/5) with the SAS video series.
Conclusions: While the SAS videos resulted in high user satisfaction, measured knowledge gains were small within a participant population that was already receiving perinatal health messages through antenatal clinics. The higher knowledge scores observed in older participants with higher education levels suggest that boosting maternal knowledge in younger mothers with lower education levels should continue to be a public health priority in South Africa. Given the high maternal satisfaction among the SAS video-users in this study,

policy makers should consider integrating similar approaches into existing, broad-reaching perinatal health programs, such as MomConnect, to boost satisfaction and potentially enhance maternal engagement. While previous studies have shown the promise of animated video health education, most of this research has been conducted in high-income countries. More research in underresourced settings is urgently needed, especially as access to mobile technology increases in the Global South. Future studies should explore the effect of SAS videos on maternal knowledge in hard-to-reach populations with limited access to antenatal care, although real-world logistical challenges persist when implementing studies in underresourced South African populations.

J Mother Child. 2023 Jul 6;27(1):64-71.
doi: 10.34763/jmotherandchild.20232701.d-22-00025. eCollection 2023 Jun 1.

Impact of Early Exposure to Play Materials on Motor Development in High-Risk Infants: A Randomised Controlled Trial

Mrunmayi S Gadre [1], Vinuta R Deshpande [1]

Abstract

Background: The purpose of this study was to determine the impact of early exposure to play materials on motor development in high-risk infants.

Materials and methods: A 1:1 parallel group randomised control study was conducted. A total of 36 participants were recruited, with 18 in each group. The intervention lasted 6 weeks for both groups, with follow-ups in the 2nd and 4th weeks. The Peabody Developmental Motor Scale 2nd Edition (PDMS-2) was used as an outcome measure. The data was analysed using the Likelihood Ratio test, Chi-square test, independent sample t-test, and paired t-test.

Results: There was no difference between the groups except for the raw reflex scores ($t = 3.29$, $p = 0.002$), raw stationary scores ($t = 4.26$, $p < 0.001$), standard stationary scores ($t = 2.57$, $p = 0.015$), and Gross Motor Quotient (GMQ) ($t = 3.275$, $p = 0.002$). Statistical significance within the experimental group was observed in the raw reflex ($t = -5.16$, $p < 0.001$), stationary ($t = -10.5$, $p < 0.001$), locomotion ($t = -5.67$, $p < 0.001$), grasp ($t = -4.68$, $p < 0.001$), and visual motor ($t = -5.03$, $p < 0.001$) scores, as well as the standard stationary ($t = -2.87$, $p = 0.010$), locomotion ($t = -3.43$, $p = 0.003$), grasp ($t = -3.28$, $p = 0.004$), and visual motor ($t = -5.03$, $p < 0.001$) scores. Quotients were the GMQ ($t = -7.31$, $p < 0.001$), Total Motor Quotient (TMQ) ($t = -5.71$, $p < 0.001$), Fine Motor Quotient (FMQ) ($t = -6.48$, $p < 0.001$). Conclusions: The current study concludes that a six-week treatment of early exposure to age-appropriate toys is advantageous in enhancing motor development in high-risk neonates.

Res Dev Disabil. 2024 Apr:147:104696.
doi: 10.1016/j.ridd.2024.104696. Epub 2024 Feb 14.

Parent coaching to enhance community participation in young children with developmental disabilities: A pilot randomized controlled trial

Chi-Wen Chien [1], Chung-Ying Lin [2], Cynthia Yuen Yi Lai [3], Fiona Graham [4]

Abstract

Background: Parent coaching emerges as a preferred approach for enhancing performance and participation of children with developmental disabilities (DD), but limited clinical trials examine its effects on community participation.
Aim: To evaluate whether parent coaching, specifically using Occupational Performance Coaching (OPC), enhances community participation among young children with DD.
Method and procedures: A pilot double-blind randomized controlled trial was conducted. Parents of 50 children with DD (31 male, 19 female, mean age 4 years 10 months) were randomly assigned to the OPC group (n = 25) or parent consultation group (n = 25). Each parent received a maximum of eight coaching sessions or consultations. The primary outcome was children's community participation as assessed through parent-report measures at baseline, pre-intervention, post-intervention, and an 8-week follow-up.
Outcomes and results: Both groups showed significant improvements in parent-identified, goal-specific community participation after the intervention (mean difference [MD]=2.26-2.56), and these improvements were sustained during the follow-up. Despite a trend favoring parent coaching, the group difference in the improvements was not evident (MD=0.18-0.28). Both groups displayed positive improvements in children's overall community involvement post-intervention (MD=0.32); however, the time effects were not statistically significant.
Conclusions and implications: OPC, by coaching parents, could enhance goal-specific community participation in children with DD, producing effects similar to those achieved through parent consultation.

Lancet Glob Health. 2023 Aug;11(8):e1269-e1276.
doi: 10.1016/S2214-109X(23)00271-1.

Promoting early childhood development in Viet Nam: cost-effectiveness analysis alongside a cluster-randomised trial

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Abstract
Background: Economic evaluations are critical to ensure effective resource use to implement and scale up child development interventions. This study aimed to estimate the cost-effectiveness of a multicomponent early childhood development intervention in rural Viet Nam.
Methods: We did a cost-effectiveness study alongside a cluster-randomised trial with a 30-month time horizon. The study included 669 mothers from 42 communes in the intervention group, and 576 mothers from 42 communes in the control group. Mothers in the intervention group attended Learning Clubs sessions from mid-pregnancy to 12 months after delivery. The primary outcomes were child cognitive, language, motor, and social-emotional development at age 2 years. In this analysis, we estimated the incremental cost-effectiveness ratios (ICERs) of the intervention compared with the usual standard of care from the service provider and household perspectives. We used non-parametric bootstrapping to examine uncertainty, and applied a 3% discount rate.
Findings: The total intervention cost was US$169 898 (start-up cost $133 692 and recurrent cost $36 206). The recurrent cost per child was $58 (1 341 741 Vietnamese dong). Considering the recurrent cost alone, the base-case ICER was $14 and mean ICER of 1000 bootstrap

samples was $14 (95% CI -0·48 to 30) per cognitive development score gained with a 3% discount rate to costs. The ICER per language and motor development score gained was $22 and $20, respectively, with a 3% discount rate to costs.
Interpretation: The intervention was cost-effective: the ICER per child cognitive development score gained was 0·5% of Viet Nam's gross domestic product per capita, alongside other benefits in language and motor development. This finding supports the scaling up of this intervention in similar socioeconomic settings.

Health Policy Plan. 2023 Sep 18;38(8):916-925.
doi: 10.1093/heapol/czad057.

Considering equity and cost-effectiveness in assessing a parenting intervention to promote early childhood development in rural Vietnam

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Abstract
Considering equity in early childhood development (ECD) is important to ensure healthy development for every child. Equity-informative cost-effectiveness analysis can further guide decision makers to maximize outcomes with limited resources while promoting equity. This cost-effectiveness study aimed to examine the equity impacts of a multicomponent ECD intervention in rural Vietnam. We estimated the cost-effectiveness of the intervention with a 30-month time horizon from the service provider and household perspectives with equity considerations. Data were from a cluster-randomized controlled trial comparing the intervention with the local standard of care. The incremental cost-effectiveness ratios (ICERs) per child cognitive development score gained were estimated by household wealth quintile and maternal education level, adjusted for cluster effects and baseline characteristics such as maternal parity and age. A 3% discount rate was applied to costs, and non-parametric cluster bootstrapping was used to examine uncertainty around ICERs. Children in the intervention had higher cognitive development scores than those in the control arm across all subgroups. Based on intervention recurrent cost, the ICER per cognitive development score gained was lower in children from the poorest quintile (-US$6) compared to those from the richest quintile (US$16). Similarly, the ICER per cognitive development score gained was lower in children whose mothers had the lowest education level (-US$0.02) than those with mothers who had the highest education level (US$7). Even though our findings should be interpreted with caution due to the insufficient study power, the findings suggest that the intervention could promote equity while improving child cognitive development with greater cost-effectiveness in disadvantaged groups.

Front Pediatr. 2023 Jul 7:11:1120253.
doi: 10.3389/fped.2023.1120253. eCollection 2023.

Maternal time investment in caregiving activities to promote early childhood development: evidence from rural India

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Zafar[8], Gauri Divan[3], Zelee Hill[1], Bilal Iqbal Avan[2], Atif Rahman[6], Betty Kirkwood[2], Jolene Skordis[1]

Abstract

Introduction: Intervention strategies that seek to improve early childhood development outcomes are often targeted at the primary caregivers of children, usually mothers. The interventions require mothers to assimilate new information and then act upon it by allocating sufficient physical resources and time to adopt and perform development promoting behaviours. However, women face many competing demands on their resources and time, returning to familiar habits and behaviours. In this study, we explore mothers' allocation of time for caregiving activities for children under the age of 2, nested within a cluster randomised controlled trial of a nutrition and care for development intervention in rural Haryana, India.

Methods: We collected quantitative maternal time use data at two time points in rural Haryana, India, using a bespoke survey instrument. Data were collected from 704 mothers when their child was 12 months old, and 603 mothers when their child was 18 months old. We tested for significant differences in time spent by mothers on different activities when children are 12 months of age vs. 18 months of age between arms as well as over time, using linear regression. As these data were collected within a randomised controlled trial, we adjusted for clusters using random effects when testing for significant differences between the two time points.

Results: At both time points, no statistically significant difference in maternal time use was found between arms. On average, mothers spent most of their waking time on household chores (over 6 h and 30 min) at both time points. When children were aged 12 months, approximately three and a half hours were spent on childcare activities for children under the age of 2 years. When children were 18 months old, mothers spent more time on income generating activities (30 min) than when the children were 12 years old, and on leisure (approximately 4 h and 30 min). When children were 18 months old, less time was spent on feeding/breastfeeding children (30 min less) and playing with children (15 min). However, mothers spent more time talking or reading to children at 18 months than at 12 months.

Conclusion: We find that within a relatively short period of time in early childhood, maternal (or caregiver) time use can change, with time allocation being diverted away from childcare activities to others. This suggests that changing maternal time allocation in resource poor households may be quite challenging, and not allow the uptake of new and/or optimal behaviours.

Child Care Health Dev. 2023 Jul;49(4):750-759.
doi: 10.1111/cch.13089. Epub 2022 Dec 20.

Scaling-up an early childhood parenting intervention by integrating into government health care services in rural Bangladesh: A cluster-randomised controlled trial

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Abstract

Aims: We evaluated the feasibility and effectiveness of utilising government health supervisors to train and supervise primary health care workers (HWs) in community clinics to deliver parenting sessions as part of their usual duties.
Methods: We randomly allocated 16 unions in the Mymensing district of Bangladesh 1:1 to an intervention or control group. HWs in clinics in the eight intervention unions (n = 59 health workers, n = 24 clinics) were trained to deliver a group-based parenting intervention, with training and supervision provided by government supervisors. In each of the 24 intervention clinics, we recruited 24 mothers of children aged 6-24 months to participate in the parenting sessions (n = 576 mother/child dyads). Mother/child dyads attended fortnightly parenting sessions at the clinic in groups of four to five participants for 6 months (13 sessions). We collected data on supervisor and HW compliance in implementing the intervention, mothers' attendance and the observed quality of parenting sessions in all intervention clinics and HW burnout at endline in all clinics. We randomly selected 32 clinics (16 intervention, 16 control) and 384 mothers (192 intervention, 192 control) to participate in the evaluation on mother-reported home stimulation, measured at baseline and endline.
Results: Supervisors and HWs attended all training, 46/59 health workers (78%) conducted the majority of parenting sessions, (only two HWs [3.4%] refused) and mothers' attendance rate was 86%. However, supervision levels were low: only 32/57 (56.1%) of HWs received at least one supervisory visit. Intervention HWs delivered the parenting sessions with acceptable levels of quality on most items. The intervention significantly benefitted home stimulation (effect size = 0.53SD, 95% confidence interval: 0.50, 0.56, $p < 0.001$). HW burnout was low in both groups.
Conclusion: Integration into the primary health care service is a promising approach for scaling early childhood development programmes in Bangladesh, although further research is required to identify feasible methods for facilitator supervision.

PLoS One. 2023 Aug 18;18(8):e0290379.
doi: 10.1371/journal.pone.0290379. eCollection 2023.

Cognitive development among children in a low-income setting: Cost-effectiveness analysis of a maternal nutrition education intervention in rural Uganda

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Abstract
Inadequate nutrition and insufficient stimulation in early childhood can lead to long-term deficits in cognitive and social development. Evidence for policy and decision-making regarding the cost of delivering nutrition education is lacking in low and middle-income countries (LMIC). In rural Uganda, we conducted a cluster-randomized controlled trial (RCT) examining the effect of a maternal nutrition education intervention on developmental outcomes among children aged 6-8 months. This intervention led to significantly improved cognitive scores when the children reached the age of 20-24 months. When considering the potential for this intervention's future implementation, the desired effects should be weighed against the increased costs. This study therefore aimed to assess the cost-effectiveness of this education intervention compared with current practice. Health outcome data were based on the RCT. Cost data were initially identified by reviewing publications from the RCT, while more detailed information was obtained by interviewing researchers involved in processing the intervention. This study considered a healthcare provider

perspective for an 18-months' time horizon. The control group was considered as the current practice for the future large-scale implementation of this intervention. A cost-effectiveness analysis was performed, including calculations of incremental cost-effectiveness ratios (ICERs). In addition, uncertainty in the results was characterized using one-way and probabilistic sensitivity analyses. The ICER for the education intervention compared with current practice was USD ($) 16.50 per cognitive composite score gained, with an incremental cost of $265.79 and an incremental cognitive composite score of 16.11. The sensitivity analyses indicated the robustness of these results. The ICER was sensitive to changes in cognitive composite score and the cost of personnel. The education intervention can be considered cost-effective compared with the current practice. The outcome of this study, including the cost analysis, health outcome, cost-effectiveness, and sensitivity analysis, can be useful to inform policymakers and stakeholders about effective resource allocation processes in Uganda and possibly other LMIC.

J Mother Child. 2023 Jul 6;27(1):64-71.
doi: 10.34763/jmotherandchild.20232701.d-22-00025. eCollection 2023 Jun 1.

Impact of Early Exposure to Play Materials on Motor Development in High-Risk Infants: A Randomised Controlled Trial

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Abstract

Background: The purpose of this study was to determine the impact of early exposure to play materials on motor development in high-risk infants.

Materials and methods: A 1:1 parallel group randomised control study was conducted. A total of 36 participants were recruited, with 18 in each group. The intervention lasted 6 weeks for both groups, with follow-ups in the 2nd and 4th weeks. The Peabody Developmental Motor Scale 2nd Edition (PDMS-2) was used as an outcome measure. The data was analysed using the Likelihood Ratio test, Chi-square test, independent sample t-test, and paired t-test.

Results: There was no difference between the groups except for the raw reflex scores ($t = 3.29$, $p = 0.002$), raw stationary scores ($t = 4.26$, $p < 0.001$), standard stationary scores ($t = 2.57$, $p = 0.015$), and Gross Motor Quotient (GMQ) ($t = 3.275$, $p = 0.002$). Statistical significance within the experimental group was observed in the raw reflex ($t = -5.16$, $p < 0.001$), stationary ($t = -10.5$, $p < 0.001$), locomotion ($t = -5.67$, $p < 0.001$), grasp ($t = -4.68$, $p < 0.001$), and visual motor ($t = -5.03$, $p < 0.001$) scores, as well as the standard stationary ($t = -2.87$, $p = 0.010$), locomotion ($t = -3.43$, $p = 0.003$), grasp ($t = -3.28$, $p = 0.004$), and visual motor ($t = -5.03$, $p < 0.001$) scores. Quotients were the GMQ ($t = -7.31$, $p < 0.001$), Total Motor Quotient (TMQ) ($t = -5.71$, $p < 0.001$), Fine Motor Quotient (FMQ) ($t = -6.48$, $p < 0.001$). Conclusions: The current study concludes that a six-week treatment of early exposure to age-appropriate toys is advantageous in enhancing motor development in high-risk neonates.

Pediatrics. 2023 Oct 1;152(4):e2023061383.
doi: 10.1542/peds.2023-061383.

Effects of a Parenting and Nutrition Intervention on Siblings: A Cluster-RCT

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Abstract
Objectives: The majority of the evidence about the effectiveness of early parenting and nutrition interventions pertains to 1 targeted index child in a given household. We evaluated whether nontargeted sibling children benefited from a bundled parenting and nutrition intervention.
Methods: We designed a sub-study within a broader cluster-randomized trial that evaluated the effects of engaging both mothers and fathers and bundling parenting and nutrition interventions in Mara, Tanzania. Trained community health workers delivered interventions to parents through peer groups and home visits. Interventions encompassed various content including responsive parenting, infant and young child feeding, and positive couples' relationships. The main trial enrolled mothers and fathers and 1-index children <18 months of age in 80 clusters. Between June and July 2021, in 32 clusters (16 intervention, 16 control), we reenrolled 222 households (118 intervention, 104 control) from the main trial that had another child <6 years of age (ie, sibling to the index child). We compared caregiving practices and child development and nutrition outcomes among siblings in intervention versus control households.
Results: Compared with control siblings, intervention siblings had improved expressive language development (β = 0.33 [95% confidence interval: 0.03 to 0.62]) and dietary intake (β = 0.52 [0.10 to 0.93]) and reduced internalizing behaviors (β = -0.56 [-1.07 to -0.06]). Intervention caregivers reported greater maternal stimulation (β = 0.31 [0.00 to 0.61]) and paternal stimulation (β = 0.33 [0.02 to 0.65]) and displayed more responsive caregiving behaviors (β = 0.40 [0.09 to 0.72]) with sibling children.
Conclusions: A father-inclusive, bundled parenting and nutrition intervention can achieve positive spillover effects on sibling children's developmental and nutritional outcomes.

Early Hum Dev. 2023 Aug;183:105795.
doi: 10.1016/j.earlhumdev.2023.105795. Epub 2023 May 30.

Effects of acute moderate-intensity exercise on executive function in children with preterm birth: A randomized crossover study

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Abstract
Background: Acute exercise appears to promote executive function (EF) in children. However, the effect of acute exercise on EF in children with preterm birth (PB) remains unclear.
Objective: To investigate whether acute moderate-intensity exercise improves EF in children with PB.
Methods: Twenty child participants with PB (age = 10.95 ± 1.19 years, birth age = 31.71 ± 3.64 weeks) completed exercise and control sessions in a randomized crossover design. In the exercise session, participants completed a 30-minute period of moderate-intensity aerobic exercise. In the control session, participants watched a video for appropriately 30 min. Following each session immediately, inhibitory control, an aspect of EF, was assessed with the Numerical Stroop task.
Results: Response time (RT) for the Stroop's incongruent condition was shorter after the exercise session than after the control session. However, no differences were observed in RT

for the congruent condition. Accuracy rate (ACC) in both congruent and incongruent conditions did not differ between exercise and control session.
Conclusion: The findings support the beneficial effect of acute exercise on executive function (EF) in children with PB, particularly in terms of improving inhibitory control.

Lancet Glob Health. 2023 Aug;11(8):e1269-e1276.
doi: 10.1016/S2214-109X(23)00271-1.

Promoting early childhood development in Viet Nam: cost-effectiveness analysis alongside a cluster-randomised trial

Yeji Baek[1], Zanfina Ademi[2], Thach Tran[1], Alice Owen[1], Trang Nguyen[3], Stanley Luchters[4], David B Hipgrave[5], Sarah Hanieh[6], Tuan Tran[3], Ha Tran[3], Beverley-Ann Biggs[6], Jane Fisher[7]

Abstract

Background: Economic evaluations are critical to ensure effective resource use to implement and scale up child development interventions. This study aimed to estimate the cost-effectiveness of a multicomponent early childhood development intervention in rural Viet Nam.
Methods: We did a cost-effectiveness study alongside a cluster-randomised trial with a 30-month time horizon. The study included 669 mothers from 42 communes in the intervention group, and 576 mothers from 42 communes in the control group. Mothers in the intervention group attended Learning Clubs sessions from mid-pregnancy to 12 months after delivery. The primary outcomes were child cognitive, language, motor, and social-emotional development at age 2 years. In this analysis, we estimated the incremental cost-effectiveness ratios (ICERs) of the intervention compared with the usual standard of care from the service provider and household perspectives. We used non-parametric bootstrapping to examine uncertainty, and applied a 3% discount rate.
Findings: The total intervention cost was US$169 898 (start-up cost $133 692 and recurrent cost $36 206). The recurrent cost per child was $58 (1 341 741 Vietnamese dong). Considering the recurrent cost alone, the base-case ICER was $14 and mean ICER of 1000 bootstrap samples was $14 (95% CI -0·48 to 30) per cognitive development score gained with a 3% discount rate to costs. The ICER per language and motor development score gained was $22 and $20, respectively, with a 3% discount rate to costs.
Interpretation: The intervention was cost-effective: the ICER per child cognitive development score gained was 0·5% of Viet Nam's gross domestic product per capita, alongside other benefits in language and motor development. This finding supports the scaling up of this intervention in similar socioeconomic settings.

Indian Pediatr. 2023 Oct 15;60(10):811-815.
Epub 2023 Jun 21.

Impact of a Brief Healthcare-based Intervention to Support Early Childhood Development in India: A Pilot Randomized Controlled Trial

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Abstract

Objectives: To study the impact of a brief early childhood develop-ment (ECD) intervention, Sit Down and Play (SDP), integrated within routine healthcare visits on parent and child outcomes.
Methods: Between April, 2018 and March, 2019, caregivers and their infants aged 5-6 months attending a well-baby clinic were enrolled and randomized to intervention (n=26) or control (n=26) groups. Intervention families received SDP at recruitment and two subsequent immunization visits (8 months and 10 months). Control families received usual care. ECD outcomes were assessed through in-person assessments at the age of 12 months using the Stim Q subscales to assess parenting behaviors, and the Developmental Assessment Scale for Indian Infants (DASII) for neurodevelopment.
Results: There was a significant improvement in parent-child stimulation activities and verbal interactions in the intervention group compared with the control group [6.1(1.4) vs 4.9 (1.3); P=0.002]. Infants in the intervention group had significantly higher DASII scores in multivariable analyses [108.0 (103.0-111.3) vs 102.0 (96.8-108.0); P=0.04].
Conclusion: Our findings suggest a brief healthcare intervention supports opportunities for early learning among caregivers and neurodevelopmental outcomes in their infants.

Child Care Health Dev. 2023 Oct 26.
doi: 10.1111/cch.13189. Online ahead of print.

A cluster randomised controlled trial of an early childhood parenting programme delivered through early childhood education centres in rural Zimbabwe

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Abstract
Background: Early childhood is a critical period for child development. Effective approaches to support families in low-resource settings in the use of responsive and stimulating parenting are needed.
Aim: The aim of this study was to examine the effects of the Reach Up early childhood parenting programme on children's development, parenting attitudes and practices, when delivered through early childhood development (ECD) centres in Zimbabwe.
Methods: A cluster randomised controlled trial was conducted in Sanyati, a rural district in Zimbabwe. Twenty-four of 51 available centres were randomised to intervention (n = 12) or control (n = 12) groups. Sixteen mothers with a child aged 12-30 months were recruited from each centre's catchment area (n = 189 intervention; n = 193 control). The intervention comprised two home visits per month delivered by centre teaching assistants over a period of 27 months. Primary outcomes were child Developmental Quotient (DQ), Language, Eye and Hand coordination, Performance and Practical Reasoning subscale scores assessed at follow-up. Secondary outcomes were mothers' attitudes about child development, parenting practices and maternal depressive symptoms all measured at baseline and follow-up. Intention to treat analyses was conducted using mixed-effects regression models with the standard error adjusted for cluster and inverse proportionality weights to adjust for attrition. Significance was set at $P < 0.05$.
Results: A total of 285 (74.6%) of 382 children enrolled were tested, with 97 children lost to follow-up. The intervention improved the children's DQ by 3.55 points (95% CI 0.82 to 6.28), Eye and Hand by 3.58 (95% CI 0.59 to 6.56) and Practical Reasoning by 4.19 (95% CI 0.96 to

7.42). No significant improvements to Performance or Language scores, parenting attitudes, parenting practices and depressive symptoms were identified.
Conclusions: A home visiting intervention delivered by ECD teaching assistants promoted children's development. This suggests that outreach from preschools may be an effective platform for delivery of parenting interventions.

JAMA. 2024 Jan 2;331(1):28-37.
doi: 10.1001/jama.2023.23727.

Child Neurodevelopment After Multidomain Interventions From Preconception Through Early Childhood: The WINGS Randomized Clinical Trial

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Abstract

Importance: Multidomain interventions in pregnancy and early childhood have improved child neurodevelopment, but little is known about the effects of additional preconception interventions.
Objective: To evaluate the effect of a multifaceted approach including health; nutrition; water, sanitation, and hygiene (WASH); and psychosocial support interventions delivered during the preconception period and/or during pregnancy and early childhood on child neurodevelopment.
Design, setting, and participants: In this randomized trial involving low- and middle-income neighborhoods in Delhi, India, 13 500 participants were assigned to preconception interventions or routine care for the primary outcome of preterm births and childhood growth. Participants who became pregnant were randomized to pregnancy and early childhood interventions or routine care. Neurodevelopmental assessments, the trial's secondary outcome reported herein, were conducted in a subsample of children at age 24 months, including 509 with preconception, pregnancy, and early childhood interventions; 473 with preconception interventions alone; 380 with pregnancy and early childhood interventions alone; and 350 with routine care. This study was conducted from November 1, 2000, through February 25, 2022.
Interventions: Health, nutrition, psychosocial care and support, and WASH interventions delivered during preconception, pregnancy, and early childhood periods.
Main outcomes and measures: Cognitive, motor, language, and socioemotional performance at age 24 months, assessed using the Bayley Scales of Infant and Toddler Development 3 tool.
Results: The mean age of participants at enrollment was 23.8 years (SD, 3.0 years). Compared with the controls at age 24 months, children in the preconception intervention groups had higher cognitive scores (mean difference [MD], 1.16; 98.3% CI, 0.18-2.13) but had similar language, motor, and socioemotional scores as controls. Those receiving pregnancy and early childhood interventions had higher cognitive (MD, 1.48; 98.3% CI, 0.49-2.46), language (MD, 2.29; 98.3% CI, 1.07-3.50), motor (MD, 1.53; 98.3% CI, 0.65-2.42), and socioemotional scores (MD, 4.15; 98.3% CI, 2.18-6.13) than did controls. The pregnancy and early childhood group also had lower incidence rate ratios (RRs) of moderate to severe delay in cognitive (incidence RR, 0.62; 98.3% CI, 0.40-0.96), language (incidence RR, 0.73; 98.3% CI,

0.57-0.93), and socioemotional (incidence RR, 0.49; 98.3% CI, 0.24-0.97) development than did those in the control group. Children in the preconception, pregnancy, and early childhood intervention group had higher cognitive (MD, 2.60; 98.3% CI, 1.08-4.12), language (MD, 3.46; 98.3% CI, 1.65-5.27), motor (MD, 2.31; 98.3% CI, 0.93-3.69), and socioemotional (MD, 5.55; 98.3% CI, 2.66-8.43) scores than did those in the control group.
Conclusions and relevance: Multidomain interventions during preconception, pregnancy and early childhood led to modest improvements in child neurodevelopment at 24 months. Such interventions for enhancing children's development warrant further evaluation.

Child protection and family violence

EClinicalMedicine. 2023 Sep 26:64:102233.
doi: 10.1016/j.eclinm.2023.102233. eCollection 2023 Oct.

Long-term impacts of the Bandebereho programme on violence against women and children, maternal health-seeking, and couple relations in Rwanda: a six-year follow-up of a randomised controlled trial

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Abstract
Background: Programmes that work with parents to build couple relationship and parenting skills and include critical reflection on gender norms are a promising approach for reducing violence against women and children. However, there is limited evidence of their longer-term impact. In Rwanda, the Bandebereho programme engaged expectant and current parents of children under five years. At 21-months, Bandebereho demonstrated positive impacts on intimate partner violence (IPV), child physical punishment, maternal health-seeking, and couple relations. This study seeks to explore whether those outcomes are sustained six years later.
Methods: A six-year follow-up to a two-arm, multi-site randomised controlled trial was conducted in four districts of Rwanda between May and September 2021. At baseline, couples were randomly assigned to either the 15-session intervention (n = 575) or a control group (n = 624). At this follow-up, 1003 men and 1021 women were included in intention to treat analysis. Generalised estimating equations with robust standard errors were used to fit the models. This study was registered with Clinicaltrials.gov (NCT04861870).
Findings: Bandebereho has lasting effects on IPV and physical punishment of children, alongside multiple health and relationship outcomes. Compared to the control group: intervention women report less past-year physical (OR = 0.45, 95% CI 0.34-0.60 p < 0.001), sexual (OR = 0.50, 95% CI 0.37-0.67, p < 0.001), economic (OR = 0.47 95% CI 0.34-0.64, p < 0.001), and moderate or severe emotional (OR = 0.40 95% CI 0.29-0.56, p < 0.001) IPV. Intervention couples report less child physical punishment (OR = 0.72, p = 0.009 for men; OR = 0.68, p = 0.017 for women), fewer depressive symptoms (OR = 0.52, p < 0.001 for men; OR = 0.50, p < 0.001 for women), less harmful alcohol use, and improved maternal health-seeking, father engagement, and division of household labour and decision-making.

Interpretation: Our study expands the evidence, demonstrating that programmes engaging men and women to promote collaborative and non-violent couple relations can result in sustained reductions in family violence six years later.

Trauma Violence Abuse. 2023 Nov 18:15248380231207965.
doi: 10.1177/15248380231207965. Online ahead of print.

Parenting Interventions That Promote Child Protection and Development for Preschool-Age Children with Developmental Disabilities: A Global Systematic Review and Meta-Analysis

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Abstract

Global guidelines emphasize the critical role of responsive caregiving in terms of reducing violence against children and promoting early childhood development. However, there is an absence of global evidence synthesis on the effects of early childhood parenting programs for children with developmental disabilities. This systematic review and meta-analysis aims to investigate the effectiveness of parenting interventions delivered for preschool-age children with developmental disabilities in reducing violence against children, altering violence-related factors, and promoting child development. We searched for randomized controlled trials with inactive control. Estimates were pooled using robust variance estimations. Meta-regressions were conducted to explore sources of heterogeneity. In all, 33 studies met the inclusion criteria. The results showed that parenting programs improved child behavior, parental mental health, parenting practices, parental self-efficacy, parent-child interaction, child language skills, and child social skills post-intervention. No studies provided data on the actual occurrence of violence against children. Effects might vary by diagnosis, delivery modality, and world region. The findings supported the delivery of parenting programs to alter factors associated with violence against children and promote child language and social skills for families of young children with developmental disabilities, especially attention deficit hyperactivity disorder, autism, intellectual disability, and language disorders. More research using rigorous methods, long-term follow-ups, and transparent reporting is needed, particularly within more low- and middle-income countries.

Complimentary medicine

J Asthma. 2024 Mar;61(3):249-259.
doi: 10.1080/02770903.2023.2267113. Epub 2024 Feb 8.

Efficacy of Bhramari pranayama and Om chanting on asthma control, quality of life, and airway inflammation in asthmatic children: an open-label randomized controlled trial

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Abstract

Objectives: To explore the efficacy of combination of *Bhramari pranayama* and *om* chanting as an adjunct to standard pharmacological treatment on asthma control, quality of life, pulmonary function, and airway inflammation in asthmatic children.
Methods: Children (*n* = 110; 8-15 years) with uncontrolled or partly controlled asthma were recruited from the Pediatric Chest Clinic of All India Institute of Medical Sciences, New Delhi. Eligible participants were randomized to either home-based online *Bhramari pranayama* and *om* chanting plus standard treatment (YI + ST) group, or standard treatment (ST) alone group. Primary outcome measures were 12-week change in level of asthma symptom control; asthma control questionnaire (ACQ) score, spirometry indices, impulse oscillometry parameters, and pediatric asthma quality of life questionnaire (PAQLQ) score. Secondary outcome was a change in fractional exhaled nitric oxide (FeNO) levels at 12 weeks. Beginning from the enrollment, every participant was evaluated at 0, 2, 6, and 12 weeks.
Results: After 12 weeks of intervention, higher proportion (68.2%) of children were found to have controlled asthma symptoms in the YI + ST group as compared to ST group (38.5%) according to per protocol analysis ($p = 0.03$). When compared to ST group, children in YI + ST group showed significantly lower ACQ score, higher PAQLQ score and reduced FeNO levels. No significant changes were observed for the lung function parameters.
Conclusion: Children practicing *Bhramari pranayama* and o*m chanting* for 12 weeks have better asthma symptom control, quality of life, and reduced airway inflammation than those taking standard pharmacotherapy alone.

BMC Complement Med Ther. 2024 Jan 2;24(1):5.
doi: 10.1186/s12906-023-04292-2.

Effects of acupressure on sleep quality and anxiety of patients with second- or third-degree burns: a randomized sham-controlled trial

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Abstract
Background: Although acupressure is proposed to boost sleep quality and alleviate anxiety in various disorders, no trials have yet documented these consequences in burn victims. Considering the high importance of managing sleep quality and anxiety among burn patients utilizing adjunctive non-pharmacological measures, this study sought to investigate the impacts of acupressure on sleep quality and anxiety among a population of Iranian patients with burn injuries.
Methods: This trial was performed on 72 patients with second- or third-degree burns, who were divided into two equal arms to receive routine care plus 10-minute acupressure on either real acupoints (i.e., Yintang and Shen men) or sham points for three consecutive nights. Sleep quality and anxiety were investigated at baseline (T1) and on the fourth day (T2) by using St. Mary's Hospital Sleep Questionnaire (SMHSQ) and Spielberger's State-Trait Anxiety Inventory for State Anxiety (STAI-S), respectively.
Results: The mean scores of SMHSQ and STAI-S were significantly lower in the real acupressure arm at T2 ($P < 0.001$ in two cases), implying better sleep quality improvement and higher anxiety alleviation. Also, the reduction in mean changes of SMHSQ and STAI-S scores from T1 to T2 was significantly more in the real acupressure arm ($P < 0.001$ in two cases).

Conclusion: Acupressure, as a low-cost complementary method, could be potentially helpful in enhancing sleep quality and decreasing the anxiety of burn patients. Additional long-term trials are required to identify the sustainability of the findings.

J Ethnopharmacol. 2024 Jan 10;318(Pt A):116862.
doi: 10.1016/j.jep.2023.116862. Epub 2023 Jul 10.

The hydroalcoholic extract of Nasturtium officinale reduces oxidative stress markers and increases total antioxidant capacity in patients with asthma

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Abstract

Ethnopharmacological relevance: Asthma is a common chronic disease characterized by inflammation of the airways. One of the most devastating consequences of this inflammatory process is the production of reactive oxygen species responsible for oxidative stress. Nasturtium officinale commonly known as watercress has traditionally been applied in Iranian folk medicine to treat respiratory disorders and diseases mainly bronchitis and asthma. In accordance with these ethnopharmacological reports, through our previous in vivo experiment, we have confirmed significant effect of its hydroalcoholic extract in reducing lung inflammation and oxidative stress in an ovalbumin-induced asthmatic rat model.

Aim of the study: The aim of the present study was to investigate the anti-inflammatory and antioxidant effects of N. officinale hydroalcoholic extract (NOE) in patients with asthma, in order to confirm our findings of the previous performed in vivo study.

Material and methods: The NOE capsules (500 mg) were treated twice daily for 4 weeks as a supplementary treatment in a randomized, double-blind, and placebo-controlled trial in asthmatics. The primary outcome was Asthma Control Test score. The blood samples were taken at the beginning and end of the study. Then, the level of inflammatory markers, oxidative stress markers and antioxidant enzyme activity were measured.

Results: Treatment with NOE for one month caused a reduction in the levels of MDA, PCO and NO metabolite markers compared to the placebo group. In addition, FRAP levels as an indicator of total antioxidant capacity in the intervention group was significantly increased at the end of the treatment period compared to pre-treatment values.

Conclusion: Findings demonstrated that NOE may have a therapeutic effect on asthma by improving oxidative stress. However, more studies are required to support these results. Moreover, bio-assay guided fractionation and isolation approach can be conducted to identify major bioactive compound/s.

J Complement Integr Med. 2024 Apr 23.
doi: 10.1515/jcim-2020-0246. Online ahead of print.

Galactagogue activity of poly-herbal decoction from Indonesia: a randomized open label controlled trial

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Abstract
Objectives: Indonesia have several herbs empirically used as galactagogue. However there are limited clinical evidence regarding the efficacy and safety of this herbs especially poly-herb. The aim of this study was to assess the efficacy and safety of polyherbal galactagogue (PHG) consist of katuk leaves, torbangun leaves and papaya leaves compared to commercial galactagogue capsules (CGC) that contain a single plant extract, katuk leaves.
Methods: This study was an open label randomized controlled trial with 120 subjects that randomly assigned into two groups, PHG and CGC. This study was conducted at the herbal medicine research house (Rumah Riset Jamu/RRJ) Hortus Medicus and 30 subsites in Central Java and Jogjakarta provinces from July to November 2018. Duration of intervention 28 days. Parameter of efficacy breast milk volume, baby weight, prolactin level and parameter of safety ALT, AST, Urea, Creatinin were performed at baseline, day 14 and 28. The symptom of side effects also recorded every week.
Results: Breast milk volume and infant's weight increased at day-14 and 28 in both groups. However, prolactin level in both groups decreased. There were no significant differences of efficacy parameters at baseline in both groups. At three times measurement of ALT, AST, Urea and Ceratinin average levels were within the normal range. About 3-5% mothers experience higher ALT, AST and nausea that can tolerated well. No side effect was found in infants.
Conclusions: PHG and CGC have the equal efficacy and safety as a galactagogue. The optimal used is for 14 days.

Dengue

(see Vaccines - dengue)

Cochrane Database Syst Rev. 2024 Apr 10;4(4):CD015636.
doi: 10.1002/14651858.CD015636.pub2.

Wolbachia-carrying Aedes mosquitoes for preventing dengue infection

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Abstract
Background: Dengue is a global health problem of high significance, with 3.9 billion people at risk of infection. The geographic expansion of dengue virus (DENV) infection has resulted in increased frequency and severity of the disease, and the number of deaths has increased in recent years. Wolbachia, an intracellular bacterial endosymbiont, has been under investigation for several years as a novel dengue-control strategy. Some dengue vectors (Aedes mosquitoes) can be transinfected with specific strains of Wolbachia, which decreases their fitness (ability to survive and mate) and their ability to reproduce, inhibiting the replication of dengue. Both laboratory and field studies have demonstrated the potential effect of Wolbachia deployments on reducing dengue transmission, and modelling studies have suggested that this may be a self-sustaining strategy for dengue prevention, although long-term effects are yet to be elucidated.

Objectives: To assess the efficacy of Wolbachia-carrying Aedes speciesdeployments (specifically wMel-, wMelPop-, and wAlbB- strains of Wolbachia) for preventing dengue virus infection.
Search methods: We searched CENTRAL, MEDLINE, Embase, four other databases, and two trial registries up to 24 January 2024.
Selection criteria: Randomized controlled trials (RCTs), including cluster-randomized controlled trials (cRCTs), conducted in dengue endemic or epidemic-prone settings were eligible. We sought studies that investigated the impact of Wolbachia-carrying Aedes deployments on epidemiological or entomological dengue-related outcomes, utilizing either the population replacement or population suppression strategy.
Data collection and analysis: Two review authors independently selected eligible studies, extracted data, and assessed the risk of bias using the Cochrane RoB 2 tool. We used odds ratios (OR) with the corresponding 95% confidence intervals (CI) as the effect measure for dichotomous outcomes. For count/rate outcomes, we planned to use the rate ratio with 95% CI as the effect measure. We used adjusted measures of effect for cRCTs. We assessed the certainty of evidence using GRADE.
Main results: One completed cRCT met our inclusion criteria, and we identified two further ongoing cRCTs. The included trial was conducted in an urban setting in Yogyakarta, Indonesia. It utilized a nested test-negative study design, whereby all participants aged three to 45 years who presented at healthcare centres with a fever were enrolled in the study provided they had resided in the study area for the previous 10 nights. The trial showed that wMel-Wolbachia infected Ae aegypti deployments probably reduce the odds of contracting virologically confirmed dengue by 77% (OR 0.23, 95% CI 0.15 to 0.35; 1 trial, 6306 participants; moderate-certainty evidence). The cluster-level prevalence of wMel Wolbachia-carrying mosquitoes remained high over two years in the intervention arm of the trial, reported as 95.8% (interquartile range 91.5 to 97.8) across 27 months in clusters receiving wMel-Wolbachia Ae aegypti deployments, but there were no reliable comparative data for this outcome. Other primary outcomes were the incidence of virologically confirmed dengue, the prevalence of dengue ribonucleic acid in the mosquito population, and mosquito density, but there were no data for these outcomes. Additionally, there were no data on adverse events.
Authors' conclusions: The included trial demonstrates the potential significant impact of wMel-Wolbachia-carrying Ae aegypti mosquitoes on preventing dengue infection in an endemic setting, and supports evidence reported in non-randomized and uncontrolled studies. Further trials across a greater diversity of settings are required to confirm whether these findings apply to other locations and country settings, and greater reporting of acceptability and cost are important.

Diarrhoea

(See also: Vaccines and immunization - Rotavirus vaccine, Hygiene and Environmental health, Malnutrition, Dengue, Nutrition - Environmental enteric dysfunction)

Treatment of diarrhoea

Acta Paediatr. 2023 Aug;112(8):1755-1763.

doi: 10.1111/apa.16810. Epub 2023 May 15.

Open-label, randomised controlled trial found that a green banana mixed rice suji diet was most effective for persistent diarrhoea in children in Bangladesh

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Abstract

Aim: Persistent diarrhoea continues for at least 14 days and kills more children than acute diarrhoea. We assessed whether rice suji, green banana mixed rice suji or 75% rice suji improved persistent diarrhoea in young children.

Methods: This open-labelled randomised controlled trial was carried out between December 2017 and August 2019 at the Dhaka Hospital of icddr,b, Bangladesh, with 135 children aged 6-35 months with persistent diarrhoea. The children were randomly assigned to green banana mixed rice suji, rice suji or 75% rice suji, with 45 in each group. The primary outcome was the percentage who recovered from diarrhoea by day 5 using an intention-to-treat analysis.

Results: The children's median age was 8 months (interquartile range: 7-10 months). By day 5, the recovery rate was 58%, 31% and 58% for children in the green banana mixed rice suji, rice suji and 75% rice suji groups, respectively. The green banana mixed rice suji group had fewer relapses (7%) than the 75% rice suji group (24%). Enteroaggregative Escherichia coli, rotavirus, norovirus, Enteropathogenic Escherichia coli, astrovirus and Campylobacter were the major pathogens for persistent diarrhoea.

Conclusion: Green banana mixed rice suji was the most effective option for managing persistent diarrhoea in young children.

Sci Rep. 2024 Mar 18;14(1):6422.
doi: 10.1038/s41598-024-56627-9.

Promising clinical and immunological efficacy of Bacillus clausii spore probiotics for supportive treatment of persistent diarrhea in children

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Abstract

Persistent diarrhea is a severe gastroenteric disease with relatively high risk of pediatric mortality in developing countries. We conducted a randomized, double-blind, controlled clinical trial to evaluate the efficacy of liquid-form Bacillus clausii spore probiotics (LiveSpo CLAUSY; 2 billion CFU/5 mL ampoule) at high dosages of 4-6 ampoules a day in supporting treatment of children with persistent diarrhea. Our findings showed that B. clausii spores significantly improved treatment outcomes, resulting in a 2-day shorter recovery period ($p < 0.05$) and a 1.5-1.6 folds greater efficacy in reducing diarrhea symptoms, such as high frequency of bowel movement of ≥ 3 stools a day, presence of fecal mucus, and diapered infant stool scale types 4-5B. LiveSpo CLAUSY supportive treatment achieved 3 days ($p < 0.0001$) faster recovery from diarrhea disease, with 1.6-fold improved treatment efficacy. At day 5 of treatment, a significant decrease in blood levels of pro-inflammatory cytokines TNF-α, IL-17, and IL-23 by 3.24% ($p = 0.0409$), 29.76% ($p = 0.0001$), and 10.87% ($p = 0.0036$), respectively, was observed in the Clausy group. Simultaneously, there was a significant 37.97% decrease ($p = 0.0326$) in the excreted IgA in stool at day 5 in the Clausy group. Overall,

the clinical study demonstrates the efficacy of B. clausii spores (LiveSpo CLAUSY) as an effective symptomatic treatment and immunomodulatory agent for persistent diarrhea in children.

J Infect Dis. 2024 Apr 12;229(4):988-998.
doi: 10.1093/infdis/jiad252.

Azithromycin for Bacterial Watery Diarrhea: A Reanalysis of the AntiBiotics for Children With Severe Diarrhea (ABCD) Trial Incorporating Molecular Diagnostics

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Abstract

Background: Bacterial pathogens cause substantial diarrhea morbidity and mortality among children living in endemic settings, yet antimicrobial treatment is only recommended for dysentery or suspected cholera.

Methods: AntiBiotics for Children with severe Diarrhea was a 7-country, placebo-controlled, double-blind efficacy trial of azithromycin in children 2-23 months of age with watery diarrhea accompanied by dehydration or malnutrition. We tested fecal samples for enteric pathogens utilizing quantitative polymerase chain reaction to identify likely and possible bacterial etiologies and employed pathogen-specific cutoffs based on genomic target quantity in previous case-control diarrhea etiology studies to identify likely and possible bacterial etiologies.

Results: Among 6692 children, the leading likely etiologies were rotavirus (21.1%), enterotoxigenic Escherichia coli encoding heat-stable toxin (13.3%), Shigella (12.6%), and Cryptosporidium (9.6%). More than one-quarter (1894 [28.3%]) had a likely and 1153 (17.3%) a possible bacterial etiology. Day 3 diarrhea was less common in those randomized to azithromycin versus placebo among children with a likely bacterial etiology (risk difference [RD]likely, -11.6 [95% confidence interval {CI}, -15.6 to -7.6]) and possible bacterial etiology (RDpossible, -8.7 [95% CI, -13.0 to -4.4]) but not in other children (RDunlikely, -0.3% [95% CI, -2.9% to 2.3%]). A similar association was observed for 90-day hospitalization or death (RDlikely, -3.1 [95% CI, -5.3 to -1.0]; RDpossible, -2.3 [95% CI, -4.5 to -.01]; RDunlikely, -0.6 [95% CI, -1.9 to .6]). The magnitude of risk differences was similar among specific likely bacterial etiologies, including Shigella.

Conclusions: Acute watery diarrhea confirmed or presumed to be of bacterial etiology may benefit from azithromycin treatment.

Diarrhoea prevention

(also see Hygiene and Environmental health; Water, Sanitation and Hygiene)

Open Forum Infect Dis. 2023 Nov 21;10(11):ofad535.
doi: 10.1093/ofid/ofad535. eCollection 2023 Nov.

Better Existing Water, Sanitation, and Hygiene Can Reduce the Risk of Cholera in an Endemic Setting: Results From a Prospective Cohort Study From Kolkata, India

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Abstract

Background: Global cholera control efforts rely heavily on effective water, sanitation, and hygiene (WASH) interventions in cholera-endemic settings.

Methods: Using data from a large, randomized controlled trial of oral cholera vaccine conducted in Kolkata, India, we evaluated whether natural variations in WASH in an urban slum setting were predictive of cholera risk. From the control population (n = 55 086), baseline WASH data from a randomly selected "training subpopulation" (n = 27 634) were analyzed with recursive partitioning to develop a dichotomous ("better" vs "not better") composite household WASH variable from several WASH features collected at baseline, and this composite variable was then evaluated in a mutually exclusive "validation population" (n = 27 452). We then evaluated whether residents of better WASH households in the entire population (n = 55 086) experienced lower cholera risk using Cox regression models. Better WASH was defined by a combination of 4 dichotomized WASH characteristics including safe source of water for daily use, safe source of drinking water, private or shared flush toilet use, and always handwashing with soap after defecation.

Results: Residence in better WASH households was associated with a 30% reduction in risk of cholera over a 5-year period (adjusted hazard ratio, 0.70 [95% confidence interval, .49-.99]; *P* = .048). We also found that the impact of better WASH households on reducing cholera risk was greatest in young children (0-4 years) and this effect progressively declined with age.

Conclusions: The evidence suggests that modest improvements in WASH facilities and behaviors significantly modify cholera risk and may be an important component of cholera prevention and elimination strategies in endemic settings.

PLoS Negl Trop Dis. 2024 May 13;18(5):e0012157.
doi: 10.1371/journal.pntd.0012157. Online ahead of print.

Influence of hydrometeorological risk factors on child diarrhea and enteropathogens in rural Bangladesh

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Abstract
Background: A number of studies have detected relationships between weather and diarrhea. Few have investigated associations with specific enteric pathogens. Understanding pathogen-specific relationships with weather is crucial to inform public health in low-resource settings that are especially vulnerable to climate change.
Objectives: Our objectives were to identify weather and environmental risk factors associated with diarrhea and enteropathogen prevalence in young children in rural Bangladesh, a population with high diarrheal disease burden and vulnerability to weather shifts under climate change.
Methods: We matched temperature, precipitation, surface water, and humidity data to observational longitudinal data from a cluster-randomized trial that measured diarrhea and enteropathogen prevalence in children 6 months-5.5 years from 2012-2016. We fit generalized additive mixed models with cubic regression splines and restricted maximum likelihood estimation for smoothing parameters.
Results: Comparing weeks with 30°C versus 15°C average temperature, prevalence was 3.5% higher for diarrhea, 7.3% higher for Shiga toxin-producing Escherichia coli (STEC), 17.3% higher for enterotoxigenic E. coli (ETEC), and 8.0% higher for Cryptosporidium. Above-median weekly precipitation (median: 13mm; range: 0-396mm) was associated with 29% higher diarrhea (adjusted prevalence ratio 1.29, 95% CI 1.07, 1.55); higher Cryptosporidium, ETEC, STEC, Shigella, Campylobacter, Aeromonas, and adenovirus 40/41; and lower Giardia, sapovirus, and norovirus prevalence. Other associations were weak or null.
Discussion: Higher temperatures and precipitation were associated with higher prevalence of diarrhea and multiple enteropathogens; higher precipitation was associated with lower prevalence of some enteric viruses. Our findings emphasize the heterogeneity of the relationships between hydrometeorological variables and specific enteropathogens, which can be masked when looking at composite measures like all-cause diarrhea. Our results suggest that preventive interventions targeted to reduce enteropathogens just before and during the rainy season may more effectively reduce child diarrhea and enteric pathogen carriage in rural Bangladesh and in settings with similar meteorological characteristics, infrastructure, and enteropathogen transmission.

Ear disease and hearing loss

Sensors (Basel). 2023 Jul 22;23(14):6601.
doi: 10.3390/s23146601.

Use of Virtual Reality-Based Games to Improve Balance and Gait of Children and Adolescents with Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis

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Abstract
Background: Children and adolescents with sensorineural hearing loss (SNHL) often experience motor skill disturbances, particularly in balance and gait, due to potential vestibular dysfunctions resulting from inner ear damage. Consequently, several studies have

proposed the use of virtual reality-based games as a technological resource for therapeutic purposes, aiming to improve the balance and gait of this population.
Objective: The objective of this systematic review is to evaluate the quality of evidence derived from randomized or quasi-randomized controlled trials that employed virtual reality-based games to enhance the balance and/or gait of children and adolescents with SNHL.
Methods: A comprehensive search was conducted across nine databases, encompassing articles published in any language until 1 July 2023. The following inclusion criteria were applied: randomized or quasi-randomized controlled trials involving volunteers from both groups with a clinical diagnosis of bilateral SNHL, aged 6-19 years, devoid of physical, cognitive, or neurological deficits other than vestibular dysfunction, and utilizing virtual reality-based games as an intervention to improve balance and/or gait outcomes.
Results: Initially, a total of 5984 articles were identified through the searches. Following the removal of duplicates and screening of titles and abstracts, eight studies remained for full reading, out of which three trials met the eligibility criteria for this systematic review. The included trials exhibited a very low quality of evidence concerning the balance outcome, and none of the trials evaluated gait. The meta-analysis did not reveal significant differences in balance improvement between the use of traditional balance exercises and virtual reality-based games for adolescents with SNHL (effect size: -0.48; [CI: -1.54 to 0.57]; $p = 0.37$; $I^2 = 0\%$).
Conclusion: Virtual reality-based games show promise as a potential technology to be included among the therapeutic options for rehabilitating the balance of children and adolescents with SNHL. However, given the methodological limitations of the trials and the overall low quality of evidence currently available on this topic, caution should be exercised when interpreting the results of the trials analyzed in this systematic review.

Ebola and viral haemorrhagic fever

Endocrine disorders and bone health

Diabetes

BMJ Open. 2024 May 6;14(5):e075554.
doi: 10.1136/bmjopen-2023-075554.

Feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi: a randomised controlled trial

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Abstract

Objectives: To assess the feasibility and change in clinical outcomes associated with continuous glucose monitoring (CGM) use among a rural population in Malawi living with type 1 diabetes.
Design: A 2:1 open randomised controlled feasibility trial.
Setting: Two Partners In Health-supported Ministry of Health-run first-level district hospitals in Neno, Malawi.
Participants: 45 people living with type 1 diabetes (PLWT1D).
Interventions: Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received diabetes education.
Outcomes: Primary outcomes included fidelity, appropriateness and severe adverse events. Secondary outcomes included change in haemoglobin A1c (HbA1c), acceptability, time in range (CGM arm only) SD of HbA1c and quality of life.
Results: Participants tolerated CGM well but were unable to change their own sensors which resulted in increased clinic visits in the CGM arm. Despite the hot climate, skin rashes were uncommon but cut-out tape overpatches were needed to secure the sensors in place. Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change suggestions than those in the UC arm. Participants in the CGM arm wore their CGM on average 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the time. There were three hospitalisations all in the CGM arm, but none were related to the intervention.
Conclusions: This is the first randomised controlled trial conducted on CGM in a rural region of a low-income country. CGM was feasible and appropriate among PLWT1D and providers, but inability of participants to change their own sensors is a challenge.

Diabetes Res Clin Pract. 2024 Apr:210:111610.
doi: 10.1016/j.diabres.2024.111610. Epub 2024 Mar 12.

Impact of short-term application of continuous glucose monitoring system(CGMS) on long-term glycemic profile in adolescents and adults with type 1 diabetes mellitus: An open-label randomized control cross over study

Ashish Gupta [1], Soham Mukherjee [2], Sanjay Kumar Bhadada [1], Sant Ram [3], Rimesh Pal [1], Naresh Sachdeva [1], Pinaki Dutta [1]

Abstract
Aims: The use of Continuous Glucose Monitoring System (CGMS) improves glycemic parameters in Type 1 Diabetes Mellitus (T1D), but the cost is prohibitive. Here, we investigated the effect of short-term application of real-time and intermittently-scanned CGMS (rt and is-CGMS) in T1D individuals on change in HbA1c at the end of 3 months.
Methods: T1D individuals were randomized into three groups in a ratio of 1:1:2 - Group A (rt-CGMS for 2 weeks initially, followed by is-CGMS for 2 weeks at 3 months), Group B (is-CGMS for 2 weeks initially followed by rt-CGMS for 2 weeks at 3 months) and Group C (only self-monitoring of blood glucose), respectively. HbA1c at baseline, 3, and 6 months were compared.
Results: Out of a total 68 T1D patients, HbA1c decreased significantly in groups A and B at 6 months compared to the baseline, but not in group C. HbA1c was significantly lower in Group A compared to Group C at 3 and 6 months. Fructosamine levels significantly decreased in

Group B before and after cross-over. Glycemic variability indices improved significantly after cross-over from is-CGMS to rt-CGMS.
Conclusion: Intermittent application of CGMS for 2 weeks improves short- and long-term blood glucose control in T1D.

Indian J Pediatr. 2024 Apr 1.
doi: 10.1007/s12098-024-05074-5. Online ahead of print.

Supplementation of High-Strength Oral Probiotics Improves Immune Regulation and Preserves Beta Cells among Children with New-Onset Type 1 Diabetes Mellitus: A Randomised, Double-Blind Placebo Control Trial

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Abstract
Objectives: To investigate the mechanism of glycemic control in children with type 1 diabetes (T1D) following high-strength probiotics supplementation by assessing immune-regulatory markers.
Methods: In this single-centre randomised double-blinded placebo-controlled study, children with new-onset T1D on regular insulin therapy were randomised into probiotic or placebo groups with 30 children each. The probiotics group received oral powder of Vivomixx®, and the placebo group received corn starch for six months. The primary outcome parameters included induced T regulatory cells (i-Tregs) percentage, insulin autoantibodies (IAA), insulinoma associated 2 autoantibodies (IA2), glutamic acid decarboxylase autoantibodies (GAD 65) and plasma interleukin-10 (IL-10) levels. The secondary outcome variables were changes in plasma C-peptide levels and glycemic control parameters.
Results: Twenty-three children in the placebo group and 27 in the probiotic group completed the study. There was a significant increase in the percentage of iTregs (3.40 in the probiotic vs. 2.46 in the placebo group; p = 0.034). Median glycated hemoglobin (HbA1c) levels significantly decreased from 68 mmol/mol (8.35%) in the placebo group to 60 mmol/mol (7.55%) in the probiotic group (p = 0.017). Median C-peptide levels were significantly higher in probiotics (0.72 ng/ml) vs. placebo group (0.11 ng/ml) (p = 0.036). The plasma IL-10 levels significantly increased in the probiotic group after six months of treatment (p = 0.002).
Conclusions: The high-strength probiotics improved the immunoregulatory milieu, thereby preserving the beta-cell function and better glycemic control.

Indian J Pediatr. 2023 Oct 3.
doi: 10.1007/s12098-023-04850-z. Online ahead of print.

Carbohydrate Counting vs. Fixed Meal Plan in Indian Children with Type 1 Diabetes Mellitus: A Randomized Controlled Trial

Rajni Sharma [1], Babita Upadhyay [1], Nitika Lal [1], Rajesh Sagar [2], Vandana Jain [3]

Abstract
Objectives: To study the impact of carbohydrate counting vs. fixed-meal plan on glycemic control, quality of life (QoL) and diabetes-related emotional distress in children with Type 1 diabetes mellitus (T1DM).

Methods: Children aged 6-18 y with T1DM of duration >1 y were eligible for the study if they were on multiple daily injections of insulin and regularly monitoring blood glucose. Those with celiac disease, hypothyroidism, any underlying chronic renal/liver/systemic disease or HbA1c >13% were excluded. Both groups received education on diabetes management and healthy diet. In the intervention arm, parents were taught to quantify carbohydrate content and modify insulin doses according to insulin-carbohydrate ratio. The control arm had dietary prescription according to recommended dietary allowance and food exchange list. Standard validated questionnaires were used to assess the QoL and emotional distress related to diabetes.
Results: One hundred twenty five patients (61 intervention, 64 controls) were enrolled and 91.8% and 84.3%, respectively, completed 6-mo follow-up. There was a reduction in HbA1c in both the groups, but was not statistically significant within or between groups {Intervention: 8.9 (1.4) to 8.6 (1.5) vs. control: 9.1 (1.6) to 8.8 (1.9), [95% CI 8.3-9.3 vs. 8.3-9.0, intention to treat (ITT), p = 0.63]}. There was a significant reduction in diabetes distress in the intervention group; DAWN Problem Areas in Diabetes Questionnaire (PAID) score with a median (interquartile range) of 21 (11-33) vs. control: 27 (20-40), (p = 0.04).
Conclusions: Patients in the carbohydrate-counting group demonstrated lower diabetes distress scores and less emotional burnout compared to fixed-meal plan over a 6 mo period though overall glycemic control was comparable between groups.

J Clin Densitom. 2024 Jan 26;27(2):101468.
doi: 10.1016/j.jocd.2024.101468. Online ahead of print.

Effect of Calcium and Vitamin D Supplementation (Dairy vs. Pharmacological) on Bone Health of Underprivileged Indian Children and Youth with Type-1 Diabetes: A Randomized Controlled Trial

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Abstract

Background: Bone health is affected by chronic childhood disorders including type-1 diabetes mellitus (T1DM). We conducted this randomized controlled trial with the objective of investigating the effect of 1-year supplementation of vitamin-D with milk or with pharmacological calcium on bone mass accrual in underprivileged Indian children and youth with T1DM.
Methods: 5 to 23year old (n = 203) underprivileged children and youth with T1DM were allocated to one of three groups: Milk (group A-received 200 ml milk + 1000 international unit (IU) vitamin-D3/day), Calcium supplement (group B-received 500 mg of calcium carbonate + 1000 IU of vitamin-D3/day) or standard of care/control (group C). Anthropometry, clinical details, biochemistry, diet (3-day 24-h recall), physical activity (questionnaires adapted for Indian children) and bone health parameters (using dual-energy X-ray absorptiometry and peripheral quantitative computed tomography- DXA and pQCT respectively) were evaluated at enrolment and end of 12 month intervention.
Results: Total body less head(TBLH) bone mineral content (BMC(g)) and bone mineral density (BMD(gm/cm^2)) were significantly higher at end of study in girls in both supplemented groups (TBLHBMC-A-1011.8 ± 307.8, B-983.2 ± 352.9, C-792.8 ± 346.8. TBLHBMD-A-± 0.2, B-0.8 ± 0.2, C-0.6 ± 0.2, p < 0.05). Z score of lumbar spine bone mineral

apparent density of supplemented participants of both sexes was significantly higher than controls (Boys- A-0.7 ± 1.1, B-0.6 ± 1.4, C- -0.7 ± 1.1; Girls- A-1.1 ± 1.1, B-0.9 ± 3.4, C- -1.7 ± 1.3, $p < 0.05$). A significantly higher percentage increase was found in cortical thickness in girls in both supplemented groups (A-17.9 ± 28.6, B-15.3 ± 16.5, C-7.6 ± 26.2); the differences remained after adjusting for confounders.
Conclusion: Supplementation with milk or pharmacological calcium (+vitaminD3) improved bone outcomes-particularly geometry in children with T1DM with more pronounced effect in girls. Pharmacological calcium may be more cost effective in optimising bone health in T1DM in resource limited settings.

Front Clin Diabetes Healthc. 2024 Apr 19:5:1353279.
doi: 10.3389/fcdhc.2024.1353279. eCollection 2024.

Effect of metformin adjunct therapy on cardiometabolic parameters in Indian adolescents with type 1 diabetes: a randomized controlled trial

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Abstract
Introduction: Insulin resistance is being increasingly reported in type-1 Diabetes (T1D) and is known to accelerate microvascular complications. The Asian Indian population has a higher risk of double diabetes development compared to Caucasians. Hence, we studied the effect of adding Metformin to standard insulin therapy on glycemic control, insulin sensitivity (IS), cardiometabolic parameters and body composition in Indian adolescents with T1D.
Methods: A Randomized controlled trial was conducted spanning 9 months (Registration number:CTRI/2019/11/022126). Inclusion: Age 10-19 years, T1D duration>1year, HbA1c>8% Exclusion: Uncontrolled vascular complications/comorbidities, Metformin intolerance, concomitant drugs affecting insulin sensitivity. Participants were randomized to Metformin/Placebo (n=41 each) groups and age, sex, duration-matched. Assessments were performed at baseline, 3 and 9 months.
Results: 82 participants aged 14.7 ± 3years (40 females) were enrolled, with a mean diabetes duration of 5.2 ± 2.3 years. Over 9 months, HbA1c decreased significantly by 0.8 (95% confidence interval: -1.2 to -0.3) from 9.8 ± 1.8% to 9.1 ± 1.7% on Metformin but remained largely unchanged (difference of 0.2, 95% confidence interval: -0.7 to 0.2) i.e. 9.9 ± 1.6% and 9.7 ± 2.2% on placebo. HbA1c improvement correlated negatively with baseline IS (EGDR:r= -0.3;SEARCH:r = -0.24, $p<0.05$) implying better HbA1c-lowering in those with decreased initial IS. CGM-based glycemic variability (standard deviation) reduced by 6.3 mg/dL (95% confidence interval: -12.9 to 0.2) from 100.2 ± 19.1 mg/dL to 93.7 ± 19.9 mg/dL in those on Metformin (p=0.05) but not placebo (94.0 ± 20.5; 90.0 ± 22.6 mg/dL). Insulin sensitivity: CACTIexa & SEARCH scores demonstrated no change with Metformin but significant worsening on placebo. Significant increase in LDL-C(42%), total cholesterol(133.6 to 151.1 mg/dL), triglyceride (60.0 to 88.0 mg/dL) and carotid intima-media thickness was noted on placebo but not Metformin. Weight, BMI, fat Z-scores increased significantly on placebo but not Metformin. Adverse events (AE) were minor; AE, compliance and safety parameters were similar between the two groups.
Conclusion: Metformin as an adjunct to insulin in Asian Indian adolescents with T1D demonstrated beneficial effect on glycemic control, glycemic variability, IS, lipid profile,

vascular function, weight and body fat, with a good safety profile when administered for 9 months.

Ann Pediatr Endocrinol Metab. 2024 Jan 2.
doi: 10.6065/apem.2346162.081. Online ahead of print.

Safety and tolerability of sodium glucose cotransporter-2 inhibitors in children and young adults: A systematic review and meta-analysis

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Abstract

Purpose: Sodium glucose co-transporter-2 inhibitors (SGLT2i) have been evaluated in children with type-2 diabetes (T2DM), Type-1 diabetes (T1DM) and several other non-diabetic conditions. Potential tolerability issues have been preventing us from routinely using SGLT2i in children with diabetes. No meta-analysis till date has evaluated the safety and tolerability of SGLT2i in children. This systematic review and meta-analysis aimed to address this knowledge-gap.

Methods: Databases were searched for randomized controlled trials (RCTs), case-control and cohort studies involving children receiving SGLT2i in intervention-arm. Primary outcome was occurrence of treatment-emergent adverse events (TAEs). Secondary outcomes were evaluation of glycaemic efficacy and occurrence of severe adverse-events (SAEs), hypoglycaemia, ketosis, genital or urinary infections and any other adverse-events.

Results: From initially screened 27 articles, data from 4 RCT (258 children) was analyzed. In children with T2DM, occurrence of TAEs [OR 1.77(95%CI:0.93-3.36);P=0.08;I2=0%], SAEs [OR 0.45(95%CI:0.08-2.54);P=0.37;I2=0%], ketoacidosis [OR 0.33(95%CI:0.01-8.37);P=0.50], urinary tract infections [OR 2.34(95%CI:0.44-12.50);P=0.32;I2=0%] and severe hypoglycaemia [OR 4.47(95%CI:0.21-96.40);P=0.34] were comparable among SGLTi group and placebo. Compared to placebo, T2DM children receiving SGLTi had significantly lower HbA1C at 24-26 weeks [MD -0.79%(95%CI:-1.33--0.26);P=0.004;I2=0%]. In T1DM children, ß-hydroxybutyrate levels were significantly higher in SGLTi group compared to placebo [MD 0.11mmol/L(95%CI:0.05-0.17);P=0.0005;I2=53%]. In T1DM, there was not a single report of SAE, ketoacidosis, severe hypoglycaemia among both groups, with time in range considerably greater in SGLT2i group (68%±6% vs. 50%±13%;P<0.001).

Conclusion: This study provides us with reassuring data on safety of use of SGLT2i in children and young adults.

Thyroid disease

J Pediatr Endocrinol Metab. 2024 Jan 1.
doi: 10.1515/jpem-2023-0165. Online ahead of print.

Effect of daily zinc supplementation for 12 weeks on serum thyroid auto-antibody levels in children and adolescents with autoimmune thyroiditis - a randomized controlled trial

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Abstract

Objectives: To assess the effect of daily zinc supplementation for 12 weeks on thyroid auto-antibodies - thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb), and oxidative stress in children with autoimmune thyroid disease (AITD) compared to standard therapy.

Methods: This open-labeled, parallel, randomized controlled trial was done in a tertiary care teaching institute in south India. Children aged 3-18 years with AITD were randomized to receive 25 mg elemental zinc daily for 12 weeks or standard therapy alone. The change in thyroid function tests (thyroid stimulating hormone, free T3, free T4), thyroid auto-antibody (TPOAb, TgAb) titers, oxidative stress markers (glutathione peroxidase, malondialdehyde, superoxide dismutase, and total antioxidant capacity) were compared.

Results: 40 children, 20 in each arm, were recruited in the study. We observed a female-to-male ratio of 7:1. Median duration of disease was 2 (0.25, 4.25) years. A total of 37 (92.5 %) children were hypothyroid, two hyperthyroid, and one euthyroid at enrolment. A total of 13 children (32.5 %) had associated co-morbidities, most commonly type 1 diabetes mellitus and systemic lupus erythematosus, three (7.5 %) each. We did not find any significant change in thyroid function tests, thyroid auto-antibody titers, and oxidative stress markers. However, the requirement of levothyroxine dose was significantly increased in the control arm, compared to the zinc group (p=0.03). Only four (20 %) children had minor adverse effects like nausea, metallic taste, and body ache.

Conclusions: Zinc supplementation did not have any effect on thyroid auto-antibodies and oxidative stress. Zinc-supplemented children did not require escalation in levothyroxine dose.

Bone health

J Bone Miner Res. 2024 Apr 19;39(3):211-221.
doi: 10.1093/jbmr/zjae007.

Influence of vitamin D supplementation on bone mineral content, bone turnover markers, and fracture risk in South African schoolchildren: multicenter double-blind randomized placebo-controlled trial (ViDiKids)

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Abstract

Randomized controlled trials (RCTs) to determine the influence of vitamin D on BMC and fracture risk in children of Black African ancestry are lacking. We conducted a sub-study (n = 450) nested within a phase 3 RCT of weekly oral supplementation with 10 000 IU vitamin D3 vs placebo for 3 yr in HIV-uninfected Cape Town schoolchildren aged 6-11 yr. Outcomes were BMC at the whole body less head (WBLH) and LS and serum 25-hydroxyvitamin D3

(25(OH)D3), PTH, alkaline phosphatase, C-terminal telopeptide, and PINP. Incidence of fractures was a secondary outcome of the main trial (n = 1682). At baseline, mean serum 25(OH)D3 concentration was 70.0 nmol/L (SD 13.5), and 5.8% of participants had serum 25(OH)D3 concentrations <50 nmol/L. Among sub-study participants, end-trial serum 25(OH)D3 concentrations were higher for participants allocated to vitamin D vs placebo (adjusted mean difference [aMD] 39.9 nmol/L, 95% CI, 36.1 to 43.6) and serum PTH concentrations were lower (aMD -0.55 pmol/L, 95% CI, -0.94 to -0.17). However, no interarm differences were seen for WBLH BMC (aMD -8.0 g, 95% CI, -30.7 to 14.7) or LS BMC (aMD -0.3 g, 95% CI, -1.3 to 0.8) or serum concentrations of bone turnover markers. Fractures were rare among participants in the main trial randomized to vitamin D vs placebo (7/755 vs 10/758 attending at least 1 follow-up; adjusted odds ratio 0.70, 95% CI, 0.27 to 1.85). In conclusion, a 3-yr course of weekly oral vitamin D supplementation elevated serum 25(OH)D3 concentrations and suppressed serum PTH concentrations in HIV-uninfected South African schoolchildren of Black African ancestry but did not influence BMC or serum concentrations of bone turnover markers. Fracture incidence was low, limiting power to detect an effect of vitamin D on this outcome.

Epilepsy and acute seizures

Epilepsy

Naunyn Schmiedebergs Arch Pharmacol. 2024 Jul;397(7):5233-5240.
doi: 10.1007/s00210-024-02954-7. Epub 2024 Jan 24.

Safety and efficacy of levetiracetam and carbamazepine monotherapy in the management of pediatric focal epilepsy: a randomized clinical trial

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Abstract

Due to the limited number of studies in children with focal epilepsy and the importance of choosing the most suitable drug to control seizures in children, the administration of the most effective medication with the most negligible adverse events is vital. This study aimed to evaluate the effectiveness and adverse events of carbamazepine vs. levetiracetam monotherapy in children with focal seizures. A monocentric, randomized, controlled, double-blind, parallel-group clinical trial was designed. This study was approved by the Iranian Registry of Clinical Trials (registration number: IRCT20170216032603N2) on June 19, 2020, and conducted at the neurology department of Imam Ali Hospital, Karaj, Iran, from February 2020 to March 2021. This study assessed 120 patients with recently diagnosed focal seizures aged 2 to 14. Patients were randomly divided into two groups, who received carbamazepine (CBZ) 15 to 20 mg/kg and levetiracetam (LEV) 20 to 40 mg/kg daily, respectively. Patients were evaluated for improvement and complications at weeks 4, 12, and 24. Out of 120 patients included in the study, six patients were excluded due to various complications of CBZ. The mean number of seizures at the end of the fourth, twelfth, and

twenty-fourth weeks were 1.09 ± 0.75, 0.62 ± 0.27, and 0.39 ± 0.12 in the carbamazepine group and 1.11 ± 0.63, 0.52 ± 0.21, and 0.37 ± 0.11 in the LEV group, respectively (P > 0.05). Similarly, the number of seizure-free patients was 34, 44, and 48 in the CBZ group compared to 41, 50, and 54 in the LEV group, respectively (P > 0.05). On the other hand, the frequency of somnolence, dermatologic complications, and agitation was considerably higher in the CBZ group (P < 0.05). Although both medicines were equally effective in seizure control, CBZ was associated with considerably more adverse events and less patient compliance. Physicians should be aware of this difference to prevent unwanted consequences.

Epilepsy Behav. 2023 Dec 31:151:109598.
doi: 10.1016/j.yebeh.2023.109598. Online ahead of print.

Feasibility of mobile phone application "Epilepsy care" for self-management of children and adolescents with epilepsy in Phramongkutklao hospital: A randomized controlled trial

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Abstract

Epilepsy is a common neurological disorder in children. Mobile applications have shown potential in improving self-management for patients with chronic illnesses. To address language barriers, we developed the first Thai version of the "Epilepsy care" mobile application for children and adolescents with epilepsy in Thailand. A prospective, randomized controlled trial with 220 children and adolescents living with epilepsy who had a smartphone and were treated at the pediatric neurology clinic was conducted, with one group using the mobile application and the other receiving standard epilepsy guidance. The primary outcome assessed epilepsy self-management using the Pediatric Epilepsy Self-Management Questionnaire (PEMSQ) in the Thai version, which comprised 27 questions. These questions aimed to determine knowledge, adherence to medications, beliefs about medication efficacy, and barriers to medication adherence. The secondary outcome evaluated seizure frequency at baseline, 3, and 6 months after initiation of an application. Eighty-five participants who were randomized to a mobile application achieved significantly higher PEMSQ scores in the domain of barriers to medication adherence (p < 0.05) at 6 months follow-up. Other domains of PEMSQ showed no statistically significant difference. Baseline median seizure frequencies per month were 7 in the control group and 5.5 in the intervention group. At 3 and 6 months, these decreased significantly to 1.5 and 1 for the control group and 2.5 and 1 for the intervention group (p < 0.001). In addition, the study revealed that 94.9 % of the participants in a mobile application group were highly satisfied with using application. These findings suggest that the mobile application "Epilepsy care" may serve as an effective adjunctive therapy to enhance self-management and seizure control in children and adolescents with epilepsy.

Indian J Pediatr. 2023 Oct;90(10):969-973.
doi: 10.1007/s12098-023-04527-7. Epub 2023 May 26.

Modified Atkins Diet vs. Ketogenic Diet in the Management of Children with Epileptic Spasms Refractory to First Line Treatment: An Open Labelled, Randomized Controlled Trial

Shobhna Sharma [1], Surekha Dabla [2], Jaya Shankar Kaushik [3]

Abstract

Objective: To compare the efficacy and tolerability of modified Atkins diet (mAD) and ketogenic diet (KD) among children aged 9 mo to 3 y with epileptic spasms refractory to the first line treatment.

Methods: An open labelled, randomized controlled trial with parallel group assignment was conducted among children aged 9 mo to 3 y with epileptic spasms refractory to the first line treatment. They were randomized to either receive the mAD along with conventional anti-seizure medications (n = 20) or KD with conventional anti-seizure medications (n = 20). Primary outcome measure was proportion of children who achieved "spasm freedom" at 4 wk and 12 wk. Secondary outcome measures were proportion of children who achieved >50% and >90% reduction in spasms at 4 wk and 12 wk, nature and proportion of the adverse effects as per parental reports.

Results: Proportion of children achieving spasm freedom [mAD {4 (20%)} vs. KD {3 (15%)}: OR (95% CI) 1.42 (0.27-7.34); P = 0.67], >50% spasm reduction [mAD {3 (15%)} vs. KD {5 (25%)}: OR (95% CI) 0.53 (0.11-2.59); P = 0.63] and >90% spasm reduction [mAD {4 (20%)} vs. KD {2 (10%)}: OR (95% CI) 2.25 (0.36-13.97); P = 0.41] was comparable between the two groups at 12 wk. The diet was well tolerated in both the groups with vomiting and constipation being the most common reported adverse effect.

Conclusions: mAD is an effective alternative to KD in the management of children with epileptic spasms refractory to first line treatment. However, further studies with adequately powered sample size and longer follow-up are required.

Epilepsy Res. 2024 Mar:201:107322.
doi: 10.1016/j.eplepsyres.2024.107322. Epub 2024 Feb 15.

Efficacy of daily versus intermittent low glycemic index therapy diet in children with drug-resistant epilepsy: A randomized controlled trial

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Abstract

Introduction: The predominant reason for the discontinuation of low glycemic index therapy (LGIT) in children with epilepsy is the dietary restrictions imposed therein. This trial intended to compare the efficacy of daily and intermittent LGIT in children with drug-resistant epilepsy (DRE).

Methods: This study was performed between February 2018 and January 2019 to compare the efficacy of daily and intermittent LGIT in children aged 1-15 years with DRE following 24 weeks of dietary therapy. Compliance, the difficulty faced by caregivers, adverse effects, impact on behaviour, and social quotient in both arms were compared. Children in the intermittent LGIT arm received a liberalized diet for two days every week (Saturday and Sunday), which also allowed medium glycemic index foods. Carbohydrate calories were allowed up to 20% of the total caloric requirement in the liberalized diet, as compared to only 10% in standard LGIT.

Results: Out of 132 children randomized (66 in each group), 122 completed 24 weeks follow up. Mean weekly seizure frequency reduction at 24 weeks in the intermittent LGIT group was comparable with that of the daily LGIT group in both intention-to-treat (ITT) and per-protocol analysis (-50.95%± 22.34% vs -47.16%± 23.41%, p=0.36 in ITT and -53.88%±20.54% vs -49.20%±21.87%, p=0.23) in per-protocol analysis for intermittent and daily LGIT group respectively). The proportion with ≥50% reduction in seizure frequency was also comparable between both groups (p=0.73 and 0.56 in ITT and per protocol analysis respectively). The proportion of patients with adverse events and satisfactory compliance rate also had a trend towards favoring intermittent LGIT (p=0.06 and 0.51, respectively), while caregiver difficulty was lower with intermittent LGIT (p=0.001).
Conclusions: Intermittent LGIT is comparable to daily LGIT in terms of seizure frequency reduction after 24 weeks of dietary therapy.

Childs Nerv Syst. 2023 Nov 27.
doi: 10.1007/s00381-023-06216-4. Online ahead of print.

Is intraoperative electrocorticography (ECoG) for long-term epilepsy-associated tumors (LEATs) more useful in children?-A Randomized Controlled Trial

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Abstract

Objectives: The utility of intraoperative electrocorticography (ECoG)-guided resective surgery for pediatric long-term epilepsy-associated tumors (LEATs) with antiseizure medication (ASM) resistant epilepsy is not supported by robust evidence. As epilepsy networks and their ramifications are different in children from those in adults, the impact of intraoperative ECoG-based tailored resections in predicting prognosis and influencing outcomes may also differ. We evaluated this hypothesis by comparing the outcomes of resections with and without the use of ECoG in children and adults by a randomized study.
Methods: From June 2020 to January 2022, 42 patients (17 children and 25 adults) with LEATs and antiseizure medication (ASM)-resistant epilepsy were randomly assigned to one of the 2 groups (ECoG or no ECoG), prior to surgical resection. The 'no ECoG' arm underwent gross total lesion resection (GTR) without ECoG guidance and the ECoG arm underwent GTR with ECoG guidance and further additional tailored resections, as necessary. Factors evaluated were tumor location, size, lateralization, seizure duration, preoperative antiepileptic drug therapy, pre- and postresection ECoG patterns and tumor histology. Postoperative Engel score and adverse event rates were compared in the pediatric and adult groups of both arms. Eloquent cortex lesions and re-explorations were excluded to avoid confounders.
Results: Forty-two patients were included in the study of which 17 patients were in the pediatric cohort (age < 18 years) and 25 in the adult cohort. The mean age in the pediatric group was 11.11 years (SD 4.72) and in the adult group was 29.56 years (SD 9.29). The mean duration of epilepsy was 9.7 years (SD 4.8) in the pediatric group and 10.96 (SD 8.8) in the adult group. The ECoG arm of LEAT resections had 23 patients (9 children and 14 adults) and

the non-ECoG arm had 19 patients (8 children and 11 adults). Three children and 3 adults from the ECoG group further underwent ECoG-guided tailored resections (average 1.33 additional tailored resections/per patient.).The histology of the tailored resection specimen was unremarkable in 3/6 (50%).Overall, the commonest histology in both groups was ganglioglioma and the temporal lobe, the commonest site of the lesion. 88.23% of pediatric cases (n = 15/17) had an excellent outcome (Engel Ia) following resection, compared to 84% of adult cases (n = 21/25) at a mean duration of follow-up of 25.76 months in children and 26.72 months in adults (p = 0.405).There was no significant difference in seizure outcomes between the ECoG and no ECoG groups both in children and adults, respectively (p > 0.05). Additional tailored resection did not offer any seizure outcome benefit when compared to the non-tailored resections.
Conclusions: The use of intraoperative electrocorticography in LEATs did not contribute to postoperative seizure outcome benefit in children and adults. No additional advantage or utility was offered by ECoG in children when compared to its use in adults. ECoG-guided additional tailored resections did not offer any additional seizure outcome benefit both in children and adults.

Acute seizures and status epilepticus

Seizure. 2024 Apr 18:118:110-116.
doi: 10.1016/j.seizure.2024.04.015. Online ahead of print.
Efficacy and safety of phenytoin and levetiracetam for acute symptomatic seizures in children with acute encephalitis syndrome: an open label, randomised controlled trial
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Abstract
Introduction: Seizures represent a significant comorbidity in children with acute encephalitis syndrome (AES). Despite this, there is a notable absence of randomized controlled trials (RCTs) directly comparing antiseizure medications (ASMs) in children with AES.
Materials and methods: This RCT aimed to assess the efficacy and safety of phenytoin and levetiracetam in controlling seizures among children with AES. Both ASMs were administered with a loading followed by maintenance dose. After a 12-week period, children exhibiting a normal electroencephalogram and no seizure recurrence underwent tapering and discontinuation of ASM. Clinical follow-up occurred daily for the first week, and subsequently at 4, 12, and 24 weeks, evaluating seizure recurrence, incidence of status epilepticus, cognition, behavior, functional status, ASM acquisition cost, and adverse effects.
Results: A total of 100 children (50 in each group) were enrolled. Within the first week, 5 and 3 children in the phenytoin and levetiracetam groups expired. Up to 1 week or death (whichever occurred earliest), 46 (92 %) and 44 (88 %) children remained seizure-free. Intention-to-treat analysis for both best and worst-case scenarios showed insignificant differences (p=0.52 and 1.0). No children experienced seizure recurrence after 1 week in either group. The number of patients with breakthrough status epilepticus, need for mechanical ventilation, duration of hospital stay, presence of epileptiform abnormalities in repeat electroencephalogram at 12 weeks, functional outcomes at 1, 12, and 24 weeks, as

well as cognition and behavioral profiles at 24 weeks, were comparable in both groups (p>0.05 for all). However, the incidence of treatment-emergent adverse events (TEAEs) causally related to study medications was significantly higher in the phenytoin group (p=0.04).
Conclusion: Levetiracetam and phenytoin are comparable in efficacy in terms of achieving clinical seizure control in children with acute encephalitis syndrome, although levetiracetam group demonstrated fewer adverse effects.

Epilepsy Res. 2024 May:202:107360.
doi: 10.1016/j.eplepsyres.2024.107360. Epub 2024 Apr 12.
Early versus late switch over of antiseizure medications from intravenous to the oral route in children with seizures: Single-blinded, randomized controlled trial (ELAIO trial)
Prateek Kumar Panda [1], Sanjot Bhardwaj [1], Vignesh Kaniyappan Murugan [1], Aman Elwadhi [1], Puneet Dhamija [2], Lokesh Tiwari [3], Indar Kumar Sharawat [4]
Abstract
Introduction: Early switch-over of anti-seizure medications (ASMs) from intravenous to oral route may reduce the duration of hospitalization, drug acquisition costs, and behavioral upset in hospitalized children with seizures.
Objective: The primary objective was to compare short-term seizure recurrence within 1 week in hospitalized children aged 1 month to 18 years with new-onset/breakthrough seizures after an early versus late switch-over from intravenous to the oral route of ASMs. Secondary objectives were to compare the incidence of status epilepticus, duration of hospital stay, drug acquisition costs, and caregiver-reported satisfaction scores in both groups.
Methods: In this single-blind randomized controlled trial, patients with seizures were categorized based on the number of ASMs required and the history of status epilepticus. Patients in each category were randomized in a 1:1 ratio into either early or late switch-over (ES or LS) groups. In the ES groups, ASMs were tapered one-by-one between 0 and 24 hours of seizure freedom, while in the LS groups, they were tapered one-by-one between 24 and 48 hours of seizure freedom.
Results: A total of 112 children were enrolled in the study, with 56 in each arm. Seizure recurrence at 1 week and 12 weeks was comparable in ES and LS groups (3/55 vs. 1/54 at 1 week, p=0.61; 7/49 vs. 6/49 at 12 weeks, p=0.98). Drug acquisition costs were significantly lower in the ES group (393±274 vs. 658±568 INR, p=0.002). Thrombophlebitis and dysphoria were significantly more common in the LS group (p=0.008 and 0.03, respectively).
Conclusion: The early switch-over of ASMs from intravenous to oral route is safe without any significant increased risk of short-term seizure recurrence and also associated with a reduction in the incidence of thrombophlebitis and ASM acquisition costs.

Economics, equity and poverty alleviation

Arch Dis Child. 2024 Apr 24:archdischild-2022-325222.

doi: 10.1136/archdischild-2022-325222. Online ahead of print.

Cost of childhood severe pneumonia management in selected public inpatient care facilities in Bangladesh: a provider perspective

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Abstract

Objective: To estimate inpatient care costs of childhood severe pneumonia and its urban-rural cost variation, and to predict cost drivers.

Design: The study was nested within a cluster randomised trial of childhood severe pneumonia management. Cost per episode of severe pneumonia was estimated from a healthcare provider perspective for children who received care from public inpatient facilities. A bottom-up micro-costing approach was applied and data collected using structured questionnaire and review of the patient record. Multivariate regression analysis determined cost predictors and sensitivity analysis explored robustness of cost parameters.

Setting: Eight public inpatient care facilities from two districts of Bangladesh covering urban and rural areas.

Patients: Children aged 2-59 months with WHO-classified severe pneumonia.

Results: Data on 1252 enrolled children were analysed; 795 (64%) were male, 787 (63%) were infants and 59% from urban areas. Average length of stay (LoS) was 4.8 days (SD ±2.5) and mean cost per patient was US$48 (95% CI: US$46, US$49). Mean cost per patient was significantly greater for urban tertiary-level facilities compared with rural primary-secondary facilities (mean difference US$43; 95% CI: US$40, US$45). No cost variation was found relative to age, sex, malnutrition or hypoxaemia. Type of facility was the most important cost predictor. LoS and personnel costs were the most sensitive cost parameters.

Conclusion: Healthcare provider cost of childhood severe pneumonia was substantial for urban located public health facilities that provided tertiary-level care. Thus, treatment availability at a lower-level facility at a rural location may help to reduce overall treatment costs.

Environmental health

Water, Sanitation and Hygiene

Am J Trop Med Hyg. 2023 Jul 24;109(3):676-685.
doi: 10.4269/ajtmh.21-0555. Print 2023 Sep 6.

Assessing the Impact of a Handwashing Knowledge and Practices Program among Poor Households in Rural Bangladesh: A Cluster-Randomized Pre-Post Study

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Abstract

Improvement in hand hygiene has been strongly associated with positive outcomes in maternal and child health. Although Bangladesh has a high level of awareness of key hygiene

messages, the practice of handwashing, the most effective hygiene behavior, is low. Suchana, a multisectoral nutrition program, aims to increase knowledge and practices around various water, sanitation, and hygiene settings in Sylhet region, the northeast of rural Bangladesh. This study aimed to investigate the changes in indicators related to handwashing knowledge and practices among Suchana beneficiaries in final compared with baseline evaluations. Data were derived from the baseline and final cross-sectional evaluation survey. The following handwashing knowledge and practices were considered: handwashing before preparing food, before eating food and feeding children, before serving food, after defecation, and after touching animals. The descriptive findings indicate that Suchana intervention improved handwashing knowledge and practices in the intervention area compared with the control. The odds of having knowledge of hand washing before preparing food (adjusted odds ratio [aOR]: 1.60; 95% CI: 1.30-1.98), before eating food and feeding children (aOR: 1.68; 95% CI: 1.25-2.25), before serving food (aOR: 1.35; 95% CI: 1.04-1.76), after defecation (aOR: 1.74; 95% CI: 1.25-2.41), and after touching animals (aOR: 1.67; 95% CI: 1.29-2.16) were higher in intervention area than the control area. Similarly, the impact on maternal handwashing practices at final evaluation indicated successful effects of the intervention. These results suggest scaling-up of similar interventions for larger populations living in vulnerable areas of rural Bangladesh.

J Epidemiol Glob Health. 2024 Mar 20.
doi: 10.1007/s44197-024-00210-y. Online ahead of print.

Improved Child Feces Management Mediates Reductions in Childhood Diarrhea from an On-Site Sanitation Intervention: Causal Mediation Analysis of a Cluster-Randomized Trial in Rural Bangladesh

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Abstract

Background: The WASH benefits Bangladesh trial multi-component sanitation intervention reduced diarrheal disease among children < 5 years. Intervention components included latrine upgrades, child feces management tools, and behavioral promotion. It remains unclear which components most impacted diarrhea.

Methods: We conducted mediation analysis within a subset of households (n = 720) from the sanitation and control arms. Potential mediators were categorized into indicators of latrine quality, latrine use practices, and feces management practices. We estimated average causal mediation effects (ACME) as prevalence differences (PD), defined as the intervention's effect on diarrhea through its effect on the mediator.

Results: The intervention improved all indicators compared to controls. We found significant mediation through multiple latrine use and feces management practice indicators. The strongest mediators during monsoon seasons were reduced open defecation among children aged < 3 and 3-8 years, and increased disposal of child feces into latrines. The strongest mediators during dry seasons were access to a flush/pour-flush latrine, reduced open defecation among children aged 3-8 years, and increased disposal of child feces into latrines. Individual mediation effects were small (PD = 0.5-2 percentage points) compared to the overall intervention effect but collectively describe significant mediation pathways.

Discussion: The effect of the WASH Benefits Bangladesh sanitation intervention on diarrheal disease was mediated through improved child feces management and reduced child open defecation. Although the intervention significantly improved latrine quality, relatively high latrine quality at baseline may have limited benefits from additional improvements. Targeting safe child feces management may increase the health benefits of rural sanitation interventions.

Nat Commun. 2024 Feb 20;15(1):1556.
doi: 10.1038/s41467-024-45624-1.

WASH interventions and child diarrhea at the interface of climate and socioeconomic position in Bangladesh

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Abstract

Many diarrhea-causing pathogens are climate-sensitive, and populations with the lowest socioeconomic position (SEP) are often most vulnerable to climate-related transmission. Household Water, Sanitation, and Handwashing (WASH) interventions constitute one potential effective strategy to reduce child diarrhea, especially among low-income households. Capitalizing on a cluster randomized trial population (360 clusters, 4941 children with 8440 measurements) in rural Bangladesh, one of the world's most climate-sensitive regions, we show that improved WASH substantially reduces diarrhea risk with largest benefits among children with lowest SEP and during the monsoon season. We extrapolated trial results to rural Bangladesh regions using high-resolution geospatial layers to identify areas most likely to benefit. Scaling up a similar intervention could prevent an estimated 734 (95% CI 385, 1085) cases per 1000 children per month during the seasonal monsoon, with marked regional heterogeneities. Here, we show how to extend large-scale trials to inform WASH strategies among climate-sensitive and low-income populations.

Environ Health Perspect. 2024 Apr;132(4):47006.
doi: 10.1289/EHP13807. Epub 2024 Apr 11.

Influence of Temperature and Precipitation on the Effectiveness of Water, Sanitation, and Handwashing Interventions against Childhood Diarrheal Disease in Rural Bangladesh: A Reanalysis of the WASH Benefits Bangladesh Trial

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Abstract

Background: Diarrheal disease is a leading cause of childhood morbidity and mortality globally. Household water, sanitation, and handwashing (WASH) interventions can reduce exposure to diarrhea-causing pathogens, but meteorological factors may impact their effectiveness. Information about effect heterogeneity under different weather conditions is critical to refining these targeted interventions.

Objectives: We aimed to determine whether temperature and precipitation modified the effect of low-cost, point-of-use WASH interventions on child diarrhea.
Methods: We analyzed data from a trial in rural Bangladesh that compared child diarrhea prevalence between clusters (N=720*N*=720) that were randomized to different WASH interventions between 2012 and 2016 (NCT01590095). We matched temperature and precipitation measurements to diarrhea outcomes (N=12,440*N*=12,440 measurements, 6,921 children) by geographic coordinates and date. We estimated prevalence ratios (PRs) using generative additive models and targeted maximum likelihood estimation to assess the effectiveness of each WASH intervention under different weather conditions.
Results: Generally, WASH interventions most effectively prevented diarrhea during monsoon season, particularly following weeks with heavy rain or high temperatures. The PR for diarrhea in the WASH interventions group compared with the control group was 0.49 (95% CI: 0.35, 0.68) after 1 d of heavy rainfall, with a less-protective effect [PR=0.87PR=0.87 (95% CI: 0.60, 1.25)] when there were no days with heavy rainfall. Similarly, the PR for diarrhea in the WASH intervention group compared with the control group was 0.60 (95% CI: 0.48, 0.75) following above-median temperatures vs. 0.91 (95% CI: 0.61, 1.35) following below-median temperatures. The influence of precipitation and temperature varied by intervention type; for precipitation, the largest differences in effectiveness were for the sanitation and combined WASH interventions.
Discussion: WASH intervention effectiveness was strongly influenced by precipitation and temperature, and nearly all protective effects were observed during the rainy season. Future implementation of these interventions should consider local environmental conditions to maximize effectiveness, including targeted efforts to maintain latrines and promote community adoption ahead of monsoon seasons.

Matern Child Nutr. 2023 Oct;19(4):e13528.
doi: 10.1111/mcn.13528. Epub 2023 May 27.

Effects of an integrated poultry value chain, nutrition, gender and WASH intervention (SELEVER) on hygiene and child morbidity and anthropometry in Burkina Faso: A secondary outcome analysis of a cluster randomised trial

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Abstract
Nutrition-sensitive agriculture programmes have the potential to improve child nutrition outcomes, but livestock intensification may pose risks related to water, sanitation and hygiene (WASH) conditions. We assessed the impact of SELEVER, a nutrition- and gender-sensitive poultry intervention, with and without added WASH focus, on hygiene practices, morbidity and anthropometric indices of nutrition in children aged 2-4 years in Burkina Faso. A 3-year cluster randomised controlled trial was implemented in 120 villages in 60 communes (districts) supported by the SELEVER project. Communes were randomly assigned using restricted randomisation to one of three groups: (1) SELEVER intervention (n = 446 households); (2) SELEVER plus WASH intervention (n = 432 households); and (3) control without intervention (n = 899 households). The study population included women aged 15-

49 years with an index child aged 2-4 years. We assessed the effects 1.5-years (WASH substudy) and 3-years (endline) post-intervention on child morbidity and child anthropometry secondary trial outcomes using mixed effects regression models. Participation in intervention activities was low in the SELEVER groups, ranging from 25% at 1.5 years and 10% at endline. At endline, households in the SELEVER groups had higher caregiver knowledge of WASH-livestock risks (Δ = 0.10, 95% confidence interval [CI] [0.04-0.16]) and were more likely to keep children separated from poultry (Δ = 0.09, 95% CI [0.03-0.15]) than in the control group. No differences were found for other hygiene practices, child morbidity symptoms or anthropometry indicators. Integrating livestock WASH interventions alongside poultry and nutrition interventions can increase knowledge of livestock-related risks and improve livestock-hygiene-related practices, yet may not be sufficient to improve the morbidity and nutritional status of young children.

Nat Commun. 2024 Apr 26;15(1):3572.
doi: 10.1038/s41467-024-47896-z.

A cluster-randomized trial of water, sanitation, handwashing and nutritional interventions on stress and epigenetic programming

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Abstract

A regulated stress response is essential for healthy child growth and development trajectories. We conducted a cluster-randomized trial in rural Bangladesh (funded by the Bill & Melinda Gates Foundation, ClinicalTrials.gov NCT01590095) to assess the effects of an integrated nutritional, water, sanitation, and handwashing intervention on child health. We previously reported on the primary outcomes of the trial, linear growth and caregiver-reported diarrhea. Here, we assessed additional prespecified outcomes: physiological stress response, oxidative stress, and DNA methylation (N = 759, ages 1-2 years). Eight neighboring pregnant women were grouped into a study cluster. Eight geographically adjacent clusters were block-randomized into the control or the combined nutrition, water, sanitation, and handwashing (N + WSH) intervention group (receiving nutritional counseling and lipid-based nutrient supplements, chlorinated drinking water, upgraded sanitation, and handwashing with soap). Participants and data collectors were not masked, but analyses were masked. There were 358 children (68 clusters) in the control group and 401 children (63 clusters) in the intervention group. We measured four F2-isoprostanes isomers (iPF(2α)-III; 2,3-dinor-iPF(2α)-III; iPF(2α)-VI; 8,12-iso-iPF(2α)-VI), salivary alpha-amylase and cortisol, and methylation of the glucocorticoid receptor (NR3C1) exon 1F promoter including the NGFI-A binding site. Compared with control, the N + WSH group had lower concentrations of F2-isoprostanes isomers (differences ranging from -0.16 to -0.19 log ng/mg of creatinine, P < 0.01), elevated post-stressor cortisol (0.24 log μg/dl; P < 0.01), higher cortisol residualized gain scores (0.06 μg/dl; P = 0.023), and decreased methylation of the NGFI-A binding site (-

0.04; P = 0.037). The N + WSH intervention enhanced adaptive responses of the physiological stress system in early childhood.

Food Nutr Bull. 2023 Dec;44(2_suppl):S119-S123.
doi: 10.1177/03795721231195427.

The Livestock for Health Study: A Field Trial on Livestock Interventions to Prevent Acute Malnutrition Among Women and Children in Pastoralist Communities in Northern Kenya

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Abstract

Background: Livestock-dependent communities in Africa's drylands disproportionately experience acute malnutrition, especially during drought seasons. We detail the design and implementation of the Livestock for Health (L4H) study aimed at determining the effect of providing livestock feed and nutritional counselling to prevent seasonal spikes of acute malnutrition.

Methods: The L4H study employed a 3-arm cluster randomized controlled trial to compare households in pastoralist settings in northern Kenya receiving livestock feeds during critical dry periods, with or without nutritional counseling, with control households. Over 4 dry seasons, 2019 to 2021, the study collected data on household milk production, consumption patterns, mothers'/children's nutritional status, household socioeconomic status, herd dynamics, and human and animal health status every 6 weeks.

Results: L4H recruited 1734 households, with 639, 585, and 510 households assigned to intervention arms 1 and 2 and control arm 3, respectively. From these households, 1734 women and 1748 children younger than 3 years were recruited. In total, 19 419 household visits were completed, obtaining anthropometric measures 9 times on average for each child and mother. Eighty-one households (5%) were lost from the study due to the mother's death, child's death, migration, and withdrawal for other reasons.

Discussion: L4H's success in a challenging environment was possible due to strong community engagement, formative studies to inform trial design, collaboration with local authorities, and effective interdisciplinary collaboration. Subsequent manuscripts will report the study findings.

J Infect Public Health. 2024 Apr:17 Suppl 1:34-41.
doi: 10.1016/j.jiph.2023.04.003. Epub 2023 Apr 7.

The relationship between hand hygiene and rates of acute respiratory infections among Umrah pilgrims: A pilot randomised controlled trial

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Abstract

Background: There is a lack of randomised controlled trials (RCTs) investigating the role of hand hygiene in preventing and containing acute respiratory infections (ARIs) in mass gatherings. In this pilot RCT, we assessed the feasibility of establishing a large-scale trial to explore the relationship between practising hand hygiene and rates of ARI in Umrah pilgrimage amidst the COVID-19 pandemic.
Methods: A parallel RCT was conducted in hotels in Makkah, Saudi Arabia, between April and July 2021. Domestic adult pilgrims who consented to participate were randomised 1:1 to the intervention group who received alcohol-based hand rub (ABHR) and instructions, or to the control group who did not receive ABHR or instructions but were free to use their own supplies. Pilgrims in both groups were then followed up for seven days for ARI symptoms. The primary outcome was the difference in the proportions of syndromic ARIs among pilgrims between the randomised groups.
Results: A total of 507 (control: intervention = 267: 240) participants aged between 18 and 75 (median 34) years were randomised; 61 participants were lost to follow-up or withdrew leaving 446 participants (control: intervention = 237:209) for the primary outcome analysis; of whom 10 (2.2 %) had developed at least one respiratory symptom, three (0.7 %) had 'possible ILI' and two (0.4 %) had 'possible COVID-19'. The analysis of the primary outcome found no evidence of difference in the proportions of ARIs between the randomised groups (odds ratio 1.1 [0.3-4.0] for intervention relative to control).
Conclusion: This pilot trial suggests that conducting a future definitive RCT to assess the role of hand hygiene in the prevention of ARIs is feasible in Umrah setting amidst such a pandemic; however, outcomes from this trial are inconclusive, and such a study would need to be very large given the low rates of outcomes observed here.

Pollutants

Environ Res. 2023 Jul 1;228:115784.
doi: 10.1016/j.envres.2023.115784. Epub 2023 Apr 1.

Predictors of serum- per- and polyfluoroalkyl substance (PFAS) concentrations among infants in Guinea-Bissau, West Africa

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Abstract
Background: Knowledge about PFAS exposure in Africa is limited. We have previously detected six types of PFAS in the serum of infants from Guinea-Bissau, West Africa. The aim of this study was to identify predictors of the infant serum-PFAS concentrations.
Methods: This cross-sectional study was based on a subset of data from a randomized controlled trial of early measles vaccination performed in 2012-2015 in three rural regions of Guinea-Bissau. Blood samples were obtained from 237 children aged 4-to-7 months, and six types of PFAS were quantified in serum. Location of residence was recorded, and information about predictors related to socioeconomic status as well as maternal and child characteristics were obtained through structured interviews with the mothers through routine surveillance. Associations between potential predictors and infant serum-PFAS

concentrations were examined in linear regression models while adjusting for potential confounding and mediating factors as identified in a directed acyclic graph.
Results: Infants from the Cacheu region had the lowest concentrations of perfluorooctanoic acid (PFOA), while infants from the Oio region had the lowest concentrations of all other PFAS. Compared to infants from Oio, infant serum-perfluorooctane sulfonic acid (PFOS) concentrations were 94.1% (95% CI: 52.4, 147.1%) and 81.9% (95% CI: 45.7, 127.1%) higher in Cacheu and Biombo, respectively. Higher maternal age and lower parity were associated with slightly higher child-serum perfluorohexane sulfonic acid (PFHxS) concentrations, while infants with higher socioeconomic status and infants breastfed without supplementary solid foods at inclusion had higher average concentrations of most PFAS, although the confidence intervals were wide and overlapped zero.
Discussion: Location of residence was the most important determinant of serum-PFAS concentrations among Guinea-Bissau infants, indicating a potential role of diet as affected by the global spread of PFAS, but future studies should explore reasons for the regional differences in PFAS exposure.

Editor's Note:
The Environmental Protection Authority in the US says this about PFAS
https://www.epa.gov/pfas/pfas-explained

- *PFAS are widely used, long lasting chemicals, components of which break down very slowly over time.*
- *Because of their widespread use and their persistence in the environment, many PFAS are found in the blood of people and animals all over the world and are present at low levels in a variety of food products and in the environment.*
- *PFAS are found in water, air, fish, and soil at locations across the nation and the globe.*
- *Scientific studies have shown that exposure to some PFAS in the environment may be linked to harmful health effects in humans and animals.*
- *There are thousands of PFAS chemicals, and they are found in many different consumer, commercial, and industrial products. This makes it challenging to study and assess the potential human health and environmental risks.*

Indoor air pollution

(see also Pneumonia prevention)

Int J Environ Res Public Health. 2024 Apr 17;21(4):490.
doi: 10.3390/ijerph21040490.
Multicomponent Behavioural Intervention during Pregnancy to Reduce Home Exposure to Second-Hand Smoke: A Pilot Randomised Controlled Trial in Bangladesh and India
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Abstract

Background: Pregnant women exposed to second-hand smoke (SHS) are at increased risk of poor birth outcomes. We piloted multicomponent behavioural intervention and trial methods in Bangalore, India, and Comilla, Bangladesh.
Methods: A pilot individual randomised controlled trial with economic and process evaluation components was conducted. Non-tobacco-using pregnant women exposed to SHS were recruited from clinics and randomly allocated to intervention or control (educational leaflet) arms. The process evaluation captured feedback on the trial methods and intervention components. The economic component piloted a service use questionnaire. The primary outcome was saliva cotinine 3 months post-intervention.
Results: Most pregnant women and many husbands engaged with the intervention and rated the components highly, although the cotinine report elicited some anxiety. Forty-eight (Comilla) and fifty-four (Bangalore) women were recruited. The retention at 3 months was 100% (Comilla) and 78% (Bangalore). Primary outcome data were available for 98% (Comilla) and 77% (Bangalore).
Conclusions: The multicomponent behavioural intervention was feasible to deliver and was acceptable to the interventionists, pregnant women, and husbands. With the intervention, it was possible to recruit, randomise, and retain pregnant women in Bangladesh and India. The cotinine data will inform sample size calculations for a future definitive trial.

Lancet Glob Health. 2024 May;12(5):e815-e825.
doi: 10.1016/S2214-109X(24)00033-0.

Cooking with liquefied petroleum gas or biomass and fetal growth outcomes: a multi-country randomised controlled trial

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Abstract
Background: Household air pollution might lead to fetal growth restriction during pregnancy. We aimed to investigate whether a liquefied petroleum gas (LPG) intervention to reduce personal exposures to household air pollution during pregnancy would alter fetal growth.
Methods: The Household Air Pollution Intervention Network (HAPIN) trial was an open-label randomised controlled trial conducted in ten resource-limited settings across Guatemala, India, Peru, and Rwanda. Pregnant women aged 18-34 years (9-19 weeks of gestation) were randomly assigned in a 1:1 ratio to receive an LPG stove, continuous fuel delivery, and behavioural messaging or to continue usual cooking with biomass for 18 months. We conducted ultrasound assessments at baseline, 24-28 weeks of gestation (the first pregnancy visit), and 32-36 weeks of gestation (the second pregnancy visit), to measure fetal size; we monitored 24 h personal exposures to household air pollutants during these visits; and we

weighed children at birth. We conducted intention-to-treat analyses to estimate differences in fetal size between the intervention and control group, and exposure-response analyses to identify associations between household air pollutants and fetal size. This trial is registered with ClinicalTrials.gov (NCT02944682).
Findings: Between May 7, 2018, and Feb 29, 2020, we randomly assigned 3200 pregnant women (1593 to the intervention group and 1607 to the control group). The mean gestational age was 14·5 (SD 3·0) weeks and mean maternal age was 25·6 (4·5) years. We obtained ultrasound assessments in 3147 (98·3%) women at baseline, 3052 (95·4%) women at the first pregnancy visit, and 2962 (92·6%) at the second pregnancy visit, through to Aug 25, 2020. Intervention adherence was high (the median proportion of days with biomass stove use was 0·0%, IQR 0·0-1·6) and pregnant women in the intervention group had lower mean exposures to particulate matter with a diameter less than 2·5 μm ($PM_{2·5}$; 35·0 [SD 37·2] μg/m^3vs 103·3 [97·9] μg/m^3) than did women in the control group. We did not find differences in averaged post-randomisation Z scores for head circumference (0·30 vs 0·39; p=0·04), abdominal circumference (0·38 vs 0·39; p=0·99), femur length (0·44 vs 0·45; p=0·73), and estimated fetal weight or birthweight (-0·13 vs -0·12; p=0·70) between the intervention and control groups. Personal exposures to household air pollutants were not associated with fetal size.
Interpretation: Although an LPG cooking intervention successfully reduced personal exposure to air pollution during pregnancy, it did not affect fetal size. Our findings do not support the use of unvented liquefied petroleum gas stoves as a strategy to increase fetal growth in settings were biomass fuels are used predominantly for cooking.

Environ Res. 2023 Aug 15;231(Pt 1):115991.
doi: 10.1016/j.envres.2023.115991. Epub 2023 Apr 29.

Who benefits most from a prenatal HEPA filter air cleaner intervention on childhood cognitive development? The UGAAR randomized controlled trial

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Abstract
Background: Air pollution exposure during pregnancy affects children's brain function. Maternal stress and nutrition, socioeconomic status, and the child's sex may modify this relationship.
Objective: To identify characteristics of children with the largest increases in full-scale IQ (FSIQ) after their mothers used HEPA filter air cleaners during pregnancy.
Methods: In this randomized controlled trial we randomly assigned women to receive 1-2 air cleaners or no air cleaners during pregnancy. We analyzed maternal hair samples for cortisol and dehydroepiandrosterone (DHEA). When the children were 48 months old, we measured FSIQ with the Wechsler Preschool and Primary Scale of Intelligence. We evaluated ten potential modifiers of the intervention-FSIQ relationship using interaction terms in separate regression models. To account for correlations between modifiers, we also used a single regression model containing main effects and intervention x modifier terms for all potential modifiers.
Results: Among 242 mother-child dyads with complete data, the intervention was associated with a 2.3-point increase (95% CI: -1.5, 6.0 points) in mean FSIQ. The intervention

improved mean FSIQ among children of mothers in the bottom (5.4 points; 95% CI: -0.8, 11.5) and top (6.1 points; 95% CI: 0.5, 11.8) cortisol tertiles, but not among those whose mothers were in the middle tertile. The largest between-group difference in the intervention's effect was a 7.5-point (95% CI: -0.7, 15.7) larger increase in mean FSIQ among children whose mothers did not take vitamins than among children whose mothers did take vitamins (interaction p-value = 0.07). We also observed larger benefits among children whose mothers did not complete university, and those with lower hair DHEA concentrations, hair cortisol concentrations outside the middle tertile, or more perceived stress.
Conclusion: The benefits of reducing air pollution during pregnancy on brain development may be greatest for children whose mothers who do not take vitamins, experience more stress, or have less education.

N Engl J Med. 2024 Jan 4;390(1):44-54.
doi: 10.1056/NEJMoa2302687.

Effects of Cooking with Liquefied Petroleum Gas or Biomass on Stunting in Infants

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Abstract

Background: Household air pollution is associated with stunted growth in infants. Whether the replacement of biomass fuel (e.g., wood, dung, or agricultural crop waste) with liquefied petroleum gas (LPG) for cooking can reduce the risk of stunting is unknown.
Methods: We conducted a randomized trial involving 3200 pregnant women 18 to 34 years of age in four low- and middle-income countries. Women at 9 to less than 20 weeks' gestation were randomly assigned to use a free LPG cookstove with continuous free fuel delivery for 18 months (intervention group) or to continue using a biomass cookstove (control group). The length of each infant was measured at 12 months of age, and personal exposures to fine particulate matter (particles with an aerodynamic diameter of ≤2.5 μm) were monitored starting at pregnancy and continuing until the infants were 1 year of age. The primary outcome for which data are presented in the current report - stunting (defined as a length-for-age z score that was more than two standard deviations below the median of a growth standard) at 12 months of age - was one of four primary outcomes of the trial. Intention-to-treat analyses were performed to estimate the relative risk of stunting.
Results: Adherence to the intervention was high, and the intervention resulted in lower prenatal and postnatal 24-hour personal exposures to fine particulate matter than the control (mean prenatal exposure, 35.0 μg per cubic meter vs. 103.3 μg per cubic meter; mean postnatal exposure, 37.9 μg per cubic meter vs. 109.2 μg per cubic meter). Among 3061 live births, 1171 (76.2%) of the 1536 infants born to women in the intervention group and 1186 (77.8%) of the 1525 infants born to women in the control group had a valid length

measurement at 12 months of age. Stunting occurred in 321 of the 1171 infants included in the analysis (27.4%) of the infants born to women in the intervention group and in 299 of the 1186 infants included in the analysis (25.2%) of those born to women in the control group (relative risk, 1.10; 98.75% confidence interval, 0.94 to 1.29; P = 0.12).
Conclusions: An intervention strategy starting in pregnancy and aimed at mitigating household air pollution by replacing biomass fuel with LPG for cooking did not reduce the risk of stunting in infants.

Environ Pollut. 2024 Jan 27:345:123414.
doi: 10.1016/j.envpol.2024.123414. Online ahead of print.

Effects of a liquefied petroleum gas stove intervention on stillbirth, congenital anomalies and neonatal mortality: A multi-country household air pollution intervention network trial

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Abstract
Household air pollution (HAP) from cooking with solid fuels used during pregnancy has been associated with adverse pregnancy outcomes. The Household Air Pollution Intervention Network (HAPIN) trial was a randomized controlled trial that assessed the impact of a liquefied petroleum gas (LPG) stove and fuel intervention on health in Guatemala, India, Peru, and Rwanda. Here we investigated the effects of the LPG stove and fuel intervention on stillbirth, congenital anomalies and neonatal mortality and characterized exposure-response relationships between personal exposures to fine particulate matter ($PM_{2.5}$), black carbon (BC) and carbon monoxide (CO) and these outcomes. Pregnant women (18 to <35 years of age; gestation confirmed by ultrasound at 9 to <20 weeks) were randomly assigned to intervention or control arms. We monitored these fetal and neonatal outcomes and personal exposure to $PM_{2.5}$, BC and CO three times during pregnancy, we conducted intention-to-treat (ITT) and exposure-response (E-R) analyses to determine if the HAPIN intervention and corresponding HAP exposure was associated with the risk of fetal/neonatal outcomes. A total of 3200 women (mean age 25.4 ± 4.4 years, mean gestational age at randomization 15.4 ± 3.1 weeks) were included in this analysis. Relative risks for stillbirth, congenital anomaly and neonatal mortality were 0.99 (0.60, 1.66), 0.92 (95 % CI 0.52, 1.61), and 0.99 (0.54, 1.85), respectively, among women in the intervention arm compared to controls in an ITT analysis. Higher mean personal exposures to $PM_{2.5}$, CO and BC during pregnancy were associated with a higher, but statistically non-significant, incidence of adverse outcomes. The LPG stove and fuel intervention did not reduce the risk of these outcomes nor did we find evidence supporting an association between personal exposures to HAP and stillbirth, congenital anomalies and neonatal mortality.

BMC Pregnancy Childbirth. 2024 Mar 12;24(1):192.
doi: 10.1186/s12884-024-06363-9.

Effect of a chimney-fitted improved stove on pregnancy outcomes in Northwest Ethiopia: a randomized controlled trial

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Abstract

Background: Exposure to household air pollution during pregnancy has been linked to adverse pregnancy outcomes. Improved stove was implemented in Ethiopia to reduce this exposure and related health problems. However, the effects of improved stove interventions on pregnancy outcomes remains uncertain.

Method: Individually randomized stove replacement trial was conducted among 422 households in six low-income rural kebeles of Northwestern Ethiopia. Pregnant women without known health conditions were recruited at ≤ 24 weeks gestation and randomized to an intervention or control group with a 1:1 ratio. A baseline survey was collected and a balance test was done. Two-sided independent samples t-test for continuous outcomes and chi-square for categorical variables were used to compare the effect of the intervention between the groups. Mean differences with 95% CIs were calculated and a p-value of < 0.05 was considered statistically significant.

Result: In this study, the mean birth weight was 3065 g (SD = 453) among the intervention group and not statistically different from 2995 g (SD = 541) of control group. After adjusting for covariates, infants born from intervention group weighed 55 g more [95% CI: - 43 to 170) than infants born from the control group, but the difference was not statistically significant (P = 0.274). The respective percentages for low birth weight were 8% and 10.3% for intervention and control groups respectively (P = 0.346). However, the average gestational age at delivery was higher among improved stove users (38 weeks (SD = 8.2) compared to control groups 36.5 weeks (SD = 9.6) with statistically significant difference at 0.91 weeks (95% CI: 0.52 to 1.30 weeks, p < 0.001). The corresponding difference in risk ratio for preterm birth is 0.94 (95% CI:0.92 to 0.97; p < 0.001). The percentages for maternal complications, stillbirth, and miscarriage in the intervention group were not statistically different from the control group.

Conclusions: While the increase in average birth weight among babies born to mothers using improved stoves was not statistically significant, babies had a longer gestational age on average, offering valuable health benefits. However, the study didn't find a significant impact on other pregnancy outcomes like stillbirth, miscarriage, or maternal complications.

Lancet Respir Med. 2024 Feb 1:S2213-2600(23)00427-7.
doi: 10.1016/S2213-2600(23)00427-7. Online ahead of print.

Estimated health effects from domestic use of gaseous fuels for cooking and heating in high-income, middle-income, and low-income countries: a systematic review and meta-analyses

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Abstract

Background: Exposure to household air pollution from polluting domestic fuel (solid fuel and kerosene) represents a substantial global public health burden and there is an urgent need for rapid transition to clean domestic fuels. Gas for cooking and heating might possibly affect child asthma, wheezing, and respiratory health. The aim of this review was to synthesise the evidence on the health effects of gaseous fuels to inform policies for scalable clean household energy.

Methods: In this systematic review and meta-analysis, we summarised the health effects from cooking or heating with gas compared with polluting fuels (eg, wood or charcoal) and clean energy (eg, electricity and solar energy). We searched PubMed, Scopus, Web of Science, MEDLINE, Cochrane Library (CENTRAL), Environment Complete, GreenFile, Google Scholar, Wanfang DATA, and CNKI for articles published between Dec 16, 2020, and Feb 6, 2021. Studies eligible for inclusion had to compare gas for cooking or heating with polluting fuels (eg, wood or charcoal) or clean energy (eg, electricity or solar energy) and present data for health outcomes in general populations. Studies that reported health outcomes that were exacerbations of existing underlying conditions were excluded. Several of our reviewers were involved in screening studies, data extraction, and quality assessment (including risk of bias) of included studies; 20% of studies were independently screened, extracted and quality assessed by another reviewer. Disagreements were reconciled through discussion with the wider review team. Included studies were appraised for quality using the Liverpool Quality Assessment Tools. Key health outcomes were grouped for meta-analysis and analysed using Cochrane's RevMan software. Primary outcomes were health effects (eg, acute lower respiratory infections) and secondary outcomes were health symptoms (eg, respiratory symptoms such as wheeze, cough, or breathlessness). This study is registered with PROSPERO, CRD42021227092.

Findings: 116 studies were included in the meta-analysis (two [2%] randomised controlled trials, 13 [11%] case-control studies, 23 [20%] cohort studies, and 78 [67%] cross-sectional studies), contributing 215 effect estimates for five grouped health outcomes. Compared with polluting fuels, use of gas significantly lowered the risk of pneumonia (OR 0·54, 95% CI 0·38-0·77; p=0·00080), wheeze (OR 0·42, 0·30-0·59; p<0·0001), cough (OR 0·44, 0·32-0·62; p<0·0001), breathlessness (OR 0·40, 0·21-0·76; p=0·0052), chronic obstructive pulmonary disease (OR 0·37, 0·23-0·60; p<0·0001), bronchitis (OR 0·60, 0·43-0·82; p=0·0015), pulmonary function deficit (OR 0·27, 0·17-0·44; p<0·0001), severe respiratory illness or death (OR 0·27, 0·11-0·63; p=0·0024), preterm birth (OR 0·66, 0·45-0·97; p=0·033), and low birth weight (OR 0·70, 0·53-0·93; p=0·015). Non-statistically significant effects were observed for asthma in children (OR 1·04, 0·70-1·55; p=0·84), asthma in adults (OR 0·65, 0·43-1·00; p=0·052), and small for gestational age (OR 1·04, 0·89-1·21; p=0·62). Compared with electricity, use of gas significantly increased risk of pneumonia (OR 1·26, 1·03-1·53; p=0·025) and chronic obstructive pulmonary disease (OR 1·15, 1·06-1·25; p=0·0011), although smaller non-significant effects were observed for higher-quality studies. In addition, a small increased risk of asthma in children was not significant (OR 1·09, 0·99-1·19; p=0·071) and no significant associations were found for adult asthma, wheeze, cough, and breathlessness (p>0·05). A significant decreased risk of bronchitis was observed (OR 0·87, 0·81-0·93; p<0·0001).

Interpretation: Switching from polluting fuels to gaseous household fuels could lower health risk and associated morbidity and mortality in resource-poor countries where reliance on polluting fuels is greatest. Although gas fuel use was associated with a slightly higher risk for some health outcomes compared with electricity, gas is an important transitional option

for health in countries where access to reliable electricity supply for cooking or heating is not feasible in the near term.

Environ Res. 2024 Jun 1:250:118488.
doi: 10.1016/j.envres.2024.118488. Epub 2024 Feb 20.

The effect of chimney fitted improved stove on kitchen fine particulate matter (PM2.5) concentrations in rural Ethiopia: Evidence from a randomized controlled trial

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Abstract

Background: Millions of Ethiopian people cook with biomass fuels using traditional stoves, releasing harmful pollutants and contributing to a significant public health crisis. Improved stoves offer a potential escape route, but their effectiveness needs close scrutiny. This study delves into the impact of chimney-fitted stoves on kitchen $PM_{2.5}$ concentrations in rural Ethiopian households.

Method: We conducted a randomized controlled trial with 86 households equally divided (1:1 ratio) between intervention and control groups. The 24-h average kitchen $PM_{2.5}$ concentrations was measured using Particle and Temperature Sensor (PATS+) at baseline and after intervention. All relevant sociodemographic and cooking related characteristics were collected at baseline and dynamic characteristics were updated during air monitoring visits. Three distinct statistical models, including independent sample t-tests, paired sample t-tests and one-way analysis of variance were used to analyze the data using Statistical Package for the Social Sciences (SPSS) software for Windows (v 24.0).

Result: At baseline, the average 24-h kitchen $PM_{2.5}$ concentrations were 482 μg/m^3 (95% CI: 408, 557) for the control and 405 μg/m^3 (95% CI: 318, 492) for the intervention groups. Despite remaining elevated at 449 μg/m3 (95% CI: 401, 496) in the control group, $PM_{2.5}$ concentrations reduced to 104 μg/m3 (95% CI: 90,118) in the intervention group, indicating a statistically significant difference ($t = 6.97$, $p < 0.001$). All three statistical analyses delivered remarkably consistent results, estimating a $PM_{2.5}$ reductions of 74% with the before-and-after approach, 76% when comparing groups, and 74% for difference in difference analysis. Beyond the overall reduction, homes with primary school completed women, larger kitchens, smaller family size, and those specifically baking Injera (the traditional energy-intensive staple food), witnessed even greater drops in $PM_{2.5}$ levels.

Conclusion: Pregnant women in our study encountered dangerously high $PM_{2.5}$ exposures in their kitchens. While the intervention achieved a significant $PM_{2.5}$ reductions, unfortunately remained above the WHO's safe limit, highlighting the need for further interventions.

Exercise and physical activity

J Phys Act Health. 2023 Aug 22;20(12):1102-1108.
doi: 10.1123/jpah.2023-0062. Print 2023 Dec 1.

Effects of a School-Based Physical Activity Intervention on Adolescents' Mental Health: A Cluster Randomized Controlled Trial

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Abstract

Background: The aim of this study was to evaluate the effectiveness of a school-based multicomponent physical activity intervention on mental health of adolescents.

Methods: A clustered, randomized, controlled trial was employed in 8 high schools in Dhaka, Bangladesh, which were randomly assigned to either an intervention or control group; 40 students in grades 8 and 9 from each school took part in the trial (n = 160/group). Students in the intervention schools participated in a 12-week physical activity intervention with multiple components (eg, supervised circuits, lunchtime sports, health education, infographics), while control schools received no intervention. Participants completed baseline and postintervention surveys measuring depressive symptoms (Center for Epidemiologic Studies Depression Scale) and life satisfaction (Cantril Ladder), along with other sociodemographic and behavioral characteristics. Linear mixed-effects modeling was used to evaluate the intervention effects.

Results: Depressive symptoms in the intervention group decreased at postintervention, but remained stable in the control group. There was an increase in life satisfaction in the intervention group and a decrease in the control group. Multivariable modeling showed that students in the intervention group had a significantly lower level of depressive symptoms (β = -4.60; 95% confidence interval, -5.76 to -3.46) and higher level of life satisfaction (β = 1.43; 95% confidence interval, 0.77 to 2.10) compared with their counterparts in the control group. Sensitivity analyses supported the positive effects of the intervention.

Conclusions: Our school-based, multicomponent physical activity intervention is effective in improving mental health indicators in adolescents. Future trials should be ramped up to include schools in rural and regional settings, using robust measures of mental well-being.

Am J Prev Med. 2024 Feb 1:S0749-3797(24)00027-8.
doi: 10.1016/j.amepre.2024.01.017. Online ahead of print.

Randomized Trial to Improve Body Composition and Micronutrient Status Among South African Children

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Abstract

Introduction: Physical activity (PA) promotion combined with multimicronutrient supplementation (MMNS) among school-age children may reduce fat mass accrual and increase muscle mass through different mechanisms and so benefit child health. This study determined the efficacy of combined interventions on body composition among South African schoolchildren and determined if micronutrients mediate these effects.

Study design: Longitudinal cluster randomized controlled trial of children followed from 2019 to 2021. Statistical analyses carried from 2022 to 2023.

Setting/participants: A total of 1,304 children 6-12 years of age recruited from public schools in Gqeberha, South Africa.

Intervention: Children were randomized by classes to either: (a) a physical activity group (PA); (b) a MMNS group; (c) a physical activity + multimicronutrient supplementation group (PA + MMNS); and (d) a placebo control group.

Main outcome measures: Trajectories of overall and truncal fat free mass (FFM) and fat mass (FM) estimates in modeled at 9 and 21 months using latent growth curve models (LGCM). Changes in micronutrient concentrations at 9 months from baseline.
Results: An increased FFM trajectory was found among children in the MMNS arm at 9 months (Beta 0.16, 95% CI = 0.12, 0.31). The PA and MMNS arms both had positive indirect effects on this trajectory at 9 months (Beta 0.66, 95% CI = 0.44, 0.88 and Beta 0.32 95% CI = 0.1 0.5, respectively) and similarly at 21 months when mediated by zinc concentration changes. A reduced FM trajectory was found among children in the PA promotion arm at 9 months when using this collection point as the referent intercept. This arm was inversely associated with the FM trajectory at 9 months when mediated by zinc changes.
Conclusions: PA and MMNS promotion in school-based interventions directly contributed to reductions in FM and increased FFM among South African children and indirectly through changes in micronutrient status.

BMC Pediatr. 2024 May 29;24(1):371.
doi: 10.1186/s12887-024-04845-5.

Sustainable effects of a motor skill programme on physical activity levels in 7-8 years old children, in the Eastern Cape Province of South Africa

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Abstract
Background: Deteriorating global physical activity (PA) levels among children warrants new and sustainable approaches to increase PA levels. This study aimed to determine the immediate and sustainable influences of a 9-week movement program on the PA levels in 7 to 8-year-old school children in the Raymond Mhlaba Municipality in the Eastern Cape Province of South Africa.
Methods: A randomized control trial including two groups (control group (CG) and intervention group (IG)), pre-post-retest (after six months of no intervention) design was used. Seventy school children, mean age 7.12 years (± 0.71) (n = 35 IG; n = 35 CG) participated in the study. A 9-week movement program was followed twice a week for 30 min during school hours. PA was measured for 7 consecutive days using a hip-mounted wGT3X-BT Actigraph accelerometer. The Test of Gross Motor Development-Third Edition (TGMD-3) was used to assess motor skills. Hierarchical Linear Modelling (HLM) was applied to analyze the data with time, sex, and group as predictors. Effect sizes were computed using Cohen's d-cut points to assess the practical significance of changes over time. Estimated regression coefficients were also computed to determine the strength of the relationship between moderate-to-vigorous physical activity (MVPA) and fundamental movement skills (FMS).
Results: Before the intervention, 60% of the IG met the 60 min of daily MVPA guideline, while light physical activity (LPA) per day was also higher than sedentary behavior (SB) in both groups. No immediate ($p < 0.01$) or sustainable ($p < 0.01$) increases in MVPA levels were found and no positive associations emerged between FMS and MVPA levels.
Conclusions: This intervention had little to no effect on children's MVPA. More understanding of the activity behavior and interests of children is needed to improve their PA behavior through the content of movement programs. Strategies are also needed to communicate clear messages at a personalized but also parental level, focusing on enhancing health through regular PA, especially to promote PA in young children.

J Phys Act Health. 2023 Nov 6:1-9.
doi: 10.1123/jpah.2023-0182. Online ahead of print.

Effect of Yoga or Physical Exercise on Muscle Function in Rural Indian Children: A Randomized Controlled Trial

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Abstract

Background: Synergistic effects of yoga or physical exercise (PE) along with protein supplementation on children's muscle function in rural India have not been studied. Hence, we aimed to study the effect of yoga and PE along with protein supplementation on muscle function in healthy 6- to 11-year-old rural Indian children post 6 months of intervention.

Methods: A randomized controlled trial on 232 children, recruited into 3 groups, each receiving 1 protein-rich ladoo (148 kcal, 7 g protein/40 g ladoo-an Indian sweet snack) daily and performing (1) yoga (n = 78) for 30 minutes 5 times per week, (2) PE (n = 76) for 30 minutes 5 times per week, or (3) control group (n = 78) no additional exercise. Maximum power, maximum voluntary force (Fmax), and grip strength (GS) were measured. Data were analyzed using paired t tests and a 2-way mixed analysis of variance with post hoc Bonferroni adjustment.

Results: GS, maximum power, and Fmax within yoga group increased significantly (P < .05) from baseline to endline. GS and Fmax increased significantly within PE group postintervention (P < .001). In controls, GS increased (P < .05) at endline. No significant effect of the intervention was observed on the change in maximum power (P > .05) postintervention. The 2 exercise groups showed significant increase in Fmax compared with the control group (P < .05). Similarly, increase in GS was significantly higher in both the exercise groups compared with the control group (P < .05). No significant difference was observed in change in muscle function between the 2 exercise groups (P > .05).

Conclusions: Structured physical activity along with protein supplementation resulted in improved muscle function in children. Yoga and PE showed a comparable impact on muscle force.

Family planning

Lancet Glob Health. 2023 Dec;11(12):e1943-e1954.
doi: 10.1016/S2214-109X(23)00453-9.

Partnerships with religious leaders to promote family planning in rural Tanzania: an open-label, cluster randomised trial

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Abstract

Background: Family planning benefits maternal-child health, education, and economic wellbeing. Despite global efforts, an unsatisfied demand for family planning persists in sub-Saharan Africa. Based on previous successful partnerships, the aim of this study was to determine whether an educational intervention for religious leaders would increase community knowledge, demand for, and ultimately uptake of family planning.
Methods: In this open-label, cluster randomised trial in Tanzania, 24 communities were randomised (1:1) to intervention or control arm. Communities, defined as the catchment area of a single public health facility, were eligible if they were at least 15 km from Mwanza City and had not previously participated in a health intervention for religious leaders. Random allocations were determined by coin toss and were not revealed to clinicians at health facilities in intervention and control communities, nor to the data entry team; however, due to the nature of the intervention, masking of religious leaders in the intervention communities was not possible. All Christian religious institutions were invited to send four leaders to an educational intervention that incorporated cultural, theological, and medical teaching about family planning. The primary outcome was contraceptive uptake at the community health facility during the year post intervention versus the year before the intervention. This trial was registered at clinicaltrials.gov, NCT03594305.
Findings: 75 communities in three districts were assessed for eligibility. 19 communities were excluded and 56 were eligible for study inclusion and were placed in random order to be invited to participate. The first 24 communities that were invited agreed to participate and were randomly assigned to receive the educational intervention either during the trial or after trial completion. Between July 10, 2018 and Dec 11, 2021, we provided the intervention in 12 communities and compared contraceptive uptake with 12 control communities. All were followed up for 12 months. In intervention communities, contraceptive uptake increased by a factor of 1·47 (95% CI 1·41-1·53) in the post-intervention (prospective) versus pre-intervention (historical) year (geometric mean of contraceptive uptake, 466 in the prospective year vs 312 in the historical year), versus 1·24 (95% CI 1·20-1·29) in control communities (geometric mean, 521 in the prospective year vs 429 in the historical year). The rate of change in contraceptive uptake was greater in intervention communities (between-group ratio of geometric mean ratios over time, 1·19 [95% CI 1·12-1·25]; p<0·0001). The COVID-19 pandemic was associated with decreased contraceptive uptake (geometric mean, 365 during the pandemic in communities that had the majority of their prospective 12-month data collection periods occur after March 16, 2020, vs 494 before the pandemic; geometric mean ratio, 0·72 [95% CI 0·57-0·90]; p=0·0040).
Interpretation: This intervention offers a scalable model, leveraging influence of trusted religious leaders to increase knowledge and uptake of family planning. New strategies such as this could help to overcome setbacks that occurred during the COVID-19 pandemic.

Fever

Clin Infect Dis. 2023 Jul 25;77(Suppl 2):S156-S170.
doi: 10.1093/cid/ciad341.

Impact of the Introduction of a Package of Diagnostic Tools, Diagnostic Algorithm, and Training and Communication on Outpatient Acute Fever Case Management at 3 Diverse Sites in Uganda: Results of a Randomized Controlled Trial

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Abstract

Background: Increasing trends of antimicrobial resistance are observed around the world, driven in part by excessive use of antimicrobials. Limited access to diagnostics, particularly in low- and middle-income countries, contributes to diagnostic uncertainty, which may promote unnecessary antibiotic use. We investigated whether introducing a package of diagnostic tools, clinical algorithm, and training-and-communication messages could safely reduce antibiotic prescribing compared with current standard-of-care for febrile patients presenting to outpatient clinics in Uganda.

Methods: This was an open-label, multicenter, 2-arm randomized controlled trial conducted at 3 public health facilities (Aduku, Nagongera, and Kihihi health center IVs) comparing the proportions of antibiotic prescriptions and clinical outcomes for febrile outpatients aged ≥1 year. The intervention arm included a package of point-of-care tests, a diagnostic and treatment algorithm, and training-and-communication messages. Standard-of-care was provided to patients in the control arm.

Results: A total of 2400 patients were enrolled, with 49.5% in the intervention arm. Overall, there was no significant difference in antibiotic prescriptions between the study arms (relative risk [RR]: 1.03; 95% CI: .96-1.11). In the intervention arm, patients with positive malaria test results (313/500 [62.6%] vs 170/473 [35.9%]) had a higher RR of being prescribed antibiotics (1.74; 1.52-2.00), while those with negative malaria results (348/688 [50.6%] vs 376/508 [74.0%]) had a lower RR (.68; .63-.75). There was no significant difference in clinical outcomes.

Conclusions: This study found that a diagnostic intervention for management of febrile outpatients did not achieve the desired impact on antibiotic prescribing at 3 diverse and representative health facility sites in Uganda.

Clin Infect Dis. 2023 Jul 25;77(Suppl 2):S145-S155.
doi: 10.1093/cid/ciad328.

Impact of Point-of-Care Rapid Diagnostic Tests on Antibiotic Prescription Among Patients Aged <18 Years in Primary Healthcare Settings in 2 Peri-Urban Districts in Ghana: Randomized Controlled Trial Results

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Abstract

Background: Inappropriate antibiotic prescriptions are a known driver of antimicrobial resistance in settings with limited diagnostic capacity. This study aimed to assess the impact of diagnostic algorithms incorporating rapid diagnostic tests on clinical outcomes and antibiotic prescriptions compared with standard-of-care practices, of acute febrile illness cases at outpatient clinics in Shai-Osudoku and Prampram districts in Ghana.

Methods: This was an open-label, centrally randomized controlled trial in 4 health facilities. Participants aged 6 months to <18 years of both sexes with acute febrile illness were

randomized to receive a package of interventions to guide antibiotic prescriptions or standard care. Clinical outcomes were assessed on day 7.
Results: In total, 1512 patients were randomized to either the intervention (n = 761) or control (n = 751) group. Majority were children aged <5 years (1154 of 1512, 76.3%) and male (809 of 1512, 53.5%). There was 11% relative risk reduction of antibiotic prescription in intervention group (RR, 0.89; 95% CI, .79 to 1.01); 14% in children aged <5 years (RR, 0.86; 95% CI, .75 to .98), 15% in nonmalaria patients (RR, 0.85; 95% CI, .75 to .96), and 16% in patients with respiratory symptoms (RR, 0.84; 95% CI, .73 to .96). Almost all participants had favorable outcomes (759 of 761, 99.7% vs 747 of 751, 99.4%).
Conclusions: In low- and middle-income countries, the combination of point-of-care diagnostics, diagnostic algorithms, and communication training can be used at the primary healthcare level to reduce antibiotic prescriptions among children with acute febrile illness, patients with nonmalarial fevers, and respiratory symptoms.

Clin Infect Dis. 2023 Jul 25;77(Suppl 2):S134-S144.
doi: 10.1093/cid/ciad331.

A Randomized Trial to Assess the Impact of a Package of Diagnostic Tools and Diagnostic Algorithm on Antibiotic Prescriptions for the Management of Febrile Illnesses Among Children and Adolescents in Primary Health Facilities in Burkina Faso

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Abstract
Background: Low- and middle-income countries face significant challenges in differentiating bacterial from viral causes of febrile illnesses, leading to inappropriate use of antibiotics. This trial aimed to evaluate the impact of an intervention package comprising diagnostic tests, a diagnostic algorithm, and a training-and-communication package on antibiotic prescriptions and clinical outcomes.
Methods: Patients aged 6 months to 18 years with fever or history of fever within the past 7 days with no focus, or a suspected respiratory tract infection, arriving at 2 health facilities were randomized to either the intervention package or standard practice. The primary outcomes were the proportions of patients who recovered at day 7 (D7) and patients prescribed antibiotics at day 0.
Results: Of 1718 patients randomized, 1681 (97.8%; intervention: 844; control: 837) completed follow-up: 99.5% recovered at D7 in the intervention arm versus 100% in standard practice (P = .135). Antibiotics were prescribed to 40.6% of patients in the intervention group versus 57.5% in the control arm (risk ratio: 29.3%; 95% CI: 21.8-36.0%; risk difference [RD]: -16.8%; 95% CI: -21.7% to -12.0%; P < .001), which translates to 1 additional antibiotic prescription saved every 6 (95% CI: 5-8) consultations. This reduction was significant regardless of test results for malaria, but was greater in patients without malaria (RD: -46.0%; -54.7% to -37.4%; P < .001), those with a respiratory diagnosis (RD: -38.2%; -43.8% to -32.6%; P < .001), and in children 6-59 months old (RD: -20.4%; -26.0% to -14.9%; P < .001). Except for the period July-September, the reduction was consistent across the other quarters (P < .001).
Conclusions: The implementation of the package can reduce inappropriate antibiotic prescription without compromising clinical outcomes.

Clin Infect Dis. 2023 Jul 25;77(Suppl 2):S199-S205.
doi: 10.1093/cid/ciad324.

Synthesis and Meta-analysis of 3 Randomized Trials Conducted in Burkina Faso, Ghana, and Uganda Comparing the Effects of Point-of-Care Tests and Diagnostic Algorithms Versus Routine Care on Antibiotic Prescriptions and Clinical Outcomes in Ambulatory Patients <18 Years of Age With Acute Febrile Illness

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Abstract

This meta-analysis included 3 randomized trials conducted in sub-Saharan Africa comparing the effects of point-of-care tests and diagnostic algorithms versus routine care on antibiotic prescriptions and clinical outcomes in ambulatory patients presenting at outpatient facilities with acute uncomplicated febrile illness.

Fluid management

Indian J Pediatr. 2023 Dec 29.
doi: 10.1007/s12098-023-04925-x. Online ahead of print.

Additional Bicarbonate Infusion Complements WHO Rehydration Therapy in Children with Acute Diarrhea and Severe Dehydration Presenting with Severe Non-anion Gap Metabolic Acidemia: An Open Label Randomized Trial

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Abstract

Objectives: To assess the efficacy and safety of bicarbonate infusion in children with Acute Diarrhea and Severe Dehydration (ADSD) having severe Non-Anion Gap Metabolic Acidemia (sNAGMA).

Methods: Children (aged 1-144 mo) with ADSD and sNAGMA (pH ≤7.2 and/or serum bicarbonate ≤15 mEq/L) were enrolled in an open-label randomized design. Controls (n = 25) received WHO-recommended rehydration therapy with Ringer Lactate, while intervention group (n = 25) received additional bicarbonate deficit correction. Primary outcome was time taken to resolve metabolic acidemia (pH >7.30 and/or bicarbonate >15 mEq/L). Secondary outcome measures were adverse outcome [composite of pediatric intensive care unit (PICU) transfer and deaths], acute care area free days in 5 d ($ACAFD_5$), hospital stay, and adverse effects.

Results: Time taken to resolve metabolic acidemia was significantly lesser with intervention [median (IQR); 8 h (4, 12) vs. 12 h (8, 24); p = 0.0067]. Intervention led to acidemia resolution in significantly more children by 8 h and 16 h (17/25 vs. 9/25, p = 0.035 and 23/25 vs. 17/24, p = 0.018, respectively). Patients with fluid refractory shock needed lesser inotropes in intervention group [median Vasoactive Inotrope Score (VIS), 10.5 vs. 34]. Intervention led to

significantly lesser adverse outcome (0/25 vs. 5/25, p = 0.049), and noticeably more $ACAFD_5$ [median (IQR); 2 (1, 2) vs. 1 (1, 2); p = 0.12]. Two patients died in the control group while none in the intervention group. No adverse effect was documented.
Conclusions: Additional calculated dose of bicarbonate infusion led to significantly early resolution of metabolic acidemia, lesser utilization of critical care facilities, and lesser adverse outcome in children with ADSD and sNAGMA, compared to standard therapy, with no adverse effect.

Indian J Pediatr. 2023 Oct 18.
doi: 10.1007/s12098-023-04867-4. Online ahead of print.
Restricted versus Usual/Liberal Maintenance Fluid Strategy in Mechanically Ventilated Children: An Open-Label Randomized Trial (ReLiSCh Trial)
Shubham Charaya [1], Suresh Kumar Angurana [2], Karthi Nallasamy [3], Muralidharan Jayashree [3]
Abstract
Objectives: To assess the impact of restricted vs. usual/liberal maintenance fluid strategy on fluid overload (FO) among mechanically ventilated children.
Methods: This open-label randomized controlled trial was conducted over a period of 1 y (October 2020-September 2021) in a Pediatric intensive care unit (PICU) in North India. Hemodynamically stable mechanically ventilated children were randomized to 40% (restricted group, n = 50) and 70-80% (usual/liberal group, n = 50) of maintenance fluids. The primary outcome was cumulative fluid overload percentage (FO%) on day 7. Secondary outcomes were FO% >10%; vasoactive inotropic score, sequential organ failure assessment score, pediatric logistic organ dysfunction score and oxygenation index from day 1-7; ventilation free days (VFDs) and PICU free days (PFDs) through day 28; and mortality.
Results: The restricted group had statistically non-significant trend towards lower cumulative FO% at day 7 [7.6 vs. 9.5, p = 0.40]; and proportion of children with FO% >10% (12% vs. 26%, p = 0.21) as compared to usual/liberal group. The increase in FO% from day 1-7 was significant in usual/liberal group as compared to restricted group (p <0.001 and p = 0.134, respectively). Restricted group received significantly lower amount of fluid in the first 5 d; had significantly higher VFDs (23 vs. 17 d, p = 0.008) and PFDs (19 vs. 15 d, p = 0.007); and trend towards lower mortality (8% vs. 16%, p = 0.21).
Conclusions: Restricted as compared to usual/liberal maintenance fluid strategy among mechanically ventilated children was associated with a trend towards lower rate and severity of FO and mortality; and significantly lower fluid volume received, and higher VFDs and PFDs.

Indian J Pediatr. 2024 Feb 26.
doi: 10.1007/s12098-024-05059-4. Online ahead of print.
Pattern of Fluid Overload and its Impact on Mortality Among Mechanically Ventilated Children: Secondary Analysis of the ReLiSCh Trial
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Abstract
Objectives: To assess the pattern of fluid overload (FO) and its impact on mortality among mechanically ventilated children.
Methods: In this secondary analysis of an open-label randomized controlled trial (ReLiSCh trial, October 2020-September 2021), hemodynamically stable mechanically ventilated children (n = 100) admitted to a tertiary level pediatric intensive care unit (PICU) in North India were enrolled. The primary outcome was pattern of FO (FO% >10% and cumulative FO% from day 1-7); and secondary outcomes were pattern of FO among survivors and non-survivors, and prescription practices of maintenance fluid.
Results: The median (IQR) age was 3.5 (0.85-7.5) y and 57% were males. Common diagnoses were pneumonia (27%), scrub typhus (14%), Landry-Guillain-Barré syndrome (9%), dengue (8%), central nervous system infections (7%) and staphylococcal sepsis (6%). Common organ dysfunction included acute respiratory distress syndrome (ARDS) (41%), shock (38%), and acute kidney injury (AKI) (9%). The duration PICU stay was 11 (7-17) d and mortality was 12%. The FO% >10% was noted in 19% children; and there was significant increase in cumulative FO% from day 1-7 [1.2 (0.2-2.6)% to 8.5 (1.7-14.3)%, (p = 0.000)]. Among non-survivors, higher proportion had FO% >10% (66.7% vs. 12.5%, p 0.0001); and trend towards higher cumulative FO% on first seven days. From day 1-7, the percentage of maintenance fluid received increased from 60 (50-71)% to 70 (60-77)% (p = 0.691).
Conclusions: One-fifth of mechanically ventilated children had FO% >10% and there was significant increase in cumulative FO% from day 1-7. Non-survivors had significantly higher degree of FO.

Paediatr Anaesth. 2024 Feb 13.
doi: 10.1111/pan.14856. Online ahead of print.

Goal-directed fluid therapy guided by plethysmographic variability index versus conventional liberal fluid therapy in neonates undergoing abdominal surgery: A prospective randomized controlled trial

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Abstract
Background: Intraoperative fluid therapy maintains normovolemia, normal tissue perfusion, normal metabolic function, normal electrolytes, and acid-base status. Plethysmographic variability index has been shown to predict fluid responsiveness but its role in guiding intraoperative fluid therapy is still elusive.
Aims: The aim of the present study was to compare intraoperative goal-directed fluid therapy based on plethysmographic variability index with liberal fluid therapy in term neonates undergoing abdominal surgeries.
Methods: A prospective randomized controlled study was conducted in a tertiary care centre, over a period of 18 months. A total of 30 neonates completed the study out of 132 neonates screened. Neonates with tracheoesophageal fistula, congenital diaphragmatic hernia, congenital heart disease, respiratory disorders, creatinine clearance <90 mL/min and who were hemodynamically unstable were excluded. Neonates were randomized to goal-directed fluid therapy group where the plethysmographic variability index was targeted at <18 or liberal fluid therapy group. Primary outcome was comparison of total amount of fluid

infused intraoperatively in both the groups. Secondary outcomes included intraoperative and postoperative arterial blood gas parameters, biochemical parameters, use of vasopressors, number of fluid boluses, complications and duration of hospital stay.
Results: There was no significant difference in total intraoperative fluid infused [90 (84-117.5 mL) in goal-directed fluid therapy and 105 (85.5-144.5 mL) in liberal fluid therapy group (p = .406)], median difference (95% CI) -15 (-49.1 to 19.1). There was a decrease in serum lactate levels in both groups from preoperative to postoperative 24 h. The amount of fluid infused before dopamine administration was significantly higher in liberal fluid therapy group (58 [50.25-65 mL]) compared to goal-directed fluid therapy group (36 [22-44 mL], p = .008), median difference (95% CI) -22 (-46 to 2). In postoperative period, the total amount of fluid intake over 24 h was comparable in two groups (222 [204-253 mL] in goal-directed fluid therapy group and 224 [179.5-289.5 mL] in liberal fluid therapy group, p = .917) median difference (95% CI) cutoff -2 (-65.3 to 61.2).
Conclusion: Intraoperative plethysmographic variability index-guided goal-directed fluid therapy was comparable to liberal fluid therapy in terms of total volume of fluid infused in neonates during perioperative period. More randomized controlled trials with higher sample size are required.

Crit Care Med. 2023 Nov 1;51(11):1449-1460.
doi: 10.1097/CCM.0000000000005952. Epub 2023 Jun 9.

Multiple Electrolytes Solution Versus Saline as Bolus Fluid for Resuscitation in Pediatric Septic Shock: A Multicenter Randomized Clinical Trial

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Abstract
Objective: To determine if initial fluid resuscitation with balanced crystalloid (e.g., multiple electrolytes solution [MES]) or 0.9% saline adversely affects kidney function in children with septic shock.
Design: Parallel-group, blinded multicenter trial.
Setting: PICUs of four tertiary care centers in India from 2017 to 2020.
Patients: Children up to 15 years of age with septic shock.
Methods: Children were randomized to receive fluid boluses of either MES (PlasmaLyte A) or 0.9% saline at the time of identification of shock. All children were managed as per standard protocols and monitored until discharge/death. The primary outcome was new and/or progressive acute kidney injury (AKI), at any time within the first 7 days of fluid resuscitation. Key secondary outcomes included hyperchloremia, any adverse event (AE), at 24, 48, and 72 hours, and all-cause ICU mortality.
Interventions: MES solution (n = 351) versus 0.9% saline (n = 357) for bolus fluid resuscitation during the first 7 days.
Measurements and main results: The median age was 5 years (interquartile range, 1.3-9); 302 (43%) were girls. The relative risk (RR) for meeting the criteria for new and/or progressive AKI was 0.62 (95% CI, 0.49-0.80; p < 0.001), favoring the MES (21%) versus the saline (33%)

group. The proportions of children with hyperchloremia were lower in the MES versus the saline group at 24, 48, and 72 hours. There was no difference in the ICU mortality (33% in the MES vs 34% in the saline group). There was no difference with regard to infusion-related AEs such as fever, thrombophlebitis, or fluid overload between the groups.
Conclusions: Among children presenting with septic shock, fluid resuscitation with MES (balanced crystalloid) as compared with 0.9% saline resulted in a significantly lower incidence of new and/or progressive AKI during the first 7 days of hospitalization.

J Pediatr Gastroenterol Nutr. 2024 Feb;78(2):360-368.
doi: 10.1002/jpn3.12082. Epub 2023 Dec 11.

Faster discharge with lactated ringers than normal saline in first 72 h of acute pancreatitis: A multicenter randomized trial

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Abstract
Objectives: Data driven strategies for acute pancreatitis (AP) in pediatrics are limited; adult data suggests lactated ringers (LR) compared to normal saline (NS) resulted in favorable outcomes, but has not been studied in pediatrics. Our objective was to evaluate the efficacy of LR during the first 48 h of an AP episode compared with NS.
Study design: A multisite randomized controlled clinical trial, from 2015 to 2020 (Clinical Trials.gov NCT03242473). Patients were randomized to exclusively LR or NS for the first 48 h. Primary outcomes were serial C-reactive protein (CRP) values. Secondary outcomes included other lab values, time to feeds, length of stay (LOS), systemic inflammatory response syndrome (SIRS) development, and progression to severe AP (SAP).
Results: We studied 76 patients (38 LR, 38 NS). CRP at 24 and 48 h were not significantly different between LR or NS group. Additionally, there were no differences in trends of BUN, amylase, lipase, SIRS status, or SAP development between the LR and NS group at 24 and 48 h. A higher proportion of LR patients (32%, 12/38) were discharged before 48 h compared to NS (13%, 5/38). The LR group had a significantly higher rate of discharge within the first 72 h compared to the NS group ($p = 0.02$).
Conclusion: The use of LR was associated with a faster rate of discharge during the intervention period and in the first 72 h, but no other differences compared to NS. This reduction in length of hospitalization has significant implications for patients and healthcare costs.

Health promotion

Health services

Appl Nurs Res. 2023 Dec:74:151744.
doi: 10.1016/j.apnr.2023.151744. Epub 2023 Oct 4.

Application of "Partnership Care Model" in chronically ill adults and children: A systematic review and dose-response meta-analysis of randomized controlled trials

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Abstract

Background: "Partnership Care Model (PCM)", which is the first partnership conceptual framework founded on the Iranian culture to control chronic diseases, has been recently used in different fields of nursing research with no levels of valid evidence to support its application. Therefore, this systematic review and meta-analysis sought to clarify the impacts of interventions developed based on PCM on quality of life (QoL), sleep quality, anxiety, and depression among adults and children with chronic diseases.

Methods: International data sources (e.g., PubMed, Web of Science, Scopus) and national databases (e.g., SID, MagIran, IranDoc, IRCT) were searched from 2001 to September 23, 2023, to find Randomized Controlled Trials (RCTs) on PCM-driven interventions for the experimental groups versus no intervention or standard care groups. The studies' methodological quality and evidence quality were rated utilizing the Cochrane risk of bias instruction and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Data were pooled by a random-effects approach employing STATA (vers. 11.2).

Result: Eighteen RCTs, reported in 22 publications, were qualified. The PCM compared to the standard care significantly improved the QoL among both adults (10 effect sizes [ESs], mean difference [MD]: 3.17, P < 0.001) and children (4 ESs, MD: 4.45, P < 0.001). Likewise, the intervention enhanced adults' sleep quality (3 ESs, MD: 7.15, P < 0.001). The anxiety of adults and children was also significantly lower in the PCM group (4 ESs, MD: -4.52, P = 0.001; 2 ESs, MD: -4.04, P < 0.001, respectively). However, regarding depression, a significant effect of PCM was found only among children (3 ESs, MD: -7.99, P = 0.011). The methodological quality of the studies and the evidence quality were undesirable.

Conclusion: The PCM had a promising influence on the caring of adults and children suffering from chronic diseases. However, additional high-quality RCTs are needed to generate a higher quality of evidence concerning the clinical benefits of the PCM.

Child Care Health Dev. 2023 Dec 4.
doi: 10.1111/cch.13192. Online ahead of print.

Telehealth services for children with neuro-developmental disabilities in the Asia-Pacific region: A systematic review

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Abstract

Background: In recent years telehealth became a popular and a rational health service delivery approach, especially amidst multiple challenges posed while providing health care interventions during the COVID-19 pandemic.
Aim: We synthesized available evidence on telehealth for managing children with NDDs in the Asia-Pacific region with the aim of identifying successful methods.
Methodology: We systematically reviewed six electronic databases: MEDLINE, AMED, EMBASE, PsychInfo, Web of Science, and (CINAHL plus) using the keywords and database-specific subject headings from their inception to 25th August 2021. Review findings were synthesized narratively, and harvest plots were used to demonstrate the effect of interventions. The protocol and reporting the findings of this review adhered to PRISMA 2020 guidelines. PROSPERO registration: CRD 340690.
Results: We harvested 30,823 records; 17,563 duplicates were removed, and 196 full-text articles were assessed for eligibility. 16 studies with multiple research designs were included in the review. Eight were from the Pacific region and eight represented Asia. The interventions targeted families and children with a variety of NDDs (autism spectrum disorder, Down syndrome, cleft lip and palate, hearing impairment, cerebral palsy etc.) via telehealth. Telehealth packages consisted of direct and indirect methods of synchronous, asynchronous, and hybrid approaches. All studies used parent-led intervention strategies. Telehealth reported a positive effect in 7/16 studies while five showed a neutral effect.
Conclusions: According to published evidence telehealth for children with NDDs is an evolving, evidence-based service facilitation modality in the Asia-Pacific region, with only a few published randomized controlled trials. The systematic review shows promising telehealth practices emerging across the region despite the diversity in NDDs studied.

Health worker education

BMC Health Serv Res. 2024 Feb 8;24(1):177.
doi: 10.1186/s12913-024-10547-6.

Electronic Integrated Management of Childhood Illness (eIMCI): a randomized controlled trial to evaluate an electronic clinical decision-making support system for management of sick children in primary health care facilities in South Africa

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Abstract
Background: Electronic clinical decision-making support systems (eCDSS) aim to assist clinicians making complex patient management decisions and improve adherence to evidence-based guidelines. Integrated management of Childhood Illness (IMCI) provides guidelines for management of sick children attending primary health care clinics and is widely implemented globally. An electronic version of IMCI (eIMCI) was developed in South Africa.
Methods: We conducted a cluster randomized controlled trial comparing management of sick children with eIMCI to the management when using paper-based IMCI (pIMCI) in one district in KwaZulu-Natal. From 31 clinics in the district, 15 were randomly assigned to intervention (eIMCI) or control (pIMCI) groups. Computers were deployed in eIMCI clinics,

and one IMCI trained nurse was randomly selected to participate from each clinic. eIMCI participants received a one-day computer training, and all participants received a similar three-day IMCI update and two mentoring visits. A quantitative survey was conducted among mothers and sick children attending participating clinics to assess the quality of care provided by IMCI practitioners. Sick child assessments by participants in eIMCI and pIMCI groups were compared to assessment by an IMCI expert.
Results: Self-reported computer skills were poor among all nurse participants. IMCI knowledge was similar in both groups. Among 291 enrolled children: 152 were in the eIMCI group; 139 in the pIMCI group. The mean number of enrolled children was 9.7 per clinic (range 7-12). IMCI implementation was sub-optimal in both eIMCI and pIMCI groups. eIMCI consultations took longer than pIMCI consultations (median duration 28 minutes vs 25 minutes; p = 0.02). eIMCI participants were less likely than pIMCI participants to correctly classify children for presenting symptoms, but were more likely to correctly classify for screening conditions, particularly malnutrition. eIMCI participants were less likely to provide all required medications (124/152; 81.6% vs 126/139; 91.6%, p= 0.026), and more likely to prescribe unnecessary medication (48/152; 31.6% vs 20/139; 14.4%, p = 0.004) compared to pIMCI participants.
Conclusions: Implementation of eIMCI failed to improve management of sick children, with poor IMCI implementation in both groups. Further research is needed to understand barriers to comprehensive implementation of both pIMCI and eIMCI.

Haematological disorders

(See also Anaemia and iron deficiency, Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

Sickle cell disease

Lancet Haematol. 2024 Apr 30:S2352-3026(24)00078-4.
doi: 10.1016/S2352-3026(24)00078-4. Online ahead of print.
Hydroxyurea dose optimisation for children with sickle cell anaemia in sub-Saharan Africa (REACH): extended follow-up of a multicentre, open-label, phase 1/2 trial
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Abstract
Background: Realizing Effectiveness Across Continents with Hydroxyurea (REACH) is an open-label non-randomised trial of hydroxyurea (hydroxycarbamide) in children with sickle cell anaemia in sub-Saharan Africa. The short-term results of REACH on safety, feasibility, and effectiveness of hydroxyurea were published previously. In this paper we report results from extended hydroxyurea treatment in the REACH cohort up to 8 years.

Methods: In this open-label, non-randomised, phase 1/2 trial, participants were recruited from four clinical sites in Kilifi, Kenya; Mbale, Uganda; Luanda, Angola; and Kinshasa, Democratic Republic of Congo. Eligible children were 1-10 years old with documented haemoglobin SS or haemoglobin Sβ zero thalassaemia, weighing at least 10 kg. Participants received fixed-dose hydroxyurea of 17.5 (±2.5) mg/kg per day for 6 months (fixed-dose phase), followed by 6 months of dose escalation (2·5-5·0 mg/kg increments every 8 weeks) as tolerated, up to 20-35 mg/kg per day (maximum tolerated dose; MTD), defined as mild myelosuppression. After the MTD was reached, hydroxyurea dosing was optimised for each participant on the basis of changes in bodyweight and laboratory values over time (MTD with optimisation phase). After completion of the first 12 months, children with an acceptable toxicity profile and favourable responses were given the opportunity to continue hydroxyurea until the age of 18 years. The safety and feasibility results after 3 years has been reported previously. Here, haematological responses, clinical events, and toxicity rates were compared across the dosing phases (fixed-dose hydroxyurea vs MTD with optimisation phase) as protocol-specified outcomes. REACH is registered on ClinicalTrials.gov (NCT01966731) and is ongoing.

Findings: We enrolled 635 children between July 4, 2014, and Nov 11, 2016. 606 children were given hydroxyurea and 522 (86%; 266 [51%] boys and 256 [49%] girls) received treatment for a median of 93 months (IQR 84-97) with 4340 patient-years of treatment. The current (Oct 5, 2023) mean dose is 28·2 (SD 5·2) mg/kg per day with an increased mean haemoglobin concentration (7·3 [SD 1·1] g/dL at baseline to 8·5 [1·5] g/dL) and mean fetal haemoglobin level (10·9% [SD 6·8] to 23·3% [9·5]) and decreased absolute neutrophil count (6·8 [3·0] × 10^9 cells per L to 3·6 [2·2] × 10^9 cells per L). Incidence rate ratios (IRR) comparing MTD with fixed-dose hydroxyurea indicate decreased vaso-occlusive episodes (0·60; 95% CI 0·52-0·70; p<0·0001), acute chest syndrome events (0·21; 0·13-0·33; p<0·0001), recurrent stroke events (0·27; 0·07-1·06; p=0·061), malaria infections (0·58; 0·46-0·72; p<0·0001), non-malarial infections (0·52; 0·46-0·58; p<0·0001), serious adverse events (0·42; 0·27-0·67; p<0·0001), and death (0·70; 0·25-1·97; p=0·50). Dose-limiting toxicity rates were similar between the fixed-dose (24·1 per 100 patient-years) and MTD phases (23·2 per 100 patient-years; 0·97; 0·70-1·35; p=0·86). Grade 3 and 4 adverse events were infrequent (18·5 per 100 patient-years) and included malaria infection, non-malarial infections, vaso-occlusive pain, and acute chest syndrome. Serious adverse events were uncommon (3·6 per 100 patient-years) and included malaria infections, parvovirus-associated anaemia, sepsis, and stroke, with no treatment-related deaths.

Interpretation: Hydroxyurea dose escalation to MTD with dose optimisation significantly improved clinical responses and treatment outcomes, without increasing toxicities in children with sickle cell anaemia in sub-Saharan Africa.

SAGE Open Med. 2023 Sep 15:11:20503121231197866.
doi: 10.1177/20503121231197866. eCollection 2023.

Evidence-based interventions for reducing sickle cell disease-associated morbidity and mortality in sub-Saharan Africa: A scoping review

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Abstract

Objective: Sickle cell disease is a lifelong illness affecting millions of people globally, but predominantly burdensome in sub-Saharan Africa, where most affected children do not live to adulthood, despite available evidence-based interventions that reduce the disease burden in high-income countries.
Method: We reviewed studies evaluating evidence-based interventions that decrease sickle cell disease-related morbidity and mortality among children living in sub-Saharan Africa. We used the Joanna Briggs scoping review methodological framework and grouped identified evidence-based interventions into preventative pharmacotherapeutic agents, newborn screening and comprehensive healthcare, disease-modifying agents, nutritional supplementation, systemic treatment, supportive agents and patient/carer/population education.
Results: We included 36 studies: 18 randomized controlled trials, 11 observational studies, 5 before-and-after studies and 2 economic evaluation studies, with most of the studies performed in West African countries. Included studies suggest evidence-based interventions effectively to reduce the common morbidities associated with sickle cell disease such as stroke, vaso-occlusive crisis, acute chest syndrome, severe anaemia and malaria infection. Evidence-based interventions also improve survival among study participants. Specifically, our review shows hydroxyurea increases haemoglobin and foetal haemoglobin levels, a finding with practical implications given the challenges with blood transfusion in this setting. The feasibility of implementing individual interventions is hampered by challenges such as affordability, accessibility and the availability of financial and human resources.
Conclusion: Our review suggests that regular use of low-dose hydroxyurea therapy, sulphadoxine-pyrimethamine chemoprophylaxis, L-arginine and Omega-3 fatty acid supplementation and establishment of specialist stand-alone sickle cell clinics could reduce the sickle cell disease-associated morbidity and mortality in sub-Saharan Africa countries.

Blood Adv. 2023 Jul 11;7(13):3023-3031.
doi: 10.1182/bloodadvances.2022008539.

Zinc for infection prevention in children with sickle cell anemia: a randomized double-blind placebo-controlled trial

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DOI: 10.1182/bloodadvances.2022008539

Abstract

Data from small clinical trials in the United States and India suggest zinc supplementation reduces infection in adolescents and adults with sickle cell anemia (SCA), but no studies of zinc supplementation for infection prevention have been conducted in children with SCA living in Africa. We conducted a randomized double-blind placebo-controlled trial to assess zinc supplementation for prevention of severe or invasive infections in Ugandan children 1.00-4.99 years with SCA. Of 252 enrolled participants, 124 were assigned zinc (10 mg) and 126 assigned placebo once daily for 12 months. The primary outcome was incidence of protocol-defined severe or invasive infections. Infection incidence did not differ between treatment arms (282 vs. 270 severe or invasive infections per 100 person-years, respectively, incidence rate ratio of 1.04 [95% confidence interval (CI), 0.81, 1.32, p=0.78]), adjusting for

hydroxyurea treatment. There was also no difference between treatment arms in incidence of serious adverse events or SCA-related events. Children receiving zinc had increased serum levels after 12-months, but at study exit, 41% remained zinc deficient (<65 µg/dL). In post-hoc analysis, occurrence of stroke or death was lower in the zinc treatment arm (adjusted hazard ratio (95% CI), 0.22 (0.05, 1.00); p=0.05). Daily 10 mg zinc supplementation for 12 months did not prevent severe or invasive infections in Ugandan children with SCA, but many supplemented children remained zinc deficient. Optimal zinc dosing and the role of zinc in preventing stroke or death in SCA warrant further investigation.

Blood Adv. 2023 Oct 24;7(20):6024-6034.
doi: 10.1182/bloodadvances.2023010789.

Feasibility trial for the management of severe acute malnutrition in older children with sickle cell anemia in Nigeria

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Abstract

Children with sickle cell anemia (SCA) living in Nigeria are at an increased risk of malnutrition, which contributes to increased morbidity and mortality. However, evidence-based guidelines for managing malnutrition in children with SCA are lacking. To address this gap, we conducted a multicenter, randomized controlled feasibility trial to assess the feasibility and safety of treating children with SCA aged from 5 to 12 years and having uncomplicated severe acute malnutrition (body mass index z score of <-3.0). Children with SCA and uncomplicated severe acute malnutrition were randomly allocated to receive supplemental ready-to-use therapeutic food (RUTF) with or without moderate-dose hydroxyurea therapy (20 mg/kg per day). Over a 6-month enrollment period, 3190 children aged from 5 to 12 years with SCA were evaluated for eligibility, and 110 of 111 children who were eligible were enrolled. During the 12-week trial, no participants withdrew or missed visits. One participant died of unrelated causes. Adherence was high for hydroxyurea (94%, based on pill counts) and RUTF (100%, based on the number of empty sachets returned). No refeeding syndrome event or hydroxyurea-related myelosuppression occurred. At the end of the trial, the mean change in body mass index z score was 0.49 (standard deviation = 0.53), and 39% of participants improved their body mass index z score to ≥-3.0. Our findings demonstrate the feasibility, safety, and potential of outpatient treatment for uncomplicated severe acute malnutrition in children with SCA aged from 5 to 12 years in a low-resource setting. However, RUTF sharing with household and community members potentially confounded the response to malnutrition treatment.

Thalassaemia

J Pharm Pract. 2023 Aug;36(4):749-755.
doi: 10.1177/08971900211038301. Epub 2022 Apr 27.

Efficacy and Tolerability of Twice-Daily Dosing Schedule of Deferasirox in Transfusion-Dependent Paediatric Beta-Thalassaemia Patients: A Randomized Controlled Study

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Abstract

Background: Deferasirox has proved good efficacy and acceptable safety for the management of thalassaemia patients. However, some patients are unresponsive or intolerant to once-daily administration of deferasirox even at a high dose. The current study evaluated the effectiveness and tolerability of twice-daily dosing of deferasirox among transfusion-dependent paediatric beta-thalassaemia patients. **Methods:** This prospective randomized single-blinded parallel study included all transfusion-dependent paediatric beta-thalassaemia patients prescribed with deferasirox, who visit the study site for their regular blood transfusions and follow-up. The enrolled patients were randomized into intervention and control groups by using a simple block randomization method. In the intervention group, the once-daily dosing of deferasirox was changed to twice-daily dosing with the same total daily dose. Whereas, in the control group, the patients continued with the once-daily deferasirox dosing. The serum ferritin levels of both groups were determined on the enrolment day and after 6 months of follow-up. **Results:** Forty-one patients were included for analysis. A statistically significant mean decrease in serum ferritin levels was detected in the intervention group, while the serum ferritin levels of the control group significantly increased from baseline. The twice-daily dosing of deferasirox was better tolerated by the thalassaemia patients when compared to once-daily dosing. **Conclusion:** This study concludes that twice-daily dosing of deferasirox with the same total daily dose significantly enhances the iron chelation efficacy and tolerability among transfusion-dependent paediatric beta-thalassaemia patients when compared to once-daily regimen.

Heart disease

Rheumatic heart disease

Int J Cardiol. 2024 Mar 15:399:131662.
doi: 10.1016/j.ijcard.2023.131662. Epub 2023 Dec 22.

Outcomes of latent rheumatic heart disease: External validation of a simplified score in patients with and without secondary prophylaxis

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Abstract

Background: Secondary antibiotic prophylaxis reduces progression of latent rheumatic heart disease (RHD) but not all children benefit. Improved risk stratification could refine recommendations following positive screening. We aimed to evaluate the performance of a

previously developed echocardiographic risk score to predict mid-term outcomes among children with latent RHD.
Methods: We included children who completed the GOAL, a randomized trial of secondary antibiotic prophylaxis among children with latent RHD in Uganda. Outcomes were determined by a 4-member adjudication panel. We applied the point-based score, consisting of 5 variables (mitral valve (MV) anterior leaflet thickening (3 points), MV excessive leaflet tip motion (3 points), MV regurgitation jet length ≥ 2 cm (6 points), aortic valve focal thickening (4 points) and any aortic regurgitation (5 points)), to panel results. Unfavorable outcome was defined as progression of diagnostic category (borderline to definite, mild definite to moderate/severe definite), worsening valve involvement or remaining with mild definite RHD.
Results: 799 patients (625 borderline and 174 definite RHD) were included, with median follow-up of 24 months. At total 116 patients (14.5%) had unfavorable outcome per study criteria, 57.8% not under prophylaxis. The score was strongly associated with unfavorable outcome (HR = 1.26, 95% CI 1.16-1.37, p < 0.001). Unfavorable outcome rates in low (≤6 points), intermediate (7-9 points) and high-risk (≥10 points) children at follow-up were 11.8%, 30.4%, and 42.2%, (p < 0.001) respectively (C-statistic = 0.64 (95% CI 0.59-0.69)).
Conclusions: The simple risk score provided an accurate prediction of RHD status at 2-years, showing a good performance in a population with milder RHD phenotypes.

Congenital heart disease and cardiac surgery

BMC Med. 2024 Feb 6;22(1):27.
doi: 10.1186/s12916-023-03242-6.
Effects of 6-month customized home-based exercise on motor development, bone strength, and parental stress in children with simple congenital heart disease: a single-blinded randomized clinical trial
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Abstract
Background: New "noncardiac" problems in children with congenital heart disease (CHD), such as developmental delay or long-term neurodevelopmental impairments, have attracted considerable attention in recent years. It is hypothesized that exercise might attenuate CHD-associated neurodevelopmental impairments; however, this has not been thoroughly investigated. The objective of this prospective, single-blinded, randomized controlled experiment was to evaluate the impact of customized home-based exercise for children with CHD.
Methods: Children aged 0-5 years with echocardiography-confirmed simple CHD subtypes who were scheduled to undergo cardiac catheterization were screened for enrolment. Among 420 screened CHD children, 192 were enrolled and randomly assigned at a 1:1 ratio to receive a 6-month intervention (30 min daily customized home-based exercise program with supervision for no less than 5 days per week, combined with home-based exercise education) or control treatment (home-based education). The primary outcome was motor development (gross motor quotient (GMQ), fine motor quotient (FMQ), and total motor

quotient (TMQ)). The secondary outcomes were cardiac function and structure, bone quality, physical development, parental anxiety, caregiver burden, and quality of life. Children and their families were assessed before and 1, 3, and 6 months after catheterization; 183 (95.3%) children were included in the primary analysis.
Results: After 6-month treatment, the intervention group significantly increased their motor quotient, which was consistently higher than that of the control group (GMQ $p < 0.0001$, FMQ $p = 0.02$, TMQ $p < 0.001$). The physical developments in height, weight, and circumferences of the upper-arm, chest, and head were also significantly improved by exercise (all $p < 0.017$). No significant improvements in the bone strength or the cardiac structure and function were found among patients in the intervention group (all $p > 0.017$). For parents, higher quality of life level (total score $p = 0.016$) was observed in the intervention group; while effects of exercise on the anxiety (rude score $p = 0.159$, standard score $p = 0.159$) or the Zarit caregiver burden scale score ($p = 0.404$) were non-significant. No adverse events occurred during the study period.
Conclusions: Customized home-based exercise improved motor development in children with CHD. While the long-term effects of parent training in home-based exercise are unknown, the study results suggest positive outcomes.

Pediatr Cardiol. 2024 Jun;45(5):1100-1109.
doi: 10.1007/s00246-024-03465-1. Epub 2024 Mar 26.

Triiodothyronine Supplementation for Children Undergoing Cardiopulmonary Bypass: A Meta-Analysis

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Abstract
Specific pediatric populations have exhibited disparate responses to triiodothyronine (T3) repletion during and after cardiopulmonary bypass (CPB). Objective: To determine if T3 supplementation improves outcomes in children undergoing CPB. We searched randomized controlled trials (RCT) evaluating T3 supplementation in children aged 0-3 years undergoing CPB between 1/1/2000 and 1/31/2022. We calculated Hazard ratios (HR) for time to extubation (TTE), ICU length of stay (LOS), and hospital LOS. 5 RCTs met inclusion criteria with available patient-level data. Two were performed in United States (US) and 3 in Indonesia with 767 total subjects (range 29- 220). Median (IQR) age 4.1 (1.6, 8.0) months; female 43%; RACHS-1 scores: 1-1%; 2-55%; 3-27%; 4-13%; 5-0.1%; 6-3.9%; 54% of subjects in US vs 46% in Indonesia. Baseline TSH and T3 were lower in Indonesia ($p < 0.001$). No significant difference occurred in TTE between treatment groups overall [HR 1.09 (CI, 0.94-1.26)]. TTE numerically favored T3-treated patients aged 1-5 months [HR 1.24 (CI, 0.97-1.60)]. TTE HR for the Indonesian T3 group was 1.31 (CI, 1.04-1.65) vs. 0.95 (CI, 0.78-1.15) in US. The ICU LOS HR for the Indonesian T3 group was 1.19 vs. 0.89 in US ($p = 0.046$). There was a significant T3 effect on hospital LOS [HR 1.30 (CI, 1.01-1.67)] in Indonesia but not in US [HR 0.99 (CI, 0.78-1.23)]. T3 supplementation in children undergoing CPB is simple, inexpensive, and safe, showing benefit in resource-limited settings. Differences in effects between settings likely relate to depression in baseline thyroid function often associated with malnutrition.

Curr Probl Cardiol. 2024 Jul;49(7):102567.

doi: 10.1016/j.cpcardiol.2024.102567. Epub 2024 Apr 8.

The effect of individualized nutrition training of children with congenital heart disease (CHD) on their growth and development a randomized controlled trial

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Abstract

Objective: This study investigated the effectiveness of individualized nutrition training for mothers of children who underwent congenital heart disease (CHD) surgery on their children's growth and development.

Methods: The researchers conducted a randomized controlled trial at Çukurova University Medical Faculty Balcalı Hospital in Adana, Turkey, between January 20th, 2021, and June 30th, 2021. They recruited 42 children with CHD and their families. Researchers used a personal information form, growth parameter measurements, and the Ankara Developmental Screening Inventory to assess the children. Participants were randomly divided into three groups. Control group, received standard care. Experimental group 1 (orally fed), received family-centered care and individualized nutrition training focused on age-appropriate food content, preparation methods, and meeting children's caloric needs. Experimental group 2 (orally and nutritionally fed), received the same interventions as group 1. The training programs for the experimental groups included information on strengthening breast milk and additional nutritional nutrition support. The training programs for the experimental groups likely addressed feeding challenges specific to children with CHD.

Results: The study found a statistically significant difference in weight gain between the first and third follow-ups within the training group (children who received individualized nutrition education). This suggests that the training may have positively impacted weight gain. Additionally, the children in the training groups who were breastfed for longer than 12 months had better growth parameters and developmental scores compared to those with shorter breastfeeding durations.

Conclusion: This study suggests that individualized nutrition training for mothers of children with CHD surgery may support their children's growth and development, particularly when combined with prolonged breastfeeding.

HIV / AIDS

HIV diagnosis and disclosure

(See also: Vaccines – BCG vaccine and delayed administration in HIV exposed infants)

J Acquir Immune Defic Syndr. 2023 Dec 1;94(4):371-380.
doi: 10.1097/QAI.0000000000003292.

Pediatric HIV Disclosure Intervention Improves Immunologic Outcome at 48 Weeks: The Sankofa Trial Experience

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Abstract

Background: The World Health Organization recommends disclosure of HIV status to children and adolescents living with HIV (CALWH). HIV disclosure improves adherence to antiretroviral therapy and immunologic and virologic outcomes. However, the prevalence of HIV disclosure is low in sub-Saharan Africa. We assessed the longitudinal effect of the Sankofa Pediatric HIV disclosure intervention on immunologic and virologic outcomes among CALWH in Ghana.
Methods: We conducted a secondary analysis of a two-arm site-randomized clinical trial among CALWH aged 7-18 years. Data were collected at baseline, 24, and 48 weeks. Generalized linear mixed models were used to compare immunologic (CD4) and virologic (viral load) outcomes as both continuous and categorical variables by disclosure status and by intervention group.
Results: Among participants who had their HIV status disclosed during this study, the proportion with CD4 percent >25% increased from 56.5% at baseline to 75.4% at week 48 (P = 0.03), with a slight increase in the undisclosed group (69.5% vs. 74.3%, P = 0.56). In the intervention arm, there was a steady increase in proportion with CD4 percent >25% from 47.1% at baseline to 67.8% at week 48 (P = 0.01) while it remained unchanged in the control arm (80.5% vs. 81.3% [P = 0.89]). Concurrently, declines in detectable viral load were observed in both disclosed (63.3% vs. 51.5%, P = 0.16) and undisclosed (69.9% vs. 62.0%, P = 0.17) groups while the intervention group experienced a meaningful drop from 72.9% to 57.6% at 24 weeks (P = 0.04), which was maintained at 48 weeks.

Lancet HIV. 2024 Jan;11(1):e42-e51.
doi: 10.1016/S2352-3018(23)00265-5.

A community-based child health and parenting intervention to improve child HIV testing, health, and development in rural Lesotho (Early Morning Star): a cluster-randomised, controlled trial

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Abstract
Background: When caregivers live in remote settings characterised by extreme poverty, poor access to health services, and high rates of HIV/AIDS, their caregiving ability and children's development might be compromised. We aimed to test the effectiveness of a community-based child health and parenting intervention to improve child HIV testing, health, and development in rural Lesotho.
Methods: We implemented a matched cluster-randomised, controlled trial in the Mokhotlong district in northeastern Lesotho with 34 community clusters randomly assigned to intervention or wait-list control groups within a pair. Eligible clusters were villages with non-governmental organisation partner presence and an active preschool. Participants were caregiver-child dyads, where the child was 12-60 months old at baseline. The intervention consisted of eight group sessions delivered at informal preschools to all children in each village. Mobile health events were hosted for all intervention (n=17) and control (n=17) clusters, offering HIV testing and other health services to all community members. Primary outcomes were caregiver-reported child HIV testing, child language development, and child attention. Assessments were done at baseline, immediately post-intervention (3 months

post-baseline), and 12 months post-intervention. We assessed child language by means of one caregiver-report measure (MacArthur-Bates Communicative Development Inventory [CDI]) and used two observational assessments of receptive language (the Mullen Scales of Early Learning receptive language subscale, and the Peabody Picture Vocabulary Test 4th edn). Child attention was assessed by means of the Early Childhood Vigilance Task. Assessors were masked to group assignment. Analysis was by intention to treat. This trial was registered with ISRCTN.com, ISRCTN16654287 and is completed.
Findings: Between Aug 8, 2015, and Dec 10, 2017, 1040 children (531 intervention; 509 control) and their caregivers were enrolled in 34 clusters (17 intervention; 17 control). Compared with controls, the intervention group reported significantly higher child HIV testing at the 12-month follow-up (relative risk [RR] 1·46, 95% CI 1·29 to 1·65, p<0·0001), but not immediately post-intervention. The intervention group showed significantly higher child receptive language on the caregiver report (CDI) at immediate (effect size 3·79, 95% CI 0·78 to 6·79, p=0·028) but not at 12-month follow-up (effect size 2·96, 95% CI -0·10 to 5·98, p=0·056). There were no significant group differences for the direct assessments of receptive language. Child expressive language and child attention did not differ significantly between groups.
Interpretation: Integrated child health and parenting interventions, delivered by trained and supervised lay health workers, can improve both child HIV testing and child development.

J Acquir Immune Defic Syndr. 2024 Apr 15;95(5):431-438.
doi: 10.1097/QAI.0000000000003379. Epub 2024 Mar 11.

Integration of HIV Testing in a Community Intervention for Tuberculosis Screening Among Household Contacts of Patients with Tuberculosis in Cameroon and Uganda

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Abstract
Introduction: People living with HIV are considered at higher risk of developing severe forms of tuberculosis (TB) disease. Providing HIV testing to TB-exposed people is therefore critical. We present the results of integrating HIV testing into a community-based intervention for household TB contact management in Cameroon and Uganda.
Methods: Trained community health workers visited the households of index patients with TB identified in 3 urban/semiurban and 6 rural districts or subdistricts as part of a cluster-randomized trial and provided TB screening to all household contacts. Voluntary HIV counseling and testing were offered to contacts aged 5 years or older with unknown HIV status. We describe the cascade of care for HIV testing and the factors associated with the acceptance of HIV testing.
Results: Overall, 1983 household contacts aged 5 years or older were screened for TB. Of these contacts, 1652 (83.3%) did not know their HIV status, 1457 (88.2%) accepted HIV testing, and 1439 (98.8%) received testing. HIV testing acceptance was lower among adults than children [adjusted odds ratio (aOR) = 0.35, 95% confidence interval (CI): 0.22 to 0.55], those living in household of an HIV-positive vs HIV-negative index case (aOR = 0.56, 95% CI: 0.38 to 0.83), and contacts requiring a reassessment visit after the initial TB screening visit vs

asymptomatic contacts (aOR = 0.20, 95% CI: 0.06 to 0.67) and was higher if living in Uganda vs Cameroon (aOR = 4.54, 95% CI: 1.17 to 17.62) or if another contact of the same index case was tested for HIV (aOR = 9.22, 95% CI: 5.25 to 16.18).
Conclusion: HIV testing can be integrated into community-based household TB contact screening and is well-accepted.

Prevention of mother to child transmission of HIV and early infant diagnosis

Lancet. 2024 Apr 6;403(10434):1362-1371.
doi: 10.1016/S0140-6736(23)02464-9. Epub 2024 Mar 11.
Optimised prevention of postnatal HIV transmission in Zambia and Burkina Faso (PROMISE-EPI): a phase 3, open-label, randomised controlled trial
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Abstract
Background: Transmission through breastfeeding accounts for more than half of the unacceptably high number of new paediatric HIV infections worldwide. We hypothesised that, in addition to maternal antiretroviral therapy (ART), extended postnatal prophylaxis with lamivudine, guided by point-of-care assays for maternal viral load, could reduce postnatal transmission.
Methods: We did a phase 3, open-label, randomised controlled trial at four health-care facilities in Zambia and four health-care facilities in Burkina Faso. Mothers with HIV and their breastfed infants without HIV attending the second visit of the Expanded Programme of Immunisation (EPI-2; infant age 6-8 weeks) were randomly assigned 1:1 to intervention or control groups. In the intervention group, maternal viral load was measured using Xpert HIV viral load assay at EPI-2 and at 6 months, with results provided immediately. **Infants whose mothers had a viral load of 1000 copies per mL or higher were started on lamivudine syrup twice per day for 12 months or 1 month after breastfeeding discontinuation.** The control group followed national guidelines for prevention of postnatal transmission of HIV. The primary outcome assessed by modified intention to treat was infant HIV infection at age 12 months, with HIV DNA point-of-care testing at 6 months and at 12 months. This trial is registered with ClinicalTrials.gov (NCT03870438).
Findings: Between Dec 12, 2019 and Sept 30, 2021, 34 054 mothers were screened for HIV. Among them, 1506 mothers with HIV and their infants without HIV, including 1342 mother and infant pairs from Zambia and 164 from Burkina Faso, were eligible and randomly assigned 1:1 to the intervention (n=753) or control group (n=753). At baseline, the median age of the mothers was 30·6 years (IQR 26·0-34·7), 1480 (98·4%) of 1504 were receiving ART, and 169 (11·5%) of 1466 had a viral load ≥1000 copies/mL. There was one case of HIV

transmission in the intervention group and six in the control group, resulting in a transmission incidence of 0·19 per 100 person-years (95% CI 0·005-1·04) in the intervention group and 1·16 per 100 person-years (0·43-2·53) in the control group, which did not reach statistical significance (p=0·066). HIV-free survival and serious adverse events were similar in both groups.

Interpretation: Our intervention, initiated at EPI-2 and based on extended single-drug postnatal prophylaxis guided by point-of-care maternal viral load could be an important strategy for paediatric HIV elimination.

AIDS. 2024 Jul 15;38(9):1304-1313.
doi: 10.1097/QAD.0000000000003878. Epub 2024 Mar 1.

Effects of preterm birth, maternal ART and breastfeeding on 24-month infant HIV-free survival in a randomized trial

Sufia Dadabhai[1,2], Victoria B Chou[3], Mauricio Pinilla[4], Lameck Chinula[5,6], Maxensia Owor[7], Avy Violari[8], Dhayendre Moodley[9], Lynda Stranix-Chibanda[10,11], Taguma Allen Matubu[12], Gift Tafadzwa Chareka[13], Gerhard Theron[12], Aarti Avinash Kinikar[13], Mwangelwa Mubiana-Mbewe[14], Lee Fairlie[15], Raziya Bobat[16], Blandina Theophil Mmbaga[17], Patricia M Flynn[18], Taha E Taha[1], Katie S McCarthy[19], Renee Browning[20], Lynne M Mofenson[21], Sean S Brummel[4], Mary Glenn Fowler[3]; IMPAACT PROMISE 1077BF/FF team

Abstract

Background: IMPAACT 1077BF/FF (PROMISE) compared the safety/efficacy of two HIV antiretroviral therapy (ART) regimens to zidovudine (ZDV) alone during pregnancy for HIV prevention. PROMISE found an increased risk of preterm delivery (<37 weeks) with antepartum triple ART (TDF/FTC/LPV+r or ZDV/3TC/LPV+r) compared with ZDV alone. We assessed the impact of preterm birth, breastfeeding, and antepartum ART regimen on 24-month infant survival.

Methods: We compared HIV-free and overall survival at 24 months for liveborn infants by gestational age, time-varying breastfeeding status, and antepartum ART arm at 14 sites in Africa and India. Kaplan-Meier survival probabilities and Cox proportional hazards ratios were estimated.

Results: Three thousand four hundred and eighty-two live-born infants [568 (16.3%) preterm and 2914 (83.7%) term] were included. Preterm birth was significantly associated with lower HIV-free survival [0.85; 95% confidence interval (CI) 0.82-0.88] and lower overall survival (0.89; 95% CI 0.86-0.91) versus term birth (0.96; 95% CI 0.95-0.96). Very preterm birth (<34 weeks) was associated with low HIV-free survival (0.65; 95% CI 0.54-0.73) and low overall survival (0.66; 95% CI 0.56-0.74). Risk of HIV infection or death at 24 months was higher with TDF-ART than ZDV-ART (adjusted hazard ratio 2.37; 95% CI 1.21-4.64). Breastfeeding initiated near birth decreased risk of infection or death at 24 months (adjusted hazard ratio 0.05; 95% CI 0.03-0.08) compared with not breastfeeding.

Conclusion: Preterm birth and antepartum TDF-ART were associated with lower 24-month HIV-free survival compared with term birth and ZDV-ART. Any breastfeeding strongly promoted HIV-free survival, especially if initiated close to birth. Reducing preterm birth and promoting infant feeding with breastmilk among HIV/antiretroviral drug-exposed infants remain global health priorities.

Lancet Glob Health. 2023 Aug;11(8):e1217-e1224.
doi: 10.1016/S2214-109X(23)00216-4.

Incorporating the HIV Infant Tracking System into standard-of-care early infant diagnosis of HIV services in Kenya: a cost-effectiveness analysis of the HITSystem randomised trial

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Abstract

Background: The HITSystem efficacy trial showed significant improvements in early infant diagnosis retention, return and notification of infant test results, and earlier antiretroviral therapy (ART) initiation compared with standard-of-care early infant diagnosis services in Kenya. This study aimed to analyse data from the HITSystem trial to assess the cost-effectiveness of the intervention in Kenya.

Methods: In this analysis, we extrapolated results from the HITSystem cluster randomised controlled trial to model early infant diagnosis outcomes and cost-effectiveness if the HITSystem was scaled up nationally in Kenya, compared with standard-of-care outcomes. We used a micro-costing method to collect cost data, which were analysed from a health-system perspective, reflecting the investment required to add HITSystem to existing early infant diagnosis services and infrastructure. The base model used to calculate cost-effectiveness was deterministic and calculated the progression of infants through early infant diagnosis. Differences in progression across study arms were used to establish efficacy outcomes. The number of life-years gained per infant successfully initiating ART were based on the Cost Effectiveness of Preventing AIDS Complications model in east Africa. HITSystem cost data were integrated into the model, and the incremental cost-effectiveness ratio was calculated in terms of cost per life-year gained. Sensitivity analyses were done using the deterministic model with triangular stochastic probability functions for key model parameters added. The number of life-years gained was discounted at 3% and costs were adjusted to 2021 values.

Findings: The cost per life-year gained from the HITSystem was US$82·72. Total cost for national HITSystem coverage in Kenya was estimated to be around $2·6 million; covering 82 230 infants exposed to HIV at a cost of $31·38 per infant and a yield of 1133 infants receiving timely ART, which would result in 31 189 life-years gained. With sensitivity analyses, the cost per life-year gained varied from $40·13 to $215·05. 90% of model values across iterations ranged between $55·58 (lower 5% threshold) and $132·38 (upper 95% threshold).

Interpretation: The HITSystem would be very cost-effective in Kenya and can optimise the return on the existing investment in the national early infant diagnosis programme.

AIDS Behav. 2023 Sep;27(9):2902-2914.
doi: 10.1007/s10461-023-04014-2. Epub 2023 Mar 13.

Effects of M-DEPTH Model of Depression Care on Maternal HIV Viral Suppression and Adherence to the PMTCT Care Continuum Among HIV-Infected Pregnant Women in Uganda: Results from a Cluster Randomized Controlled Trial at Pregnancy Completion

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Kashesya [7,8], Juliet Nakku [9], Leticia Kyohangirwe [9], Linda Kisaakye Nabitaka [10], Hafsa Lukwata [10], Barbara Mukasa [11], Rhoda K Wanyenze [2]

Abstract

Perinatal depression has been shown to impede adherence to antiretroviral therapy (ART) and the prevention of mother-to-child transmission (PMTCT) care continuum; therefore, treating perinatal depression may result in increased viral suppression and PMTCT adherence. We examined the effects of the M-DEPTH (Maternal Depression Treatment in HIV) depression care model (including antidepressants and individual Problem Solving Therapy) on depression, maternal viral suppression and adherence to PMTCT care processes in an ongoing cluster-randomized controlled trial of 391 HIV-infected pregnant women (200 usual care; 191 intervention) with at least mild depressive symptoms enrolled across 8 antenatal care clinics in Uganda. At baseline, 68.3% had clinical depression and 41.7% had detectable HIV viral load. Adjusted repeated-measures multivariable regression models found that the intervention group was nearly 80% less likely to be clinically depressed [Adjusted OR (95% CI) 0.22 (0.05, 0.89)] at the 2-month post-pregnancy assessment, compared to the control group. However, the intervention and control groups did not differ meaningfully on maternal viral suppression, ART adherence, and other PMTCT care processes and outcomes. In this sample of women who were mostly virally suppressed and ART adherent at baseline, the depression care model had a strong effect on depression alleviation, but no downstream effects on viral suppression or other PMTCT care processes.

J Acquir Immune Defic Syndr. 2024 Apr 15;95(5):447-455.
doi: 10.1097/QAI.0000000000003383. Epub 2024 Mar 11.

Randomized Trial of Dynamic Choice HIV Prevention at Antenatal and Postnatal Care Clinics in Rural Uganda and Kenya

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Abstract

Background: Pregnant and postpartum women in Sub-Saharan Africa are at high risk of HIV acquisition. We evaluated a person-centered dynamic choice intervention for HIV prevention (DCP) among women attending antenatal and postnatal care.

Setting: Rural Kenya and Uganda.

Methods: Women (aged 15 years or older) at risk of HIV acquisition seen at antenatal and postnatal care clinics were individually randomized to DCP vs. standard of care (SEARCH; NCT04810650). The DCP intervention included structured client choice of product (daily oral pre-exposure prophylaxis or postexposure prophylaxis), service location (clinic or out of facility), and HIV testing modality (self-test or provider-administered), with option to switch over time and person-centered care (phone access to clinician, structured barrier assessment and counseling, and provider training). The primary outcome was biomedical prevention coverage-proportion of 48-week follow-up with self-reported pre-exposure prophylaxis or postexposure prophylaxis use, compared between arms using targeted maximum likelihood estimation.

Results: Between April and July 2021, we enrolled 400 women (203 intervention and 197 control); 38% were pregnant, 52% were aged 15-24 years, and 94% reported no pre-exposure prophylaxis or postexposure prophylaxis use for ≥6 months before baseline. Among 384/400

participants (96%) with outcome ascertained, DCP increased biomedical prevention coverage 40% (95% CI: 34% to 47%; P < 0.001); the coverage was 70% in intervention vs. 29% in control. DCP also increased coverage during months at risk of HIV (81% in intervention, 43% in control; 38% absolute increase; 95% CI: 31% to 45%; P < 0.001).
Conclusion: A person-centered dynamic choice intervention that provided flexibility in product, testing, and service location more than doubled biomedical HIV prevention coverage in a high-risk population already routinely offered access to biomedical prevention options.

PLoS One. 2024 Apr 19;19(4):e0297652.
doi: 10.1371/journal.pone.0297652. eCollection 2024.

Enhanced peer-group strategies to support the prevention of mother-to-child HIV transmission leads to increased retention in care in Uganda: A randomized controlled trial

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Abstract
Introduction: Despite the scale-up of Option B+, long-term retention of women in HIV care during pregnancy and the postpartum period remains an important challenge. We compared adherence to clinic appointments and antiretroviral therapy (ART) at 6 weeks, 6, and and 24 months postpartum among pregnant women living with HIV and initiating Option B+. Women were randomized to a peer group support, community-based drug distribution and income-generating intervention called "Friends for Life Circles" (FLCs) versus the standard of care (SOC). Our secondary outcome was infant HIV status and HIV-free survival at 6 weeks and 18 months postpartum.
Methods: Between 16 May 2016 and 12 September 2017, 540 ART-naïve pregnant women living with HIV at urban and rural health facilities in Uganda were enrolled in the study at any gestational age. Participants were randomized 1:1 to the unblinded FLC intervention or SOC at enrolment and assessed for adherence to the prevention of mother-to-child HIV transmission (PMTCT) clinic appointments at 6 weeks, 12, and 24 months postpartum, self-reported adherence to ART at 6 weeks, 6 and 24 months postpartum and supported by plasma HIV-1 RNA viral load (VL) measured at the same time points, retention in care through the end of study, and HIV status and HIV-free survival of infants at 18 months postpartum. The FLC groups were formed during pregnancy within 4 months of enrollment and held monthly meetings in their communites, and were followed up until the last group participant reached 24 months post delivery. We used Log-rank and Chi-Square p-values to test the equality of Kaplan-Meier survival probabilities and hazard rates (HR) for failure to retain in care for any reason by study arm.
Results: There was no significant difference in adherence to PMTCT clinic visits or to ART or in median viral loads between FLC and SOC arms at any follow-up time points. Retention in care through the end of study was high in both arms but significantly higher among participants randomized to FLC (86.7%) compared to SOC (79.3%), p = 0.022. The adjusted HR of visit dropout was 2.4 times greater among participants randomized to SOC compared to FLC (aHR = 2.363, 95% CI: 1.199-4.656, p = 0.013). Median VL remained < 400 copies/ml in both arms at 6 weeks, 6, and 24 months postpartum. Eight of the 431 infants tested at 18

months were HIV positive (1.9%), however, this was not statistically different among mothers enrolled in the FLC arm compared to those in the SOC arm. At 18 months, HIV-free survival of children born to mothers in the FLC arm was significantly higher than that of children born to mothers in the SOC arm.
Conclusions: Our findings suggest that programmatic interventions that provide group support, community-based ART distribution, and income-generation activities may contribute to retention in PMTCT care, HIV-free survival of children born to women living with HIV, and ultimately, to the elimination of mother-to-child HIV transmission (EMTCT).

J Acquir Immune Defic Syndr. 2023 Aug 15;93(5):431-437.
doi: 10.1097/QAI.0000000000003218.

Bone and Renal Health in Infants With or Without Breastmilk Exposure to Tenofovir-Based Maternal Antiretroviral Treatment in the PROMISE Randomized Trial

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Abstract
Background: We assessed bone and kidney outcomes in infants randomized postdelivery as mother-infant pairs within the IMPAACT PROMISE trial to maternal tenofovir disoproxil fumarate-based antiretroviral treatment (mART) or infant nevirapine prophylaxis (iNVP) to prevent breastfeeding HIV transmission.
Methods: Infants were coenrolled in the P1084s substudy on randomization day and followed through Week 74. Lumbar spine bone mineral content (LS-BMC) was assessed at entry (6-21 age days) and Week 26 by dual-energy x-ray absorptiometry. Creatinine clearance (CrCl) was calculated at entry; Weeks 10, 26, and 74. Student t tests compared mean LS-BMC and CrCl at Week 26 and mean change from entry between arms.
Results: Of 400 enrolled infants, the mean (SD; n) for entry LS-BMC was 1.68 g (0.35; n = 363) and CrCl was 64.2 mL/min/1.73 m 2 (24.6; n = 357). At Week 26, 98% of infants were breastfeeding and 96% on their assigned HIV prevention strategy. The mean (SD) Week 26 LS-BMC was 2.64 g (0.48) for mART and 2.77 g (0.44) for iNVP; mean difference (95% confidence interval [CI]) -0.13 g (-0.22 to -0.04), P = 0.007, n = 375/398 (94%). Mean absolute (-0.14 g [-0.23 to -0.06]) and percent (-10.88% [-18.53 to -3.23]) increase in LS-BMC from entry was smaller for mART than iNVP. At Week 26, the mean (SD) CrCl was 130.0 mL/min/1.73 m 2 (34.9) for mART vs. 126.1 mL/min/1.73 m 2 (30.0) for iNVP; mean difference (95% CI) 3.8 (-3.0 to 10.7), P = 0.27, n = 349/398 (88%).
Conclusion: Week 26 mean LS-BMC was lower in infants in the mART group compared with the iNVP group. However, this difference (∼0.23 g) was less than one-half SD, considered potentially clinically relevant. No infant renal safety concerns were observed.

BMC Pregnancy Childbirth. 2024 Feb 21;24(1):153.
doi: 10.1186/s12884-024-06332-2.

Impact of training and case manager support for traditional birth attendants in the linkage of care among HIV-positive pregnant women in Southwest Nigeria: a 3-arm cluster randomized control trial

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Abstract

Background: Mother-to-child transmission (MTCT) accounts for 90% of all new paediatric HIV infections in Nigeria and for approximately 30% of the global burden. This study aimed to determine the effectiveness of a training model that incorporated case managers working closely with traditional birth attendants (TBAs) to ensure linkage to care for HIV-positive pregnant women.

Methods: This study was a 3-arm parallel design cluster randomized controlled trial in Ifo and Ado-Odo Ota, Ogun State, Nigeria. The study employed a random sampling technique to allocate three distinct TBA associations as clusters. Cluster 1 received training exclusively; Cluster 2 underwent training in addition to the utilization of case managers, and Cluster 3 served as a control group. In total, 240 TBAs were enrolled in the study, with 80 participants in each of the intervention and control groups. and were followed up for a duration of 6 months. We employed a one-way analysis of variance (ANOVA) statistical test to evaluate the differences between baseline and endline HIV knowledge scores and PMTCT practices. Additionally, bivariate analysis using the chi-square test was used to investigate linkage to care. Furthermore, logistic regression analysis was utilized to identify TBA characteristics associated with various PMTCT interventions, including the receipt of HIV test results and repeat testing at term for HIV-negative pregnant women. The data analysis was performed using Stata version 16.1.877, and we considered results statistically significant when p values were less than 0.05.

Results: At the end of this study, there were improvements in the TBAs' HIV and PMTCT-related knowledge within the intervention groups, however, it did not reach statistical significance ($p > 0.05$). The referral of pregnant clients for HIV testing was highest (93.5%) within cluster 2 TBAs, who received both PMTCT training and case manager support ($p \leq 0.001$). The likelihood of HIV-negative pregnant women at term repeating an HIV test was approximately 4.1 times higher when referred by TBAs in cluster 1 (AOR = 4.14; 95% CI [2.82-5.99]) compared to those in the control group and 1.9 times in cluster 2 (AOR = 1.93; 95% CI [1.3-2.89]) compared to the control group. Additionally, older TBAs (OR = 1.62; 95% CI [1.26-2.1]) and TBAs with more years of experience in their practice (OR = 1.45; 95% CI [1.09-1.93]) were more likely to encourage retesting among HIV-negative women at term.

Conclusions: The combination of case managers and PMTCT training was more effective than training alone for TBAs in facilitating the linkage to care of HIV-positive pregnant women, although this effect did not reach statistical significance. Larger-scale studies to further investigate the benefits of case manager support in facilitating the linkage to care for PMTCT of HIV are recommended.

AIDS. 2024 Feb 26.
doi: 10.1097/QAD.0000000000003877. Online ahead of print.

Systemic inflammation in pregnant women with HIV: relationship with HIV treatment regimen and preterm delivery

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Abstract

Objective: : HIV treatment regimen during pregnancy was associated with preterm delivery (PTD) in the PROMISE 1077 BF trial. Systemic inflammation among pregnant women with HIV could help explain differences in PTD by treatment regimen. We assessed associations between inflammation, treatment regimen, and PTD.

Design/methods: : A nested 1:1 case-control study (N = 362) was conducted within a multi-country randomized trial comparing three HIV regimens in pregnant women: zidovudine alone, or combination antiretroviral therapy (ART) with lopinavir/ritonavir and either zidovudine or tenofovir. Cases were women with PTD (<37 weeks of gestational age). The following inflammatory biomarkers were measured in plasma samples using immunoassays: soluble CD14 (sCD14) and sCD163, intestinal fatty acid-binding protein, interleukin (IL)-6, interferon γ, and tumor necrosis factor α. We fit regression models to assess associations between second trimester biomarkers (measured before ART initiation at 13-23 weeks of gestational age and 4 weeks later), treatment regimen, and PTD. We also assessed whether inflammation was a mediator in the relationship between ART regimen and PTD.

Results: : Persistently high interleukin-6 was associated with increased PTD. Compared to zidovudine alone, the difference in biomarker concentration between week 0 and week 4 was significantly higher ($p < 0.05$) for both PI-based regimens. However, the estimated proportion of the ART effect on increased PTD mediated by persistently high biomarker levels was ≤5% for all biomarkers.

Conclusions: Persistently high IL-6 during pregnancy was associated with PTD. While PI-based ART was associated with increases in inflammation, factors other than inflammation likely explain the increased PTD in ART-based regimens compared to zidovudine alone.

AIDS. 2024 Mar 4.
doi: 10.1097/QAD.0000000000003878. Online ahead of print.

Effects of preterm birth, maternal ART and breastfeeding on 24-month infant HIV-free survival in a randomized trial

Sufia Dadabhai [1 2], Victoria B Chou [3], Mauricio Pinilla [4], Lameck Chinula [5], Maxensia Owor [6], Avy Violari [7], Dhayendre Moodley [8], Lynda Stranix-Chibanda [9 10], Taguma Allen Matubu [10], Gift Tafadzwa Chareka [10], Gerhard Theron [11], Aarti Avinash Kinikar [12], Mwangelwa Mubiana-Mbewe [13], Lee Fairlie [14], Raziya Bobat [15], Blandina Theophil Mmbaga [16], Patricia M Flynn [17], Taha E Taha [1], Katie S McCarthy [18], Renee Browning [19], Lynne M Mofenson [20], Sean S Brummel [4], Mary Glenn Fowler [3]; IMPAACT PROMISE 1077BF/FF team.

Abstract

Background: IMPAACT 1077BF/FF compared the safety/efficacy of two HIV antiretroviral therapy (ART) regimens to zidovudine (ZDV) alone during pregnancy for HIV prevention. PROMISE found an increased risk of preterm delivery (<37 weeks) with antepartum triple ART (TDF/FTC/LPV+r or ZDV/3TC/LPV+r) compared to ZDV alone. We assessed the impact of preterm birth, breastfeeding and antepartum ART regimen on 24-month infant survival.

Methods: We compared HIV-free and overall survival at 24-months for liveborn infants by gestational age, time-varying breastfeeding status, and antepartum ART arm at 14 sites in

Africa and India. Kaplan-Meier survival probabilities and Cox proportional hazards ratios (HR) were estimated.
Results: 3,482 live-born infants (568 [16 3%] preterm and 2,914 [83 7%] term) were included. Preterm birth was significantly associated with lower HIV-free survival (0·85; 95% CI: 0·82-0·88) and lower overall survival (0·89; 95% CI: 0·86-0·91) versus term birth (0·96; 95% CI: 0·95-0·96). Very preterm birth (<34 weeks) was associated with low HIV-free survival (0·65; 95% CI: 0·54-0·73) and low overall survival (0·66; 95% CI: 0·56-0·74). Risk of HIV infection or death at 24-months was higher with TDF-ART than ZDV-ART (adjusted HR 2·37; 95% CI: 1·21-4·64). Breastfeeding initiated near birth decreased risk of infection or death at 24 months (adjusted HR 0·05; 95% CI: 0·03-0·08) compared to not breastfeeding.
Conclusion: Preterm birth and antepartum TDF-ART were associated with lower 24-month HIV-free survival compared to term birth and ZDV-ART. Any breastfeeding strongly promoted HIV-free survival, especially if initiated close to birth. Reducing preterm birth and promoting infant feeding with breastmilk among HIV/ARV-exposed infants remain global health priorities.

Antiretroviral therapy (ART)

Int J STD AIDS. 2024 Apr;35(5):389-396.
doi: 10.1177/09564624241226489. Epub 2024 Jan 12.
Effect of the timing of antiretroviral treatment initiation on CD4 count in children and youths living with HIV in North India
Mukesh Vir Singh [1], Sukesh Sharma [1], Anubha Shrivastava [1], Santosh Kumar Shukla [1], Shahid Akhtar Siddiqui [1], Manisha Maurya [1], Nandita Mishra [1], Rajesh Kumar Yadav [1]
Abstract
Background: Immediate start of antiretroviral treatment (ART) among non-hospitalized outpatient children living with HIV may improve or worsen clinical outcomes due to immune reconstitution.
Objective: Role of immediate versus post-stabilization start of antiretroviral treatment in children and youths living with HIV on CD4 count and viral load suppression.
Methods: This was a single blinded, randomized controlled trial conducted on outpatients attending a tertiary care hospital associated HIV clinic in North India. We enrolled ART-naive children and youths living with HIV aged 18 months to 21 years in a 1:1 ratio. Block randomization was done using computerized software. Children and youths living with HIV were either started with ART on diagnosis immediately within 24 h (Group A) or post stabilization at 2 weeks (Group B) as per National AIDS Control Organization (NACO) India guidelines. Both groups were comparable for baseline characteristics.
Results: There was no significant difference seen in CD4 counts between two groups at 6 months follow up. CD4 count increased significantly in immediate group but not in post-stabilization group at 6 months. No significant changes/differences was seen in WHO clinical staging or anthropometry; one patient developed tuberculosis in both groups. Viral load at 6 months in both the groups did not differ significantly.

Conclusion: Immediate ART in children and youths living with HIV results in significant increase in CD4 count at 6 months follow up exemplifying immunological response to ART.

Clin Infect Dis. 2023 Sep 18;77(6):875-882.
doi: 10.1093/cid/ciad267.

First Pharmacokinetic Data of Tenofovir Alafenamide Fumarate and Tenofovir With Dolutegravir or Boosted Protease Inhibitors in African Children: A Substudy of the CHAPAS-4 Trial

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Abstract

Background: We evaluated the pharmacokinetics of tenofovir alafenamide fumarate (TAF) and tenofovir in a subset of African children enrolled in the CHAPAS-4 trial.

Methods: Children aged 3-15 years with human immunodeficiency virus infection failing first-line antiretroviral therapy were randomized to emtricitabine/TAF versus standard-of-care nucleoside reverse transcriptase inhibitor combination, plus dolutegravir, atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. Daily emtricitabine/TAF was dosed according to World Health Organization (WHO)-recommended weight bands: 120/15 mg in children weighing 14 to <25 kg and 200/25 mg in those weighing ≥25 kg. At steady state, 8-9 blood samples were taken to construct pharmacokinetic curves. Geometric mean (GM) area under the concentration-time curve (AUC) and the maximum concentration (Cmax) were calculated for TAF and tenofovir and compared to reference exposures in adults.

Results: Pharmacokinetic results from 104 children taking TAF were analyzed. GM (coefficient of variation [CV%]) TAF AUClast when combined with dolutegravir (n = 18), darunavir/ritonavir (n = 34), or lopinavir/ritonavir (n = 20) were 284.5 (79), 232.0 (61), and 210.2 (98) ng*hour/mL, respectively, and were comparable to adult reference values. When combined with atazanavir/ritonavir (n = 32), TAF AUClast increased to 511.4 (68) ng*hour/mL. For each combination, tenofovir GM (CV%) AUCtau and Cmax remained below reference values in adults taking 25 mg TAF with a boosted protease inhibitors.

Conclusions: In children, TAF combined with boosted PIs or dolutegravir and dosed according to WHO-recommended weight bands provides TAF and tenofovir concentrations previously demonstrated to be well tolerated and effective in adults. These data provide the first evidence for use of these combinations in African children.

Viruses. 2023 Oct 12;15(10):2083.
doi: 10.3390/v15102083.

HIV Drug Resistance Patterns and Characteristics Associated with Clinically Significant Drug Resistance among Children with Virologic Failure on Antiretroviral Treatment in Kenya: Findings from the Opt4Kids Randomized Controlled Trial

Lisa Abuogi [1], Patrick Oyaro [2 3], Garoma Wakjira [4], Katherine K Thomas [5], Andrea J Scallon [5], Irene Mukui [6], Bhavna H Chohan [5 7], Evelyn Brown [8], Enericah Karauki [8], Nashon Yongo [8], Bilaal Ahmed [1], Shukri A Hassan [4], James Wagude [9], Eunice Kinywa [10], Linda Otieno [11], Leonard Kingwara [12], Boaz Oyaro [13], Lisa M Frenkel [4 5 14 15], Grace John-Stewart [4 5 14], Rena C Patel [4 5]

Abstract

Increasing HIV drug resistance (DR) among children with HIV (CHIV) on antiretroviral treatment (ART) is concerning. CHIV ages 1-14 years enrolled from March 2019 to December 2020 from five facilities in Kisumu County, Kenya, were included. Children were randomized 1:1 to control (standard-of-care) or intervention (point-of-care viral load (POC VL) testing every three months with targeted genotypic drug resistance testing (DRT) for virologic failure (VF) (≥1000 copies/mL)). A multidisciplinary committee reviewed CHIV with DRT results and offered treatment recommendations. We describe DR mutations and present logistic regression models to identify factors associated with clinically significant DR. We enrolled 704 children in the study; the median age was 9 years (interquartile range (IQR) 7, 12), 344 (49%) were female, and the median time on ART was 5 years (IQR 3, 8). During the study period, 106 (15%) children had DRT results (84 intervention and 22 control). DRT detected mutations associated with DR in all participants tested, with 93 (88%) having major mutations, including 51 (54%) with dual-class resistance. A history of VF in the prior 2 years (adjusted odds ratio (aOR) 11.1; 95% confidence interval (CI) 6.3, 20.0) and less than 2 years on ART at enrollment (aOR 2.2; 95% CI 1.1, 4.4) were associated with increased odds of major DR. DR is highly prevalent among CHIV on ART with VF in Kenya. Factors associated with drug resistance may be used to determine which children should be prioritized for DRT.

Clin Infect Dis. 2023 Nov 11;77(9):1312-1317.
doi: 10.1093/cid/ciad346.

Pharmacokinetic Data of Dolutegravir in Second-line Treatment of Children With Human Immunodeficiency Virus: Results From the CHAPAS4 Trial

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Abstract

Background: Dolutegravir (DTG), combined with a backbone of 2 nucleoside reverse transcriptase inhibitors, is currently the preferred first-line treatment for human immunodeficiency virus (HIV) in childhood. CHAPAS4 is an ongoing randomized controlled trial investigating second-line treatment options for children with HIV. We did a nested pharmacokinetic (PK) substudy within CHAPAS4 to evaluate the DTG exposure in children with HIV taking DTG with food as part of their second-line treatment.

Methods: Additional consent was required for children on DTG enrolled in the CHAPAS4 trial to participate in this PK substudy. Children weighing 14-19.9 kg took 25 mg DTG as dispersible tablets and children ≥20 kg took 50 mg film-coated tablets. Steady-state 24-hour DTG plasma concentration-time PK profiling was done at t = 0 and 1, 2, 4, 6, 8, 12, and 24 hours after observed DTG intake with food. Reference adult PK data and pediatric data from the ODYSSEY trial were used primarily for comparison. The individual target trough concentration (Ctrough) was defined as 0.32 mg/L.

Results: Thirty-nine children on DTG were included in this PK substudy. The geometric mean (GM) area under the concentration-time curve over the dosing interval (AUC0-24h) was 57.1 hours × mg/L (coefficient of variation [CV%], 38.4%), which was approximately 8% below the average AUC0-24h in children in the ODYSSEY trial with comparable dosages, but above the adult reference. The GM (CV%) Ctrough was 0.82 mg/L (63.8%), which was comparable to ODYSSEY and adult reference values.
Conclusions: This nested PK substudy shows that the exposure of DTG taken with food in children on second-line treatment is comparable with that of children in the ODYSSEY trial and adult references.

BMC Public Health. 2023 Jul 3;23(1):1280.
doi: 10.1186/s12889-023-16181-x.

Effectiveness of a community-based intervention (Konga model) to address factors contributing to low viral load suppression among children living with HIV in Tanzania: a preliminary, cluster, randomized clinical trial report

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Abstract
Background: Despite effective antiretroviral therapy (ART) coverage in other groups living with human immunodeficiency virus (HIV) in Tanzania, virologic suppression among HIV-positive children receiving ART remains unacceptably low. This study evaluated the effectiveness of a community-based intervention (Konga model) in addressing the factor contributing to low viral load suppression among children living with HIV in the Simiyu region, Tanzania.
Methods: This study used a parallel cluster randomized trial. The cluster was only eligible if the health facility provided HIV care and treatment. All eligible resident children aged 2–14 years who attended the cluster with a viral load > 1,000 cells/mm were enrolled. The intervention included three distinct activities: adherence counseling, psychosocial support, and co-morbidity screening such as tuberculosis. The evaluation was based on patient-centered viral load outcomes measured at baseline and 6 months later. Using a pre- and post-test design, we compared the means of participants in the intervention and control groups. We performed an analysis of covariance. The effect of a Konga was calculated using omega-squared. We used F-tests, with their corresponding p-values, as measures of improvement.
Results: We randomly assigned 45 clusters to the treatment (15) and control (30) groups. We enrolled 82 children with amedian age of 8.8 years(interquartile range(IQR);5.5-11.2), and a baseline median viral load of 13,150 cells/mm (interquartile range (IQR);3600-59,200). After the study, both children in each group had good adherence, with children in the treatment group scoring slightly higher than those in the control group, 40 (97.56%) versus 31(75%61), respectively. At the end of the study, the difference in viral load suppression between the two groups was significant. The median viral load suppression at the end of the study was 50 cells/mm [IQR, (20-125)]. After adjusting for the viral load before the intervention, the effect size of the Konga intervention explained 4% (95% confidence interval [0%, 14.1%]) of the viral load variation at the end of the intervention.

Conclusion: The Konga model demonstrated significant positive effects that improved viral load suppression. We recommend implementing the Konga model trial in other regions to improve the consistency of results.

Lancet Child Adolesc Health. 2023 Oct;7(10):718-727.
doi: 10.1016/S2352-4642(23)00164-5. Epub 2023 Aug 8.

Neuropsychiatric manifestations and sleep disturbances with dolutegravir-based antiretroviral therapy versus standard of care in children and adolescents: a secondary analysis of the ODYSSEY trial

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Abstract

Background: Cohort studies in adults with HIV showed that dolutegravir was associated with neuropsychiatric adverse events and sleep problems, yet data are scarce in children and adolescents. We aimed to evaluate neuropsychiatric manifestations in children and adolescents treated with dolutegravir-based treatment versus alternative antiretroviral therapy.

Methods: This is a secondary analysis of ODYSSEY, an open-label, multicentre, randomised, non-inferiority trial, in which adolescents and children initiating first-line or second-line antiretroviral therapy were randomly assigned 1:1 to dolutegravir-based treatment or standard-of-care treatment. We assessed neuropsychiatric adverse events (reported by clinicians) and responses to the mood and sleep questionnaires (reported by the participant or their carer) in both groups. We compared the proportions of patients with neuropsychiatric adverse events (neurological, psychiatric, and total), time to first neuropsychiatric adverse event, and participant-reported responses to questionnaires capturing issues with mood, suicidal thoughts, and sleep problems.

Findings: Between Sept 20, 2016, and June 22, 2018, 707 participants were enrolled, of whom 345 (49%) were female and 362 (51%) were male, and 623 (88%) were Black-African. Of 707 participants, 350 (50%) were randomly assigned to dolutegravir-based antiretroviral therapy and 357 (50%) to non-dolutegravir-based standard-of-care. 311 (44%) of 707 participants started first-line antiretroviral therapy (ODYSSEY-A; 145 [92%] of 157 participants had efavirenz-based therapy in the standard-of-care group), and 396 (56%) of 707 started second-line therapy (ODYSSEY-B; 195 [98%] of 200 had protease inhibitor-based therapy in the standard-of-care group). During follow-up (median 142 weeks, IQR 124-159), 23 participants had 31 neuropsychiatric adverse events (15 in the dolutegravir group and eight in the standard-of-care group; difference in proportion of participants with ≥1 event p=0·13). 11 participants had one or more neurological events (six and five; p=0·74) and 14 participants had one or more psychiatric events (ten and four; p=0·097). Among 14 participants with psychiatric events, eight participants in the dolutegravir group and four in standard-of-care group had suicidal ideation or behaviour. More participants in the

dolutegravir group than the standard-of-care group reported symptoms of self-harm (eight vs one; p=0·025), life not worth living (17 vs five; p=0·0091), or suicidal thoughts (13 vs none; p=0·0006) at one or more follow-up visits. Most reports were transient. There were no differences by treatment group in low mood or feeling sad, problems concentrating, feeling worried or feeling angry or aggressive, sleep problems, or sleep quality.
Interpretation: The numbers of neuropsychiatric adverse events and reported neuropsychiatric symptoms were low. However, numerically more participants had psychiatric events and reported suicidality ideation in the dolutegravir group than the standard-of-care group. These differences should be interpreted with caution in an open-label trial. Clinicians and policy makers should consider including suicidality screening of children or adolescents receiving dolutegravir.

ART therapeutic monitoring

J Acquir Immune Defic Syndr. 2023 Aug 15;93(5):403-412.
doi: 10.1097/QAI.0000000000003212.
Point-of-Care Viral Load Testing to Manage HIV Viremia During the Rollout of Dolutegravir-Based ART in South Africa: A Randomized Feasibility Study (POwER)
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Abstract
Background: Data are required regarding the feasibility of conducting a randomized trial of point-of-care viral load (VL) testing to guide management of HIV viremia and to provide estimates of effect to guide potential future trial design.
Setting: Two public South African clinics during the dolutegravir-based antiretroviral therapy (ART) rollout.
Methods: We randomized adults receiving first-line ART, with recent VL ≥1000 copies/mL, in a 1:1 ratio to receive point-of-care Xpert HIV-1 VL versus standard-of-care laboratory VL testing after 12 weeks. Feasibility outcomes included proportions of eligible patients enrolled and completing follow-up and VL process outcomes. Estimates of effect were assessed using the trial primary outcome of VL <50 copies/mL after 24 weeks.
Results: From August 2020 to March 2022, we enrolled 80 eligible participants, an estimated 24% of those eligible. 47 of 80 (58.8%) were women, and the median age was 38.5 years (interquartile range [IQR], 33-45). 44 of 80 (55.0%) were receiving dolutegravir, and 36 of 80 (465.0%) were receiving efavirenz. After 12 weeks, point-of-care participants received VL results after median 3.1 hours (IQR 2.6-3.8), versus 7 days (IQR 6-8, P < 0.001) in standard of care. Twelve-week follow-up VL was ≥1000 copies/mL in 13 of 39 (33.3%) point-of-care participants and in 16 of 41 (39.0%) standard-of-care participants; 11 of 13 (84.6%) and 12 of 16 (75.0%) switched to second-line ART. After 24 weeks, 76 of 80 (95.0%) completed follow-up. 27 of 39 (69.2% [95% CI: 53.4 to 81.4]) point-of-care participants achieved VL <50 copies/mL versus 29 of 40 (72.5% [57.0 to 83.9]) standard-of-care participants. Point-of-care participants had median 3 (IQR, 3-4) clinical visits versus 4 (IQR, 4-5) in standard-of-care participants (P < 0.001).

Conclusions: It was feasible to conduct a trial of point-of-care VL testing to manage viremia. Point-of-care VL lead to quicker results and fewer clinical visits, but estimates of 24-week VL suppression were similar between arms.

HIV exposed infants and children

AIDS Behav. 2023 Dec;27(12):3831-3843.
doi: 10.1007/s10461-023-04097-x. Epub 2023 Jun 12.

Why do Integrated Maternal HIV and Infant Healthcare Services work? A Secondary Analysis of a Randomised Controlled Trial in South Africa

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Abstract

In a randomised trial, we found that integrated maternal HIV and infant health services through the end of breastfeeding were significantly associated with the primary outcome of engagement in HIV care and viral suppression at 12 months postpartum, compared to the standard of care. Here, we quantitatively explore potential psychosocial modifiers and mediators of this association. Our findings suggest that the intervention was significantly more effective among women experiencing an unintended pregnancy but did not improve outcomes among women reporting risky alcohol use. Although not statistically significant, our results suggest that the intervention may also be more effective among women experiencing higher levels of poverty and HIV-related stigma. We observed no definitive mediator of the intervention effect, but women allocated to integrated services reported better relationships with their healthcare providers through 12 months postpartum. These findings point to high-risk groups that may benefit the most from integrated care, as well as groups for whom these benefits are hampered and that warrant further attention in intervention development and evaluation.

Chronic comorbidity in paediatric HIV

HIV Med. 2023 Oct 7.
doi: 10.1111/hiv.13565. Online ahead of print.

Exhaled nitric oxide is associated with inflammatory biomarkers and risk of acute respiratory exacerbations in children with HIV-associated chronic lung disease

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Abstract

Objectives: Chronic lung disease is a recognized complication in children with HIV. Acute respiratory exacerbations (ARE) are common among this group and cause significant morbidity. Exhaled nitric oxide (eNO) is a known marker of local airway inflammation. We investigated the association between eNO and ARE, biomarkers of systemic inflammation, and the effect of azithromycin on eNO levels.

Methods: Individuals aged 6-19 years with HIV-associated chronic lung disease in Harare, Zimbabwe, were enrolled in a placebo-controlled randomized trial investigating the effect of 48-week azithromycin treatment on lung function and ARE. eNO levels and biomarkers were measured at inclusion and after treatment in a consecutively enrolled subset of participants. Linear regression and generalized linear models were used to study associations between eNO and ARE, biomarkers, and the effect of azithromycin on eNO levels.
Results: In total, 172 participants were included in this sub-study, 86 from the placebo group and 86 from the azithromycin group. Participants experiencing at least one ARE during follow-up had significantly higher eNO levels at baseline than participants who did not (geometric mean ratio 1.13, 95% confidence interval [CI] 1.03-1.24, p = 0.015), adjusted for trial arm, age, sex and history of tuberculosis. Matrix metalloproteinase (MMP)-3, -7, and -10 were significantly associated with higher baseline eNO levels. At 48 weeks, azithromycin treatment did not affect eNO levels (geometric mean ratio 0.86, 95% CI 0.72-1.03, p = 0.103).
Conclusion: Higher baseline eNO levels were a risk factor for ARE. eNO was associated with proinflammatory biomarkers previously found to contribute to the development of chronic lung disease. The potential use of eNO as a marker of inflammation and risk factor for ARE in HIV-associated chronic lung disease needs further investigation.

Nutrition, growth and development of children with HIV

Cotrimoxazole preventative therapy

HIV-TB coinfection

PLOS Glob Public Health. 2023 Jul 14;3(7):e0001473.
doi: 10.1371/journal.pgph.0001473. eCollection 2023.
The impact of a combined TB/HIV intervention on the incidence of TB infection among adolescents and young adults in the HPTN 071 (PopART) trial communities in Zambia and South Africa
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Abstract
Background: HPTN071 (PopART) was a cluster randomized trial conducted in Zambian and South African (SA) communities, between 2013-2018. The PopART intervention (universal HIV-testing and treatment (UTT) combined with population-level TB symptom screening) was implemented in 14 communities. The TREATS study (2017-2021) was conducted to evaluate the impact of the PopART intervention on TB outcomes. We report on the impact of the combined TB/HIV intervention on the incidence of TB infection in a cohort of adolescents and young adults (AYA) aged 15-24 years.

Methods: A random sample of AYA was enrolled between July 2018 and July 2019 in 7 intervention vs 7 standard-of-care communities. We collected questionnaire data on risk factors for TB, and blood for measuring TB infection using QuantiFERON (QFT) Plus. AYA were seen at months 12 and 24 with all procedures repeated. Primary outcome was incidence of TB infection comparing intervention and standard-of-care communities. An incident case was defined as a participant with QFT interferon-gamma response of < 0.2 IU/ml plasma ('negative') at baseline and a QFT interferon-gamma response of > = 0.7 IU/ml ('positive') at follow up.
Results: We enrolled 4,648 AYA, 2,223 (47.8%) had a negative QFT-plus result at baseline, 1,902 (85.6%) had a follow up blood sample taken at 12 months or 24 months. Among the 1,902 AYA, followed for 2,987 person-years, 213 had incident TB infection giving (7.1 per 100 person-years). TB infection incidence rates were 8.7 per 100 person-years in intervention communities compared to 6.0 per 100 person-years in standard-of-care communities. There was no evidence the intervention reduced the transmission of TB (incidence-rate-ratio of 1.45, 95%CI 0.97-2.15, p = 0.063).
Conclusion: In our trial setting, we found no evidence that UTT combined with TB active case finding reduced the incidence of TB infection at population level. Our data will inform future modelling work to better understand the population level dynamics of HIV and TB.

Helminth and other gastrointestinal disorders

(See also Anaemia, Diarrhoea, Micronutrients and food fortification, Malaria and HIV)

J Epidemiol Glob Health. 2024 May 2.
doi: 10.1007/s44197-024-00231-7. Online ahead of print.

Efficacy of Albendazole and Mebendazole Against Soil Transmitted Infections among Pre-School and School Age Children: A Systematic Review and Meta-Analysis

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Abstract
Background: Soil-transmitted helminthic (STH) infections are the leading cause of stunting among children. To lessen the burden, the World Health Organization (WHO) recommended a periodic deworming program through the use of single-dose therapy in the endemic regions. Therefore, the purpose of this study was to synthesize evidence about the efficacy of anthelminthic drugs against STH infections among preschool and school-age children.
Methods: The Preferred Reposting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed in this study. Relevant electronic databases, including PubMed, Scopus, Embase, DOAJ, Science Direct, the WHO Clinical Trials.gov library, Google Scholar, and AJOL databases, were searched for relevant publications. Randomized controlled trials (RCTs) and non-randomized interventional studies focused on the efficacy of albendazole and mebendazole against STHs in children were included in the study. Review Manager was used to analyze the data. A random effects model was used to obtain the pooled estimated efficacy. To evaluate heterogeneity, the I^2 test and Cochrane Q (χ^2) were employed. The risk of publication bias was investigated using Egger's test and the funnel

plot. The protocol of this review was registered at the PROSPERO international prospective register of systematic reviews (CRD42023401196).
Results: Of the 69 publications selected for the systematic review, 66 with complete data were included in the meta-analysis. Single doses of albendazole and mebendazole have shown satisfactory efficacy [egg reduction rate (ERR)] against Ascaris lumbricoides [95.54% (95% CI: 88.75-102.34%) and 98.69% (95% CI: 97.68-99.65%), respectively. The effectiveness of these two drugs against Trichuris trichiura and hookworms was comparatively low (< 80% ERR), except for albendazole, which showed high ERRs [93.44% (95%CI: 92.39-94.49%)] against hookworms. The cure rate (CR) of albendazole against T. trichiura, A. lumbricoides, and hookworms were 50.8%, 91.3%, and 78.32%, respectively. Likewise, mebendazole showed CRs of 48.15%, 92.8%, and 49.32% against T. trichiura, A. lumbricoides, and hookworms, respectively. Subgroups such as studies conducted after 2000, diagnostic type (McMaster), and longer follow-up weeks significantly reduced the efficacy of the two drugs against T. trichura. While the combination of albendazole or mebendazole with other drugs and RCT showed significantly improved efficacy against T. trichura. The count of eggs per gram of stool (EPG) was identified as one of the variables that negatively and significantly influenced the efficacy of albendazole or mebendazole against A. lumbricoides.
Conclusion: Despite the wide range of ERRs and CR reported in the different articles included in this review, the pooled estimated efficacy of albendazole and mebendazole against STHs falls in the satisfactory category of WHO recommendations. Further evaluation of the combination of anthelminthic drugs as a preventive chemotherapy option and routine drug efficacy testing are necessary to prevent the emergence and widespread use of drug-resistant STHs.

PLoS Negl Trop Dis. 2023 Jul 3;17(7):e0011439.
doi: 10.1371/journal.pntd.0011439. eCollection 2023 Jul.

The impact of dual- versus single-dosing and fatty food co-administration on albendazole efficacy against hookworm among children in Mayuge district, Uganda: Results from a 2x2 factorial randomised controlled trial

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Abstract
Background: Mass Drug Administration (MDA) is the main strategy for control of soil-transmitted helminth (STH) infections, with single-dose benzimidazole (albendazole or mebendazole) the principal MDA option. In Mayuge district, Uganda, an MDA programme has been in place for over fifteen years but hookworm infection remains common and there is concern that the effectiveness of single-dose albendazole as currently used for MDA may be sub-optimal. This study aims to assess the efficacy of dual- versus single-dose albendazole, with and without fatty food co-administration against hookworm, the dominant form of STHs in Mayuge district, Uganda.
Methodology: This was a 2x2 factorial randomised controlled trial to investigate two interventions simultaneously; 1) dual-dose versus single-dose albendazole, 2) taking albendazole with or without fatty food (200 grams of avocado eaten directly after medication). School children with hookworm infection were randomised in a 1:1:1:1 ratio to the four possible treatment groups. Three weeks after the treatment, stool samples were

collected from trial participants to evaluate trial outcomes: cure rate and egg reduction rate (ERR).
Principal findings: A total of 225 participants were enrolled, and 222 (98.7%) seen at 3 weeks. The cure rate in the dual-dose group was 96.4% (95% CI: 90.9-99%), higher than 83.9% (95% CI: 75.7-90.2%) in the single-dose group (OR: 5.07, 95% CI:1.61-15.96, p = 0.002). The ERR was 97.6% and 94.5% in the dual-dose group and single-dose drug group, respectively (ERR difference 3.1%, 95% CI: -3.89-16.39%, p = 0.553). The cure rates among participants taking albendazole with and without avocado were 90.1% and 89.1%, respectively, with no statistical difference between the two groups (OR: 1.24, 95% CI: 0.51-3.03, p = 0.622). The ERR was 97.0% and 94.2% in the group receiving albendazole with and without avocado, respectively, and the difference in ERR between the two groups was 2.8% (95% CI -8.63-14.3%, p = 0.629).
Conclusions/significance: In Ugandan school children, dual-dose albendazole improves the cure rate of hookworm compared to single-dose albendazole. However, there was no significant improvement in cure rate or egg reduction rate of hookworm with fatty-food co-administration. Dual-dose albendazole is a feasible alternative for improving drug effectiveness against hookworm infection and minimising drug resistance.

Clin Infect Dis. 2023 Nov 11;77(9):1294-1302.
doi: 10.1093/cid/ciad387.
Efficacy and Safety of Moxidectin-Albendazole and Ivermectin-Albendazole Combination Therapy Compared to Albendazole Monotherapy in Adolescents and Adults Infected with Trichuris trichiura: A Randomized, Controlled Superiority Trial
Viviane P Sprecher[1,2], Jean T Coulibaly[3,4], Eveline Hürlimann[1,2], Jan Hattendorf[2,5], Jennifer Keiser[1,2]
Abstract
Background: The currently recommended benzimidazole monotherapy is insufficiently effective to control infection with the soil-transmitted helminth Trichuris trichiura. Ivermectin-albendazole combination has shown promising, but setting-dependent efficacy, with therapeutic underperformance in Côte d'Ivoire. We evaluated whether moxidectin-albendazole could serve as an alternative to albendazole monotherapy in Côte d'Ivoire.
Methods: In this community-based, randomized, placebo-controlled, parallel-group superiority trial, individuals aged 12-60 years were screened for T. trichiura eggs in their stool using quadruplicate Kato-Katz thick smears. Diagnostically and clinically eligible participants were randomly assigned (1:1:1) to receive single oral doses of moxidectin (8 mg) and albendazole (400 mg), ivermectin (200 µg/kg) and albendazole (400 mg), or albendazole (400 mg) and placebo. The primary outcome was proportion cured, ie, cure rate (CR), assessed at 2-3 weeks post-treatment. Safety endpoints were assessed pre-treatment and at 3 and 24 hours post-treatment.
Results: For the 210 participants with primary outcome data, we observed CRs of 15.3% in the moxidectin-albendazole arm and 22.5% in the ivermectin-albendazole arm, which did not differ significantly from the CR of 13.4% in the albendazole arm (differences: 1.8%-points [95% confidence interval: -10.1 to 13.6] and 9.1%-points [-3.9 to 21.8], respectively). Most common adverse events were abdominal pain (range across arms: 11.9%-20.9%), headache (4.7%-14.3%), and itching (5.8%-13.1%), which were predominantly mild and transient.

Conclusions: All therapies showed similar low efficacy in treating trichuriasis in Côte d'Ivoire. Alternative treatment options need to be evaluated, and further analyses should be conducted to understand the lack of enhanced activity of the combination therapies in Côte d'Ivoire.

Am J Trop Med Hyg. 2024 Jan 9;110(2):263-269.
doi: 10.4269/ajtmh.23-0010. Print 2024 Feb 7.

Effectiveness of a School Intervention Based on Knowledge, Attitude, and Practice of Soil-Transmitted Helminths

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Abstract

More than 1.5 billion people are infected by soil-transmitted helminths (STHs) worldwide, comprising one of the world's most serious public health problems. School-age children are the most affected as a result of precarious hygienic habits, especially in economically poor areas that lack appropriate sanitation. Therefore, this study aimed to evaluate a didactic method via a health education approach as a complement to the school curriculum of the sixth-grade students of public schools, distributed among six cities in the state of São Paulo, Brazil. For this, a didactic booklet was elaborated with educational explanatory activities about worms, their life cycle, and how to avoid infections. The intervention was measured by the change caused by knowledge, attitude, and practice (KAP), in students before and after using the notebook, through a questionnaire with high validity and internal consistency. Schools were assigned randomly into intervention and control groups, receiving both the didactic material and the questionnaires, versus the questionnaires only, respectively. The results were submitted to an analysis of covariance that revealed a significant difference pre- and postintervention for knowledge ($P < 0.001$), with greater means (0.54) compared with the control group (0.44); attitude ($P < 0.005$), with respective means of 0.56 versus 0.48; and practice ($P < 0.001$), with means of 0.75 versus 0.57. These findings set the didactic material as a potential tool to complement the school curriculum through KAP without disrupting the teaching system, in addition to assisting teachers in health education at schools aiming to prevent children's infections by STHs.

J Trop Med Hyg. 2024 Mar 12:tpmd230676.
doi: 10.4269/ajtmh.23-0676. Online ahead of print.

Adolescents' Perspective Regarding a Community-Wide Mass Drug Administration Program for Soil-Transmitted Helminths in India

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Abstract

This study was undertaken to understand the perspective of adolescents in endemic communities of India regarding soil-transmitted helminth (STH) infections and community-wide mass drug administration (cMDA). A multicountry community-based cluster-randomized trial, the Deworm3 trial, tested the feasibility of interrupting STH transmission with cMDA, where all individuals aged 1-99 are treated empirically with albendazole. Using a guideline based on the Consolidated Framework for Implementation Research, eight focus

group discussions were conducted among 57 adolescents from the trial site in India and analyzed on ATLAS.ti 8.0 software using an a priori thematic codebook. Adolescents believed that adults could be a source of STH infection because they were not routinely dewormed like the children through the national deworming program. Perceived benefits of cMDA for all were better health and increased work efficiency. Perceived barriers to adults' participation in cMDA was their mistrust about the program, fear of side effects, perceived low risk of infection, and absence during drug distribution. To encourage adult participation in cMDAs, adolescents suggested community outreach activities, engaging village influencers and health workers, and tailoring drug distribution to when adults would be available. Adolescents were confident in their ability to be change agents within their households for treatment compliance. Adolescents provided insights into potential barriers and solutions to improve adult participation in cMDA, identified best practices of cMDA delivery, and suggested that they have unique roles as change agents to increase their household participation in cMDA.

Hepatitis and chronic liver disease

Acta Med Okayama. 2024 Apr;78(2):107-113.
doi: 10.18926/AMO/66913.

Evaluation of the Efficacy and Safety of Tenofovir Disoproxil Fumarate in Intercepting Mother-to-Child Transmission of Hepatitis B Virus

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Abstract

Vertical transmission of hepatitis B virus (HBV), especially in Asia, is a key target in the global elimination of HBV. This study assessed the effects of tenofovir disoproxil fumarate (TDF) in pregnant women for mother-to-infant transmission of HBV. A total of 122 pregnant women at our hospital met the inclusion criteria for high HBV DNA viral loads. They were randomly divided into TDF-treatment (n=70) and placebo (n=52) groups. Maternal liver function and serum HBV DNA load were tested before and after treatment. Clinical and laboratory data of infants were assayed at delivery and 7-months post-partum visit and compared between the two groups. There was no difference in clinical characteristics of participants between the two groups. There were no significant differences in liver function markers, including alanine aminotransferase, total bilirubin, blood creatinine, and blood urea nitrogen levels before and after TDF treatment. The serum HBV DNA viral load of the TDF-treated group became significantly lower than those of the control group and their own pre-medication levels. Infants showed no significant difference in body growth, including weight, height, head size, and five-min Apgar score. At 7 months after birth, 94.29% of infants in the TDF group and 86.54% of control-group infants had protective HBsAb levels ≥ 10 mIU/ml ($p>0.05$). The HBV infection rate of infants in the TDF-treated group was lower than that in the non-treated group. In high-HBV-DNA-load pregnant women, TDF administered from 28 weeks gestational age to delivery was associated with a lower risk of mother-to-infant transmission of HBV.

Trans R Soc Trop Med Hyg. 2023 Dec 4:trad084.
doi: 10.1093/trstmh/trad084. Online ahead of print.

Impact of lamivudine treatment in late pregnancy on the development of the foetal immune response to hepatitis B virus: a meta-analysis in R with the metafor package

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Abstract

Background: Hepatitis B virus (HBV) infection is a worldwide public health burden, especially in Asia and Africa. Concerns were raised that foetal exposure to HBV and antiretroviral therapy (ART) might suppress the innate immune response and reduce the production of hepatitis B surface antibody (HBsAb) in foetuses and infants. We therefore conducted the current study to evaluate the impact of ART on the development of the immune response to HBV in foetuses and infants.

Methods: We selected lamivudine instead of telbivudine or tenofovir as the intervention measurement because it was the oldest and most widely used ART during pregnancy and its safety data have been sufficiently documented. A comprehensive search was conducted in eight electronic databases, including four Chinese and four English databases. Studies that met the following eligibility criteria were included: human randomized controlled trials (RCTs); participants in the treatment group were exclusively exposed to lamivudine; participants in the control group were exposed to placebo, no treatment or hepatitis B immunoglobulin; all participants were HBV-positive pregnant women with a high viral load and the main outcome of interest was neonatal HBsAb seropositivity. Data were tabulated and analysed using R software.

Results: Nine RCTs were included and analysed. Compared with controls, lamivudine significantly decreased HBsAb seronegativity in the newborn within 24 h after birth (indicating the foetal immune response to HBV). Similar results were noted in infants within 6-7 months after birth and infants within 12 months (indicating the neonatal immune response to HBV vaccine).

Conclusions: Lamivudine treatment in late pregnancy boosted the foetal immune response to HBV in utero and enhanced the neonatal immune response to hepatitis B vaccine after birth.

J Pediatr Gastroenterol Nutr. 2024 Feb;78(2):350-359.
doi: 10.1002/jpn3.12077. Epub 2023 Dec 11.

Midodrine reduces new-onset acute kidney injury and hyponatremia in children with cirrhosis and ascites awaiting liver transplantation: Results from an open-label RCT

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Abstract

Objectives: Midodrine, an oral α-1-adrenergic receptor agonist, counters arterial hypovolemia and reduces complications in adult patients with cirrhosis. This randomized controlled trial (RCT) aimed to assess the efficacy and safety of midodrine in preventing complications and improving survival in children with cirrhosis and ascites who are awaiting liver transplantation (LT).

Methods: This open-label RCT conducted from January 2022 to May 2023 included children under 18 years with cirrhosis and ascites. Patients were randomized to receive either

midodrine plus standard medical therapies (SMTs) or SMT alone. The primary outcome measure was the incidence of cirrhosis-related complications within 6 months.
Results: Thirty-five subjects were enrolled and randomized. Patients in the midodrine arm had a lower incidence of new-onset acute kidney injury (AKI) compared with the SMT arm (11.1% vs. 41.2%). Patients in the midodrine arm showed a decline in serum creatinine and improvement in glomerular filtration rate, whereas no changes were observed in the SMT arm. There was a lower incidence of new-onset hyponatremia in the midodrine arm (20% vs. 56%). Midodrine led to reduction in plasma rennin activity (PRA) and improvement in systemic hemodynamics. There was no difference in the rate of resolution of ascites, recurrence of ascites, requirement of therapeutic paracentesis, cumulative albumin infusion requirement, episodes of spontaneous bacterial peritonitis, and hepatic encephalopathy between the two arms.
Conclusion: Midodrine, when added to SMT, was effective in reducing the incidence of new-onset AKI and hyponatremia in pediatric cirrhotics awaiting LT. It also improved systemic hemodynamics and showed a trend towards reducing PRA.

Injury prevention

Traffic Inj Prev. 2024 Feb 7:1-8.
doi: 10.1080/15389588.2024.2305426. Online ahead of print.
Driver yield and safe child pedestrian crossing behavior promotion by a school traffic warden program at primary school crossings: A cluster-randomized trial
Jimmy Osuret [1], Ashley Van Niekerk [2 3], Olive Kobusingye [1], Lynn Atuyambe [4], Victoria Nankabirwa [5]
Abstract
Objective: To determine the effect of a school traffic warden program on increasing driver yield and safe child pedestrian crossing behavior in Kampala, Uganda.
Methods: We designed and implemented a school traffic warden program in specific school zones in Kampala, Uganda. We randomly assigned 34 primary schools in Kampala, in a 1:1 ratio, using a computer-generated randomization sequence, to control or intervention arms in a cluster randomized trial. Each school in the intervention group received one trained adult traffic warden stationed at roads adjacent to schools to help young children safely cross. The control schools continued with the standard of care. We extracted and coded outcome data from video recordings on driver yield and child crossing behavior (defined as waiting at the curb, looking both ways for oncoming vehicles, not running while crossing, and avoiding illegal crossing between vehicles) at baseline and after 6 months. Using a mixed effect modified Poisson regression model, we estimated the prevalence ratio to assess whether being in a school traffic warden program was associated with increased driver yield and safe crossing behavior.
Results: A higher proportion of drivers yielded to child pedestrians at crossings with a school traffic warden (aPR 7.2; 95% CI 4.42-11.82). Children were 70% more likely to demonstrate safe crossing behavior in the intervention clusters than in control clusters (aPR 1.7; 95% CI 1.04-2.85). A higher prevalence was recorded for walking while crossing (aPR 1.2; 95% CI 1.08-1.25) in the intervention clusters.

Conclusion: The school traffic warden program is associated with increased driver yield and safe child pedestrian crossing behavior, i.e., stopping at the curb, walking while crossing, and not crossing between vehicles. Therefore, the school traffic warden program could be promoted to supplement other road safety measures, such as pedestrian safety road infrastructure, legislation, and enforcement that specifically protects children in school zones.

Kidney disease

Kidney Int. 2024 May;105(5):1113-1123.
doi: 10.1016/j.kint.2024.01.028. Epub 2024 Feb 13.

An open label non-inferiority randomized controlled trial evaluated alternate day prednisolone given daily during infections vs. levamisole in frequently relapsing nephrotic syndrome

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Abstract

Initial therapies for children with frequently relapsing nephrotic syndrome include alternate-day prednisolone that is given daily during infections, or levamisole. In this open label, non-inferiority trial, 160 patients, 2 to 18-years-old with frequent relapses, were randomly assigned to receive either prednisolone (0.5-0.7 mg/kg/alternate-day, given daily during infections), or levamisole (2-2.5 mg/kg/alternate-days) for one-year. Patients with relapses on alternate day prednisolone at over 1 mg/kg, prior use of potent steroid-sparing therapies, eGFR under 60 ml/min/1.73 m^2 and significant steroid toxicity were excluded. Primary outcome was the proportion of patients with frequent relapses, defined as three-relapses in one-year, or two-relapses within six-months if associated with significant steroid toxicity or loss to follow up. Eighty patients each were randomized to receive prednisolone and levamisole. Baseline features showed preponderance of young patients presenting within two-years of disease onset. On intention-to-treat analysis, frequent relapses were more common in patients administered prednisolone (40% versus 22.5%; risk difference 17.5%; 95% confidence interval 3.4-31.6%). Prednisolone was not non-inferior to levamisole in preventing frequent relapses. However, the two groups showed similar proportions of patients in sustained remission, comparable frequency of relapses, and low frequency of adverse events. The decline in steroid requirement from baseline was higher in the levamisole group. Per-protocol analysis showed similar results. These results have implications for choice of therapy for frequently relapsing nephrotic syndrome. Although therapy with alternate-day prednisolone was not non-inferior to levamisole in preventing frequent relapses, both therapies were effective in other outcome measures. Thus, levamisole was relatively steroid-sparing and may be preferred in patients at risk of steroid toxicity.

Pediatr Nephrol. 2024 Jun 1.
doi: 10.1007/s00467-024-06402-9. Online ahead of print.

Daily compared with alternate-day levamisole in pediatric nephrotic syndrome: an open-label randomized controlled study

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Abstract

Background: Levamisole is less expensive and has a better toxicity profile compared to other steroid sparing agents used in nephrotic syndrome. It has a plasma half-life of 2.0 to 5.6 hours, but is conventionally administered on alternate days. We aimed to assess whether daily levamisole is safe and more effective than standard alternate-day therapy in maintaining remission in children with frequently relapsing or steroid-dependent nephrotic syndrome (FR/SDNS).

Methods: An open-label randomized controlled trial was conducted in children with FR/SDNS. Group A received daily while Group B received alternate-day levamisole (2-3 mg/kg/dose) for 12 months. Prednisolone was tapered off by 3 months. Patients were monitored for relapses, further steroid requirement, and adverse effects.

Results: A total of 190 children with FR/SDNS (94 in Group A and 96 in Group B) were analyzed. Sustained remission for 12 months was observed in 36% of Group A and 27% of Group B patients (p = 0.18). Numbers completing 12 months in the study were 67% in Group A and 56% in Group B (p = 0.13). Time to first relapse, persistent FR/SDNS, and withdrawal due to poor compliance were statistically similar in both groups, while relapse rate and cumulative steroid dosage were significantly lower in Group A compared to Group B (p = 0.03 and p = 0.02, respectively). The incidence of adverse effects was comparable in both groups, with reversible leucopenia and hepatic transaminitis being the commonest.

Conclusions: Daily levamisole therapy was not superior to alternate-day therapy in maintaining sustained remission over 12 months. Nevertheless, relapse rate and cumulative steroid dosage were significantly lower without increased adverse effects.

J Pediatr Urol. 2023 Dec;19(6):688-695.
doi: 10.1016/j.jpurol.2023.08.013. Epub 2023 Aug 22.

Mini-versus standard percutaneous nephrolithotomy in pediatric population: A randomized controlled trial

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Abstract

Introduction: Mini PCNL has gained popularity in adult patients due to reduction in the complication rate with comparable stone free rate. There is paucity of level 1 evidence regarding the benefit of mini PCNL in the pediatric group.

Objective: We performed a randomised study to compare mini PCNL (mPCNL) with standard PCNL (sPCNL) for the management of renal calculi in patients less than 18 years of age in terms of safety, efficacy, and stone-free rate (SFR).

Materials and methods: A randomised controlled trial was performed on 50 children who underwent PCNL from June 2015 to March 2021, who were divided into two groups. Group I had 25 patients managed with mPCNL (sheath size 16.5 Fr) and Group II had 25 patients who underwent sPCNL (sheath size 26 Fr). Primary outcomes including stone free rates (SFR) and hemoglobin drop and secondary outcomes like operative time, complications, pain score,

need of analgesia, incidence of nephrostomy site leak, hospital stay in days were compared between the two groups.
Results: The mean age of patients in groups I and II was 9.4 ± 2.6 and 10.4 ± 2.26 years, respectively (p = 0.15). The mean stone sizes in both groups I and II were 18.6 ± 2.56 and 20.2 ± 3.58 mm, respectively (p > 0.05). The stone free rate for group I was 88% and for group II, 92% (p = 0.64). The average drop in hemoglobin was higher in group II compared to group I (1.1 ± 0.31 g/dl and 1.7 ± 0.23 g/dl respectively; p < 0.0001), however the mean blood transfusion rate was not significantly different in both groups. The operating time was shorter in group II compared to group I (p-value - 0.0030). The pain scores were lesser for the group I. Grade I complications were higher in group II as compared to group I (p-0.047); however, grade II complications were comparable in both groups. The mean hospital stay was not significantly different in both groups.
Discussion: This study confirms the role of mini PCNL in pediatric patients with renal stones. The stone clearance rate of mini PCNL is equivalent to standard PCNL, with lesser blood loss and postoperative complications, however with longer operative time during mPCNL. The small number of the participants in both arms is a limitation of this study and may also reflect fewer children with urolithiasis being treated surgically even in a tertiary care referral centre.
Conclusions: Mini-PCNL offers equivalent stone free outcome with lower complications rate compared to the standard PCNL for all types of renal stones.

Leishmaniasis

J Antimicrob Chemother. 2023 Sep 20:dkad286.
doi: 10.1093/jac/dkad286. Online ahead of print.
Population pharmacokinetics of a combination of miltefosine and paromomycin in Eastern African children and adults with visceral leishmaniasis
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Abstract
Objectives: To improve visceral leishmaniasis (VL) treatment in Eastern Africa, 14- and 28-day combination regimens of paromomycin plus allometrically dosed miltefosine were evaluated. As the majority of patients affected by VL are children, adequate paediatric exposure to miltefosine and paromomycin is key to ensuring good treatment response.
Methods: Pharmacokinetic data were collected in a multicentre randomized controlled trial in VL patients from Kenya, Sudan, Ethiopia and Uganda. Patients received paromomycin (20 mg/kg/day for 14 days) plus miltefosine (allometric dose for 14 or 28 days). Population pharmacokinetic models were developed. Adequacy of exposure and target attainment of paromomycin and miltefosine were evaluated in children and adults.
Results: Data from 265 patients (59% ≤12 years) were available for this pharmacokinetic analysis. Paromomycin exposure was lower in paediatric patients compared with adults [median (IQR) end-of-treatment AUC0-24h 187 (162-203) and 242 (217-328) μg·h/mL, respectively], but were both within the IQR of end-of-treatment exposure in Kenyan and

Sudanese adult patients from a previous study. Cumulative miltefosine end-of-treatment exposure in paediatric patients and adults [AUCD0-28 517 (464-552) and 524 (456-567) µg·day/mL, respectively] and target attainment [time above the in vitro susceptibility value EC90 27 (25-28) and 30 (28-32) days, respectively] were comparable to previously observed values in adults.
Conclusions: Paromomycin and miltefosine exposure in this new combination regimen corresponded to the desirable levels of exposure, supporting the implementation of the shortened 14 day combination regimen. Moreover, the lack of a clear exposure-response and exposure-toxicity relationship indicated adequate exposure within the therapeutic range in the studied population, including paediatric patients.

BMC Public Health. 2024 May 13;24(1):1304.
doi: 10.1186/s12889-024-18810-5.

A community based intervention to modify preventive behaviors of cutaneous leishmaniasis in children: a randomized controlled trial based on PRECEDE PROCEED model

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Abstract
Objectives: Iran ranks among the top six countries globally with a significant incidence of Cutaneous Leishmaniasis (CL). Using planning models is one community-based intervention to promote preventive behaviors. The purpose of our study was to evaluate the effectiveness of the PRECEDE-PROCEED model (PPM) in modifying preventive behaviors related to CL in children through mother training in a community intervention.
Methods: A randomized controlled trial based on the PPM model was conducted on 168 mothers (intervention (n = 84) and control group (n = 84) with 10 years old children in the rural areas of Iran. Mothers from 7 village areas were randomly allocated to the intervention (2 village) and control groups (5 village). The intervention group received a program comprising eight 90-minute training sessions and environmental interventions. In this study, we utilized the PPM as a framework to design the questionnaires on Leishmaniosis prevention behavior. Participants in both groups completed the questionnaires at baseline (before the intervention), immediately after the intervention, and at the 2-month follow-up. Analysis of the data was conducted utilizing $SPSS_{20}$, with statistical significance set at $p < 0.05$.
Results: Compared to the control group, the intervention group showed significant increases in knowledge, enabling factors, reinforcing factors, attitude, and preventive behaviors related to Cutaneous Leishmaniasis over time from baseline to follow-up ($P < 0.001$). No significant differences ($P > 0.05$) were observed in the alterations of the PPM construct, knowledge, and preventive behaviors within the control group from pre-intervention to follow-up.
Conclusions: Community (education and environmental) intervention based on PPM is feasible and acceptable to modify preventive behaviors of Cutaneous Leishmaniasis in children by increasing a mother's knowledge and attitude as well as changing enabling and reinforcing factors.

PLoS Negl Trop Dis. 2024 Jun 20;18(6):e0012242.
doi: 10.1371/journal.pntd.0012242. eCollection 2024 Jun.

A phase II, non-comparative randomised trial of two treatments involving liposomal amphotericin B and miltefosine for post-kala-azar dermal leishmaniasis in India and Bangladesh

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Abstract

Background: In Southeast Asia, treatment is recommended for all patients with post-kala-azar dermal leishmaniasis (PKDL). Adherence to the first-line regimen, twelve weeks of miltefosine (MF), is low and ocular toxicity has been observed with this exposure period. We assessed the safety and efficacy of two shorter-course treatments: liposomal amphotericin B (LAmB) alone and combined with MF.

Methodology/principal findings: An open-label, phase II, randomized, parallel-arm, non-comparative trial was conducted in patients with parasitologically confirmed PKDL, 6 to ≤60 years. Patients were assigned to 20 mg/kg LAmB (total dose, in five injections over 15 days) alone or combined with allometric MF (3 weeks). The primary endpoint was definitive cure at 12 months, defined as complete resolution of papular and nodular lesions and >80% re-pigmentation of macular lesions. Definitive cure at 24 months was a secondary efficacy endpoint. 118/126 patients completed the trial. Definitive cure at 12 months was observed in 29% (18/63) patients receiving LAmB and 30% (19/63) receiving LAmB/MF (mITT), increasing to 58% and 66%, respectively, at 24 months. Most lesions had resolved/improved at 12 and 24 months for patients receiving LAmB (90%, 83%) and LAmB/MF (85%, 88%) by qualitative assessment. One death, unrelated to study drugs, was reported; no study drug-related serious adverse events were observed. The most frequent adverse drug reactions were MF-related vomiting and nausea, and LAmB-related hypokalaemia and infusion reactions. Most adverse events were mild; no ocular adverse events occurred.

Lymphatic filariasis

Leprosy

Lancet Glob Health. 2024 Jun;12(6):e1017-e1026.
doi: 10.1016/S2214-109X(24)00062-7.

Post-exposure prophylaxis in leprosy (PEOPLE): a cluster randomised trial

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Andrianarivelo [6], Hanitra Harinjatovo [3], Philip Supply [7], Rian Snijders [5], Carolien Hoof [5], Achilleas Tsoumanis [5], Philip Suffys [8], Tahinamandranto Rasamoelina [6], Paul Corstjens [9], Nimer Ortuno-Gutierrez [10], Annemieke Geluk [9], Emmanuelle Cambau [11], Bouke Catharina de Jong [5]

Abstract

Background: Post-exposure prophylaxis (PEP) using single-dose rifampicin reduces progression from infection with Mycobacterium leprae to leprosy disease. We compared effectiveness of different administration modalities, using a higher (20 mg/kg) dose of rifampicin-single double-dose rifampicin (SDDR)-PEP.

Methods: We did a cluster randomised study in 16 villages in Madagascar and 48 villages in Comoros. Villages were randomly assigned to four study arms and inhabitants were screened once a year for leprosy, for 4 consecutive years. All permanent residents (no age restriction) were eligible to participate and all identified patients with leprosy were treated with multidrug therapy (SDDR-PEP was provided to asymptomatic contacts aged ≥2 years). Arm 1 was the comparator arm, in which no PEP was provided. In arm 2, SDDR-PEP was provided to household contacts of patients with leprosy, whereas arm 3 extended SDDR-PEP to anyone living within 100 m. In arm 4, SDDR-PEP was offered to household contacts and to anyone living within 100 m and testing positive to anti-phenolic glycolipid-I. The main outcome was the incidence rate ratio (IRR) of leprosy between the comparator arm and each of the intervention arms. We also assessed the individual protective effect of SDDR-PEP and explored spatial associations. This trial is registered with ClinicalTrials.gov, NCT03662022, and is completed.

Findings: Between Jan 11, 2019, and Jan 16, 2023, we enrolled 109 436 individuals, of whom 95 762 had evaluable follow-up data. Our primary analysis showed a non-significant reduction in leprosy incidence in arm 2 (IRR 0·95), arm 3 (IRR 0·80), and arm 4 (IRR 0·58). After controlling for baseline prevalence, the reduction in arm 3 became stronger and significant (IRR 0·56, p=0·0030). At an individual level SDDR-PEP was also protective with an IRR of 0·55 (p=0·0050). Risk of leprosy was two to four times higher for those living within 75 m of an index patient at baseline.

Interpretation: SDDR-PEP appears to protect against leprosy but less than anticipated. Strong spatial associations were observed within 75 m of index patients. Targeted door-to-door screening around index patients complemented by a blanket SDDR-PEP approach will probably have a substantial effect on transmission.

Malaria

Malaria diagnosis

Insecticide-treated bed nets and other materials

Lancet Infect Dis. 2023 Sep 27:S1473-3099(23)00420-6.
doi: 10.1016/S1473-3099(23)00420-6. Online ahead of print.

Effectiveness of long-lasting insecticidal nets with pyriproxyfen-pyrethroid, chlorfenapyr-pyrethroid, or piperonyl butoxide-pyrethroid versus pyrethroid only against malaria in Tanzania: final-year results of a four-arm, single-blind, cluster-randomised trial

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Abstract

Background: New classes of long-lasting insecticidal nets (LLINs) containing two active ingredients have been recently recommended by WHO in areas where malaria vectors are resistant to pyrethroids. This policy was based on evidence generated by the first 2 years of our recently published trial in Tanzania. In this Article, we report the final third-year trial findings, which are necessary for assessing the long-term effectiveness of new classes of LLIN in the community and the replacement intervals required.

Methods: A third year of follow-up of a four-arm, single-blind, cluster-randomised controlled trial of dual active ingredient LLINs was conducted between July 14, 2021, and Feb 10, 2022, in Misungwi, Tanzania. Restricted randomisation was used to assign 84 clusters to the four LLIN groups (1:1:1:1) to receive either standard pyrethroid (PY) LLINs (reference), chlorfenapyr-PY LLINs, pyriproxyfen-PY LLINs, or piperonyl butoxide (PBO)-PY LLINs. All households received one LLIN for every two people. Data collection was done in consenting households in the cluster core area with at least one child between 6 months and 15 years of age who permanently resided in the selected household. Exclusion criteria were householders absent during the visit, living in the cluster buffer area, no adult caregiver capable of giving informed consent, or eligible children who were severely ill. Field staff and study participants were masked to allocation, and those analysing data were not. The primary 24-month endpoint was reported previously; here, we present the secondary outcome, malaria infection prevalence in children at 36 months post LLIN distribution, reported in the intention-to-treat analysis. The trial was registered with ClinicalTrials.gov (NCT03554616) and is now complete.

Findings: Overall usage of study nets was 1023 (22·3%) of 4587 people at 36 months post distribution. In the standard PY LLIN group, malaria infection was prevalent in 407 (37·4%) of 1088 participants, compared with 261 (22·8%) of 1145 in the chlorfenapyr-PY LLIN group (odds ratio 0·57, 95% CI 0·38-0·86; p=0·0069), 338 (32·2%) of 1048 in the PBO-PY LLIN group (0·95, 0·64-1·42; p=0·80), and 302 (28·8%) of 1050 in the pyriproxyfen-PY LLIN group (0·82, 0·55-1·23; p=0·34). None of the participants or caregivers reported side-effects.

Interpretation: Despite low coverage, the protective efficacy against malaria offered by chlorfenapyr-PY LLINs was superior to that provided by standard PY LLINs over a 3-year LLIN lifespan. Appropriate LLIN replacement strategies to maintain adequate usage of nets will be necessary to maximise the full potential of these nets.

Malar J. 2023 Oct 3;22(1):294.
doi: 10.1186/s12936-023-04727-8.

Effectiveness of piperonyl butoxide and pyrethroid-treated long-lasting insecticidal nets (LLINs) versus pyrethroid-only LLINs with and without indoor residual spray

against malaria infection: third year results of a cluster, randomised controlled, two-by-two factorial design trial in Tanzania

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Abstract

Background: After decades of success in reducing malaria through the scale-up of pyrethroid long-lasting insecticidal nets (LLINs), the decline in the malaria burden has stalled, coinciding with the rapid spread of pyrethroid resistance. In a previously reported study, nets treated with a pyrethroid and a synergist, piperonyl butoxide (PBO), demonstrated superior efficacy compared to standard pyrethroid LLINs (std-LLINs) against malaria. Evidence was used to support the public health recommendation of PBO-Pyrethroid-LLIN by the World Health Organization in 2018. This study looks at the third year of rollout of these nets in Muleba district, Tanzania to inform whether policy guidelines need to be updated.

Methods: A four-group cluster randomized trial (CRT) using a two-by-two factorial design was carried out between January 2014 and December 2017. A total of 48 clusters, were randomized in a 1:1:1:1 ratio to the following treatment groups, each intervention being provided once in 2015: 1/std-LLIN; 2/PBO-pyrethroid LLIN; 3/std-LLIN + Indoor Residual Spraying (IRS) and 4/PBO-Pyrethroid-LLIN + IRS. During the third year follow-up, malaria infection prevalence in 80 children per cluster, aged 6 months to 14 years, was measured at 28- and 33-months post-intervention and analysed as intention-to-treat (ITT) and per protocol (PP). Mosquito collections were performed monthly in all clusters, using CDC light traps in 7 randomly selected houses per cluster.

Results: At 28 and 33 months, study net usage among household participants was only 47% and 31%, respectively. In ITT analysis, after 28 months malaria infection prevalence among 7471 children was 80.9% in the two std-LLIN groups compared to 69.3% in the two PBO-Pyrethroid-LLIN (Odds Ratio: 0.45, 95% Confidence Interval: 0.21-0.95, p-value: 0.0364). After 33 months the effect was weaker in the ITT analysis (prevalence 59.6% versus 49.9%, OR: 0.60, 95%CI:0.32-1.13, p-value: 0.1131) but still evident in the PP analysis (57.2% versus 44.2%, OR: 0.34, 95%CI: 0.16-0.71, p-value: 0.0051). Mean number of Anopheles per night collected per house was similar between PBO-Pyrethroid-LLIN groups (5.48) and std-LLIN groups (5.24) during the third year.

Conclusions: Despite low usage of PBO- Pyrethroid LLIN, a small impact of those nets on malaria infection prevalence was still observed in the 3rd year with the most protection offered to children still using them. To maximize impact, it is essential that net re-distribution cycles are aligned with this LLIN lifespan to maintain maximum coverage.

Lancet Infect Dis. 2024 Jun;24(6):619-628.
doi: 10.1016/S1473-3099(24)00002-1. Epub 2024 Feb 21.

Effectiveness of pyriproxyfen-pyrethroid and chlorfenapyr-pyrethroid long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs for malaria control in the third year post-distribution: a secondary analysis of a cluster-randomised controlled trial in Benin

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Free article

Abstract

Background: Malaria continues to kill approximately 650 000 people each year. There is evidence that some second-generation insecticide-treated nets, which combine insecticide formulations with different modes of action, are protective against malaria while the nets are new; however, evidence for their impact over 3 years is scarce. In this study, we report the third-year results of a cluster-randomised controlled trial assessing the long-term effectiveness of dual-active ingredient long-lasting insecticidal nets (LLINs).

Methods: This is a secondary analysis of a cluster-randomised controlled trial, carried out between May 23, 2019, and April 30, 2023, in southern Benin. Restricted randomisation was used to assign 60 clusters (villages or groups of villages with a minimum of 100 households) to the three study groups (1:1:1) to evaluate the efficacy of pyriproxyfen-pyrethroid LLINs and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs (reference) against malaria transmission. The study staff and communities were masked to the group allocation. The primary outcome was malaria incidence measured over the third year after LLIN distribution, in a cohort of children aged 6 months to 9 years at the time of enrolment, in the intention-to-treat population. Here, we present the data of the third year post-LLIN distribution. The trial was registered with ClinicalTrials.gov, NCT03931473.

Findings: Study net use declined over the 3 years and was consistently lowest in the pyriproxyfen-pyrethroid LLIN group (at 36 months: 889 [39·4%] of 2257 participants vs 1278 [52·2%] of 2450 participants for the chlorfenapyr-pyrethroid LLIN group and 1400 [57·6%] of 2430 participants for the pyrethroid-only LLIN group). The cohort of children for the third year of follow-up (600 per group) were enrolled between April 9 and 30, 2022. Mean malaria incidence during the third year after distribution was 1·19 cases per child-year (95% CI 1·09-1·29) in the pyrethroid-only LLIN reference group, 1·21 cases per child-year (1·12-1·31) in the pyriproxyfen-pyrethroid LLIN group (hazard ratio [HR] 1·02, 95% CI 0·71-1·44; p=0·92), and 0·96 cases per child-year (0·88-1·05) in the chlorfenapyr-pyrethroid LLIN group (HR 0·80, 0·56-1·17; p=0·25). No adverse events related to study nets were reported by participants.

Interpretation: During the third year, as was also observed during the first 2 years, the pyriproxyfen-pyrethroid LLIN group did not have superior protection against malaria cases compared with the standard LLIN group. In the third year, people living in the chlorfenapyr-pyrethroid LLIN group no longer benefited from greater protection against malaria cases and infections than those living in the pyrethroid-only LLIN group. This was probably influenced by lower study net use than previous years and the declining concentration of partner insecticides in the nets.

BMC Infect Dis. 2023 Jul 20;23(1):486.
doi: 10.1186/s12879-023-08464-w.

Effect of malaria prevention education on bed net utilization, incidence of malaria and treatment seeking among school-aged children in Southern Ethiopia; cluster randomized controlled trial

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Abstract

Background: School-aged children (SAC) have an increased risk to contract malaria and play a major role in its transmission dynamics. However, their malaria prevention experience is poor. Thus, the effect of malaria prevention education (MPE) on bed net utilization, treatment seeking from a health facility and cumulative incidence of malaria was evaluated in Southern Ethiopia.

Methods: A two arm cluster randomized controlled trial was conducted by recruiting 2038 SAC from 32 schools. Structured questionnaire was used to collect data on socio-demographic, economic, bed net ownership, bed net utilization, whether the participated child suffered from malaria and has got treatment from a health facility. Generalized mixed effect logistic regression using school as random variable was used to assess the effect of the intervention on the outcome variables.

Results: The ownership of bed net in households of the control and intervention schools was similar respectively with 84.6 and 88.6% (Crude Odds Ratio (COR): 1.5; 95%CI: 0.5-4.8). The percentage of SAC slept under the bed net the night before the survey was also similar (55.1% versus 54.0%); COR:1.04; 95%CI: 0.5-2.4). Bed net utilization was affected by household size to the bed net ratio ≤ 2 (Adjusted Odds Ratio (AOR) = 1.6; 95%CI:1.3-2.1), bed net utilization at baseline of the study (AOR = 2.3; 95%CI:1.5-3.6), and history of malaria attack in the last twelve months (AOR = 1.3; 95%CI:1.01-1.8). Reported cumulative incidence of malaria and treatment seeking from a health facility by SAC was similar between intervention and control arms: -2.1% (COR = 0.8; 95%CI: 0.5-1.5) and 9.6% (COR = 1.4; 95%CI: 0.4-4.3) respectively. The reported incidence of malaria was affected by altitude (AOR = 0.5; 95%CI: 0.3-0.8), low and medium wealth index (AOR = 0.7; 95%CI: 0.5-0.96 and AOR = 0.7; 95%CI: 0.5-0.98), adequate bed net number for household members (AOR = 0.7; 95%CI:0.5-0.9) and bed net utilization (AOR = 1.3; 95%CI:1.1-1.8).

Conclusions: MPE had no significant effect on the use of malaria prevention measures considered, treatment seeking from a health facility and reported cumulative incidence of malaria though bed net use was associated with malaria incidence. Before organizing any health education program, sustainable implementation efforts have to be warranted especially in SAC, a neglected but relevant vulnerable and reservoirs.

Intermittent preventative treatment and seasonal malaria prophylaxis

N Engl J Med. 2024 May 2;390(17):1549-1559.
doi: 10.1056/NEJMoa2312775. Epub 2024 Apr 26.

Subcutaneous Administration of a Monoclonal Antibody to Prevent Malaria

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Abstract

Background: Subcutaneous administration of the monoclonal antibody L9LS protected adults against controlled *Plasmodium falciparum* infection in a phase 1 trial. Whether a monoclonal antibody administered subcutaneously can protect children from *P. falciparum* infection in a region where this organism is endemic is unclear.

Methods: We conducted a phase 2 trial in Mali to assess the safety and efficacy of subcutaneous administration of L9LS in children 6 to 10 years of age over a 6-month malaria season. In part A of the trial, safety was assessed at three dose levels in adults, followed by assessment at two dose levels in children. In part B of the trial, children were randomly assigned, in a 1:1:1 ratio, to receive 150 mg of L9LS, 300 mg of L9LS, or placebo. The primary efficacy end point, assessed in a time-to-event analysis, was the first *P. falciparum* infection, as detected on blood smear performed at least every 2 weeks for 24 weeks. A secondary efficacy end point was the first episode of clinical malaria, as assessed in a time-to-event analysis.

Results: No safety concerns were identified in the dose-escalation part of the trial (part A). In part B, 225 children underwent randomization, with 75 children assigned to each group. No safety concerns were identified in part B. *P. falciparum* infection occurred in 36 participants (48%) in the 150-mg group, in 30 (40%) in the 300-mg group, and in 61 (81%) in the placebo group. The efficacy of L9LS against *P. falciparum* infection, as compared with placebo, was 66% (adjusted confidence interval [95% CI], 45 to 79) with the 150-mg dose and 70% (adjusted 95% CI, 50 to 82) with the 300-mg dose (P<0.001 for both comparisons). Efficacy against clinical malaria was 67% (adjusted 95% CI, 39 to 82) with the 150-mg dose and 77% (adjusted 95% CI, 55 to 89) with the 300-mg dose (P<0.001 for both comparisons).

Conclusions: Subcutaneous administration of L9LS to children was protective against *P. falciparum* infection and clinical malaria over a period of 6 months.

Lancet Glob Health. 2023 Aug;11(8):e1277-e1289.
doi: 10.1016/S2214-109X(23)00204-8.

Effectiveness and safety of intermittent preventive treatment with dihydroartemisinin-piperaquine or artesunate-amodiaquine for reducing malaria and related morbidities in schoolchildren in Tanzania: a randomised controlled trial

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Abstract

Background: In high transmission settings, most school-aged children harbour malaria parasites without showing symptoms, often leading to anaemia and possibly impaired psychomotor and cognitive abilities. We aimed to assess the effectiveness and safety of

intermittent preventive treatment for malaria in school-aged children (IPTsc) living in highly endemic areas.
Methods: We did an open-label randomised controlled trial in seven primary schools in northeastern Tanzania. Schoolchildren aged 5-15 years were individually randomly assigned (1:1:1) to receive dihydroartemisinin-piperaquine, artesunate-amodiaquine, or standard of care (control) using a balanced block design. Drugs were administered by schoolteachers, with supervision from study nurses, at months 0 (baseline), 4, and 8, and were given in line with manufacturer's recommendations with dose based on the child's bodyweight. The primary endpoints were change from baseline in mean haemoglobin concentration at months 12 and 20, and clinical incidence of malaria and prevalence of parasitaemia at months 12 and 20 in the intervention groups versus the control group. The outcome data were collected through longitudinal surveys conducted every 4 months. Data were analysed on the basis of intention to treat (including all randomised participants) and per protocol (comprising children who completed the full 3-day regimen of all three IPTsc treatment rounds as assigned). This study is registered with ClinicalTrials.gov (NCT03640403).
Findings: Of the 1797 children scheduled for clinical screening, 1566 were enrolled and randomly allocated (526 to receive dihydroartemisinin-piperaquine, 527 to receive artesunate-amodiaquine, and 513 to receive standard of care). Due to COVID-19-related school closures, only two schools were visited at month 12 (135 children in the dihydroartemisinin-piperaquine group, 131 in the artesunate-amodiaquine group, and 118 in the control group). At month 12, compared with the control group, the change from baseline in mean haemoglobin concentration was increased by 0·5 g/dL (95% CI 0·2 to 0·8; p<0·0001) in the dihydroartemisinin-piperaquine group and 0·5 g/dL (0·2 to 0·7; p=0·0020) in the artesunate-amodiaquine group in the intention-to-treat analysis (with similar findings in the per protocol analysis). In the same period, in the intention-to-treat analysis, the prevalence of malaria parasitaemia increased from 28·5% (138 of 485 participants) to 33·6% (39 of 116) in the control group, but decreased from 28·0% (139 of 497) to 12·0% (15 of 125) in the dihydroartemisinin-piperaquine group (-21·6 percentage points [95% CI -31·9 to -11·3], p=0·0001 vs control at month 12) and from 24·7% (124 of 502) to 16·0% (20 of 125) in the artesunate-amodiaquine group (-17·6 percentage points [-28·4 to -6·9], p=0·0015). The decrease for artesunate-amodiaquine was larger in the per protocol analysis (-25·3 percentage points [-36·3 to -14·2], p<0·0001). The protective effect of IPTsc against malaria parasitaemia was 64% (95% CI 39 to 79; p<0·0001) for dihydroartemisinin-piperaquine and 52% (23 to 70; p=0·0015) for artesunate-amodiaquine in the intention-to-treat analysis, and was slightly higher on per protocol analysis. The protective effect against clinical malaria at month 12 was 20% (95% CI 9 to 29; p=0·0002) for dihydroartemisinin-piperaquine and 19% (8 to 28; p=0·0004) for artesunate-amodiaquine. No significant differences in any primary outcomes between the intervention and control groups were noted at month 20. Dihydroartemisinin-piperaquine and artesunate-amodiaquine were associated with a small number of mild adverse events, and there were no treatment-related serious adverse events or deaths.
Interpretation: IPTsc with dihydroartemisinin-piperaquine or artesunate-amodiaquine is a safe and effective approach to reducing malaria parasitaemia, clinical malaria, and related morbidities, and is feasible to implement through programmes delivered by schoolteachers.

Malar J. 2023 Oct 18;22(1):315.

doi: 10.1186/s12936-023-04745-6.

Enhanced effect of seasonal malaria chemoprevention when coupled with nutrients supplementation for preventing malaria in children under 5 years old in Burkina Faso: a randomized open label trial

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Abstract

Background: In rural African settings, most of the children under the coverage of Seasonal Malaria Chemoprevention (SMC) are also undernourished at the time of SMC delivery, justifying the need for packaging malarial and nutritional interventions. This study aimed at assessing the impact of SMC by coupling the intervention with nutrients supplementation for preventing malaria in children less than 5 years old in Burkina Faso.

Methods: A randomized trial was carried out between July 2020 and June 2021 in the health district of Nanoro, Burkina Faso. Children (n = 1059) under SMC coverage were randomly assigned to one of the three study arms SMC + Vitamin A (SMC-A, n = 353) or SMC + Vitamin A + Zinc (SMC-AZc, n = 353) or SMC + Vitamin A + PlumpyDoz(tm) (SMC-APd, n = 353)-a medium quantity-lipid-based nutrient supplement (MQ-LNS). Children were followed up for one year that included an active follow-up period of 6 months with scheduled monthly home visits followed by 6 months passive follow-up. At each visit, capillary blood sample was collected for malaria diagnosis by rapid diagnosis test (RDT).

Results: Adding nutritional supplements to SMC had an effect on the incidence of malaria. A reduction of 23% (adjusted IRR = 0.77 (95%CI 0.61-0.97) in the odds of having uncomplicated malaria in SMC-APd arm but not with SMC-AZc arm adjusted IRR = 0.82 (95%CI 0.65-1.04) compare to control arm was observed. A reduction of 52%, adjusted IRR = 0.48 (95%CI 0.23-0.98) in the odds of having severe malaria was observed in SMC-APd arm compared to control arm. Besides the effect on malaria, this combined strategy had an effect on all-cause morbidity. More specifically, a reduction of morbidity odds of 24%, adjusted IRR = 0.76 (95%CI 0.60-0.94) in SMC-APd arm compared to control arm was observed. Unlike clinical episodes, no effect of nutrient supplementation on cross sectional asymptomatic infections was observed.

Conclusion: Adding nutritional supplements to SMC significantly increases the impact of this intervention for preventing children from malaria and other childhood infections.

J Infect Dis. 2024 Jan 12;229(1):189-197.
doi: 10.1093/infdis/jiad387.

Randomized Field Trial to Assess the Safety and Efficacy of Dihydroartemisinin-Piperaquine for Seasonal Malaria Chemoprevention in School-Aged Children in Bandiagara, Mali

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Abstract

Background: Owing to the increased cases of malaria in older children, the World Health Organization has recently recommended extending seasonal malaria chemoprevention (SMC) to children >5 years of age and using other effective drugs for malaria. In this study, we report the safety and efficacy of dihydroartemisinin-piperaquine (DHA-PQ) for SMC in school-aged children in Mali.
Method: This randomized, controlled trial included 345 participants aged 6-15 years randomized to receive DHA-PQ, sulfadoxine-pyrimethamine plus amodiaquine (SP-AQ), or no chemoprevention (albendazole) at a 1:1:1 ratio. Four rounds of SMC were conducted from September to December 2021. The participants were assessed 7 days after each round for safety and efficacy of the interventions.
Results: Abdominal pain (11.8% vs 29.2%), headache (11.2% vs 19.2%), and vomiting (5.7% vs 15.2%) were frequently reported in the DHA-PQ and SP-AQ arms. On Day 120 of follow up, the incidence of clinical malaria was 0.01 episodes/person-month in the DHA-PQ and SP-AQ arms and 0.17 episodes/person-month in the control arm (P < .0001). Gametocytes were detected in 37 participants in all arms.
Conclusions: Children in DHA-PQ arm reported less adverse events compared to the SP-AQ arm. Both drugs were effective against clinical malaria and infection.

Sci Rep. 2024 Jan 25;14(1):2143.
doi: 10.1038/s41598-024-52706-z.

Dihydroartemisinin-piperaquine effectiveness for seasonal malaria chemoprevention in settings with extended seasonal malaria transmission in Tanzania

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Abstract
Effectiveness of dihydroartemisinin-piperaquine (DP) as seasonal malaria chemoprevention (SMC) was assessed in Nanyumbu and Masasi Districts. Between March and June 2021, children aged 3-59 months were enrolled in a cluster randomized study. Children in the intervention clusters received a monthly, 3-days course of DP for three consecutive months regardless of malaria infection status, and those in the control clusters received no intervention. Malaria infection was assessed at before the first-round and at 7 weeks after the third-round of DP in both arms. Malaria prevalence after the third-round of DP administration was the primary outcome. Chi-square tests and logistic regression model were used to compare proportions and adjust for explanatory variables. Before the intervention, malaria prevalence was 13.7% (161/1171) and 18.2% (212/1169) in the intervention and control clusters, respectively, p < 004. Malaria prevalence declined to 5.8% (60/1036) in the intervention clusters after three rounds of DP, and in the control clusters it declined to 9.3% (97/1048), p = 0.003. Unadjusted and adjusted prevalence ratios between the intervention and control arms were 0.42 (95%CI 0.32-0.55, p < 0.001) and 0.77 (95%CI 0.53-1.13, p = 0.189), respectively. SMC using DP was effective for control of malaria in the two Districts.

Lancet Glob Health. 2024 Jan;12(1):e33-e44.

doi: 10.1016/S2214-109X(23)00492-8.

Post-discharge malaria chemoprevention in children admitted with severe anaemia in malaria-endemic settings in Africa: a systematic review and individual patient data meta-analysis of randomised controlled trials

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Abstract

Background: Severe anaemia is associated with high in-hospital mortality among young children. In malaria-endemic areas, surviving children also have an increased risk of mortality or readmission after hospital discharge. We conducted a systematic review and individual patient data meta-analysis to determine the efficacy of monthly post-discharge malaria chemoprevention in children recovering from severe anaemia.

Methods: This analysis was conducted according to PRISMA-IPD guidelines. We searched multiple databases on Aug 28, 2023, without date or language restrictions, for randomised controlled trials comparing monthly post-discharge malaria chemoprevention with placebo or standard of care among children (aged <15 years) admitted with severe anaemia in malaria-endemic Africa. Trials using daily or weekly malaria prophylaxis were not eligible. The investigators from all eligible trials shared pseudonymised datasets, which were standardised and merged for analysis. The primary outcome was all-cause mortality during the intervention period. Analyses were performed in the modified intention-to-treat population, including all randomly assigned participants who contributed to the endpoint. Fixed-effects two-stage meta-analysis of risk ratios (RRs) was used to generate pooled effect estimates for mortality. Recurrent time-to-event data (readmissions or clinic visits) were analysed using one-stage mixed-effects Prentice-Williams-Peterson total-time models to obtain hazard ratios (HRs). This study is registered with PROSPERO, CRD42022308791.

Findings: Our search identified 91 articles, of which 78 were excluded by title and abstract, and a further ten did not meet eligibility criteria. Three double-blind, placebo-controlled trials, including 3663 children with severe anaemia, were included in the systematic review and meta-analysis; 3507 (95·7%) contributed to the modified intention-to-treat analysis. Participants received monthly sulfadoxine-pyrimethamine until the end of the malaria transmission season (mean 3·1 courses per child [range 1-6]; n=1085; The Gambia), monthly artemether-lumefantrine given at the end of weeks 4 and 8 post discharge (n=1373; Malawi), or monthly dihydroartemisinin-piperaquine given at the end of weeks 2, 6, and 10 post discharge (n=1049; Uganda and Kenya). During the intervention period, post-discharge malaria chemoprevention was associated with a 77% reduction in mortality (RR 0·23 [95% CI 0·08-0·70], p=0·0094, I^2=0%) and a 55% reduction in all-cause readmissions (HR 0·45 [95% CI 0·36-0·56], p<0·0001) compared with placebo. The protective effect was restricted to the intervention period and was not sustained after the direct pharmacodynamic effect of the drugs had waned. The small number of trials limited our ability to assess heterogeneity, its sources, and publication bias.

Interpretation: In malaria-endemic Africa, post-discharge malaria chemoprevention reduces mortality and readmissions in recently discharged children recovering from severe anaemia. Post-discharge malaria chemoprevention could be a valuable strategy for the management of this group at high risk. Future research should focus on methods of delivery, options to prolong the protection duration, other hospitalised groups at high risk, and interventions targeting non-malarial causes of post-discharge morbidity.

Treatment of uncomplicated malaria

(also see Community child health)

BMC Med. 2024 Jun 10;22(1):231.
doi: 10.1186/s12916-024-03441-9.

Expanding community case management of malaria to all ages can improve universal access to malaria diagnosis and treatment: results from a cluster randomized trial in Madagascar

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Abstract

Background: Global progress on malaria control has stalled recently, partly due to challenges in universal access to malaria diagnosis and treatment. Community health workers (CHWs) can play a key role in improving access to malaria care for children under 5 years (CU5), but national policies rarely permit them to treat older individuals. We conducted a two-arm cluster randomized trial in rural Madagascar to assess the impact of expanding malaria community case management (mCCM) to all ages on health care access and use.

Methods: Thirty health centers and their associated CHWs in Farafangana District were randomized 1:1 to mCCM for all ages (intervention) or mCCM for CU5 only (control). Both arms were supported with CHW trainings on malaria case management, community sensitization on free malaria care, monthly supervision of CHWs, and reinforcement of the malaria supply chain. Cross-sectional household surveys in approximately 1600 households were conducted at baseline (Nov-Dec 2019) and endline (Nov-Dec 2021). Monthly data were collected from health center and CHW registers for 36 months (2019-2021). Intervention impact was assessed via difference-in-differences analyses for survey data and interrupted time-series analyses for health system data.

Results: Rates of care-seeking for fever and malaria diagnosis nearly tripled in both arms (from less than 25% to over 60%), driven mostly by increases in CHW care. Age-expanded mCCM yielded additional improvements for individuals over 5 years in the intervention arm (rate ratio for RDTs done in 6-13-year-olds, $RR_{RDT6\text{-}13\ years}$ = 1.65; 95% CIs 1.45-1.87), but increases were significant only in health system data analyses. Age-expanded mCCM was associated with larger increases for populations living further from health centers ($RR_{RDT6\text{-}13\ years}$ = 1.21 per km; 95% CIs 1.19-1.23).

Conclusions: Expanding mCCM to all ages can improve universal access to malaria diagnosis and treatment. In addition, strengthening supply chain systems can achieve significant improvements even in the absence of age-expanded mCCM.

Malar J. 2024 Apr 3;23(1):92.
doi: 10.1186/s12936-024-04922-1.

Efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine and prevalence of molecular markers of anti-malarial drug resistance in children in Togo in 2021

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Abstract

Background: Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) are the currently recommended first- and second-line therapies for uncomplicated Plasmodium falciparum infections in Togo. This study assessed the efficacy of these combinations, the proportion of Day3-positive patients (D3 +), the proportion of molecular markers associated with P. falciparum resistance to anti-malarial drugs, and the variable performance of HRP2-based malaria rapid diagnostic tests (RDTs).

Methods: A single arm prospective study evaluating the efficacy of AL and DP was conducted at two sites (Kouvé and Anié) from September 2021 to January 2022. Eligible children were enrolled, randomly assigned to treatment at each site and followed up for 42 days after treatment initiation. The primary endpoint was polymerase chain reaction (PCR) adjusted adequate clinical and parasitological response (ACPR). At day 0, samples were analysed for mutations in the Pfkelch13, Pfcrt, Pfmdr-1, dhfr, dhps, and deletions in the hrp2/hrp3 genes.

Results: A total of 179 and 178 children were included in the AL and DP groups, respectively. After PCR correction, cure rates of patients treated with AL were 97.5% (91.4-99.7) at day 28 in Kouvé and 98.6% (92.4-100) in Anié, whereas 96.4% (CI 95%: 89.1-98.8) and 97.3% (CI 95%: 89.5-99.3) were observed at day 42 in Kouvé and Anié, respectively. The cure rates of patients treated with DP at day 42 were 98.9% (CI 95%: 92.1-99.8) in Kouvé and 100% in Anié. The proportion of patients with parasites on day 3 (D3 +) was 8.5% in AL and 2.6% in DP groups in Anié and 4.3% in AL and 2.1% DP groups in Kouvé. Of the 357 day 0 samples, 99.2% carried the Pfkelch13 wild-type allele. Two isolates carried nonsynonymous mutations not known to be associated with artemisinin partial resistance (ART-R) (A578S and A557S). Most samples carried the Pfcrt wild-type allele (97.2%). The most common Pfmdr-1 allele was the single mutant 184F (75.6%). Among dhfr/dhps mutations, the quintuple mutant haplotype N51I/C59R/S108N + 437G/540E, which is responsible for SP treatment failure in adults and children, was not detected. Single deletions in hrp2 and hrp3 genes were detected in 1/357 (0.3%) and 1/357 (0.3%), respectively. Dual hrp2/hrp3 deletions, which could affect the performances of HRP2-based RDTs, were not observed.

Conclusion: The results of this study confirm that the AL and DP treatments are highly effective. The absence of the validated Pfkelch13 mutants in the study areas suggests the absence of ART -R, although a significant proportion of D3 + cases were found. The absence of dhfr/dhps quintuple or sextuple mutants (quintuple + 581G) supports the continued use of SP for IPTp during pregnancy and in combination with amodiaquine for seasonal malaria chemoprevention.

Nat Commun. 2024 May 7;15(1):3817.
doi: 10.1038/s41467-024-48210-7.

Persistent and multiclonal malaria parasite dynamics despite extended artemether-lumefantrine treatment in children

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Abstract

Standard diagnostics used in longitudinal antimalarial studies are unable to characterize the complexity of submicroscopic parasite dynamics, particularly in high transmission settings. We use molecular markers and amplicon sequencing to characterize post-treatment stage-specific malaria parasite dynamics during a 42 day randomized trial of 3- versus 5 day artemether-lumefantrine in 303 children with and without HIV (ClinicalTrials.gov number NCT03453840). The prevalence of parasite-derived 18S rRNA is >70% in children throughout follow-up, and the ring-stage marker SBP1 is detectable in over 15% of children on day 14 despite effective treatment. We find that the extended regimen significantly lowers the risk of recurrent ring-stage parasitemia compared to the standard 3 day regimen, and that higher day 7 lumefantrine concentrations decrease the probability of ring-stage parasites in the early post-treatment period. Longitudinal amplicon sequencing reveals remarkably dynamic patterns of multiclonal infections that include new and persistent clones in both the early post-treatment and later time periods. Our data indicate that post-treatment parasite dynamics are highly complex despite efficacious therapy, findings that will inform strategies to optimize regimens in the face of emerging partial artemisinin resistance in Africa.

BMC Med. 2023 Oct 20;21(1):397.
doi: 10.1186/s12916-023-03105-0.

Factors affecting haemoglobin dynamics in African children with acute uncomplicated Plasmodium falciparum malaria treated with single low-dose primaquine or placebo

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Abstract

Background: Single low-dose primaquine (SLDPQ) effectively blocks the transmission of Plasmodium falciparum malaria, but anxiety remains regarding its haemolytic potential in patients with glucose-6-phopshate dehydrogenase (G6PD) deficiency. We, therefore, examined the independent effects of several factors on haemoglobin (Hb) dynamics in falciparum-infected children with a particular interest in SLDPQ and G6PD status.

Methods: This randomised, double-blind, placebo-controlled, safety trial was conducted in Congolese and Ugandan children aged 6 months-11 years with acute uncomplicated P. falciparum and day (D) 0 Hbs ≥ 6 g/dL who were treated with age-dosed SLDPQ/placebo and weight-dosed artemether lumefantrine (AL) or dihydroartemisinin piperaquine (DHAPP).

Genotyping defined G6PD (G6PD c.202T allele), haemoglobin S (HbS), and α-thalassaemia status. Multivariable linear and logistic regression assessed factor independence for continuous Hb parameters and Hb recovery (D42 Hb > D0 Hb), respectively.
Results: One thousand one hundred thirty-seven children, whose median age was 5 years, were randomised to receive: AL + SLDPQ (n = 286), AL + placebo (286), DHAPP + SLDPQ (283), and DHAPP + placebo (282). By G6PD status, 284 were G6PD deficient (239 hemizygous males, 45 homozygous females), 119 were heterozygous females, 418 and 299 were normal males and females, respectively, and 17 were of unknown status. The mean D0 Hb was 10.6 (SD 1.6) g/dL and was lower in younger children with longer illnesses, lower mid-upper arm circumferences, splenomegaly, and α-thalassaemia trait, who were either G6PDd or heterozygous females. The initial fractional fall in Hb was greater in younger children with higher D0 Hbs and D0 parasitaemias and longer illnesses but less in sickle cell trait. Older G6PDd children with lower starting Hbs and greater factional falls were more likely to achieve Hb recovery, whilst lower D42 Hb concentrations were associated with younger G6PD normal children with lower fractional falls, sickle cell disease, α-thalassaemia silent carrier and trait, and late treatment failures. Ten blood transfusions were given in the first week (5 SLDPQ, 5 placebo).
Conclusions: In these falciparum-infected African children, posttreatment Hb changes were unaffected by SLDPQ, and G6PDd patients had favourable posttreatment Hb changes and a higher probability of Hb recovery. These reassuring findings support SLDPQ deployment without G6PD screening in Africa.

Treatment of severe malaria

Int J Infect Dis. 2024 Feb:139:34-40.
doi: 10.1016/j.ijid.2023.11.031. Epub 2023 Nov 25.
Adjunctive rosiglitazone treatment for severe pediatric malaria: A randomized placebo-controlled trial in Mozambican children
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Abstract
Objectives: We tested the hypothesis that adjunctive rosiglitazone treatment would reduce levels of circulating angiopoietin-2 (Angpt-2) and improve outcomes of Mozambican children with severe malaria.
Methods: A randomized, double-blind, placebo-controlled trial of rosiglitazone vs placebo as adjunctive treatment to artesunate in children with severe malaria was conducted. A 0.045 mg/kg/dose of rosiglitazone or matching placebo were administered, in addition to standard of malaria care, twice a day for 4 days. The primary endpoint was the rate of decline of Angpt-2 over 96 hours. Secondary outcomes included the longitudinal dynamics of angiopoietin-1 (Angpt-1) and the Angpt-2/Angpt-1 ratio over 96 hours, parasite clearance kinetics, clinical outcomes, and safety metrics.

Results: Overall, 180 children were enrolled; 91 were assigned to rosiglitazone and 89 to placebo. Children who received rosiglitazone had a steeper rate of decline of Angpt-2 over the first 96 hours of hospitalization compared to children who received placebo; however, the trend was not significant (P = 0.28). A similar non-significant trend was observed for Angpt-1 (P = 0.65) and the Angpt-2/Angpt-1 ratio (P = 0.34). All other secondary and safety outcomes were similar between groups (P >0.05).
Conclusion: Adjunctive rosiglitazone at this dosage was safe and well tolerated but did not significantly affect the longitudinal kinetics of circulating Angpt-2.

Int J Infect Dis. 2023 Sep;134:240-247.
doi: 10.1016/j.ijid.2023.06.022. Epub 2023 Jul 5.

Prostration and the prognosis of death in African children with severe malaria

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Abstract

Objectives: Malaria is still one of the main reasons for hospitalization in children living in sub-Saharan Africa. Rapid risk stratification at admission is essential for optimal medical care and improved prognosis. Whereas coma, deep breathing, and, to a lesser degree, severe anemia are established predictors of malaria-related death, the value of assessing prostration for risk stratification is less certain.
Methods: Here we used a retrospective multi-center analysis comprising over 33,000 hospitalized children from four large studies, including two observational studies from the Severe Malaria in African Children network, a randomized controlled treatment study, and the phase-3-clinical RTS,S-malaria vaccine trial, to evaluate known risk factors of mortality and with a specific emphasis on the role of prostration.
Results: Despite comparable age profiles of the participants, we found significant inter- and intra-study variation in the incidence of fatal malaria as well as in the derived risk ratios associated with the four risk factors: coma, deep breathing, anemia, and prostration. Despite pronounced variations, prostration was significantly associated with an increased risk of mortality (P <0.001) and its consideration resulted in improved predictive performance, both in a multivariate model and a univariate model based on the Lambaréné Organ Dysfunction Score.
Conclusion: Prostration is an important clinical criterion to determine severe pediatric malaria with possible fatal outcomes.

Malnutrition

(Papers in past years listed in this section refer to the management of protein-energy malnutrition. For other relevant studies of nutrition see also Nutrition, Vitamin A, Vitamin D, Zinc, Maternal health, Anaemia and iron deficiency)

Clin Nutr. 2023 Aug 6;42(9):1778-1787.
doi: 10.1016/j.clnu.2023.08.003. Online ahead of print.

Changes in polyunsaturated fatty acids during treatment of malnourished children may be insufficient to reach required essential fatty acid levels - A randomised controlled trial

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Abstract

Background & aims: Severe acute malnutrition (SAM) is a global concern. Studies on the impact of ready-to-use therapeutic foods (RUTFs) on polyunsaturated fatty acids (PUFA) are almost non-existent. The aim was to investigate the change in whole-blood PUFA and nutrition and health markers among Cambodian children with SAM after treatment with RUTFs.

Methods: The trial was an 8-week randomised clinical trial of the effectiveness of locally produced fish-based RUTF (L-RUTF) vs standard milk-based RUFT (S-RUTF). Whole-blood fatty acids were analysed using dried blood spots. Nutrition and health markers were assessed using anthropometric assessment and blood samples for markers of inflammation. The trial was conducted at the National Pediatric Hospital, Phnom Penh, Cambodia, with one hundred and twenty-one 6-59-month-old children in treatment for SAM.

Results: L-RUTF had a higher content of n-3 PUFA and a higher content of arachidonic acid (AA) and docosahexaenoic acid (DHA), while S-RUTF had the highest content of n-6 PUFA. At baseline, the children presented with a Mead acid level in whole-blood of around 0.08% of total fatty acids (FA%) and an omega-3 index of ~0.91 ± 0.44. After eight weeks of S-RUTF treatment, linoleic acid (LA), AA, n-6/n-3 PUFA ratio, and Mead acid levels were increased. The L-RUTF intervention did not change the whole-blood PUFAs from baseline. At discharge, the children in the L-RUTF group had a lower n-6/n-3 PUFA ratio than the children in the S-RUTF group, driven by a lower alpha-linolenic acid (ALA) (0.20 vs 0.27 FA%, p = 0.004) and lower LA (15.77 vs 14.21 FA%, p = 0.018) with no significant differences in AA or DHA levels. Weight-for-height z-score at discharge was negatively associated with total PUFA (β -1.4 FA%, 95%CI. -2.7; -0.1), n-6 LCPUFA (β -1.3 FA%, 95%CI. -1.3; -0.3), and AA (β -0.6 FA%, 95%CI. -1.0; -0.2). Age-adjusted height was negatively associated with the Mead acid:AA ratio (β -1.2 FA%, 95%CI. -2.2; -0.2). No significant change was seen in inflammation markers within groups or between groups during treatment, and n-3 and n-6 PUFAs were not associated with markers of inflammation or haemoglobin status at discharge.

Conclusion: The trial found that whole-blood markers of PUFA status were low in children at admission and discharge from SAM treatment, indicating that the currently recommended composition of RUTFs are not able to correct their compromised essential fatty acid status. The higher content of DHA and AA in L-RUTF did not give rise to any improvement in PUFA status. No changes in health markers or associations between PUFA and health markers were found.

Indian J Pediatr. 2023 Oct;90(10):994-999.
doi: 10.1007/s12098-023-04614-9. Epub 2023 Jun 1.

A Randomized Controlled Trial on Comparison of Clinical Outcome in Uncomplicated SAM Managed with and without Antibiotics

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Abstract

Objectives: To assess the clinical outcome of management of uncomplicated severe acute malnutrition (SAM) at community level with antibiotics vs. without antibiotics.

Methods: A randomized controlled trial was conducted on children aged 6 to 59 mo with uncomplicated SAM, selected randomly from rural areas of Kanpur. A total of 100 children were enroled and were randomized into two groups, the intervention group who were given antibiotics for a week and the control group who were not given antibiotics. Rest of the management was same. Demographic, clinical and anthropometric details of each child were taken.

Results: Gender and socio-economic status was comparable in both the groups. Anthropometric parameters (mean weight for age, height for age and weight for height) in both the groups were not significantly different at the time of enrolment and also at two weeks follow-up. At 2 wk follow-up, weight/height Z score in the intervention and control group were -1.29±0.84 and -1.45±0.93, respectively (p value = 0.436).

Conclusions: It was concluded that whether antibiotics were given or not in the management of children with uncomplicated SAM, improvement in clinical and anthropometric parameters was seen without any significant difference.

Nutrients. 2023 Jul 17;15(14):3166.
doi: 10.3390/nu15143166.

Ready-to-Use Therapeutic Foods (RUTFs) Based on Local Recipes Are as Efficacious and Have a Higher Acceptability than a Standard Peanut-Based RUTF: A Randomized Controlled Trial in Indonesia

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Abstract

To strengthen community-based treatment of severe acute malnutrition (SAM) in Indonesia, locally produced ready-to-use therapeutic foods (RUTFs) are needed, but data on their acceptability and effectiveness are lacking. We conducted an individually randomized controlled trial in 302 children (6-59 months old) with uncomplicated SAM receiving 8 weeks of a standard RUTF (CON) or one of four alternative RUTFs produced with locally available ingredients: soybean (SOY), mungbean (MUN1, MUN2) or peanuts (PEA). The main outcomes were weight gain and product acceptability. Children consumed on average 2.2 kg of standard RUTF, but up to 4.5 kg of the local products (MUN2, $p < 0.05$). Mean weight gain did not differ across the groups ($p > 0.05$). Controlled for consumption, children receiving either CON or SOY RUTF gained >2 g/kg body weight (BW)/day compared with 1.6 g/kg BW/day in children receiving the other RUTF products ($p > 0.05$). Overall drop-out was 29.1%, ranging from 21.3% (MUN2) to 38.3% (CON, $p > 0.05$). Mean time to drop out was 19 days in the CON group, significantly shorter than in the PEA group (33.6 days, $p < 0.05$). Thus, with no

difference in weight gain and better acceptance, the development of locally produced RUTFs in Indonesia is warranted to strengthen the community-based treatment of SAM.

Matern Child Nutr. 2024 Apr;20(2):e13602.
doi: 10.1111/mcn.13602. Epub 2024 Jan 8.

Efficacy of ready-to-use food supplement for treatment of moderate acute malnutrition among children aged 6 to 59 months

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Abstract

Moderate acute malnutrition (MAM) is a persistent public health problem in Tanzania. The current approach for its management is nutrition counselling. However, there has been no commercial production of ready-to-use supplementary foods for the management of MAM in the country but rather imported from companies outside the country. The objective of the study was to determine the ability of a ready-to-use food supplementation versus corn soya blend (CSB+) to manage MAM. The randomised controlled trial employed three parallel arm approach. The first arm received CSB+ and infant and young child feeding (IYCF) counselling, the second arm received ready-to-use food (RUF) and IYCF counselling and the third arm, a control group, received IYCF as standard care for three consecutive months. Results indicated that the overall proportion of children who recovered from MAM was 65.6%. There was a significant difference ($p < 0.001$) in the proportion of children who recovered from MAM between the three arms (CSB+, RUF and standard care). Results revealed further a high recovery rate of 83.7% in the RUF arm, followed by 71.9% in the CSB+ arm and 41% in the standard care arm. The risk differences for RUF compared with CSB+ and standard care were 11.8% and 42.7%, respectively. RUFs can be used as an alternative supplement to conventional CSB+ for the management of MAM in children and, thus, has the potential to scale up its use to address the problem of MAM among 6 to 59 months' children.

Nutr Rev. 2024 Feb 13:nuad177.
doi: 10.1093/nutrit/nuad177. Online ahead of print.

Perspective on alternative therapeutic feeds to treat severe acute malnutrition in children aged between 6 and 59 months in sub-Saharan Africa: a narrative review

Marie-Claire Charlotte Nitschke [1], Martin Smollich [2]

Abstract

Worldwide, nearly 200 million children younger than 5 years old suffer from stunting and wasting, 2 different types of undernutrition. Moreover, 45% of deaths among children in that age group are associated with these conditions. Severe acute malnutrition (SAM) refers to children with a weight-for-height z score < -3, a midupper arm circumference < 115 mm, or the presence of bilateral edema, and is especially prevalent in low- and middle-income countries. Undernutrition in children can have a major impact on both their physical and cognitive development. It can lead to infections and death if it remains undetected or untreated. The use of therapeutic feeds is an important component in the management of

SAM, which remains a challenge in poorly resourced countries. The aim of this review was to assess the alternatives to the standard therapeutic foods used to treat SAM and to summarize their advantages and disadvantages, providing an overview of current research. A literature search was performed from September to November 2022 using PubMed, the Trip medical database, and the German Institute for Medical Documentation and Information (DIMDI). This review includes 13 randomized controlled trials testing alternatives to the standard therapeutic foods used to treat SAM by using alternative ingredients or a reduced dosage. The results show that, while a few alternative ready-to-use therapeutic food formulas lead to recovery rates similar to those seen with the standard protocol, many alternatives were less effective in the affected children. Thus, the evidence is not yet strong enough to change the World Health Organization's guidelines. The review identifies promising results of treatment alternatives related to treatment outcomes and costs. Additional research should focus on the interventions that positively impact the recovery process of severely malnourished children to facilitate the treatment and enable greater treatment coverage worldwide.

Matern Child Nutr. 2024 May 27:e13670.
doi: 10.1111/mcn.13670. Online ahead of print.

Effect of a simplified approach on recovery of children 6-59 months with wasting in Ethiopia: A noninferiority, cluster randomized controlled trial

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Abstract

Worldwide, nearly 45 million children under the age of 5 years were affected by wasting in 2022. Ethiopia has been challenged by disasters increasing the caseload of children with wasting. This study aimed to determine the effect of a simplified approach on recovery of children with acute malnutrition as compared with the standard protocol. A cluster randomized, controlled, noninferiority trial was carried out in three regions of Ethiopia from December 4, 2021, to July 30, 2022. A total of 58 clusters (health posts) were randomized into intervention and control groups. Children with SAM in the intervention groups received two sachets of Ready-to-Use Therapeutic Food (RUTF), whereas children in the control groups received RUTF based on their body weight. Children with moderate acute malnutrition (MAM) received one sachet of RUTF and one sachet of Ready-to-Use Supplementary Food (RUSF) daily in the intervention and control groups, respectively. Per protocol (PP) and intention-to-treat analysis were used to compare recovery at a noninferiority margin of 15%. Data were collected from 55 health posts and 1032 children. In the PP analysis, the recovery rate of children with wasting among the simplified group (97.8%) was noninferior to the standard protocol group (97.7%), p = 0.399. The RUTF cost per treatment of child with SAM was 56.55 USD for the standard versus 42.78 USD for the simplified approach. The simplified approach is noninferior to the standard protocol in terms of recovery and has a lower cost of RUTF. Further study is recommended to assess the effectiveness of the simplified approach in emergency contexts.

Front Public Health. 2024 Feb 21:12:1283148.
doi: 10.3389/fpubh.2024.1283148. eCollection 2024.

Effectiveness of decentralizing outpatient acute malnutrition treatment with community health workers and a simplified combined protocol: a cluster randomized controlled trial in emergency settings of Mali

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Abstract

Background: Outpatient treatment of acute malnutrition is usually centralized in health centers and separated into different programs according to case severity. This complicates case detection, care delivery, and supply chain management, making it difficult for families to access treatment. This study assessed the impact of treating severe and moderate cases in the same program using a simplified protocol and decentralizing treatment outside health centers through community health workers (CHWs).

Methods: A three-armed cluster randomized controlled trial under a non-inferiority hypothesis was conducted in the Gao region of Mali involving 2,038 children between 6 and 59 months of age with non-complicated acute malnutrition. The control arm consisted of 549 children receiving standard treatment in health centers from nursing staff. The first intervention arm consisted of 800 children treated using the standard protocol with CHWs added as treatment providers. The second intervention arm consisted of 689 children treated by nurses and CHWs under the ComPAS simplified protocol, considering mid-upper arm circumference as the sole anthropometric criterion for admission and discharge and providing a fixed dose of therapeutic food for severe and moderate cases. Coverage was assessed through cross-sectional surveys using the sampling evaluation of access and coverage (SLEAC) methodology for a wide area involving several service delivery units.

Results: The recovery rates were 76.3% in the control group, 81.8% in the group that included CHWs with the standard protocol, and 92.9% in the group that applied the simplified protocol, confirming non-inferiority and revealing a significant risk difference among the groups. No significant differences were found in the time to recovery (6 weeks) or in anthropometric gain, whereas the therapeutic food expenditure was significantly lower with the simplified combined program in severe cases (43 sachets fewer than the control). In moderate cases, an average of 35 sachets of therapeutic food were used. With the simplified protocol, the CHWs had 6% discharge errors compared with 19% with the standard protocol. The treatment coverage increased significantly with the simplified combined program (SAM +42.5%, MAM +13.8%).

Implications: Implementing a simplified combined treatment program and adding CHWs as treatment providers can improve coverage while maintaining non-inferior effectiveness, reducing the expenditure on nutritional intrants, and ensuring the continuum of care for the most vulnerable children.

Hum Resour Health. 2024 Mar 29;22(1):22.
doi: 10.1186/s12960-024-00904-1.

Cost-effectiveness of severe acute malnutrition treatment delivered by community health workers in the district of Mayahi, Niger

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Abstract

Background: A non-randomized controlled trial, conducted from June 2018 to March 2019 in two rural communes in the health district of Mayahi in Niger, showed that including community health workers (CHWs) in the treatment of severe acute malnutrition (SAM) resulted in a better recovery rate (77.2% vs. 72.1%) compared with the standard treatment provided solely at the health centers. The present study aims to assess the cost and cost-effectiveness of the CHWs led treatment of uncomplicated SAM in children 6-59 months compared to the standard national protocol.

Methods: To account for all relevant costs, the cost analysis included activity-based costing and bottom-up approaches from a societal perspective and on a within-trial time horizon. The cost-effectiveness analysis was conducted through a decision analysis network built with OpenMarkov and evaluated under two approaches: (1) with recovery rate and cost per child admitted for treatment as measures of effectiveness and cost, respectively; and (2) assessing the total number of children recovered and the total cost incurred. In addition, a multivariate probabilistic sensitivity analysis was carried out to evaluate the effect of uncertainty around the base case input data.

Results: For the base case data, the average cost per child recovered was 116.52 USD in the standard treatment and 107.22 USD in the CHWs-led treatment. Based on the first approach, the CHWs-led treatment was more cost-effective than the standard treatment with an average cost per child admitted for treatment of 82.81 USD vs. 84.01 USD. Based on the second approach, the incremental cost-effectiveness ratio of the transition from the standard to the CHWs-led treatment amounted to 98.01 USD per additional SAM case recovered.

Conclusions: In the district of Mayahi in Niger, the CHWs-led SAM treatment was found to be cost-effective when compared to the standard protocol and provided additional advantages such as the reduction of costs for households.

Health Policy Plan. 2024 Jun 5:czae036.
doi: 10.1093/heapol/czae036. Online ahead of print.

The Impacts of Task Shifting on the Management and Treatment of Malnourished Children in Northern Kenya: A Cluster-Randomized Controlled Trial

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Abstract

Treating children with acute malnutrition can be challenging, particularly regarding access to healthcare facilities during treatment. Task shifting, a strategy of transferring specific tasks to health workers with shorter training and fewer qualifications, is being considered as an effective approach to enhancing health outcomes in primary healthcare. This study aimed to assess the effectiveness of integrating the treatment of acute malnutrition by community health volunteers into integrated community case management in two sub-counties in

northern Kenya (Loima and Isiolo). We conducted a two-arm non-inferiority cluster-randomized controlled trial across 20 community health units. Participants were children aged 6-59 months with uncomplicated acute malnutrition. In the intervention group, community health volunteers used simplified tools and protocols to identify and treat eligible children at home and provided the usual integrated community case management package. In the control group, community health volunteers provided the usual integrated community case management package only (screening and referral of the malnourished children to the health facilities). The primary outcome was recovery (MUAC ≥12.5 cm for two consecutive weeks). Results show that children in the intervention group were more likely to recover than those in the control group [73 vs. 50; risk difference (RD)=26% (95% CI 12 to 40) and risk ratio (RR)=2 (95% CI 1.2 to 1.9)]. The probability of defaulting was lower in the intervention group than in the control group: RD=-21% (95% CI -31 to -10) and RR=0.3 (95% CI 0.2 to 0.5). The intervention reduced the length of stay by about 13 days, although this was not statistically significant and varied substantially by sub-county. Integrating the treatment of acute malnutrition by community health volunteers into the integrated community case management program led to better malnutrition treatment outcomes. There is a need to integrate acute malnutrition treatment into integrated community case management and review policies to allow community health volunteers to treat uncomplicated acute malnutrition.

J Pediatr Gastroenterol Nutr. 2023 Oct 2.
doi: 10.1097/MPG.0000000000003953. Online ahead of print.

Probiotic supplementation for promotion of growth in undernourished children: A systematic review and meta-analysis

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Abstract

Objectives: Probiotic supplementation has been proposed as a therapeutic intervention to improve growth outcomes in children with undernutrition. The objective of this review to synthesize the current evidence on probiotic supplementation for promotion of growth in undernourished children.

Methods: We searched MEDLINE, Cochrane CENTRAL, CINAHL, Embase, LILACS, and Scopus for randomized controlled trials (RCTs) that administered probiotics or eligible comparators to undernourished children below 5 years of age. Our primary outcomes of interest were weight-for-age, height-for-age, and weight-for-height at the longest follow-up points reported. Random-effects meta-analysis was used to calculate standardized mean differences (SMD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to assess certainty of the evidence.

Results: Nine RCTs with 5,295 children in total were included. Durations of treatment ranged from 1 month to 1 year. Pooled analyses from seven studies showed that probiotics may have little to no effect on weight-for-age (SMD 0.05 standard deviation [SD], 95% CI -0.04 to 0.13, n = 2115 children; low-certainty evidence) and height-for-age (SMD -0.04 SD, 95% CI -0.14 to 0.07, n = 1357 children; low-certainty evidence). The evidence was very uncertain about the effect on weight-for-height.

Conclusions: Probiotics may have little to no effect on anthropometry in undernourished children, though there is considerable heterogeneity among the trials reviewed thus far. The interaction between gut microbiota and human nutrition is complex, and further research is needed to determine how the gut microbiome may contribute to undernutrition and how probiotics may affect growth in this vulnerable population.

BMJ Open. 2023 Nov 24;13(11):e076805.
doi: 10.1136/bmjopen-2023-076805.

Solutions to Enhance Health with Alternative Treatments (SEHAT) protocol: a double-blinded randomised controlled trial for gut microbiota-targeted treatment of severe acute malnutrition using rice bran in ready-to-use therapeutic foods in Indonesia

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Abstract

Introduction: Current formulations of ready-to-use therapeutic foods (RUTFs) to treat severe acute malnutrition (SAM) in children focus on nutrient density and quantity. Less attention is given to foods targeting gut microbiota metabolism and mucosal barrier functions. Heat-stabilised rice bran contains essential nutrients, prebiotics, vitamins and unique phytochemicals that have demonstrated favourable bioactivity to modulate gut microbiota composition and mucosal immunity. This study seeks to examine the impact of RUTF with rice bran on the microbiota during SAM treatment, recovery and post-treatment growth outcomes in Jember, Indonesia. Findings are expected to provide insights into rice bran as a novel food ingredient to improve SAM treatment outcomes.

Methods and analysis: A total of 200 children aged 6-59 months with uncomplicated SAM (weight-for-height z-scores (WHZ) <-3, or mid-upper arm circumference (MUAC) <115 mm or having bilateral pitting oedema +/++) or approaching SAM (WHZ<-2.5) will be enrolled in a double-blinded, randomised controlled trial. Children in the active control arm will receive a locally produced RUTF; those in the intervention arm will receive the local RUTF with 5% rice bran. Children will receive daily RUTF treatment for 8 weeks and be monitored for 8 weeks of follow-up. Primary outcomes include the effectiveness of RUTF as measured by changes in weight, WHO growth z-scores, MUAC and morbidity. Secondary outcomes include modulation of the gut microbiome and dried blood spot metabolome, the percentage of children recovered at weeks 8 and 12, and malnutrition relapse at week 16. An intention-to-treat analysis will be conducted for each outcome.

Lancet Child Adolesc Health. 2024 Apr;8(4):280-289.
doi: 10.1016/S2352-4642(23)00339-5. Epub 2024 Feb 15.

Long-term outcomes after severe childhood malnutrition in adolescents in Malawi (LOSCM): a prospective observational cohort study

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Abstract

Background: Research on long-term outcomes of severe childhood malnutrition is scarce. Existing evidence suggests potential associations with cardiometabolic disease and impaired cognition. We aimed to assess outcomes in adolescents who were exposed to severe childhood malnutrition compared with peers not exposed to severe childhood malnutrition.

Methods: In Long-term Outcomes after Severe Childhood Malnutrition (LOCSM), we followed up adolescents who had 15 years earlier received treatment for severe childhood malnutrition at Queen Elizabeth Central Hospital in Blantyre, Malawi. Adolescents with previous severe childhood malnutrition included in LOCSM had participated in an earlier follow-up study (ChroSAM) at 7 years after treatment for severe childhood malnutrition, where they were compared to siblings and age-matched children in the community without previous severe childhood malnutrition. We measured anthropometry, body composition, strength, glucose tolerance, cognition, behaviour, and mental health during follow-up visits between Sept 9, 2021, and July 22, 2022, comparing outcomes in adolescents exposed to previous severe childhood malnutrition with unexposed siblings and adolescents from the community assessed previously (for ChroSAM) and newly recruited during current follow-up. We used a linear regression model to adjust for age, sex, disability, HIV, and socioeconomic status. This study is registered with the International Standard Randomised Controlled Trial Number Registry (ISRCTN17238083).

Findings: We followed up 168 previously malnourished adolescents (median age 17·1 years [IQR 16·5 to 18·0]), alongside 123 siblings (18·2 years [15·0 to 20·5]), and 89 community adolescents (17·1 years [16·3 to 18·1]). Since last measured 8 years previously, mean height-for-age Z (HAZ) scores had improved in previously malnourished adolescents (difference 0·33 [95% CI 0·20 to 0·46]) and siblings (0·32 [0·09 to 0·55]), but not in community adolescents (difference -0·01 [-0·24 to 0·23]). Previously malnourished adolescents had sustained lower HAZ scores compared with siblings (adjusted difference -0·32 [-0·58 to -0·05]) and community adolescents (-0·21 [-0·52 to 0·10]). The adjusted difference in hand-grip strength between previously malnourished adolescents and community adolescents was -2·0 kg (-4·2 to 0·3). For child behaviour checklist internalising symptom scores, the adjusted difference for previously malnourished adolescents was 2·8 (0·0 to 5·5) compared with siblings and 2·1 (-0·1 to 4·3) compared with community adolescents. No evidence of differences between previously malnourished adolescents and unexposed groups were found in any of the other variables measured.

Interpretation: Catch-up growth into adolescence was modest compared with the rapid improvement seen in childhood, but provides optimism for ongoing recovery of height deficits. We found little evidence of heightened non-communicable disease risk in adolescents exposed to severe childhood malnutrition, although long-term health implications need to be monitored. Further investigation of associated home and environmental factors influencing long-term outcomes is needed to tailor preventive and treatment interventions.

Editor's note: this is not a randomised trial but gives us important long-term information about outcomes of severe malnutrition.

Maternal health

(see also Malaria)

Antenatal care

JMIR Form Res. 2023 Jul 20;7:e44362.
doi: 10.2196/44362.

A Mobile Clinical Decision Support System for High-Risk Pregnant Women in Rural India (SMARThealth Pregnancy): Pilot Cluster Randomized Controlled Trial

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in women in India. Early identification is crucial to reducing deaths. Hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) carry independent risks for future CVD, and antenatal care is a window to screen and counsel high-risk women. In rural India, community health workers (CHWs) deliver antenatal and postnatal care. We developed a complex intervention (SMARThealth Pregnancy) involving mobile clinical decision support for CHWs and evaluated it in a pilot cluster randomized controlled trial (cRCT).

Objective: The aim of the study is to co-design a theory-informed intervention for CHWs to screen, refer, and counsel pregnant women at high risk of future CVD in rural India and evaluate its feasibility and acceptability.

Methods: In phase 1, we used qualitative methods to explore community priorities for high-risk pregnant women in rural areas of 2 diverse states in India. In phase 2, informed by behavior change theory and human-centered design, we used these qualitative data to develop the intervention components and implementation strategies for SMARThealth Pregnancy in an iterative process with end users. In phase 3, using mixed methods, we evaluated the intervention in a cRCT with an embedded qualitative substudy across 4 primary health centres: 2 in Jhajjar district, Haryana, and 2 in Guntur district, Andhra Pradesh.

Results: SMARThealth Pregnancy embedded a total of 15 behavior change techniques and included (1) community awareness programs; (2) targeted training, including point-of-care blood pressure and hemoglobin measurement; and (3) mobile clinical decision support for CHWs to screen women in their homes. The intervention focused on 3 priority conditions: anemia, HDP, and GDM. The evaluation involved a total of 200 pregnant women, equally randomized to intervention or enhanced standard care (control). Recruitment was completed within 5 months, with minimal loss to follow-up (4/200, 2%) at 6 weeks postpartum. A total of 4 primary care doctors and 54 CHWs in the intervention clusters took part in the study. Fidelity to intervention practices was 100% prepandemic. Over half the study population was affected by moderate to severe anemia at baseline. The prevalence of HDP (2.5%) and GDM (2%) was low in our study population. Results suggest a possible improvement in mean hemoglobin (anemia) in the intervention group, although an adequately powered trial is needed. The model of home-based care was feasible and

acceptable for pregnant or postpartum women and CHWs, who perceived improvements in quality of care, self-efficacy, and professional recognition.
Conclusions: SMARThealth Pregnancy is an innovative model of home-based care for high-risk pregnant women during the transitions between antenatal and postnatal care and adult health services. The use of theory and co-design during intervention development facilitated acceptability of the intervention and implementation strategies. Our experience has informed the decision to initiate a larger-scale cRCT.

Birth. 2024 Jun;51(2):319-325.
doi: 10.1111/birt.12788. Epub 2023 Oct 30.

Promoting childbirth in a rural health facility: A quasi-experimental study in western Kenya

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Abstract
Background: The high maternal and neonatal mortality rate in sub-Saharan Africa could be reduced by using navigation by means of mobile devices to increase the number of women who choose to give birth in a health center (HC) with a skilled healthcare practitioner.
Methods: A quasi-experimental design was used to test a midwife-delivered navigation by means of mobile phone. A total of 208 women were randomized to two groups (intervention and control). Women in the intervention group received up to three navigation calls from midwives. Women in the control group received usual antenatal education during prenatal visits. Data were collected using semistructured questionnaires. Childbirth location was determined through medical records.
Results: Overall, 180 (87%) women gave birth in a HC with a 3% advantage for the intervention group. A total of 86% (88/102) of the control group gave birth in a HC versus 89% (92/103) for the intervention group ($X^2 = 0.44$, p-value = 0.51), with an unadjusted odds ratio of 1.33 (95% CI: 0.57, 3.09). Among those with personal phones, 91% (138/152) had a birth in a HC versus 79% (42/53) in those without a personal phone ($X^2 = 4.89$, p-value = 0.03).
Conclusions: The results of this study indicate that it is feasible to deliver phone-based navigation to support birth in a HC; personal phone ownership may be a factor in the success of this strategy.

Lancet Glob Health. 2024 Apr;12(4):e641-e651.
doi: 10.1016/S2214-109X(24)00004-4.

Point-of-care testing and treatment of sexually transmitted and genital infections to improve birth outcomes in high-burden, low-resource settings (WANTAIM): a pragmatic cluster randomised crossover trial in Papua New Guinea

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Rogerson[17], Suzanne M Garland[16], Rebecca J Guy[3], Rosanna W Peeling[18], William S Pomat[1], John M Kaldor[3], Andrew J B Vallely[19]; WANTAIM study group

Abstract

Background: Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, and bacterial vaginosis have been associated with adverse maternal and perinatal outcomes, but there is conflicting evidence on the benefits of antenatal screening and treatment for these conditions. We aimed to determine the effect of antenatal point-of-care testing and immediate treatment of C trachomatis, N gonorrhoeae, T vaginalis, and bacterial vaginosis on preterm birth, low birthweight, and other adverse maternal and perinatal outcomes compared with current standard of care, which included symptom-based treatment without laboratory confirmation.

Methods: In this pragmatic cluster randomised crossover trial, we enrolled women (aged ≥16 years) attending an antenatal clinic at 26 weeks' gestation or earlier (confirmed by obstetric ultrasound), living within approximately 1 h drive of a study clinic, and able to provide reliable contact details at ten primary health facilities and their catchment communities (clusters) in Papua New Guinea. Clusters were randomly allocated 1:1 to receive either the intervention or control (standard care) in the first phase of the trial. Following an interval (washout period) of 2-3 months at the end of the first phase, each cluster crossed over to the other group. Randomisation was stratified by province. Individual participants were informed about trial group allocation only after completing informed consent procedures. The primary outcome was a composite of preterm birth (livebirth before 37 weeks' gestation), low birthweight (<2500 g), or both, analysed according to the intention-to-treat population. This study is registered with ISRCTN Registry, ISRCTN37134032, and is completed.

Findings: Between July 26, 2017, and Aug 30, 2021, 4526 women were enrolled (2210 [63·3%] of 3492 women in the intervention group and 2316 [62·8%] of 3687 in the control group). Primary outcome data were available for 4297 (94·9%) newborn babies of 4526 women. The proportion of preterm birth, low birthweight, or both, in the intervention group, expressed as the mean of crude proportions across clusters, was 18·8% (SD 4·7%) compared with 17·8% in the control group (risk ratio [RR] 1·06, 95% CI 0·78-1·42; p=0·67). There were 1052 serious adverse events reported (566 in the intervention group and 486 in the control group) among 929 trial participants, and no differences by trial group.

Interpretation: Point-of-care testing and treatment of C trachomatis, N gonorrhoeae, T vaginalis, and bacterial vaginosis did not reduce preterm birth or low birthweight compared with standard care. Within the subgroup of women with N gonorrhoeae, there was a substantial reduction in the primary outcome.

BMJ Open. 2024 Feb 7;14(2):e070798.
doi: 10.1136/bmjopen-2022-070798.

Can an integrated intervention package including peer support increase the proportion of health facility births? A cluster randomised controlled trial in Northern Uganda

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Abstract
Objective: To assess the effect of an integrated intervention package compared with routine government health services on the frequency of health facility births.
Setting: Three subcounties of Lira district in Northern Uganda.
Design: A cluster randomised controlled trial where a total of 30 clusters were randomised in a ratio of 1:1 to intervention or standard of care.
Participants: Pregnant women at ≥28 weeks of gestation.
Interventions: Participants in the intervention arm received an integrated intervention package of peer support, mobile phone messaging and birthing kits during pregnancy while those in the control arm received routine government health services ('standard of care').
Primary and secondary outcome measures: The primary outcome was the proportion of women giving birth at a health facility in the intervention arm compared with the control arm. Secondary outcomes were perinatal and neonatal deaths.
Results: In 2018-2019, 995 pregnant women were included in 15 intervention clusters and 882 in 15 control clusters. The primary outcome was ascertained for all except one participant who died before childbirth. In the intervention arm, 754/994 participants (76%) gave birth at a health facility compared with 500/882 (57%) in the control arm. Participants in the intervention arm were 35% more likely to give birth at a health facility compared with participants in the control arm, (risk ratio 1.35 (95% CI 1.20 to 1.51)) and (risk difference 0.20 (95% CI 0.13 to 0.27)). Adjusting for baseline differences generated similar results. There was no difference in secondary outcomes (perinatal or neonatal mortality or number of postnatal visits) between arms.
Conclusion: The intervention was successful in increasing the proportion of facility-based births but did not reduce perinatal or neonatal mortality.

Birth. 2023 Sep;50(3):587-595.
doi: 10.1111/birt.12681. Epub 2022 Oct 13.

Effects of an educational intervention on Nigerian midwives' intention to provide planned home birth care

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Abstract
Background: The majority of women in Sokoto, Nigeria prefer homebirths, but midwives are reluctant to provide care in the home setting. As such, many women continue to give birth at home alone or assisted by untrained attendants, which is associated with an increased risk for maternal and neonatal morbidity and mortality.
Methods: A randomized controlled trial was conducted among 226 midwives from 10 health care facilities. The intervention group received an educational program on home birth. A validated questionnaire that evaluated knowledge, attitudes, norms, perceived control, and intention to provide planned home birth care was given at baseline, immediately after the intervention, and at three-months follow-up. Data were analyzed using linear mixed-effect model statistics.
Results: Following the intervention, the intervention group demonstrated higher knowledge and more positive attitudes, norms, perceived control, and intention to provide planned

home birth care compared with the control group (P < 0.05). No significant changes in the scores of the control group were observed during the study duration (P > 0.05).
Discussion: Educating midwives on planned home birth increases their willingness to provide planned home birth care. Health system administrators, policymakers, and researchers may use similar interventions to promote skilled home birth attendance by midwives. Increasing the number of midwives who are willing to attend planned home births provides women at low risk for medical complications with safer options for labor, delivery, and postpartum care.

BMC Public Health. 2023 Aug 4;23(1):1491.
doi: 10.1186/s12889-023-16376-2.

Effects of a community-level intervention on maternal health care utilization in a resource-poor setting of Northern Ghana

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Abstract

Background: This study aimed to assess the effects of health education and community-level participatory interventions at the community level and the use of community maternal health promoters on the utilization of maternal health care services in poor rural settings of northern Ghana.
Methods: A randomized controlled survey design was conducted from June 2019 to July 2020 in two rural districts of northern Ghana. A multistage cluster sampling technique was used to select the participants. Data were collected from a repeated cross-sectional household survey. Descriptive analysis, bivariate and covariates adjusted simple logistic regression analyses were performed using STATA version 16 statistical software.
Results: At post-intervention, the two groups differed significantly in terms of ANC (p = 0.001), skilled delivery (SD) (p = 0.003), and PNC (p < 0.0001). Women who received health education on obstetric danger signs had improved knowledge by 50% at the end of the study. Women who received the health education intervention (HEI) on practices related to ANC and skilled delivery had increased odds to utilize ANC (AOR = 4.18; 95% CI = 2.48-7.04) and SD (AOR = 3.90; 95% CI = 1.83-8.29) services. Institutional delivery and PNC attendance for at least four times significantly increased from 88.5 to 97.5% (p < 0.0001), and 77.3-96.7% (p < 0.0001) respectively at postintervention. Women who had received the HEI were significantly more likely to have good knowledge about obstetric danger signs (AOR = 10.17; 95% CI = 6.59-15.69), and BPCR (AOR = 2.10; 95% CI = 1.36-3.24). Women who had obtained tertiary education were significantly more likely to make at least four visits to ANC (AOR = 2.38; 95% CI = 0.09-1.67).
Conclusions: This study suggests that the use of health education and participatory sessions led by community-based facilitators could be a potentially effective intervention to improve the knowledge of women about obstetric danger signs and encourage the uptake of maternity care services in resource-poor settings of Ghana.

JAMA Netw Open. 2024 Feb 5;7(2):e2356609.
doi: 10.1001/jamanetworkopen.2023.56609.

Effect of Maternal and Newborn Care Service Package on Perinatal and Newborn Mortality: A Cluster Randomized Clinical Trial

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Abstract

Importance: In resource-constrained settings where the neonatal mortality rate (NMR) is high due to preventable causes and health systems are underused, community-based interventions can increase newborn survival by improving health care practices.

Objectives: To develop and evaluate the effectiveness of a community-based maternal and newborn care services package to reduce perinatal and neonatal mortality in rural Pakistan.

Design, setting, and participants: This cluster randomized clinical trial was conducted between November 1, 2012, and December 31, 2013, in district Rahim Yar Khan in the province of Punjab. A cluster was defined as an administrative union council. Any consenting pregnant resident of the study area, regardless of gestational age, was enrolled. An ongoing pregnancy surveillance system identified 12 529 and 12 333 pregnancies in the intervention and control clusters, respectively; 9410 pregnancies were excluded from analysis due to continuation of pregnancy at the end of the study, loss to follow-up, or miscarriage. Participants were followed up until the 40th postpartum day. Statistical analysis was performed from January to May 2014.

Intervention: A maternal and newborn health pack, training for community- and facility-based health care professionals, and community mobilization through counseling and education sessions.

Main outcomes and measures: The primary outcome was perinatal mortality, defined as stillbirths per 1000 births and neonatal death within 7 days per 1000 live births. The secondary outcome was neonatal mortality, defined as death within 28 days of life per 1000 live births. Systematic random sampling was used to allocate 10 clusters each to intervention and control groups. Analysis was conducted on a modified intention-to-treat basis.

Results: For the control group vs the intervention group, the total number of households was 33 188 vs 34 315, the median number of households per cluster was 3092 (IQR, 3018-3467) vs 3469 (IQR, 3019-4075), the total population was 229 155 vs 234 674, the mean (SD) number of residents per household was 6.9 (9.5) vs 6.8 (9.6), the number of males per 100 females (ie, the sex ratio) was 104.2 vs 103.7, and the mean (SD) number of children younger than 5 years per household was 1.0 (4.2) vs 1.0 (4.3). Altogether, 7598 births from conrol clusters and 8017 births from intervention clusters were analyzed. There was no significant difference in perinatal mortality between the intervention and control clusters (rate ratio, 0.86; 95% CI, 0.69-1.08; P = .19). The NMR was lower among the intervention than the control clusters (39.2/1000 live births vs 52.2/1000 live births; rate ratio, 0.75; 95% CI, 0.58-0.95; P = .02). The frequencies of antenatal visits and facility births were similar between the 2 groups. However, clean delivery practices were higher among intervention clusters than control clusters (63.2% [2284 of 3616] vs 13.2% [455 of 3458]; P < .001). Chlorhexidine use was also more common among intervention clusters than control clusters (55.9% [4271 of 7642] vs 0.3% [19 of 7203]; P < .001).

Conclusions and relevance: This pragmatic cluster randomized clinical trial demonstrated a reduction in NMR that occurred in the background of improved household intrapartum and newborn care practices. However, the effect of the intervention on antenatal visits, facility births, and perinatal mortality rates was inconclusive, highlighting areas requiring further research. Nevertheless, the improvement in NMR underscores the effectiveness of community-based programs in low-resource settings.

BMC Womens Health. 2024 Mar 26;24(1):200.
doi: 10.1186/s12905-024-03009-y.

Effect of behavior change communication through the health development army on birth weight of newborns in Ambo district, Ethiopia: a cluster randomized controlled community trial

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Abstract

Background: Poor behavior change communication on maternal nutrition and health throughout pregnancy is thought to be to blame for Ethiopia's high rate of low birthweight babies, and this has implications for neonatal morbidity and mortality. The effect of behavior change communication on birth weight in the study district was not examined. This study was to determine whether improving neonatal birthweight using nutrition and health behavior change communication (NHBCC) interventions was successful.

Methods: A cluster randomized controlled trial was conducted in the Ambo district of Ethiopia from May 5, 2018-January 30, 2019. At the beginning of the study, 385 women in the 24 intervention groups and 385 women in the 24 control groups were recruited. In the intervention group, health development armies delivered the NHBCC core message every two weeks for four months by grouping pregnant women in specific clusters. Pregnant women in the control group received the routine treatment offered by the healthcare system during their ANC visits. Within 24 h of birth, the birthweights of 302 and 292 neonates in the intervention and control groups, respectively, were measured at the end point of the study. A binary generalized linear model analysis was employed.

Result: The control group had a larger absolute risk of neonates with low birthweight (0.188 vs. 0.079, $p < 0.001$) than the intervention group. Pregnant women in the intervention group had an absolute risk difference of 10.9% for low birthweight. Pregnant women who received the intervention were 62% less likely to have low-risk birthweight compared to pregnant women who were in the control group (ARR = 0.381, 95% CI: 0.271-0.737).

Conclusion: Nutrition and health behavior change Communication by health development armies improves birthweight. The findings demonstrated that to improve birthweight, NHBCC must be administered to pregnant women in groups via health development armies in their communities.

BMC Pregnancy Childbirth. 2024 Jan 5;24(1):37.
doi: 10.1186/s12884-023-06224-x.

Improving health literacy through group antenatal care: results from a cluster randomized controlled trial in Ghana

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Abstract

Background: Although the majority of Ghanaian women receive antenatal care (ANC), many exhibit low health literacy by misinterpreting and incorrectly operationalizing ANC messages, leading to poor maternal and newborn health outcomes. Prior research in low-resource settings has found group antenatal care (G-ANC) feasible for women and providers. This study aims to determine the effect of G-ANC on increasing maternal health literacy. We hypothesized that pregnant women randomized into G-ANC would exhibit a greater increase in maternal health literacy than women in routine, individual ANC.

Methods: A 5-year cluster randomized controlled trial was conducted in 14 rural and peri-urban health facilities in the Eastern Region of Ghana. Facilities were paired based on patient volume and average gestational age at ANC enrollment and then randomized into intervention (G-ANC) vs. control (routine, individual ANC); 1761 pregnant women were recruited. Data collection occurred at baseline (T0) and post-birth (T2) using the Maternal Health Literacy scale, a 12-item composite scale to assess maternal health literacy. Logistic regression compared changes in health literacy from T0 to T2.

Results: Overall, women in both the intervention and control groups improved their health literacy scores over time ($p < 0.0001$). Women in the intervention group scored significantly higher on 3 individual items and on overall composite scores ($p < 0.0001$) and were more likely to attend 8 or more ANC visits.

Conclusion: While health literacy scores improved for all women attending ANC, women randomized into G-ANC exhibited greater improvement in overall health literacy post-birth compared to those receiving routine individual care. Life-saving information provided during ANC must be presented in an understandable format to prevent women and newborns from dying of preventable causes.

PLOS Glob Public Health. 2024 Feb 27;4(2):e0002693.
doi: 10.1371/journal.pgph.0002693. eCollection 2024.

Association of maternal, obstetric, fetal, and neonatal mortality outcomes with Lady Health Worker coverage from a cross-sectional survey of >10,000 households in Gilgit-Baltistan, Pakistan

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Abstract

Pakistan has among the highest rates of maternal, perinatal, and neonatal mortality globally. Many of these deaths are potentially preventable with low-cost, scalable interventions delivered through community-based health worker programs to the most remote communities. We conducted a cross-sectional survey of 10,264 households during the baseline phase of a cluster randomized controlled trial (cRCT) in Gilgit-Baltistan, Pakistan from June-August 2021. The survey was conducted through a stratified, two-stage sampling design with the objective of estimating the neonatal mortality rate (NMR) within the study

catchment area, and informing implementation of the cRCT. Study outcomes were self-reported and included neonatal death, stillbirth, health facility delivery, maternal death, postpartum hemorrhage (PPH), and Lady Health Worker (LHW) coverage. Summary statistics (proportions and rates) were weighted according to the sampling design, and mixed-effects Poisson regression was conducted to explore the relationship between LHW coverage and maternal/newborn outcomes. We identified 7,600 women who gave birth in the past five years, among whom 13% reported experiencing PPH. The maternal mortality ratio was 225 maternal deaths per 100,000 live births (95% confidence interval [CI] 137-369). Among 12,376 total births, the stillbirth rate was 41.4 per 1,000 births (95% CI 36.8-46.7) and the perinatal mortality rate was 53.0 per 1,000 births (95% CI 47.6-59.0). Among 11,863 live births, NMR was 16.2 per 1,000 live births (95% CI 13.6-19.3) and 65% were delivered at a health facility. LHW home visits were associated with declines in PPH (risk ratio [RR] 0.89 per each additional visit, 95% CI 0.83-0.96) and late neonatal mortality (RR 0.80, 95% CI 0.67-0.97). Intracluster correlation coefficients were also estimated to inform the planning of future trials. The high rates of maternal, perinatal, and neonatal death in Gilgit-Baltistan continue to fall behind targets of the 2030 Sustainable Development Goals.

Maternal mental health

J Affect Disord. 2023 Oct 15;339:82-88.
doi: 10.1016/j.jad.2023.07.047. Epub 2023 Jul 10.

Antenatal depression and adverse birth outcomes among pregnant women living with HIV in Dar es Salaam, Tanzania

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Abstract

Background: Women who experience antenatal depression may be at increased risk of adverse birth outcomes. Few studies have examined this association among women living with HIV (WHIV).

Methods: We conducted a prospective cohort study of 2298 pregnant WHIV on antiretroviral therapy (ART) in Dar es Salaam, Tanzania, who were participants in a randomized trial of vitamin D_3 supplementation. Depressive symptoms were assessed at 12-27 weeks gestation using the Hopkins Symptoms Checklist (HSCL-25). Generalized estimating equations to account for twins were used to assess the relative risks of adverse birth outcomes.

Results: Approximately 67 % of the women in our study population reported symptoms consistent with depression. We observed a 4.0 % prevalence of stillbirth and a 25.1 % prevalence of preterm birth. We found that low social support, higher education, and more recent initiation of ART were associated with a greater risk of antenatal depression. There was no association of antenatal depression with risk of fetal loss, stillbirth, low birth weight, birth weight, preterm birth, gestational age at delivery, or small-for-gestational age.

Limitations: Depression was self-reported and only collected at one timepoint in pregnancy. Our findings may not be generalizable to all WHIV.

Conclusions: Our findings illustrate the high risk of both depression and adverse birth outcomes among WHIV and underscore the need for interventions to improve their mental health and the health of their infants; however, the relationship between depression and birth outcomes remains unclear. Further research on this topic is merited, particularly examining the chronicity and timing of depression in pregnancy.

J Affect Disord. 2023 Oct 15;339:325-332.
doi: 10.1016/j.jad.2023.07.020. Epub 2023 Jul 12.

Association between the continuum of care and postpartum depression among Angolan mothers

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Abstract

Background: This study investigated the association between maternal and child health service utilization patterns and postpartum depression (PPD).

Methods: This study analyzed a dataset of women who participated in a randomized controlled trial to examine the effectiveness of the Maternal and Child Health Handbook in Angola. We defined probable PPD as an Edinburgh Postpartum Depression Scale (EPDS) score ≥ 10. The EPDS was administered at approximately 6 months postpartum. Service utilization patterns were defined using numbers of antenatal care (ANC), facility delivery, and vaccination visits by 6 months postpartum. The association between service utilization patterns and PPD was examined using logistic regression analyses adjusting for socioeconomic factors and parity. The continuum of care (CoC) complete pattern (four ANC/facility delivery/four vaccination) was used as a reference.

Results: The data of 7087 participants whose children were alive and aged 6 months or older at the endline survey were analyzed. Prevalence of PPD was 17.9 % in urban and 43.2 % in rural municipalities. In urban municipalities, dropouts from the CoC at delivery and after delivery had significantly higher odds of PPD (AOR = 1.45, 95 % CI = 1.00-2.10; AOR = 1.57, 95 % CI = 1.24-1.99). In rural municipalities, dropouts from the CoC after delivery (AOR = 1.60, 95 % CI = 1.12-2.28) had significantly higher odds of PPD.

Limitations: The onset of depressive symptoms was not assessed. The EPDS was validated in some Portuguese speaking countries but not in Angola.

Conclusion: PPD was associated with irregular service utilization patterns such as dropouts from the CoC. Therefore, CoC and mental health must be promoted simultaneously.

Midwifery. 2024 Jan:128:103864.
doi: 10.1016/j.midw.2023.103864. Epub 2023 Oct 31.

Development and content validation of yoga module for the mental health of NICU mothers

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Abstract

Background: Postnatal yoga has been found to be effective for maternal mental health management. But a validated yoga module for the mental health of early postpartum mothers with infants admitted to the Neonatal Intensive Care Unit (NICU) is lacking.
Aim: To design and validate a yoga module for the mental health of early postpartum mothers having infants admitted to the NICU.
Materials and methods: First phase: A yoga module was designed through a review of published research articles and yogic texts for NICU mothers. Second phase: thirty-eight yoga experts validated the yoga module. Lawshe's formula was used to calculate each item's content validity ratio (CVR). The intra-class correlation coefficient was determined for the validated yoga module. Third phase: The validated yoga module was pilot-tested with a sample size of 20 NICU mothers.
Results: Thirty-eight yoga experts validated the yoga module for NICU mothers. Thirteen practices included in the module indicated good content validity (cutoff value: 0.316). The module's content validity index (CVI) and intra-class correlation coefficient were 0.672 and 0.924, respectively. Ten days of practicing the yoga module resulted in a significant reduction in maternal stress levels in the yoga group ($p < 0.001$) compared to the control group ($p = 0.427$).
Conclusion: The present study suggests good content validity of the yoga module for the mental health of NICU mothers. However, future randomized controlled trials must be carried out to determine both the feasibility and clinical efficacy of the Yoga Module for NICU mothers.

Maternal malaria prevention

Clin Infect Dis. 2023 Jul 5;77(1):127-134.
doi: 10.1093/cid/ciad128.

Effectiveness of Intermittent Screening and Treatment of Malaria in Pregnancy on Maternal and Birth Outcomes in Selected Districts in Rwanda: A Cluster Randomized Controlled Trial

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Abstract
Background: Malaria during pregnancy can cause serious consequences including maternal anemia and low birthweight (LBW). Routine antenatal care (ANC) in Rwanda includes malaria symptom screening at each ANC visit. This cluster randomized controlled trial investigated whether adding intermittent screening with a malaria rapid diagnostic test at each routine ANC visit and treatment of positives during pregnancy (ISTp) is more effective than routine ANC for reducing malaria prevalence at delivery.
Methods: Between September 2016 and June 2018, pregnant women initiating ANC at 14 health centers in Rwanda were enrolled into ISTp or control arms. All women received an insecticide-treated bed net at enrollment. Hemoglobin concentration, placental and peripheral parasitemia, newborn outcome, birthweight, and prematurity were assessed at delivery.

Results: Nine hundred seventy-five women were enrolled in ISTp and 811 in the control group. Routine ANC plus ISTp did not significantly reduce polymerase chain reaction-confirmed placental malaria compared to control (adjusted relative risk [aRR], 0.94 [95% confidence interval {CI}, .59-1.50]; P = .799). ISTp had no impact on anemia (aRR, 1.08 [95% CI, .57-2.04]; P = .821). The mean birthweight of singleton newborns was not significantly different between arms (3054 g vs 3096 g, P = .395); however, women in the ISTp arm had a higher proportion of LBW (aRR, 1.59 [95% CI, 1.02-2.49]; P = .042).
Conclusions: This is the only study to compare ISTp to symptomatic screening at ANC in a setting where intermittent preventive treatment is not routinely provided. ISTp did not reduce the prevalence of malaria or anemia at delivery and was associated with an increased risk of LBW.

Malar J. 2023 Oct 21;22(1):320.
doi: 10.1186/s12936-023-04757-2.

Safety and tolerability of repeated doses of dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnancy: a systematic review and an aggregated data meta-analysis of randomized controlled trials

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Abstract

Background: Malaria infection during pregnancy is an important cause of maternal and infant mortality and morbidity with the greatest effect being concentrated in sub-Saharan Africa. In areas of moderate to high malaria transmission, the World Health Organization (WHO) recommends the administration of intermittent preventive treatment of malaria in pregnancy (IPTp) using sulfadoxine-pyrimethamine (SP) to be given to all pregnant women at each scheduled antenatal care visit at monthly intervals. However, there is concern that increased resistance has compromised its effectiveness. This has led to a need for evaluation of alternatives to SP for IPTp with dihydroartemisinin-piperaquine (DP) emerging as a very promising candidate. Thus, this systematic review and aggregated data meta-analysis was conducted to establish the safety and tolerability of repeated doses with DP in IPTp.
Methods: A systematic review and aggregated data meta-analysis of randomized controlled trials (RCTs) was performed by searching electronic databases of PubMed, Science Direct, ClinicalTrials.gov and Google Scholar. RCTs comparing IPTp DP versus recommended standard treatment for IPTp with these outcome measures were analyzed; change in QTc interval, serious adverse events (SAE), grade 3 or 4 adverse events possibly related to study drug and vomiting within 30 min after study drug administration. The search was performed up to 24th June 2023. Data was extracted from eligible studies and an aggregated data meta-analysis was carried out with data pooled as risk ratio (RR) with a 95% confidence interval (CI), using RevMan software (5.4). This study is registered with PROSPERO, CRD42022310041.
Results: Six RCTs involving 7969 participants were included in this systematic review and aggregated data meta-analysis. The pooled analysis showed that DP was associated with a change from baseline of the QTc interval although this change was not associated with cardiotoxicity. There was no statistically significant difference in the risk of occurrence of SAEs among participants in both treatment groups (RR = 0.80, 95% CI [0.52-1.24], P = 0.32). However, significant difference was observed in grade 3 or 4 AEs possibly related to study

drug where analysis showed that subjects on IPT DP were statistically significantly more likely to experience an AE possibly related to study drug than subjects on IPT SP (RR = 6.65, 95% CI [1.18-37.54], P = 0.03) and in vomiting within 30 min after study drug administration where analysis showed that the risk of vomiting is statistically significantly higher in subjects receiving IPT DP than in subjects receiving IPT SP (RR = 1.77, 95% CI [1.02-3.07], P = 0.04).
Conclusion: DP was associated with a higher risk of grade 3 or 4 AEs possibly related to study drug and a higher risk of vomiting within 30 min after study drug administration. However, these were experienced in a very small percentage of women and did not affect adherence to study drugs. DP was also better tolerated in these studies as compared to most alternatives that have been proposed to replace SP which have proved to be too poorly tolerated in IPTp use.

Lancet. 2024 Jan 27;403(10424):365-378.
doi: 10.1016/S0140-6736(23)02631-4. Epub 2024 Jan 12.

Chemoprevention for malaria with monthly intermittent preventive treatment with dihydroartemisinin-piperaquine in pregnant women living with HIV on daily co-trimoxazole in Kenya and Malawi: a randomised, double-blind, placebo-controlled trial

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Abstract

Background: The efficacy of daily co-trimoxazole, an antifolate used for malaria chemoprevention in pregnant women living with HIV, is threatened by cross-resistance of Plasmodium falciparum to the antifolate sulfadoxine-pyrimethamine. We assessed whether addition of monthly dihydroartemisinin-piperaquine to daily co-trimoxazole is more effective at preventing malaria infection than monthly placebo plus daily co-trimoxazole in pregnant women living with HIV.
Methods: We did an individually randomised, two-arm, placebo-controlled trial in areas with high-grade sulfadoxine-pyrimethamine resistance in Kenya and Malawi. Pregnant women living with HIV on dolutegravir-based combination antiretroviral therapy (cART) who had singleton pregnancies between 16 weeks' and 28 weeks' gestation were randomly assigned (1:1) by computer-generated block randomisation, stratified by site and HIV status (known positive vs newly diagnosed), to daily co-trimoxazole plus monthly dihydroartemisinin-piperaquine (three tablets of 40 mg dihydroartemisinin and 320 mg piperaquine given daily for 3 days) or daily co-trimoxazole plus monthly placebo. Daily co-trimoxazole consisted of one tablet of 160 mg sulfamethoxazole and 800 mg trimethoprim. The primary endpoint was the incidence of Plasmodium infection detected in the peripheral (maternal) or placental (maternal) blood or tissue by PCR, microscopy, rapid diagnostic test, or placental histology (active infection) from 2 weeks after the first dose of dihydroartemisinin-piperaquine or placebo to delivery. Log-binomial regression was used for binary outcomes, and Poisson regression for count outcomes. The primary analysis was by modified intention to treat, consisting of all randomised eligible participants with primary endpoint data. The safety analysis included all women who received at least one dose of study drug. All investigators,

laboratory staff, data analysts, and participants were masked to treatment assignment. This trial is registered with ClinicalTrials.gov, NCT04158713.
Findings: From Nov 11, 2019, to Aug 3, 2021, 904 women were enrolled and randomly assigned to co-trimoxazole plus dihydroartemisinin-piperaquine (n=448) or co-trimoxazole plus placebo (n=456), of whom 895 (99%) contributed to the primary analysis (co-trimoxazole plus dihydroartemisinin-piperaquine, n=443; co-trimoxazole plus placebo, n=452). The cumulative risk of any malaria infection during pregnancy or delivery was lower in the co-trimoxazole plus dihydroartemisinin-piperaquine group than in the co-trimoxazole plus placebo group (31 [7%] of 443 women vs 70 [15%] of 452 women, risk ratio 0·45, 95% CI 0·30-0·67; p=0·0001). The incidence of any malaria infection during pregnancy or delivery was 25·4 per 100 person-years in the co-trimoxazole plus dihydroartemisinin-piperaquine group versus 77·3 per 100 person-years in the co-trimoxazole plus placebo group (incidence rate ratio 0·32, 95% CI 0·22-0·47, p<0·0001). The number needed to treat to avert one malaria infection per pregnancy was 7 (95% CI 5-10). The incidence of serious adverse events was similar between groups in mothers (17·7 per 100 person-years in the co-trimoxazole plus dihydroartemisinin-piperaquine group [23 events] vs 17·8 per 100 person-years in the co-trimoxazole group [25 events]) and infants (45·4 per 100 person-years [23 events] vs 40·2 per 100 person-years [21 events]). Nausea within the first 4 days after the start of treatment was reported by 29 (7%) of 446 women in the co-trimoxazole plus dihydroartemisinin-piperaquine group versus 12 (3%) of 445 women in the co-trimoxazole plus placebo group. The risk of adverse pregnancy outcomes did not differ between groups.
Interpretation: Addition of monthly intermittent preventive treatment with dihydroartemisinin-piperaquine to the standard of care with daily unsupervised co-trimoxazole in areas of high antifolate resistance substantially improves malaria chemoprevention in pregnant women living with HIV on dolutegravir-based cART and should be considered for policy.

Lancet Infect Dis. 2024 May;24(5):476-487.
doi: 10.1016/S1473-3099(23)00738-7. Epub 2024 Jan 12.

Safety and efficacy of dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women with HIV from Gabon and Mozambique: a randomised, double-blind, placebo-controlled trial

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Abstract

Background: The cornerstone of malaria prevention in pregnancy, intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine, is contraindicated in women with HIV who are receiving co-trimoxazole prophylaxis. We assessed whether IPTp with dihydroartemisinin-piperaquine is safe and effective in reducing the risk of malaria infection in women with HIV receiving co-trimoxazole prophylaxis and antiretroviral drugs.
Methods: For this randomised, double-blind, placebo-controlled clinical trial, women with HIV attending the first antenatal care clinic visit, resident in the study area, and with a gestational age up to 28 weeks were enrolled at five sites in Gabon and Mozambique.

Participants were randomly assigned (1:1) to receive either IPTp with dihydroartemisinin-piperaquine at each scheduled antenatal care visit plus daily co-trimoxazole (intervention group) or placebo at each scheduled antenatal care visit plus daily co-trimoxazole (control group). Randomisation was done centrally via block randomisation (block sizes of eight), stratified by country. IPTp was given over 3 days under direct observation by masked study personnel. The number of daily IPTp tablets was based on bodyweight and according to the treatment guidelines set by WHO (target dose of 4 mg/kg per day [range 2-10 mg/kg per day] of dihydroartemisinin and 18 mg/kg per day [range 16-27 mg/kg per day] of piperaquine given once a day for 3 days). At enrolment, all participants received co-trimoxazole (fixed combination drug containing 800 mg trimethoprim and 160 mg sulfamethoxazole) for daily intake. The primary study outcome was prevalence of peripheral parasitaemia detected by microscopy at delivery. The modified intention-to-treat population included all randomly assigned women who had data for the primary outcome. Secondary outcomes included frequency of adverse events, incidence of clinical malaria during pregnancy, and frequency of poor pregnancy outcomes. All study personnel, investigators, outcome assessors, data analysts, and participants were masked to treatment assignment. This study is registered with ClinicalTrials.gov, NCT03671109.

Findings: From Sept 18, 2019, to Nov 26, 2021, 666 women (mean age 28·5 years [SD 6·4]) were enrolled and randomly assigned to the intervention (n=332) and control (n=334) groups. 294 women in the intervention group and 308 women in the control group had peripheral blood samples taken at delivery and were included in the primary analysis. Peripheral parasitaemia at delivery was detected in one (<1%) of 294 women in the intervention group and none of 308 women in the control group. The incidence of clinical malaria during pregnancy was lower in the intervention group than in the control group (one episode in the intervention group vs six in the control group; relative risk [RR] 0·12, 95% CI 0·03-0·52, p=0·045). In a post-hoc analysis, the composite outcome of overall malaria infection (detected by any diagnostic test during pregnancy or delivery) was lower in the intervention group than in the control group (14 [5%] of 311 women vs 31 [10%] of 320 women; RR 0·48, 95% CI 0·27-0·84, p=0·010). The frequency of serious adverse events and poor pregnancy outcomes (such as miscarriages, stillbirths, premature births, and congenital malformations) did not differ between groups. The most frequently reported drug-related adverse events were gastrointestinal disorder (reported in less than 4% of participants) and headache (reported in less than 2% of participants), with no differences between study groups.

Interpretation: In the context of low malaria transmission, the addition of IPTp with dihydroartemisinin-piperaquine to co-trimoxazole prophylaxis in pregnant women with HIV did not reduce peripheral parasitaemia at delivery. However, the intervention was safe and associated with a decreased risk of clinical malaria and overall Plasmodium falciparum infection, so it should be considered as a strategy to protect pregnant women with HIV from malaria.

Obstetric care and delivery

BMC Pregnancy Childbirth. 2024 Apr 17;24(1):283.

doi: 10.1186/s12884-024-06449-4.

Effect of implementation of the WHO intrapartum care model on maternal and neonatal outcomes: a randomized control trial

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Abstract

Background: In 2018, the World Health Organization published a set of recommendations for further emphasis on the quality of intrapartum care to improve the childbirth experience. This study aimed to determine the effects of the WHO intrapartum care model on the childbirth experience, fear of childbirth, the quality of intrapartum care (primary outcomes), as well as post-traumatic stress disorder symptoms, postpartum depression, the duration of childbirth stages, the frequency of vaginal childbirth, Apgar score less than 7, desire for subsequent childbearing, and exclusive breastfeeding in the 4 to 6 weeks postpartum period (secondary outcomes).

Methods: This study was a randomized controlled trial involving 108 pregnant women admitted to the maternity units of Al-Zahra and Taleghani hospitals in Tabriz-Iran. Participants were allocated to either the intervention group, which received care according to the ' 'intrapartum care model, or the control group, which received the' 'hospital's routine care, using the blocked randomization method. A Partograph chart was drawn for each participant during pregnancy. A delivery fear scale was completed by all participants both before the beginning of the active phase (pre-intervention) and during 7 to 8 cm dilation (post-intervention). Participants in both groups were followed up for 4 to 6 weeks after childbirth and were asked to complete questionnaires on childbirth experience, postpartum depression, and post-traumatic stress disorder symptoms, as well as the pregnancy and childbirth questionnaire and checklists on the desire to have children again and exclusive breastfeeding. The data were analyzed using independent T and Mann-Whitney U tests and analysis of covariance ANCOVA with adjustments for the parity variable and the baseline scores or childbirth fear.

Results: The average score for the childbirth experience total was notably higher in the intervention group (Adjusted Mean Difference (AMD) (95% Confidence Interval (CI)): 7.0 (0.6 to 0.8), $p < 0.001$). Similarly, the intrapartum care quality score exhibited a significant increase in the intervention group (AMD (95% CI): 7.0 (4.0 to 10), $p < 0.001$). Furthermore, the post-intervention fear of childbirth score demonstrated a substantial decrease in the intervention group (AMD (95% CI): -16.0 (-22.0 to -10.0), $p < 0.001$). No statistically significant differences were observed between the two groups in terms of mean scores for depression, PTSD symptoms, duration of childbirth stages, frequency of vaginal childbirth, Apgar score less than 7, and exclusive breastfeeding in the 4 to 6 weeks postpartum ($p > 0.05$).

Conclusion: The intrapartum care model endorsed by the World Health Organization (WHO) has demonstrated effectiveness in enhancing childbirth experiences and increasing maternal satisfaction with the quality of obstetric care. Additionally, it contributes to the reduction of fear associated with labor and childbirth. Future research endeavors should explore strategies to prioritize and integrate respectful, high-quality care during labor and childbirth alongside clinical measures.

Birth. 2023 Sep;50(3):616-626.
doi: 10.1111/birt.12709. Epub 2023 Feb 12.

Improved obstetric management after implementation of a scaled-up quality improvement intervention: A nested before-after study in three public hospitals in Nepal

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Abstract

Background: We assessed the change in obstetric management after implementation of a quality improvement intervention, the Nepal Perinatal Quality Improvement Package (NePeriQIP).

Methods: The Nepal Perinatal Quality Improvement Package was a stepped-wedge cluster-randomized controlled trial conducted in 12 public hospitals in Nepal between April 2017 and October 2018. In this study, three hospitals allocated at different time points to the intervention were selected for a nested before-after analysis. We used bivariate and multivariate analyses to compare obstetric management in the control vs intervention group.

Results: There were 25 977 deliveries in the three hospitals during the study period: 10 207 (39%) in the control and 15 770 (61%) in the intervention group. After adjusting for maternal age, ethnicity, education, gestational age, stage of labor at admission, complications during labor, and birthweight, the intervention group had a higher proportion of fetal heart rate monitoring performed as per protocol (adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 1.12-1.27), shorter time intervals between each fetal heart rate monitoring (aOR 2.09, 95% CI 1.96-2.23), a higher likelihood of abnormal fetal heart rate being detected (aOR 1.53, 95% CI 1.25-1.68), progress of labor more often being recorded immediately after per vaginal examination (aOR 2.73, 95% CI 2.55-2.93), and partograph filled as per standards (aOR 3.18, 95% CI 2.98-3.50). The cesarean birth rate was 2.5% in the control group and 8.2% in the intervention group (aOR 3.12, 95% CI 2.64-3.68).

BMC Pregnancy Childbirth. 2023 Sep 18;23(1):669.
doi: 10.1186/s12884-023-05978-8.

Efficacy of midwife-led role orientation of birth companions on maternal satisfaction and birth outcomes: a randomized control trial in Uganda

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Abstract

Background: The World Health Organization recommends birth companionship for all women in labor. There is insufficient evidence on birth companionship in low-income settings and it is not clear if role orientation impacts effectiveness. The aim of this study was to assess the efficacy of midwife-led role orientation of birth companions of on maternal satisfaction and birth outcomes in a sub-region in Uganda.

Methods: A stepped wedge cluster randomized trial conducted (control n = 240), intervention n = 235) from 4 clusters. Women who had a birth companion, in spontaneously established labor and, expecting a vaginal delivery were eligible. The intervention was "midwife-provided orientation of birth companions". The admitting midwife provided an orientation session for the birth companion on supportive labor techniques. The primary

outcome was the chance of having a spontaneous vaginal delivery. Assessors were not blinded. Independent t-test and Chi-Square tests were used to assess the differences by study period.
Results: Mean maternal satisfaction rate was significantly higher in the intervention period compared to the control period (P > 0.001). High maternal satisfaction levels were noted among the women who were; at the regional referral hospital, younger, first-time mothers, and unmarried (P < 0.001). Satisfaction with pain management was rated lowest across study periods. Satisfaction with humaneness was rated highest with a higher score in the intervention period (93%) than the control (79.5%). There were no statistically significant differences in the mode of delivery, need to augment labor, length of labor and Apgar scores.
Conclusion: Midwife-led role orientation of birth companions increased maternal satisfaction. Nevertheless, no significant effect was noted in the mode of delivery, length of labor, Apgar score, and need to augment labor. Findings could inform the integration of birth companions in the admission process of the woman in labor in similar settings.

BMC Health Serv Res. 2023 Oct 14;23(1):1100.
doi: 10.1186/s12913-023-10082-w.

A clustered randomized control trial to assess feasibility, acceptability, and impact of implementing the birth companion intervention package in Ethiopia, Kenya, and Nigeria: study protocol

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Abstract
Background: A birth companion is a simple and low-cost intervention that can improve both maternal and newborn health outcomes. The evidence that birth companionship improves labor outcomes and experiences of care has been available for many years. Global and national policies exist in support of birth companions. Many countries including Ethiopia, Kenya, and Nigeria have not yet incorporated birth companions into routine practice in health facilities. This paper presents the protocol for a trial that aims to assess if a package of interventions that addresses known barriers can increase the coverage of birth companions.
Methods: This two parallel arm cluster randomized controlled trial will evaluate the impact of a targeted intervention package on scale-up of birth companionship at public sector health facilities in Ethiopia (five study sites encompassing 12 facilities), Kenya (two sites encompassing 12 facilities in Murang'a and 12 facilities in Machakos counties), and Nigeria (two sites encompassing 12 facilities in Kano and 12 facilities in Nasarawa states). Baseline and endline assessments at each site will include 744 women who have recently given birth in the quantitative component. We will interview a maximum of 16 birth companions, 48 health care providers, and eight unit managers quarterly for the qualitative component in each country.
Discussion: Ample evidence supports the contribution of birth companions to positive health outcomes for mothers and newborns. However, limited data are available on effective strategies to improve birth companion coverage and inform scale-up efforts. This trial tests a

birth companion intervention package in diverse clinical settings and cultures to identify possible barriers and considerations to increasing uptake of birth companions. Findings from this study may provide valuable evidence for scaling up birth companionship in similar settings.

Reprod Health. 2023 Nov 18;20(1):169.
doi: 10.1186/s12978-023-01713-w.

Evaluation of a community-based intervention package to improve knowledge of obstetric danger signs, birth preparedness, and institutional delivery care utilization in Arba Minch Zuria District, Ethiopia: a cluster-randomized trial

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Abstract

Introduction: Maternal healthcare utilization, particularly the institutional delivery, is disproportionately low in rural Ethiopia. This study aimed to evaluate the effectiveness of an integrated package of community-based interventions on the improved knowledge of obstetric danger signs, birth preparedness, and institutional delivery services utilization in rural areas of Gamo zone, southern Ethiopia.

Methods: We conducted cluster-randomized controlled trial (NCT05385380) from 2019 to 2021 at the Arba Minch Health and Demographic Surveillance System site. We randomly assigned the 10 kebele clusters to intervention and control arm. We used a package of interventions, which included providing information on safe motherhood via video and/or audio with a birth preparedness card for pregnant women, training for community volunteers and health extension workers, and improving maternity waiting home services. Women in the control arm received routine services only. We used generalized mixed-effects logistic regression models to evaluate the effectiveness of the intervention on the outcome variables.

Results: The study enrolled 727 pregnant women across the 10 clusters, with a 617 (84.9%) successful follow-up rate. The proportion of institutional delivery in the intervention arm was increased by 16.1% from 36.4% (174/478) at the baseline to 52.5% (224/427) at the endline (Adjusted odds ratio [AOR] for McNemar's Test = 1.5; 95% confidence interval [CI]: 1.1 to 2; $p < 0.001$). In the control arm, however, there was a 10.3% fall in the proportion of institutional delivery (from 164/249 to 105/190). Pregnant women who received the intervention were significantly more likely to give birth in a health institution than those who did not (AOR 2.8; 95% CI: 1.2, 6.4).

Conclusion: The study demonstrates that an integrated community-based intervention package that included video-based storytelling and upgrading maternity waiting homes increased institutional delivery care utilization among rural women. We recommend that audio-visual storytelling, starting during pregnancy and continuing postpartum, be incorporated into routine maternal healthcare services to address access to care inequalities in rural settings.

Maternal nutrition and micronutrient supplementation

Am J Clin Nutr. 2024 Mar;119(3):730-739.
doi: 10.1016/j.ajcnut.2023.07.023. Epub 2023 Nov 30.

The effects of prenatal and postnatal high-dose vitamin B-12 supplementation on human milk vitamin B-12: a randomized, double-blind, placebo-controlled trial in Tanzania

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Abstract

Background: Vitamin B-12 status in human milk (HM) has critical implications for infant growth and development. Few studies have separately evaluated the effects of prenatal and postnatal maternal high-dose vitamin B-12 supplementation on HM vitamin B-12 concentration.

Objectives: This randomized controlled trial aimed to assess the effects of prenatal and postnatal vitamin B-12 supplementation on HM vitamin B-12 at 6 wk and 7 mo postpartum.

Methods: Pregnant women were enrolled in Dar es Salaam, Tanzania, between 2001 and 2004. From recruitment (12-27 weeks of gestation) through 6 wk postpartum, participants were randomly assigned to daily oral multiple micronutrient supplementation or placebo. From 6 wk to 18 mo postpartum, a subset of participants was randomly assigned to a postnatal supplement or placebo. The supplement included 50 μg/d of vitamin B-12 and various other vitamins. HM vitamin B-12 concentrations were analyzed at 6 wk and 7 mo postpartum for 412 participants.

Results: The prevalence of HM vitamin B-12 of <310 pmol/L was 73.3% and 68.4% at 6 wk and 7 mo postpartum, respectively. Prenatal supplementation increased HM vitamin B-12 concentration (percent difference: 34.4; 95% CI: 17.0, 54.5; P < 0.001) at 6 wk; this effect was not present at 7 mo. Postnatal supplementation increased HM vitamin B-12 concentration (percent difference: 15.9; 95% CI: 1.91, 31.9; P = 0.025) at 7 mo. Effect modification between prenatal and postnatal supplementation on HM vitamin B-12 status at 7 mo was found, with the effects of prenatal and postnatal supplements more pronounced among those receiving control during the other period; the prenatal supplement had a greater effect with postnatal control, and the postnatal supplement had a greater effect with prenatal control.

Conclusions: Prenatal maternal vitamin B-12 supplementation has benefits on short-term HM status, and postnatal maternal vitamin B-12 supplementation has benefits on long-term HM status

N Engl J Med. 2024 Jan 11;390(2):143-153.
doi: 10.1056/NEJMoa2307212.

Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy

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Abstract

Background: The World Health Organization recommends 1500 to 2000 mg of calcium daily as supplementation, divided into three doses, for pregnant persons in populations with low dietary calcium intake in order to reduce the risk of preeclampsia. The complexity of the dosing scheme, however, has led to implementation barriers.

Methods: We conducted two independent randomized trials of calcium supplementation, in India and Tanzania, to assess the noninferiority of a 500-mg daily dose to a 1500-mg daily dose of calcium supplementation. In each trial, the two primary outcomes were preeclampsia and preterm birth, and the noninferiority margins for the relative risks were 1.54 and 1.16, respectively.

Results: A total of 11,000 nulliparous pregnant women were included in each trial. The cumulative incidence of preeclampsia was 3.0% in the 500-mg group and 3.6% in the 1500-mg group in the India trial (relative risk, 0.84; 95% confidence interval [CI], 0.68 to 1.03) and 3.0% and 2.7%, respectively, in the Tanzania trial (relative risk, 1.10; 95% CI, 0.88 to 1.36) - findings consistent with the noninferiority of the lower dose in both trials. The percentage of live births that were preterm was 11.4% in the 500-mg group and 12.8% in the 1500-mg group in the India trial (relative risk, 0.89; 95% CI, 0.80 to 0.98), which was within the noninferiority margin of 1.16; in the Tanzania trial, the respective percentages were 10.4% and 9.7% (relative risk, 1.07; 95% CI, 0.95 to 1.21), which exceeded the noninferiority margin.

Conclusions: In these two trials, low-dose calcium supplementation was noninferior to high-dose calcium supplementation with respect to the risk of preeclampsia. It was noninferior with respect to the risk of preterm live birth in the trial in India but not in the trial in Tanzania.

PLoS Med. 2023 Jul 24;20(7):e1004242.
doi: 10.1371/journal.pmed.1004242. eCollection 2023 Jul.

Effect of prenatal micronutrient-fortified balanced energy-protein supplementation on maternal and newborn body composition: A sub-study from the MISAME-III randomized controlled efficacy trial in rural Burkina Faso

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Abstract

Background: Micronutrient-fortified balanced energy-protein (BEP) supplements are promising interventions to prevent intrauterine growth retardation in low- and middle-income countries. On the other hand, one concern with blanket prenatal supplementation programs using energy-dense supplements is that they could lead to more maternal and/or infant overweight. However, evidence is lacking on the potential effect of BEP on maternal and offspring body composition. This study evaluates the effects of micronutrient-fortified BEP supplementation during pregnancy on body composition of mothers and their newborns in rural Burkina Faso.

Methods and findings: The MISAME-III study is an open label individually randomized controlled trial where pregnant women (n = 1,897) of gestational age <21 weeks received either a combination of micronutrient-fortified BEP and iron-folic acid (IFA) tablets (i.e., intervention) or IFA alone (i.e., control). The prenatal phase of the MISAME-III study was conducted between the first enrollment in October 2019 and the last delivery in August 2021. In a sub-study nested under the MISAME-III trial, we evaluated anthropometry and body composition in newborns who were born starting from 17 November 2020 (n: control = 368 and intervention = 352) and their mothers (n: control = 185 and intervention = 186). Primary study outcomes were newborn and maternal fat-free mass (FFMI) and fat-mass (FMI) indices. We used the deuterium dilution method to determine FFMI and FMI and %FFM and %FM of total body weight within 1 month postpartum. Our main analysis followed a modified intention-to-treat approach by analyzing all subjects with body composition data available. Univariable and multivariable linear regression models were fitted to compare the intervention and control arms, with adjusted models included baseline maternal age, height, arm fat index, hemoglobin concentration and primiparity, household size, wealth and food security indices, and newborn age (days). At study enrollment, the mean ± SD maternal age was 24.8 ± 6.13 years and body mass index (BMI) was 22.1 ± 3.02 kg/m2 with 7.05% of the mothers were underweight and 11.5% were overweight. Prenatal micronutrient-fortified BEP supplementation resulted in a significantly higher FFMI in mothers (MD (mean difference): 0.45; 95% CI (confidence interval): 0.05, 0.84; P = 0.026) and newborns (MD: 0.28; 95% CI: 0.06, 0.50; P = 0.012), whereas no statistically significant effects were found on FMI. The effect of micronutrient-fortified BEP on maternal FFMI was greater among mothers from food secure households and among those with a better nutritional status (BMI ≥21.0 kg/m2 or mid-upper arm circumference (MUAC) ≥23 cm). Key limitations of the study are the relatively high degree of missing data (approximately 18%), the lack of baseline maternal body composition values, and the lack of follow-up body composition measurements to evaluate any long-term effects.
Conclusions: Micronutrient-fortified BEP supplementation during pregnancy can increase maternal and newborn FFMI, without significant effects on FMI.

Curr Dev Nutr. 2023 Jul 4;7(8):101969.
doi: 10.1016/j.cdnut.2023.101969. eCollection 2023 Aug.

Micronutrient status during pregnancy is associated with child immune status in rural Bangladesh

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Abstract

Background: Poor immune function increases children's risk of infection and mortality. Several maternal factors during pregnancy may affect infant immune function during the postnatal period.
Objectives: We aimed to evaluate whether maternal micronutrients, stress, estriol, and immune status during the first or second trimester of pregnancy were associated with child immune status in the first two years after birth.
Methods: We conducted observational analyses within the water, sanitation, and hygiene (WASH) Benefits Bangladesh randomized controlled trial. We measured biomarkers in 575 pregnant women and postnatally in their children. Maternal biomarkers measured during the first and second trimester of pregnancy included nutrition status via vitamin D (25-hydroxy-D [25(OH)D]), ferritin, soluble transferrin receptor (sTfR), and retinol-binding protein (RBP); cortisol; estriol. Immune markers were assessed in pregnant women at enrollment and their children at ages 14 and 28 mo, including C-reactive protein (CRP), alpha-1-acid glycoprotein (AGP), and 13 cytokines (including IFN-γ). We generated a standardized sum score of log-transformed cytokines. We analyzed IFN-γ individually because it is a critical immunoregulatory cytokine. All outcomes were prespecified. We used generalized additive models and reported the mean difference and 95% confidence intervals at the 25th and 75th percentiles of exposure distribution.
Results: At child age 14 mo, concentrations of maternal RBP were inversely associated with the cytokine sum score in children (-0.34 adjusted difference between the 25th and 75th percentile [95% confidence interval -0.61, -0.07]), and maternal vitamin A deficiency was positively associated with the cytokine sum score in children (1.02 [0.13, 1.91]). At child age of 28 mo, maternal RBP was positively associated with IFN-γ in children (0.07 [0.01, 0.14]), whereas maternal vitamin A deficiency was negatively associated with child AGP (-0.07 [-0.13, -0.02]). Maternal iron deficiency was associated with higher AGP concentrations in children at age 14 mo (0.13 [0.04, 0.23]), and maternal sTfR concentrations were positively associated with child CRP concentrations at age 28 mo (0.18 [0, 0.36]).
Conclusion: Maternal deficiencies in vitamin A or iron during the first 2 trimesters of pregnancy may shape the trajectory of a child's immune status.

J Nutr. 2024 Jun;154(6):1917-1926.
doi: 10.1016/j.tjnut.2024.04.018. Epub 2024 Apr 16.

Zinc Supplementation Initiated Prior to or During Pregnancy Modestly Impacted Maternal Status and High Prevalence of Hypozincemia in Pregnancy and Lactation: The Women First Preconception Maternal Nutrition Trial

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Abstract
Background: Data regarding effects of small-quantity-lipid-based nutrient supplements (SQ-LNS) on maternal serum zinc concentrations (SZC) in pregnancy and lactation are limited.
Objectives: The objectives of this study were to evaluate the effect of preconception compared with prenatal zinc supplementation (compared with control) on maternal SZC and

hypozincemia during pregnancy and early lactation in women in low-resource settings, and assess associations with birth anthropometry.
Methods: From ~100 women/arm at each of 3 sites (Guatemala, India, and Pakistan) of the Women First Preconception Maternal Nutrition trial, we compared SZC at 12- and 34-wk gestation (n = 651 and 838, respectively) and 3-mo postpartum (n = 742) in women randomly assigned to daily SQ-LNS containing 15 mg zinc from ≥3 mo before conception (preconception, arm 1), from ~12 wk gestation through delivery (early pregnancy, arm 2) or not at all (control, arm 3). Birth anthropometry was examined for newborns with ultrasound-determined gestational age. Statistical analyses were performed separately for each time point.
Results: At 12-wk gestation and 3-mo postpartum, no statistical differences in mean SZC were observed among arms. At 34-wk, mean SZC for arms 1 and 2 were significantly higher than for arm 3 (50.3, 50.8, 47.8 μg/dL, respectively; P = 0.005). Results were not impacted by correction for inflammation or albumin concentrations. Prevalence of hypozincemia at 12-wk (<56 μg/dL) was 23% in Guatemala, 26% in India, and 65% in Pakistan; at 34 wk (<50 μg/dL), 36% in Guatemala, 48% in India, and 74% in Pakistan; and at 3-mo postpartum (<66 μg/dL) 79% in Guatemala, 91% in India, and 92% in Pakistan. Maternal hypozincemia at 34-wk was associated with lower birth length-for-age Z-scores (all sites P = 0.013, Pakistan P = 0.008) and weight-for-age Z-scores (all sites P = 0.017, Pakistan P = 0.022).
Conclusions: Despite daily zinc supplementation for ≥7 mo, high rates of maternal hypozincemia were observed. The association of hypozincemia with impaired fetal growth suggests widespread zinc deficiency in these settings

Eur J Clin Nutr. 2023 Jul;77(7):710-730.
doi: 10.1038/s41430-022-01232-0. Epub 2022 Nov 9.

Micronutrient supplementation interventions in preconception and pregnant women at increased risk of developing pre-eclampsia: a systematic review and meta-analysis

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Abstract
Background: Pre-eclampsia can lead to maternal and neonatal complications and is a common cause of maternal mortality worldwide. This review has examined the effect of micronutrient supplementation interventions in women identified as having a greater risk of developing pre-eclampsia.
Methods: A systematic review was performed using the PRISMA guidelines. The electronic databases MEDLINE, EMBASE and the Cochrane Central Register of Controlled trials were searched for relevant literature and eligible studies identified according to a pre-specified criteria. A meta-analysis of randomised controlled trials (RCTs) was conducted to examine the effect of micronutrient supplementation on pre-eclampsia in high-risk women.
Results: Twenty RCTs were identified and supplementation included vitamin C and E (n = 7), calcium (n = 5), vitamin D (n = 3), folic acid (n = 2), magnesium (n = 1) and multiple micronutrients (n = 2). Sample size and recruitment time point varied across studies and a

variety of predictive factors were used to identify participants, with a previous history of pre-eclampsia being the most common. No studies utilised a validated prediction model. There was a reduction in pre-eclampsia with calcium (risk difference, -0.15 (-0.27, -0.03, $I^2 = 83.4\%$)), and vitamin D (risk difference, -0.09 (-0.17, -0.02, $I^2 = 0.0\%$)) supplementation.
Conclusion: Our findings show a lower rate of pre-eclampsia with calcium and vitamin D, however, conclusions were limited by small sample sizes, methodological variability and heterogeneity between studies. Further higher quality, large-scale RCTs of calcium and vitamin D are warranted. Exploration of interventions at different time points before and during pregnancy as well as those which utilise prediction modelling methodology, would provide greater insight into the efficacy of micronutrient supplementation intervention in the prevention of pre-eclampsia in high-risk women.

Front Nutr. 2023 Jul 4;10:1144709.
doi: 10.3389/fnut.2023.1144709. eCollection 2023.

Effects of intensive nutrition education and counseling on nutritional status of pregnant women in East Shoa Zone, Ethiopia

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Abstract
Background: Nutritional status is defined as an individual's health condition as it is influenced by the intake and utilization of nutrients. Maternal malnutrition is widespread throughout the world, with Sub-Saharan Africa and Asia bearing the brunt of the burden. The objective of this study was to evaluate the effect of intensive nutrition education and counseling on nutritional status during pregnancy.
Methods and materials: The study was a one-year, two-arm parallel design cluster randomized controlled trial conducted in the East Shoa zone, Ethiopia, from January 1, 2021, to February 30, 2022. A total of 374 participants were enrolled in the intervention ($n = 185$) and control ($n = 189$) groups. End-line data were collected from 163 women, from each group. The intervention package provided three counseling sessions by trained midwives, three-page take-home brochures prepared in local languages, and the delivery of 18 weekly serial short text messages. The women in the control group received routine nutrition education from the health facilities. After adjusting for potential confounders, a linear mixed-effects model was employed to assess the intervention effect.
Results: After the intervention, the mean mid-upper arm circumference in the intervention group increased by 1.8% (23.08 vs. 23.44, $p < 0.01$). Similarly, the proportion of undernutrition in the intervention group was 11% (25 vs. 36%, $p = 0.02$) lower compared to the control arm. At the end of the trial, women in the intervention arm had significantly better nutritional status than women in the control group ($\beta = 0.47$, $p < 0.01$).
Conclusion: The findings showed that intensive nutrition education and counseling using the health belief model was effective in improving nutritional status and reducing undernutrition among pregnant women. As a result, nutrition education and counseling using HBM constructs, as well as regular reminder messages, should be provided to pregnant women as part of the routine antenatal care service.

Eur J Obstet Gynecol Reprod Biol X. 2023 Sep 9:20:100235.
doi: 10.1016/j.eurox.2023.100235. eCollection 2023 Dec.

Telephonic intervention to combat non-adherence to oral iron-folic acid supplementation in pregnancy: A randomized controlled trial

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Abstract

Introduction: Iron deficiency anemia is a public health problem globally attributing to high incidences of maternal and infant mortality and morbidity. Iron and folic acid supplementation (IFAS) is essential and provided free of cost by the public health sectors, however, a systematic review shows that the national-level adherence to oral Iron-Folic Acid Supplementation (IFAS) is less than half in pregnant women, and the significant obstacles to non-adherence are fear of side effects and forgetfulness. This trial was designed to mitigate the side effects and tackle forgetfulness with telephonic intervention. The objectives were to investigate the effectiveness of the telephonic intervention on oral IFAS adherence and hemoglobin and the reasons for non-adherence to oral IFAS, to find out the proportion of anemia in the study population, and to assess the effectiveness of the intervention on maternal and neonatal outcomes.

Methods: Hospital-based open-label multi-centric parallel-group randomized controlled trial, used block randomization and allocated treatment in a 1:1 ratio recruited 286 anemic pregnant women between 14 and 24 weeks of gestation with hemoglobin level < 11 g/dl having smartphones at a secondary hospital and a tertiary hospital in Eastern India. The experimental group received telephonic intervention for one month via structured text reminders, WhatsApp audio messages, and phone calls. The standard course of treatment was given to the control group.

Results: 286 women (n_1 =143, n_2 =143) were randomized, 36 had attrition leaving 250 for analysis (n_1 =123, n_2 =127), the experimental group experienced a 44.9 % and the control group 13.8 % increase in adherence ($P < 0.001$). The leading reasons for non-adherence were forgetfulness (24 %), nausea and vomiting (23.2 %), and constipation (18.8 %). Hemoglobin level increased by 0.8 g/dl ($P < 0.001$) in the experimental group and 0.2 g/dl ($P < 0.807$) in the control group.

Conclusion: In addition to improving adherence to oral IFAS, telephonic intervention mitigates side effects and enhances hemoglobin in anemic pregnant women. The increase in adherence was threefold in the experimental group compared to a marginal rise in the control group. This study recommends the implementation of a telephonic intervention to promote adherence to oral IFAS among anemic pregnant women.

Arch Dis Child. 2023 Aug;108(8):622-631.
doi: 10.1136/archdischild-2023-325352. Epub 2023 May 4.

Neurodevelopment, vision and auditory outcomes at age 2 years in offspring of participants in the 'Women First' maternal preconception nutrition randomised controlled trial

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Abstract

Background: Maternal nutrition in preconception and early pregnancy influences fetal growth. Evidence for effects of prenatal maternal nutrition on early child development (ECD) in low-income and middle-income countries is limited.

Objectives: To examine impact of maternal nutrition supplementation initiated prior to or during pregnancy on ECD, and to examine potential association of postnatal growth with ECD domains.

Design: Secondary analysis regarding the offspring of participants of a maternal multicountry, individually randomised trial.

Setting: Rural Democratic Republic of the Congo, Guatemala, India and Pakistan.

Participants: 667 offspring of Women First trial participants, aged 24 months.

Intervention: Maternal lipid-based nutrient supplement initiated preconceptionally (arm 1, n=217), 12 weeks gestation (arm 2, n=230) or not (arm 3, n=220); intervention stopped at delivery.

Main outcome measures: The INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) cognitive, language, gross motor, fine motor, positive and negative behaviour scores; visual acuity and contrast sensitivity scores and auditory evoked response potentials (ERP). Anthropometric z-scores, family care indicators (FCI) and sociodemographic variables were examined as covariates.

Results: No significant differences were detected among the intervention arms for any INTER-NDA scores across domains, vision scores or ERP potentials. After adjusting for covariates, length-for-age z-score at 24 months (LAZ_{24}), socio-economic status, maternal education and FCI significantly predicted vision and INTER-NDA scores (R^2=0.11-0.38, p<0.01).

Conclusions: Prenatal maternal nutrition supplementation was not associated with any neurodevelopmental outcomes at age 2 years. Maternal education, family environment and LAZ_{24} predicted ECD. Interventions addressing multiple components of the nurturing care model may offer greatest impact on children's developmental potential.

BMJ Paediatr Open. 2023 Nov;7(1):e002229.
doi: 10.1136/bmjpo-2023-002229.

Supplementation with fortified balanced energy-protein during pregnancy and lactation and its effects on birth outcomes and infant growth in southern Nepal: protocol of a 2×2 factorial randomised trial

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Abstract

Introduction: Many women in low and middle-income countries enter pregnancy with low nutritional reserves with increased risk of fetal growth restriction and poor birth outcomes, including small-for-gestational-age (SGA) and preterm birth. Balanced energy-protein (BEP) supplements have shown reductions in risk of stillbirth and SGA, yet variations in intervention format and composition and limited evidence on the impact of BEP during lactation on growth outcomes warrant further study. This paper describes the protocol of the Maternal Infant Nutrition Trial (MINT) Study, which aims to evaluate the impact of a fortified

BEP supplement during pregnancy and lactation on birth outcomes and infant growth in rural Nepal.
Methods and analysis: MINT is a 2×2 factorial, household randomised, unblinded, efficacy trial conducted in a subarea of Sarlahi District, Nepal. The study area covers six rural municipalities with about 27 000 households and a population of approximately 100 000. Married women (15-30 years) who become pregnant are eligible for participation in the trial and are randomly assigned at enrolment to supplementation with fortified BEP or not and at birth to fortified BEP supplementation or not until 6 months post partum. The primary pregnancy outcome is incidence of SGA, using the INTERGROWTH-21st standard, among live born infants with birth weight measured within 72 hours of delivery. The primary infant growth outcome is mean length-for-age z-score at 6 months using the WHO international growth reference.

Family planning and birth spacing

Contraception. 2023 Sep;125:110096.
doi: 10.1016/j.contraception.2023.110096. Epub 2023 Jun 22.
A pilot quasi-experimental controlled trial of a community-based, multilevel family planning intervention for couples in rural Uganda: evidence of feasibility, acceptability, and effect on contraceptive uptake among those with an unmet need for family planning
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Abstract
Objectives: Effective interventions to reduce the unmet need for family planning in low-income settings are limited. This study aimed to establish the feasibility, acceptability, and preliminary effects of Family Health=Family Wealth (FH=FW), a multilevel intervention aimed to increase high-efficacy contraceptive uptake among couples wanting to delay pregnancy.
Study design: A pilot quasi-experimental controlled trial was conducted in rural Uganda, with 70 couples wanting to delay pregnancy but not using contraceptives (n = 140). Two matched clusters (communities) were randomly allocated to receive FH=FW or a comparator intervention via coin toss. FH=FW included health system strengthening elements and four facilitated group sessions. Interviewer-administered questionnaires were conducted at baseline and at ~7-month and ~10-month follow-up, and process data gathered feasibility/acceptability outcomes.
Results: Of 121 households visited in the intervention community, 63 couples were screened, and 35 enrolled. In the comparator, 61 households were visited, 45 couples screened, and 35 enrolled. Intervention attendance was 99%, fidelity was 96%, and 100% of participants reported being satisfied with the intervention. From no use at baseline, there was 31% more high efficacy contraceptive uptake at 7 months and 40% more at 10 months in intervention versus comparator couples (adjusted odds ratio = 1.68, 95% confidence interval = 0.78-3.62, p = 0.19). A decline in fertility desires was observed in intervention versus

comparator participants from baseline (Wald $\chi^2 = 9.87$, p = 0.007; Cohen's d: 7 months, 0.06; 10 months, 0.49).
Conclusions: FH=FW is a feasible and acceptable intervention with strong promise in its effect on contraceptive uptake to be established in a future trial.
Implications: The FH=FW intervention addresses multilevel family planning barriers through four group dialogs with couples paired with efforts to reduce health system barriers. A quasi-experimental controlled trial provides preliminary support for its feasibility, acceptability, contraceptive uptake and fertility desire effects, and success in engaging both women and men.

Meningitis and encephalitis

Mental health and child psychiatry

J Am Acad Child Adolesc Psychiatry. 2023 Jul;62(7):777-790.
doi: 10.1016/j.jaac.2022.12.028. Epub 2023 Mar 8.
Short-Term Impact of "Amaka Amasanyufu" Multiple Family Group Intervention on Mental Health Functioning of Children With Disruptive Behavior Disorders in Uganda
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Abstract
Objective: We evaluate the mid-intervention (8 weeks) and short-term (16 weeks) impact of a culturally adapted multiple family group (MFG) intervention, "Amaka Amasanyufu," on the mental health of children with disruptive behavior disorders (DBDs) and primary caregivers in Uganda.
Method: We analyzed data from the Strengthening mental health and research training in Sub-Saharan Africa (SMART) Africa-Uganda study. Schools were randomized to the following: a control group; an MFG facilitated by parent peers (MFG-PP); or an MFG facilitated by community health workers (MFG:CHW). All participants were blinded to interventions provided to other participants and study hypotheses. At 8 weeks and 16 weeks, we evaluated differences in depressive symptoms and self-concept among children and in mental health and caregiving-related stress among caregivers. Three-level linear mixed-effects models were fitted. Pairwise comparisons of post-baseline group means were performed using the Sidak adjustment for multiple comparisons and standardized mean differences. Data from 636 children with DBDs and caregivers (controls: n = 243, n = 10 schools; MFG-PP: n = 194, n = 8 schools; MFG-CHW: n = 199, n = 8 schools) were analyzed.
Results: There were significant group-by-time interactions for all outcomes, and differences were observed mid-intervention, with short-term effects at 16 weeks (end-intervention). MFG-PP and MFG-CHW children had significantly lower depressive symptoms and higher self-concept, whereas caregivers had significantly lower caregiving-related stress and fewer mental health problems, than controls. There was no difference between intervention groups.

Conclusion: Amaka Amasanyufu MFG intervention is effective for reducing depressive symptoms and improving self-concept among children with DBDs while reducing parental stress and mental health problems among caregivers. Given the paucity of culturally adapted mental health interventions, this provides support for adaptation and scale-up in Uganda and other low-resource settings.

J Child Psychol Psychiatry. 2023 Oct 2.
doi: 10.1111/jcpp.13891. Online ahead of print.

Research Review: Psychological and psychosocial interventions for children and adolescents with depression, anxiety, and post-traumatic stress disorder in low- and middle-income countries - a systematic review and meta-analysis

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Abstract

Background: The incidence of depression, anxiety, and post-traumatic stress disorder (PTSD) among children and adolescents residing in low- and middle-income countries (LMICs) poses a significant public health concern. However, there is variation in the evidence of effective psychological interventions. This meta-analysis aims to provide a complete overview of the current body of evidence in this rapidly evolving field.

Methods: We conducted searches on PubMed, Embase.com, and EBSCO/APA PsycInfo databases up to June 23, 2022, identify randomized controlled trials (RCTs) investigating the effectiveness of psychological interventions in LMICs that targeted children and adolescents with elevated symptoms above a cut-off score for depression, anxiety, and PTSD, comparing a psychological or psychosocial intervention with other control conditions. We conducted random effects meta-analyses for depression, anxiety, and PTSD symptoms. Sensitivity analysis for outliers and high-risk studies, and analyses for the publication bias were carried out. Subgroup analyses investigated how the intervention type, intervention format, the facilitator, study design, and age group of the participant predicted effect sizes.

Results: Thirty-one RCTs (6,123 participants) were included. We found a moderate effect of interventions on depression outcomes compared to the control conditions (g = 0.53; 95% CI: 0.06-0.99; NNT = 6.09) with a broad prediction interval (PI) (-1.8 to 2.86). We found a moderate to large effect for interventions on anxiety outcomes (g = 0.88; 95% CI: -0.03 to 1.79; NNT = 3.32) with a broad PI (-3.14 to 4.9). Additionally, a moderate effect was observed on PTSD outcomes (g = 0.54; 95% CI: 0.19-0.9; NNT = 5.86) with a broad PI (-0.64 to 1.72).

Conclusions: Psychological and psychosocial interventions aimed at addressing depression, anxiety, and PTSD among children and adolescents in LMICs have demonstrated promising results. However, future studies should consider the variation in evidence and incorporate long-term outcomes to better understand the effectiveness of these interventions.

AIDS Behav. 2023 Oct 9.
doi: 10.1007/s10461-023-04179-w. Online ahead of print.

Effectiveness of trauma-focused cognitive behavioral therapy compared to psychosocial counseling in reducing HIV risk behaviors, substance use, and mental health problems among orphans and vulnerable children in Zambia: a community-based randomized controlled trial

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Abstract

Orphans and vulnerable children (OVC) in sub-Saharan Africa are at high risk for HIV infection and transmission. HIV prevention and treatment efforts with OVC are hindered by mental health and substance use problems. This randomized controlled trial compared a mental health intervention, Trauma Focused Cognitive Behavioral Therapy (TF-CBT), to an enhanced version of an existing HIV Psychosocial Counseling (PC+) program among 610 adolescents who met PEPFAR criteria for OVC and had HIV risk behaviors in Lusaka, Zambia. Outcomes included HIV risk behaviors (e.g., risky sexual behaviors), mental health (internalizing symptoms, externalizing behaviors, PTSD) and substance use. At 12-month follow-up, there were significant within group reductions in both groups for all outcomes, with the only significant between group difference being for substance use, in which OVC who received TF-CBT had significantly greater reductions than OVC who received PC+. In a subgroup analysis of OVC with high levels of PTSD symptoms, TF-CBT was superior to PC + in reducing internalizing symptoms, functional impairment, and substance use. Findings support TF-CBT for reducing substance use among OVC. Subgroup analysis results suggest that a robust intervention such as TF-CBT is warranted for OVC with significant mental and behavioral health comorbidities. The similar performance of TF-CBT and PC + in the overall sample for risky sexual behavior and mild mental health problems indicates that enhancing existing psychosocial programs, such as PC, with standard implementation factors like having a defined training and supervision schedule (as was done to create PC+) may improve the efficacy of HIV risk reduction efforts.

J Pediatr Nurs. 2023 Jul-Aug;71:e57-e69.
doi: 10.1016/j.pedn.2023.04.015. Epub 2023 May 8.

Caregiver engagement interventions on reducing the anxiety and depression of children with chronic health conditions and their caregivers: A meta-analysis of randomized controlled trials

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Abstract

Background: Anxiety and depression are common debilitating mental health issues in families of children with chronic health conditions. It is essential to consider the mediating role of caregivers between children and healthcare workers. Previous research has evaluated the effectiveness of caregiver engagement interventions in reducing anxiety and depression in chronically ill children and their caregivers, but their overall impact awaits a synthesis of the available evidence.

Methods: We performed a comprehensive search using PubMed, Embase, Web of Science, Cochrane Library, Ovid, PsycINFO, APA PsycArticles, and Cumulative Index of Nursing and Allied Health Literature (CINAHL).

Results: Twenty-nine studies were included. The results demonstrated that caregiver engagement interventions significantly decreased anxiety (standardized mean difference [SMD] = -0.49; 95% confidence interval [CI], -0.77 to -0.22; P < 0.001) and depression (SMD = -

0.37; 95% CI, -0.55 to -0.18; P < 0.001) among caregivers, particularly in developing countries. However, no improvements in the anxiety (SMD = 0.00; 95% CI, -0.46 to 0.46; P = 0.99) and depression (SMD = -0.14; 95% CI, -0.32 to 0.04; P = 0.14) of children were observed.
Conclusions: Significant evidence exists regarding the positive effects of caregiver engagement interventions on caregivers' anxiety and depression. Further recommendations for future research should focus on engagement interventions that reduce the anxiety and depression for children with chronic conditions.
Implications: Clinicians should concentrate on the mental health of chronically ill children and their caregivers and extend caregiver engagement therapies to improve anxiety and depression resulting from managing the disease.

J Am Acad Child Adolesc Psychiatry. 2023 Nov;62(11):1217-1232.
doi: 10.1016/j.jaac.2023.02.013. Epub 2023 Mar 20.

Systematic Review and Meta-analysis: Group-Based Interventions for Treating Posttraumatic Stress Symptoms in Children and Adolescents

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Affiliations collapse

Abstract
Objective: Trauma exposure in childhood is common and can lead to a range of negative mental health outcomes, including posttraumatic stress disorder (PTSD). In many settings, resources to address this distress are scarce. Group-based interventions require minimal resources and training, can be delivered by non-mental health specialists, and target larger numbers of children and adolescents. This meta-analysis sought to establish whether such an approach is an effective method for targeting PTSD symptoms and to identify potential moderators of effectiveness.
Method: PubMed, PsycNET, and PTSDPubs were searched for randomized controlled trials that used a group-based PTSD intervention with children and adolescents aged 6 to 18 years. Data were extracted for PTSD symptoms and depression symptoms. A random-effects meta-analysis was conducted to obtain between-group pooled effect size estimates. This study was registered on PROSPERO (CRD42020187214).
Results: The initial search identified 9,650 studies, of which 42 were eligible for inclusion (N = 5,998). Children randomized to a group-based intervention had significantly lower PTSD symptoms after treatment compared with a control group, with a medium pooled effect (g = -0.55, 95% CI [-0.76, -0.35]). Group interventions were superior when compared with either active or passive controls, at follow-up, and for depression symptoms. There was a large amount of heterogeneity, but no evidence that this was explained by whether the intervention was delivered in a low- and middle-income or high-income country, included caregivers, or was universal or targeted.
Conclusion: Group PTSD interventions, particularly cognitive-behavioral therapy-based interventions, are effective at targeting posttrauma distress in children and adolescents. There was evidence of effectiveness when delivered in highly complex and resource-scarce settings and to a range of trauma-exposed groups, including groups exposed to war/conflict, natural disasters, and abuse.

Medicine (Baltimore). 2023 Jul 7;102(27):e34168.
doi: 10.1097/MD.0000000000034168.

Raising the self-esteem and reducing irrational beliefs of schoolchildren: The moderating and main effect study

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Abstract

Background: Several systematic reviews and meta-analyses studies have called for moderators of treatment outcomes and their main effect with regard to disadvantaged populations. In view of that, this study investigated the impacts and moderators of rational emotive behavior therapy (REBT) on the self-esteem and irrational beliefs of Schoolchildren in Ebonyi State Nigeria.

Methods: A group randomized controlled design was utilized to assign 55 schoolchildren to the treatment group and 55 schoolchildren to waitlisted control group. Two self-report measures (Self-Esteem Scale and Children Adolescent Scale of Irrationality) were used to assess the participants. There were pretest, posttest, and follow-up tests given at different intervals to ascertain the baseline, main effect, and long-term effects of the treatment. The data collected were analyzed using a 2-way analysis of covariance statistic.

Results: The results of the 2-way analysis of covariance demonstrated a difference between participants in the waitlisted control group at the pretest, posttest, and follow-up test and a positive improvement in schoolchildren with illogical beliefs as a result of exposure to REBT intervention. It was discovered that the REBT intervention changed schoolchildren's self-esteem and irrational views into rational ones. A later test result supported the intervention's consistent and significant effects in lowering illogical beliefs and raising students' self-esteem. The results also showed that there is no connection between gender and group membership.

Conclusion: This study suggests that REBT is a significant treatment strategy that reduces irrational beliefs and improves the self-esteem of primary school children. Based on these outcomes, further studies should replicate the study in other cultures with such a disadvantaged group.

Mobile phones and Apps

Front Public Health. 2024 Feb 8:12:1175262.
doi: 10.3389/fpubh.2024.1175262. eCollection 2024.

Using the health beliefs model to implement mobile puberty health education in Iranian adolescent boys: a randomized controlled trial

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Abstract

Introduction: Given boys' low health knowledge and their unhealthy behavior during puberty, which can cause many physical, mental, and psychological problems, it is important to prevent these complications. This study was therefore aimed to determine the efficacy of

a mobile health educational intervention based on the Health Beliefs Model (HBM) on Iranian adolescent boys.
Materials and methods: This randomized controlled trial involved junior high school boys (n = 148) in Iran studying during the 2020-2021 school year. Educational content concerning healthy behaviors during puberty (e.g., the importance of bathing) was developed based on HBM and sent to the intervention group via mobile phone. HBM addresses multiple factors (e.g., perceived disease risk) that explain health behaviors. The intervention was delivered in five sessions over four weeks using real-time Internet communication and texting. The control group did not receive any intervention. One school was randomly selected from each of the four districts of the study site. The schools were then randomized into intervention and control groups. The boys were then randomly selected from each school to participate in the study. Data collected at baseline and 2-month follow-up assessments included demographic information, health knowledge (e.g., physical changes during puberty), health behaviors (e.g., bathing), and HBM constructs (e.g., self-efficacy to perform healthy behaviors). Data analysis was done using the chi-square, independent and paired t-tests, and analysis of covariance (ANCOVA).
Results: The two groups did not differ in terms of demographic characteristics. Before the intervention, the two groups were slightly different in terms of knowledge, health behavior, and HBM constructs. Following the intervention, the scores of the intervention group improved significantly ($p < 0.05$). After adjusting for pre-intervention knowledge, HBM, and health behavior scores, the intervention group remained superior to the control group in terms of improvement of knowledge, HBM constructs, and healthy behaviors ($p < 0.05$). Effect sizes ranged from medium to large (0.25-0.86).
Conclusion: Mobile phone education based on the HBM is efficacious in encouraging healthy behavior in boys during puberty. Organizations interested in encouraging healthy behaviors in boys should consider the use of such a program.

BMC Public Health. 2024 Mar 7;24(1):737.
doi: 10.1186/s12889-024-18241-2.

Efficacy of a facial-aging web app on sun protection behaviors among primary school students in Iran: a randomized controlled trial

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Abstract
Background: Skin cancers resulting from excessive exposure to solar ultraviolet (UV) radiation are on the rise. This study aims to investigate the impact of facial-aging app intervention on promoting safe and healthy behaviors and its influence on reducing students' UV exposure.
Method: Utilizing a Pretest-Posttest repeated-measures design, we developed a theory-guided web app on the WhatsApp platform, named the Sunshine and Skin Health app. This app allows users to visualize their altered faces in three stages of adolescence, middle age, and old age based on sun protection behavior. The intervention continued within WhatsApp, incorporating 27 health messages grounded in the PMT theory, eight educational files, and a skin cancer video clip. The primary outcome is the change in sun protection behavior between the two groups (intervention and control) immediately after the intervention (T2) and the secondary outcome is the change in sun protection behavior between the two

groups at 3 months follow-up (T3). The data are analyzed in SPSS 22 and a significance level of 0.05 is considered.
Results: The results revealed no significant difference between the two groups before the intervention. However, in the intervention group, there were significant differences in the utilization of sunglasses, hats, and sunscreen in the last month, as well as sunscreen reapplication after washing their hands and face, both immediately after the intervention and at the 3-month follow-up, compared to the control group (P = 0.001). Furthermore, a significant intervention effect, time effect, and interaction effect between group and time were observed in behaviors related to using sunscreen in the last month and sunscreen reapplication after washing hands and face (P = 0.001). Specifically, the intervention group exhibited a significant difference from Time 1 to 2 and from Time 1 to 3 (p = 0.001), but no significant difference from Time 2 to 3. In contrast, the control group did not show any significant differences over time.
Conclusions: This study indicated that the Facial-Aging web app can effectively encourage safe behaviors in sunlight. To ensure the maintenance and sustainability of these behaviors over the long term, it is crucial to consider implementing booster sessions.

Mortality – post discharge

Neurology

Indian J Pediatr. 2023 Sep;90(9):867-872.
doi: 10.1007/s12098-022-04327-5. Epub 2022 Sep 1.
A Randomized, Controlled, Noninferiority Trial Comparing Vitamin B12 Monotherapy Versus Combination Multinutrient Therapy with Vitamin B12 for Efficacy in Treatment of Infantile Tremor Syndrome
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Abstract
Objectives: To compare the mean Likert (caregiver impression of change) and CAPUTE scores in children with ITS treated with daily injectable vitamin B12 alone versus injectable vitamin B12 with other multinutrients at 1 wk and 1 mo of therapy.
Methods: This was an open-label, active-controlled, assessor-blinded, noninferiority, randomized clinical trial. The participants included children aged 3 mo to 2 y with infantile tremor syndrome. Children were randomized to receive either 1 mg of daily injectable vitamin B12 or 1 mg of daily injectable vitamin B12 with other multinutrients (B12 + MV). Primary outcome measure was the mean Likert score in the two arms at 1 wk. Secondary outcome measures were mean change in CAPUTE scores at 1 wk of therapy; and mean change in CAPUTE and Vineland Social Maturity Scale (VSMS) scores after 1 mo of treatment.
Results: Seventy-two (N = 72) of the 160 screened were enrolled and randomized. The mean (SD) Likert score in the B12 group (n = 38) was 16.1 (3.7) and in the B12 + MV group (n = 34) was 14.9 (3.7); p = 0.237. Mean (SD) change in CAPUTE (CAT/CLAMS) at 1 mo in the groups was not statistically different. The mean (SD) change in social quotient in the B12

monotherapy group, 35.0 (20.7) was significantly higher than the B12 + multinutrient group 23.5 (15.4); p=0.01.
Conclusion: Injectable vitamin B12 monotherapy in ITS resulted in an improvement that was noninferior to combination multinutrient therapy, strongly supporting vitamin B12 deficiency as the cause of infantile tremor syndrome.

Cephalalgia. 2024 Apr;44(4):3331024241230963.
doi: 10.1177/03331024241230963.

A comparative study on prophylactic efficacy of cinnarizine and amitriptyline in childhood migraine: a randomized double-blind clinical trial

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Abstract

Background: Pediatric migraine prophylaxis is indicated when headaches are frequent and/or disabling. We aimed to conduct a study to compare the efficacy of cinnarizine and amitriptyline in pediatric migraine prophylaxis.
Methods: In a randomized, double-blind trial, patients aged 4-17 years with migraine who were eligible for prophylaxis enrolled. The primary outcome was a reduction response rate of ≥50% with $p < 0.005$ with respect to headache characteristics. The secondary outcome was migraine disability assessment. We evaluated patients every four weeks for three months: T1: week 4, T2: week 8 and T3: week 12. The safety profile was also assessed.
Results: Thirty patients were randomly assigned to each group. However, 43 patients completed the trial. Headache frequency decreased in amitriptyline group more effectively in T1 ($p = 0.004$). Amitriptyline was more successful in reducing the headache duration in all three periods ($p < 0.005$). There was no significant difference in severity improvement and reducing disability score between the two groups ($p > 0.005$). No serious adverse events were observed.
Conclusions: Both medications are effective in ameliorating migraine headaches and related disabilities. However, amitriptyline appears be a preferable option over cinnarizine, given its faster onset of action, efficacy in reducing headache duration and longer-lasting effects.

Lancet Glob Health. 2024 Jul;12(7):e1149-e1158.
doi: 10.1016/S2214-109X(24)00102-5. Epub 2024 May 13.

Doxycycline for the treatment of nodding syndrome: a randomised, placebo-controlled, phase 2 trial

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Abstract

Background: Nodding syndrome is a poorly understood neurological disorder that predominantly occurs in Africa. We hypothesised that nodding syndrome is a neuroinflammatory disorder, induced by antibodies to Onchocerca volvulus or its Wolbachia symbiont, cross-reacting with host neuronal proteins (HNPs), and that doxycycline can be used as treatment.
Methods: In this randomised, double-blind, placebo-controlled, phase 2 trial, we recruited participants from districts affected by nodding syndrome in northern Uganda. We included children and adolescents aged 8-18 years with nodding syndrome, as defined by WHO consensus criteria. Participants were randomly assigned (1:1) to receive either 100 mg doxycycline daily or placebo for 6 weeks via a computer-generated schedule stratified by skin microscopy results, and all parties were masked to group assignment. Diagnoses of O volvulus and antibodies to HNPs were made using luciferase immunoprecipitation system assays and immunohistochemistry. The primary outcome was change in the proportion with antibodies to HNPs, assessed at 24 months. All participants were included in safety analyses, and surviving participants (those with samples at 24 months) were included in primary analyses. Secondary outcomes were: change in concentrations of antibodies to HNPs at 24 months compared with baseline; proportion of participants testing positive for antibodies to O volvulus-specific proteins and concentrations of Ov16 or OVOC3261 antibodies at 24 months compared with baseline; change in seizure burden, proportion achieving seizure freedom, and the proportions with interictal epileptiform discharges on the diagnostic EEG; overall quality of life; disease severity at 24 months; and incidence of all-cause adverse events, serious adverse events, and seizure-related mortality by 24 months. This trial is registered with ClinicalTrials.gov, NCT02850913.
Findings: Between Sept 1, 2016, and Aug 31, 2018, 329 children and adolescents were screened, of whom 240 were included in the study. 140 (58%) participants were boys and 100 (42%) were girls. 120 (50%) participants were allocated to receive doxycycline and 120 (50%) to receive placebo. At recruitment, the median duration of symptoms was 9 years (IQR 6-10); 232 (97%) participants had O volvulus-specific antibodies and 157 (65%) had autoantibodies to HNPs. The most common plasma autoantibodies were to human protein deglycase DJ-1 (85 [35%] participants) and leiomodin-1 (77 [32%] participants) and, in cerebrospinal fluid (CSF), to human DJ-1 (27 [11%] participants) and leiomodin-1 (14 [6%] participants). On immunohistochemistry, 46 (19%) participants had CSF autoantibodies to HNPs, including leiomodin-1 (26 [11%]), γ-aminobutyric acid B receptors (two [<1%]), CASPR2 (one [<1%]), or unknown targets (28 [12%]). At 24 months, 161 (72%) of 225 participants had antibodies to HNPs compared with 157 (65%) of 240 at baseline. 6 weeks of doxycycline did not affect the concentration of autoantibodies to HNPs, seizure control, disease severity, or quality of life at the 24-month follow-up but substantially decreased Ov16 antibody concentrations; the median plasma signal-to-noise Ov16 ratio was 16·4 (95% CI 6·4-38·4), compared with 27·9 (8·2-65·8; p=0·033) for placebo. 14 (6%) participants died and, other than one traffic death, all deaths were seizure-related. Acute seizure-related hospitalisations (rate ratio [RR] 0·43 [95% CI 0·20-0·94], p=0·028) and deaths (RR 0·46 [0·24-0·89], p=0·028) were significantly lower in the doxycycline group. At 24 months, 96 (84%) of 114 participants who received doxycycline tested positive for antibodies to Ov16, compared with 97 (87%) of 111 on placebo (p=0·50), and 74 (65%) participants on doxycycline tested positive for antibodies to OVOC3261, compared with 57 (51%) on placebo (p=0·039). Doxycycline was safe; there was no difference in the incidence of grade 3-5 adverse events across the two groups.

Interpretation: Nodding syndrome is strongly associated with O volvulus and the pathogenesis is probably mediated through an O volvulus induced autoantibody response to multiple proteins. Although it did not reverse disease symptoms, doxycycline or another prophylactic antibiotic could be considered as adjunct therapy to antiseizure medication, as it might reduce fatal complications from acute seizures and status epilepticus induced by febrile infections.

Neurodevelopmental conditions and cerebral palsy

Autism

Explore (NY). 2023 Jul-Aug;19(4):594-599.
doi: 10.1016/j.explore.2022.12.004. Epub 2022 Dec 25.

Effect of yoga on the social responsiveness and problem behaviors of children with ASD in special schools: A randomized controlled trial

Sindhu Shanker[1], Balaram Pradhan[2]

Abstract

Context: Autism spectrum disorder (ASD) is the most common neurodevelopmental disorder and is increasingly reported among school-age children in India. Many children with ASD attend special schools which extend support for learning basic functional and academic skills. Problem behaviors and lack of social responsiveness are frequently associated with children with ASD in a school environment. Many evidence-based studies have explored various interventions in mitigating the lack of social responsiveness and problem behaviors in children. Few studies have examined the impact of yoga on social responsiveness and problem behaviors in special schools.

Objective: The objective of the study was to highlight the effect of school-based yoga on the social responsiveness and problem behaviors of children with ASD in special schools. Forty-three children with ASD from four special schools participated in the study.

Design: A randomized controlled trial (RCT) design was employed for the study. Children with ASD (n = 43) from four special schools were assessed by their teachers for social responsiveness and problem behaviors with the Social Responsiveness Scale-2 (SRS-2) and Aberrant Behavior Checklist-2 (ABC-2) at the baseline and after the yoga intervention.

Intervention: Structured yoga of 45 min for 12 weeks was conducted across four special schools with simple yoga practices conducive to children with ASD.

Results: Significant changes were observed post-intervention in the mean scores of the social communication aspect in social responsiveness (p = .021), irritability (p = .041), and social withdrawal (p = .047) aspects of problem behaviors.

Asian J Psychiatr. 2024 Apr 16:96:104052.
doi: 10.1016/j.ajp.2024.104052. Online ahead of print.

Comparative efficacy of family mediated intervention versus early intensive behavioural intervention on symptom domains in children with autism spectrum disorder: A randomized controlled trial

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Abstract

Background: Family Mediated Intervention (FMI) and Early Intensive Behavioural Intervention (EIBI) are found to be standard of care for children with Autism Spectrum Disorder (ASD). Comparison of their efficacy were assessed using ISAA as primary outcome measure.

Methods: This study was a parallel arm, open label, randomized active- controlled non-inferiority clinical trial. 50 Children diagnosed with ASD were randomized into FMI and EIBI groups. Clinical status was checked by using Indian scale for assessment of autism (ISAA), Oro- motor and sensory profile at baseline, after three and six months.

Results: Difference between change in mean ISAA score between FMI and EIBI group at the end of 6 months as per protocol (PP) analysis was -7.23 (CI=-18.41, 3.94), which was within pre-defined clinically relevant non-inferiority (NI) margin of - 24. FMI was found to be non-inferior to EIBI at the end of 6 months as the lower bound of 95% CI (-18.41) for ISAA score was higher than NI margin. ISAA scores were found to be statistically lower in both FMI and EIBI groups at the end point compared to baseline which indicated improvement in symptom severity.

Conclusion: FMI was non-inferior to EIBI as therapy for children with ASD at the end of six months. Finding also indicated longer duration of treatment is required for FMI to be superior. FMI can be recommended for children with ASD in view of improved ISAA scores reported in our study.

BMC Pediatr. 2024 Apr 25;24(1):270.
doi: 10.1186/s12887-024-04752-9.

Comparison of the efficacy of parent-mediated NDBIs on developmental skills in children with ASD and fidelity in parents: a systematic review and network meta-analysis

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Abstract

Background: Recently, studies on behavioral interventions for autism have gained popularity. Naturalistic Developmental Behavior Interventions (NDBIs) are among the most effective, evidence-based, and widely used behavior interventions for autism. However, no research has been conducted on which of the several NDBI methods is most effective for parents and children with autism spectrum disorders. Therefore, we conducted a network meta-analysis to compare the specific effects of each type of parental-mediated NDBI on children's developmental skills and parent fidelity.

Methods: PubMed, Embase, Cochrane Library, Medline, Web of Science, China National Knowledge Infrastructure (CNKI), CINAHL, and Wanfang databases were searched from inception to August 30, 2023. A total of 32 randomized controlled trial studies that examined the efficacy of different NDBIs were included.

Results: Parents of children with ASD who received Pivotal Response Treatment (PRT) reported significant improvements in their children's social skills (SUCRA, 74.1%), language skills (SUCRA, 88.3%), and parenting fidelity (SUCRA, 99.5%). Moreover, parents who received Early Start Denver Model (ESDM) reported significant improvements in their children's language (SMD = 0.41, 95% CI: 0.04, 0.79) and motor skills (SMD = 0.44, 95% CI: 0.09, 0.79). In terms of the efficacy of improving parent fidelity, the results showed that the Improving Parents as Communication Teachers (ImPACT) intervention significantly improved parent fidelity when compared with the treatment-as-usual group (TAU) (SMD = 0.90, 95% CI: 0.39, 1.42) and the parental education intervention (PEI) (SMD = 1.10, 95% CI:0.28, 1.91).There was a difference in parent fidelity among parents who received PRT(SMD = 3.53, 95% CI: 2.26, 4.79) or ESDM(SMD = 1.42, 95% CI: 0.76, 2.09) training compared with PEI.
Conclusion: In conclusion, this study revealed that parents can achieve high fidelity with the ImPACT intervention, and it can serve as an early first step for children newly diagnosed with ASD. It also showed that parent-mediated ESDM is effective in improving language and motor skills for children with ASD and can be used as part of the second stage of parent training. Parent-mediated PRT can also be used as a third stage of parent training with sufficient training intensity to further improve language, social, and motor skills.

Ital J Pediatr. 2024 Jun 21;50(1):120.
doi: 10.1186/s13052-024-01692-z.

Effect of probiotics on children with autism spectrum disorders: a meta-analysis

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Abstract

Background: Researches have found that alteration of intestinal flora may be closely related to the development of autism spectrum disorder (ASD). However, whether probiotics supplementation has a protective effect on ASD remains controversial. This meta-analysis aimed to analyze the outcome of probiotics in the treatment of ASD children.
Methods: The Pubmed, Cochrane Library, Web of Science and Embase were searched until Sep 2022. Randomized controlled trials (RCTs) relevant to the probiotics and placebo treatment on ASD children were screened. Quality assessment of the included RCTs was evaluated by the Cochrane collaboration's tool. The primary outcomes were ASD assessment scales, including ABC (aberrant behavior checklist) and CBCL (child behavior checklist) for evaluating the behavior improvement, SRS (social responsiveness scale) for social assessment, DQ (developmental quotient) for physical and mental development and CGI-I (clinical global impression improvement) for overall improvement. The secondary outcome was total 6-GSI (gastrointestinal severity index).
Results: In total, 6 RCTs from 6 studies with 302 children were included in the systemic review. Total 6-GSI (MD=-0.59, 95%CI [-1.02,-0.17], P < 0.05) decreased significantly after oral administration of probiotics. Whereas, there was no statistical difference in ABC, CBCL, SRS, DQ and CGI-I between probiotics and placebo groups in ASD children.
Conclusion: Probiotics treatment could improve gastrointestinal symptoms, but there was no significant improvement in ASD.

Cerebral palsy

Pediatrics. 2024 Apr 1;153(4):e2023063854.
doi: 10.1542/peds.2023-063854.

Efficacy of Early Intervention for Infants With Cerebral Palsy in an LMIC: An RCT

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Abstract

Objective: To test efficacy of a parent-delivered multidomain early intervention (Learning through Everyday Activities with Parents [LEAP-CP]) for infants with cerebral palsy (CP) compared with equal-dose of health advice (HA), on (1) infant development; and (2) caregiver mental health. It was hypothesized that infants receiving LEAP-CP would have better motor function, and caregivers better mental health.

Methods: This was a multisite single-blind randomized control trial of infants aged 12 to 40 weeks corrected age (CA) at risk for CP (General Movements or Hammersmith Infant Neurologic Examination). Both LEAP-CP and HA groups received 15 fortnightly home-visits by a peer trainer. LEAP-CP is a multidomain active goal-directed intervention. HA is based on Key Family Practices, World Health Organization. Primary outcomes: (1) infants at 18 months CA: Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDI-CAT mobility); and (2) caregiver: Depression Anxiety and Stress Scale.

Results: Of eligible infants, 153 of 165 (92.7%) were recruited (86 males, mean age 7.1±2.7 months CA, Gross Motor Function Classification System at 18 m CA: I = 12, II = 25, III = 9, IV = 18, V = 32). Final data were available for 118 (77.1%). Primary (PEDI-CAT mobility mean difference = 0.8 (95% CI -1.9 to 3.6) P = .54) and secondary outcomes were similar between-groups. Modified-Intention-To-Treat analysis on n = 96 infants with confirmed CP showed Gross Motor Function Classification System I and IIs allocated to LEAP-CP had significantly better scores on PEDI-CAT mobility domain (mean difference 4.0 (95% CI = 1.4 to 6.5), P = .003) compared with HA.

Conclusions: Although there was no overall effect of LEAP-CP compared with dose-matched HA, LEAP-CP lead to superior improvements in motor skills in ambulant children with CP, consistent with what is known about targeted goal-directed training.

Dev Med Child Neurol. 2024 Jun 25.
doi: 10.1111/dmcn.16007. Online ahead of print.

Functioning and activity outcomes of the Akwenda Intervention Program for children and young adults with cerebral palsy in Uganda: A cluster-randomized trial

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Abstract

Aim: To evaluate the efficacy of the Akwenda Intervention Program on motor, self-care, and social function of children and young people with cerebral palsy (CP).

Method: This was a cluster-randomized, controlled, single-blinded, intervention study of 100 participants with CP (2-23 years; 52 males) in rural eastern Uganda. Half were allocated to the intervention program, the remainder served as waitlist controls. Gross Motor Function Measure-66 (GMFM-66) and the Ugandan version of Pediatric Evaluation of Disability Inventory (PEDI-UG) were collected before group allocation and after intervention. General linear models and t-tests were used to compare changes within and between groups. Cohen's d estimated the effect size of group differences. Change scores were evaluated by age and mobility subgroups.
Results: Significant group by time interactions were found for GMFM-66 ($p = 0.003$) and PEDI-UG outcomes ($p < 0.001$), except mobility, with the intervention group demonstrating greater changes. Both groups increased their scores on the GMFM-66 and child PEDI-UG, while only the intervention group had significant increases in caregiver assistance scores and across all age and mobility subgroups. Cohen's d showed large effect sizes ($d > 0.8$) of differences for PEDI-UG outcomes except mobility.
Interpretation: The Akwenda Intervention Program had a large positive impact on functioning and activity across age and mobility levels.

Indian J Pediatr. 2023 Sep;90(9):873-879.
doi: 10.1007/s12098-022-04265-2. Epub 2022 Jul 22.

Gabapentin as Add-on Therapy to Trihexyphenidyl in Children with Dyskinetic Cerebral Palsy: A Randomized, Controlled Trial

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Abstract
Objective: To compare the efficacy of gabapentin as add-on therapy to trihexyphenidyl in the treatment of children with dyskinetic cerebral palsy (CP).
Methods: An open-labelled, randomized, controlled trial was conducted among children aged 3-9 y with dyskinetic CP [Gross Motor Functional Classification System (GMFCS) 4-5]. Participants were assigned into two groups: gabapentin with trihexyphenidyl (n = 30) and trihexyphenidyl alone (n = 30). Dyskinesia Impairment Scale (DIS), Dystonia Severity Assessment Plan (DSAP), and International Classification of Functioning, Disability, and Health-Children and Youth Version (ICF-CY) were measured at baseline, 4 and 12 wk.
Results: There was significant reduction in baseline dystonia in both the groups (DIS: $p < 0.001$; DSAP: $p = 0.007$; ICF-CY: $p < 0.001$) but when data were compared between the groups, there was no significant difference in the severity of dystonia at 4 wk and at 12 wk (DIS: $p = 0.09$; DSAP: $p = 0.49$; ICF-CY: $p = 0.25$). Constipation was the commonest side effect observed in both the groups [3 (11.5%) vs. 4 (14.3%)].
Conclusion: Trihexyphenidyl alone is as effective as combination of gabapentin with trihexyphenidyl in decreasing the severity of dystonia at 12 wk. Hence, there is no added benefit of gabapentin as add-on therapy for dystonia among children with dyskinetic CP.

Ther Clin Risk Manag. 2024 Feb 14:20:95-109.
doi: 10.2147/TCRM.S432249. eCollection 2024.

Effectivity of Virtual Reality to Improve Balance, Motor Function, Activities of Daily Living, and Upper Limb Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis

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Abstract

Background: Cerebral palsy (CP) is the most common motor disorder in childhood. CP limits movement, which can interfere with children's daily activities. As a technology that provides intensive mass practice to children, virtual reality (VR) can create an interactive and motivating environment. With the intensity set by the therapist and feedback that can be used to produce individualized therapy, VR has great potential to improve CP patients' quality of life, especially in a safe, enjoyable, and playful environment.

Purpose: This systematic review and meta-analysis sought to determine the effectiveness of VR for children with CP.

Methods: We conducted a comprehensive literature search based on the PRISMA guidelines through PubMed, Scopus, Embase, Wiley, and ProQuest to assess the efficacy of VR in managing children with CP up to 15 September 2022. Risk assessment of bias was performed using Cochrane RoB 2.

Results: Nineteen randomized controlled trials with 467 and 427 patients with CP were included in the intervention and control groups in qualitative and quantitative analyses. Participants consisted of cerebral palsy with hemiplegia (n=7), diplegia (n=2), a combination of both (n=4), and undefined (n=13). From all studies conducted, VR showed significant results where VR could improve balance (MD: 2.71[1.95, 3.48]; $p < 0.00001$), motor function (MD: 3.73 [1.67, 5.79]; $p = 0.0004$), and activity daily living (MD: 10.05 [2.89, 17.22]. However, VR showed not effective in improving upper limb function.

Conclusion: With its advantages and excellent effectiveness, VR may improve functional mobility and the quality of life of children with CP.

Spina bifida

Am J Obstet Gynecol MFM. 2023 Aug;5(8):100983.
doi: 10.1016/j.ajogmf.2023.100983. Epub 2023 Apr 24.

Prenatal predictors of need for cerebrospinal fluid diversion in infants following prenatal repair of open spina bifida; systematic review and meta-analysis

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Abstract

Objective: This study aimed to investigate prenatal predictors of the need for cerebrospinal fluid diversion in infants following prenatal repair of open spina bifida.

Data sources: A systematic search was performed to identify relevant studies published from inception until June 2022 in the English language using the databases PubMed, Scopus, and Web of Science.

Study eligibility criteria: We included retrospective and prospective cohort studies and randomized controlled trials reporting on prenatal repair of open spina bifida.

Methods: The random-effects model was used to pool the mean differences or odds ratios and the corresponding 95% confidence intervals. Heterogeneity was assessed using the I^2 value.
Results: A total of 9 studies including 948 pregnancies undergoing prenatal repair of open spina bifida were included in the final analysis. Prenatal factors that were significantly associated with the need for postnatal cerebrospinal fluid diversion were gestational age at surgery ≥25 weeks (odds ratio, 4.2; 95% confidence interval, 1.8-9.9; I^2=54%; P=.001), myeloschisis (odds ratio, 2.2; 95% confidence interval, 1.1-4.1; I^2=0.0%; P=.02), preoperative lateral ventricle width ≥15 mm (odds ratio, 4.5; 95% confidence interval, 2.9-6.9; I^2=0.0%; P<.0001), predelivery lateral ventricle width (mm) (mean difference, 8.3; 95% confidence interval, 6.4-10.2; I^2=0.0%; P<.0001), and preoperative lesion level at T12-L2 (odds ratio, 2.5; 95% confidence interval, 1.03-6.3; I^2=68%; P=.04). Factors that significantly reduced the need for postnatal shunt placement were gestational age at surgery <25 weeks (odds ratio, 0.3; 95% confidence interval, 0.15-0.6; I^2=67%; P=.001) and preoperative lateral ventricle width <15 mm (odds ratio, 0.3; 95% confidence interval, 0.2-0.4; I^2=0.0%; P<.0001).
Conclusion: This study demonstrated that among fetuses that underwent surgical repair of open spina bifida, having gestational age at surgery of ≥25 weeks, preoperative lateral ventricle width of ≥15 mm, myeloschisis lesion type, and preoperative lesion level above L3 was predictive of the need for cerebrospinal fluid diversion during the first year of life.

Neuro-rehabilitation medicine

Assist Technol. 2023 Oct 5:1-8.
doi: 10.1080/10400435.2023.2267626. Online ahead of print.

Application of remodeled glove puppetry for children with developmental disabilities: a randomized controlled trial

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Abstract
This study aimed to improve hand performance and play behavior in children with developmental disabilities (DD) using a remodeled glove puppetry approach. Overall, 62 children with DD were randomly assigned to experimental and control groups (n = 31 each). The experimental group underwent a 12-week rehabilitation program by playing with the remodeled glove puppetry, while the children in the control group played with non-remodeled glove puppetry. The Chinese puppet was remodeled using a Lego EV3® robot. Hand kinematics were analyzed through the Siliconcoach® Pro 7 software, which measured the force produced by the baseline ® hydraulic pinch gauge. Play behavior was measured using the Knox Preschool Play Scale-revised (KPPS-r). The experimental group exhibited significant improvements compared to the control group in hand kinematics (wrist range of motion [ROM], p < .05; metacarpophalangeal ROM, p < .05; proximal interphalangeal ROM, p < .05) and KPPS-r scores (space management, p < .05; material management, p < .05; pretense-symbolic, p < .05; participation, p < .05). After the 12-week rehabilitation with the remodeled glove puppetry, the experimental group exhibited significant improvement in kinematics and KPPS-r scores.

J Spinal Cord Med. 2023 Nov;46(6):964-974.
doi: 10.1080/10790268.2021.2012053. Epub 2021 Dec 22.

Effectiveness of immersive virtual reality training to improve sitting balance control among individuals with acute and sub-acute paraplegia: A randomized clinical trial

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Abstract

Objectives: Spinal cord injury (SCI) is a disabling condition with physical, psychological, and financial consequences. The study's goal is to compare the effectiveness of immersive virtual reality (VR) training in balance among individuals with incomplete paraplegia to that of functional electrical stimulation (FES).

Design: Two groups, randomized clinical trial.

Setting: Neurological Physiotherapy Out Patient Department, Tertiary Care Hospital.

Participants: Eighteen people aged 18-60 years with incomplete SCI.

Interventions: VR training along with conventional physical therapy (CPT) and FES for Rectus Abdominis and Erector Spinae with CPT five times a week for 4 weeks.

Outcome measures: The outcome measures were Modified Functional Reach Test (mFRT) and Function in Sitting Test (FIST) to assess sitting balance and Spinal Cord Independence Measure III (SCIM III) for the level of independence. Assessments were taken before initiating treatment and at the end of the 2 and 4 weeks after treatment. Within-group analyses for the mFRT values were performed using Repeated Measures ANOVA test, and between-group analyses were performed using the independent *t*-test test. Friedman and Mann-Whitney *U*-tests were used for analyzing FIST and SCIM III.

Results: All variables (mFRT and FIST) improved significantly in both groups ($P < 0.05$), with the VR + CPT group showing a more significant result than the FES + CPT group (P value < 0.05), except for SCIM III.

Conclusion: VR as an adjunct to CPT demonstrated proved to be an effective treatment to improve balance among individuals with incomplete paraplegia.

Newborn care

Essential newborn care

Avoiding hypothermia

Int Breastfeed J. 2024 May 3;19(1):31.
doi: 10.1186/s13006-024-00635-y.

Implementation of early essential neonatal care for newborns delivered by cesarean section in Jiaxing: a single-center prospective randomized controlled trial

Jianping Xu[1], Min Zhang[2], Yi Li[3], Shuiqin Gu[4]

Abstract

Background: As an essential part of Early Essential Newborn Care, 90 minutes of mother-infant skin-to-skin contact is significant in improving maternal and infant outcomes. However, due to human resource constraints and the consideration of maternal and infant safety, it is difficult to achieve continuous uninterrupted skin-to-skin contact for at least 90 minutes during and after cesarean delivery. The aim of this study was to investigate the efficacy and safety of the continuous uninterrupted skin-to-skin contact for at least 90 minutes during and after cesarean section for exclusive breastfeeding rate during hospitalization and maternal and infant health indicators during and after cesarean delivery.
Methods: This is a single-center, prospective randomized controlled trial conducted in one tertiary care hospital in China. We selected 280 cases of elective cesarean delivery in a tertiary maternal and child specialty hospital in Zhejiang Province from September 2018 to August 2022, which were randomly divided into two groups: in the conventional group, doulas performed at least 30 minutes for early continuous SSC within 10-30 minutes during and after cesarean delivery. In the EENC group, with immediate continuous SSC within 5-10 minutes of neonatal delivery until surgery is completed and continued SSC after returning to the ward. Exclusive breastfeeding rate during hospitalization and maternal and infant health indicators were compared between the groups.
Results: A total of 258 cases were analyzed. Compared with the control group, the EENC group had earlier first breastfeeding initiation (13.7 ± 3.6 vs 62.8 ± 6.5 minutes, P < 0.001), longer duration of first breastfeeding (42.6 ± 9.0 vs 17.9 ± 7.5 minutes, P < 0.001), earlier onset of lactogenesis II (73.7 ± 3.6 vs 82.5 ± 7.4 hours, P < 0.001), higher breastfeeding self-efficacy score (128.6 ± 8.9 vs 104.4 ± 8.5, P < 0.001), higher Exclusive breastfeeding rate during hospitalization (88% vs 81%, P = 0.018), higher maternal satisfaction scores (18.9 ± 1.1 vs 14.0 ± 2.7, P < 0.001). Meanwhile the EENC group showed lower incidence of neonatal hypothermia (0% vs 4.6%, P = 0.014), lower neonatal hypoglycemia (0% vs 5.4%, P = 0.007) and less cumulative blood loss within 24 hours postpartum (254.2 ± 43.6 vs 282.8 ± 63.8 ml, P < 0.001).
Conclusion: The implementation of EENC up to 90 minutes by caesarean doula company nurses is feasible and beneficial to maternal and infant health.

Lancet. 2024 May 13:S0140-6736(24)00064-3.
doi: 10.1016/S0140-6736(24)00064-3. Online ahead of print.

Effectiveness of kangaroo mother care before clinical stabilisation versus standard care among neonates at five hospitals in Uganda (OMWaNA): a parallel-group, individually randomised controlled trial and economic evaluation

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Abstract

Background: Preterm birth is the leading cause of death in children younger than 5 years worldwide. WHO recommends kangaroo mother care (KMC); however, its effects on mortality in sub-Saharan Africa and its relative costs remain unclear. We aimed to compare the

effectiveness, safety, costs, and cost-effectiveness of KMC initiated before clinical stabilisation versus standard care in neonates weighing up to 2000 g.
Methods: We conducted a parallel-group, individually randomised controlled trial in five hospitals across Uganda. Singleton or twin neonates aged younger than 48 h weighing 700-2000 g without life-threatening clinical instability were eligible for inclusion. We randomly assigned (1:1) neonates to either KMC initiated before stabilisation (intervention group) or standard care (control group) via a computer-generated random allocation sequence with permuted blocks of varying sizes, stratified by birthweight and recruitment site. Parents, caregivers, and health-care workers were unmasked to treatment allocation; however, the independent statistician who conducted the analyses was masked. After randomisation, neonates in the intervention group were placed prone and skin-to-skin on the caregiver's chest, secured with a KMC wrap. Neonates in the control group were cared for in an incubator or radiant heater, as per hospital practice; KMC was not initiated until stability criteria were met. The primary outcome was all-cause neonatal mortality at 7 days, analysed by intention to treat. The economic evaluation assessed incremental costs and cost-effectiveness from a disaggregated societal perspective. This trial is registered with ClinicalTrials.gov, NCT02811432.
Findings: Between Oct 9, 2019, and July 31, 2022, 2221 neonates were randomly assigned: 1110 (50·0%) neonates to the intervention group and 1111 (50·0%) neonates to the control group. From randomisation to age 7 days, 81 (7·5%) of 1083 neonates in the intervention group and 83 (7·5%) of 1102 neonates in the control group died (adjusted relative risk [RR] 0·97 [95% CI 0·74-1·28]; p=0·85). From randomisation to 28 days, 119 (11·3%) of 1051 neonates in the intervention group and 134 (12·8%) of 1049 neonates in the control group died (RR 0·88 [0·71-1·09]; p=0·23). Even if policy makers place no value on averting neonatal deaths, the intervention would have 97% probability from the provider perspective and 84% probability from the societal perspective of being more cost-effective than standard care.
Interpretation: KMC initiated before stabilisation did not reduce early neonatal mortality; however, it was cost-effective from the societal and provider perspectives compared with standard care. Additional investment in neonatal care is needed for increased impact, particularly in sub-Saharan Africa.

Resuscitation. 2023 Aug;189:109840.
doi: 10.1016/j.resuscitation.2023.109840. Epub 2023 May 15.

Immediate skin-to-skin contact versus care under radiant warmer at birth in moderate to late preterm neonates - A randomized controlled trial

Kuldeep Singh[1], Deepak Chawla[2], Suksham Jain[1], Supreet Khurana[1], Navneet Takkar[3]

Abstract

Objective: To compare the effect of immediate care at birth in skin-to-skin contact (SSC) or under a radiant warmer on cardiorespiratory stability at 60 minutes of age in moderate-to-late preterm neonates.
Methods: In this open-label, parallel-group, randomized controlled trial, neonates born at $33^{0/7}$ to $36^{6/7}$ weeks of gestation by vaginal delivery and breathing or crying were randomized to receive care at birth in SSC (n = 50) or under a radiant warmer (n = 50). In the SSC group, immediate care at birth including drying and clearing of the airway was provided in SSC over the mother's abdomen. SSC was maintained for an observational period of 60 minutes after

birth. In the radiant warmer group, care at birth and post-birth observation was performed under an overhead radiant warmer. The primary outcome of the study was the stability of the cardio-respiratory system in late preterm infants (SCRIP) score at 60 minutes of age.
Results: Baseline variables were similar in the two study groups. The SCRIP score at 60 minutes of age was similar in the two study groups (median: 5.0, IQR: 5-6 vs. 5.0, 5-6). The mean axillary temperature at 60 minutes of age was significantly lower in the SSC group (°C; 36.4 ± 0.4 vs. 36.6 ± 0.4, P = 0.004).
Conclusion: It was feasible to provide immediate care at birth in moderate and late preterm neonates while being positioned in SSC with the mother. However, in comparison to care under a radiant warmer, this did not lead to better cardiorespiratory stability at 60 minutes of age.

Acta Paediatr. 2023 Oct 31.
doi: 10.1111/apa.17021. Online ahead of print.
90 versus 60 min of early skin-to-skin contact on exclusive breastfeeding rate in healthy infants' ≥35 weeks: A randomised controlled trial
Shalini Raj Kumawat[1], Himanshu Vyas[1], Remiya Mohan[1], Rohit Sasidharan[2], Bharti Yadav[2], Neeraj Gupta[2]
Abstract
Aim: To compare the effect of 90 versus 60 min of early skin-to-skin contact (SSC) among vaginally born healthy infants ≥35 weeks of gestation on their exclusive breastfeeding rates and breastfeeding behaviour.
Methods: This parallel-group, open-label, randomised controlled trial enrolled healthy term and late preterm infants born vaginally. Infants in the intervention group received early SSC for 90 min compared to 60 min in the control group. The primary outcome was the proportion of infants on exclusive breastfeeding at 60 ± 12 h.
Results: One hundred ninety-eight mother-infant dyads were randomised (99 in each group). The infants in the 90-min SSC group were more likely to be exclusively breastfed at 60 ± 12 h as compared to the 60-min SSC group (RR, 95% CI-1.44, [1.15-1.79], p < 0.01). The modified infant breastfeeding assessment tool score at 60 ± 12 h was significantly higher in the 90-min SSC group (median [IQR]-9, [8, 10] versus 8 [7, 10], p = 0.03]. The proportion of infants on exclusive breastfeeding at 6, 10, and 14 weeks of age was also significantly higher in the 90-min SSC group (RR, 95% CI-1.39 [1.11-1.74], 1.36 [1.08-1.07], and 1.38 [1.08-1.75], respectively).
Conclusion: Increasing the duration of early SSC showed a dose-response benefit on exclusive breastfeeding rates and breastfeeding behaviour.

Am J Obstet Gynecol MFM. 2023 Aug;5(8):101033.
doi: 10.1016/j.ajogmf.2023.101033. Epub 2023 May 26.
Association of duration of skin-to-skin contact after cesarean delivery in China: a superiority, multicentric randomized controlled trial

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Abstract

Background: In China, the rates of early initiation and exclusive breastfeeding are low. The high cesarean delivery rates further contribute to low breastfeeding outcomes. Skin-to-skin contact, a key component of early essential newborn care, is known to be associated with improved breastfeeding initiation and exclusivity; however, the necessary duration has not been subjected to a randomized control trial.

Objective: This study aimed to determine the association of the duration of skin-to-skin contact after cesarean delivery with breastfeeding outcomes and maternal and neonatal health outcomes in China.

Study design: This was a multicentric randomized controlled trial that was conducted at 4 hospitals in China. A total of 720 participants at ≥37 gestational weeks with a singleton pregnancy and who received an elective cesarean delivery with epidural anesthesia or spinal anesthesia or combined spinal-epidural anesthesia were randomly divided into 4 groups at a ratio of 1:1:1:1. The control group received routine care. Intervention group 1 (G1), 2 (G2), and 3 (G3) received 30, 60, and 90 minutes of skin-to-skin contact immediately after the cesarean delivery, respectively.

Results: Between January 3 and October 14, 2021, 659 participants were recruited, including 173 in the control group, 176 in G1, 146 in G2, and 164 in G3. Among G1, G2, and G3, the rate of early initiation of breastfeeding within 60 minutes of birth was 56%, 71%, and 72%, respectively, compared with 22% in the control group (P<.001). The exclusive breastfeeding rate at discharge was 69%, 62%, and 71%, respectively, compared with 57% in the control group (P=.003). Early essential newborn care practices were associated with a reduction in postpartum blood loss and neonatal intensive care unit or neonatal ward admission (P<.001; P=.022) .

Conclusion: Our findings highlight that prolonged skin-to-skin contact after a cesarean delivery was associated with higher initiation and exclusive breastfeeding at discharge rates. It also found associations with reduced postpartum blood loss and neonatal intensive care unit or neonatal ward admission.

Resuscitation. 2023 Aug 17;109934.
doi: 10.1016/j.resuscitation.2023.109934. Online ahead of print.

Maintaining normothermia immediately after birth in preterm infants < 34 weeks' gestation: A Systematic review and meta-analysis

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Abstract

Aim: To evaluate delivery room (DR) interventions to prevent hypothermia and improve outcomes in preterm newborn infants < 34 weeks' gestation.

Methods: Medline, Embase, CINAHL and CENTRAL were searched till 22nd July 2022. Randomized controlled trials (RCTs), non-RCTs and quality improvement studies were

considered. A random effects meta-analysis was performed, and the certainty of evidence was evaluated using GRADE guidelines.
Results: DR temperature of ≥ 23°C compared to standard care improved temperature outcomes without an increased risk of hyperthermia (low certainty), whereas radiant warmer in servo mode compared to manual mode decreased mean body temperature (MBT) (moderate certainty). Use of a plastic bag or wrap (PBW) improved normothermia (low certainty), but with an increased risk of hyperthermia (moderate certainty). Plastic cap improved normothermia (moderate certainty) and when combined with PBW improved MBT (low certainty). Use of a cloth cap decreased moderate hypothermia (low certainty). Though thermal mattress (TM) improved MBT, it increased risk of hyperthermia (low certainty). Heated-humidified gases (HHG) for resuscitation decreased the risk of moderate hypothermia and severe intraventricular hemorrhage (very low to low certainty). None of the interventions was shown to improve survival, but sample sizes were insufficient.
Conclusions: DR temperature of ≥ 23°C, radiant warmer in manual mode, use of a PBW and a head covering is suggested for preterm newborn infants < 34 weeks' gestation. HHG and TM could be considered in addition to PBW provided resources allow, in settings where hypothermia incidence is high. Careful monitoring to avoid hyperthermia is needed.

Pediatr Res. 2024 Mar 5.
doi: 10.1038/s41390-024-03115-5. Online ahead of print.
Temperature probe placement in very preterm infants during delivery room stabilization: an open-label randomized trial
Pranav R Jani[#1,2], Rajesh Maheshwari[#3,4], Hannah Skelton[3,5], Patricia Viola[3], Sheela Thomas[3], Lynette Ryder[6], Mihaela Culcer[3,4], Umesh Mishra[3,4], Swapnil Shah[3,4], Jane Baird[3], James Elhindi[4,7], Ann-Maree Padernia[3], Traci-Anne Goyen[3], Daphne D'Cruz[3], Melissa Luig[3], Dharmesh Shah[3,4]
Abstract
Background: Variation in practice exists for temperature probe positioning during stabilization of very preterm infants (<32 weeks gestation). We explored the influence of temperature probe sites on thermoregulation.
Methods: An open-label, stratified, balanced, parallel, randomized trial was conducted. Inborn infants were randomly assigned temperature probe to the axilla or to the upper back. The primary outcome was normothermia (local range: 36.8-37.3 °C and World Health Organization (WHO) range: 36.5-37.5 °C) at admission to the neonatal intensive care unit.
Results: Between 1 November 2018 and 4 July 2022, 178 infants were randomly assigned to one of the two sites (n = 89 each), 175 included in the final analysis. Normothermia (local range) was achieved for 39/87 infants (44.8%) assigned to the upper back compared to 28/88 infants (31.8%) assigned to the axilla [risk difference:13%; 95% CI -1.3-27.3]. Normothermia (WHO range) was achieved for 78/87 infants (89.7%) assigned to the upper back compared to 70/88 infants (79.6%) assigned to the axilla [risk difference:10.1%; 95% CI -0.5-20.7]. No infant recorded temperatures >38 °C or developed skin injury.
Conclusions: In very preterm infants, upper back site was equally effective as the axilla in maintaining normothermia, with no increase in adverse events.

Avoiding hypoglycaemia

Neonatology. 2024 Jan 9:1-16.
doi: 10.1159/000535503. Online ahead of print.

Early Feeding for the Prevention of Neonatal Hypoglycaemia: A Systematic Review and Meta-Analysis

Lily F Roberts [1], Jane E Harding [2], Caroline A Crowther [2], Estelle Watson [2], Zeke Wang [2], Luling Lin [2]

Abstract

Background: Poor feeding, among other factors, predisposes neonates to hypoglycaemia. Early feeding is widely recommended to prevent hypoglycaemia in those at risk, but the effectiveness of this is uncertain. This review aimed to summarise and analyse the evidence on the effectiveness of early feeding for prevention of neonatal hypoglycaemia.

Methods: Four databases and three clinical trial registries were searched from inception to May 24, 2023. Published and unpublished randomised controlled trials (RCTs), quasi-RCTs, cluster randomised trials, non-randomised studies of interventions, and observational studies with comparison groups were considered for inclusion with no language or publication date restrictions. We included studies of neonates who were fed early (within 60 min of birth or study defined) versus delayed. Study quality was assessed using the Cochrane Risk of Bias 1 tool or Effective Public Health Practice Project Quality Assessment tool. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. RevMan 5.4.1 or R was used to synthesise results in random-effects meta-analyses. This review was registered prospectively with PROSPERO (CRD42022378904).

Results: A total of 175,392 participants were included across 19 studies, of which two were RCTs, 14 cohort studies, two cross-sectional studies, and one a case-control study. Most studies (13/19) were conducted in low- or lower-middle-income countries. Early feeding may be associated with reduced neonatal hypoglycaemia (four cohort studies, 744 infants, odds ratio [OR] 0.19 (95% CI: 0.10-0.35), p < 0.00001, I2 = 44%) and slightly reduced duration of initial hospital stay (one cohort study, 1,673 infants, mean difference: -0.20 days [95% CI: -0.31 to -0.09], p = 0.0003), but the evidence is very uncertain. One RCT found early feeding had little or no effect on the risk of neonatal mortality, but three cohort studies found early feeding may be associated with reduced risk (136,468 infants, OR 0.51 [95% CI: 0.37-0.72]; low certainty evidence; p <0.0001; I2 = 54%).

Conclusion: We found that early feeding may reduce the incidence of neonatal hypoglycaemia, but the evidence is very uncertain. Given its many other benefits, early feeding should continue to be recommended.

Indian J Pediatr. 2024 May 23.
doi: 10.1007/s12098-024-05138-6. Online ahead of print.

Does the 3C (Counselling, Checking and Certification) Initiative Prevent Hypoglycemia Among At-Risk Stable Late Preterm and Term Neonates? - A Randomized Controlled Trial

Abhinavya Egala [1], Sindhu Sivanandan [1], Adhisivam Bethou [2]

Abstract
Objective: To evaluate whether the 3C (Counselling, Checking, Certification) initiative helps in preventing hypoglycemia among at-risk neonates compared to standard care.
Methods: This randomised controlled trial included 222 mother-newborn dyads with risk factors for neonatal hypoglycemia-Small for gestational age (SGA) babies, infants of diabetic mothers (IDM), large for gestational age (LGA) babies and late preterm infants (LPI). They were randomized to two groups. Group A received standard care while mothers in group B were administered 3C intervention. Early initiation of breastfeeding, incidence of neonatal hypoglycemia within 24 h, and exclusive breastfeeding rate at 6 mo were evaluated.
Results: Early initiation of breastfeeding was higher in the 3C group compared to standard care group (94.6% vs. 55.9% p <0.001). The incidence of hypoglycemia within 24 h was lower in the intervention group compared to standard care (3.6% vs. 15.3%, p <0.05). However, there was no significant difference in exclusive breastfeeding rates at 6 mo between the two groups (61% and 66% in group A and B respectively).
Conclusions: The 3C intervention decreases the incidence of hypoglycemia among at-risk neonates. Early initiation of breast-feeding is higher among mothers who receive the 3C intervention.

Acta Paediatr. 2024 Feb;113(2):183-190.
doi: 10.1111/apa.17026. Epub 2023 Nov 5.

Maternal ethnicity and gestational age at birth predict hypoglycaemia among neonates of mothers with gestational diabetes

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Abstract
Aim: Hypoglycaemia is common in neonates born to mothers with gestational diabetes mellitus (GDM). We aimed to determine predictors of hypoglycaemia among neonates of women with GDM and association with short-term outcomes.
Methods: We conducted a secondary cohort analysis of data from a multi-centre randomised trial (the TARGET trial) conducted across ten maternity hospitals in New Zealand between May 2015 and November 2017. Data were analysed using univariate analysis and multivariable forward stepwise logistic regression.
Results: Among 1085 neonates, those born to Asian mothers had reduced odds of hypoglycaemia (OR [95% CI]: 0.54 [0.38, 0.75], p = 0.001), as did those born at higher gestational ages (0.76 [0.68, 0.85], p < 0.001). Neonates born to Pacific mothers had increased odds of hypoglycaemia (OR [95% CI]: 1.57 [1.04, 2.39], p = 0.034). Neonates who experienced hypoglycaemia were more likely to experience neonatal intensive care unit admission (8.3% vs. 2.1%; p ≤ 0.001), hyperbilirubinaemia (8.6% vs. 3.3%; p ≤ 0.001) and receive respiratory support (11.4% vs. 4.8%; p ≤ 0.001) and less likely to be breastfed at discharge (92.4% vs. 96.2%; p = 0.009).
Conclusion: Among neonates of women with GDM, maternal ethnicity and gestation at birth are independent predictors of hypoglycaemia, and hypoglycaemia is associated with short-term comorbidities. Additional surveillance may be appropriate for neonates in these high-risk groups.

* Although not from a low-medium income country, this study has widespread relevance to a common neonatal problem, and highlights some ethnic differences in the risk of hypoglycaemia.

Cord management

Eur J Pediatr. 2023 Jul 13.
doi: 10.1007/s00431-023-05105-x. Online ahead of print.
Effects of umbilical cord milking versus delayed cord clamping on systemic blood flow in intrauterine growth-restricted neonates: A randomized controlled trial
Chaitra Angadi[1], Poonam Singh[2], Yash Shrivastava[3], Mayank Priyadarshi[1], Suman Chaurasia[1], Jaya Chaturvedi[4], Sriparna Basu[1]
Abstract
Recommendations for umbilical cord management in intrauterine growth-restricted (IUGR) neonates are lacking. The present randomized controlled trial compared hemodynamic effects of umbilical cord milking (UCM) with delayed cord clamping (DCC) in IUGR neonates > 28 weeks of gestation, not requiring resuscitation. One hundred seventy IUGR neonates were randomly allocated to intact UCM (4 times squeezing of 20 cm intact cord; n = 85) or DCC (cord clamping after 60 s; n = 85) immediately after delivery. The primary outcome variable was superior vena cava (SVC) blood flow at 24 ± 2 h. Secondary outcomes assessed were anterior cerebral artery (ACA) and superior mesenteric artery (SMA) blood flow indices, right ventricular output (RVO), regional cerebral oxygen saturation ($CrSO_2$) and venous hematocrit at 24 ± 2 h, peak total serum bilirubin (TSB), incidences of in-hospital complications, need and duration of respiratory support, and hospital stay. SVC flow was significantly higher in UCM compared to DCC (111.95 ± 33.54 and 99.49 ± 31.96 mL/kg/min, in UCM and DCC groups, respectively; $p < 0.05$). RVO and ACA/SMA blood flow indices were comparable whereas $CrSO_2$ was significantly higher in UCM group. Incidences of polycythemia and jaundice requiring phototherapy were similar despite significantly higher venous hematocrit and peak TSB in UCM group. The need for non-invasive respiratory support was significantly higher in UCM group though the need and duration of mechanical ventilation and other outcomes were comparable.
Conclusions: UCM significantly increases SVC flow, venous hematocrit, and $CrSO_2$ compared to DCC in IUGR neonates without any difference in other hemodynamic parameters and incidences of polycythemia and jaundice requiring phototherapy; however, the need for non-invasive respiratory support was higher with UCM.

Eur J Pediatr. 2024 Jun;183(6):2791-2796.
doi: 10.1007/s00431-024-05550-2. Epub 2024 Apr 6.
A randomised controlled trial comparing umbilical cord milking to delayed cord clamping at birth in preterm infants 28-36 weeks gestational age
Nitin Narayan Rao[1], Kulkarni Poornima Prakash[2], Anita Nyamagoudar[3]
Abstract
Delayed cord clamping (DCC) is an established practice in perinatology with multiple benefits. However, in instances where the implementation of DCC is not viable, it needs

alternatives, especially during caesarean deliveries. A non-inferiority randomized, non-blinded, trial was conducted at a tertiary care referral unit in South India among the preterm newborns (28-36 weeks) randomized to DCC as opposed to intact-umbilical cord milking (UCM). The primary objective was to compare the mean haemoglobin values between the two groups, and the secondary outcome was to compare death and/or major IVH (> Grade II). Of the 132 eligible newborn infants, 99 were randomized to two study groups. Of the 59 and 40 randomised to UCM and DCC, 54 and 36 received the allocated intervention respectively. Preterm infants who underwent UCM had significantly higher haemoglobin (19.97 ± 1.44) as compared to DCC group (18.62 ± 0.98) p-0.0001. The rates of mortality and/or major IVH were comparable between the two groups.
Conclusion: UCM may be a feasible alternative to DCC especially in settings where the latter is not achievable, without increasing the risk of adverse effects to the preterm infants, this finding needing further confirmation with larger sample.

J Pediatr Surg. 2023 Sep;58(9):1843-1848.
doi: 10.1016/j.jpedsurg.2023.03.007. Epub 2023 Mar 15.

Treatment of Umbilical Granuloma in Infants With Topical Application of Common Salt: A Scoping Review

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Abstract
Background: Common salt is a safe, effective and cheap home-made remedy for umbilical granuloma. The aim of this scoping review is to identify and summarize the available evidence and examine the research conducted on salt treatment for umbilical granuloma.
Methods: A literature search was performed in the second week of September, 2022 using Google scholar, PubMed, MEDLINE and EMBASE databases using the keywords 'umbilical granuloma' and 'salt treatment' to identify all English articles pertaining to salt treatment for umbilical granuloma. Tables were made to summarize the methodological characteristics, results and the dosage regimens of salt used by different authors. The Cochrane Collaboration's tool was used for assessing risk of bias in RCTs. The indexing statuses of the journals publishing these studies were also noted. The overall efficacy with the use of common salt was calculated by adding the success rates mentioned in each study.
Results: Twenty-four articles (2 systematic reviews, 6 Randomized Controlled Trials, 11 prospective cohort studies, 1 case control study, 3 retrospective case series and 1 case report) were included. An overall 93.91% success rate (1033/1100) was seen with common salt application, without any reports of complications/recurrences.
Conclusion: Topical application of common salt for umbilical granulomas is simple, effective and inexpensive. This scoping review provides a broader outlook at the existing level of evidence and may help in planning interventional comparative studies, so that recommendations can be formulated. It also highlights a lack of properly designed randomized controlled trials on this topic.

Eur J Pediatr. 2024 Apr 6.
doi: 10.1007/s00431-024-05550-2. Online ahead of print.

A randomised controlled trial comparing umbilical cord milking to delayed cord clamping at birth in preterm infants 28-36 weeks gestational age

Nitin Narayan Rao [1], Kulkarni Poornima Prakash [2], Anita Nyamagoudar [3]

Abstract

Delayed cord clamping (DCC) is an established practice in perinatology with multiple benefits. However, in instances where the implementation of DCC is not viable, it needs alternatives, especially during caesarean deliveries. A non-inferiority randomized, non-blinded, trial was conducted at a tertiary care referral unit in South India among the preterm newborns (28-36 weeks) randomized to DCC as opposed to intact-umbilical cord milking (UCM). The primary objective was to compare the mean haemoglobin values between the two groups, and the secondary outcome was to compare death and/or major IVH (> Grade II). Of the 132 eligible newborn infants, 99 were randomized to two study groups. Of the 59 and 40 randomised to UCM and DCC, 54 and 36 received the allocated intervention respectively. Preterm infants who underwent UCM had significantly higher haemoglobin (19.97 ± 1.44) as compared to DCC group (18.62 ± 0.98) p-0.0001. The rates of mortality and/or major IVH were comparable between the two groups.

Conclusion: UCM may be a feasible alternative to DCC especially in settings where the latter is not achievable, without increasing the risk of adverse effects to the preterm infants, this finding needing further confirmation with larger sample.

Lancet. 2023 Nov 14:S0140-6736(23)02468-6.
doi: 10.1016/S0140-6736(23)02468-6. Online ahead of print.

Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis

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Abstract

Background: Umbilical cord clamping strategies at preterm birth have the potential to affect important health outcomes. The aim of this study was to compare the effectiveness of deferred cord clamping, umbilical cord milking, and immediate cord clamping in reducing neonatal mortality and morbidity at preterm birth.

Methods: We conducted a systematic review and individual participant data meta-analysis. We searched medical databases and trial registries (from database inception until Feb 24, 2022; updated June 6, 2023) for randomised controlled trials comparing deferred (also known as delayed) cord clamping, cord milking, and immediate cord clamping for preterm births (<37 weeks' gestation). Quasi-randomised or cluster-randomised trials were excluded. Authors of eligible studies were invited to join the iCOMP collaboration and share individual participant data. All data were checked, harmonised, re-coded, and assessed for risk of bias following prespecified criteria. The primary outcome was death before hospital discharge. We performed intention-to-treat one-stage individual participant data meta-analyses accounting for heterogeneity to examine treatment effects overall and in prespecified subgroup analyses. Certainty of evidence was assessed with Grading of Recommendations

Assessment, Development, and Evaluation. This study is registered with PROSPERO, CRD42019136640.
Findings: We identified 2369 records, of which 48 randomised trials provided individual participant data and were eligible for our primary analysis. We included individual participant data on 6367 infants (3303 [55%] male, 2667 [45%] female, two intersex, and 395 missing data). Deferred cord clamping, compared with immediate cord clamping, reduced death before discharge (odds ratio [OR] 0·68 [95% CI 0·51-0·91], high-certainty evidence, 20 studies, n=3260, 232 deaths). For umbilical cord milking compared with immediate cord clamping, no clear evidence was found of a difference in death before discharge (OR 0·73 [0·44-1·20], low certainty, 18 studies, n=1561, 74 deaths). Similarly, for umbilical cord milking compared with deferred cord clamping, no clear evidence was found of a difference in death before discharge (0·95 [0·59-1·53], low certainty, 12 studies, n=1303, 93 deaths). We found no evidence of subgroup differences for the primary outcome, including by gestational age, type of delivery, multiple birth, study year, and perinatal mortality.
Interpretation: This study provides high-certainty evidence that deferred cord clamping, compared with immediate cord clamping, reduces death before discharge in preterm infants. This effect appears to be consistent across several participant-level and trial-level subgroups. These results will inform international treatment recommendations.

J Neonatal Perinatal Med. 2023 Nov 22.
doi: 10.3233/NPM-230069. Online ahead of print.
Delayed cord clamping versus cord milking in vigorous neonates ≥35 weeks gestation born via cesarean: A Randomized clinical trial
Mithuna Murali [1], Giridhar Sethuraman [2], Jaishree Vasudevan [1], L Umadevi [1], Usha Devi [3]
Abstract
Background: Delayed cord clamping (DCC) is the recommended strategy in neonates not requiring resuscitation, but umbilical cord milking (UCM) can also be used in term babies. DCC has been found to offer advantages more than just placental transfusion.
Objective: To compare the neonatal outcomes of DCC and UCM at birth in vigorous neonates ≥35 weeks born via cesarean section.
Methods: We included all vigorous neonates born ≥35 weeks of gestation through the cesarean section in this open-label randomized controlled trial. They were randomized into Group-A (DCC-cord was clamped 60 s after birth) or Group B(UCM). For neonates in Group B, the intact cord was milked at 25 cm from the stump 3 times towards the neonate and then clamped. The primary outcome was hematocrit at 72 h of life. Secondary outcomes were serum ferritin between 6 and 10 weeks of life, serum bilirubin at 72 h of life, need and duration of phototherapy, respiratory distress, hypoglycemia, hypotension, and sepsis.
Results: Baseline characteristics were similar in both the groups. The mean hematocrit at 72 h was more in the DCC group compared to the UCM group [(55.60±4.50) vs (53.89±4.44), MD (95% CI) = 1.71 (0.26, 3.16); p = 0.021]. There was no significant difference in median serum ferritin between the groups [102.88(84.67-173.24) vs 137.93(85.15-230.40); p = 0.173]. There was no significant difference in clinical outcomes.
Conclusion: In neonates born via cesarean section, DCC resulted in improved hematocrit levels by 72 hours compared to UCM. DCC results in better placental transfusion.

Analgesia in newborn care

Indian J Pediatr. 2023 Nov 22.
doi: 10.1007/s12098-023-04900-6. Online ahead of print.

Comparison of Sucrose vs. Swaddling in Pain Management during Birth Dose of Hepatitis B Vaccine: A Randomized Control Trial

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Abstract

Objectives: To evaluate the efficacy of pain management of 1 ml of 24% sucrose given orally compared to routine care given one minute before vaccination for reduction of pain.

Methods: This double-blind randomized controlled trial included term neonates visiting Pediatric OPD for immunization. Neonates were randomly assigned into two groups (Group A- Sucrose, Group B- Swaddling). Commercially available sucrose solution (StayHappi solution 24%) was given in a dose of 1 ml to the neonates. Video recording of the neonate's facial expression was done during the procedure. Duration of cry, latency of onset of cry as well Modified Neonatal Facial Coding Score (MFCS) were the outcome variables.

Results: The mean (SD) of birth weight and gestational age was 2729 (321.6) g and 38.24 (0.84) d, respectively. Analysis showed significant difference in total MFCS across the groups (P <0.001). Total MFCS was significantly lower in sucrose group [4.88 (1.07) vs. 7.17 (0.95)]. The duration of cry (in seconds) was also found to be significantly lower in sucrose group.

Neonatal sepsis

Acta Paediatr. 2023 Sep 13.
doi: 10.1111/apa.16972. Online ahead of print.

Short course of intravenous antibiotics in the treatment of uncomplicated proven neonatal bacterial sepsis: A systematic review

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Abstract

Aim: To evaluate the efficacy and harms of a short (7-10 days) compared with a standard (10-14 days) duration of antibiotics in culture-proven neonatal sepsis for reducing all-cause mortality, treatment failure and duration of hospitalisation.

Methods: Medline, EMBASE and Cochrane CENTRAL were searched for randomised trials.

Results: We included five studies, all conducted in India (447 infants with a gestational age greater than 32 weeks). Except for one study, all studies were at high risk of bias. All-cause mortality was reported in three studies with only one death reported in the standard duration regimen arm (243 patients, very low certainty). A meta-analysis showed no evidence of the effect on treatment failure (RR of 1.47 [95% CI 0.48-4.50], 440 patients, five studies, very low certainty) of short-term antibiotics. Short-term antibiotic regimen shortened the duration of hospitalisation by 4 days (mean difference of -4.04 days [95% CI -5.47 to -2.61]; 4 studies; 371 patients; very low certainty).

Conclusion: Among studies focused on infants born with a gestational age greater than 32 weeks, short-term administration of antibiotics may shorten the duration of hospitalisation,

but the evidence is very uncertain. The evidence on other predefined outcomes is very uncertain to draw definite conclusions.

J Trop Pediatr. 2024 Feb 7;70(2):fmae002.
doi: 10.1093/tropej/fmae002.

Efficacy and safety of short- vs. standard-course antibiotics for culture-negative neonatal sepsis: a systematic review and meta-analysis

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Abstract

Objectives: To conduct a systematic review and meta-analysis of evidence from randomized controlled trials (RCTs) comparing a short course of antibiotics (2-4 days), to a standard course (5-7 days), for the treatment of culture-negative neonatal sepsis.

Methods: Relevant databases were searched for RCTs comparing short- vs. standard-course of antibiotics for culture-negative sepsis. The primary outcomes were mortality and treatment failure, defined as the reappearance of clinical signs suggestive of sepsis within 7 days of stoppage of antibiotics. Secondary outcomes included neurological impairment, duration of hospital stay, need for oxygen, respiratory support and double-volume exchange transfusion (DVET).

Results: Seven RCTs were included in the review with 729 neonates >30 weeks gestational age at birth. No mortality occurred in either of the groups (2 studies; 276 neonates). Treatment failure rates were similar in the short- and standard-course antibiotic groups [7 studies; 729 neonates; risk ratio (RR) = 1.01; 95% confidence interval (CI), 0.55 to 1.86; very low certainty]. The short course of antibiotics resulted in a shorter hospital stay [3 studies; 293 neonates; mean difference (MD), -2.46 days; 95% CI, -3.16 to -1.75]. There was no difference in the need for oxygen supplementation (2 studies; 258 neonates; RR, 1.40; 95% CI, 0.40 to 4.91), any respiratory support (2 studies; 258 neonates; RR, 1.04; 95% CI, 0.92 to 1.17) or DVET (2 studies; 258 neonates; RR, 1.29; 95% CI, 0.56 to 2.95).

Conclusion: Very-low certainty evidence suggests that a short antibiotic course, compared to a standard course, does not affect treatment failure rates in culture-negative neonatal sepsis. There is a need for well-designed RCTs powered enough to assess critical outcomes such as mortality and neurological sequelae to generate stronger evidence and inform guidelines.

BMJ Glob Health. 2024 Feb 29;9(2):e013691.
doi: 10.1136/bmjgh-2023-013691.

Impact of topical applications of sunflower seed oil on neonatal mortality and morbidity in southern Nepal: a community-based, cluster-randomised trial

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Abstract

Introduction: Hospital-based studies have demonstrated topical applications of sunflower seed oil (SSO) to skin of preterm infants can reduce nosocomial infections and improve survival. In South Asia, replacing traditional mustard with SSO might have similar benefits.

Methods: 340 communities in Sarlahi, Nepal were randomised to use mustard oil (MO) or SSO for community practice of daily newborn massage. Women were provided oil in late pregnancy and the first month post partum, and visited daily through the first week of life to encourage massage practice. A separate data collection team visited on days 1, 3, 7, 10, 14, 21 and 28 to record vital status and assess serious bacterial infection.
Results: Between November 2010 and January 2017, we enrolled 39 479 pregnancies. 32 114 live births were analysed. Neonatal mortality rates (NMRs) were 31.8/1000 (520 deaths, 16 327 births) and 30.5/1000 (478 deaths, 15 676 births) in control and intervention, respectively (relative risk (RR)=0.95, 95% CI: 0.84, 1.08). Among preterm births, NMR was 90.4/1000 (229 deaths, 2533 births) and 79.2/1000 (188 deaths, 2373 births) in control and intervention, respectively (RR=0.88; 95% CI: 0.74, 1.05). Among preterm births <34 weeks, the RR was 0.83 (95% CI: 0.67, 1.02). No statistically significant differences were observed in incidence of serious bacterial infection.
Conclusions: We did not find any neonatal mortality or morbidity benefit of using SSO instead of MO as emollient therapy in the early neonatal period. Further studies examining whether very preterm babies may benefit are warranted.

Low birth weight and prematurity

(also see Ophthalmology – Retinopathy of Prematurity)

BMC Pediatr. 2024 May 11;24(1):326.
doi: 10.1186/s12887-024-04778-z.

A mixed-methods study to investigate feasibility and acceptability of an early warning score for preterm infants in neonatal units in Kenya: results of the NEWS-K study : Neonatal early warning scores in Kenya

Eleanor J Mitchell [1], Jalemba Aluvaala [2], Lucy Bradshaw [3], Jane P Daniels [3], Caren Emadau [4], Bernadine Muthumbi [5], Helen Nabwera [6], Ednah Ojee [2], Jacqueline Opira [7], Phoebe Pallotti [8], Zahida Qureshi [9], Mark Sigei [9], Yuanfei Su [3], Richard Swinden [3], Fredrick Were [2], Shalini Ojha [10]

Abstract
Preterm birth (< 37 weeks gestation) complications are the leading cause of neonatal mortality. Early-warning scores (EWS) are charts where vital signs (e.g., temperature, heart rate, respiratory rate) are recorded, triggering action. To evaluate whether a neonatal EWS improves clinical outcomes in low-middle income countries, a randomised trial is needed. Determining whether the use of a neonatal EWS is feasible and acceptable in newborn units, is a prerequisite to conducting a trial. We implemented a neonatal EWS in three newborn units in Kenya. Staff were asked to record infants' vital signs on the EWS during the study, triggering additional interventions as per existing local guidelines. No other aspects of care were altered. Feasibility criteria were pre-specified. We also interviewed health professionals (n = 28) and parents/family members (n = 42) to hear their opinions of the EWS. Data were collected on 465 preterm and/or low birthweight (< 2.5 kg) infants. In addition to qualitative

study participants, 45 health professionals in participating hospitals also completed an online survey to share their views on the EWS. 94% of infants had the EWS completed at least once during their newborn unit admission. EWS completion was highest on the day of admission (93%). Completion rates were similar across shifts. 15% of vital signs triggered escalation to a more senior member of staff. Health professionals reported liking the EWS, though recognised the biggest barrier to implementation was poor staffing. Newborn unit infant to staff ratios varied between 10 and 53 staff per 1 infant, depending upon time of shift and staff type. A randomised trial of neonatal EWS in Kenya is possible and acceptable, though adaptations are required to the form before implementation.

Indian Pediatr. 2024 May 15;61(5):435-440.
Epub 2024 Mar 5.

Nurse-Guided Maternal Interventional Package for Neonatal Stress - A Randomized Controlled Trial

- Sanjoli[1], Anupama Choudhary[1], Kanya Mukhopadhyay[2], Seema Chopra[3]

Abstract

Objective: To assess the role of nurse-guided maternal interventional package for reducing stress behaviour among preterm neonates admitted in neonatal intensive care unit (NICU).

Methods: A randomized controlled trial was conducted among 100 mothers and their newborns delivered preterm and admitted consecutively in the NICU over 4 months. Mothers in the intervention group (n = 50) received education and demonstration regarding the use of maternal touch, facilitated tucking, kangaroo mother care (KMC), non-nutritive sucking (NNS), nesting and maternal voice alongwith a handout in local language for five consecutive days, while those in the control group (n = 50) received routine care including KMC and NNS for five consecutive days. Neonates were assessed before and five days after enrolment or intervention by using modified Infant Positioning Assessment Tool (IPAT), Neonatal Stress Scale and Preterm Neonate's Behaviour Assessment Scale.

Results: The mean (SD) score of positioning was significantly higher in the intervention group as compared to control group [9.62 (1.17) vs 6.58 (1.72), P < 0.001]. The median (IQR) score of stress was significantly lower in the intervention group compared to the control group [7 (7,10) vs 11(8,12.75), P = 0.004]. The mean (SD) scores for the autonomic and visceral subsystem behavioral response were significantly higher in the intervention group [5.28 (1.4) vs 3.25 (1.0), P < 0.001]. Mean (SD) attention interaction subsystem behavioral response score in the intervention group was significantly higher compared to the control group [2.96 (1.2) vs 1.85 (0.9), P = 0.001].

Conclusion: Mothers can be guided by nurses on neonatal stress behaviour and how to handle neonates in NICU, which significantly improves positioning and behavioral scores and reduces stress scores.

Indian J Pediatr. 2024 Feb 28.
doi: 10.1007/s12098-024-05066-5. Online ahead of print.

Does Early Fortification of Human Milk Decrease Time to Regain Birth Weight as Compared to Late Fortification Among Preterm Infants? - A Randomized Controlled Trial

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Abstract

Objectives: To compare the duration required to regain birth weight following early fortification of human milk vs. late fortification among preterm infants.
Methods: This randomized controlled trial included hemodynamically stable 120 preterm infants (≤32 wk of gestation). The intervention and comparator groups received standard fortification with human milk fortifier when enteral feeds reached 30 ml/kg/d (early fortification) and 80 ml/kg/d (late fortification) respectively. Neonates in both the groups received feed increments as per standard NICU protocol. Anthropometric measurements (weight, length, and head circumference) at birth and during postnatal follow-up were done following standard precautions and plotted on the sex-specific Fenton growth charts. Primary outcome was the mean duration required to regain birth weight. Secondary outcomes included weight gain velocity, linear growth, increase in head circumference and occurrence of sepsis, feed intolerance and necrotizing enterocolitis.
Results: Preterm neonates who received early fortification regained birth weight earlier compared to those in the late fortification group (10.13 ± 2.90 vs. 11.26 ± 3.06, p <0.05). The weight gain velocity, linear growth and increase in head circumference were better in the early fortification group. There was no increased risk of culture proven sepsis, feed intolerance and necrotizing enterocolitis in the early fortification group compared to late fortification.
Conclusions: Standard fortification with human milk fortifier when enteral feeds reach 30 ml/kg/d helps preterm neonates regain birth weight earlier. Early fortification is well tolerated and safe for the population studied.

Indian J Pediatr. 2024 Jan 11.
doi: 10.1007/s12098-023-04989-9. Online ahead of print.

Comparative Growth Outcomes in Very Low Birth Weight Infants: Evaluating Different Feeding Strategies

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Abstract
Objectives: To assess the growth pattern of preterm, very low birth weight (VLBW) appropriate for gestational age (AGA) infants on three different feeding regimens.
Methods: This prospective open label three-arm parallel randomized controlled trial was conducted at neonatal intensive care unit, Kasturba Hospital, Manipal. One hundred twenty VLBW (weight between 1000-1500 g and gestational age 28-32 wk) preterm AGA infants admitted from April 2021 through September 2022 were included. Three feeding regimens were compared: Expressed breast milk (EBM); EBM supplemented with Human milk fortifier (HMF); EBM supplemented with Preterm formula feed (PTF). Primary outcome measure was assessing the growth parameters such as weight, length, head circumference on three different feeding regimens at birth 2, 3, 4, 5 and 6 wk/discharge. Secondary outcomes included incidence of co-morbidities and cost-effectiveness.
Results: Of 112 infants analyzed, Group 2 supplemented with HMF showed superior growth outcomes by 6th wk/discharge of intervention, with mean weight of 2053±251 g, mean length of 44.6±1.9 cm, and mean head circumference of 32.9±1.4 cm. However, infants in Group 3, supplemented with PTF, registered mean weight of 1968±203 g, mean length of 43.6±2.0 cm, and mean head circumference of 32.0±1.6 cm. Infants exclusively on EBM presented with

mean weight of 1873±256 g, mean length of 43.0±2.0 cm and mean head circumference of 31.4±1.6 cm.
Conclusions: Addition of 1 g of HMF to 25 ml of EBM in neonates weighing 1000-1500 g showed better weight gain and head circumference at 6 wk/discharge, which was statistically significant. However, no significant differences in these parameters were observed at postnatal or 2, 3, 4, and 5 wk.

Front Nutr. 2024 Feb 26:11:1348225.
doi: 10.3389/fnut.2024.1348225. eCollection 2024.

Growth patterns of preterm and small for gestational age children during the first 10 years of life

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Abstract

Background: Preterm and small for gestational age (SGA) remain significant public health concerns worldwide. Yet limited evidence exists on their growth patterns during childhood from low-or middle-income countries.
Objectives: We investigated the postnatal growth patterns of preterm and SGA compared to term appropriate for gestational age (AGA) children from birth to 10-11y, and examined the impact of birth status on child nutritional status during the school age years.
Methods: Children born to women who participated in a double-blinded randomized controlled trial of preconception micronutrient supplementation in Vietnam were classified into three groups: preterm AGA (*n* = 130), full-term SGA (*n* = 165) and full-term AGA (*n* = 1,072). Anthropometric data (weight and height) were collected prospectively at birth, 3, 6, 12, 18, 24 months and at 6-7 and 10-11y. We used ANOVA and multiple regression models to examine the differences in growth patterns from birth to 10-11y as well as child undernutrition and overnutrition by birth status.
Results: Children who were born preterm exhibited rapid postnatal growth, but still had lower HAZ at 1y and 2y and showed catch up to the AGA group at 6y. Compared to those born AGA, SGA infants had higher risk of thinness (BMIZ < -2) at 2y and 6y (adjusted Odds Ratio, AOR [95% CI] 2.5 [1.0, 6.1] and 2.6 [1.4, 4.6], respectively); this risk reduced at 10-11y (1.6 [0.9, 2.8]). The risk of stunting (HAZ < -2) was also 2.4 [1.5, 3.8] and 2.3 times [1.2, 4.1] higher in SGA than AGA group at ages 2y and 6-7y, respectively, with no differences at 10y. Although preterm children had higher rates of thinness and stunting at 2y compared to AGA children, these differences were not statistically significant. No associations were found between preterm or SGA and overweight /obesity at age 10-11y.
Conclusion: Children who were born term-SGA continued to demonstrate deficits in weight and height during childhood whereas those born preterm showed catch-up growth by age 6-7y. Additional efforts to reduce the burden of these conditions are needed, particularly during school-age and early adolescents when children are exposed to challenging environments and have higher demands for nutrition.

BMJ Open 2023 Aug 31;13(8):e064678.
doi: 10.1136/bmjopen-2022-064678.

Growth and neurodevelopmental outcomes of preterm and low birth weight infants in rural Kenya: a cross-sectional study

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Abstract

Objective: Data on long-term outcomes of preterm (PT) and low birth weight (LBW) infants in countries with high rates of neonatal mortality and childhood stunting are limited, especially from community settings. The current study sought to explore growth and neurodevelopmental outcomes of PT/LBW infants from a rural community-based setting of Kenya up to 18 months adjusted age.

Design: Cross-sectional study.

Setting: Migori County, Kenya.

Participants: Three hundred and eighty-two PT/LBW infants (50.2% of those identified as eligible) from a cluster randomised control trial evaluating a package of facility-based intrapartum quality of care interventions for newborn survival consented for follow-up.

Outcome measures: Caregiver interviews and infant health, growth and neurodevelopmental assessments were completed at 6, 12 or 18 months±2 weeks. Data included sociodemographic information, medical history, growth measurements and neurodevelopmental assessment using the Ten Questions Questionnaire, Malawi Developmental Assessment Tool and Hammersmith Infant Neurological Examination. Analyses were descriptive and univariate regression models. No alterations were made to planned data collection.

Results: The final sample included 362 PT/LBW infants, of which 56.6% were moderate to late PT infants and 64.4% were LBW. Fewer than 2% of parents identified their child as currently malnourished, but direct measurement revealed higher proportions of stunting and underweight than in national demographic and health survey reports. Overall, 22.7% of caregivers expressed concern about their child's neurodevelopmental status. Neurodevelopmental delays were identified in 8.6% of infants based on one or more standardised tools, and 1.9% showed neurological findings indicative of cerebral palsy.

Conclusions: Malnutrition and neurodevelopmental delays are common among PT/LBW infants in this setting. Close monitoring and access to early intervention programmes are needed to help these vulnerable infants thrive.

Int J Infect Dis. 2023 Oct:135:28-40.
doi: 10.1016/j.ijid.2023.07.012. Epub 2023 Jul 28.

Fetal growth and birth weight are independently reduced by malaria infection and curable sexually transmitted and reproductive tract infections in Kenya, Tanzania, and Malawi: A pregnancy cohort study

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Abstract

Objectives: Malaria and sexually transmitted and reproductive tract infections (STIs/RTIs) are highly prevalent in sub-Saharan Africa and associated with poor pregnancy outcomes. We investigated the individual and combined effects of malaria and curable STIs/RTIs on fetal growth in Kenya, Tanzania, and Malawi.
Methods: This study was nested within a randomized trial comparing monthly intermittent preventive treatment for malaria in pregnancy with sulfadoxine-pyrimethamine vs dihydroartemisinin-piperaquine, alone or combined with azithromycin. Fetal weight gain was assessed by serial prenatal ultrasound. Malaria was assessed monthly, and Treponema pallidum, Neisseria gonorrhoeae, Trichomonas vaginalis, Chlamydia trachomatis, and bacterial vaginosis at enrollment and in the third trimester. The effect of malaria and STIs/RTIs on fetal weight/birthweight Z-scores was evaluated using mixed-effects linear regression.
Results: In total, 1435 pregnant women had fetal/birth weight assessed 3950 times. Compared to women without malaria or STIs/RTIs (n = 399), malaria-only (n = 267), STIs/RTIs only (n = 410) or both (n = 353) were associated with reduced fetal growth (adjusted mean difference in fetal/birth weight Z-score [95% confidence interval]: malaria = -0.18 [-0.31,-0.04], P = 0.01; STIs/RTIs = -0.14 [-0.26,-0.03], P = 0.01; both = -0.20 [-0.33,-0.07], P = 0.003). Paucigravidae experienced the greatest impact.
Conclusion: Malaria and STIs/RTIs are associated with poor fetal growth especially among paucigravidae women with dual infections. Integrated antenatal interventions are needed to reduce the burden of both malaria and STIs/RTIs.

Respir Res. 2024 May 24;25(1):219.
doi: 10.1186/s12931-024-02850-x.

Rates of bronchopulmonary dysplasia in very low birth weight neonates: a systematic review and meta-analysis

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Abstract
Importance: Large-scale estimates of bronchopulmonary dysplasia (BPD) are warranted for adequate prevention and treatment. However, systematic approaches to ascertain rates of BPD are lacking.
Objective: To conduct a systematic review and meta-analysis to assess the prevalence of BPD in very low birth weight (≤ 1,500 g) or very low gestational age (< 32 weeks) neonates.
Data sources: A search of MEDLINE from January 1990 until September 2019 using search terms related to BPD and prevalence was performed.
Study selection: Randomized controlled trials and observational studies evaluating rates of BPD in very low birth weight or very low gestational age infants were eligible. Included studies defined BPD as positive pressure ventilation or oxygen requirement at 28 days (BPD28) or at 36 weeks postmenstrual age (BPD36).
Data extraction and synthesis: Two reviewers independently conducted all stages of the review. Random-effects meta-analysis was used to calculate the pooled prevalence. Subgroup analyses included gestational age group, birth weight group, setting, study period,

continent, and gross domestic product. Sensitivity analyses were performed to reduce study heterogeneity.
Main outcomes and measures: Prevalence of BPD defined as BPD28, BPD36, and by subgroups.
Results: A total of 105 articles or databases and 780,936 patients were included in this review. The pooled prevalence was 35% (95% CI, 28-42%) for BPD28 (n = 26 datasets, 132,247 neonates), and 21% (95% CI, 19-24%) for BPD36 (n = 70 studies, 672,769 neonates). In subgroup meta-analyses, birth weight category, gestational age category, and continent were strong drivers of the pooled prevalence of BPD.
Conclusions and relevance: This study provides a global estimation of BPD prevalence in very low birth weight/low gestation neonates.

PLoS One. 2024 May 14;19(5):e0302969.
doi: 10.1371/journal.pone.0302969. eCollection 2024.

Effect of topical emollient oil application on weight of preterm newborns: A systematic review and meta-analysis

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Abstract
Background: Synthesizing current evidence on interventions to improve survival outcomes in preterm infants is crucial for informing programs and policies. The objective of this study is to investigate the impact of topical emollient oil application on the weight of preterm infants.
Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. To identify relevant studies, comprehensive searches were conducted across multiple databases, including PubMed, Cochrane, Scopus, Clinical trials, ProQuest Central, Epistemonikos, and gray literature sources. The inclusion criteria were based on the PICO (Population, Intervention, Comparison, and Outcomes) format. Study quality was assessed using the Cochrane risk of bias tool for randomized trials (RoB 2.0). Data analysis was performed using StataCrop MP V.17 software, which included evaluating heterogeneity, conducting subgroup analysis, sensitivity analysis, and meta-regression. The findings were reported in accordance with the PRISMA checklist, and the review was registered with PROSPERO (CRD42023413770).
Results: Out of the initial pool of 2734 articles, a total of 18 studies involving 1454 preterm neonates were included in the final analysis. Fourteen of these studies provided data that contributed to the calculation of the pooled difference in mean weight gain in preterm neonates. The random effects meta-analysis revealed a significant pooled difference in mean weight gain of 52.15 grams (95% CI: 45.96, 58.35), albeit with high heterogeneity (I2 > 93.24%, p 0.000). Subgroup analyses were conducted, revealing that preterm infants who received massages three times daily with either sunflower oil or coconut oil exhibited greater mean differences in weight gain. Meta-regression analysis indicated that the type of emollient oil,

duration of therapy, and frequency of application significantly contributed to the observed heterogeneity. A sensitivity analysis was performed, excluding two outlier studies, resulting in a pooled mean weight difference of 78.57grams (95% CI: 52.46, 104.68). Among the nine studies that reported adverse events, only two mentioned occurrences of rash and accidental slippage in the intervention groups.
Conclusion: The available evidence suggests that the application of topical emollient oil in preterm neonates is likely to be effective in promoting weight gain, with a moderate-to-high level of certainty. Based on these findings, it is recommended that local policymakers and health planners prioritize the routine use of emollient oils in newborn care for preterm infants. By incorporating emollient oils into standard care protocols, healthcare providers can provide additional support to promote optimal growth and development in preterm infants.

Indian Pediatr. 2024 Jan 9:S097475591600579.
Mustard Seed Pillow for Prevention of Deformational Plagiocephaly in ≤ 32 Weeks' Gestational Age Infants: An Open Label Randomized Controlled Trial
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Abstract
Objectives: To assess the effectiveness of using mustard seed filled pillows in preventing deformational plagiocephaly (DP) in premature infants.
Methods: A prospective open label randomized trial was conducted in a tertiary care hospital in south India. Eligible preterm infants born at ≤32 weeks and <1500 g admitted in the neonatal intensive care unit (NICU) were randomly allocated to the intervention and control groups. In addition to standard nesting, the intervention group was positioned using a mustard pillow, while the control group was positioned using nesting alone. Plagiocephaly was assessed using the Cranial Index (CI), Cranial Vault Asymmetry Index (CVAI) and Argenta classification within the first week and at 4 weeks postnatal age.
Results: Twenty-eight infants, each in the control and intervention groups, were included for analysis. At 4 weeks postnatal age, the intervention group had lower mean (SD) CVAI scores when compared to the control group [3.16 (1.89 vs 7.85 (2.63)] with adjusted odds ratio, aOR (95% CI) of 28.2 (3.8, 210.01), P < 0.01. More number of infants in the control group had plagiocephaly measured using Argenta classification [aOR (95% CI) 25.70 (2.80, 235.67), P < 0.01]. There were no differences in the Cranial Index scores in the intervention and control groups [aOR (95% CI) 0.41 (0.11, 1.52), P = 0.184].
Conclusion: A mustard seed pillow is an easily available and a cost-effective intervention for preventing plagiocephaly in hospitalized preterm infants.

Neonatal intensive care

Cochrane Database Syst Rev. 2023 Oct 31;10(10):CD013830.

doi: 10.1002/14651858.CD013830.pub2.

Methylxanthine for the prevention and treatment of apnea in preterm infants

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Abstract

Background: Very preterm infants often require respiratory support and are therefore exposed to an increased risk of chronic lung disease and later neurodevelopmental disability. Although methylxanthines are widely used to prevent and treat apnea associated with prematurity and to facilitate extubation, there is uncertainty about the benefits and harms of different types of methylxanthines.

Objectives: To assess the effects of methylxanthines on the incidence of apnea, death, neurodevelopmental disability, and other longer-term outcomes in preterm infants (1) at risk for or with apnea, or (2) undergoing extubation.

Search methods: We searched CENTRAL, MEDLINE, Embase, two other databases, and three trial registers (November 2022).

Selection criteria: We included randomized trials in preterm infants, in which methylxanthines (aminophylline, caffeine, or theophylline) were compared to placebo or no treatment for any indication (i.e. prevention of apnea, treatment of apnea, or prevention of re-intubation).

Data collection and analysis: We used standard Cochrane methods and GRADE to assess the certainty of evidence.

Main results: We included 18 studies (2705 infants), evaluating the use of methylxanthine in preterm infants for: any indication (one study); prevention of apnea (six studies); treatment of apnea (five studies); and to prevent re-intubation (six studies). Death or major neurodevelopmental disability (DMND) at 18 to 24 months. Only the Caffeine for Apnea of Prematurity (CAP) study (enrolling 2006 infants) reported on this outcome. Overall, caffeine probably reduced the risk of DMND in preterm infants treated with caffeine for any indication (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.78 to 0.97; risk difference (RD) -0.06, 95% CI -0.10 to -0.02; number needed to treat for an additional beneficial outcome (NNTB) 16, 95% CI 10 to 50; 1 study, 1869 infants; moderate-certainty evidence). No other trials reported DMND. Results from the CAP trial regarding DMND at 18 to 24 months are less precise when analyzed based on treatment indication. Caffeine probably results in little or no difference in DMND in infants treated for prevention of apnea (RR 1.00, 95% CI 0.80 to 1.24; RD -0.00, 95% CI -0.10 to 0.09; 1 study, 423 infants; moderate-certainty evidence) and probably results in a slight reduction in DMND in infants treated for apnea of prematurity (RR 0.85, 95% CI 0.71 to 1.01; RD -0.06, 95% CI -0.13 to 0.00; NNTB 16, 95% CI 7 to > 1000; 1 study, 767 infants; moderate-certainty evidence) or to prevent re-intubation (RR 0.85, 95% CI 0.73 to 0.99; RD -0.08, 95% CI -0.15 to -0.00; NNTB 12, 95% CI 6 to >1000; 1 study, 676 infants; moderate-certainty evidence). Death. In the overall analysis of any methylxanthine treatment for any indication, methylxanthine used for any indication probably results in little or no difference in death at hospital discharge (RR 0.99, 95% CI 0.71 to 1.37; I^2 = 0%; RD -0.00, 95% CI -0.02 to 0.02; I^2 = 5%; 7 studies, 2289 infants; moderate-certainty evidence). Major neurodevelopmental disability at 18 to 24 months. In the CAP trial, caffeine probably reduced the risk of major neurodevelopmental disability at 18 to 24 months (RR 0.85, 95% CI 0.76 to 0.96; RD -0.06, 95% CI -0.10 to -0.02; NNTB 16, 95% CI 10 to 50; 1 study, 1869 infants; moderate-certainty evidence), including a reduction in the risk of cerebral palsy or gross motor disability (RR 0.60, 95% CI 0.41 to 0.88; RD -0.03, 95% CI -0.05 to -0.01; NNTB 33, 95% CI

20 to 100; 1 study, 1810 infants; moderate-certainty evidence) and a marginal reduction in the risk of developmental delay (RR 0.88, 95% CI 0.78 to 1.00; RD -0.05, 95% CI -0.09 to -0.00; NNTB 20, 95% CI 11 to > 1000; 1 study, 1725 infants; moderate-certainty evidence). Any apneic episodes, failed apnea reduction after two to seven days (< 50% reduction in apnea) (for infants treated with apnea), and need for positive-pressure ventilation after institution of treatment. Methylxanthine used for any indication probably reduces the occurrence of any apneic episodes (RR 0.31, 95% CI 0.18 to 0.52; I^2 = 47%; RD -0.38, 95% CI -0.51 to -0.25; I^2 = 49%; NNTB 3, 95% CI 2 to 4; 4 studies, 167 infants; moderate-certainty evidence), failed apnea reduction after two to seven days (RR 0.48, 95% CI 0.33 to 0.70; I^2 = 0%; RD -0.31, 95% CI -0.44 to -0.17; I^2 = 53%; NNTB 3, 95% CI 2 to 6; 4 studies, 174 infants; moderate-certainty evidence), and may reduce receipt of positive-pressure ventilation after institution of treatment (RR 0.61, 95% CI 0.39 to 0.96; I^2 = 0%; RD -0.06, 95% CI -0.11 to -0.01; I^2 = 49%; NNTB 16, 95% CI 9 to 100; 9 studies, 373 infants; low-certainty evidence). Chronic lung disease. Methylxanthine used for any indication reduces chronic lung disease (defined as the use of supplemental oxygen at 36 weeks' postmenstrual age) (RR 0.77, 95% CI 0.69 to 0.85; I^2 = 0%; RD -0.10, 95% CI -0.14 to -0.06; I^2 = 18%; NNTB 10, 95% CI 7 to 16; 4 studies, 2142 infants; high-certainty evidence). Failure to extubate or the need for re-intubation within one week after initiation of therapy. Methylxanthine used for the prevention of re-intubation probably results in a large reduction in failed extubation compared with no treatment (RR 0.48, 95% CI 0.32 to 0.71; I^2 = 0%; RD -0.27, 95% CI -0.39 to -0.15; I^2 = 69%; NNTB 4, 95% CI 2 to 6; 6 studies, 197 infants; moderate-certainty evidence).

Authors' conclusions: Caffeine probably reduces the risk of death, major neurodevelopmental disability at 18 to 24 months, and the composite outcome DMND at 18 to 24 months. Administration of any methylxanthine to preterm infants for any indication probably leads to a reduction in the risk of any apneic episodes, failed apnea reduction after two to seven days, cerebral palsy, developmental delay, and may reduce receipt of positive-pressure ventilation after institution of treatment. Methylxanthine used for any indication reduces chronic lung disease (defined as the use of supplemental oxygen at 36 weeks' postmenstrual age).

BMC Pediatr. 2023 Dec 1;23(1):608.
doi: 10.1186/s12887-023-04406-2.

Comparison of the efficacy of two natural surfactants (BERAKSURF and BLES) in the treatment of respiratory distress syndrome among preterm neonates

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Abstract

Background: The benefit of surfactant replacement therapy for respiratory distress syndrome (RDS) has been demonstrated. However, some surfactants are expensive and usually inaccessible. Consequently, the Iranian Survanta was produced, but its effect on complications and mortality of RDS is unknown. This study aimed to compare the therapeutic outcomes of Iranian surfactant (beraksurf) and BLES (bovine lipid extract surfactant) on RDS treatment among preterm neonates.

Methods: This triple blinded randomized controlled trial study was performed on 128 eligible neonates diagnosed with RDS in Afzalipour hospital in Kerman, Iran. Diagnosis of

RDS, gestational age of 28-34 weeks and weight ≥ 1 kg were considered as inclusion criteria. Congenital anomalies such as congenital cyanotic heart diseases, digestive system anomalies and chromosome abnormalities were the exclusion criteria Neonates were randomly assigned into two equal groups: (1) those treated with BLES (n = 64) and (2) those treated with beraksurf (n = 64). Complications including patent ductus arteriosus (PDA), sepsis, intraventricular hemorrhage (IVH), pneumothorax, pulmonary hemorrhage, mortality, and also, the number of days required for invasive mechanical ventilation (using ventilator) and non-invasive continuous positive airway pressure (CPAP) were evaluated for all neonates. The risk ratio (RR) was calculated at 95% of confidence intervals (CI).
Results: Compared with BLES group, the RR estimate among neonates in beraksurf group was 0.89 (0.66-1.20) for PDA, 0.71 (0.23-2.13) for IVH, 0.44 (0.14-1.36) for sepsis, 0.35 (0.13-0.93) for pneumothorax, 0.33 (0.12-0.86) for pulmonary hemorrhage, and 0.55 (0.28-1.05) for mortality.
Conclusions: Despite advances in the use of exogenous surfactants for the treatment of neonatal respiratory distress syndrome; There are still some controversial topics in this field. The results obtained in the present study showed that the two types of surfactant (BERAKSURF and BLES) have similar efficacy for the treatment and short-term outcomes in preterm infants with respiratory distress syndrome. Therefore, due to the cost-effectiveness of BRAKSURF compared to BLES, We recommend choosing BERAKSURF in terms of treatment.

Paediatr Anaesth. 2024 Feb 2.
doi: 10.1111/pan.14845. Online ahead of print.

Randomized controlled trial to evaluate the rate of successful neonatal endotracheal intubation performed with a stylet versus without a stylet

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Abstract
Introduction: Neonates in intensive care units often require endotracheal intubation and mechanical ventilation. During this intubation procedure, a stylet is frequently used along with an endotracheal tube. Despite the widespread use of a stylet, it is still not known whether its use increases the intubation success rate. This study examined the association between stylet use and the intubation success rate in surgical neonates.
Methodology: This single-center study was conducted between December 2021 and December 2022 in the Neonatal surgical intensive care unit of a tertiary care center in Northern India. Infants were randomized to have the endotracheal intubation procedure performed using either an endotracheal tube alone or with a stylet. The primary outcome of the study was to assess the successful first-attempt neonatal endotracheal intubation rate with and without using a stylet. Apart from the rate of successful intubation, the duration of the intubation and complications during the intubation procedures as measured by bradycardia, desaturation episodes, and local trauma were also recorded. Both groups were thus compared on above mentioned outcomes.
Results: The total number of neonates enrolled were 200, and the overall success rate (81% in the stylet group vs. 73% in the non-stylet group) was not statistically significant. Intubation time was however less, when stylet was used (16.2 ± 4.3 vs. 17.5 ± 5.0 s, p = .046). When the endotracheal tube size was 3 or less, the success rate was substantially higher in

the stylet group (80%) than the non-stylet group (63%), p = .03. No statistical difference was recorded for bleeding and local trauma, though the esophageal intubation rate was higher when intubation was attempted without the stylet.
Conclusion: Endotracheal intubation using a stylet did not significantly improve the success rate of the procedure, however, intubation time significantly varied between groups and in different conditions. The rigidity and curvature provided by the stylet may facilitate the process of intubation when smaller caliber endotracheal tubes are used.

Indian J Pediatr. 2023 Aug 14.
doi: 10.1007/s12098-023-04756-w. Online ahead of print.

Functional Duration of Peripheral Intravenous Cannula in Neonates with or without Splint: A Randomized Controlled Trial

Nadella Lakshmi Thushara [1,2], Poonam Singh [3], Mayank Priyadarshi [1], Suman Chaurasia [1], Nowneet Kumar Bhat [2], Sriparna Basu [1]

Abstract
Objectives: To determine the effect of splint on the functional duration of peripheral intravenous cannula (PIVC) in neonates.
Methods: The trial was prospectively registered with the Clinical Trial Registry of India (CTRI/2021/09/036337). One-hundred-fifty cannulations in 71 neonates were randomized to splint (n = 75) and no-splint (n = 75) groups, respectively. The median (interquartile range, IQR) functional duration of PIVC was calculated from the time of PIVC insertion till removal due to the development of signs of PIVC failure or treatment completion. Kaplan-Meier survival analysis was used to compute the time to complication of PIVC. Complications related to PIVC were noted and multivariate Cox-proportion hazard analysis was done to find the predictors associated with PIVC failure.
Results: Median (IQR) functional duration of PIVC in the splint and the no-splint group was 28 (23-48) and 30 (25-48) h, respectively (p = 0.477). PIVC duration was higher in the splint group in term neonates and the no-splint group in preterm neonates; however, the differences were not statistically significant. No difference was observed in continuous vs. intermittent infusion subgroups. Time to complication development was also comparable between the groups.
Conclusions: Splint application did not affect functional PIVC duration and its related complications in neonates.

J Pediatr. 2024 Mar 4:114002.
doi: 10.1016/j.jpeds.2024.114002. Online ahead of print.

Effect of minimization of early blood sampling losses among extremely premature neonates- A randomized clinical trial

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Abstract
Objective: To evaluate the effect of blood sampling stewardship on transfusion requirements among infants born extremely preterm.

Study design: In this single-center, randomized controlled trial, infants born at <28 weeks of gestation and birth weight of <1000 g were randomized at 24 hours of age to two different blood sampling approaches: restricted sampling versus conventional sampling. The stewardship intervention in the restricted sampling group included targeted reduction in blood sampling volume and frequency and point of care testing methods in the first six weeks after birth. Both groups received early recombinant erythropoietin from day three of age. Primary outcome was the rate of early red blood cell (RBC) transfusions in the first six postnatal weeks.
Results: A total of 102 infants (mean gestational age: 26 weeks; birth weight: 756 g) were enrolled. Fidelity to the sampling protocol was achieved in 95% of the infants. Sampling losses in the first six weeks were significantly lower in the restricted sampling group (16.8 ml/kg vs 23.6 ml/kg, P<0.001). The restricted sampling group had a significantly lower rate of early postnatal RBC transfusion (41% versus 73%, RR: 0.56 [0.39-0.81], P=0.001). The hazard of needing a transfusion during NICU stay was reduced by 55% by restricted sampling. Mortality and neonatal morbidities were similar between the two groups.
Conclusion: Minimization of blood sampling losses by approximately one third in the first six weeks after birth leads to substantial reduction in the early RBC transfusion rate in infants born extremely preterm who weighed <1000 g at birth.

Biomed Hub. 2024 Jan 3;9(1):1-8.
doi: 10.1159/000535096. eCollection 2024 Jan-Dec.

Comparison of Ultrasound-Guided Umbilical Venous Catheter Insertion with Blind Method: A Randomized Controlled Trial

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Abstract
Introduction: Ultrasonography (USG) can be used in neonates to manipulate and place the umbilical catheter in the correct position. Although chest radiograph (CXR) is the gold standard, a noninvasive method like USG without radiation exposure may be an alternative bedside armamentarium to the clinician. The purpose of the study was to evaluate whether USG-guided umbilical venous catheter (UVC) insertion is superior to the conventional method for the successful insertion of UVC.
Method: The neonates born between 25 and 42 weeks of gestation requiring parenteral fluids and admission to neonatal intensive care unit (NICU) between September 2020 and November 2022 were randomized in two weight-based strata: ≤1,200 and >1,200 g. USG-guided UVC insertion was done in the intervention group and blind UVC insertion was done in the control group.
Results: Out of 112 enrolled neonates, 58 were in the USG-guided group and 54 in the blind group. There was no significant difference in the failure rate between the intervention and control groups (20% versus 29% [RR: 0.69, 95% CI: 0.36-1.33]). The sensitivity and specificity of USG in locating tip position were 97 and 46.8%, respectively. The mean procedure time in USG and blind groups was 8.9 and 8.3 min, respectively (*p* value 0.56).
Conclusion: USG does not reduce the failure rates during the insertion of umbilical catheters. However, being a safe, noninvasive procedure, it can be considered a rescue modality to CXR in NICUs equipped with portable USG for guiding UVC insertion.

EClinicalMedicine. 2023 Jul 20;62:102097.
doi: 10.1016/j.eclinm.2023.102097. eCollection 2023 Aug.

Clinical decision thresholds for surfactant administration in preterm infants: a systematic review and network meta-analysis

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Abstract

Background: The ideal threshold at which surfactant administration in preterm neonates with respiratory distress syndrome (RDS) is most beneficial is contentious. The aim of this systematic review was to determine the optimal clinical criteria to guide surfactant administration in preterm neonates with RDS.

Methods: The systematic review was registered in PROSPERO (CRD42022309433). Medline, Embase, CENTRAL and CINAHL were searched from inception till 16th May 2023. Only randomized controlled trials (RCTs) were included. A Bayesian random effects network meta-analysis (NMA) evaluating 33 interventions was performed. The primary outcome was requirement of invasive mechanical ventilation (IMV) within 7 days of life.

Findings: 58 RCTs were included. In preterm neonates ≤30 weeks after adjusting for the confounding factor of modality of surfactant administration, an arterial alveolar oxygen tension ratio (aAO_2) <0.36 (FiO_2: 37-55%) was ranked the best threshold for decreasing the risk of IMV, very low certainty. Further, surfactant administration at an FiO_2 40-45% possibly decreased mortality compared to rescue treatment when respiratory failure was diagnosed, certainty very low. The reasonable inference that could be drawn from these findings is that surfactant administration may be considered in preterm neonates of ≤30 weeks' with RDS requiring an $FiO_2 \geq 40\%$. There was insufficient evidence for the comparison of FiO_2 thresholds: 30% vs. 40%. The evidence was sparse for surfactant administration guided by lung ultrasound. For the sub-group >30 weeks, nebulized surfactant administration at an $FiO_2 < 30\%$ possibly increased the risk of IMV compared to Intubate-Surfactant-Extubate at $FiO_2 < 30\%$ and 40%, and less invasive surfactant administration at FiO_2 40%, certainty very low.

Interpretation: Surfactant administration may be considered in preterm neonates of ≤30 weeks' with RDS if the FiO_2 requirement is ≥40%. Future trials are required comparing lower FiO_2 thresholds of 30% vs. 40% and that guided by lung ultrasound.

Pediatr Pulmonol. 2023 Aug 2.
doi: 10.1002/ppul.26624. Online ahead of print.

Nonsynchronized nasal intermittent positive pressure ventilation versus continuous positive airway pressure as a primary mode of respiratory support in neonates (26-40 weeks) admitted in a tertiary care center: A randomized controlled trial

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Abstract

Introduction: Continuous positive airway pressure (CPAP) is a standard respiratory care for neonates for last few decades but it too has a high failure rate. Nasal intermittent positive pressure ventilation (NIPPV) is proven to be superior to CPAP in maintaining higher mean airway pressure in neonates with Respiratory Distress Syndrome. The main objective of this study was to compare failure within 72 h of initiation of primary respiratory support between nonsynchronized NIPPV and CPAP in all causes of respiratory distress in newborn infants. Secondarily feed intolerance, Necrotizing enterocolitis (NEC > stage II), hemodynamically significant patent ductus arteriosus, intraventricular hemorrhage (IVH > gradeIII), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), duration of support and mortality were also compared.
Methods: This was a single center randomized controlled trial. Stratified randomization was done for 216 neonates, based on the gestational age in two subgroups 26-33 weeks and 34-40 weeks whopresented with respiratory distress within 5 days of birth, to receive either NIPPV or CPAP. Primary and secondary outcomes were documented.
Results: Statisticalsignificant difference was noted for primary outcome (RR 0.48 [confidence interval = 0.301-0.786], p = 0.003) but not for other secondary outcomes. NIPPV appeared superior in respect to noninvasiveventilation days, BPD occurrence and hospitalization duration.
Conclusion: As a primary mode, nonsynchronized NIPPV was more efficacious than CPAP in preventing intubation within 72 h of initiation of respiratory support. Further multicenter studies are warranted to explore the benefits of this respiratory support.

Cochrane Database Syst Rev. 2023 Oct 12;10(10):CD012642.
doi: 10.1002/14651858.CD012642.pub2.

Higher versus lower sodium intake for preterm infants

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Abstract

Background: Infants born preterm are at increased risk of early hypernatraemia (above-normal blood sodium levels) and late hyponatraemia (below-normal blood sodium levels). There are concerns that imbalances of sodium intake may impact neonatal morbidities, growth and developmental outcomes.
Objectives: To determine the effects of higher versus lower sodium supplementation in preterm infants.
Search methods: We searched CENTRAL in February 2023; and MEDLINE, Embase and trials registries in March and April 2022. We checked reference lists of included studies and systematic reviews where subject matter related to the intervention or population examined in this review. We compared early (< 7 days following birth), late (≥ 7 days following birth), and early and late sodium supplementation, separately.
Selection criteria: We included randomised, quasi-randomised or cluster-randomised controlled trials that compared nutritional supplementation that included higher versus lower sodium supplementation in parenteral or enteral intake, or both. Eligible participants were preterm infants born before 37 weeks' gestational age or with a birth weight less than 2500 grams, or both. We excluded studies that had prespecified differential water intakes between groups.

Data collection and analysis: Two review authors independently assessed eligibility and risk of bias, and extracted data. We used the GRADE approach to assess the certainty of evidence.
Main results: We included nine studies in total. However, we were unable to extract data from one study (20 infants); some studies contributed to more than one comparison. Eight studies (241 infants) were available for quantitative meta-analysis. Four studies (103 infants) compared early higher versus lower sodium intake, and four studies (138 infants) compared late higher versus lower sodium intake. Two studies (103 infants) compared intermediate sodium supplementation (≥ 3 mmol/kg/day to < 5 mmol/kg/day) versus no supplementation, and two studies (52 infants) compared higher sodium supplementation (≥ 5 mmol/kg/day) versus no supplementation. We assessed only two studies (63 infants) as low risk of bias. Early (less than seven days following birth) higher versus lower sodium intake Early higher versus lower sodium intake may not affect mortality (risk ratio (RR) 1.02, 95% confidence interval (CI) 0.38 to 2.72; I^2 = 0%; 3 studies, 83 infants; low-certainty evidence). Neurodevelopmental follow-up was not reported. Early higher versus lower sodium intake may lead to a similar incidence of hyponatraemia < 130 mmol/L (RR 0.68, 95% CI 0.40 to 1.13; I^2 = 0%; 3 studies, 83 infants; low-certainty evidence) but an increased incidence of hypernatraemia ≥ 150 mmol/L (RR 1.62, 95% CI 1.00 to 2.65; I^2 = 0%; 4 studies, 103 infants; risk difference (RD) 0.17, 95% CI 0.01 to 0.34; number needed to treat for an additional harmful outcome 6, 95% CI 3 to 100; low-certainty evidence). Postnatal growth failure was not reported. The evidence is uncertain for an effect on necrotising enterocolitis (RR 4.60, 95% CI 0.23 to 90.84; 1 study, 46 infants; very low-certainty evidence). Chronic lung disease at 36 weeks was not reported. Late (seven days or more following birth) higher versus lower sodium intake Late higher versus lower sodium intake may not affect mortality (RR 0.13, 95% CI 0.01 to 2.20; 1 study, 49 infants; very low-certainty evidence). Neurodevelopmental follow-up was not reported. Late higher versus lower sodium intake may reduce the incidence of hyponatraemia < 130 mmol/L (RR 0.13, 95% CI 0.03 to 0.50; I^2 = 0%; 2 studies, 69 infants; RD -0.42, 95% CI -0.59 to -0.24; number needed to treat for an additional beneficial outcome 2, 95% CI 2 to 4; low-certainty evidence). The evidence is uncertain for an effect on hypernatraemia ≥ 150 mmol/L (RR 7.88, 95% CI 0.43 to 144.81; I^2 = 0%; 2 studies, 69 infants; very low-certainty evidence). A single small study reported that later higher versus lower sodium intake may reduce the incidence of postnatal growth failure (RR 0.25, 95% CI 0.09 to 0.69; 1 study; 29 infants; low-certainty evidence). The evidence is uncertain for an effect on necrotising enterocolitis (RR 0.07, 95% CI 0.00 to 1.25; 1 study, 49 infants; very low-certainty evidence) and chronic lung disease (RR 2.03, 95% CI 0.80 to 5.20; 1 study, 49 infants; very low-certainty evidence). Early and late (day 1 to 28 after birth) higher versus lower sodium intake for preterm infants Early and late higher versus lower sodium intake may not have an effect on hypernatraemia ≥ 150 mmol/L (RR 2.50, 95% CI 0.63 to 10.00; 1 study, 20 infants; very low-certainty evidence). No other outcomes were reported.
Authors' conclusions: Early (< 7 days following birth) higher sodium supplementation may result in an increased incidence of hypernatraemia and may result in a similar incidence of hyponatraemia compared to lower supplementation. We are uncertain if there are any effects on mortality or neonatal morbidity. Growth and longer-term development outcomes were largely unreported in trials of early sodium supplementation. Late (≥ 7 days following birth) higher sodium supplementation may reduce the incidence of hyponatraemia. We are uncertain if late higher intake affects the incidence of hypernatraemia compared to lower supplementation. Late higher sodium intake may reduce postnatal growth failure. We are

uncertain if late higher sodium intake affects mortality, other neonatal morbidities or longer-term development. We are uncertain if early and late higher versus lower sodium supplementation affects outcomes.

BMC Pediatr. 2024 Jan 12;24(1):35.
doi: 10.1186/s12887-023-04516-x.

Continuous versus intermittent bolus infusion of calcium in preterm infants receiving total parenteral nutrition: a randomized blind clinical trial

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Abstract

Background: Premature neonates need adequate nutritional support to provide sufficient essential nutrients for optimal growth. Calcium (Ca) is one of the important nutrients in parental nutrition support of premature infants. This study aimed to compare the effect of continuous and intermittent bolus infusion of Ca on the incidence of metabolic bone disease (MBD) in preterm infants.

Methods: This randomized double-blind clinical trial was conducted on ninety preterm infants in the NICU of Al-Zahra Hospital in Tabriz, Iran. The preterm infants were randomly allocated to either a continuous infusion group (received 4-5 ml/kg/day of Ca gluconate 10% by PN solution in a 24-h period) or an intermittent bolus administration group (received 1-2 ml/kg/day Ca gluconate 10% three to four times per day). Serial serum levels of Ca, phosphorous, alkaline phosphatase (ALP), vitamin D and parathyroid hormone (PTH) were assessed on the 7th day, 30th day and 45th day of life.

Results: A total of 78 infants completed the study. The serum ALP level on the 45th day after birth was 753.28 ± 304.59 IU/L and 988.2 ± 341.3 IU/L in the continuous infusion and intermittent bolus administration groups, respectively ($P < 0.05$). MBD in preterm infants with ALP levels above 900 IU/L on the 45th day of life was significantly lower in the continuous infusion group than in the intermittent bolus administration group ($p < 0.05$). The mean serum levels of calcium, phosphorus, vitamin D and PTH in 45-day-old infants were not significantly different between the two groups.

Conclusion: The MBD in preterm infants who received continuous infusion of Ca was lower than that in preterm infants who received intermittent bolus administration of Ca.

Indian Pediatr. 2023 Nov 15;60(11):893-898.
Epub 2023 Jun 21.

Neonatal Pain Response to Various Heel Prick Devices: A Randomized Controlled Trial

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Abstract

Background: Heel prick is a commonly performed painful intervention in neonates. Though different devices are available, there is a need to compare the procedural pain response elicited by them.

Objective: To compare the neonatal pain response to three different heel prick devices; automatic lancet, manual lancet, and 26-gauge (G) hypodermic needle.

Design: Parallel-group three-arm randomized controlled trial.
Participants: Clinically stable neonates of gestational age >28 weeks and birth weight >800 g undergoing heel prick for estimation of random blood sugar.
Methods: One hundred and eighty neonates were randomized to automatic lancet (n=59), manual lancet (n=59), or needle (n=62) groups between March, 2021 and August, 2022. The primary outcome was the premature infant pain profile-revised (PIPP-R) score. Secondary outcomes were post-intervention cerebral regional oxygen saturation (CrSO2), changes in CrSO2 (DCrSO2), the time for CrSO2 normalization using near-infrared spectroscopy, duration of audible cry, and the number of squeezes and pricks needed. Intention-to-treat analysis was done.
Results: Median (IQR) of PIPP-R scores were comparable in the automatic lancet [6 (4, 7.5)], manual lancet [5.5 (3.5, 8)], and needle [6 (3-9.6)] groups; P=0.59. No difference was observed in post-intervention CrSO2, DCrSO2, and the number of pricks. However, the time required for CrSO2 normalization and the number of squeezes were significantly higher with the needle.
Conclusion: All three devices induced similar pain responses to heel prick in neonates; though, the number of squeezes needed was higher with the needle.

Neonatal nutrition

Cochrane Database Syst Rev. 2024 Jan 26;1(1):CD008771.
doi: 10.1002/14651858.CD008771.pub3.
Early versus late administration of amino acids in preterm infants receiving parenteral nutrition
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Abstract
Background: Observational studies in preterm newborns suggest that delay in administering amino acids (AA) could result in a protein catabolic state and impact on growth and development.
Objectives: The objective of this review was to compare the efficacy and safety of early versus late administration of intravenous AA in neonates born at < 37 weeks of gestation.
Search methods: We searched CENTRAL, MEDLINE, Embase, and trial registries in March 2023. We checked the reference lists of included studies and studies/systematic reviews where subject matter related to the intervention or population examined in this review.
Selection criteria: We included randomised controlled trials (RCTs) comparing early administration of AA with late administration in premature newborn infants. We defined early administration of AA solution as the administration of AA in isolation or with total parenteral nutrition within the first 24 hours of birth, and late administration as the administration of AA in isolation or with total parenteral nutrition after the first 24 hours of birth.
Data collection and analysis: We used standard Cochrane methodological procedures. We used the GRADE approach to assess the certainty of the evidence.
Main results: Nine studies (383 participants) were eligible for inclusion in the review. All study participants were born at < 37 weeks of gestation and were inpatients in neonatal

intensive care units. No studies reported growth during the first months of life as assessed by difference in weight. Early administration of AA may have little or no effect on growth in the first month of life as measured by length (mean difference (MD) 0.00, 95% confidence interval (CI) -0.41 to 0.41; 1 study; 21 participants; low-certainty evidence) and head circumference (MD 0.05, 95% CI -0.03 to 0.14; 2 studies; 87 participants; low-certainty evidence). No studies reported the discharge weight outcome. Early administration of AA may result in little to no difference in neurodevelopmental outcome assessed by Mental Developmental Index (MDI) of < 70 at two years of age (odds ratio 0.83, 95% CI 0.21 to 3.28; 1 study; 111 participants; low-certainty evidence). No studies reported all-cause mortality at 28 days and before discharge. Early administration of AA may result in a large increase in positive nitrogen balance in the first three days of life (MD 250.42, 95% CI 224.91 to 275.93; 4 studies; 93 participants; low-certainty evidence).

Authors' conclusions: Low-certainty evidence suggests that there may be little to no difference between early and late administration of AA in growth (measured by length and head circumference during the first month after birth) and neurodevelopmental outcome (assessed by MDI of < 70). No RCTs reported on weight in the first month of life, mortality (all-cause mortality at 28 days and before discharge), or discharge weight. Low-certainty evidence suggests a large increase in positive nitrogen balance in preterm infants who received AA within 24 hours of birth. The clinical relevance of this observation is unknown. The number of infants in the RCTs included in the review was small, and there was clinical heterogeneity amongst trials. Adequately powered trials in infants < 37 weeks' gestation are required to determine optimal timing of initiation of AA. We identified two ongoing studies. Both studies will be recruiting infants ≥ 34 weeks of gestation and may or may not add to the outcome data for this review.

Fundam Clin Pharmacol. 2024 Feb 11.
doi: 10.1111/fcp.12993. Online ahead of print.

Ursodeoxycholic acid for preventing parenteral nutrition-associated cholestasis in neonates: A systematic review and meta-analysis

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Abstract

Background: While ursodeoxycholic acid is used in treating parenteral nutrition-associated cholestasis (PNAC) in neonates, its role in prevention is unclear.

Objectives: In this systematic review and meta-analysis, we attempted to determine the role of ursodeoxycholic acid in preventing PNAC in neonates.

Methods: PubMed, Embase, Cochrane Library, Scopus, and CINAHL databases were searched on September 16, 2023, for interventional studies comparing ursodeoxycholic acid with placebo.

Results: Of the 6180 unique records identified, five studies were eligible for inclusion (three randomised and two nonrandomised). Evidence from randomised trials showed that ursodeoxycholic acid prophylaxis did not reduce cholestasis, mortality, sepsis, and necrotising enterocolitis. Ursodeoxycholic acid prophylaxis reduced feed intolerance (RR 0.23 (0.09, 0.64); 1 RCT, 102 neonates), peak conjugated bilirubin levels (MD -0.13 (-0.22, -0.04) mg/dL; 1 RCT, 102 neonates), and time to full enteral feeds (MD -2.7 (-5.09, -0.31) days; 2 RCTs, 76 neonates). There was no decrease in hospital stay and parenteral nutrition

duration. Data from nonrandomised studies did not show benefit in any of the outcomes. The certainty of the evidence was low to very low.
Conclusion: Because of the very low-quality evidence and lack of evidence on critical outcomes, definitive conclusions could not be made on using ursodeoxycholic acid to prevent parenteral nutrition-associated cholestasis in neonates.

PLoS One. 2024 Apr 16;19(4):e0302267.
doi: 10.1371/journal.pone.0302267. eCollection 2024.

Effects of implementing non-nutritive sucking on oral feeding progression and outcomes in preterm infants: A systematic review and meta-analysis

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Abstract

Background: Preterm infants have imperfect neurological development, uncoordinated sucking-swallowing-breathing, which makes it difficult to realize effective oral feeding after birth. How to help preterm infants achieve complete oral feeding as soon as possible has become an important issue in the management of preterm infants. Non-nutritive sucking (NNS), as a useful oral stimulation, can improve the effect of oral feeding in preterm infants. This review aimed to explore the effect of NNS on oral feeding progression through a meta-analysis.
Methods: We systematically searched PubMed, CINHAL, Web of Science, Embase, Cochrane databases, China's National Knowledge Infrastructure (CNKI), Wanfang and VIP database from inception to January 20, 2024. Search terms included 'non-nutritive sucking' 'oral feeding' and 'premature.' Eligibility criteria involved randomized controlled studies in English or Chinese. Studies were excluded if they were reviews, case reports, or observational studies from which valid data could not be extracted or outcome indicators were poorly defined. The meta-analysis will utilize Review Manager 5.3 software, employing either random-effects or fixed-effects models based on observed heterogeneity. We calculated the mean difference (MD) and 95% confidence interval (CI) for continuous data, and estimated pooled odds ratios (ORs) for dichotomous data. Sensitivity and publication bias analyses were conducted to ensure robust and reliable findings. We evaluated the methodological quality of randomized controlled trials (RCTs) utilizing the assessment tool provided by the Cochrane Collaboration.
Results: A total of 23 randomized controlled trials with 1461 preterm infants were included. The results of the meta-analysis showed that NNS significantly shortened time taken to achieve exclusive oral feeding (MD = -5.37,95%CI = -7.48 to-3.26, p<0.001), length of hospital stay(MD = -4.92, 95% CI = -6.76 to -3.09, p<0.001), time to start oral feeding(MD = -1.41, 95% CI = -2.36 to -0.45, p = 0.004), time to return to birth weight(MD = -1.72, 95% CI = -2.54 to -0.91, p<0.001). Compared to the NNS group, the control group had significant weight gain in preterm infants, including weight of discharge (MD = -61.10, 95% CI = -94.97 to -27.23, p = 0.0004), weight at full oral feeding (MD = -86.21, 95% CI = -134.37 to -38.05, p = 0.0005). In addition, NNS reduced the incidence of feeding intolerance (OR = 0.22, 95% CI = 0.14 to 0.35, p<0.001) in preterm infants.
Conclusion: NNS improves oral feeding outcomes in preterm infants and reduces the time to reach full oral feeding and hospitalization length. However, this study was limited by the relatively small sample size of included studies and did not account for potential

confounding factors. There was some heterogeneity and bias between studies. More studies are needed in the future to validate the effects on weight gain and growth in preterm infants. Nevertheless, our meta-analysis provides valuable insights, updating existing evidence on NNS for improving oral feeding in preterm infants and promoting evidence-based feeding practices in this population.

JAMA Netw Open. 2024 Apr 1;7(4):e247145.
doi: 10.1001/jamanetworkopen.2024.7145.

Breast Milk Enema and Meconium Evacuation Among Preterm Infants: A Randomized Clinical Trial

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Abstract

Importance: Delayed meconium evacuation and delayed achievement of full enteral feeding among premature infants are associated with poor short- and long-term outcomes. Identifying a more effective and safer enema for meconium evacuation is imperative for improving neonatal care.

Objective: To examine whether breast milk enemas can shorten the time to complete meconium evacuation and achievement of full enteral feeding for preterm infants.

Design, setting, and participants: This randomized, open-label, parallel-group, single-center clinical trial was conducted from September 1, 2019, to September 30, 2022, among 286 preterm infants with a gestational age of 23 to 30 weeks in the neonatal ward of the Shengjing Hospital of China Medical University in Shenyang.

Interventions: Preterm infants were randomly assigned to receive either breast milk enemas or normal saline enemas 48 hours after birth.

Main outcome and measures: The primary outcomes were time to complete meconium evacuation and time to achieve full enteral feeding. Secondary outcomes were duration of hospitalization, weight at discharge, and duration of total parenteral nutrition. Intention-to-treat and per-protocol analyses were conducted.

Results: In total, 286 preterm infants (mean [SD] gestational age, 198.8 [7.9] days; 166 boys [58.0%]) were eligible and included in this study. A total of 145 infants were randomized to the normal saline group, and 141 were randomized to the breast milk group. The time to achieve complete meconium evacuation was significantly shorter in the breast milk group than in the normal saline group (-2.2 days; 95% CI, -3.2 to -1.2 days). The time to achieve full enteral feeding was also significantly shorter in the breast milk group than in the normal saline group (-4.6 days; 95% CI, -8.0 to -1.2 days). The duration of total parenteral nutrition was significantly shorter in the breast milk group than in the normal saline group (-4.6 days; 95% CI, -8.6 to -1.0 days). There were no clinically notable differences in any other secondary or safety outcomes between the 2 groups.

Conclusions and relevance: In this randomized clinical trial testing the effects of breast milk enema on meconium evacuation, breast milk reduced the time to achieve complete meconium evacuation and achieve full enteral feeding for preterm infants with a gestational age of 23 to 30 weeks. Subgroup analyses highlight the need for tailored interventions based on gestational age considerations.

Asia Pac J Clin Nutr. 2024 Jun;33(2):194-199.
doi: 10.6133/apjcn.202406_33(2).0006.

Phentolamine and B vitamins for feeding intolerance in late preterm infants: a randomised trial

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Abstract

Background and objectives: Feeding intolerance (FI) is a common problem in late preterm infants (34 weeks ≤ gestational age < 37 weeks). This study aimed to evaluate the efficacy and safety of phentolamine combined with B vitamins in treating FI in late preterm infants and to explore its effects on gastrointestinal symptoms, inflammation and complications.

Methods and study design: We randomly assigned 118 late preterm infants with FI to a treatment group (n = 56) or a control group (n = 62). The treatment group received intravenous phentolamine and intramuscular B vitamins, whereas the control group received basic treatment only. We measured the time of disappearance of gastrointestinal symptoms, the time of basal at-tainment, the time of hospitalisation, the incidence of complications, the concentrations of inflammatory markers and the overall effective rate of treatment.

Results: The treatment group had a shorter duration of gastrointestinal symptoms than did the control group ($p < 0.01$). The treatment group also had lower concentrations of inflammatory markers and a higher overall effective rate than did the control group ($p < 0.05$). There was no difference between the two groups in the time of hospitalisation, basal attainment, weight re-covery and the incidence of complications ($p > 0.05$).

Conclusions: Phentolamine and B vitamins can reduce gastrointestinal symptoms and inflammation in late preterm infants with FI but do not affect the occurrence of complications.

Neonatal respiratory distress syndrome

Am J Obstet Gynecol. 2023 Jul 11:S0002-9378(23)00454-4.
doi: 10.1016/j.ajog.2023.07.006. Online ahead of print.

A comparison of 2 doses of antenatal dexamethasone for the prevention of respiratory distress syndrome: an open-label, noninferiority, pragmatic randomized trial

Saifon Chawanpaiboon[1], Ronnakorn Chukaew[2], Julaporn Pooliam[3]

Abstract

Background: Antenatal corticosteroids have been used for the prevention of respiratory complications, intraventricular hemorrhage, necrotizing enterocolitis, and other adverse neonatal outcomes for over 50 years, with limited evidence about their optimal doses. Higher steroid doses or frequencies of antenatal corticosteroids in preterm newborns pose adverse effects such as prolonged adrenal suppression, negative effects on fetal programming and metabolism, and increased risks of neurodevelopmental and neuropsychological impairments. Conversely, lower doses of antenatal corticosteroids may be an effective alternative to induce fetal lung maturation with less risk to the fetus. Late

preterm births represent the largest population of all preterm neonates, with a respiratory distress syndrome risk of 8.83%. Therefore, determining the optimal antenatal corticosteroid dosage is of particular importance for this population.
Objective: This study aimed to compare the efficacy of 5-mg and 6-mg dexamethasone in preventing neonatal respiratory distress syndrome in women with preterm births at 32^0 to 36^6 weeks of gestation.
Study design: This was an open-label, randomized, controlled, noninferiority trial. Singleton pregnant women (n=370) at 32^0 to 36^6 weeks of gestation with spontaneous preterm labor or preterm premature rupture of membranes were enrolled. They were randomly assigned (1:1) to a 5-mg or 6-mg dexamethasone group. Dexamethasone was administered intramuscularly every 12 hours for 4 doses or until delivery. The primary outcome was the reduction in neonatal respiratory distress syndrome cases, whereas the secondary outcomes were any adverse maternal or neonatal events.
Results: Between December 2020 and April 2022, 370 eligible women, anticipating deliveries within the gestational range of 32 0/7 to 36 6/7 weeks, willingly participated in the study. They were evenly split, with 185 women assigned to the 5-mg group and 185 to the 6-mg group. The study revealed that the demographic profiles of the participants in the 2 groups were remarkably similar, with no statistically significant disparities (P>.05). It is noteworthy that most of these women gave birth after 34 weeks of gestation. Despite a substantial proportion not completing the full course of steroid treatment, the 5-mg dose exhibited noninferiority compared with the 6-mg dose of dexamethasone, as indicated by a modest proportional difference of 0.5% (95% confidence interval, -2.8 to 43.9). Neonatal respiratory distress syndrome occurred in a relatively low percentage of newborns in both groups, affecting 2.2% in the 5-mg group and 1.6% in the 6-mg group. Notably, the risk difference of 0.6% fell comfortably within the predefined noninferiority threshold of 10%.
Conclusion: Our study suggests that a 5-mg dexamethasone dose is noninferior to a standard 6-mg dose in preventing neonatal respiratory distress syndrome in preterm births.

Obstet Gynecol. 2024 Feb 8.
doi: 10.1097/AOG.0000000000005520. Online ahead of print.

Late Preterm Antenatal Steroids for Reduction of Neonatal Respiratory Complications: A Randomized Controlled Trial

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Abstract
Objective: To evaluate the efficacy of antenatal corticosteroids in reducing neonatal respiratory complications when administered to those at risk of preterm delivery between 34 and 36 6/7 weeks of gestation.
Methods: This was a single-center, triple-blind, randomized, placebo-controlled trial in southern India enrolling pregnant participants at risk of preterm delivery between 34 and 36 6/7 weeks of gestation. Computer-generated block randomization was used with participants randomized to either one course of intramuscular betamethasone or placebo. The primary outcome was a composite of treatment for respiratory distress in the neonate, defined as need for oxygen or continuous positive airway pressure or mechanical ventilation for at least 2 hours in the first 72 hours of life. Neonatal secondary outcomes were transient tachypnea of the newborn, respiratory distress syndrome, necrotizing enterocolitis, sepsis,

hyperbilirubinemia, hypoglycemia, stillbirth, and early neonatal death; maternal secondary outcomes were chorioamnionitis, postpartum hemorrhage, puerperal fever, and length of hospitalization. All analyses were based on intention to treat. A sample size of 1,200 was planned with 80% power to detect a 30% reduction in rates of respiratory distress. After a planned interim analysis, enrollment was stopped for futility.
Results: From March 2020 to August 2022, 847 participants were recruited, with 423 participants randomized to betamethasone and 424 participants randomized to placebo. There were 22 individuals lost to follow-up. There was no statistically significant difference in the primary outcome (betamethasone 4.9% vs placebo 4.8%, relative risk 1.03, 95% CI, 0.57-1.84, number needed to treat 786). There were no statistically significant differences in secondary neonatal or maternal outcomes.
Conclusion: Betamethasone administered in the late preterm period to those at risk for preterm delivery did not reduce the need for treatment of neonatal respiratory distress.

J Perinatol. 2024 Apr 12.
doi: 10.1038/s41372-024-01962-y. Online ahead of print.
Comparison of efficacy between beractant and poractant alfa in respiratory distress syndrome among preterm infants (28-33^{+6} weeks gestational age) using the less invasive surfactant administration (LISA) technique: A randomized controlled trial
Ashadur Zamal[1], Md Habibullah Sk[1], Bijan Saha[2], Avijit Hazra[3]
Abstract
Objective: Exogenous surfactant therapy is vital in managing respiratory distress syndrome (RDS) in preterm infants, with less invasive surfactant administration (LISA) gaining popularity. This study aimed to assess the efficacy and short-term outcomes of LISA using beractant and poractant alfa.
Study design: In a randomized controlled trial, we enrolled preterm infants (28-33^{+6} weeks) with RDS requiring surfactant. LISA was employed, with beractant at 100 mg/kg or poractant-alfa at 200 mg/kg. Primary outcome was the need for intubation within 72 hours.
Results: Among 120 infants, 3.3% in both groups required intubation within 72 hours (p value 1.00, 95% CI 0.14-6.86). No significant differences in secondary outcomes were noted. However, beractant was significantly more economical than poractant-alfa, with a significantly lower surfactant cost and total care cost for infant hospital stays.
Conclusion: Beractant and poractant-alfa exhibit similar efficacy in LISA for preterm infants with RDS. Economic considerations, especially in LMICs, favour beractant.

BMC Pediatr. 2024 Apr 20;24(1):262.
doi: 10.1186/s12887-024-04736-9.
The impact of combined administration of surfactant and intratracheal budesonide compared to surfactant alone on bronchopulmonary dysplasia (BPD) and mortality rate in preterm infants with respiratory distress syndrome: a single-blind randomized clinical trial
Asghar Marzban[1], Samira Mokhtari[1], Pouria Tavakkolian[2], Reza Mansouri[3], Nahid Jafari[1], Azam Maleki[4]

Abstract

Background: Respiratory distress syndrome (RDS) is one of the most important and common disorders among premature infants.

Objective: This study aimed to compare the effect of the combination of surfactant and budesonide with surfactant alone on Bronchopulmonary dysplasia (BPD) and mortality rate among premature infants with RDS.

Method: An outcome assessor-blind randomized clinical trial was conducted on 134 premature infants with RDS who were born in Ayatollah Mousavi Hospital, Zanjan, Iran in 2021. The covariate adaptive randomization method was utilized to allocate participants into two groups (surfactant alone and a combination of surfactant and budesonide). The primary outcomes were BPD and Mortality rate from admission to hospital discharge. The data in this study were analyzed using SPSS software version 18.

Results: Overall the comparison of mortality rate and BPD between the two groups did not show a significant difference($p > 0.05$). The subgroup results showed that administering surfactant with budesonide to infants under 30 weeks of age significantly reduced the number of deaths compared to using surfactant alone (5 vs. 17). Similar positive effects were observed for the occurrence of Pulmonary Hemorrhage, the need for a second dose of surfactant, oxygen index, mean blood pressure and mean arterial pressure (MAP) in infants under 34 weeks of age compared to more than 34 weeks ($p < 0.05$).

Conclusion: These findings suggest that the combination therapy of surfactant and budesonide may be beneficial, particularly in preterm infants with less than 34 weeks gestational age and 1500 birth weight. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these results and assess long-term outcomes.

Curr Pediatr Rev. 2024 Apr 15.
doi: 10.2174/0115733963279420240402083916. Online ahead of print.

Effects of Vitamin D and E Supplementation on Prevention of Bronchopulmonary Dysplasia (BPD) in Premature Neonates: A Systematic Review and Meta-Analysis

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Abstract

Background: Bronchopulmonary Dysplasia (BPD) has a multifactorial etiology. Vitamin E and vitamin D play an important role in lung development and can potentially be beneficial in the prevention of BPD.

Objective: The study aimed to compare the risk of BPD occurrence in preterm neonates supplemented with vitamin D or E versus those who did not get supplementation.

Methods: The literature search was conducted for this systematic review by searching the PubMed, Scopus, and Web of Science databases up to December 2022. Randomized controlled trials involved administering vitamin D or E to preterm neonates and examining the occurrence of BPD. We excluded non-English articles, and articles with non-relevant and insufficient data. We used the Critical Appraisal Skills Programme (CASP) checklist to assess the quality of the included studies. We used Egger's test to evaluate the risk of bias among the included studies. Heterogeneity was also assessed through Q-test and I2. We applied the

random effect model for analysis. A P-value less than 0.05 was considered as significant. All the statistical analysis in the current study was performed using STATA 14. The Relative Risk (RR) was calculated as the effect size with 95% Confidence Interval (CI).
Results: Three eligible studies seeking the role of vitamin D in the prevention of BPD were analysed. Meta-analysis revealed that receiving vitamin D supplementation can significantly reduce the risk of BPD in preterm infants (RR = 0.357, 95% CI: 0.189-0.675, I2 = 0.0%; p = 0.002). Similarly, for assessing the role of Vitamin E in the prevention of BPD, three eligible studies were analysed. Vitamin E supplementation was not found to play a significant role in the reduction of BPD (RR = 0.659, 95%CI = 0.243-1.786, I2 = 38.7%; p = 0.412).
Conclusion: Vitamin D supplementation could be beneficial in preventing BPD in preterm infants. However, evidence is not enough regarding vitamin E's role in reducing the incidence of BPD in preterm infants.

Neonatal resuscitation

Eur J Pediatr. 2023 Oct 4.
doi: 10.1007/s00431-023-05230-7. Online ahead of print.
T-Piece resuscitator versus self-inflating bag for delivery room resuscitation in preterm neonates: a randomized controlled trial
Bhrajishna Pallapothu[1], Mayank Priyadarshi[1], Poonam Singh[1], Sourabh Kumar[1], Suman Chaurasia[1], Sriparna Basu[2]
Abstract
The establishment of adequate ventilation is the cornerstone of neonatal resuscitation in the delivery room (DR). This parallel-group, accessor-blinded randomized controlled trial compared the changes in peripheral oxygen saturation (SpO_2), heart rate (HR), and cerebral regional oxygen saturation ($crSO_2$) with the use of a T-piece resuscitator (TPR) versus self-inflating bag (SIB) as a mode of providing positive pressure ventilation (PPV) during DR resuscitation in preterm neonates. Seventy-two preterm neonates were randomly allocated to receive PPV with TPR (n = 36) or SIB (n = 36). The primary outcome was SpO_2 (%) at 5 min. The secondary outcomes included the time to achieve a $SpO_2 \geq 80\%$ and > 85%, HR > 100/min, fractional-inspired oxygen (FiO_2) requirement, minute-specific SpO_2, HR and FiO_2 trends for the first 5 min of life, need for DR-intubation, $crSO_2$, need and duration of respiratory support, and other in-hospital morbidities. Mean SpO_2 at 5 min was 74.5 ± 17.8% and 69.4 ± 22.4%, in TPR and SIB groups, respectively [Mean difference, 95% Confidence Interval 5.08 (-4.41, 14.58); p = 0.289]. No difference was observed in the time to achieve a $SpO_2 \geq 80\%$ and > 85%, HR > 100/min, the requirement of FiO_2, DR-intubation, and the need and duration of respiratory support. There was no significant difference in the minute-specific SpO_2, HR, and FiO_2 requirements for the first 5 min. $CrSO_2$ (%) at one hour was lower by 5% in the TPR group compared to SIB; p = 0.03. Other complications were comparable.
Conclusions: TPR and SIB resulted in comparable SpO_2 at 5 min along with similar minute-specific SpO_2, HR, and FiO_2 trends.

Am J Perinatol. 2023 Nov 9.

doi: 10.1055/a-1933-7235. Online ahead of print.

Providing Positive End-Expiratory Pressure during Neonatal Resuscitation: A Meta-analysis

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Abstract

Our objective was to conduct a systematic review and meta-analysis evaluating the effects of administering positive end-expiratory pressure (PEEP) during neonatal resuscitation at birth. Medline, Web of Science, Scopus, Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov databases were systematically searched from inception to 15 December 2020. Randomized controlled trials and cohort studies were held eligible. Studies were included if they compared the administration of PEEP using either a T-piece resuscitator or a self-inflating bag with a PEEP valve versus resuscitation via a self-inflating bag without a PEEP valve. Data were extracted by two reviewers independently. The credibility of evidence was appraised with the Grading of Recommendations, Assessment, Development, and Evaluations approach. Random-effects models were fitted to provide pooled estimates of risk ratio (RR) and 95% confidence intervals (CIs). Overall, 10 studies were included, comprising 4,268 neonates. This included five randomized controlled trials, one quasi-randomized trial, and four cohort studies. The administration of PEEP was associated with significantly lower rates of mortality till discharge (odds ratio [OR]: 0.60, 95% CI: 0.49-0.74, moderate quality of evidence). The association was significant in preterm (OR: 0.57, 95% CI: 0.46-0.69) but not in term (OR: 1.03, 95% CI: 0.52-2.02) neonates. Low-to-moderate quality evidence suggests that providing PEEP during neonatal resuscitation is associated with lower rates of mortality in preterm neonates. Evidence regarding term neonates is limited and inconclusive. Future research is needed to determine the optimal device and shed more light on the long-term effects of PEEP administration during neonatal resuscitation.

Children (Basel). 2023 Nov 4;10(11):1782.
doi: 10.3390/children10111782.

Impact of an Educational Clinical Video Combined with Standard Helping Babies Breathe Training on Acquisition and Retention of Knowledge and Skills among Ethiopian Midwives

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Abstract

Helping Babies Breathe (HBB) is an evidence-based neonatal resuscitation program designed for implementation in low-resource settings. While HBB reduces rates of early neonatal mortality and stillbirth, maintenance of knowledge and skills remains a challenge. The extent to which the inclusion of educational clinical videos impacts learners' knowledge and skills acquisition, and retention is largely unknown. We conducted a cluster-randomized controlled trial at two public teaching hospitals in Addis Ababa, Ethiopia. We randomized small training group clusters of 84 midwives to standard HBB vs. standard HBB training supplemented with exposure to an educational clinical video on newborn resuscitation. Midwives were followed over a 7-month time period and assessed on their knowledge and skills using standard HBB tools. When comparing the intervention to the control group, there was no difference in outcomes across all assessments, indicating that the addition of the

video did not influence skill retention. Pass rates for both the control and intervention group on bag and mask skills remained low at 7 months despite frequent assessments. There is more to learn about the use of educational videos along with low-dose, high-frequency training and how it relates to retention of knowledge and skills in learners.

Indian Pediatr. 2023 Sep 15;60(9):719-725.
Epub 2023 Mar 20.

Impact of Delivery Room Gastric Lavage on Exclusive Breastfeeding Rates Among Neonates Born Through Meconium-Stained Amniotic Fluid: A Randomized Controlled Trial

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Abstract

Background: Delivery-room gastric lavage reduces feeding intolerance and respiratory distress in neonates born through meconium-stained amniotic fluid (MSAF).

Objectives: To evaluate the effects of gastric lavage on exclusive breastfeeding and skin-to-skin contact in neonates delivered through MSAF.

Design: Randomized controlled trial.

Participants: 110 late preterm and term neonates delivered through MSAF not requiring resuscitation beyond initial steps.

Methods: Participants randomized into gastric lavage (GL) (n=55) and no-GL (n=55) groups. The primary outcome was the rate of exclusive breastfeeding at 72±12 hours of life. Secondary outcomes were time to initiate breastfeeding and establish exclusive breastfeeding, rate of exclusive breastfeeding at discharge, time to initiate skin-to-skin contact and its duration, rates of respiratory distress, feeding intolerance, and the procedure-related complications of gastric lavage monitored by pulse oximetry and videography.

Results: Both the groups were similar in baseline characteristics. 49 (89.1%) neonates in GL group could achieve exclusive breast-feeding at 72 hours compared to 48 (87.3%) in no-GL group [RR (95% CI) 1.02 (0.89-1.17); P=0.768]. Initiation of skin-to-skin contact was significantly delayed and the total duration was significantly less in GL group compared to no-GL group. No difference in respi-ratory distress and feeding intolerance was observed. Procedure-related complications included retching, vomiting, and mild desaturation.

Conclusion: Gastric lavage did not help to establish exclusive breastfeeding, delayed the initiation of skin-to-skin contact in delivery room and reduced its total duration. Moreover, the procedure of gastric lavage was associated with neonatal discomfort.

Perinatal asphyxia

J Pediatr. 2023 Jul 17;113610.
doi: 10.1016/j.jpeds.2023.113610. Online ahead of print.

Outcomes of Neonates with Hypoxic-ischemic Encephalopathy Treated with Magnesium Sulfate: A Systematic Review with Meta-Analysis

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Abstract

Objective: To assess magnesium sulfate (MgSO4) as a neuroprotective agent in hypoxic-ischemic encephalopathy.

Study design: For this systematic review, PubMed, EMBASE, Cochrane Library, EMCARE. and MedNar were searched in November 2022 for randomized controlled trials (RCTs). Meta-analysis was conducted using Stata 16.0 and RevMan 5.3.

Results: Twenty RCTs with a total sample size of 1485) were included, of which 16 were from settings where therapeutic hypothermia (TH) was not offered. Regarding MgSO4 in settings where TH was not offered, only one study evaluated composite outcome of "death or disability" at ≥18 months and reported such poor outcome in 8 out of 14 control infants and 4 out of 8 in the MgSO4 group. MgSO4 was not associated with mortality (RR: 0.86, CI: 0.72-1.03, 13RCTs) or hypotension (RR:1.02, CI:0.88-1.18, 5RCTs). Thirteen studies reported that MgSO4 improved in-hospital outcomes, such as reduced seizure burden, and improved neurological status at discharge. MgSO4 reduced the risk of poor suck feeds (RR: 0.52, 95%CI: 0.40-0.68, 6RCTs) and abnormal EEG (RR: 0.64, CI: 0.45-0.93, 5RCTs). Certainty of Evidence (COE) was "moderate" for mortality and "low/very low" for other outcomes. For studies with MgSO4 as an adjunct to TH, none reported on "death or neurodevelopmental disability" at ≥18 months. MgSO4 was not associated with mortality (RR 0.65, CI: 0.34-1.27, 3RCTs) or hypotension (RR: 1.0, CI: 0.71-1.40, 3RCTs).

Conclusions: Evidence around long-term outcomes of MgSO4 when used with or without TH was scant. MgSO4 therapy may improve in-hospital neurological outcomes without affecting mortality in settings where TH is not offered. Well-designed RCTs for neuroprotection are needed, especially in low-resource settings.

Obstet Gynecol. 2024 Jun 3.
doi: 10.1097/AOG.0000000000005644. Online ahead of print.

Magnesium Sulfate Before Preterm Birth for Neuroprotection: An Updated Cochrane Systematic Review

Emily S Shepherd [1], Shona Goldsmith, Lex W Doyle, Philippa Middleton, Stéphane Marret, Dwight J Rouse, Peter Pryde, Hanne T Wolf, Caroline A Crowther

Abstract

Objective: To systematically review the evidence for the effectiveness and safety of magnesium sulfate as a fetal neuroprotective agent when given to individuals at risk of preterm birth.

Data sources: We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (through March 17, 2023), and reference lists of relevant studies.

Methods of study selection: Randomized controlled trials (RCTs) assessing magnesium sulfate for fetal neuroprotection in pregnant participants at risk of imminent preterm birth were eligible. Two authors assessed RCTs for inclusion, extracted data, and evaluated risk of bias, trustworthiness, and evidence certainty (GRADE [Grading of Recommendations Assessment, Development and Evaluation]).

Tabulation, integration, and results: We included six RCTs (5,917 pregnant participants and 6,759 fetuses at less than 34 weeks of gestation at randomization). They were conducted in high-income countries (two in the United States, two across Australia and New Zealand, and one each in Denmark and France) and commenced between 1995 and 2018. Primary outcomes: up to 2 years of corrected age, magnesium sulfate compared with placebo reduced the risk of cerebral palsy (risk ratio [RR] 0.71, 95% CI, 0.57-0.89; six RCTs, 6,107 children) and death or cerebral palsy (RR 0.87, 95% CI, 0.77-0.98; six RCTs, 6,481 children) (high-certainty evidence). Magnesium sulfate had little or no effect on death up to 2 years of corrected age (moderate-certainty evidence) or these outcomes at school age (low-certainty evidence). Although there was little or no effect on death or cardiac or respiratory arrest for pregnant individuals (low-certainty evidence), magnesium sulfate increased adverse effects severe enough to stop treatment (RR 3.21, 95% CI, 1.88-5.48; three RCTs, 4,736 participants; moderate-certainty evidence). Secondary outcome: magnesium sulfate reduced the risk of severe neonatal intraventricular hemorrhage (moderate-certainty evidence).
Conclusion: Magnesium sulfate for preterm fetal neuroprotection reduces cerebral palsy and death or cerebral palsy for children. Further research is required on longer-term benefits and harms for children, effect variation by participant and treatment characteristics, and the generalizability of findings to low- and middle-income countries.

Arch Dis Child Fetal Neonatal Ed. 2024 May 10:fetalneonatal-2024-327107.
doi: 10.1136/archdischild-2024-327107. Online ahead of print.

Early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy: a multicentre double-blind pilot randomised controlled trial

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Abstract
Objective: To examine the feasibility of early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy (HIE).
Design: Double-blind pilot randomised controlled trial.
Setting: Eight neonatal units in South Asia.
Patients: Neonates (≥36 weeks) with moderate or severe HIE admitted between 31 December 2022 and 3 May 2023.

Interventions: Erythropoietin (500 U/kg daily) or to the placebo (sham injections using a screen) within 6 hours of birth and continued for 9 days. MRI at 2 weeks of age.
Main outcomes and measures: Feasibility of randomisation, drug administration and assessment of brain injury using MRI.
Results: Of the 154 neonates screened, 56 were eligible; 6 declined consent and 50 were recruited; 43 (86%) were inborn. Mean (SD) age at first dose was 4.4 (1.2) hours in erythropoietin and 4.1 (1.0) hours in placebo. Overall mortality at hospital discharge occurred in 5 (19%) vs 11 (46%) (p=0.06), and 3 (13%) vs 9 (40.9%) (p=0.04) among those with moderate encephalopathy in the erythropoietin and placebo groups. Moderate or severe injury to basal ganglia, white matter and cortex occurred in 5 (25%) vs 5 (38.5%); 14 (70%) vs 11 (85%); and 6 (30%) vs 2 (15.4%) in the erythropoietin and placebo group, respectively. Sinus venous thrombosis was seen in two (10%) neonates in the erythropoietin group and none in the control group.
Conclusions: Brain injury and mortality after moderate or severe HIE are high in South Asia. Evaluation of erythropoietin monotherapy using MRI to examine treatment effects is feasible in these settings.

BMC Pediatr. 2024 Jan 15;24(1):46.
doi: 10.1186/s12887-024-04523-6.

Biochemical profiles and organ dysfunction in neonates with hypoxic-ischemic encephalopathy post-hoc analysis of the THIN trial

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Abstract
Background: Therapeutic hypothermia for infants with moderate to severe hypoxic-ischemic encephalopathy is well established as standard of care in high-income countries. Trials from low- and middle-income countries have shown contradictory results, and variations in the level of intensive care provided may partly explain these differences. We wished to evaluate biochemical profiles and clinical markers of organ dysfunction in cooled and non-cooled infants with moderate/severe hypoxic-ischemic encephalopathy.
Methods: This secondary analysis of the THIN (Therapeutic Hypothermia in India) study, a single center randomized controlled trial, included 50 infants with moderate to severe hypoxic-ischemic encephalopathy randomized to therapeutic hypothermia (n = 25) or standard care with normothermia (n = 25) between September 2013 and October 2015. Data were collected prospectively and compared by randomization groups. Main outcomes were metabolic acidosis, coagulopathies, renal function, and supportive treatments during the intervention.
Results: Cooled infants had lower pH than non-cooled infants at 6-12 h (median (IQR) 7.28 (7.20-7.32) vs 7.36 (7.31-7.40), respectively, p = 0.003) and 12-24 h (median (IQR) 7.30 (7.24-7.35) vs 7.41 (7.37-7.43), respectively, p < 0.001). Thrombocytopenia (< 100 000) was, though not statistically significant, twice as common in cooled compared to non-cooled infants (4/25 (16%) and 2/25 (8%), respectively, p = 0.67). No significant difference was found in the use of vasopressors (14/25 (56%) and 17/25 (68%), p = 0.38), intravenous bicarbonate (5/25 (20%) and 3/25 (12%), p = 0.70) or treatment with fresh frozen plasma (10/25 (40%) and 8/25 (32%), p = 0.56)) in cooled and non-cooled infants, respectively. Urine output < 1 ml/kg/h was

less common in cooled infants compared to non-cooled infants at 0-24 h (7/25 (28%) vs. 16/23 (70%) respectively, p = 0.004).
Conclusions: This post hoc analysis of the THIN study support that cooling of infants with hypoxic-ischemic encephalopathy in a level III neonatal intensive care unit in India was safe. Cooled infants had slightly lower pH, but better renal function during the first day compared to non-cooled infants. More research is needed to identify the necessary level of intensive care during cooling to guide further implementation of this neuroprotective treatment in low-resource settings.

Pediatr Res. 2024 May 20.
doi: 10.1038/s41390-024-03261-w. Online ahead of print.

Prevalence of hearing impairment in neonatal encephalopathy due to hypoxia-ischemia: a systematic review and meta-analysis

Dinesh Pawale[1], Anurag Fursule[1], Jason Tan[1 2], Deepika Wagh[1 2], Sanjay Patole[2 3], Shripada Rao[4 5]

Abstract
Background: This systematic review was undertaken to estimate the overall prevalence of hearing impairment in survivors of neonatal HIE.
Methods: PubMed, EMBASE, CINAHL, EMCARE and Cochrane databases, mednar (gray literature) were searched till January 2023. Randomized controlled trials and observational studies were included. The main outcome was estimation of overall prevalence of hearing impairment in survivors of HIE.
Results: A total of 71 studies (5821 infants assessed for hearing impairment) were included of which 56 were from high income countries (HIC) and 15 from low- or middle-income countries (LMIC). Overall prevalence rate of hearing impairment in cooled infants was 5% (95% CI: 3-6%, n = 4868) and 3% (95% CI: 1-6%, n = 953) in non-cooled HIE infants. The prevalence rate in cooled HIE infants in LMICs was 7% (95% CI: 2-15%) and in HICs was 4% (95% CI: 3-5%). The prevalence rate in non-cooled HIE infants in LMICs was 8% (95% CI: 2-17%) and HICs was 2% (95% CI: 0-4%).
Conclusions: These results would be useful for counseling parents, and in acting as benchmark when comparing institutional data, and while monitoring future RCTs testing new interventions in HIE. There is a need for more data from LMICs and standardization of reporting hearing impairment.
Impact: The overall prevalence rate of hearing impairment in cooled infants with HIE was 5% (95% CI: 3-6%) and 3% (95% CI: 1-6%) in the non-cooled infants. The prevalence rate in cooled HIE infants in LMICs was 7% (95% CI: 2-15%) and in HICs was 4% (95% CI: 3-5%). The prevalence rate in non-cooled HIE infants in LMICs was 8% (95% CI: 2-17%) and HICs was 2% (95% CI: 0-4%). These results would be useful for counseling parents, and in acting as benchmark when comparing institutional data, and while monitoring future RCTs testing new interventions in HIE.

Neonatal seizures

Cochrane Database Syst Rev. 2023 Oct 24;10(10):CD014967.
doi: 10.1002/14651858.CD014967.pub2.

Anti-seizure medications for neonates with seizures

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Abstract

Background: Newborn infants are more prone to seizures than older children and adults. The neuronal injury caused by seizures in neonates often results in long-term neurodevelopmental sequelae. There are several options for anti-seizure medications (ASMs) in neonates. However, the ideal choice of first-, second- and third-line ASM is still unclear. Further, many other aspects of seizure management such as whether ASMs should be initiated for only-electrographic seizures and how long to continue the ASM once seizure control is achieved are elusive.

Objectives: 1. To assess whether any ASM is more or less effective than an alternative ASM (both ASMs used as first-, second- or third-line treatment) in achieving seizure control and improving neurodevelopmental outcomes in neonates with seizures. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately. 2. To assess maintenance therapy with ASM versus no maintenance therapy after achieving seizure control. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately. 3. To assess treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates.

Search methods: We searched MEDLINE, Embase, CENTRAL, Epistemonikos and three databases in May 2022 and June 2023. These searches were not limited other than by study design to trials.

Selection criteria: We included randomised controlled trials (RCTs) that included neonates with EEG-confirmed or clinically diagnosed seizures and compared (1) any ASM versus an alternative ASM, (2) maintenance therapy with ASM versus no maintenance therapy, and (3) treatment of clinical or EEG seizures versus treatment of clinical seizures alone.

Data collection and analysis: Two review authors assessed trial eligibility, risk of bias and independently extracted data. We analysed treatment effects in individual trials and reported risk ratio (RR) for dichotomous data, and mean difference (MD) for continuous data, with respective 95% confidence interval (CI). We used GRADE to assess the certainty of evidence.

Main results: We included 18 trials (1342 infants) in this review. Phenobarbital versus levetiracetam as first-line ASM in EEG-confirmed neonatal seizures (one trial) Phenobarbital is probably more effective than levetiracetam in achieving seizure control after first loading dose (RR 2.32, 95% CI 1.63 to 3.30; 106 participants; moderate-certainty evidence), and after maximal loading dose (RR 2.83, 95% CI 1.78 to 4.50; 106 participants; moderate-certainty evidence). However, we are uncertain about the effect of phenobarbital when compared to levetiracetam on mortality before discharge (RR 0.30, 95% CI 0.04 to 2.52; 106 participants; very low-certainty evidence), requirement of mechanical ventilation (RR 1.21, 95% CI 0.76 to 1.91; 106 participants; very low-certainty evidence), sedation/drowsiness (RR 1.74, 95% CI 0.68 to 4.44; 106 participants; very low-certainty evidence) and epilepsy post-discharge (RR 0.92, 95% CI 0.48 to 1.76; 106 participants; very low-certainty evidence). The trial did not

report on mortality or neurodevelopmental disability at 18 to 24 months. Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures (one trial) We are uncertain about the effect of phenobarbital versus phenytoin on achieving seizure control after maximal loading dose of ASM (RR 0.97, 95% CI 0.54 to 1.72; 59 participants; very low-certainty evidence). The trial did not report on mortality or neurodevelopmental disability at 18 to 24 months. Maintenance therapy with ASM versus no maintenance therapy in clinically diagnosed neonatal seizures (two trials) We are uncertain about the effect of short-term maintenance therapy with ASM versus no maintenance therapy during the hospital stay (but discontinued before discharge) on the risk of repeat seizures before hospital discharge (RR 0.76, 95% CI 0.56 to 1.01; 373 participants; very low-certainty evidence). Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on mortality before discharge (RR 0.69, 95% CI 0.39 to 1.22; 373 participants; low-certainty evidence), mortality at 18 to 24 months (RR 0.94, 95% CI 0.34 to 2.61; 111 participants; low-certainty evidence), neurodevelopmental disability at 18 to 24 months (RR 0.89, 95% CI 0.13 to 6.12; 108 participants; low-certainty evidence) and epilepsy post-discharge (RR 3.18, 95% CI 0.69 to 14.72; 126 participants; low-certainty evidence). Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates (two trials) Treatment of both clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on seizure burden during hospitalisation (MD -1871.16, 95% CI -4525.05 to 782.73; 68 participants; low-certainty evidence), mortality before discharge (RR 0.59, 95% CI 0.28 to 1.27; 68 participants; low-certainty evidence) and epilepsy post-discharge (RR 0.75, 95% CI 0.12 to 4.73; 35 participants; low-certainty evidence). The trials did not report on mortality or neurodevelopmental disability at 18 to 24 months. We report data from the most important comparisons here; readers are directed to Results and Summary of Findings tables for all comparisons.

Authors' conclusions: Phenobarbital as a first-line ASM is probably more effective than levetiracetam in achieving seizure control after the first loading dose and after the maximal loading dose of ASM (moderate-certainty evidence). Phenobarbital + bumetanide may have little or no difference in achieving seizure control when compared to phenobarbital alone (low-certainty evidence). Limited data and very low-certainty evidence preclude us from drawing any reasonable conclusion on the effect of using one ASM versus another on other short- and long-term outcomes. In neonates who achieve seizure control after the first loading dose of phenobarbital, maintenance therapy compared to no maintenance ASM may have little or no effect on all-cause mortality before discharge, mortality by 18 to 24 months, neurodevelopmental disability by 18 to 24 months and epilepsy post-discharge (low-certainty evidence). In neonates with hypoxic-ischaemic encephalopathy, treatment of both clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on seizure burden during hospitalisation, all-cause mortality before discharge and epilepsy post-discharge (low-certainty evidence). All findings of this review apply only to term and late preterm neonates. We need well-designed RCTs for each of the three objectives of this review to improve the precision of the results. These RCTs should use EEG to diagnose seizures and should be adequately powered to assess long-term neurodevelopmental outcomes. We need separate RCTs evaluating the choice of ASM in preterm infants.

Indian J Pediatr. 2023 Nov 8.
doi: 10.1007/s12098-023-04905-1. Online ahead of print.

Levetiracetam versus Phenobarbitone for Management of Neonatal Seizures: A Systematic Review and Meta-analysis

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Abstract

Objectives: To review whether levetiracetam is non-inferior to phenobarbitone as the first-choice antiseizure medication (ASM).

Methods: The authors searched Medline, Embase, Web of Science, Scopus, and Cochrane Library for randomized controlled trials (RCTs) published until May 31, 2023. RCTs comparing the efficacy and safety of levetiracetam and phenobarbitone as first-line ASM in neonatal seizures were included. Random effects meta-analysis was performed, and the Risk of Bias version 2 tool was used for quality assessment.

Results: Eleven RCTs enrolling 821 neonates [mostly term, with hypoxic-ischemic encephalopathy (HIE)] were included. There was no significant difference in seizure control between levetiracetam and phenobarbitone (10 RCTs, 786 participants; relative risk RR: 1.11; 95% CI: 0.79, 1.54; I^2- 88%). Neonates in the levetiracetam group had a significantly lower incidence of hypotension (RR: 0.28; 95% CI: 0.09, 0.86), respiratory depression (RR: 0.36, 95% CI: 0.19, 0.66), and depressed sensorium (RR: 0.52, 95% CI: 0.27, 1.00). Three studies compared neurodevelopmental outcomes; however two of them were cross-over trials where infants received both drugs. Only one RCT enrolled pure cohorts and showed better neurodevelopment in the levetiracetam group at one month of age.

Conclusions: With the limitation of very-low certainty evidence, the results of this systematic review suggest that levetiracetam may be non-inferior to phenobarbitone for managing neonatal seizures. Considering a better safety profile and marginally better neurodevelopment in the short term, levetiracetam may be considered an initial choice for managing neonatal seizures.

Neonatal sepsis

J Trop Pediatr. 2023 Oct 5;69(6):fmad036.
doi: 10.1093/tropej/fmad036.

Ten- vs. 14-day antibiotic therapy for culture-positive neonatal sepsis

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Abstract

Background: Neonatal sepsis is a major determinant of neonatal mortality. There is a scarcity of evidence-based guidelines for the duration of antibiotics in culture-positive sepsis.

Objectives: The aim of this study was to compare the efficacy of 10- and 14-day antibiotic therapies in the management of culture-positive neonatal sepsis.

Methods: This randomized controlled trial was conducted in the neonatal intensive care unit of a tertiary care center among the neonates suffering from culture-positive sepsis (with

signs of clinical remission on day 9 of antibiotic) between January 2023 and May 2023. Newborns with major congenital anomaly, deep-seated infections, multi-organ dysfunction, associated fungal infections/infection by multiple organisms and severe birth asphyxia were excluded. Two hundred and thirty-four newborns were randomized into two groups-study (received 10 days of antibiotics) and control (received 14 days of antibiotics). Treatment failure, hospital stay and adverse effects were compared between the two groups. $p < 0.05$ was taken as the limit of statistical significance.
Results: Median [interquartile range (IQR)] birth weight and gestational age of the study population (53.8% boys) were 2.424 kg (IQR: 2.183-2.695) and 37.3 weeks (IQR: 35.5-38.1), respectively. Acinetobacter was the most commonly isolated species (56, 23.9%). The baseline characteristics of both groups were almost similar. Treatment failure was similar in the study and control groups (3.8% vs. 1.7%, $p = 0.40$), with a shorter hospital stay [median (IQR): 14 (13-16) vs. 18 (17-19) days, $p < 0.001$].
Conclusion: Ten-day antibiotic therapy was comparable with 14-day antibiotic therapy in efficacy, with a shorter duration of hospital stay and without any significant increase in adverse effects.

Jaundice

Cochrane Database Syst Rev. 2024 May 28;5(5):CD011060.
doi: 10.1002/14651858.CD011060.pub2.
Transcutaneous bilirubinometry for detecting jaundice in term or late preterm neonates
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Abstract
Background: The American Academy of Pediatrics and the Canadian Paediatric Society both advise that all newborns should undergo bilirubin screening before leaving the hospital, and this has become the standard practice in both countries. However, the US Preventive Task Force has found no strong evidence to suggest that this practice of universal screening for bilirubin reduces the occurrence of significant outcomes such as bilirubin-induced neurologic dysfunction or kernicterus.
Objectives: To evaluate the effectiveness of transcutaneous screening compared to visual inspection for hyperbilirubinemia to prevent the readmission of newborns (infants greater than 35 weeks' gestation) for phototherapy.
Search methods: We searched CENTRAL, MEDLINE, Embase, CINAHL, ClinicalTrials.gov, ICTRP, and ISRCTN in June 2023. We also searched conference proceedings, and the reference lists of included studies.
Selection criteria: We included randomized controlled trials (RCTs), quasi-randomized, cluster-randomized, or prospective cohort studies with control arm that evaluated the use of transcutaneous bilirubin (TcB) screening for hyperbilirubinemia in newborns before hospital discharge.
Data collection and analysis: We used standard methodologic procedures expected by Cochrane. We evaluated treatment effects using a fixed-effect model with risk ratio (RR) and 95% confidence intervals (CI) for categorical data and mean, standard deviation (SD), and

mean difference (MD) for continuous data. We used the GRADE approach to evaluate the certainty of evidence.
Main results: We identified one RCT (1858 participants) that met our inclusion criteria. The study included 1858 African newborns at 35 weeks' gestation or greater who were receiving routine care at a well-baby nursery, and were randomly recruited prior to discharge to undergo TcB screening. The study had good methodologic quality. TcB screening versus visual assessment of hyperbilirubinemia in newborns: - may reduce readmission to the hospital for hyperbilirubinemia (RR 0.25, 95% CI 0.14 to 0.46; P < 0.0001; moderate-certainty evidence); - probably has little or no effect on the rate of exchange transfusion (RR 0.20, 95% CI 0.01 to 14.16; low-certainty evidence); - may increase the number of newborns who require phototherapy prior to discharge (RR 2.67, 95% CI 1.56 to 4.55; moderate-certainty evidence). - probably has little or no effect on the rate of acute bilirubin encephalopathy (RR 0.33, 95% CI 0.01 to 8.18; low-certainty evidence). The study did not evaluate or report cost of care.
Authors' conclusions: Moderate-certainty evidence suggests that TcB screening may reduce readmission for hyperbilirubinemia compared to visual inspection. Low-certainty evidence also suggests that TcB screening probably has little or no effect on the rate of exchange transfusion compared to visual inspection. However, moderate-certainty evidence suggests that TcB screening may increase the number of newborns that require phototherapy before discharge compared to visual inspection. Low-certainty evidence suggests that TcB screening probably has little or no effect on the rate of acute bilirubin encephalopathy compared to visual inspection. Given that we have only identified one RCT, further studies are necessary to determine whether TcB screening can help to reduce readmission and complications related to neonatal hyperbilirubinemia. In settings with limited newborn follow-up after hospital discharge, identifying newborns at risk of severe hyperbilirubinemia before hospital discharge will be important to plan targeted follow-up of these infants.

Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Growth monitoring

Cochrane Database Syst Rev. 2023 Oct 12;10(10):CD014785.
doi: 10.1002/14651858.CD014785.pub2.
The impact of growth monitoring and promotion on health indicators in children under five years of age in low- and middle-income countries
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Abstract
Background: Undernutrition in the critical first 1000 days of life is the most common form of childhood malnutrition, and a significant problem in low- and middle-income countries (LMICs). The effects of undernutrition in children aged under five years are wide-ranging and include increased susceptibility to and severity of infections; impaired physical and cognitive

development, which diminishes school and work performance later in life; and death. Growth monitoring and promotion (GMP) is a complex intervention that comprises regular measurement and charting of growth combined with promotion activities. Policymakers, particularly in international aid agencies, have differing and changeable interpretations and perceptions of the purpose of GMP. The effectiveness of GMP as an approach to preventing malnutrition remains a subject of debate, particularly regarding the added value of growth monitoring compared with promotion alone.
Objectives: To evaluate the effectiveness of child growth monitoring and promotion for identifying and addressing faltering growth, improving infant and child feeding practices, and promoting contact with and use of health services in children under five years of age in low- and middle-income countries.
Search methods: We used standard, extensive Cochrane search methods. The latest search date was 3 November 2022.
Selection criteria: We included randomised controlled trials (RCTs), cohort studies, and controlled before-after studies that compared GMP with standard care or nutrition education alone in non-hospitalised children aged under five years.
Data collection and analysis: We used standard Cochrane methods to conduct a narrative synthesis. Our primary outcomes were anthropometric indicators, infant and child feeding practices, and health service usage. Secondary outcomes were frequency and severity of childhood illnesses, and mortality. We used GRADE to assess the certainty of evidence for each primary outcome.
Main results: We included six studies reported in eight publications. We grouped the findings according to intervention. Community-based growth monitoring and promotion (without supplementary feeding) versus standard care We are unsure if GMP compared to standard care improves infant and child feeding practices, as measured at 24 months by the proportion of infants who have fluids other than breast milk introduced early (49.7% versus 70.5%; 1 study; 4296 observations; very low-certainty evidence). We are unsure if GMP improves health service usage, as measured at 24 months by the proportion of children who receive vitamin A (72.5% versus 62.9%; 1 study; 4296 observations; very low-certainty evidence) and the proportion of children who receive deworming (29.2% versus 14.6%; 1 study; 4296 observations; very low-certainty evidence). No studies reported selected anthropometric indicators (weight-for-age z-score or height-for-age z-score) at 12 or 24 months, infant and child feeding practices at 12 months, or health service usage at 12 months. Community-based growth monitoring and promotion (with supplementary feeding) versus standard care Two studies (with 569 participants) reported the mean weight-for-age z-score at 12 months, providing very low-certainty evidence: in one study, there was little or no difference between GMP and standard care (mean difference (MD) -0.07, 95% confidence interval (CI) -0.19 to 0.06); in the other study, mean weight-for-age z-score worsened in both groups, but we were unable to calculate a relative effect. GMP versus standard care may make little to no difference to the mean height-for-age z-score at 12 months (MD -0.15, 95% CI -0.34 to 0.04; 1 study, 337 participants; low-certainty evidence). Two studies (with 564 participants) reported a range of outcome measures related to infant and child feeding practices at 12 months, showing little or no difference between the groups (very low-certainty evidence). No studies reported health service usage at 12 or 24 months, feeding practices at 24 months, or selected anthropometric indicators at 24 months.
Authors' conclusions: There is limited uncertain evidence on the effectiveness of GMP for identifying and addressing faltering growth, improving infant and child feeding practices,

and promoting contact with and use of health services in children aged under five years in LMICs. Future studies should explore the reasons for the apparent limited impact of GMP on key child health indicators. Reporting of GMP interventions and important outcomes must be transparent and consistent.

Nutritional education

PLoS One. 2024 Mar 15;19(3):e0300334.
doi: 10.1371/journal.pone.0300334. eCollection 2024.

Care groups in an integrated nutrition education intervention improved infant growth among South Sudanese refugees in Uganda's West Nile post-emergency settlements: A cluster randomized trial

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Abstract

Objective: This study examined the effects of a peer-led integrated nutrition education intervention with maternal social support using Care Groups on infant growth among South Sudanese refugees in Uganda.

Methods: A community-based cluster-randomized trial (RCT) was conducted among 390 pregnant women (third trimester). Two intervention study arms were Mothers-only(n = 131) and Parents-combined (n = 142) with a Control (n = 117). WHO infant growth standards defined length-for-age z-scores (LAZ) for stunting, weight-for-age z-scores (WAZ) for underweight and weight-for-length z-scores (WLZ) for wasting. The Medical Outcomes Study (MOS) social support index was a proxy measure for social support. A split-plot ANOVA tested the interaction effects of social support, intervention, and time on infant growth after adjusting for covariates. Further, pairwise comparisons explained mean differences in infant growth among the study arms.

Results: The mean infant birth weight was 3.1 ± 0.5 kg. Over the study period, infant stunting was most prevalent in the Control (≥ 14%) compared to Mothers-only (< 9.5%) and Parents-combined (< 7.4%) arms. There were significant interaction effects of the Care Group intervention and social support by time on infant mean LAZ ($F(6, 560) = 28.91$, $p < 0.001$), WAZ ($F(5.8, 539.4) = 12.70$, $p = < 0.001$) and WLZ ($F(5.3, 492.5) = 3.38$, $p = 0.004$). Simple main effects by the end of the study showed that the intervention improved infant mean LAZ (Mothers-only vs. Control (mean difference, MD) = 2.05, $p < 0.001$; Parents-combined vs. Control, MD = 2.00, $p < 0.001$) and WAZ (Mothers-only vs. Control, MD = 1.27, $p < 0.001$; Parents-combined vs. Control, MD = 1.28, $p < 0.001$).

Conclusion: Maternal social support with an integrated nutrition education intervention significantly improved infant stunting and underweight. Nutrition-sensitive approaches focused on reducing child undernutrition among post-emergency refugees may benefit from using Care Groups in programs.

Front Public Health. 2023 Nov 13:11:1277471.
doi: 10.3389/fpubh.2023.1277471. eCollection 2023.

Effectiveness of a positive deviance approach to improve mother's nutritional knowledge, attitude, self-efficacy, and child's nutritional status in Maji District, West Omo Zone, South West region, Ethiopia: a cluster randomized control trial

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Abstract

Background: Achieving appropriate feeding for infants and young children continues to be a struggle. These impediments are not only due to limited food availability but also inadequate knowledge, unfavorable attitudes, and low self-efficacy. A positive deviant approach (PDA) addressing positive and possible solutions inherent in a community focusing on problems is applied in Africa and particularly to Ethiopia. Therefore, this trial is aimed at evaluating the effectiveness of PDA in improving mothers' nutritional knowledge, attitudes, self-efficacy, and children's nutritional status.

Method: This was a cluster randomized control trial in which 516 mothers were randomly assigned to either an intervention or control group after collecting baseline data. The trial participants in the intervention cluster received a positive deviant intervention for 6 months, whereas those in the control group received only the usual care. Trained positive deviant mothers (PDM) delivered the intervention. A pretested, structured, interviewer-administered questionnaire was used for data collection. Generalized estimating equation regression analysis adjusted for baseline covariates and clustering was used to test the intervention effect.

Result: The results showed that PDA improved breastfeeding outcomes in the intervention groups compared to their counterparts. A mean difference (MD) of breastfeeding (BF) knowledge (MD = 6.47; 95% CI: 6.45-6.49), BF attitude (MD = 12.68; 95% CI: 11.96-13.40), and BF self-efficacy (MD = 3.13; 95% CI: 3.05-3.21) was observed favoring the intervention. The intervention group showed better improvement in complementary feeding (*CF*) knowledge, attitude, and self-efficacy among mothers compared to the control group. A mean difference in *CF* knowledge (MD = 4.53, 95% CI: 4.31-4.75), *CF* attitude (MD = 9.14, 95% CI: 8.52-9.75), and *CF* self-efficacy (MD = 11.64, 95% CI: 11.16-12.12) were observed favoring the intervention. At the end of the 6-month follow-up, children in the intervention group showed a lower prevalence of underweight (18.23%) (95% CI: 4.55, 22.54%; $p = 0.004$) compared with the control group.

Conclusion: PDA was effective in improving mothers' nutritional knowledge, attitude, and self-efficacy and reducing children's underweight in the intervention area

Micronutients, multivitamins, and food fortification

(See also Vitamin A)

Br J Nutr. 2023 Oct 5:1-13.
doi: 10.1017/S0007114523002234. Online ahead of print.

Ten2Twenty-Ghana: a randomised controlled trial on the efficacy of multiple micronutrient-fortified biscuits on the micronutrient status of adolescent girls

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Abstract

Adolescent girls are an important target group for micronutrient interventions particularly in Sub-Saharan Africa where adolescent pregnancy and micronutrient deficiencies are common. When consumed in sufficient amounts and at levels appropriate for the population, fortified foods may be a useful strategy for this group, but little is known about their effectiveness and timing (regarding menarche), particularly in resource-poor environments. We evaluated the effect of consuming multiple micronutrient-fortified biscuits (MMB), sold in the Ghanaian market, 5 d/week for 26 weeks compared with unfortified biscuits (UB) on the micronutrient status of female adolescents. We also explored to what extent the intervention effect varied before or after menarche. Ten2Twenty-Ghana was a 26-week double-blind, randomised controlled trial among adolescent girls aged 10-17 years (*n* 621) in the Mion District, Ghana. Biomarkers of micronutrient status included concentrations of Hb, plasma ferritin (PF), soluble transferrin receptor (TfR) and retinol-binding protein (RBP), including body-iron stores. Intention-to-treat analysis was supplemented by protocol-specific analysis. We found no effect of the intervention on PF, TfR and RBP. MMB consumption did not affect anaemia and micronutrient deficiencies at the population level. MMB consumption increased the prevalence of vitamin A deficiency by 6·2 % (95 % CI (0·7, 11·6)) among pre-menarche girls when adjusted for baseline micronutrient status, age and height-for-age *Z*-score, but it decreased the prevalence of deficient/low vitamin A status by -9·6 % (95 % CI (-18·9, -0·3)) among post-menarche girls. Consuming MMB available in the market did not increase iron status in our study, but reduced the prevalence of deficient/low vitamin A status in post-menarcheal girls.

Am J Prev Med. 2024 Jun;66(6):1078-1088.
doi: 10.1016/j.amepre.2024.01.017. Epub 2024 Feb 1.

Randomized Trial to Improve Body Composition and Micronutrient Status Among South African Children

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Abstract

Introduction: Physical activity (PA) promotion combined with multimicronutrient supplementation (MMNS) among school-age children may reduce fat mass accrual and increase muscle mass through different mechanisms and so benefit child health. This study determined the efficacy of combined interventions on body composition among South African schoolchildren and determined if micronutrients mediate these effects.

Study design: Longitudinal cluster randomized controlled trial of children followed from 2019 to 2021. Statistical analyses carried from 2022 to 2023.

Setting/participants: A total of 1,304 children 6-12 years of age recruited from public schools in Gqeberha, South Africa.

Intervention: Children were randomized by classes to either: (a) a physical activity group (PA); (b) a MMNS group; (c) a physical activity + multimicronutrient supplementation group (PA + MMNS); and (d) a placebo control group.

Main outcome measures: Trajectories of overall and truncal fat free mass (FFM) and fat mass (FM) estimates in modeled at 9 and 21 months using latent growth curve models (LGCM). Changes in micronutrient concentrations at 9 months from baseline.

Results: An increased FFM trajectory was found among children in the MMNS arm at 9 months (Beta 0.16, 95% CI = 0.12, 0.31). The PA and MMNS arms both had positive indirect effects on this trajectory at 9 months (Beta 0.66, 95% CI = 0.44, 0.88 and Beta 0.32 95% CI = 0.1 0.5, respectively) and similarly at 21 months when mediated by zinc concentration changes. A reduced FM trajectory was found among children in the PA promotion arm at 9 months when using this collection point as the referent intercept. This arm was inversely associated with the FM trajectory at 9 months when mediated by zinc changes.
Conclusions: PA and MMNS promotion in school-based interventions directly contributed to reductions in FM and increased FFM among South African children and indirectly through changes in micronutrient status.

Br J Nutr. 2023 Sep 14;130(5):868-877.
doi: 10.1017/S0007114522003944. Epub 2022 Dec 21.

Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomised controlled trial in India

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Abstract
Inadequate protein intake and lack of micronutrients may affect neurodevelopment in infants. This randomised controlled trial was conducted to measure the effect of two milk-cereal mixes with modest and high amounts of protein and enriched with multiple micronutrients, given between 6 and 12 months, on cognitive, language, motor and behavioural scores at 12 and 24 months of age, compared with no-supplementation. The two supplements were also compared with each other. The study was conducted in urban Delhi, India, and the infants were randomised in a 1:1:1 ratio to the three study groups. At 12 and 24 months of age, 1134 and 1214 children were available, respectively. At 12 months of age, compared with no-supplement group, an increase in the motor scores (mean difference, MD 1·52, 95 % CI: 0·28, 2·75) and a decrease in the infant temperament scores (MD - 2·76, 95 % CI: -4·23, -1·29) in the modest-protein group was observed. Those in the high-protein group had lower socio-emotional scores (MD - 1·40, 95 % CI: -2·43, -0·37) and higher scores on Infant Temperament Scale (MD 2·05, 95 % CI: 0·62, 3·48) when compared with modest-protein group. At 24 months, no significant differences in any of the neurodevelopment scores between the three study groups was found. In conclusion, supplementation with modest amount of protein and multiple micronutrients may lead to short-term small improvements in motor function and infant temperament. There appears no advantage of supplementing with high protein, rather negative effects on infant behaviour were observed.

Br J Nutr. 2023 Nov 14;130(9):1558-1572.
doi: 10.1017/S0007114523000739. Epub 2023 Mar 22.

Associations between maternal and infant selenium status and child growth in a birth cohort from Dhaka, Bangladesh

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Abstract
Deficiency of essential trace element, Se, has been implicated in adverse birth outcomes and in child linear growth because of its important role in redox biology and associated antioxidant effects. We used data from a randomised controlled trial conducted among a cohort of pregnant and lactating women in Dhaka, Bangladesh to examine associations between Se biomarkers in whole blood (WBSe), serum and selenoprotein P (SEPP1) in maternal delivery and venous cord (VC) blood. Associations between Se biomarkers, birth weight and infant growth outcomes (age-adjusted length, weight, head circumference and weight-for-length z-scores) at birth, 1 and 2 years of age were examined using regression analyses. WB and serum Se were negatively associated with birth weight (adjusted β, 95 % CI, WBSe delivery: −26·6 (−44·3, −8·9); WBSe VC: −19·6 (−33·0, −6·1)); however, delivery SEPP1 levels (adjusted β: −37·5 (−73·0, −2·0)) and VC blood (adjusted β: 82·3 (30·0, 134·7)) showed inconsistent and opposite associations with birth weight. Positive associations for SEPP1 VC suggest preferential transfer from mother to fetus. We found small associations between infant growth and WBSe VC (length-for-age z-score β, 95 % CI, at birth: −0·05 (−0·1, −0·01)); 12 months (β: −0·05 (−0·08, −0·007)). Weight-for-age z-score also showed weak negative associations with delivery WBSe (at birth: −0·07 (−0·1, −0·02); 12 -months: −0·05 (−0·1, −0·005)) and in WBSe VC (at birth: −0·05 (−0·08, −0·02); 12 months: −0·05 (−0·09, −0·004)). Given the fine balance between essential nutritional and toxic properties of Se, it is possible that WB and serum Se may negatively impact growth outcomes, both in utero and postpartum.

Am J Clin Nutr. 2024 Feb;119(2):470-484.
doi: 10.1016/j.ajcnut.2023.11.005. Epub 2023 Nov 11.

Effectiveness of intermittent iron and high-dose vitamin A supplementation on cognitive development of school children in southern Ethiopia: a randomized placebo-controlled trial

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Abstract
Background: Iron is an essential mineral whose deficiency results in cognitive alteration, impaired emotional behaviors, and altered myelination and neurotransmission. In animal models, it has been shown that vitamin A (VA) could affect cognition.
Objectives: The study aimed to evaluate the effectiveness of intermittent iron and VA supplementation on cognitive development of schoolchildren, and to assess the interaction between these supplementations.
Methods: Considering a 2 × 2 factorial design, 504 children were randomly assigned to 1 of the 4 arms: placebo VA and placebo iron supplement; high-dose vitamin VA and placebo iron supplement; iron supplement and placebo VA; and iron and high-dose vitamin VA supplements. Cognitive development was assessed using Raven's Coloured Progressive Matrices, digit span, Tower of London, and visual search tasks.
Results: The mean [± standard deviation (SD)] age of the enrolled children was 9.6 (±1.6) y. One-fifth of the children had iron deficiency or anemia, whereas 2.9%, 3.9%, and 12.1% of children had low iron stores, iron deficiency anemia, and VA deficiency, respectively.

Intermittent iron supplementation did not result in any significant improvement of children's cognitive development and had a negative effect on the performance index of the visual search task compared with placebo (-0.17 SD, 95% confidence interval: -0.32, -0.02). Effects were evident among children with stunting, thinness, or children coming from understimulating home environments. High-dose VA supplementation resulted in a significant improvement of digit span z-score with a mean difference of 0.30 SD (95% confidence interval: 0.14, 0.46) compared with placebo VA. VA had a more beneficial impact for girls, children infected with helminths, and those from food secure households.
Conclusion: In a population where the prevalence of iron deficiency is low, intermittent iron supplementation did not have any or negative effect on the child's cognitive development outcomes. Conversely, VA supplementation improved the child's working memory.

J Nutr. 2024 Mar 6:S0022-3166(24)00153-6.
doi: 10.1016/j.tjnut.2024.03.005. Online ahead of print.

Consumption of iron-fortified lentils is protective against declining iron status among adolescent girls in Bangladesh: evidence from a community-based double-blind, cluster-randomized controlled trial

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Abstract

Background: In many low-income countries, iron deficiency (ID) and its anemia (IDA) pose significant health challenges, particularly among women and girls. Finding sustainable and effective solutions to address this issue is critical.
Objectives: This study aimed to evaluate the efficacy of incorporating iron-fortified lentils (IFLs) into the diets of rural Bangladeshi adolescent girls on their body iron (Fe) status.
Methods: A community-based, double-blind, cluster-randomized controlled trial involved n=1195 girls aged 10-17 years. 48 adolescent clubs (n= ~ 27 girls each) were randomized into three groups: 1) 200 g cooked IFLs, 2) 200 g cooked non-iron fortified lentils (NIFLs), and 3) a control group with no lentils (usual dietary intake). The intervention, administered five days a week for 85 feeding days, provided ~8.625 mg of Fe from each serving of IFLs and 2.625 mg from NIFLs. Blood samples collected at baseline, midpoint (42 feeding days) and endpoint (85 feeding days) assessed key Fe and inflammation biomarkers. Statistical analyses were filtered for inflammation..
Results: While all groups experienced a decline in Fe status over time, the IFL group exhibited a significantly reduced decline in serum ferritin (sFer -7.2 µg/L), and total body iron level (TBI -0.48 mg/kg) compared to NIFL (sFer -14.3 µg/L and TBI -1.36 mg/kg) and usual intake group (sFer -12.8 µg/L and TBI -1.33 mg/kg). Additionally, those in the IFL group had a 57% reduced risk of developing clinical ID (sFer <15 µg/L) compared to usual intake group.
Conclusion: Our findings suggest that incorporating IFLs into the diet can help mitigate a decline in sFer, indicating a positive impact on the body Fe status of adolescent girls. This research underscores the potential role of fortified foods in addressing ID and IDA in vulnerable populations, emphasizing the significance of food-based interventions in public health.

Lipid-based nutrition supplements

Am J Clin Nutr. 2023 Aug;118(2):433-442.
doi: 10.1016/j.ajcnut.2023.05.025. Epub 2023 May 29.

Prenatal and postnatal small-quantity lipid-based nutrient supplements and children's social-emotional difficulties at ages 9-11 y in Ghana: follow-up of a randomized controlled trial

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Abstract

Background: Provision of small-quantity lipid-based nutrient supplements (SQ-LNSs) during early life improves growth and development. In the International Lipid-Based Nutrient Supplements DYAD-Ghana trial, prenatal and postnatal SQ-LNS reduced social-emotional difficulties at age 5 y, with greater effects among children in less-enriched home environments.

Objectives: We aimed to investigate the effect of prenatal and postnatal SQ-LNS on children's social-emotional problems at age 9-11 y.

Methods: In 2009-2011, 1320 pregnant women ≤20 wk gestation were randomly assigned to receive the following daily until 6 mo postpartum: 1) iron and folic acid until delivery, then placebo, 2) multiple micronutrients (MMNs), or 3) SQ-LNS (20 g/d). Children in group 3 received SQ-LNS from 6 to 18 mo. In 2021, we evaluated children's social-emotional outcomes with 6 assessment tools that used caregiver, teacher, and/or self-report to measure socioemotional difficulties, conduct problems, temperament, mood, anxiety, and emotion management.

Results: We assessed outcomes in 966 children, comprising 79.4% of 1217 participants eligible for re-enrolment. No significant differences were found between the SQ-LNS and control (non-LNS groups combined) groups. Few children (<2%) experienced high parent-reported social-emotional difficulties at 9-11 y, in contrast to the high prevalence at age 5 in this cohort (25%). Among children in less-enriched early childhood home environments, the SQ-LNS group had 0.37 SD (-0.04 to 0.82) lower self-reported conduct problems than the control group (P-interaction = 0.047).

Conclusions: Overall positive effects of SQ-LNS on social-emotional development previously found at age 5 y are not sustained to age 9-11 y; however, there is some evidence of positive effects among children in less-enriched environments. The lack of effects may be owing to low prevalence of social-emotional problems at preadolescence, resulting in little potential to benefit from early nutritional intervention at this age in this outcome domain. Follow-up during adolescence, when social-emotional problems more typically onset, may yield further insights.

Am J Clin Nutr. 2023 Aug 9;S0002-9165(23)66071-X.
doi: 10.1016/j.ajcnut.2023.08.001. Online ahead of print.

Effect of Peanut Paste-Based Ready-to-Use School Meals With and Without Milk on Fluid Cognition in Northern Ghana: A Randomized Controlled Trial

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Abstract

Background: Few studies have investigated the role of school feeding in low- and middle-income countries as a means of improving childhood cognition. Peanut-based ready-to-use foods with milk or cowpea offer an affordable, scalable option that might improve cognition.

Objective: To determine whether micronutrient-fortified peanut-based ready-to-use foods made with milk (PM-RUF) or cowpea (PC-RUF) would improve fluid cognition as assessed by 4 tests from the NIH Toolbox Cognitive Battery when compared with a micronutrient-fortified millet porridge (FP) after a year of school feeding.

Methods: An individually randomized, investigator-blinded, controlled clinical trial was conducted at 6 schools in Mion District in rural northern Ghana. 871 school children aged 5-12 years were randomized and allocated to receive PM-RUF (n = 282), PC-RUF (n = 292), or FP (n = 297), each providing approximately 400 kcal/day. The primary outcomes were 4 fluid cognition test scores: Dimensional Change Card Sort test (DCCS), Flanker Inhibitory Control and Attention test (FICA), Pattern Comparison Processing Speed test (PCPS), and a modified List Sorting Working Memory test (LSWM). Secondary outcomes included a composite median ranking of the 4 primary outcomes as well as changes in anthropometry.

Results: Among the 871 participants (median age, 8.8 years; 47% female), 795 (91%) completed endline cognitive testing. Median attendance rates exceeded 87% in all groups. PM-RUF group demonstrated better fluid cognition on DCCS (OR: 1.5; 95% CI: 1.1, 2.0; P = 0.016) and PCPS (OR: 1.4; 95% CI: 1.0, 1.9; P = 0.026) than FP, while there were no significant differences on FICA or LSWM. PC-RUF group demonstrated no improvement over FP on any cognitive tests. PM-RUF group had superior fluid cognition composite median rankings (OR: 1.5; 95% CI: 1.1, 2.0; P = 0.007).

Conclusions: Among rural Ghanaian children 5-12 years of age, PM-RUF compared with FP resulted in superior fluid cognition.

Am J Clin Nutr. 2024 Mar;119(3):829-837.
doi: 10.1016/j.ajcnut.2024.01.018. Epub 2024 Jan 24.

Effect of lipid-based nutrient supplements on micronutrient status and hemoglobin among children with stunting: secondary analysis of a randomized controlled trial in Uganda

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Abstract

Background: Micronutrient deficiencies and anemia are widespread among children with stunting.

Objectives: We assessed the effects of lipid-based nutrient supplements (LNS) containing milk protein (MP) and/or whey permeate (WP) on micronutrient status and hemoglobin (Hb) among children with stunting.

Methods: This was a secondary analysis of a randomized controlled trial. Children aged 12-59 mo with stunting were randomly assigned to LNS (100 g/d) with milk or soy protein and WP or maltodextrin for 12 wk, or no supplement. Hb, serum ferritin (S-FE), serum soluble transferrin receptor (S-TfR), plasma cobalamin (P-Cob), plasma methylmalonic acid (P-MMA), plasma folate (P-Fol), and serum retinol-binding protein (S-RBP) were measured at inclusion and at 12 wk. Data were analyzed using linear and logistic mixed-effects models.
Results: Among 750 children, with mean age ± SD of 32 ± 11.7 mo, 45% (n = 338) were female and 98% (n = 736) completed follow-up. LNS, compared with no supplementation, resulted in 43% [95% confidence interval (CI): 28, 60] greater increase in S-FE corrected for inflammation (S-FEci), 2.4 (95% CI: 1.2, 3.5) mg/L greater decline in S-TfR, 138 (95% CI: 111, 164) pmol/L greater increase in P-Cob, 33% (95% CI: 27, 39) reduction in P-MMA, and 8.5 (95% CI: 6.6, 10.3) nmol/L greater increase in P-Fol. There was no effect of LNS on S-RBP. Lactation modified the effect of LNS on markers of cobalamin status, reflecting improved status among nonbreastfed and no effects among breastfed children. LNS increased Hb by 3.8 (95% CI: 1.7, 6.0) g/L and reduced the odds of anemia by 55% (odds ratio: 0.45, 95% CI: 0.29, 0.70). MP compared with soy protein increased S-FEci by 14% (95% CI: 3, 26).
Conclusions: LNS supplementation increases Hb and improves iron, cobalamin, and folate status, but not vitamin A status among children with stunting. LNS should be considered for children with stunting. This trial was registered at ISRCTN as 13093195.

Environmental enteric dysfunction

Nature. 2024 Jan;625(7993):157-165.
doi: 10.1038/s41586-023-06838-3. Epub 2023 Dec 13.
Bioactive glycans in a microbiome-directed food for children with malnutrition
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Abstract
Evidence is accumulating that perturbed postnatal development of the gut microbiome contributes to childhood malnutrition[1-4]. Here we analyse biospecimens from a randomized, controlled trial of a microbiome-directed complementary food (MDCF-2) that produced superior rates of weight gain compared with a calorically more dense conventional ready-to-use supplementary food in 12-18-month-old Bangladeshi children with moderate acute malnutrition[4]. We reconstructed 1,000 bacterial genomes (metagenome-assembled genomes (MAGs)) from the faecal microbiomes of trial participants, identified 75 MAGs of which the abundances were positively associated with ponderal growth (change in weight-for-length Z score (WLZ)), characterized changes in MAG gene expression as a function of treatment type and WLZ response, and quantified carbohydrate structures in MDCF-2 and faeces. The results reveal that two Prevotella copri MAGs that are positively associated with WLZ are the principal contributors to MDCF-2-induced expression of metabolic pathways involved in

utilizing the component glycans of MDCF-2. The predicted specificities of carbohydrate-active enzymes expressed by their polysaccharide-utilization loci are correlated with (1) the in vitro growth of Bangladeshi P. copri strains, possessing varying degrees of polysaccharide-utilization loci and genomic conservation with these MAGs, in defined medium containing different purified glycans representative of those in MDCF-2, and (2) the levels of faecal carbohydrate structures in the trial participants. These associations suggest that identifying bioactive glycan structures in MDCFs metabolized by growth-associated bacterial taxa will help to guide recommendations about their use in children with acute malnutrition and enable the development of additional formulations.

J Nutr. 2024 Mar;154(3):949-961.
doi: 10.1016/j.tjnut.2024.01.031. Epub 2024 Feb 6.

Effects of L-Carnitine Supplementation on the Rate of Weight Gain and Biomarkers of Environmental Enteric Dysfunction in Children with Severe Acute Malnutrition: A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Background: Severe acute malnutrition (SAM) is a major public health concern among low- and middle-income countries, where the majority of the children encountering this acute form of malnutrition suffer from environmental enteric dysfunction (EED). However, evidence regarding the effects of L-carnitine supplementation on the rate of weight gain and EED biomarkers in malnourished children is limited.

Objectives: We aimed to investigate the role of L-carnitine supplementation on the rate of weight gain, duration of hospital stays, and EED biomarkers among children with SAM.

Methods: A prospective, double-blind, placebo-controlled, randomized clinical trial was conducted at the Nutritional Rehabilitation Unit (NRU) of Dhaka Hospital, International Centre for Diarrheal Disease Research, Bangladesh. Children with SAM aged 9-24 mo were randomly assigned to receive commercial L-carnitine syrup (100 mg/kg/d) or placebo for 15 d in addition to standard of care. A total of 98 children with Weight-for-Length-z-score (WLZ) < -3 Standard deviation were enrolled between October 2021 and March 2023. Analyses were conducted on an intention-to-treat basis.

Results: The primary outcome variable, "rate of weight gain," was comparable between L-carnitine and placebo groups (2.09 ± 2.23 compared with 2.07 ± 2.70; P = 0.973), which was consistent even after adjusting for potential covariates (age, sex, Weight-for-Age z-score, asset index, and WASH practices) through linear regression [ß: 0.37; 95% confidence interval (CI): -0.63,1.37; P = 0.465]. The average hospital stay was ∼4 d. The results of adjusted median regression showed that following intervention, there was no significant difference in the EED biomarkers among the treatment arms; Myeloperoxidase (ng/mL) [ß: -1342.29; 95% CI: -2817.35, 132.77; P = 0.074], Neopterin (nmol/L) [ß: -153.33; 95% CI: -556.58, 249.91; P = 0.452], alpha-1-antitrypsin (mg/mL) [ß: 0.05; 95% CI: -0.15, 0.25; P = 0.627]. Initial L-carnitine (μmol/L) levels (median, interquartile range) for L-carnitine compared with placebo were 54.84 (36.0, 112.9) and 59.74 (45.7, 96.0), whereas levels after intervention were 102.05 (60.9, 182.1) and 105.02 (73.1, 203.7).

Conclusions: Although our study findings suggest that L-carnitine bears no additional effect on SAM, we recommend clinical trials with a longer duration of supplementation, possibly with other combinations of interventions, to investigate further into this topic of interest. This trial was registered at clinicaltrials.gov as NCT05083637.

Nat Commun. 2024 Apr 17;15(1):2910.
doi: 10.1038/s41467-024-45528-0.

Malnutrition enteropathy in Zambian and Zimbabwean children with severe acute malnutrition: A multi-arm randomized phase II trial

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Abstract

Malnutrition underlies almost half of all child deaths globally. Severe Acute Malnutrition (SAM) carries unacceptable mortality, particularly if accompanied by infection or medical complications, including enteropathy. We evaluated four interventions for malnutrition enteropathy in a multi-centre phase II multi-arm trial in Zambia and Zimbabwe and completed in 2021. The purpose of this trial was to identify therapies which could be taken forward into phase III trials. Children of either sex were eligible for inclusion if aged 6-59 months and hospitalised with SAM (using WHO definitions: WLZ <-3, and/or MUAC <11.5 cm, and/or bilateral pedal oedema), with written, informed consent from the primary caregiver. We randomised 125 children hospitalised with complicated SAM to 14 days treatment with (i) bovine colostrum (n = 25), (ii) N-acetyl glucosamine (n = 24), (iii) subcutaneous teduglutide (n = 26), (iv) budesonide (n = 25) or (v) standard care only (n = 25). The primary endpoint was a composite of faecal biomarkers (myeloperoxidase, neopterin, α_1-antitrypsin). Laboratory assessments, but not treatments, were blinded. Per-protocol analysis used ANCOVA, adjusted for baseline biomarker value, sex, oedema, HIV status, diarrhoea, weight-for-length Z-score, and study site, with pre-specified significance of P < 0.10. Of 143 children screened, 125 were randomised. Teduglutide reduced the primary endpoint of biomarkers of mucosal damage (effect size -0.89 (90% CI: -1.69,-0.10) P = 0.07), while colostrum (-0.58 (-1.4, 0.23) P = 0.24), N-acetyl glucosamine (-0.20 (-1.01, 0.60) P = 0.67), and budesonide (-0.50 (-1.33, 0.33) P = 0.32) had no significant effect. All interventions proved safe. This work suggests that treatment of enteropathy may be beneficial in children with complicated malnutrition.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

Br J Nutr. 2024 Apr 14;131(7):1189-1195.
doi: 10.1017/S0007114523002702. Epub 2023 Nov 28.

Effectiveness of locally produced ready-to-use supplementary foods on the prevention of stunting in children aged 6-23 months: a community-based trial from Pakistan

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Abstract

Undernutrition is a major public health problem in developing countries. Around 40·2 % of children are stunted in Pakistan. This longitudinal study aimed to assess the effectiveness of locally produced ready-to-use supplementary foods in the prevention of stunting by detecting change in of children in intervention *v*. control arm against the 2006 WHO growth reference. A community-based non-randomised cluster-controlled trial was conducted from January 2018 to December 2020 in the district of Kurram, Khyber Pakhtunkhwa, Pakistan. A total of 80 clusters (each cluster comprising ≈ 250-300 households) were defined in the catchment population of twelve health facilities. Children aged 6-18 months were recruited *n* 1680. The intervention included a daily ration of 50 g - locally produced ready-to-use-supplementary food (Wawa-Mum). The main outcome of this study was a change in length for age z-score (LAZ) *v*. WHO growth standards. Comparison between the interventions was by *t* test and ANOVA. Cox proportional hazard models were used to assess the association between stunting occurrence and the utilisation of locally produced supplement. Out of the total 1680, fifty-one out of the total 1680, 51·1 out of the total 1680 and 51·1 % (*n* 859) were male. Mean age 13·9 months (sd + 859) were male. Mean age 13·9 months (sd + -4·4). At baseline, 36·9 % (*n* 618) were stunted. In the intervention group, mean LAZ score significantly increased from -1·13(2·2 sd) at baseline to -0·93(1·8 sd) at 6-month follow-up (*P* value 0·01) compared with the control group. The incidence rate of stunting in the intervention arm was 1·3 *v*. 3·4 per person year in the control arm. The control group had a significantly increased likelihood of stunting (Hazard Ratio (HR) 1·7, 95 % CI 1·46, 2·05, *P* value < 0·001) *v*. the intervention group. Locally produced ready-to-use supplementary food is an effective intervention for reducing stunting in children below 2 years of age. This can be provided as part of a malnutrition prevention package to overcome the alarming rates of stunting in Pakistan.

Nutr Rev. 2023 Nov 10;81(12):1501-1524.
doi: 10.1093/nutrit/nuad019.

Optimal timing of introduction of complementary feeding: a systematic review and meta-analysis

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Abstract

Context: The timing of introducing complementary feeding (CF) is crucial because premature or delayed CF can be associated with adverse health outcomes in childhood and adulthood.

Objective: This systematic review aims to evaluate the impact of the timing of CF introduction on health, nutrition, and developmental outcomes among normal-term infants.
Data sources: Electronic databases and trial registries were searched, along with the reference lists of the included studies and relevant systematic reviews.
Data extraction: Two investigators independently extracted data from the included studies on a standardized data-extraction form.
Data analysis: Data were meta-analyzed separately for randomized controlled trials (RCTs) and observational studies on the basis of early introduction of CF (< 3 months, < 4 months, < 6 months of age) or late introduction of CF (> 6 months, > 8 months of age). Evidence was summarized according to GRADE criteria. In total, 268 documents were included in the review, of which 7 were RCTs (from 24 articles) and 217 were observational studies (from 244 articles). Evidence from RCTs did not suggest an impact of early introduction, while low-certainty evidence from observational studies suggested that early introduction of CF (< 6 months) might increase body mass index (BMI) z score and overweight/obesity. Early introduction at < 3 months might increase BMI and odds of lower respiratory tract infection (LRTI), and early introduction at < 4 months might increase height, LRTI, and systolic and diastolic blood pressure (BP). For late introduction of CF, there was a lack of evidence from RCTs, but low-certainty evidence from observational studies suggests that late introduction of CF (> 6 months) might decrease height, BMI, and systolic and diastolic BP and might increase odds of intestinal helminth infection, while late introduction of CF (> 8 months) might increase height-for-age z score.
Conclusion: Insufficient evidence does suggest increased adiposity with early introduction of CF. Hence, the current recommendation of introduction of CF should stand, though more robust studies, especially from low- and middle-income settings, are needed.

PLoS One. 2023 Nov 28;18(11):e0293267.
doi: 10.1371/journal.pone.0293267. eCollection 2023.

Determinants of knowledge, attitude and self-efficacy towards complementary feeding among rural mothers: Baseline data of a cluster-randomized control trial in South West Ethiopia

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Abstract

Background: Complementary feeding (CF) is the period when exclusive breastfeeding ends and the introduction of a wide range of foods while breastfeeding should continue until the child is at least 24 months of age. Sub-optimal complementary feeding practices of infants and young children persist due to different factors, which include knowledge, attitude, and self-efficacy of index mothers. Therefore, this study aimed to assess determinants of knowledge, attitude, and self-efficacy towards complementary feeding among rural mothers with index child in rural Ethiopia.
Methods: A community-based, cross-sectional study was conducted using multistage sampling techniques followed by systematic random sampling techniques. A structured interviewer-administered questionnaire was used. The Chi-square and Fisher's exact probability tests were used to assess the baseline differences in the CF knowledge, attitude, self-efficacy and socio-demographic characteristics of the intervention and control groups. An independent sample t-test was used to determine the mean differences. Multiple linear regression models were fitted to assess the predictors of complementary feeding knowledge,

attitude, and self-efficacy. All tests were two-tailed, and a statistically significant association was considered at a p-value ≤ 0.05.
Results: Overall, 516 mothers were interviewed. 52.5% of the mothers had high complementary feeding (CF) knowledge, whereas only 47.7% and 38.9% had favorable attitude and high self-efficacy, respectively. The socio-demographic characteristics of the intervention and control groups were overall similar. However, there was a significant difference in the child's sex (p = 0.021) and age (p = 0.002). Independent t-tests found no significant difference between the two groups in terms of the mean score of CF knowledge, attitude, and self-efficacy at baseline. Maternal educational status (p = 0.0001), number of ANC visits (p = 0.025), and CF information received (p = 0.011) were significant predictors of CF knowledge. Child sex (p = 0.021) and the number of ANC visits (p = 0.01) were significant predictors of CF attitude. Family size (p = 0.008) and household food security status (p = 0.005) were significant predictors of maternal CF self-efficacy.
Conclusion: Overall, half of the mothers had high knowledge. Whereas maternal attitudes and self-efficacy toward CF were low. Maternal educational status, the number of ANC visits, and the CF information received were predictors of CF knowledge. Likewise, child sex and the number of ANC visits were predictors of CF attitude. Family size and household food security status were predictors of CF self-efficacy. These findings imply that nutrition intervention strategies are mandatory, particularly to enhance maternal knowledge, attitude, and self-efficacy towards optimum complementary feeding.

Public Health Nutr. 2023 Nov 29:1-29.
doi: 10.1017/S1368980023002604. Online ahead of print.

Effects of egg as an early complementary food on growth of 6 to 9-month-old infants: A randomised controlled trial

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Abstract
Objective: To assess the effect of daily egg consumption for six months on linear growth (primary outcome), weight-for-age, weight-for-length, mid-upper arm circumference-for-age, and head circumference-for-age Z-scores, gross motor milestones development, anaemia, and iron status (secondary outcomes) in a low socioeconomic community.
Participants/ setting: Infants aged 6 to 9-months living in peri-urban Jouberton area, in the Matlosana Municipality, South Africa.
Design: A randomised controlled trial with a parallel design was implemented. Eligible infants were randomly allocated to the intervention (n = 250) receiving one egg/day and the control group (n = 250) receiving no intervention. The participants were visited weekly to monitor morbidity and gross motor development, with information on adherence collected for the intervention group. Trained assessors took anthropometric measurements, and a blood sample was collected to assess anaemia and iron status. There was blinding of the anthropometric assessors to the groups during measurements and the statistician during the analysis.
Results: Baseline prevalence of stunting, underweight, wasting, overweight and anaemia was 23.8%, 9.8%, 1.2%, 13.8%, and 29.2%, respectively, and did not differ between groups. Overall, 230 and 216 participants in the intervention and control groups completed the

study, respectively. There was no intervention effect on length-for-age, weight-for-age, weight-for-length Z-scores, gross motor milestone development, anaemia, and iron status. **Conclusions:** Daily egg intake did not affect linear growth, underweight, wasting, motor milestones development, anaemia, and iron status. Other interventions are necessary to understand the effect of animal-source food intake on children's growth and development.

J Nutr. 2024 May 15:S0022-3166(24)00283-9.
doi: 10.1016/j.tjnut.2024.05.006. Online ahead of print.

An Egg Intervention Improves Ponderal But Not Linear Growth Among Infants 6-12 mo of Age in Rural Bangladesh

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Abstract

Background: Animal source foods are rich in multiple nutrients. Regular egg consumption may improve infant growth in low- and middle-income countries.

Objectives: To assess the impact of daily egg consumption on linear growth among 6-2-mo olds in rural Bangladesh.

Methods: We conducted a 2 × 4 factorial cluster-randomized controlled trial allocating clusters (n = 566) to treatment for enteric pathogens or placebo and a daily egg, protein supplement, isocaloric supplement, or control. All arms received nutrition education. Here, we compare the effect of the egg intervention compared with control on linear growth, a prespecified aim of the trial. Infants were enrolled at 3 mo. We measured length and weight at 6 and 12 mo and visited households weekly to distribute eggs and monitor compliance. We used linear regression models to compare 12-mo mean length, weight, and z-scores for length-for-age (LAZ), weight-for-length, and weight-for-age (WAZ), and log-binomial or robust Poisson regression to compare prevalence of stunting, wasting, and underweight between arms. We used generalized estimating equations to account for clustering and adjusted models for baseline measures of outcomes.

Results: We enrolled 3051 infants (n = 283 clusters) across arms, with complete 6 and 12 mo anthropometry data from 1228 infants (n = 142 clusters) in the egg arm and 1109 infants (n = 141 clusters) in the control. At baseline, 18.5%, 6.0%, and 16.4% were stunted, wasted, and underweight, respectively. The intervention did not have a statistically significant effect on mean LAZ (β: 0.05, 95% confidence interval [CI]: -0.01, 0.10] or stunting prevalence (β: 0.98, 95% CI: 0.89, 1.13) at 12 mo. Mean weight (β: 0.07 kg, 95% CI: 0.02, 0.11) and WAZ (β: 0.06, 95% CI: 0.02, 0.11) were significantly higher in the egg compared with control arms.

Conclusions: Provision of a daily egg for 6 mo to infants in rural Bangladesh improved ponderal but not linear growth.

Breastfeeding

Matern Child Nutr. 2024 Mar 7:e13631.
doi: 10.1111/mcn.13631. Online ahead of print.

The relationships between optimal infant feeding practices and child development and attained height at age 2 years and 6-7 years

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Abstract

Limited evidence exists on the long-term effects of early feeding practices on child growth and development. We examined the relationships between infant feeding practices and child height and development at ages 2 and 6-7 years. We studied 885 mother-child dyads from a randomized controlled trial of preconception supplementation in Vietnam. Early initiation of breastfeeding (EIBF), exclusive breastfeeding (EBF), breastfeeding (BF) duration and minimum dietary diversity (MDD) were assessed using World Health Organization (WHO) guidelines. Child development was assessed by the Bayley Scales of Infant Development-III at 2 years and the Wechsler Intelligence Scale for Children® - IV at 6-7 years. Child height-for-age z-score (HAZ) was calculated from child height and age. Multivariable regression and structural equation models were used in analyses that controlled for confounding. EIBF and EBF at 6 months occurred in 52% and 62% of children, respectively. Mean breastfeeding duration was 18 months and 83% achieved MDD at 1 year. EIBF was associated with motor (β = 0.13, 95% confidence interval [CI]: 0.00, 0.28) and cognitive development at 2 years (β = 0.12, 95% CI: -0.01, 0.26), which in turn were positively associated with cognitive development at 6-7 years. EBF was directly associated with development at 6-7 years (β = 0.21, 95% CI:0.08, 0.34) whereas motor and cognitive development at 2 years explained 41%-75% of the relationship between EIBF and development at 6-7 years. HAZ at 2 years also mediated 70% of the association between MDD at 1 year and HAZ at 6-7 years. BF duration was not associated with child development and HAZ. Early infant feeding practices, especially EIBF and EBF, have important long-term implications for optimizing child linear growth and cognition as they begin school.

Int Breastfeed J. 2024 Feb 27;19(1):15.
doi: 10.1186/s13006-024-00621-4.

Prelacteal feeding is not associated with infant size at 3 months in rural Bangladesh: a prospective cohort study

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Abstract

Background: Early and exclusive breastfeeding may reduce neonatal and post-neonatal mortality in low-resource settings. However, prelacteal feeding (PLF), the practice of giving food or liquid before breastfeeding is established, is still a barrier to optimal breastfeeding practices in many South Asian countries. We used a prospective cohort study to assess the

association between feeding non-breastmilk food or liquid in the first three days of life and infant size at 3-5 months of age.
Methods: The analysis used data from 3,332 mother-infant pairs enrolled in a randomized controlled trial in northwestern rural Bangladesh conducted from 2018 to 2019. Trained interviewers visited women in their households during pregnancy to collect sociodemographic data. Project staff were notified of a birth by telephone and interviewers visited the home within approximately three days and three months post-partum. At each visit, interviewers collected data on breastfeeding practices and anthropometric measures. Infant length and weight measurements were used to produce length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WLZ) Z-scores. We used multiple linear regression to assess the association between anthropometric indices and PLF practices, controlling for household wealth, maternal age, weight, education, occupation, and infant age, sex, and neonatal sizes.
Results: The prevalence of PLF was 23%. Compared to infants who did not receive PLF, infants who received PLF may have a higher LAZ (Mean difference (MD) = 0.02 [95% CI: -0.04, 0.08]) score, a lower WLZ (MD=-0.06 [95% CI: -0.15, 0.03]) score, and a lower WAZ (MD=-0.02 [95% CI: -0.08, 0.05]) score at 3-5 months of age, but none of the differences were statistically significant. In the adjusted model, female sex, larger size during the neonatal period, higher maternal education, and wealthier households were associated with larger infant size.
Conclusion: PLF was a common practice in this setting. Although no association between PLF and infant growth was identified, we cannot ignore the potential harm posed by PLF. Future studies could assess infant size at an earlier time point, such as 1-month postpartum, or use longitudinal data to assess more subtle differences in growth trajectories with PLF.

J Matern Fetal Neonatal Med. 2023 Dec;36(1):2185754.
doi: 10.1080/14767058.2023.2185754.
Oral domperidone versus placebo for enhancing exclusive breastfeeding among post-lower segment cesarean section mothers - a double-blind randomized controlled trial
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Abstract
Objective: To assess whether oral domperidone compared to placebo increases the rate of exclusive breastfeeding for 6 months among post-lower segment cesarean section (LSCS) mothers.
Methods: This double-blind Randomized Controlled Trial, conducted in a tertiary care teaching hospital in South India, included 366 post-LSCS mothers with delayed initiation of breastfeeding or with subjective feelings of not having enough milk. They were randomized to two groups - Group **A**: Standard lactation counseling and oral Domperidone and **Group B**: Standard lactation counseling and a placebo. The primary outcome was an exclusive breastfeeding rate at 6 months. Exclusive breastfeeding rates at 7 days and 3 months and serial weight gain of an infant were assessed in both groups.
Results: Exclusive breastfeeding rate at 7 days was statistically significant in the intervention arm. The exclusive breastfeeding rates at 3 months and 6 months were higher in the domperidone arm compared to placebo but not statistically significant.

Conclusion: Oral Domperidone along with effective breastfeeding counseling showed an increasing trend of exclusive breastfeeding rate at 7 days and at six months. Appropriate breastfeeding counseling and postnatal lactation support are important in enhancing exclusive breastfeeding.

BMC Pregnancy Childbirth. 2023 Sep 19;23(1):672.
doi: 10.1186/s12884-023-05982-y.

The effect of midwife-oriented breastfeeding counseling on self-efficacy and performance of adolescent mothers: a clinical trial study

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Abstract

Background: Breastfeeding behaviors are strongly influenced by self-efficacy. This research aimed to determine the effect of breastfeeding counseling based on the Ready Set Baby (RSB) education program on self-efficacy and breastfeeding performance in adolescent mothers.

Methods: In 2022, a parallel randomized clinical trial was carried out in Hamadan city's comprehensive health centers, involving 64 pregnant teenagers. The block randomization method was employed to divide the participants into two groups. The data collection instruments were a demographic characteristics questionnaire, a breastfeeding self-efficacy questionnaire, and the Bristol breastfeeding checklist. Three individual counseling sessions during pregnancy were conducted based on the "RSB" program. The ANCOVA was used for comparing groups. The statistical analyst was blinded to the group assignment.

Results: The study included 64 participants with a mean age of 16.97(1.30) years, data from 60 participants were analyzed. The demographic and clinical characteristics of the two groups were relatively similar ($P > 0.05$). Following the intervention, self-efficacy and breastfeeding performance scores were measured and adjusted for confounding factors. The mean scores for self-efficacy were 116.03(20.64) and 100.02(20.64) ($P < 0.005$), with effect size 0.77 [MD = 16.01 (95% CI: 5.34,26.67)], and the mean scores for breastfeeding performance were 6.30(2.07) and 4.12(2.07) ($P < 0.002$), with effect size 1.05 [MD = 2.18 (95% CI: 1.11,3.24)] in the intervention and control groups, respectively.

Conclusions: The Ready Set Baby education program's breastfeeding counseling for primiparous adolescent pregnant women significantly boosted their self-efficacy and performance in breastfeeding. Given the crucial role of breastfeeding in ensuring the well-being of both mother and child, further research is imperative to identify suitable and impactful interventions that can encourage breastfeeding practices among adolescents.

J Acquir Immune Defic Syndr. 2024 Jan 1;95(1):10-17.
doi: 10.1097/QAI.0000000000003306.

Breastfeeding Among Women Living With HIV in the Era of Lifelong ART: An Observational Multicountry Study in Eastern and Southern Africa

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Abstract

Background: Lifelong antiretroviral treatment (ART) use is recommended for pregnant and breastfeeding (BF) women living with HIV (WLWH) to prevent perinatal HIV transmission and improve maternal health. We address 2 objectives in this analysis: (1) determine timing and factors associated with BF cessation and (2) assess the impact of BF on health of WLWH on ART.

Setting: This multicountry study included 8 sites in Uganda, Malawi, Zimbabwe, and South Africa.

Methods: This was a prospective study of WLWH on lifelong ART. These women initially participated from 2011 to 2016 in a randomized clinical trial (PROMISE) to prevent perinatal HIV transmission and subsequently reenrolled in an observational study (PROMOTE, 2016-2021) to assess ART adherence, safety, and impact.

Results: The PROMOTE cohort included 1987 women on ART. Of them, 752 breastfed and were included in analyses of objective 1; all women were included in analyses of objective 2. The median time to BF cessation varied by country (11.2-19.7 months). Country of residence, age, and health status of women were significantly associated with time to BF cessation (compared with Zimbabwe: Malawi, adjusted hazard ratio [aHR] 0.50, 95% confidence interval [95% CI]: 0.40 to 0.62, P < 0.001; South Africa, aHR 1.49, 95% CI: 1.11 to 2.00, P = 0.008; and Uganda, aHR 1.77, 95% CI: 1.37 to 2.29, P < 0.001). Women who breastfed had lower risk of being "unwell" compared with women who never breastfed (adjusted rate ratio 0.87, 95% CI: 0.81 to 0.95 P = 0.030).

Conclusion: Women on lifelong ART should be encouraged to continue BF with no concern for their health. Time to BF cessation should be monitored for proper counseling in each country.

BMJ Open. 2023 Oct 10;13(10):e073385.
doi: 10.1136/bmjopen-2023-073385.

Evaluating interactive weekly mobile phone text messaging plus motivational interviewing for breastfeeding promotion among women living with HIV, giving normal birth at a primary healthcare facility in South Africa: a feasibility randomised controlled trial

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Abstract

Objectives: We assessed the feasibility of an appropriately powered randomised trial by evaluating whether participants could be recruited and retained, and sought preliminary information on exclusive breastfeeding rates.

Setting: Primary healthcare facility, serving a rural community.

Participants: Women initiating breast feeding within 24 hours of giving birth, on antiretroviral treatment and aged ≥18 years.

Interventions: We randomised mother-infant pairs to receive weekly text messaging encouraging exclusive breast feeding plus in-person individual motivational interviews post partum at weeks 2, 6 and 10, or standard infant feeding counselling.
Outcome measures: The feasibility endpoints included number of participants who consented to participate and number with complete evaluation of infant feeding practices at study visits. Exploratory endpoints included number of participants who exclusively breast fed at 24 weeks post partum and number of participants adhering to study protocol.
Results: Of 123 mothers screened, 52 participants consented for participation. We recruited an average of five participants per month over 11 months. Most participants were unemployed (75%), had some high school education (84%) and had disclosed their HIV status to someone close (88%). About 65% participants completed outcome evaluation at week 10, decreasing to 35% at week 24. Twenty participants had the week 24 visit planned between 20 March and August 2020, during COVID-19 lockdown. Of these, 4 completed the visit telephonically, 16 were lost to follow-up. Exclusive breastfeeding rate remained relatively high across both groups through week 24. The difference in exclusive breastfeeding rates between the intervention and control groups was minimal: rate difference 22.2% (95% CI -20.1% to 64.5%).
Conclusions: With a large eligible target population, recruitment targets could be achieved for a large trial. Strategies to retain participants, such as remote monitoring and in-person follow-up visits, will be essential.

Community nutrition and home gardens

Matern Child Nutr. 2023 Jul;19(3):e13495.
doi: 10.1111/mcn.13495. Epub 2023 Mar 31.

Household animal ownership is associated with infant animal source food consumption in Bangladesh

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Abstract
Context-specific research is needed on the relationship between household animal production and nutrition outcomes to inform programmes intervening in small-scale animal production. We examined associations between household animal/fishpond ownership and animal source food (ASF) consumption among 6- to 12-month-old infants enroled in the control arm of a cluster-randomised controlled trial in rural Bangladesh. We measured ASF consumption using a 7-day food frequency questionnaire at 6, 9 and 12 months and assessed household animal/fishpond ownership at 12 months. We developed negative binomial regression models with random intercepts for infant and cluster, controlling for infant age and sex, maternal age, socioeconomic status and season. Models were stratified by a dichotomised maternal decision-making score. Compared with infants in households without each animal type, those with 4-10 and ≥11 poultry consumed eggs 1.3 (95% confidence interval [CI]: 1.1, 1.6) and 1.6 (95% CI: 1.3, 2.0) times more, respectively; 2-3 and ≥4 dairy-producing animals consumed dairy 1.9 (95% CI: 1.3, 2.7) and 2.0 (95% CI: 1.3, 3.1) times more, respectively; and ≥12 meat-producing animals consumed meat 1.4 (95% CI: 1.0,

1.8) times more. It was unclear whether there was an association between fishpond ownership and fish consumption. Our results did not suggest that maternal decision-making power was a modifier in the relationship between animal/fishpond ownership and ASF consumption. In this South Asian context, strategies intervening in household animal production may increase infant consumption of eggs, dairy and meat, but not necessarily fish. Research is needed on the role of market access and other dimensions of women's empowerment.

Matern Child Nutr. 2023 Jul;19(3):e13505.
doi: 10.1111/mcn.13505. Epub 2023 Mar 24.

Impact of a Homestead Food Production program on poultry rearing and egg consumption: A cluster-randomized controlled trial in Bangladesh

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Abstract

Women and children in Bangladesh face high levels of micronutrient deficiencies from inadequate diets. We evaluated the impact of a Homestead Food Production (HFP) intervention on poultry production, as a pathway outcome, and women's and children's egg consumption, as secondary outcomes, as part of the Food and Agricultural Approaches to Reducing Malnutrition cluster-randomized trial in Sylhet division, Bangladesh. The 3-year intervention (2015-2018) promoted home gardening, poultry rearing, and nutrition counseling. We randomly allocated 96 clusters to intervention (48 clusters; 1337 women) or control (48 clusters; 1368 women). Children < 3 years old born to participants were enrolled during the trial. We analyzed poultry production indicators, measured annually, and any egg consumption (24-h recall), measured every 2-6 months for women and their children. We conducted intention-to-treat analyses using mixed-effects logistic regression models with repeat measures, with minimal adjustment to increase precision. Poultry ownership increased by 16% points (pp) and egg production by 13 pp in the final intervention year. The intervention doubled women's odds of egg consumption in the final year (Odds Ratio [OR]: 2.31, 95% CI: 1.68-3.18), with positive effects sustained 1-year post-intervention (OR: 1.58, 95% CI: 1.16-2.15). Children's odds of egg consumption were increased in the final year (OR: 3.04, 95% CI: 1.87-4.95). Poultry ownership was associated with women's egg consumption, accounting for 12% of the total intervention effect, but not with children's egg consumption. Our findings demonstrate that an HFP program can have longer-term positive effects on poultry production and women's and children's diets.

Am J Trop Med Hyg. 2023 Aug 14;109(4):945-956.
doi: 10.4269/ajtmh.23-0152. Print 2023 Oct 4.

Effect of a Homestead Food Production Program on the Prevalence of Diarrhea and Acute Respiratory Infection in Children in Sylhet, Bangladesh: A Cluster-Randomized Controlled Trial

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Abstract

Diarrhea and respiratory illness are leading causes of mortality and morbidity among young children. We assessed the impact of a homestead food production intervention on diarrhea and acute respiratory infection (ARI) in children in Bangladesh, secondary outcomes of the Food and Agricultural Approaches to Reducing Malnutrition (FAARM) cluster-randomized trial. The trial enrolled 2,705 married women and their children 3 years or younger in 96 rural settlements (geographic clusters) in Sylhet Division, Bangladesh. The intervention promoted home gardening and poultry rearing alongside child nutrition and health counseling over 3 years (2015-2018). An 8-month food hygiene behavior change component using emotional drivers was delivered beginning in mid-2017. Caregiver-reported diarrhea and symptoms of ARI in the week preceding the survey were recorded every 2 months. We analyzed 32,460 observations of 3,276 children over 4 years and found that 3.9% of children had diarrhea and 3.4% had an ARI in the prior 7 days. There was no overall effect of the intervention on 7-day diarrhea period prevalence (odds ratio [OR], 0.92; 95% CI, 0.71-1.19), diarrhea point prevalence (OR, 1.03; 95% CI, 0.78-1.36), or 7-day ARI period prevalence (OR, 1.18; 95% CI, 0.88-1.60). There was no impact on diarrhea severity or differences in health-seeking behaviors. Our findings suggest that this homestead food production program was insufficient to reduce morbidity symptoms among children in a rural setting. More comprehensive water, sanitation, and hygiene measures, and behavioral recommendations may be needed to achieve impacts on child health.

Am J Trop Med Hyg. 2023 Oct 2;109(5):1166-1176.
doi: 10.4269/ajtmh.23-0153. Print 2023 Nov 1.

Effect of a Homestead Food Production and Food Hygiene Intervention on Biomarkers of Environmental Enteric Dysfunction in Children Younger Than 24 Months in Rural Bangladesh: A Cluster-Randomized Controlled Trial

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Abstract

Poor sanitation and hygiene practices and inadequate diets can contribute to environmental enteric dysfunction (EED). We evaluated the impact of a combined homestead food production and food hygiene intervention on EED biomarkers in young children in rural Bangladesh. The analysis was conducted within the Food and Agricultural Approaches to Reducing Malnutrition (FAARM) cluster-randomized trial in Sylhet, Bangladesh. The FAARM trial enrolled 2,705 married women and their children younger than 3 years of age in 96 settlements (geographic clusters): 48 intervention and 48 control. The 3-year intervention (2015-2018) included training on gardening, poultry rearing, and improved nutrition practices and was supplemented by an 8-month food hygiene behavior change component, implemented from mid-2017. We analyzed data on 574 children age 0 to 24 months with multilevel linear regression. We assessed fecal myeloperoxidase (MPO), neopterin (NEO), and alpha-1-antitrypsin (AAT) as biomarkers of EED, and serum C-reactive protein (CRP) and

alpha-1-acid glycoprotein (AGP) as biomarkers of systemic inflammation, using ELISA. There was no intervention effect on NEO, AAT, CRP, and AGP concentrations, but, surprisingly, MPO levels were increased in children of the intervention group (0.11 log ng/mL; 95% CI, 0.001-0.22). This increase was greater with increasing child age and among intervention households with poultry that were not kept in a shed. A combined homestead food production and food hygiene intervention did not decrease EED in children in our study setting. Small-scale poultry rearing promoted by the intervention might be a risk factor for EED.

Int J Hyg Environ Health. 2023 Nov 18:255:114291.
doi: 10.1016/j.ijheh.2023.114291. Online ahead of print.

Effect of a behaviour change intervention on household food hygiene practices in rural Bangladesh: A cluster-randomised controlled trial

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Abstract

Introduction: Behavioural interventions could improve caregivers' food hygiene practices in low-resource settings. So far, evidence is limited to small-scale and short-term studies, and few have evaluated the long-term maintenance of promoted behaviours. We evaluated the effect of a relatively large-scale behaviour change intervention on medium and long-term maintenance of household food hygiene practices in Bangladesh.

Methods: We analyse a secondary outcome of the Food and Agricultural Approaches to Reducing Malnutrition (FAARM) cluster-randomised trial and its sub-study Food Hygiene to reduce Environmental Enteric Dysfunction (FHEED), conducted in Habiganj district, Sylhet division, Bangladesh. The FAARM trial used a 1:1 parallel arm design and included 2705 women in 96 settlements: 48 intervention and 48 control. Women in the intervention settlements received training in homestead gardening, poultry rearing and nutrition over three years (2015-2018), complemented by an eight-month (mid-2017 to early-2018) behaviour change component on food hygiene using motivational drivers. Nested within the FAARM trial, the FHEED sub-study evaluated several outcomes along the hygiene pathway. For this article, we evaluated household food hygiene behaviours by analysing structured observation data collected in two cross-sectional surveys, four and 16 months after the food hygiene promotion ended, from two independent subsamples of FAARM women with children aged 6-18 months. We assessed intervention effects on food hygiene practices using mixed-effects logistic regression, accounting for clustering. In exploratory analyses, we further assessed behaviour patterns - how often critical food hygiene behaviours were performed individually, in combination and consistently across events.

Results: Based on the analysis of 524 complementary feeding and 800 food preparation events in households from 571 participant women, we found that intervention households practised better food hygiene than controls four months post-intervention, with somewhat smaller differences after 16 months. Overall, the intervention positively affected food hygiene, particularly around child feeding: using soap for handwashing (odds ratio 5·8, 95% CI 2·2-15·2), cleaning feeding utensils (3·8, 1·9-7·7), and cooking fresh/reheating food (1·8, 1·1-2·8). However, the simultaneous practice of several behaviours was rare, occurring in only 10% of feeding events (intervention: 15%; control: 4%), and the practice of safe food hygiene behaviours was inconsistent between events.

Conclusion: Our findings suggest that a motivational behaviour change intervention encouraged caregivers to maintain certain safe food hygiene practices in a rural setting. However, substantial physical changes in the household environment are likely needed to make these behaviours habitual.

Lancet Planet Health. 2023 Jul;7(7):e558-e569.
doi: 10.1016/S2542-5196(23)00125-0.

Women's empowerment, production choices, and crop diversity in Burkina Faso, India, Malawi, and Tanzania: a secondary analysis of cross-sectional data

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Abstract

Background: Bolstering farm-level crop diversity is one strategy to strengthen food system resilience and achieve global food security. Women who live in rural areas play an essential role in food production; therefore, we aimed to assess the associations between women's empowerment and crop diversity.

Methods: In this secondary analysis of cross-sectional data, we used data from four cluster-randomised controlled trials done in Burkina Faso, India, Malawi, and Tanzania. We assessed women's empowerment using indicators from the Women's Empowerment in Agriculture Index. Farm-level crop diversity measures were the number of food crops grown, number of food groups grown, and if nutrient-dense crops were grown. We used a two-stage modelling approach. First, we analysed covariate-adjusted country-specific associations between women's empowerment and crop diversity indicators using multivariable generalised linear models. Second, we pooled country-specific associations using random-effects models.

Findings: The final analytic sample included 1735 women from Burkina Faso, 4450 women from India, 547 women from Malawi, and 574 women from Tanzania. Across all countries, compared with households in which women provided input into fewer productive decisions, households of women with greater input into productive decisions produced more food crops (mean difference 0·36 [95% CI 0·16-0·55]), a higher number of food groups (mean difference 0·16 [0·06-0·25]), and more nutrient-dense crops (percentage point difference 3 [95% CI 3-4]). Across all countries, each additional community group a woman actively participated in was associated with cultivating a higher number of food crops (mean difference 0·20 [0·04-0·35]) and a higher number of food groups (mean difference 0·11 [0·03-0·18]), but not more nutrient-dense crops. In pooled associations from Burkina Faso and India, asset ownership was associated with cultivating a higher number of food crops (mean difference 0·08 [0·04-0·12]) and a higher number of food groups (mean difference 0·05 [0·04-0·07]), but not more nutrient-dense crops.

Interpretation: Greater women's empowerment was associated with higher farm-level crop diversity among low-income agricultural households, suggesting that it could help enhance efforts to strengthen food system resilience.

PLoS One. 2023 Oct 20;18(10):e0288150.
doi: 10.1371/journal.pone.0288150. eCollection 2023.

Effects of nutrition education and home gardening interventions on feto-maternal outcomes among pregnant women in Jimma Zone, Southwest Ethiopia: A cluster randomized controlled trial

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Abstract

Background: Although pro-dietary practices and associated malnutrition are modifiable risk factors, they have a significant effect on maternal and neonatal health outcomes. Therefore, this study aimed to assess the effect of nutritional education and home gardening promotion on feto-maternal outcomes among pregnant women.

Methods: A three parallel arms community-based cluster randomized controlled trial was carried out in Jimma Zone, Southwest Ethiopia from August 2020 to January 2021. Eighteen selected clusters were randomly assigned into three arms: husband (pregnant woman with her husband), peers (pregnant woman with her peers), and the controls. A total of 348 pregnant women were recruited in a 1:1:1 allocation ratio to the study arms at the baseline and 336 attended the end-line survey. Three nutrition education sessions and four varieties of vegetable seeds were provided for women in the intervention arms (husband and peers) and only routine nutrition education for the controls. Data were collected using a pretested interviewer-administered structured questionnaire. Generalized estimating equation analysis (GEE) and one-way analysis of variance (ANOVA) and Kruskal Wallis test were used to evaluate the effect of the interventions. The intervention effect estimates were obtained through a difference-in-differences approach.

Result: In the final model, neonates born to women in the husband group were 232 g heavier than those in the control groups (β = 232, 95%CI: 228.00, 236.27. Similarly, women in the husband group had a 0.45 g/dl greater hemoglobin level than the control groups (β = 0.45, 95% CI: 36.48, 54.40). Likewise, a minimum diet diversity score was higher in the husband group as compared to the controls (β = 0.87 95% CI: (0.56, 1.18).

Conclusions: Therefore, nutrition education and home gardening interventions resulted in a significant positive effect on the mean birth weight and maternal hemoglobin level among the intervention groups. The findings imply the need for enhancing such interventions to improve feto-maternal outcomes.

Matern Child Nutr. 2024 Jan;20(1):e13593.
doi: 10.1111/mcn.13593. Epub 2023 Dec 2.

A cluster randomized controlled trial of a community-based initiative to reduce stunting in rural Indonesia

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Abstract

We evaluate the impacts of a $120 million project in Indonesia conducted between 2014 and 2018 that sought to reduce stunting through a combination of (1) community-driven development grants targeted at health and education outcomes, (2) training for health providers on infant and young child feeding and growth monitoring and (3) training for sanitarians on a local variation of community-led total sanitation. This cluster randomized controlled trial involved 95 treatment and 95 control subdistricts across South Sumatra,

West Kalimantan, and Central Kalimantan provinces. Overall, we find no significant impacts on stunting, the study's primary outcome measure (0.5 pp; 95% confidence interval [CI]: -3.0 to 4.1 percentage points [pp]), or other longer-term undernutrition outcomes about 1 year after the end of the project. The project had a modest impact on some secondary, more proximal outcomes related to maternal and child nutrition, including the percentage of mothers consuming the recommended number of iron-folic acid pills during pregnancy (8.7 pp; 95% CI: 4.1-13.3 pp), 0-5-month-olds being exclusively breastfed (8.7 pp; 95% CI: 1.8-15.6 pp) and 6-23-month-olds receiving the number of recommended meals per day (8.5 pp; 95% CI: 3.8-13.2 pp). However, there were no significant impacts on other proximal outcomes like the number of pre-natal and post-natal checkups, child dietary diversity, child vitamin A receipt or the incidence of child diarrhoea. Our findings highlight that successfully implementing an integrated package of interventions to reduce child stunting may be challenging in practice. Project design needs to consider implementation reality along with best practice-for example, by piloting the synchronous implementation of multifaceted interventions or phasing them in more gradually over a longer timeframe.

Obesity

Pediatr Obes. 2023 Oct;18(10):e13068.
doi: 10.1111/ijpo.13068. Epub 2023 Jul 31.

Longitudinal associations between diet quality, sedentary behaviours and physical activity and risk of overweight and obesity in preschool children: The ToyBox-study

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Abstract

Background: Lifestyle behaviours related to diet and physical activity are associated with increased risk of obesity and evidence suggests that associations might be stronger when a synergetic effect is examined.

Objective: To examine the cross-sectional and longitudinal associations between diet, screen time (ST) and step recommendations and risk of overweight and obesity in European preschoolers participating in the ToyBox-study.

Methods: In this cluster-randomized clinical trial, 718 children (51.4% boys) from six European countries participated. Parents filled out questionnaires with information on socio-demographic status, step recommendations and ST.

Results: Longitudinal results indicate that participants having a low Diet Quality Index (DQI), not meeting ST and step recommendations at T0 and T1 had higher odds of having overweight/obesity at T1 (odds ratio [OR] = 1.116; 95% confidence interval [CI] = 1.104-2.562) than those children having a high DQI and meeting ST and step recommendations at T0 and T1. Similarly, participants having a high DQI, but not meeting ST and step recommendations at T0 and T1 had increased odds of having overweight/obesity (OR = 2.515; 95% CI = 1.171-3.021).

Conclusions: The proportion of participants having a low DQI, not adhering to both step and ST recommendations was very high, and it was associated with a higher probability of having overweight and obesity.

Medicine (Baltimore). 2023 Oct 6;102(40):e34943.
doi: 10.1097/MD.0000000000034943.

Does acupuncture improve the metabolic outcomes of obese/overweight children and adolescents?: A systematic review and meta-analysis

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Abstract

Background: Although increasing evidence has revealed the efficacy of acupuncture in obesity/overweight, actual improvement in metabolism in children and adolescents is unclear. Therefore, we conducted a meta-analysis to evaluate this correlation.

Methods: A comprehensive search was conducted using multiple databases, including Medline, Cochrane, Embase, Web of Science, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Scientific Journal Database, and Wan-fang Data, to identify relevant randomized controlled trials published before February 1, 2023. General information and data for the descriptive and quantitative analyses were extracted.

Results: Fifteen randomized controlled trials of 1288 obese/overweight children and teenagers were included. All the trials were conducted in China and South Korea. Regarding quality assessment, no other significant risk of bias was found. The acupuncture groups were more likely to have improved metabolic indicators of obesity/overweight than the control groups, in terms of body mass index (standardized mean difference [SMD] = -0.45, 95% confidence interval [CI]: -0.69 to -0.21, I2 = 71.4%), body weight (SMD = -0.48, 95% CI: -0.92 to -0.05, I2 = 84.9%), and serum leptin (SMD = -0.34, 95% CI: -0.58 to -0.10, I2 = 91.8%). The subgroup analysis showed that for body mass index, the results were consistent regardless of the intervention duration, body acupuncture or auricular acupuncture combined with other interventions.

Conclusion: Our results suggest that acupuncture is effective in improving metabolic outcomes of obese/overweight children and adolescents. Owing to the limited number of trials included in this study, the results should be interpreted with caution.

Medicina (Kaunas). 2023 Oct 7;59(10):1785.
doi: 10.3390/medicina59101785.

Metabolomic Phenotype of Hepatic Steatosis and Fibrosis in Mexican Children Living with Obesity

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Abstract

Background and Objectives: Metabolic-dysfunction-associated steatotic liver disease or MASLD is the main cause of chronic liver diseases in children, and it is estimated to affect 35% of children living with obesity. This study aimed to identify metabolic phenotypes associated with two advanced stages of MASLD (hepatic steatosis and hepatic steatosis plus

fibrosis) in Mexican children with obesity. *Materials and Methods*: This is a cross-sectional analysis derived from a randomized clinical trial conducted in children and adolescents with obesity aged 8 to 16 years. Anthropometric and biochemical data were measured, and targeted metabolomic analyses were carried out using mass spectrometry. Liver steatosis and fibrosis were estimated using transient elastography (Fibroscan® Echosens, Paris, France). Three groups were studied: a non-MASLD group, an MASLD group, and a group for MASLD + fibrosis. A partial least squares discriminant analysis (PLS-DA) was performed to identify the discrimination between the study groups and to visualize the differences between their heatmaps; also, Variable Importance Projection (VIP) plots were graphed. A VIP score of >1.5 was considered to establish the importance of metabolites and biochemical parameters that characterized each group. Logistic regression models were constructed considering VIP scores of >1.5, and the receiver operating characteristic (ROC) curves were estimated to evaluate different combinations of variables. *Results*: The metabolic MASLD phenotype was associated with increased concentrations of ALT and decreased arginine, glycine, and acylcarnitine (AC) AC5:1, while MASLD + fibrosis, an advanced stage of MASLD, was associated with a phenotype characterized by increased concentrations of ALT, proline, and alanine and a decreased Matsuda Index. *Conclusions*: The metabolic MASLD phenotype changes as this metabolic dysfunction progresses. Understanding metabolic disturbances in MASLD would allow for early identification and the development of intervention strategies focused on limiting the progression of liver damage in children and adolescents.

Oncology

Pediatr Blood Cancer. 2023 Aug;70(8):e30444.
doi: 10.1002/pbc.30444. Epub 2023 May 27.

A single-blinded, randomized controlled trial of standard versus higher dose carboplatin-based intravenous chemotherapy for group D and E retinoblastoma

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Abstract

Background: Access to intra-arterial chemotherapy for retinoblastoma in low- and middle-income countries (LMICs) is limited. There is a need to optimize the efficacy of systemic chemotherapy for advanced intraocular retinoblastoma, particularly in LMICs. The aim was to compare the efficacy of standard versus higher dose carboplatin-based intravenous chemotherapy for group D and E retinoblastoma.

Methods: The single-center, single-blinded, randomized study was conducted during 2019-2021. Patients with newly diagnosed group D or E retinoblastoma were randomized to receive vincristine, etoposide, and standard versus higher dose (<36 months: 18.6 vs. 28 mg/kg; ≥36 months: 560 vs. 840 mg/m^2) carboplatin. Examination under anesthesia and ultrasonography was performed at diagnosis and following three cycles of chemotherapy. Group E eyes with poor likelihood of globe/vision salvage at diagnosis were excluded.

Results: Thirty-two eyes of 30 patients were analyzed: 17 group D and 15 group E eyes. The tumor response to chemotherapy with regards to regression pattern (p = .72), tumor

shrinkage (diameter: p = .11, height: p = .96), subretinal seeds (p = .91), and vitreous seeds (p = .9) were comparable between the two treatment arms. The globe salvage (group D [82% vs. 67%; p = .58]; group E [12.5% vs. 29%; p = .57]) and salvage of meaningful vision (group D [100% vs. 75%; p = .13]; group E [100% vs. 50%; p = .48]) were comparable between standard and higher dose arms. No excess treatment-related toxicity was observed in the higher dose arm.
Conclusions: Higher dose carboplatin-based intravenous chemotherapy did not result in superior globe or vision salvage in group D or E retinoblastoma.

Lancet Child Adolesc Health. 2023 Sep;7(9):613-620.
doi: 10.1016/S2352-4642(23)00141-4. Epub 2023 Jul 31.

Intravenous versus super-selected intra-arterial chemotherapy in children with advanced unilateral retinoblastoma: an open-label, multicentre, randomised trial

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Abstract

Background: Super-selected intra-arterial chemotherapy has increasingly been used as conservative management for retinoblastoma during the past decade. However, the absence of evidence from randomised controlled trials engendered controversy in the administration route of chemotherapy. We aimed to assess the efficacy and safety of intra-arterial chemotherapy compared with intravenous chemotherapy.
Methods: This open-label, multicentre, randomised trial was done at six hospitals in China. Patients with new-onset unilateral group D or E retinoblastoma (poorly defined, large, or very large tumours, according to the International Intraocular Retinoblastoma Classification) without high-risk clinical factors were included. Patients were randomly assigned (1:1) to receive intra-arterial chemotherapy (injections of 0·5 mg/kg [or depending on age] melphalan with 20 mg carboplatin [first and third cycles] or with 1 mg topotecan [second and fourth cycles]) or intravenous chemotherapy (0·05 mg/kg [or 1·5 mg/m^2] vincristine, 5 mg/kg [or 150 mg/m^2] etoposide, and 18·6 mg/kg [or 560 mg/m^2] carboplatin for six cycles). After intra-arterial chemotherapy, patients received a subcutaneous injection of 0·1 mL nadroparin calcium twice at a 12 h interval. Both intra-arterial and intravenous chemotherapy cycles were completed every 4 weeks. No masking was done, except of independent statisticians, who were masked to the allocation information. The primary outcome was 2-year progression-free globe salvage rate, defined as the time from randomisation to tumour progression or enucleation, whichever occurred first, and was analysed by intention to treat. We also recorded predefined safety outcomes (myelosuppression and ophthalmic arterial stenosis or occlusion) and severe adverse events likely to be related to study treatment. The study is registered with the Chinese Clinical Trial Registry, ChiCTR-IPR-15006469, and is complete.
Findings: Between June 1, 2015, and June 1, 2018, 234 patients with newly diagnosed retinoblastoma were screened and 143 eligible patients (median age 23·6 months [IQR 14·0-31·9]) were enrolled and randomly assigned to the intra-arterial chemotherapy group (n=72) or the intravenous chemotherapy group (n=71). At a median follow-up of 35·8 months (IQR 28·4-43·0), the 2-year progression-free globe salvage rate was 53% (38 of 72 patients) in the

intra-arterial chemotherapy group and 27% (19 of 71 patients) in the intravenous chemotherapy group (risk ratio 1·97, 95% CI 1·27-3·07, p=0·0020). Myelosuppression was less common in the intra-arterial chemotherapy group than in the intravenous chemotherapy group (37 [51%] of 72 patients vs 50 [70%] of 71 patients; 0·73, 95% CI 0·56-0·96, p=0·021) and less severe (p_{trend}=0·0070). In the intra-arterial chemotherapy group, two (3%) of 72 patients had ophthalmic artery occlusion and 13 (18%) patients had ophthalmic artery stenosis. **Interpretation:** Our findings show that intra-arterial chemotherapy could significantly improve the globe salvage rate in children with advanced unilateral retinoblastoma compared with intravenous chemotherapy, with mild systemic complications and no difference in overall survival rate. Intra-arterial chemotherapy could be an acceptable first-line treatment in children with advanced unilateral retinoblastoma.

J Pediatr Hematol Oncol. 2023 Oct 1;45(7):361-369.
doi: 10.1097/MPH.0000000000002737. Epub 2023 Aug 3.

Efficacy and Safety of Olanzapine for the Prevention of Chemotherapy-induced Nausea and Vomiting in Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) remain the most distressing event in patients receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). This meta-analysis was conducted to evaluate the efficacy and safety of olanzapine containing regimen in preventing CINV in children on HEC and MEC. We searched PubMed, Embase, and Cochrane central register of controlled trials electronic databases to identify randomized clinical trials that compared 2 groups who either got olanzapine (olanzapine group) or placebo/no olanzapine (control group) for the prevention of CINV in children. The primary outcome was to determine the efficacy of olanzapine (complete response). The secondary outcomes were nausea control, the need for rescue medications, and adverse events of olanzapine. Three randomized clinical trials (n=394 patients) were included in this meta-analysis (olanzapine group, n=194, and placebo/control group, n=200). The pooled analysis of this meta-analysis found that olanzapine had a higher complete response in all phases of emesis in the HEC group and only in the acute phase in HEC/MEC groups compared with the control group. Olanzapine had higher nausea control in all phases of HEC but no nausea control in HEC/MEC. Olanzapine also reduced the need for rescue medications. A significant number of patients in the olanzapine group experienced somnolence (grades 1 and 2), but none of the participants discontinued the study due to side effects. In conclusion, this meta-analysis showed that olanzapine significantly prevented CINV in HEC. There was also a lesser need for rescue medications in the olanzapine group. Somnolence was higher in the olanzapine group, but it was clinically insignificant.

Am J Blood Res. 2023 Oct 15;13(5):152-161.
eCollection 2023.

A randomized controlled trial to explore the safety and efficacy of irradiated buffy-coat granulocytes in pediatric patients with febrile neutropenia

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Abstract

Background: Transfusion of granulocytes obtained by apheresis is beneficial in febrile neutropenia (FN) but expensive and time-consuming. Buffy-coat-derived granulocytes could be an alternative. We studied the efficacy and safety of the administration of irradiated buffy-coat-derived granulocytes along with the standard of care in pediatric high-risk (HR) FN.

Methods: Sixty children ≤18 years with malignancy and chemotherapy-induced HR FN were randomized to either the granulocyte transfusion (GT) arm which received irradiated buffy-coat derived granulocyte transfusion along with the standard treatment or the standard treatment (ST) arm.

Results: Baseline characteristics, day-to-defervescence, antibiotic duration, hospital stay, and mortality were comparable between the groups. A significant difference was seen in days to achieve absolute neutrophil count (ANC) >500/mm^3 in the 2 groups: 4.5 days (3-6.5) in the GT arm v/s 8 days (4-11) in the ST arm (P=0.01).

Conclusion: Buffy-coat-derived granulocyte transfusion was safe and led to early hematological recovery but was not associated with survival benefits. Future studies with earlier initiation in the intended dose could be undertaken to generate more evidence.

BMC Nutr. 2024 Jun 19;10(1):89.
doi: 10.1186/s40795-024-00892-4.

Nutritional interventions in children with acute lymphoblastic leukemia undergoing antineoplastic treatment: a systematic review

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Abstract

Background: A compromised nutritional status jeopardizes a positive prognosis in acute lymphoblastic leukemia (ALL) patients. In low- and middle-income countries, ~ 50% of children with ALL are malnourished at diagnosis time, and undergoing antineoplastic treatment increases the risk of depleting their nutrient stores. Nutrition interventions are implemented in patients with cancer related malnutrition. We aimed to evaluate the effect of nutrition interventions in children diagnosed with ALL under treatment.

Methods: Using a predefined protocol, we searched for published or unpublished randomized controlled trials in: Cochrane CENTRAL, MEDLINE, EMBASE, LILACS, and SciELO, and conducted complementary searches. Studies where at least 50% of participants had an ALL diagnosis in children ≤ 18 years, active antineoplastic treatment, and a nutrition intervention were included. Study selection and data extraction were conducted independently by three reviewers, and assessment of the risk of bias by two reviewers. Results were synthesized in both tabular format and narratively.

Results: Twenty-five studies (out of 4097 records) satisfied the inclusion requirements. There was a high risk of bias in eighteen studies. Interventions analyzed were classified by compound/food (n = 14), micronutrient (n = 8), and nutritional support (n = 3). Within each group the interventions and components (dose and time) tested were heterogeneous. In

relation to our primary outcomes, none of the studies reported fat-free mass as an outcome. Inflammatory and metabolic markers related to nutritional status and anthropometric measurements were reported in many studies but varied greatly across the studies. For our secondary outcomes, fat mass or total body water were not reported as an outcome in any of the studies. However, some different adverse events were reported in some studies.
Conclusions: This review highlights the need to conduct high-quality randomized controlled trials for nutrition interventions in children with ALL, based on their limited number and heterogeneous outcomes.

Ophthalmology and optometry

Parasit Vectors. 2024 Mar 15;17(1):137.
doi: 10.1186/s13071-023-06087-3.
Onchocerca volvulus microfilariae in the anterior chambers of the eye and ocular adverse events after a single dose of 8 mg moxidectin or 150 µg/kg ivermectin: results of a randomized double-blind Phase 3 trial in the Democratic Republic of the Congo, Ghana and Liberia
Eric M Kanza[#1,2], Amos Nyathirombo[#3,4], Jemmah P Larbelee[#5,6], Nicholas O Opoku[7,8], Didier K Bakajika[3,9], Hayford M Howard[5,10], Germain L Mambandu[3,11], Maurice M Nigo[3,12], Deogratias Ucima Wonyarossi[3], Françoise Ngave[3], Kambale Kasonia Kennedy[1,13], Kambale Kataliko[3,14], Kpehe M Bolay[5,15], Simon K Attah[7,16,17], George Olipoh[7,18], Sampson Asare[7,19], Mupenzi Mumbere[1,20], Michel Vaillant[21], Christine M Halleux[22], Annette C Kuesel[23]
Abstract
Background: After ivermectin became available, diethylcarbamazine (DEC) use was discontinued because of severe adverse reactions, including ocular reactions, in individuals with high Onchocerca volvulus microfilaridermia (microfilariae/mg skin, SmfD). Assuming long-term ivermectin use led to < 5 SmfD with little or no eye involvement, DEC + ivermectin + albendazole treatment a few months after ivermectin was proposed. In 2018, the US FDA approved moxidectin for treatment of O. volvulus infection. The Phase 3 study evaluated SmfD, microfilariae in the anterior chamber (mfAC) and adverse events (AEs) in ivermectin-naïve individuals with ≥ 10 SmfD after 8 mg moxidectin (n = 978) or 150 µg/kg ivermectin (n = 494) treatment.
Methods: We analyzed the data from 1463 participants with both eyes evaluated using six (0, 1-5, 6-10, 11-20, 21-40, > 40) mfAC and three pre-treatment (< 20, 20 to < 50, ≥ 50) and post-treatment (0, > 0-5, > 5) SmfD categories. A linear mixed model evaluated factors and covariates impacting mfAC levels. Ocular AEs were summarized by type and start post-treatment. Logistic models evaluated factors and covariates impacting the risk for ocular AEs.
Results: Moxidectin and ivermectin had the same effect on mfAC levels. These increased from pre-treatment to Day 4 and Month 1 in 20% and 16% of participants, respectively. Six and 12 months post-treatment, mfAC were detected in ≈5% and ≈3% of participants, respectively. Ocular Mazzotti reactions occurred in 12.4% of moxidectin- and 10.2% of ivermectin-treated participants without difference in type or severity. The risk for ≥ 1 ocular Mazzotti reaction increased for women (OR 1.537, 95% CI 1.096-2.157) and with mfAC levels

pre- and 4 days post-treatment (OR 0: > 10 mfAC 2.704, 95% CI 1.27-5.749 and 1.619, 95% CI 0.80-3.280, respectively).
Conclusions: The impact of SmfD and mfAC levels before and early after treatment on ocular AEs needs to be better understood before making decisions on the risk-benefit of strategies including DEC. Such decisions should take into account interindividual variability in SmfD, mfAC levels and treatment response and risks to even a small percentage of individuals.

Eye (Lond). 2024 Apr;38(5):945-950.
doi: 10.1038/s41433-023-02809-0. Epub 2023 Nov 10.

Risk factors for corneal abrasions in Nepal: a community-based study

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Abstract
Background: South Asia is experiencing rapid urbanization, which may be changing the risk factor profile for ocular trauma. The objective of this study was to compare risk factors for traumatic corneal abrasions in rural versus urban Nepal, and to assess if any risk factors were associated with a poor outcome.
Methods: In a prospective, cross-sectional, community-based study performed as part of a cluster-randomized trial, community health workers from Nepal were trained to diagnose and treat traumatic corneal abrasions. Participants with an abrasion were invited to complete a risk factor survey. The main exposure variable was the object of eye injury, stratified by rural-urban residence. The main outcome measure was a lack of corneal healing after a three-day course of antimicrobials.
Results: Of 3657 participants diagnosed with a corneal abrasion, 2265 completed a survey. Eye trauma occurred most frequently during agricultural activities. The most common object of injury was vegetative matter, accounting for approximately 40% of injuries in rural, peri-urban, and urban communities. Wood injuries were more common in rural communities (24%) compared with urban or peri-urban communities (13%). Eye injury from an animal was more likely to result in a non-healing corneal abrasion after 3 days of treatment compared with other types of trauma (prevalence ratio 2.59, 95%CI 1.16-5.76).
Conclusions: Health promotion activities for prevention of corneal ulcers in Nepal should focus on agricultural trauma in both rural and urban areas. Community members experiencing eye trauma from an animal may benefit from early referral to an eye clinic.

Retinopathy of prematurity

Eye (Lond). 2023 Jul;37(10):2130-2134.
doi: 10.1038/s41433-022-02302-0. Epub 2022 Nov 3.

Role of fluorescein angiography guided laser treatment in aggressive retinopathy of prematurity

Prashant Kumar[1], Parijat Chandra[2], Ramesh Agarwal[3], Rohan Chawla[1], Rajpal Vohra[1]

Abstract

Purpose: To compare disease regression in cases of Fluorescein Angiography (FA) guided laser vs. conventional laser treatment in infants with Aggressive retinopathy of prematurity (AROP).

Methods: 60 eyes of 30 infants of AROP were randomized into two groups. In both the group's FA was done once. Montage of the fundus, FA images was created and the vascular area, avascular areas, and skip areas after laser treatment were demarcated and measured. In group 1, FA-guided laser treatment was done whereas in group 2 they were lasered without seeing FA. Infants were followed up every week to look for skip areas and disease regression.

Results: The mean vascular retinal area in group 1 and group 2 on fundus images was 302.7 sq. mm and 245.8 sq. mm respectively, while the same on FA was 285.2 sq. mm and 221.3 sq. mm respectively, suggesting overestimation of the vascular area on fundus imaging compared to FA which enabled more objective estimation of avascular loop areas. Retinal skip areas in group 1 and group 2 after 1st laser were 18.7 sq. mm and 73.1 sq. mm respectively ($P = 0.001$), after 2nd laser was 3.7 sq. mm and 19.2 sq. mm ($P = 0.003$), which suggests FA-guided laser led to significantly fewer skip areas. Infants had regression in 4.1 ± 0.3 wks and 4.2 ± 0.4 wks in groups 1 and 2, respectively.

Conclusion: FA-guided laser ensured lesser skip areas and more complete laser treatment, though regression was similar in both groups.

Indian J Ophthalmol. 2023 Nov;71(11):3460-3464.
doi: 10.4103/IJO.IJO_2992_22.

Role of additional posterior barrage laser in type 1 zone 2 retinopathy of prematurity: A randomized trial

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Abstract

Purpose: The efficacy of additional barrage laser posterior to ridge in advanced stage 3 or stage 4 retinopathy of prematurity (ROP) is established, but its role in early stages is not defined. The objective was to study the efficacy of additional posterior barrage laser in type I zone 2 disease.

Methods: In a randomized trial, patients with type I zone 2 ROP were recruited between February 2016 and May 2017. One eye of each baby was randomized into study and control groups, respectively. Laser photocoagulation anterior to ridge was given in the control group, and additional posterior barrage laser was performed in the study group. The outcome measures were time to complete ridge regression and final cycloplegic refraction at 3 months post-laser.

Results: Forty patients (40 eyes per group) completed the required follow-up. The mean birth weight and gestational age were 1357 ± 338 g and 29.72 ± 2.57 weeks, respectively. The mean post-conceptional age during laser was 36.67 ± 3.23 weeks. The number of eyes achieving ridge regression in control and study groups was 8/40 (20%) and 27/40 (67%) at 2

weeks (P = 0.001) and 39/40 (97%) and 40/40 (100%) at 4 weeks (P = 0.4). The mean time to complete ridge regression was 3.74 ± 1.17 weeks and 2.62 ± 0.91 weeks in control and study groups, respectively (P < 0.001). The mean spherical equivalent at 12 weeks in control and study groups was -1.9 ± 2.3 Diopters and -2.4 ± 2.6 Diopters, respectively (P = 0.41).
Conclusions: Additional posterior barrage laser leads to significantly faster regression of type 1 zone 2 ROP without increasing induced myopia and thereby might be a useful adjunct to conventional treatment in selected cases.

Eye (Lond). 2023 Oct 18.
doi: 10.1038/s41433-023-02796-2. Online ahead of print.

Efficacy comparison of 21 interventions to prevent retinopathy of prematurity: a Bayesian network meta-analysis of randomized controlled trials

Miao Zhou [#1,2], Pei-Chen Duan [#1], Dan-Lin Li [1], Jing-Hong Liang [3], Gang Liang [4], Hua Xu [5], Chen-Wei Pan [6]

Abstract
Background: The objective of this study was to evaluate the comparative efficacy of current interventions for the prevention of retinopathy of prematurity (ROP) in premature infants.
Methods: A network meta-analysis (NMA) was performed. We searched PubMed, Web of Science, Scopus, Embase, and the Cochrane Library for relevant studies from their inception to May 5, 2022. Publications were eligible for our study if they were randomized controlled trials (RCTs) involving preterm infants at <37 weeks of gestational age and reported the incidence of any-stage ROP treated with the interventions of interest. The overall effect was pooled using the random effects model.
Results: We identified 106 RCTs (involving 23894 participants). This NMA showed that vitamin A supplementation markedly reduced the incidence of ROP, in comparison with placebo (odds ratio [OR] = 0.59, 95% credible interval [95% CrI] 0.33, 0.85), fish oil-based lipid emulsion (OR = 0.57, 95% CrI 0.24, 0.90), early erythropoietin (OR = 0.51, 95% CrI 0.34, 0.98), probiotics (OR = 0.48, 95% CrI 0.32, 0.97), and human milk (OR = 0.50, 95% CrI 0.21, 0.78). Vitamin A supplementation has the highest probability of being the best option for reducing the ROP risk compared with the other 20 interventions based on its surface under the cumulative ranking curve (SUCRA) value (SUCRA = 92.50%, 95% CrI 0.71, 1.00).
Conclusions: Our findings suggest that among 21 interventions, vitamin A supplementation might be the best method of preventing ROP. This NMA offers an important resource for further efforts to develop preventive strategies for ROP.

Trachoma

Oral health / dentistry

Int J Paediatr Dent. 2024 May;34(3):229-245.

doi: 10.1111/ipd.13125. Epub 2023 Oct 15.

Effectiveness of various methods of educating children and adolescents for the maintenance of oral health: A systematic review of randomized controlled trials

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Abstract

Background: School-based oral health education has emerged as one of the most effective methods to instill a positive attitude toward oral health in children.

Aim: This systematic review (SR) aimed to assess the effectiveness of different methods of oral health education in children and adolescents.

Design: Systematic search was conducted in PubMed, Cochrane, Web of Science, LILACS, Scopus, and EMBASE on January 29, 2023. Review included only randomized controlled trials (RCTs), and their risk of bias (ROB) was assessed by Cochrane RoB-2. Data were extracted and analyzed by expert group. The GRADE approach was used to assess the quality of evidence for each outcome. Every step was conducted in duplicate, and disagreements were resolved by consulting the third reviewer.

Results: The SR included 10 RCTs with majority showing a high ROB. They included 12 methods with the commonest being the use of leaflets/flash cards. Most interventions were effective in improving oral hygiene, gingival health, and knowledge except conventional teaching methods, lecture by using PowerPoint by dentists, and e-learning interventions. The grade of evidence in the majority of outcomes was found to be low or very low.

Conclusion: Interventions using the interactive methods such as games, motivational-experiential learning, and audiovisual methods were found to be more effective than controls and other interventions. Variabilities in study methods and outcome variables must be addressed in the future.

J Dent Anesth Pain Med. 2024 Feb;24(1):37-45.
doi: 10.17245/jdapm.2024.24.1.37. Epub 2024 Feb 1.

Effect of cryoanesthesia and sweet tasting solution in reducing injection pain in pediatric patients aged 7-10 years: a randomized controlled trial

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Abstract

Background: The delivery of profound local anesthetics helps children receive successful treatment by reducing fear, anxiety, and discomfort during dental procedures. Local anesthetic injections are the most anticipated stimuli in dental surgery. Children's perceptions of pain can be altered by applying cryotherapy to precool the oral mucosa or by diverting their minds through taste distractions before administering local anesthetic injections. This study aimed to evaluate the efficacy of cryoanesthesia and xylitol sweet-tasting solution at the injection site in 7-10-year-old children.

Methods: A total of 42 participants, aged 7-10 years, who underwent dental treatment requiring local anesthesia, were enrolled in the study. The children were randomly divided into three groups. In group I, sterile water was held in the mouth for 2 minutes before anesthetic administration, similar to group II, and in group III, a xylitol sweet-tasting solution was used for 2 minutes before needle insertion. The analysis of pain perception was carried out based on the Visual Analog Scale (VAS) and the Sound, Eyes, and Motor (SEM) scale. For

VAS analysis, a one-way analysis of variance (ANOVA) was performed for intergroup comparison, and a post hoc Tukey test was performed for subgroup analysis. For the categorical SEM scale, the Kruskal-Wallis test followed by the post hoc test was performed for intergroup comparison. Where a P value of <0.05 was considered statistically significant at 95% confidence intervals.
Results: Cryoanesthesia significantly reduced pain scores on VAS (4.21 ± 1.42) when compared to those on VAS with xylitol sweet-tasting solution (5.50 ± 1.40) and that with sterile water (6.14 ± 2.47). Intergroup comparison of the VAS scores among the three groups was performed using one-way ANOVA, which demonstrated statistically significant differences (P value <0.026) on the VAS scale. Intergroup comparison of the SEM scale was performed using the Kruskal-Wallis test, followed by post hoc comparison, which exhibited statistically significant differences (P < 0.007) among the three groups for the SEM scale.
Conclusion: Cryoanesthesia demonstrated higher efficacy in reducing injection pain than that exhibited by the xylitol sweet-tasting solution.

Pain

Poisoning and toxins

Refugee health and humanitarian settings

Child Abuse Negl. 2023 Jul 1;106335.
doi: 10.1016/j.chiabu.2023.106335. Online ahead of print.
Effectiveness of the caregiver support intervention on child psychosocial wellbeing among Syrian refugees in Lebanon: Mediation and secondary analysis of a Randomized Controlled Trial
M J D Jordans [1], I Bakolis [2], M Arnous [3], G V Koppenol-Gonzalez [4], F Tossyeh [3], A Chen [5], K E Miller [6]
Abstract
Background: War and violence have a serious negative impact on the wellbeing and mental health of many children. Caregivers play an important role in mitigating or exacerbating this impact.
Objective: This study evaluates the impact of the nine session Caregiver Support Intervention on improving children's wellbeing and examines putative mediators of changes in children's psychosocial wellbeing.
Participants and setting: 240 female caregivers were randomly allocated (1:1) to the CSI or a waitlist control comparison condition. The study was implemented in Lebanon, in an area characterized by high levels of poverty and a high number of the Syrian refugees.
Methods: A parallel group Randomized Controlled Trial reporting on caregiver-reported child-level wellbeing. We used a combination of the Kid- and Kiddy-KINDL (parent version) for index children ages three to 12. Putative mediators of the CSI on children's psychosocial

wellbeing included harsh parenting, caregiver psychological distress, caregiver wellbeing. Measurements were conducted at baseline, post-intervention and 3-months follow-up.
Results: We demonstrated a statistically significant change in caregiver reported children's psychosocial wellbeing at post-intervention (Mdiff =4.39, 95 % CI = 1.12, 7.65, p < 0.01, d = 0.28) but not at follow-up (Mdiff = -0.97, 95 % CI = -4.27, 2.32, p > 0.05). The proportion of the total effect of the CSI intervention on child psychosocial wellbeing mediated by caregiver distress, caregiver wellbeing and harsh parenting was 77 %.
Conclusion: The CSI holds potential for down-stream short-term effect on improving children's psychosocial wellbeing, beyond the previously reported positive caregiver outcomes. This effect was not sustained three months post intervention. The study confirms caregiver wellbeing and parenting support as dual pathways mediating child psychosocial wellbeing. Prospective trial registration: ISRCTN22321773.

BMJ Glob Health. 2023 Oct;8(10):e012633.
doi: 10.1136/bmjgh-2023-012633.

A cluster-randomised controlled equivalence trial of the Surprise Soap handwashing intervention among older children living in a refugee settlement in Sudan

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Abstract
Introduction: Increasing handwashing with soap (HWWS) among older children in emergency settings can have a large public health impact, however, evidence on what works is limited. One promising approach is the 'Surprise Soap' intervention in which a novel soap with an embedded toy is delivered to children in a short, participatory household session that includes a glitter game and HWWS practice. Here, we evaluate this intervention against a standard intervention in a complex emergency setting.
Methods: A cluster-randomised controlled equivalence trial was conducted in Naivasha refugee settlement, Sudan. Blinding was not possible. 203 randomly selected households, with at least one child aged 5-12, were randomised to receive the Surprise Soap intervention (n=101) or a standard intervention comprising a short household session with health messaging and plain soap distribution (n=102). The primary outcome was the proportion of prespecified potential HWWS events observed for children aged 5-12, accompanied by HWWS, at baseline, 4, 12 and 16 weeks post intervention delivery.
Results: 200 households were included in the analyses: 101 intervention and 99 control. No difference in intervention effectiveness was observed at any follow-up (4 weeks: adjusted rate ratio (RR) 1.2, 95% CI 0.8 to 1.7; 12 weeks: RR 0.8, 95% CI 0.5 to 1.1; 16 weeks: RR 1.1, 95% CI 0.8 to 1.5). However, we observed increased HWWS in both arms at 4 weeks (27 and 23 percentage point increase in the intervention and control arm, respectively) that was sustained at 16 weeks.
Conclusions: We find that the Surprise Soap intervention is no more effective at increasing older children's HWWS than a standard, household-level, health-based intervention in this complex humanitarian emergency. There appears to be no marginal benefit in terms of HWWS that would justify the additional cost of implementing the Surprise Soap intervention. Further trials that include a passive control arm are needed to determine the independent effects of each intervention and guide future intervention design.

Research

Clin Trials. 2023 Dec;20(6):624-631.
doi: 10.1177/17407745231182417. Epub 2023 Jun 27.

Data monitoring committees in pediatric randomized controlled trials registered in ClinicalTrials.gov

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Abstract

Background: Data monitoring committees advise on clinical trial conduct through appraisal of emerging data to ensure participant safety and scientific integrity. While consideration of their use is recommended for trials performed with vulnerable populations, previous research has shown that data monitoring committees are reported infrequently in publications of pediatric randomized controlled trials. We aimed to assess the frequency of reported data monitoring committee adoption in ClinicalTrials.gov registry records and to examine the influence of key trial characteristics.

Methods: We conducted a cross-sectional data analysis of all randomized controlled trials performed exclusively in a pediatric population and registered in ClinicalTrials.gov between 2008 and 2021. We used the Access to Aggregate Content of ClinicalTrials.gov database to retrieve publicly available information on trial characteristics and data on safety results. Abstracted data included reported trial design and conduct parameters, population and intervention characteristics, reasons for prematurely halting, serious adverse events, and mortality outcomes. We performed descriptive analyses on the collected data and explored the influence of clinical, methodological, and operational trial characteristics on the reported adoption of data monitoring committees.

Results: We identified 13,928 pediatric randomized controlled trial records, of which 39.7% reported adopting a data monitoring committee, 49.0% reported not adopting a data monitoring committee, and 11.3% did not answer on this item. While the number of registered pediatric trials has been increasing since 2008, we found no clear time trend in the reported adoption of data monitoring committees. Data monitoring committees were more common in multicenter trials (50.6% vs 36.9% for single-center), multinational trials (60.2% vs 38.7% for single-country), National Institutes of Health-funded (60.3% vs 40.1% for industry-funded or 37.5% for other funders), and placebo-controlled (47.6% vs 37.5% for other types of control groups). Data monitoring committees were also more common among trials enrolling younger participants, trials employing blinding techniques, and larger trials. Data monitoring committees were more common in trials with at least one serious adverse event (52.6% vs 38.4% for those without) as well as for trials with reported deaths (70.3% vs 38.9% for trials without reported deaths). In all, 4.9% were listed as halted prematurely, most often due to low accrual rates. Trials with a data monitoring committee were more often halted for reasons related to scientific data than trials without a data monitoring committee (15.7% vs 7.3%).

Conclusion: According to registry records, the use of data monitoring committees in pediatric randomized controlled trials was more frequent than previously reported in

reviews of published trial reports. The use of data monitoring committees varied across key clinical and trial characteristics based on which their use is recommended. Data monitoring committees may still be underutilized in pediatric trials, and reporting of this item could be improved.

BMC Pediatr. 2024 May 27;24(1):364.
doi: 10.1186/s12887-024-04839-3.

Quality assessment of paediatric randomized controlled trials published in China from 1999 to 2022: a cross-sectional study

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Abstract

Background: Randomized controlled trials (RCTs) are usually the basis of evidence-based medicine, but whether the results of RCTs can be correctly translated into clinical practice depends on the quality of the literature reported. In this study, we evaluated the general characteristics and quality of paediatric RCTs published in China to provide evidence for the reporting of paediatric RCTs and their application in clinical practice.

Methods: We conducted a cross-sectional observational study of paediatric RCTs published in paediatric journals in China between January 1, 1999, and December 30, 2022. All RCTs that included children (younger than 18 years old) were retrieved, and the general characteristics of the RCTs were extracted and analysed. The quality of the RCTs was assessed by the Cochrane quality assessment protocol.

Results: After screening 20 available paediatric journals, 3545 RCTs were included for analysis. The average annual growth rate of the number of published paediatric RCTs from 1999 to 2022 was 7.8% ($P = 0.005$, $R^2 = 0.311$). Most of the studies were carried out in East China [1148 (32.4%]; the centres of the RCTs were mainly single-centre [3453 (97.4%], and the interventions were mainly medication [2442 (68.9%)]. Comparing RCTs published in 2017-2022 with RCTs published in 1999-2004, the quality of RCTs significantly improved in terms of random sequence generation, allocation concealment, blinding participants and personnel, incomplete outcome data and selective outcome reporting. RCTs published in multiple centres from the Chinese Science Citation Database were identified, and the approval of the ethics committee was of better quality for all the analysed risk of bias items.

Conclusion: The number and quality of paediatric RCTs reported in China have improved in recent years, but the overall quality was relatively low. Special attention should be given to allocation concealment and blinding outcome assessment, and dropouts, adverse effects and sample size calculations should be reported. Promoting government policies, strengthening the standardization of journal publishing and advancing the registration of clinical trials are feasible measures.

Trials. 2023 Aug 8;24(1):506.
doi: 10.1186/s13063-023-07397-8.

Is equipoise a useful concept to justify randomised controlled trials in the cultural context of Pakistan? A survey of clinicians in relation to a trial of talking therapy for young people who self-harm

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Abstract

Background: Clinical equipoise, also defined as the uncertainty principle, is considered essential when recruiting subjects to a clinical trial. However, equipoise is threatened when clinicians are influenced by their own preferences. Little research has investigated equipoise in the context of trial recruitment.

Methods: This cross-sectional survey sought clinicians' views (operationalised as 11 statements relating to treatments offered in a trial of a psychological intervention for young people) about equipoise and individual treatment preferences in the context of moral justification for recruiting young people at risk of self-harm or suicide to a randomised controlled trial (RCT) to evaluate the Youth Culturally Adapted Manual Assisted Psychological Intervention (Y-CMAP) in Pakistan. We compared the views of clinicians involved in Y-CMAP RCT recruitment to those of a sample of clinicians not involved in trial recruitment but treating similar patients, comparing their sociodemographic characteristics and the proportions of those in each group agreeing with each statement.

Results: There was a response rate of 96% (75/78). Findings showed that, during trial recruitment and before the RCT results were known, the majority of all responding clinicians (73.3%) considered Y-CMAP to be an effective treatment for young people at risk of self-harm or suicide. Although there was an acknowledgement of individual preferences for the intervention, there was near consensus (90%) on the need to conduct an RCT for reaching an evidence-based decision. However, there were no significant differences in the proportion of recruiting clinicians reporting a treatment preference for Y-CMAP than non-recruiting clinicians (31 (88.6%) versus 36 (90%), $p = 0.566$). A significantly higher proportion of non-recruiting clinicians (87.5%) as compared to (48.5%) in the trial ($p = 0.000$) stated that there may be other treatments that may be equally good for the patients, seemingly undermining a preference for the intervention. Those reporting a treatment preference also acknowledged that there was nothing on which this preference was based, however confident they felt about them, thus accepting clinical equipoise as ethical justification for conducting the RCT. There was a significant group difference in views that treatment overall is better as a result of young patients' participation in the Y-CMAP trial ($p = 0.015$) (i.e. more clinicians not involved in the trial agreed with this statement). Similarly, more clinicians not involved in the trial agreed on the perceived availability of other treatment options that were good for young people at risk of self-harm ($p < 0.05$).

Conclusions: The paper highlights that clinicians in Pakistan accept the notion of clinical equipoise as an ethical justification for patient participation in RCTs. The need for conducting RCTs to generate evidence base and to reduce bias was considered important by the clinical community.

Eval Rev. 2023 Oct;47(5):786-819.
doi: 10.1177/0193841X231154714. Epub 2023 Feb 2.

Intraclass Correlations Values in International Development: Evidence Across Commonly Studied Domains in sub-Saharan Africa

David Seidenfeld [1], Sudhanshu Handa [2], Thomas de Hoop [2], Mitchell Morey

Abstract

The sharp increase in the number of experimental studies evaluating development programs raises the need for accurate intraclass correlations (ICC) to conduct power calculations so that researchers can design studies to detect meaningful effects with sufficient statistical power. The intraclass correlation is an important parameter for determining the statistical power of cluster-randomized trials. The parameter is rarely available to researchers planning a study until after the design is set and data are already collected. This paper takes an important step towards helping researchers working in sub-Saharan Africa to accurately estimate appropriate sample sizes for their clustered RCTs. The study draws from rich data sets in Kenya, Malawi, Zambia, and Zimbabwe. We present ICCs for a wide range of domains common for development research. Our results suggest that ICCs for commonly studied indicators in sub-Saharan Africa are lower than is often assumed in power calculations. ICC values are especially low for indicators associated with child nutrition and food security, suggesting that cluster-RCTs might be a viable design even when faced with limited budgets because sample size requirements are not much different from an individual random assignment design.

Quality of care

Schistosomiasis

Lancet Infect Dis. 2023 Jul;23(7):867-876.
doi: 10.1016/S1473-3099(23)00048-8. Epub 2023 Mar 6.

Efficacy, safety, and palatability of arpraziquantel (L-praziquantel) orodispersible tablets in children aged 3 months to 6 years infected with Schistosoma in Côte d'Ivoire and Kenya: an open-label, partly randomised, phase 3 trial

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Abstract

Background: WHO has underlined the need for a child-friendly treatment for schistosomiasis, a prevalent parasitic disease in low-income and middle-income countries. After successful phase 1 and 2 trials, we aimed to evaluate the efficacy, safety, palatability, and pharmacokinetics of arpraziquantel (L-praziquantel) orodispersible tablets for preschool-aged children.

Methods: This open-label, partly randomised, phase 3 study was conducted at two hospitals in Côte d'Ivoire and Kenya. Children with a minimum bodyweight of 5 kg in those aged 3 months to 2 years and 8 kg in those aged 2-6 years were eligible. In cohort 1, participants aged 4-6 years infected with Schistosoma mansoni were randomly assigned (2:1) to receive a single dose of oral arpraziquantel 50 mg/kg (cohort 1a) or oral praziquantel 40 mg/kg (cohort 1b) using a computer-generated randomisation list. Cohorts 2 (aged 2-3 years) and 3 (aged 3 months to 2 years) infected with S mansoni, and the first 30 participants in cohort 4a (aged 3

months to 6 years) infected with Schistosoma haematobium, received a single dose of oral arpraziquantel 50 mg/kg. After follow-up assessments, arpraziquantel was increased to 60 mg/kg (cohort 4b). Laboratory personnel were masked to the treatment group, screening, and baseline values. S mansoni was detected using a point-of-care circulating cathodic antigen urine cassette test and confirmed using the Kato-Katz method. The primary efficacy endpoint was clinical cure rate at 17-21 days after treatment in cohorts 1a and 1b, measured in the modified intention-to-treat population and calculated using the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, NCT03845140.
Findings: Between Sept 2, 2019, and Aug 7, 2021, 2663 participants were prescreened and 326 were diagnosed with S mansoni or S haematobium. 288 were enrolled (n=100 in cohort 1a, n=50 in cohort 1b, n=30 in cohort 2, n=18 in cohort 3, n=30 in cohort 4a, and n=60 in cohort 4b), but eight participants received antimalarial drugs and were excluded from the efficacy analyses. The median age was 5·1 years (IQR 4·1-6·0) and 132 (47%) of 280 participants were female and 148 (53%) were male. Cure rates with arpraziquantel were similar to those with praziquantel (87·8% [95% CI 79·6-93·5] in cohort 1a vs 81·3% [67·4-91·1] in cohort 1b). No safety concerns were identified during the study. The most common drug-related treatment-emergent adverse events were abdominal pain (41 [14%] of 288 participants), diarrhoea (27 [9%]), vomiting (16 [6%]), and somnolence (21 [7%]).
Interpretation: Arpraziquantel, a first-line orodispersible tablet, showed high efficacy and favourable safety in preschool-aged children with schistosomiasis.

Am J Trop Med Hyg. 2024 Feb 27;110(4):677-680.
doi: 10.4269/ajtmh.23-0337. Print 2024 Apr 3.

Efficacy of a Single Oral Dose of Artesunate plus Sulfalene-Pyrimethamineversus Praziquantel in the Treatment of Schistosoma mansoni in Kenyan Children: An Open-Label, Randomized, Exploratory Trial

Erick M O Muok[1], Vincent O Were[1], Charles O Obonyo[1]

Abstract

Unlike praziquantel, artemisinin derivatives are effective against juvenile schistosome worms. We assessed the efficacy and safety of a single oral dose of artesunate plus sulfalene-pyrimethamine versus praziquantel in the treatment of Schistosoma mansoni. Seventy-three schoolchildren (aged 9-15 years) with confirmed S. mansoni infection in Rarieda, western Kenya, were randomly assigned to receive either a single oral dose of artesunate plus sulfalene-pyrimethamine (n = 39) or a single dose of praziquantel (n = 34). The cure and egg reduction rates at 4 weeks posttreatment were 69.4% (25/36) versus 80.6% (25/31) (P = 0.297) and 99.1% versus 97.5% (P = 0.607) in the artesunate plus sulfalene-pyrimethamine group versus praziquantel group, respectively. Fourteen children developed adverse events, and there were no serious adverse events. A single oral dose of artesunate plus sulfalene-pyrimethamine has efficacy comparable to that of praziquantel in the treatment of S. mansoni, but these results should be confirmed in larger randomized controlled trials.

School health and education

(See Adolescent health, Schistosomiasis)

Sch Psychol. 2024 Apr 11.
doi: 10.1037/spq0000625. Online ahead of print.

Training and coaching early childhood teachers to foster social, emotional, and behavioral competence of children in Turkey

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Abstract

A growing evidence base demonstrates the effectiveness of teacher training and coaching interventions to improve teacher- and child-level outcomes in high-income countries. However, more information is needed to show the benefits of these interventions in low- and middle-income countries (LMICs). To provide an evidence base for LMICs, we conducted a cluster-randomized controlled trial examining the efficacy of a teacher training and coaching intervention for promoting children's social, emotional, and behavioral competence, Reaching Educators and Children (REACH) Classroom Check-Up (CCU), on teachers' behaviors, teacher-child relationship quality, and children's social competence and problem behaviors. Participants included 20 early childhood teachers and 175 children (4-6 year olds) in Turkey. Findings indicate that REACH CCU increased teachers' positive behaviors and teacher behaviors that support social, emotional, and behavioral competence of children, while reducing teachers' negative behaviors. Teachers in REACH CCU demonstrated an increased level of closeness and reduced levels of conflict with children in their classrooms. Furthermore, REACH CCU improved teacher-reported social competence and reduced problem behaviors of children. Results provide evidence that REACH CCU is a promising approach for improving teachers' behaviors, teacher-child relationship quality, and children's social, emotional, and behavioral competence, especially in LMICs. (PsycInfo Database Record (c) 2024 APA, all rights reserved).

An Sist Sanit Navar. 2023 Dec 26;46(3):e1061.
doi: 10.23938/ASSN.1061.

Impact of training schoolchildren how to perform cardiopulmonary resuscitation using stories and animated cartoons

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Abstract

Background: We compared the outcome of training schoolchildren how to perform CPR by parents/legal guardians in the family environment versus by teachers at school.

Methods: Randomized study of CPR learning in primary school children (1st and 2nd grades) in the Region of Murcia. Parents/legal guardians (family group) and teachers (teacher group) trained the children using didactic material adapted for that age population (one story and one cartoon video) from the educational series Jacinto y sus Amigos©. We evaluated eight theoretical knowledge items and five practical skills.

Results: One hundred and sixty schoolchildren were selected and 116 completed the study; in the family group, 51.3% did not finish the study. Children trained by teachers obtained significantly higher median scores in comparison with the family group both in theoretical knowledge (6.7; IQR=1.8 vs 4.7; IQR=3.1, respectively; $p < 0.001$) and in all practical skills except for "recognizing an emergency situation". Children in the family group, learning CPR with one story and one cartoon video achieved significantly better scores in five theoretical knowledge items and four skills than with only the story.
Conclusions: Using non-technological educational resources, e.g., stories and animated cartoons for teaching CPR to primary school students, increases their knowledge and skills. Schoolchildren trained in the educational environment acquired more knowledge and skills than those trained by parents. Within the family environment, CPR teaching was more effective through one story and one cartoon video than when only the story was used.

Medicine (Baltimore). 2023 Jul 7;102(27):e34168.
doi: 10.1097/MD.0000000000034168.

Raising the self-esteem and reducing irrational beliefs of schoolchildren: The moderating and main effect study

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Abstract
Background: Several systematic reviews and meta-analyses studies have called for moderators of treatment outcomes and their main effect with regard to disadvantaged populations. In view of that, this study investigated the impacts and moderators of rational emotive behavior therapy (REBT) on the self-esteem and irrational beliefs of Schoolchildren in Ebonyi State Nigeria.
Methods: A group randomized controlled design was utilized to assign 55 schoolchildren to the treatment group and 55 schoolchildren to waitlisted control group. Two self-report measures (Self-Esteem Scale and Children Adolescent Scale of Irrationality) were used to assess the participants. There were pretest, posttest, and follow-up tests given at different intervals to ascertain the baseline, main effect, and long-term effects of the treatment. The data collected were analyzed using a 2-way analysis of covariance statistic.
Results: The results of the 2-way analysis of covariance demonstrated a difference between participants in the waitlisted control group at the pretest, posttest, and follow-up test and a positive improvement in schoolchildren with illogical beliefs as a result of exposure to REBT intervention. It was discovered that the REBT intervention changed schoolchildren's self-esteem and irrational views into rational ones. A later test result supported the intervention's consistent and significant effects in lowering illogical beliefs and raising students' self-esteem. The results also showed that there is no connection between gender and group membership.
Conclusion: This study suggests that REBT is a significant treatment strategy that reduces irrational beliefs and improves the self-esteem of primary school children. Based on these outcomes, further studies should replicate the study in other cultures with such a disadvantaged group.

Iran J Child Neurol. 2024 Spring;18(2):83-101.
doi: 10.22037/ijcn.v18i2.43985. Epub 2024 Mar 12.

Comparing Telerehabilitation and In-Person Interventions in School-Based Occupational Therapy for Specific Learning Disorder A Randomized Controlled Trial

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Abstract

Objective: This study investigated the efficacy of telerehabilitation (TR) in school-based Occupational Therapy (OT) for children with Specific Learning Disorder (SLD), focusing on occupational competence and parental satisfaction, aiming to contribute empirical insights to the discourse on the educational well-being of this population.

Materials & methods: The study adopted a Randomized Controlled Trial (RCT) design involving 31 children diagnosed with SLD, implementing TR and in-person interventions alongside a control group. Outcome measures included the School Self-Concept Inventory, Child Occupational Self-Assessment (COSA), and Canadian Occupational Performance Measurement (COMP), analyzed using descriptive and inferential statistics (ANOVA, post hoc tests).

Results: Both TR and in-person interventions exhibited significant enhancements in academic self-efficacy ($F=23.96$, $p<0.001$, Partial $\eta^2=0.461$), occupational competence ($F=70.59$, $p<0.001$, Partial $\eta^2=0.716$), and parent satisfaction ($F=17.03$, $p<0.001$, Partial $\eta^2=0.378$) compared to the control group. Notably, no significant differences emerged between the TR and in-person groups, emphasizing their comparable effectiveness in improving outcomes.

Conclusion: In conclusion, the study demonstrated the efficacy of TR and in-person interventions in school-based OT for children with SLD. The cohesive outcomes in academic self-efficacy, occupational competence, and parental satisfaction highlight TR as a versatile modality. This research, grounded in robust methodology, encourages further exploration of TR's transformative role in enhancing the holistic well-being of children with SLDs.

J Adolesc Health. 2023 Oct 8:S1054-139X(23)00455-X.
doi: 10.1016/j.jadohealth.2023.08.043. Online ahead of print.

Impact of Economic and Family Intervention on Adolescent Girls' Education Performance, School Absenteeism, and Behavior in School: The Suubi4Her Study

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Abstract

Purpose: Attaining education among girls is still a challenge in sub-Saharan Africa. Even those who enroll in school need additional financial and social support to promote attendance, performance, and behavior. We investigated whether (1) adolescent girls receiving an economic empowerment intervention comprising Youth Development Accounts (YDA) or a combination intervention comprising (YDA + Multiple Family Group [YDA + MFG]), participants of the Suubi4Her study, will each display better grade repetition, attendance, and behavior in school compared to girls in the control group and (2) adolescent girls in the YDA + MFG group will have better outcomes than girls receiving the YDA-only intervention.

Methods: We used longitudinal data from 1,260 Ugandan adolescent girls from the Suubi4Her cluster randomized controlled trial. To account for repeated measures at the

individual level over time and clustering at the school level, three-level mixed-effects models were fitted. For binary outcomes, we used multilevel logistic regression, while for continuous outcomes, we applied multilevel linear regression.
Results: Overall, our findings highlight the positive impact of the Suubi4Her intervention on reducing general and sickness-related absenteeism among school-attending adolescent girls who received the YDA or YDA + MFG intervention but observed no significant group differences on their grade repetition and behavior in school.
Discussion: Improving school attendance and reducing illness-related absences can translate to numerous beneficial outcomes for adolescent girls in the long-term and, hence, these interventions should be considered to improve educational outcomes among other adolescent girl populations in similar settings across sub-Saharan Africa.

Eye (Lond). 2024 Apr 2.
doi: 10.1038/s41433-024-03032-1. Online ahead of print.
Priorities in school eye health in low and middle-income countries a scoping review
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Abstract
School eye health (SEH) has been on the global agenda for many years, and there is mounting evidence available to support that school-based visual screenings are one of the most effective and cost-efficient interventions to reach children over five years old. A scoping review was conducted in MEDLINE, Web of Science, PubMed, and CINHAL between February and June 2023 to identify current priorities in recent literature on school eye health in low- and middle-income countries (LMICs). Selection of relevant publications was performed with Covidence, and the main findings were classified according to the WHO Health Promoting Schools framework (HPS). A total of 95 articles were included: cross-sectional studies (n = 55), randomised controlled trials (n = 7), qualitative research (n = 7) and others. Results demonstrate that multi-level action is required to implement sustainable and integrated school eye health programmes in low and middle-income countries. The main priorities identified in this review are: standardised and rigorous protocols; cost-effective workforce; provision of suitable spectacles; compliance to spectacle wear; efficient health promotion interventions; parents and community engagement; integration of programmes in school health; inter-sectoral, government-owned programmes with long-term financing schemes. Even though many challenges remain, the continuous production of quality data such as the ones presented in this review will help governments and other stakeholders to build evidence-based, comprehensive, integrated, and context-adapted programmes and deliver quality eye care services to children all over the world.

NPJ Sci Learn. 2023 Sep 13;8(1):37.
doi: 10.1038/s41539-023-00180-z.
Nudging parents and teachers to improve learning and reduce child labor in Cote d'Ivoire
Sharon Wolf[1], Guilherme Lichand[2]
Abstract

Whether SMS-based nudge interventions can increase parent engagement and improve child learning outcomes across diverse contexts such as rural West Africa is unknown. We conducted a school-randomized trial to test the impacts of an audio or text-message intervention (two messages per week for one school year) to parents and teachers of second and fourth grade students (N = 100 schools, 2246 students) in Cote d'Ivoire. Schools were randomly assigned to have messages sent to (i) parents only, (ii) teachers only, (iii) parents and teachers together, or (iv) control. There were statistically non-significant impacts of the parents-only treatment on learning, although with typical effect sizes (d = 0.08, p = 0.158), and marginally statistically significant increases in child labor (d = 0.11, p < 0.10). We find no impacts of the other treatment conditions. Subgroup analyses based on pre-registered subgroups show significantly larger improvements in learning for children with below-median baseline learning levels for the parents-only arm and negative impacts on learning for girls for the teachers-only arm, suggesting different conclusions regarding impacts on equity for vulnerable children.

Eval Rev. 2024 Mar 29:193841X241241354.
doi: 10.1177/0193841X241241354. Online ahead of print.

Education Experiments in Latin America: Empirical Evidence to Guide Evaluation Design

Steven Glazerman [1], Larissa Campuzano [2], Nancy Murray [2]

Abstract

Randomized experiments involving education interventions are typically implemented as cluster randomized trials, with schools serving as clusters. To design such a study, it is critical to understand the degree to which learning outcomes vary between versus within clusters (schools), specifically the intraclass correlation coefficient. It is also helpful to anticipate the benefits, in terms of statistical power, of collecting household data, testing students at baseline, or relying on administrative data on previous cohorts from the same school. We use data from multiple cluster-randomized trials in four Latin American countries to provide information on the intraclass correlations in early grade literacy outcomes. We also describe the proportion of variance explained by different types of covariates. These parameters will help future researchers conduct statistical power analysis, estimate the required sample size, and determine the necessity of collecting different types of baseline data such as child assessments, administrative data at the school level, or household surveys.

BMC Public Health. 2023 Nov 7;23(1):2187.
doi: 10.1186/s12889-023-17108-2.

Effects of health education during public health emergencies on the health literacy, emotion and coping style of Chinese junior middle school students: a randomized controlled trial

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Abstract

Background: Schools are high incidence places for public health emergencies. Good health literacy helps students cope with public health emergencies. Overall, the health literacy of

young students is relatively low. Health education can promote health literacy, but the health education related to public health emergencies for Chinese junior middle school students needs to be improved. To design and implement health education courses related to public health emergencies for junior middle school students and examine the impact on their health literacy, emotions, and coping styles.
Methods: From March to December 2022, 724 students in Grade 7 and Grade 8 of two junior middle schools in Changzhou were randomly divided into a course group (n = 359) and a control group (n = 365). The course group received an age-appropriate health education course that addressed public health emergencies; there were 12 classes, one per week. The control group received general health education. One week before and after the courses, the two groups of students were assessed with the Adolescent Health Literacy Evaluation Scale under Public Health Emergencies (AHLES-PHE), the Depression Self-Rating Scale for Children (DSRSC), the Generalized Anxiety Disorder 7-item scale (GAD-7), and the Simplified Coping Style Questionnaire (SCSQ).
Results: After the courses were completed, the scores of AHLES-PHE [156.0 (45.0,180.0) vs. 165.0 (54.0,180.0), P < 0. 05] in the course group increased significantly. The positive rate of DSRSC [81 (22.6%) vs. 57 (15.9%), P < 0.05] and GAD-7 [45 (12.5%) vs. 29 (8.1), P < 0.05]in the course group were significantly lower than those before courses. There was no significant difference in the above indices before and after courses in the control group (P > 0.05).
Conclusion: This suggests that the health education courses related to public health emergencies designed in this study has an effect on improving health literacy, depression and anxiety in junior middle school students.

Disabil Rehabil Assist Technol. 2024 Jan;19(1):9-15.
doi: 10.1080/17483107.2022.2134473. Epub 2022 Oct 19.
Mathlete: an adaptive assistive technology tool for children with dyscalculia
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Abstract
Purpose: The use of technology in teaching and learning process for children is gaining importance. Children with specific learning disabilities have shown positive results with assistive technology tools. Dyscalculia is a specific learning disability in which an individual faces problem in mathematical skills. Around 3-7% of the world population is affected with it. The aim of the current research study is to determine the effectiveness of an assistive technology tool, Mathlete on children with dyscalculia's early numeracy skills. Such assistive technology tools can serve as a boon for these children.
Method: A total of 40 children with dyscalculia *(M_{age} = 6.8 years)* were a part of the study. The group of 40 children were randomly divided into two groups: experiment group using mathlete for improving their learning (30 children) and a control group using only traditional teaching for learning (10 children). The children were screened for dyscalculia using the screening module of mathlete.
Results: The two groups showed no significant difference in terms of their socio-economic status, gender and parents education level. Children in the experiment group showed improvement from pre-test to post-test after using mathlete. Also, there was significant difference in learning of both the groups, children in experiment group could understand the concepts better than the ones in control group.

Conclusion: Mathlete helped improve the mathematical learning of children with dyscalculia from pre-test to post-test.

EClinicalMedicine. 2024 Jan 26:68:102427.
doi: 10.1016/j.eclinm.2024.102427. eCollection 2024 Feb.

A web-enabled, school-based intervention for bullying prevention (LINKlusive): a cluster randomised trial

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Abstract

Background: There is a need for more sustainable interventions and for assessing the effectiveness of school-based universal anti-bullying programmes in vulnerable populations. We assessed the efficacy of a multicomponent, web-enabled, school-based intervention that aims to improve school climate and reduce bullying (LINKlusive) relative to conventional practices (control condition).

Methods: We conducted a cluster randomised controlled trial in primary and secondary schools in Madrid, Spain. The primary outcome measure was peer-reported bullying victimisation after the 12-week intervention (study endpoint). We analysed data using longitudinal mixed-effects models. The trial was registered with the ISRCTN registry (15719015).

Findings: We included 20 schools (10 in each group); 6542 students participated at baseline; 6403 were assessed at study endpoint. After the intervention, there was a statistically significant reduction in bullying victimisation in both the intervention (OR 0.61, 95% CI [0.41, 0.90]) and control groups (OR 0.69, 95% CI [0.51, 0.92]), with no evidence of differences in the whole sample (OR 0.89, 95% CI [0.58, 1.36]; aOR 0.89, 95% CI [0.58, 1.37]). Subgroup analyses showed a statistically significant effect of LINKlusive on bullying victimisation in primary education (aOR 0.68, 95% CI [0.47, 0.98]). In students with peer-reported bullying victimisation at baseline, LINKlusive showed a statistically significant effect on depression (-1.43, 95% CI [-2.46, -0.40], adjusted standardised mean difference (SMD) -0.41) and quality of life (2.18, 95% CI [0.80, 3.56], adjusted SMD 0.45).

Interpretation: LINKlusive could be effective in reducing bullying victimisation in primary school students. Sustainable whole-school interventions to promote mental health and reduce risk factors are warranted to improve outcomes in young people, especially in the early years of education.

School nutrition

Lancet Reg Health Southeast Asia. 2024 Jan 24:21:100353.
doi: 10.1016/j.lansea.2024.100353. eCollection 2024 Feb.

Effectiveness of a school-based behavioural change intervention in reducing chronic disease risk factors in Chandigarh, India: a cluster-randomised controlled trial

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Abstract
Background: Early behavioural risk factors such as unbalanced diets, physical inactivity and tobacco and alcohol consumption lead to chronic diseases in later life. We conducted a cluster-randomised controlled trial to measure the effect of a school-based health-promotion intervention in reducing the behavioural risk factors of chronic diseases.
Methods: Twelve public schools in the Chandigarh, India were randomised to the intervention and control arm. Adolescents studying in eighth grade (n = 453), their parents (n = 395) and teachers (n = 94) were recruited for the current study. The Precede-Proceed Model was followed for intervention development. Intervention in each cluster comprised of one classroom session, four physical activity (PA) sessions every week for adolescents and four separate sessions for parents and teachers. Primary outcomes were eight binary or continuous measures of behavioural risk factors among adolescents (n = 359). Physical Activity Questionnaire-Adolescents (PAQ-A) scores were used to estimate physical activity. The ANCOVA based on cluster proportions or means was used to estimate the intervention effect accounting for baseline data.
Findings: Among adolescents, the intervention reduced salt intake by 0.5 g/d (95% CI: -0.9, -0.1), proportion of current alcohol users by 5% (95% CI: -9, -0.007), and increased fruit consumption by 18 g/d (95% CI: 5, 30) and PA by 0.2 PAQ-A score (95% CI: 0.07, 0.3). However, the intervention had no effect on the sugar and vegetable intake and on smokers and tobacco chewers. Exploratory analysis revealed that among parents, PA increased by 205 metabolic equivalents task (MET) units (95% CI: 74.5, 336), fruits intake by 20 g/d (95% CI: 6, 34), and vegetable intake by 117 g/d (95% CI: 50.5, 183). Whereas salt consumption decreased by 0.5 g/d (95% CI: 0.15, 0.9) and the proportion of current alcohol users declined by 5% (95% CI: 9, -1) among parents. Vegetable consumption increased by 149 g/d (95% CI: 12, 286) among teachers.
Interpretation: The intervention package implemented among adolescents by involving parents and teachers is an effective model for school-based behaviour-change interventions.

BMC Public Health. 2024 Feb 28;24(1):630.
doi: 10.1186/s12889-024-18114-8.

Improving adolescents' dietary behavior through teacher-delivered cancer prevention education: a school-based cluster randomized intervention trial in urban Rajasthan

Ankit Mittal[1], Neeti Rustagi[2], Prasanna Thirunavukkarasu[1], Santu Ghosh[3], Pankaja Raghav[1]

Abstract
Background: Dietary practices are one of the most common modifiable risk factors for cancers. Foods rich in dietary fibers are considered protective, meanwhile fast & junk foods are risk for common cancers. Adolescence period is marked by habit formation and is thus suited for delivering behavioral intervention. Schools offer an optimal setting for planning and executing these interventions to a large number of adolescents.
Objective: To assess the effectiveness of a teacher-delivered cancer-prevention education in changing dietary behaviors of school going adolescents.
Methods: A cluster randomized trial was conducted in government secondary and senior secondary schools with schools as clusters. A minimum required sample of 1032 students was estimated from 16 schools with 1:1 allocation in intervention and non-intervention groups. Dietary behaviors were recorded as dichotomous variable. The determinants were

recorded as per theory of planned behavior framework using Likert-scale. Two teachers from each intervention school were trained to deliver cancer prevention education with focus on role of dietary behavior. Pre-post training assessment of teachers' knowledge towards common cancers was done using a self-administered questionnaire. Gender adjusted difference-in-difference analysis was done to assess intervention effect on both healthy and unhealthy behaviors.
Results: In selected schools all students from classes 8 to 10 were approached and a total of 1224 students were enrolled, of whom 1096 completed the study. The study recorded significant improvement in scores of students from intervention group compared to non-intervention group for their attitude, subjective norms, perceived behavioral control and intention towards consuming healthy and avoiding unhealthy foods. The intervention was effective in significantly improving the proportion of students limiting fried/fast/packed food & sugar sweetened beverages (OR:1.51, 95%CI:1.08,2.12,p:0.017), and consuming fruits & vegetables daily (OR:1.55, 95%CI:1.08,2.22, p:0.017) while adjusting effect of gender.
Conclusion: Classroom-based cancer prevention education delivered through teachers during regular working hours is effective in improving dietary behaviors and its determinants among adolescent students. Thus, we recommend integrating a section focusing on the role of diet in cancer prevention and other lifestyle diseases in the existing school curriculum.

Appetite. 2024 Sep 1:200:107529.
doi: 10.1016/j.appet.2024.107529. Epub 2024 May 25.

Relaxed minds for healthier food choice at school: A field experiment in southern Mexico

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Abstract

Stress leads to unhealthy food choices since the school-age stage. Yet, there is limited evidence particularly in low- and middle-income countries regarding the impact of stress-reduction strategies on school-age children's food choices. Such aspects were crucial during the recent COVID-19 pandemic, which exacerbated psychological distress and unhealthier food choices among children. Two years after the pandemic began, we conducted a field experiment in southern Mexico to assess the impact of stress-reduction strategies on the food choices of over 1400 children aged 9-12. Half of the school-classes in the sample were randomly assigned to a stress reduction strategy namely meditation, which comprised six audios with basic relaxation techniques and intuitive messages to guide food choices. Additionally, all participants received information signalling that an amaranth snack was nutritious (i.e., the healthy snack), which was paired with a chocolate bar (i.e., the unhealthy snack) as part of a snack choice experiment. Students that practiced meditation were slightly more likely to choose the healthy snack than those in the control group, but the effect was not statistically significant. Upon collecting their snack, students had the chance to exchange their original choice for the other snack. Students that meditated were more likely to exchange their originally chosen "unhealthy snack" towards the healthy snack than students in the control group. The meditation program effectively reduced chronic stress among treated children. The effect was larger among students attending schools in lower-income areas. Our study sheds some light on the challenges to translate an improved psychological well-being into healthier food choices at school.

Lancet Child Adolesc Health. 2023 Sep 1;S2352-4642(23)00168-2.
doi: 10.1016/S2352-4642(23)00168-2. Online ahead of print.

Feasibility and impact of school-based nutrition education interventions on the diets of adolescent girls in Ethiopia: a non-masked, cluster-randomised, controlled trial

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Abstract

Background: Adolescence is a critical period of physical and psychological development, especially for girls, because poor nutrition can affect their wellbeing as well as that of their children. We aimed to assess the feasibility and impact of a package of nutrition education interventions delivered through public primary schools on the diets of adolescent girls in Ethiopia.

Methods: In this non-masked, cluster-randomised, controlled trial, primary schools (clusters) in the Southern Nations, Nationalities, and People's Region and Somali region of Ethiopia were randomly allocated to the intervention group (nutrition information provided during flag ceremonies, classroom lessons, school club meetings, peer group mentoring, BMI measurement and counselling, and parent-teacher meetings) or the control group (standard academic curriculum on health and nutrition) by use of computer-generated pseudo-random numbers. Duration of the school-based interventions was 4 months, and the key messages were related to dietary diversity (eating a variety of foods), energy adequacy (eating breakfast and healthy snacks), and healthy food choices (avoiding junk foods). Adolescent girls were eligible for participation if aged 10-14 years and enrolled in grades 4-8 in a study school. Data were collected with two independent cross-sectional surveys: baseline before the start of implementation and endline 1·5 years later. The primary outcome of impact was dietary diversity score, defined as the number of food groups (out of ten) consumed over the previous 24 h using a list-based method, and minimum dietary diversity, defined as the proportion of girls who consumed foods from at least five of the ten food groups, in the intention-to-treat population. We also assessed intervention exposure as a measure of feasibility. We estimated intervention effects using linear regression models for mean differences at endline, with SEs clustered at the school level, and controlled for adolescent age, region, household food security, and wealth. The trial is registered with ClinicalTrials.Gov, NCT04121559, and is complete.

Findings: 27 primary schools were randomly allocated to the intervention group and 27 to the control group. Between March 22 and April 29, 2021, 536 adolescent girls participated in the endline survey (270 in the intervention group and 266 in the control group), with median age of 13·3 years (IQR 12·1-14·0). At endline, the dietary diversity score was 5·37 (SD 1·66) food groups in the intervention group and 3·98 (1·43) food groups in the control group (adjusted mean difference 1·33, 95% CI 0·90-1·75, p<0·0001). Increased minimum dietary diversity was also associated with the intervention (182 [67%] of 270 in the intervention group vs 76 [29%] of 266 in the control group; adjusted odds ratio 5·37 [95% CI 3·04-9·50], p<0·0001). 256 (95%) of 270 adolescent girls in the intervention group were exposed to at least one of the five in-school intervention components.

Interpretation: Integrating nutrition interventions into primary schools in Ethiopia was feasible and increased dietary diversity incrementally among adolescent girls, but could be

limited in changing other food choice behaviours, such as junk food consumption, based on nutrition education alone.

J Health Popul Nutr. 2023 Oct 17;42(1):109.
doi: 10.1186/s41043-023-00446-7.

Evaluation of effectiveness of school-based nutrition education in improving the consumption of pulses-based food among female adolescents in Northwest Ethiopia: a cluster randomized controlled trial

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Abstract

Background: Protein undernutrition is a prevalent health problem in Ethiopia severely affecting the reproductive outcome of women. This is mainly because of inadequate consumption of protein due to the high cost of animal-origin food and the lack of knowledge about the benefits and the methods of preparation of pulses-based foods. Therefore, this trial was conducted to evaluate the effectiveness of nutrition education in improving the consumption of pulses-based foods among female adolescents.

Methods: A two-arm pragmatic cluster randomized controlled trial was conducted among female adolescents in Northwest Ethiopia. Clusters were schools assigned into intervention and control groups by cluster randomization. The trial participants were female adolescents. The intervention was pulses-based nutrition education, and the comparator was the usual dietary practice of adolescent girls. The education was delivered over four weeks on a 45-60 min session per week basis. The primary outcome of the intervention was pulses-based food consumption, and the secondary outcomes were knowledge and attitude about pulses food. Data on the outcome and the confounding variables were collected at baseline and end-line of the intervention. The analysis was based on intention-to-treat analysis, and a log-binomial logistic regression model was fitted to the data to calculate relative risk with the corresponding p value adjusted for baseline characteristics. The intervention was considered effective when the p value was < 0.05.

Results: A total of 269 intervention and 278 control participants from the four clusters completed the trial making response rates of 92.1% and 95.2%, respectively. The pulses-based nutrition education enabled participants in the intervention group to maintain their pulses-based food consumption state, while participants in the control group significantly reduced their consumption by about threefold [ARR; 95% CI 2.99 (1.87, 4.79)] from harvesting to non-harvesting season. The consumption of pulses-based food was higher by 16% among the intervention participants as compared to the control participants [ARD; 95% CI 0.16 (0.10, 0.21)].

Conclusion: Pulses-based nutrition education is effective in improving the consumption of pulses-based food among female adolescents. Therefore, policies and strategies are required to integrate this intervention in the school nutrition program.

Appetite. 2024 Feb 1:193:107118.
doi: 10.1016/j.appet.2023.107118. Epub 2023 Nov 17.

A choice architecture intervention targeting school meals and water frequency intake: A school-based randomized trial

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Abstract

Our aim was to evaluate the impact of choice architecture on school meals and water intake frequency. We conducted a school-based randomized trial in seven elementary municipal public schools (control = 3; intervention = 4) in Rio de Janeiro, Brazil. The interventions group received the following modifications: (1) banner of the daily school meal menu and two superheroes, (2) waterproof tablecloths, (3) posters on healthy eating habits, (4) displays with playful names, (5) new containers for fruits, and (6) colored footprints for one month. Changes in school meals and daily water frequency consumption were evaluated through intention-to-treat analyses, using generalized estimating equations models for repeated measures, considering the classes' cluster effect. Data from 974 students in the fifth and sixth elementary school grades were analyzed (control = 356; intervention = 618). At baseline, 47.1% of students were female, with a mean age of 12 years (SD = 1.4), 39.2% reported daily consumption of school meals, and 45.7% consumed water from the school drinking fountain three or more times a day. We observed an increase in the odds of daily water intake in the intervention group compared to the control (OR = 1.4 95% CI = 1.1-1.9), no changes in the school meals (OR = 1.2 95% CI = 0.9; 1.6). Low-complexity strategies based on choice architecture applied in the school environment can be promising in increasing water intake frequency among elementary students in public schools.

Am J Clin Nutr. 2023 Nov;118(5):977-988.
doi: 10.1016/j.ajcnut.2023.09.004. Epub 2023 Sep 15.

School-based supplementation with iron-folic acid or multiple micronutrient tablets to address anemia among adolescents in Burkina Faso: a cluster-randomized trial

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Abstract

Background: Iron-deficiency anemia is a leading cause of morbidity among adolescents (aged 10-19 y), especially in low- and middle-income settings. Few policies and programs have targeted adolescent health.

Objectives: This study aimed to evaluate the effectiveness of school-based supplementation with iron-folic acid (IFA) or multiple micronutrient supplements (MMSs) in addressing anemia among adolescents in Burkina Faso.

Methods: In this cluster-randomized trial, 3123 secondary school students aged 10 to 18 y in Burkina Faso were either supplemented with weekly IFA, daily MMSs, or received standard nutrition education as controls. Supplementation occurred between April 2021 and April 2022 over 2 supplementation periods (10 wk, then 16 wk) separated by a gap of 20 wk without supplementation. Hemoglobin was evaluated 4 times: at baseline prior to each supplementation period and at the end of each period. Anemia was categorized by the World Health Organization hemoglobin level cutoffs as none, mild, moderate, or severe. Associations between treatment arm and anemia or continuous hemoglobin (g/dL) were

assessed using multilevel mixed effects generalized linear models with schools as a random effect, controlling for baseline hemoglobin or anemia status.
Results: Baseline anemia prevalence was similar across study arms, with 32.7% in IFA, 31.2% in MMS, and 29.5% in the control arm. Over the full study period, adolescents provided IFA had hemoglobin levels higher than those in the control arm (adjusted β: 0.32; 95% CI: 0.02, 0.62). No significant associations were observed for MMS or for anemia outcomes; however, the direction and magnitude of nonsignificant associations indicate potential protective effects of IFA and MMSs on anemia.
Conclusions: The results do not provide strong evidence that weekly IFA or daily MMS alone is effective, but supplementation may play a role in addressing adolescent anemia if combined with cointerventions. Additional research is required to determine the best strategy to address anemia.

Public Health Nutr. 2023 Oct 2:1-10.
doi: 10.1017/S1368980023002094. Online ahead of print.
Efficacy of a school-based education intervention on the consumption of fruits, vegetables and carbonated soft drinks among adolescents
Kazi R Ahmed[1,2], Tracy Kolbe-Alexander[3,4,5], Asaduzzaman Khan[2]
Abstract
Objectives: To evaluate the efficacy of a school-based education intervention on the consumption of fruit, vegetables and carbonated soft drinks among adolescents.
Design: Cluster-randomised controlled trial.
Setting: Eight secondary schools from Dhaka, Bangladesh, participated in this trial and were randomly allocated to intervention (*n* 160) and control groups (*n* 160).
Participants: A total of 320 students from 8th to 9th grades participated and completed the self-reported questionnaires at baseline, and at 8 and 12 weeks. The intervention included weekly classroom-based nutrition education sessions for students and healthy eating materials for students and parents. Repeated measures ANCOVA was used to assess the effects of the intervention.
Results: Daily fresh fruit intake was more frequent in the intervention (26 %) compared to the control group (3 %) at 12 weeks ($p = 0{\cdot}006$). Participants from the intervention group also reported a significantly ($P < 0{\cdot}001$) higher (49 %) proportion of fresh vegetable intake compared to the control group (2 %) at 12 weeks. Frequency of daily carbonated soft drinks intake decreased (25 %) in the intervention group at 12 weeks compared to baseline, while it remained unchanged in the control group; the interaction effect was observed significant ($P = 0{\cdot}002$).
Conclusion: Our school-based education intervention increased the daily frequency of fresh vegetables and fruit intake and decreased carbonated soft drink consumption among adolescents in the intervention group. There is a need for scaling up the intervention to engage students and empower them to develop healthy dietary habits.

Dialogues Health. 2023 Dec;2:100123.
doi: 10.1016/j.dialog.2023.100123. Epub 2023 Mar 8.

Effect of an educational intervention on diet and physical activity among school-aged adolescents in Delhi -The i-PROMISe (PROMoting health literacy in Schools) Plus Study

Tina Rawal[1,2], Jean W M Muris[2], Vijay Kumar Mishra[1], Monika Arora[1], Nikhil Tandon[3], Onno C P van Schayck[2]

Abstract

Purpose: Emerging lifestyle changes due to rapid urbanization have led to an epidemiological transition and the rising prevalence of obesity is responsible for major non-communicable diseases (NCDs) which have further aggravated due to the COVID-19 pandemic. This study aims to assess the effectiveness of a comprehensive school-based intervention on diet and physical activity-related behavior of adolescents.

Methods: In 2019, a cluster-randomized controlled trial was conducted in randomly selected (*n* = 8) private schools. A 2-year intervention program was implemented over consecutive academic years (2019-2020 and 2020-2021) with students who were in the 6th and 7th grades when the study began. Four schools were randomly assigned to the intervention (*n* = 794) and four schools to the control group (*n* = 774).

Results: The difference in changes in diet and physical-activity-related behaviors of the students between the intervention and control schools were not significant in the intention to treat analysis probably due to the large drop-out due to COVID-19 measures: 304 students were available for follow-up in the intervention group and 122 in the control group (391 cases were excluded to make data comparable with baseline survey). The intake of vegetables (once a day) [β = 0.35, OR = 1.42, 95% CI (1.03, 1.95)] in the per-protocol analysis has increased among adolescents in the intervention group as compared to the control group.

Conclusion: The findings of this study indicated a positive effect of the intervention on diet and physical-activity-related changes in the expected direction and highlights the importance of addressing such behavior to prevent obesity among adolescents and thus NCDs in the later stage of life.

Sepsis and serious bacterial infection

J Transl Med. 2023 Oct 28;21(1):765.
doi: 10.1186/s12967-023-04592-8.

Efficacy of IVIG therapy for patients with sepsis: a systematic review and meta-analysis

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Abstract

Background: Sepsis is an overwhelming reaction to infection that comes with high morbidity and mortality. It requires urgent interventions in order to improve outcomes. Intravenous immunoglobulins (IVIG) are considered as potential therapy in sepsis patients. Results of trials on IVIG as adjunctive therapy for sepsis have been conflicting due to the variability in population characteristics, country geography and drug dosage form in different studies.

Methods: A systematic article search was performed for eligible studies published up to January, 31, 2023, through the PubMed, Embase, Cochrane Library and Chinese National Knowledge Infrastructure database. The included articles were screened by using rigorous

inclusion and exclusion criteria. Subgroup analyses were conducted according to different IVIG types, ages and economic regions. All analyses were conducted using Review Manager 5.4. Quality of studies and risk of bias were evaluated.
Results: In total, 31 randomized controlled trials were included with a sample size of 6,276 participants. IVIG could reduce the mortality (RR 0.86, 95% CI: 0.77-0.95, p = 0.005), the hospital stay (MD - 4.46, 95% CI: - 6.35 to - 2.57, p = 0.00001), and the APACHE II scores (MD - 1.65, 95% CI: - 2.89 to - 0.63, p = 0.001). Additionally, the results showed that IgM-enriched IVIG was effective in treating sepsis (RR 0.55, 95% CI: 0.40 - 0.76; p = 0.0003), while standard IVIG failed to be effective (RR 0.91, 95% CI: 0.81-1.02, p = 0.10). And the effect of IVIG in reducing neonatal mortality was inconclusive (RR 0.93, 95% CI: 0.81-1.05, p = 0.24), but it played a large role in reducing sepsis mortality in adults (RR 0.70, 95% CI: 0.57-0.86, p = 0.0006). Besides, from the subgroup of different economic regions, it indicated that IVIG was effective for sepsis in high-income (RR 0.89, 95% CI: 0.79-0.99, p = 0.03) and middle-income countries (RR 0.49, 95% CI: 0.28-0.84, p = 0.01), while no benefit was demonstrated in low-income countries (RR 0.56, 95% CI: 0.27-1.14, p = 0.11).
Conclusions: There is sufficient evidence to support that IVIG reduces sepsis mortality. IgM-enriched IVIG is effective in both adult and neonatal sepsis, while standard IVIG is only effective in adult sepsis. IVIG for sepsis has shown efficacy in high- and middle-income countries, but is still debatable in low-income countries. More RCTs are needed in the future to confirm the true clinical potential of IVIG for sepsis in low-income countries.

Eur J Pediatr. 2024 Jun 14.
doi: 10.1007/s00431-024-05624-1. Online ahead of print.

The effects of delayed appropriate antimicrobial therapy on children with Staphylococcus aureus blood infection

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Abstract
Early appropriate antimicrobial therapy plays a critical role for patients with Staphylococcus aureus bloodstream infection (SAB). We aim to determine the optimal time-window for appropriate antimicrobial therapy and evaluate the effects of delayed therapy on adverse clinical outcomes (in-hospital mortality, sepsis, and septic shock) in children with SAB by propensity score matching (PSM) analysis. Receiver-operating characteristic was used to determine the cut-off point of the time to appropriate therapy (TTAT), the patients were divided into timely and delayed appropriate antimicrobial therapy (delayed therapy) groups accordingly. The PSM was used to balance the characteristics between the two groups, controlling the effects of potential confounders. Kaplan-Meier methods and Cox proportional hazards regression were applied to the matched groups to analyze the association between delayed therapy and clinical outcomes. Inverse probability of treatment weighting and propensity score covariate adjustment were also performed to investigate the sensitivity of the results under different propensity score-based approaches. In total, 247 patients were included in this study. The optimal cut-off point of TTAT was identified as 6.4 h, with 85.0% sensitivity and 69.2% specificity (AUC 0.803, 95% confidence interval 0.702-0.904). Eighty-seven (35.22%) of the 247 patients who received delayed therapy (TTAT ≥ 6.4 h) had higher in-hospital mortality (19.54% vs 1.88%, p < 0.001), higher incidences of sepsis (44.83% vs

15.00%, p < 0.001) and septic shock (32.18% vs 6.25%, p < 0.001) when compared to timely therapy (TTAT < 6.4 h) patients. After PSM analysis, a total of 134 episodes (67 in each of the two matched groups) were further analyzed. No statistically significant difference was observed in in-hospital mortality between delayed and timely -therapy groups (log-rank test, P = 0.157). Patients with delayed therapy had a higher incidence of sepsis or septic shock than those with timely therapy (log-rank test, P = 0.009; P = 0.018, respectively). Compared to the timely-therapy group, the hazard ratio and 95% confidence interval in delayed-therapy group were 2.512 (1.227-5.144, P = 0.012) for sepsis, 3.109 (1.166-8.290, P = 0.023) for septic shock. Conclusion: Appropriate therapy delayed 6.4 h may increase the incidence of sepsis and septic shock, with similar in-hospital mortality in patients with SAB.

Skin and hair disease

Pediatr Dermatol. 2023 Jul-Aug;40(4):627-632.
doi: 10.1111/pde.15355. Epub 2023 Jun 3.

Evaluation of a paraffin-based moisturizer compared to a ceramide-based moisturizer in children with atopic dermatitis: A double-blind, randomized controlled trial

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Abstract

Background: Moisturizers are first-line therapy for treatment of atopic dermatitis (AD). Although there are multiple types of moisturizers available, head-to-head trials between different moisturizers are limited.

Objective: To evaluate if a paraffin-based moisturizer is as effective as ceramide-based moisturizer in children with AD.

Materials and methods: In this double-blind, randomized comparative trial of pediatric patients with mild to moderate AD, subjects applied either a paraffin-based or ceramide-based moisturizer twice daily. Clinical disease activity using SCOring Atopic Dermatitis (SCORAD), quality of life using Children/Infants Dermatology Life Quality Index (CDLQI/IDLQI), and transepidermal water loss (TEWL) were measured at baseline and at follow-up at 1, 3, and 6 months.

Results: Fifty-three patients were recruited (27 ceramide group and 26 paraffin group) with a mean age of 8.2 years and mean disease duration of 60 months. The mean change in SCORAD at 3 months in the ceramide-based and paraffin-based moisturizer groups was 22.1 and 21.4, respectively (p = .37). The change in CDLQI/IDLQI, TEWL over forearm and back, amount and days of topical corticosteroid required, median time to remission and disease-free days at 3 months were similar in both groups. As the 95% confidence interval (CI) of mean change in SCORAD at 3 months in both groups (0.78, 95% CI: -7.21 to 7.52) was not within the predefined margin of equivalence (-4 to +4), the conclusion of equivalence could not be proven.

Conclusion: Both the paraffin-based and ceramide-based moisturizers were comparable in improving the disease activity in children with mild to moderate AD.

Snake bite and envenomation

Surgical problems and trauma

Injury. 2023 Dec;54(12):111084.
doi: 10.1016/j.injury.2023.111084. Epub 2023 Oct 4.

Splint versus no splint after ankle fracture fixation; Results from the multi-centre post-operative ankle splint trial (PAST)

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Abstract

Background: There is considerable variation in the rehabilitation of ankle fractures. Ankle fractures treated surgically are often immobilized or splinted in the early post-operative period, despite the lack of robust evidence supporting this intervention. Thus, this randomized controlled trial aims to investigate the anecdote that splinting reduces pain and oedema.

Methods: A prospective multi-centre randomized controlled trial was performed in three trauma centres. Eligible patients were over 18 years of age that have sustained an isolated unilateral ankle fracture requiring surgical intervention. Patients were randomized to two groups receiving either; a plaster of Paris posterior back-slab or compressive bandage dressing. The post-operative rehabilitation protocol was standardized across both groups. Baseline demographics and fracture characteristics and classifications were analysed. Primary outcomes included; oedema measured by the figure-of-eight-20 technique and pain at multiple time points. Secondary outcomes included; the American Orthopaedic Foot and Ankle Society (AOFAS) score, satisfaction, unplanned emergency room (ER) visits and complications.

Results: A total of 104 comparable participants were included; 54 in the non-splint group and 50 in the splint group. There was no significance difference in ankle oedema, ankle oedema compared to contralateral ankle and pain scores between the two groups ($P = 0.56$, $P = 0.25$, $P = 0.39$ respectively). Patient satisfaction was higher in the early postoperative period in the non-splint group ($P = 0.016$). The AOFAS score was not significantly different across any time point ($P = 0.534$). In the splint group, there was a 46% rate of splint-related complaints and complications. Unplanned ER visits occurred in 46% of the splint group and 7.4% of the non-splint group ($P < 0.001$). There were 2 wound infections, 1 non-union and 1 deep vein thrombosis in the splint group. There was 1 wound infection and 1 deep vein thrombosis in the no-splint group ($P = 0.481$) CONCLUSION: The routine use of a splint does not add any perceivable benefit to the postoperative course of an ankle fracture fixation, particularly in the reduction of oedema and postoperative pain. Another key finding is that the absence of a splint does not appear to result in higher complication rates, instead leads to higher unplanned ER visits and lower early satisfaction rates.

J Pediatr Surg. 2024 Jun;59(6):1210-1218.
doi: 10.1016/j.jpedsurg.2023.12.001. Epub 2023 Dec 10.

Care of Injured Children Compared to Adults at District and Regional Hospitals in Ghana and the Impact of a Trauma Intake Form: A Stepped-Wedge Cluster Randomized Trial

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Abstract

Background: This study aimed to determine the effectiveness of a standardized trauma intake form (TIF) to improve achievement of key performance indicators (KPIs) of initial trauma care among injured children, compared to adults, at non-tertiary hospitals in Ghana.

Methods: A stepped-wedge cluster randomized trial was performed with research assistants directly observing the management of injured patients before and after introducing the TIF at emergency units of 8 non-tertiary hospitals for 17.5 months. Differences in outcomes between children and adults in periods before and after TIF introduction were determined with multivariable logistic regression. Differences in outcomes among children after TIF introduction were determined using generalized linear mixed regression.

Results: Management of 3889 injured patients was observed; 757 (19%) were children <18 years. Trauma care KPIs at baseline were lower for children compared to adults. Improvements in primary survey KPIs were observed among children after TIF introduction. Examples include airway assessment [279 (71%) to 359 (98%); adjusted odds ratio (AOR): 74.42, p = 0.005)] and chest examination [225 (58%) to 349 (95%); AOR 53.80, p = 0.002)]. However, despite these improvements, achievement of KPIs was still lower compared to adults. Examples are pelvic fracture evaluation [children: 295 (80%) vs adults: 1416 (88%), AOR: 0.56, p = 0.001] and respiratory rate assessment (children: 310 (84%) vs adults: 1458 (91%), AOR: 058, p = 0.030).

Conclusions: While the TIF was effective in improving most KPIs of pediatric trauma care, more targeted education is needed to bridge the gap in quality between pediatric and adult trauma care at non-tertiary hospitals in Ghana and other low- and middle-income countries.

Telemedicine

Indian J Pediatr. 2024 Feb 13.
doi: 10.1007/s12098-024-05028-x. Online ahead of print.

Comparison of Telemedicine versus In-Person Visit for Control of Asthma in Children aged 7-17 years: A Randomized Controlled Trial

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Abstract

Objectives: To compare asthma control between telemedicine and in-person visit in children aged 7 to 17 y.

Methods: A non-inferiority randomized-controlled trial was conducted at a pediatric chest clinic, involving a total of 192 patients, with 96 children in each group of telemedicine and in-person follow-up.

Results: There was a significant improvement in the mean asthma control test (ACT)/ Childhood asthma control test (C-ACT) scores from baseline to three months in both groups, with no significant difference in the change of means between the two groups. The mean difference in ACT/C-ACT score at three months in the telemedicine and in-person visit group

was -0.35; 95% CI (-1.30 to +0.10) [p-value 0.09]. There was a significant change in the mean Pediatric Quality of Life index (PQLI) scores from 57.2 ± 10.2 to 66.82 ± 7.99 in the telemedicine group and from 56.1 ± 11.7 to 66.71 ± 4.66 in the in-person visit group, however the mean difference in PQLI score in both the groups was not significant (p = 0.91). There was no significant difference in the number of asthma exacerbations (4 vs. 1) between telemedicine and in-person visit (p = 0.10). The mean telemedicine satisfaction questionnaire score in this study was 3.8 ± 0.7, which indicates that most of the parents were satisfied with the telemedicine follow-up process.
Conclusions: This study revealed that telemedicine is non-inferior to in-person visit for follow-up of children with asthma and can be used as an alternative to in-person visit for the management of asthma, especially in remote settings and pandemic situations.

Trypanosomiasis

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

Treatment of tuberculosis

Lancet Respir Med. 2024 Feb;12(2):117-128.
doi: 10.1016/S2213-2600(23)00389-2. Epub 2023 Nov 16.
Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial
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Collaborators, Affiliations expand
Abstract
Background: Around 500 000 people worldwide develop rifampicin-resistant tuberculosis each year. The proportion of successful treatment outcomes remains low and new treatments are needed. Following an interim analysis, we report the final safety and efficacy outcomes of the TB-PRACTECAL trial, evaluating the safety and efficacy of oral regimens for the treatment of rifampicin-resistant tuberculosis.
Methods: This open-label, randomised, controlled, multi-arm, multicentre, non-inferiority trial was conducted at seven hospital and community sites in Uzbekistan, Belarus, and South Africa, and enrolled participants aged 15 years and older with pulmonary rifampicin-resistant tuberculosis. Participants were randomly assigned, in a 1:1:1:1 ratio using variable block randomisation and stratified by trial site, to receive 36-80 week standard care; 24-week oral bedaquiline, pretomanid, and linezolid (BPaL); BPaL plus clofazimine (BPaLC); or BPaL plus moxifloxacin (BPaLM) in stage one of the trial, and in a 1:1 ratio to receive standard care

or BPaLM in stage two of the trial, the results of which are described here. Laboratory staff and trial sponsors were masked to group assignment and outcomes were assessed by unmasked investigators. The primary outcome was the percentage of participants with a composite unfavourable outcome (treatment failure, death, treatment discontinuation, disease recurrence, or loss to follow-up) at 72 weeks after randomisation in the modified intention-to-treat population (all participants with rifampicin-resistant disease who received at least one dose of study medication) and the per-protocol population (a subset of the modified intention-to-treat population excluding participants who did not complete a protocol-adherent course of treatment (other than because of treatment failure or death) and those who discontinued treatment early because they violated at least one of the inclusion or exclusion criteria). Safety was measured in the safety population. The non-inferiority margin was 12%. This trial is registered with ClinicalTrials.gov, NCT02589782, and is complete.

Findings: Between Jan 16, 2017, and March 18, 2021, 680 patients were screened for eligibility, of whom 552 were enrolled and randomly assigned (152 to the standard care group, 151 to the BPaLM group, 126 to the BPaLC group, and 123 to the BPaL group). The standard care and BPaLM groups proceeded to stage two and are reported here, post-hoc analyses of the BPaLC and BPaL groups are also reported. 151 participants in the BPaLM group and 151 in the standard care group were included in the safety population, with 138 in the BPaLM group and 137 in the standard care group in the modified intention-to-treat population. In the modified intention-to-treat population, unfavourable outcomes were reported in 16 (12%) of 137 participants for whom outcome was assessable in the BPaLM group and 56 (41%) of 137 participants in the standard care group (risk difference -29·2 percentage points [96·6% CI -39·8 to -18·6]; non-inferiority and superiority p<0·0001). 34 (23%) of 151 participants receiving BPaLM had adverse events of grade 3 or higher or serious adverse events, compared with 72 (48%) of 151 participants receiving standard care (risk difference -25·2 percentage points [96·6% CI -36·4 to -13·9]). Five deaths were reported in the standard care group by week 72, of which one (COVID-19 pneumonia) was unrelated to treatment and four (acute pancreatitis, suicide, sudden death, and sudden cardiac death) were judged to be treatment-related.

Interpretation: The 24-week, all-oral BPaLM regimen is safe and efficacious for the treatment of pulmonary rifampicin-resistant tuberculosis, and was added to the WHO guidance for treatment of this condition in 2022. These findings will be key to BPaLM becoming the preferred regimen for adolescents and adults with pulmonary rifampicin-resistant tuberculosis.

Clin Infect Dis. 2024 Apr 9:ciae193.
doi: 10.1093/cid/ciae193. Online ahead of print.

Clinical outcomes in children living with HIV treated for non-severe tuberculosis in the SHINE Trial

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Abstract

Background: Children living with HIV(CLWH) are at high risk of tuberculosis(TB) and face poor outcomes, despite antiretroviral treatment(ART). We evaluated outcomes in CLWH and HIV-uninfected children treated for non-severe TB in the SHINE trial.
Methods: SHINE was a randomized trial that enrolled children aged <16 years with smear-negative, non-severe TB who were randomized to receive 4 vs 6 months of TB treatment and followed for 72 weeks. We assessed TB relapse/recurrence, mortality, hospitalizations, grade ≥3 adverse events by HIV status, and HIV virological suppression in CLWH.
Results: Of 1204 enrolled, 127(11%) were CLWH, of similar age (median(IQR) 3.6(1.2, 10.3) vs. 3.5(1.5, 6.9)years, p= 0.07), but more underweight (WAZ; -2.3(-3.3, -0.8) vs -1.0(-1.8, -0.2), p<0.01) and anemic (hemoglobin 9.5(8.7, 10.9) vs 11.5(10.4, 12.3)g/dl, p<0.01) compared to HIV-uninfected children. 68(54%) CLWH were ART-naïve; baseline median CD4 count 719(241-1134) cells/mm3, CD4% 16(10-26)%). CLWH were more likely to be hospitalized (aOR=2.4(1.3-4.6)) and die (aHR(95%CI) 2.6(1.2,5.8)). HIV status, age <3 years (aHR 6.3(1.5,27.3)), malnutrition (aHR 6.2(2.4,15.9)) and hemoglobin <7g/dl(aHR 3.8(1.3,11.5) independently predicted mortality. Among children with available VL, 45% and 61% CLWH had VL<1000copies/ml at weeks 24 and 48, respectively. There was no difference in the effect of randomized treatment duration (4 vs 6 months) on TB treatment outcomes by HIV status (p for interaction=0.42).
Conclusions: We found no evidence of a difference in TB outcomes between 4 and 6 months of treatment for CLWH treated for non-severe TB. Irrespective of TB treatment duration, CLWH had higher rates of mortality and hospitalization than HIV-uninfected counterparts.

Clin Infect Dis. 2024 Jun 14;78(6):1601-1607.
doi: 10.1093/cid/ciad776.

Community-Wide Universal HIV Test and Treat Intervention Reduces Tuberculosis Transmission in Rural Uganda: A Cluster-Randomized Trial

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Abstract
Background: Human immunodeficiency virus (HIV) treatment reduces tuberculosis (TB) disease and mortality; however, the population-level impact of universal HIV-test-and-treat interventions on TB infection and transmission remain unclear.
Methods: In a sub-study nested in the SEARCH trial, a community cluster-randomized trial (NCT01864603), we assessed whether a universal HIV-test-and-treat intervention reduced population-level incident TB infection in rural Uganda. Intervention communities received annual, population-level HIV testing and patient-centered linkage. Control communities received population-level HIV testing at baseline and endline. We compared estimated incident TB infection by arms, defined by tuberculin skin test conversion in a cohort of persons aged 5 and older, adjusting for participation and predictors of infection, and accounting for clustering.
Results: Of the 32 trial communities, 9 were included, comprising 90 801 participants (43 127 intervention and 47 674 control). One-year cumulative incidence of TB infection was 16% in

the intervention and 22% in the control; SEARCH reduced the population-level risk of incident TB infection by 27% (adjusted risk ratio = 0.73; 95% confidence interval [CI]: .57-.92, P = .005). In pre-specified analyses, the effect was largest among children aged 5-11 years and males.
Conclusions: A universal HIV-test-and-treat intervention reduced incident TB infection, a marker of population-level TB transmission. Investments in community-level HIV interventions have broader population-level benefits, including TB reductions.

Prevention of tuberculosis, treatment of latent tuberculosis

Lancet Child Adolesc Health. 2023 Oct;7(10):708-717.
doi: 10.1016/S2352-4642(23)00174-8. Epub 2023 Aug 24.
Timing of maternal isoniazid preventive therapy on tuberculosis infection among infants exposed to HIV in low-income and middle-income settings: a secondary analysis of the TB APPRISE trial
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Abstract
Background: Infants born to women with HIV in settings with a high tuberculosis burden are at risk of tuberculosis infection and rapid progression to active disease. Maternal isoniazid preventive therapy might mitigate this risk, but optimal timing of therapy remains unclear. The TB APPRISE trial showed that initiation of isoniazid during pregnancy resulted in more frequent adverse pregnancy outcomes than when initiated postpartum. We aimed to determine the proportion of infants testing positive for tuberculosis infection born to mothers who initiated isoniazid therapy antepartum compared with postpartum using two commonly used tests, the test agreement, and predictors of test positivity.
Methods: TB APPRISE was a randomised, double-blind, placebo-controlled, non-inferiority trial done at 13 study sites across eight countries (Botswana, Haiti, India, South Africa, Tanzania, Thailand, Uganda, and Zimbabwe). Pregnant women with HIV on antiretroviral therapy were randomly assigned to receive immediate isoniazid preventive therapy (28 weeks isoniazid [300 mg daily], then placebo until week 40 after delivery) or deferred treatment (placebo until week 12 after delivery, then isoniazid [300 mg daily] for 28 weeks). Mother-infant pairs were followed up until 48 weeks after delivery. We included all liveborn infants with a tuberculin skin test or interferon-γ release assay (IGRA) at 44 weeks. The outcomes assessed in this secondary analysis were tuberculosis test positivity by study group, test agreement, and predictors of test positivity. This study was registered with ClinicalTrials.gov, NCT01494038.
Findings: Between Aug 19, 2014, and April 4, 2016, 956 mothers were randomly assigned, and 749 mother-child pairs were included in this secondary analysis. Of 749 infants, 694

(93%) received Bacille Calmette-Guérin (BCG) vaccination, 675 (90%) were born to mothers who had completed isoniazid treatment, 20 (3%) were exposed to tuberculosis, seven (1%) became HIV positive, and one (<1%) developed probable tuberculosis. 43 (6%; 95% CI 4-8]) of 732 infants had a positive IGRA test result and 55 (8%; 6-10) of 727 infants had a positive tuberculin skin test result. Test positivity did not differ by study group (p=0·88 for IGRA; p=0·44 for tuberculin skin test). Test agreement was poor (κ=0·107 [95% CI 0·002-0·212]). Infant tuberculin skin test positivity was associated with breastfeeding (adjusted odds ratio 6·63 [95% CI 1·57-27·9]), BCG vaccination (4·97 [1·50-16·43]), and maternal tuberculin skin test positivity at delivery (3·28 [1·70-6·33]); IGRA positivity was associated with female sex (2·09 [1·06-4·14]).
Interpretation: Deferral of maternal isoniazid preventive therapy to early postpartum had no effect on infant tuberculosis acquisition in our trial population, regardless of the diagnostic test used; however, tuberculosis test agreement is poor during infancy.

Lancet Glob Health. 2023 Dec;11(12):e1922-e1930.
doi: 10.1016/S2214-109X(23)00451-5. Epub 2023 Oct 30.

Cost-effectiveness of community-based household tuberculosis contact management for children in Cameroon and Uganda: a modelling analysis of a cluster-randomised trial

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Abstract
Background: WHO recommends household contact management (HCM) including contact screening and tuberculosis-preventive treatment (TPT) for eligible children. The CONTACT trial found increased TPT initiation and completion rates when community health workers were used for HCM in Cameroon and Uganda.
Methods: We did a cost-utility analysis of the CONTACT trial using a health-system perspective to estimate the health impact, health-system costs, and cost-effectiveness of community-based versus facility-based HCM models of care. A decision-analytical modelling approach was used to evaluate the cost-effectiveness of the intervention compared with the standard of care using trial data on cascade of care, intervention effects, and resource use. Health outcomes were based on modelled progression to tuberculosis, mortality, and discounted disability-adjusted life-years (DALYs) averted. Health-care resource use, outcomes, costs (2021 US$), and cost-effectiveness are presented.
Findings: For every 1000 index patients diagnosed with tuberculosis, the intervention increased the number of TPT courses by 1110 (95% uncertainty interval 894 to 1227) in Cameroon and by 1078 (796 to 1220) in Uganda compared with the control model. The intervention prevented 15 (-3 to 49) tuberculosis deaths in Cameroon and 10 (-20 to 33) in Uganda. The incremental cost-effectiveness ratio was $620 per DALY averted in Cameroon and $970 per DALY averted in Uganda.
Interpretation: Community-based HCM approaches can substantially reduce child tuberculosis deaths and in our case would be considered cost-effective at willingness-to-pay thresholds of $1000 per DALY averted. Their impact and cost-effectiveness are likely to be greatest where baseline HCM coverage is lowest.

Lancet Glob Health. 2023 Dec;11(12):e1911-e1921.
doi: 10.1016/S2214-109X(23)00430-8. Epub 2023 Oct 30.

Effectiveness of a community-based approach for the investigation and management of children with household tuberculosis contact in Cameroon and Uganda: a cluster-randomised trial

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Abstract

Background: Globally, the uptake of tuberculosis-preventive treatment (TPT) among children with household tuberculosis contact remains low, partly due to the necessity of bringing children to health facilities for investigations. This study aimed to evaluate the effect on TPT initiation and completion of community-based approaches to tuberculosis contact investigations in Cameroon and Uganda.

Methods: We did a parallel, cluster-randomised, controlled trial across 20 clusters (consisting of 25 district hospitals and primary health centres) in Cameroon and Uganda, which were randomised (1:1) to receive a community-based approach (intervention group) or standard-of-care facility-based approach to contact screening and management (control group). The community-based approach consisted of symptom-based tuberculosis screening of all household contacts by community health workers at the household, with referral of symptomatic contacts to local facilities for investigations. Initiation of TPT (3-month course of rifampicin-isoniazid) was done by a nurse in the household, and home visits for TPT follow-up were done by community health workers. Index patients were people aged 15 years or older with bacteriologically confirmed, drug-susceptible, pulmonary tuberculosis diagnosed less than 1 month before inclusion and who declared at least one child or young adolescent (aged 0-14 years) household contact. The primary endpoint was the proportion of declared child contacts in the TPT target group (those aged <5 years irrespective of HIV status, and children aged 5-14 years living with HIV) who commenced and completed TPT, assessed in the modified intention-to-treat population (excluding enrolled index patients and their contacts who did not fit the eligibility criteria). Descriptive cascade of care assessment and generalised linear mixed modelling were used for comparison. This study is registered with ClinicalTrials.gov (NCT03832023).

Findings: The study included nine clusters in the intervention group (after excluding one cluster that did not enrol any index patients for >2 months) and ten in the control group. Between Oct 14, 2019 and Jan 13, 2022, 2894 child contacts were declared by 899 index patients with bacteriologically confirmed tuberculosis. Among all child contacts declared, 1548 (81·9%) of 1889 in the intervention group and 475 (47·3%) of 1005 in the control group were screened for tuberculosis. 1400 (48·4%) child contacts were considered to be in the TPT target group: 941 (49·8%) of 1889 in the intervention group and 459 (45·7%) of 1005 in the control group. In the TPT target group, TPT was commenced and completed in 752 (79·9%) of 941 child contacts in the intervention group and 283 (61·7%) of 459 in the control group (odds ratio 3·06 [95% CI 1·24-7·53]).

Interpretation: A community-based approach using community health workers can significantly increase contact investigation coverage and TPT completion among eligible child contacts in a tuberculosis-endemic setting.

J Acquir Immune Defic Syndr. 2024 Apr 15;95(5):431-438.
doi: 10.1097/QAI.0000000000003379. Epub 2024 Mar 11.

Integration of HIV Testing in a Community Intervention for Tuberculosis Screening Among Household Contacts of Patients with Tuberculosis in Cameroon and Uganda

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Abstract

Introduction: People living with HIV are considered at higher risk of developing severe forms of tuberculosis (TB) disease. Providing HIV testing to TB-exposed people is therefore critical. We present the results of integrating HIV testing into a community-based intervention for household TB contact management in Cameroon and Uganda.

Methods: Trained community health workers visited the households of index patients with TB identified in 3 urban/semiurban and 6 rural districts or subdistricts as part of a cluster-randomized trial and provided TB screening to all household contacts. Voluntary HIV counseling and testing were offered to contacts aged 5 years or older with unknown HIV status. We describe the cascade of care for HIV testing and the factors associated with the acceptance of HIV testing.

Results: Overall, 1983 household contacts aged 5 years or older were screened for TB. Of these contacts, 1652 (83.3%) did not know their HIV status, 1457 (88.2%) accepted HIV testing, and 1439 (98.8%) received testing. HIV testing acceptance was lower among adults than children [adjusted odds ratio (aOR) = 0.35, 95% confidence interval (CI): 0.22 to 0.55], those living in household of an HIV-positive vs HIV-negative index case (aOR = 0.56, 95% CI: 0.38 to 0.83), and contacts requiring a reassessment visit after the initial TB screening visit vs asymptomatic contacts (aOR = 0.20, 95% CI: 0.06 to 0.67) and was higher if living in Uganda vs Cameroon (aOR = 4.54, 95% CI: 1.17 to 17.62) or if another contact of the same index case was tested for HIV (aOR = 9.22, 95% CI: 5.25 to 16.18).

Conclusion: HIV testing can be integrated into community-based household TB contact screening and is well-accepted.

PLoS Med. 2024 May 31;21(5):e1004393.
doi: 10.1371/journal.pmed.1004393. eCollection 2024 May.

Incidence of self-reported tuberculosis treatment with community-wide universal testing and treatment for HIV and tuberculosis screening in Zambia and South Africa: A planned analysis of the HPTN 071 (PopART) cluster-randomised trial

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Abstract

Background: HIV is a potent risk factor for tuberculosis (TB). Therefore, community-wide universal testing and treatment for HIV (UTT) could contribute to TB control, but evidence for this is limited. Community-wide TB screening can decrease population-level TB prevalence. Combining UTT with TB screening could therefore significantly impact TB control in sub-Saharan Africa, but to our knowledge there is no evidence for this combined approach.

Methods and findings: HPTN 071 (PopART) was a community-randomised trial conducted between November 2013 to July 2018; 21 Zambian and South African communities (with a total population of approximately 1 million individuals) were randomised to arms A (community-wide UTT and TB screening), B (community-wide universal HIV testing with treatment following national guidelines and TB screening), or C (standard-of-care). In a cohort of randomly selected adults (18 to 44 years) enrolled between 2013 and 2015 from all 21 communities (total size 38,474; 27,139 [71%] female; 8,004 [21%] HIV positive) and followed-up annually for 36 months to measure the population-level impact of the interventions, data on self-reported TB treatment in the previous 12 months (self-reported TB) were collected by trained research assistants and recorded using a structured questionnaire at each study visit. In this prespecified analysis of the trial, self-reported TB incidence rates were measured by calendar year between 2014 and 2017/2018. A p-value ≤0.05 on hypothesis testing was defined as reaching statistical significance. Between January 2014 and July 2018, 38,287 individuals were followed-up: 494 self-reported TB during 104,877 person-years. Overall incidence rates were similar across all arms in 2014 and 2015 (0.33 to 0.46/100 person-years). In 2016 incidence rates were lower in arm A compared to C overall (adjusted rate ratio [aRR] 0.48 [95% confidence interval (95% CI) 0.28 to 0.81; p = 0.01]), with statistical significance reached. In 2017/2018, while incidence rates were lower in arm A compared to C, statistical significance was not reached (aRR 0.58 [95% CI 0.27 to 1.22; p = 0.13]). Among people living with HIV (PLHIV) incidence rates were lower in arm A compared to C in 2016 (RR 0.56 [95% CI 0.29 to 1.08; p = 0.08]) and 2017/2018 (RR 0.50 [95% CI 0.26 to 0.95; p = 0.04]); statistical significance was only reached in 2017/2018. Incidence rates in arms B and C were similar, overall and among PLHIV. Among HIV-negative individuals, there were too few events for cross-arm comparisons. Study limitations include the use of self-report which may have been subject to under-reporting, limited covariate adjustment due to the small number of events, and high losses to follow-up over time.
Conclusions: In this study, community-wide UTT and TB screening resulted in substantially lower TB incidence among PLHIV at population-level, compared to standard-of-care, with statistical significance reached in the final study year. There was also some evidence this translated to a decrease in self-reported TB incidence overall in the population. Reduction in arm A but not B suggests UTT drove the observed effect. Our data support the role of UTT in TB control, in addition to HIV control, in high TB/HIV burden settings.

Lancet Respir Med. 2024 Jun;12(6):433-443.
doi: 10.1016/S2213-2600(24)00076-6. Epub 2024 Mar 26.

High-dose, short-duration versus standard rifampicin for tuberculosis preventive treatment: a partially blinded, three-arm, non-inferiority, randomised, controlled trial

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Abstract

Background: Tuberculosis preventive treatment (TPT) is a key component of tuberculosis elimination. To improve completion and reduce the burden for people and health systems, short, safe, and effective TPT regimens are needed. We aimed to compare safety and

treatment completion of various doses and durations of rifampicin in people who were recommended to receive TPT.
Methods: This partially blinded, parallel-arm, non-inferiority, randomised, controlled, phase 2b trial was done at seven university-affiliated clinics in Canada, Indonesia, and Viet Nam. Participants aged 10 years or older were included if they had an indication for TPT according to WHO guidelines for Indonesia and Viet Nam, or Canadian guidelines for Canadian sites, and a positive tuberculin skin test or interferon-γ release assay. Participants were randomly assigned (1:1:1) to receive oral rifampicin at 10 mg/kg once daily for 4 months (standard-dose group), 20 mg/kg daily for 2 months (20 mg/kg group), or 30 mg/kg daily for 2 months (30 mg/kg group). The randomisation sequence was computer generated with blocks of variable size (three, six, and nine) and stratified by country for Indonesia and Viet Nam, and by city within Canada. Participants and investigators were masked to dose in high-dose groups, but unmasked to duration in all groups. The two co-primary outcomes were safety (in the safety population, in which participants received at least one dose of the study drug) and treatment completion (in the modified intention-to-treat [mITT] population, excluding those ineligible after randomisation). Protocol-defined adverse events were defined as grade 3 or worse, or rash or allergy of any grade, judged by an independent and masked panel as possibly or probably related to the study. A margin of 4% was used to assess non-inferiority. This study is registered with ClinicalTrials.gov, NCT03988933 (active).
Findings: Between Sept 1, 2019, and Sept 30, 2022, 1692 people were assessed for eligibility, 1376 were randomly assigned, and eight were excluded after randomisation. 1368 participants were included in the mITT population (454 in the standard group, 461 in the 20 mg/kg group, and 453 in the 30 mg/kg group). 589 (43%) participants were male and 779 (57%) were female. 372 (82%) in the standard-dose group, 329 (71%) in the 20 mg/kg group, and 293 (65%) in the 30 mg/kg group completed treatment. No participants in the standard-dose group, one (<1%) of 441 participants in the 20 mg/kg group, and four (1%) of 423 in the 30 mg/kg group developed grade 3 hepatotoxicity. Risk of protocol-defined adverse events was higher in the 30 mg/kg group than in the standard-dose group (adjusted risk difference 4·6% [95% CI 1·8 to 7·4]) or the 20 mg/kg group (5·1% [2·3 to 7·8]). There was no difference in the risk of adverse events between the 20 mg/kg and standard-dose groups (-0·5% [95% CI -2·4 to 1·5]; non-inferiority met). Completion was lower in the 20 mg/kg group (-7·8% [95% CI -13·6 to -2·0]) and the 30 mg/kg group (-15·4% [-21·4 to -9·4]) than in the standard-dose group.
Interpretation: In this trial, 2 months of 30 mg/kg daily rifampicin had significantly worse safety and completion than 4 months of 10 mg/kg daily and 2 months of 20 mg/kg daily (the latter, a fully blinded comparison); we do not consider 30 mg/kg to be a good option for TPT. Rifampicin at 20 mg/kg daily for 2 months was as safe as standard treatment, but with lower completion. This difference remains unexplained.

Int J Infect Dis. 2023 Sep;134:63-70.
doi: 10.1016/j.ijid.2023.05.010. Epub 2023 May 20.

Vitamin D supplementation to prevent tuberculosis infection in South African schoolchildren: multicenter phase 3 double-blind randomized placebo-controlled trial (ViDiKids)

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Griffiths [2], Geeta Trilok Kumar [8], Suzanne Filteau [9], Richard L Hooper [2], Robert J Wilkinson [10], Linda-Gail Bekker [3], Adrian R Martineau [11]

Abstract

Objectives: To determine whether weekly oral supplementation with 10,000 IU vitamin D_3 for 3 years reduces the risk of sensitization to M. tuberculosis in South African schoolchildren aged 6-11 years with negative QuantiFERON-tuberculosis (TB) Gold Plus (QFT-Plus) assay results at baseline.

Methods: We conducted a phase 3 randomized placebo-controlled trial in 1682 children attending 23 primary schools in Cape Town. The primary outcome was a positive end-trial QFT-Plus result, analyzed using a mixed effects logistic regression model with the school of attendance included as a random effect.

Results: 829 vs. 853 QFT-Plus-negative children were randomized to receive vitamin D_3 vs. placebo, respectively. Mean end-study 25(OH)D concentrations in participants randomized to vitamin D vs. placebo were 104.3 vs 64.7 nmol/l, respectively (95% confidence interval for difference, 37.6 to 41.9 nmol/l). A total of 76/667 (11.4%) participants allocated to vitamin D vs. 89/687 (13.0%) participants allocated to placebo tested QFT-Plus positive at 3-year follow-up (adjusted odds ratio 0.86, 95% confidence interval 0.62-1.19, P = 0.35).

Conclusion: Weekly oral supplementation with 10,000 IU vitamin D_3 for 3 years elevated serum 25(OH)D concentrations among QFT-Plus-negative Cape Town schoolchildren but did not reduce their risk of QFT-Plus conversion.

Diagnosis of tuberculosis

Typhus

Pediatr Infect Dis J. 2023 Sep 26.
doi: 10.1097/INF.0000000000004104. Online ahead of print.

Open-Labeled Randomized Controlled Trial on Efficacy of Azithromycin Versus Doxycycline in Pediatric Scrub Typhus

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Abstract

Background: Doxycycline (DX) is the first-line therapeutic agent for scrub typhus. Macrolides, especially azithromycin (AZ), have been found to be equally efficacious as DX for treating scrub typhus in adults. We conducted this study to compare the efficacy of AZ versus DX in pediatric scrub typhus.

Study design: Open-label randomized controlled trial.

Methods: Children 1-14 years of age suffering from acute febrile illness of ≥5 days and with a positive scrub IgM serology were randomized to receive either DX (2.2 mg/kg/dose twice daily in <40 kg; 100 mg BD in >40 kg for 7 days) or AZ (10 mg/kg/day for 5 days). The primary outcome was defervescence within 7 days of DX or 5 days of AZ.

Results: We had 75 children randomized and analyzed using an intention-to-treat approach and 60 children analyzed via per-protocol analysis. The proportion of children achieving defervescence was comparable in 2 groups [per-protocol analysis: 90.9% in the DX group vs.

96.3% in the AZ group, RR: 0.94 (95% CI: 0.83-1.08)]. On Kaplan-Meier curves, AZ showed a significantly higher probability of defervescence at any time point during treatment as compared with DX (log-rank test P value 0.035).

Indian J Med Microbiol. 2023 Nov-Dec:46:100460.
doi: 10.1016/j.ijmmb.2023.100460. Epub 2023 Aug 21.

Macrolides versus other antibiotics in pediatric scrub typhus: A meta-analysis

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Abstract

Background: While Doxycycline is the recommended drug for treating scrub typhus, there is a growing trend of using Macrolides and Other antibiotics due to their perceived advantages. In this study, we compared the efficacy of Macrolides versus Other antibiotics in the treatment of pediatric scrub typhus.

Methods: Meta-analysis of randomized controlled trials (RCTs) with GRADE (Grading of Recommendations, Assessment, Development and Evaluation) application. Major databases were searched till 30th December 2022. Children of all age groups were included. Primary outcomes included mortality rate and time to defervescence (h).

Results: Of the 103 citations retrieved, 5 trials, including 383 children up to 15 years of age with probable and confirmed cases of scrub typhus, were included. None of the trials reported mortality rate. The pooled results from the trials found no significant difference between Azithromycin and Other antibiotics for any of the outcome measures. The certainty of evidence for the primary outcome was deemed to be of "very low certainty", while the certainty of evidence for the secondary outcomes ranged from "low to moderate certainty".

Conclusions: The current meta-analysis revealed that there was no significant difference between Azithromycin and Other antibiotics (such as Doxycycline and Chloramphenicol) in the treatment of scrub typhus in children. However, it's important to note that the evidence generated for the primary outcome was of "very low certainty".

Ultrasound

Anaesth Crit Care Pain Med. 2023 Oct;42(5):101247.
doi: 10.1016/j.accpm.2023.101247. Epub 2023 May 19.

Comparison between in-plane and out-of-plane techniques for ultrasound guided cannulation of the left brachiocephalic vein in pediatric population: A randomised controlled trial

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Abstract

Background and aims: Brachiocephalic vein is a novel site for central venous cannulation in infants. It becomes useful in patients where the internal jugular vein lumen is small (e.g.,

volume deficient patient), patients with a history of multiple cannulations, and in whom subclavian puncture is contraindicated.
Methods: In this randomized double-blinded study, 100 patients, aged between 0 and 1 year scheduled for elective central venous cannulation were recruited. The patients were allocated into two groups (50 patients in each). Group I patients had ultrasound (US) guided cannulation of the left brachiocephalic vein (BCV) by inserting a needle in-plane to the US probe from lateral to the medial direction, whereas Group II patients underwent cannulation of the BCV via an out-of-plane approach.
Results: The first-attempt success rate was significantly higher in Group I (74%) than in Group II (36%) ($p < 0.001$). The total success rate was higher in group I (98%) than in group II (88%) however the difference was statistically insignificant ($p > 0.05$). The mean BCV cannulation time was significantly shorter in group I (35.46 ± 25.10) than in group II (65.24 ± 40.26) ($p < 0.001$). The rate of unsuccessful BCV cannulation (12%) and hematoma development (12%) was significantly higher in group II than in group I (2%).
Conclusion: Compared to the out-of-plane approach of left BCV cannulation, US-guided in-plane cannulation of the left BCV increased the first-attempt success rate, decreased the number of puncture attempts, and decreased the time required for cannulation.

Urinary tract infection

Urology

Vaccines and immunization

Vaccine. 2024 May 22;42(14):3337-3345.
doi: 10.1016/j.vaccine.2024.04.034. Epub 2024 Apr 17.
Impact of nutritional status on vaccine-induced immunity in children living in South Africa: Investigating the B-cell repertoire and metabolic hormones
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Free article
Abstract
Objectives: We explored the role of metabolic hormones and the B-cell repertoire in the association between nutritional status and vaccine responses.
Methods: In this prospective cohort study, nested within a larger randomized open-label trial, 211 South African children received two doses of measles vaccine and two or three doses of pneumococcal conjugate vaccine (PCV). Metabolic markers (leptin, ghrelin and adiponectin) and distribution of B-cell subsets ($n = 106$) were assessed at 18 months of age.
Results: Children with a weight-for-height z-score (WHZ) ≤ -1 standard deviation (SD) at booster vaccination had a decreased mean serotype-specific PCV IgG response compared

with those with WHZ > -1 and <+1 SD or WHZ ≥ +1 SD at 9 months post-booster (18 months of age). (Naive) pre-germinal center B-cells were associated with pneumococcal antibody decay between one to nine months post-booster. Predictive performance of elastic net models for the combined effect of B-cell subsets, metabolic hormones and nutritional status (in addition to age, sex, and randomization group) on measles and PCV vaccine response had an average area under the receiver operating curve of 0.9 and 0.7, respectively.
Conclusions: The combined effect of B-cell subsets, metabolic hormones and nutritional status correlated well with the vaccination response for measles and most PCV serotypes.

Vaccine coverage and administration

Nature. 2024 Mar 13.
doi: 10.1038/s41586-024-07158-w. Online ahead of print.
Last-mile delivery increases vaccine uptake in Sierra Leone
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Abstract
Less than 30% of people in Africa received a dose of the COVID-19 vaccine even 18 months after vaccine development[1]. Here, motivated by the observation that residents of remote, rural areas of Sierra Leone faced severe access difficulties[2], we conducted an intervention with last-mile delivery of doses and health professionals to the most inaccessible areas, along with community mobilization. A cluster randomized controlled trial in 150 communities showed that this intervention with mobile vaccination teams increased the immunization rate by about 26 percentage points within 48-72 h. Moreover, auxiliary populations visited our community vaccination points, which more than doubled the number of inoculations administered. The additional people vaccinated per intervention site translated to an implementation cost of US $33 per person vaccinated. Transportation to reach remote villages accounted for a large share of total intervention costs. Therefore, bundling multiple maternal and child health interventions in the same visit would further reduce costs per person treated. Current research on vaccine delivery maintains a large focus on individual behavioural issues such as hesitancy. Our study demonstrates that prioritizing mobile services to overcome access difficulties faced by remote populations in developing countries can generate increased returns in terms of uptake of health services[3].

Cochrane Database Syst Rev. 2023 Dec 6;12(12):CD008145.
doi: 10.1002/14651858.CD008145.pub4.
Interventions for improving coverage of childhood immunisation in low- and middle-income countries
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Abstract

Background: Immunisation plays a major role in reducing childhood morbidity and mortality. Getting children immunised against potentially fatal and debilitating vaccine-preventable diseases remains a challenge despite the availability of efficacious vaccines, particularly in low- and middle-income countries. With the introduction of new vaccines, this becomes increasingly difficult. There is therefore a current need to synthesise the available evidence on the strategies used to bridge this gap. This is a second update of the Cochrane Review first published in 2011 and updated in 2016, and it focuses on interventions for improving childhood immunisation coverage in low- and middle-income countries.
Objectives: To evaluate the effectiveness of intervention strategies to boost demand and supply of childhood vaccines, and sustain high childhood immunisation coverage in low- and middle-income countries.
Search methods: We searched CENTRAL, MEDLINE, CINAHL, and Global Index Medicus (11 July 2022). We searched Embase, LILACS, and Sociological Abstracts (2 September 2014). We searched WHO ICTRP and ClinicalTrials.gov (11 July 2022). In addition, we screened reference lists of relevant systematic reviews for potentially eligible studies, and carried out a citation search for 14 of the included studies (19 February 2020).
Selection criteria: Eligible studies were randomised controlled trials (RCTs), non-randomised RCTs (nRCTs), controlled before-after studies, and interrupted time series conducted in low- and middle-income countries involving children that were under five years of age, caregivers, and healthcare providers.
Data collection and analysis: We independently screened the search output, reviewed full texts of potentially eligible articles, assessed the risk of bias, and extracted data in duplicate, resolving discrepancies by consensus. We conducted random-effects meta-analyses and used GRADE to assess the certainty of the evidence.
Main results: Forty-one studies involving 100,747 participants are included in the review. Twenty studies were cluster-randomised and 15 studies were individually randomised controlled trials. Six studies were quasi-randomised. The studies were conducted in four upper-middle-income countries (China, Georgia, Mexico, Guatemala), 11 lower-middle-income countries (Côte d'Ivoire, Ghana, Honduras, India, Indonesia, Kenya, Nigeria, Nepal, Nicaragua, Pakistan, Zimbabwe), and three lower-income countries (Afghanistan, Mali, Rwanda). The interventions evaluated in the studies were health education (seven studies), patient reminders (13 studies), digital register (two studies), household incentives (three studies), regular immunisation outreach sessions (two studies), home visits (one study), supportive supervision (two studies), integration of immunisation services with intermittent preventive treatment of malaria (one study), payment for performance (two studies), engagement of community leaders (one study), training on interpersonal communication skills (one study), and logistic support to health facilities (one study). We judged nine of the included studies to have low risk of bias; the risk of bias in eight studies was unclear and 24 studies had high risk of bias. We found low-certainty evidence that health education (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.15 to 1.62; 6 studies, 4375 participants) and home-based records (RR 1.36, 95% CI 1.06 to 1.75; 3 studies, 4019 participants) may improve coverage with DTP3/Penta 3 vaccine. Phone calls/short messages may have little or no effect on DTP3/Penta 3 vaccine uptake (RR 1.12, 95% CI 1.00 to 1.25; 6 studies, 3869 participants; low-certainty evidence); wearable reminders probably have little or no effect on DTP3/Penta 3 uptake (RR 1.02, 95% CI 0.97 to 1.07; 2 studies, 1567 participants; moderate-certainty evidence). Use of community leaders in combination with provider intervention probably increases the uptake of DTP3/Penta 3 vaccine (RR 1.37, 95% CI 1.11 to 1.69; 1 study, 2020

participants; moderate-certainty evidence). We are uncertain about the effect of immunisation outreach on DTP3/Penta 3 vaccine uptake in children under two years of age (RR 1.32, 95% CI 1.11 to 1.56; 1 study, 541 participants; very low-certainty evidence). We are also uncertain about the following interventions improving full vaccination of children under two years of age: training of health providers on interpersonal communication skills (RR 5.65, 95% CI 3.62 to 8.83; 1 study, 420 participants; very low-certainty evidence), and home visits (RR 1.29, 95% CI 1.15 to 1.45; 1 study, 419 participants; very low-certainty evidence). The same applies to the effect of training of health providers on interpersonal communication skills on the uptake of DTP3/Penta 3 by one year of age (very low-certainty evidence). The integration of immunisation with other services may, however, improve full vaccination (RR 1.29, 95% CI 1.16 to 1.44; 1 study, 1700 participants; low-certainty evidence).
Authors' conclusions: Health education, home-based records, a combination of involvement of community leaders with health provider intervention, and integration of immunisation services may improve vaccine uptake. The certainty of the evidence for the included interventions ranged from moderate to very low. Low certainty of the evidence implies that the true effect of the interventions might be markedly different from the estimated effect. Further, more rigorous RCTs are, therefore, required to generate high-certainty evidence to inform policy and practice.

PLoS One. 2023 Oct 19;18(10):e0292053.
doi: 10.1371/journal.pone.0292053. eCollection 2023.

Engagement of community health workers to improve immunization coverage through addressing inequities and enhancing data quality and use is a feasible and effective approach: An implementation study in Uganda

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Abstract
Background: Uganda, like many other developing countries, faces the challenges of unreliable estimates for its immunization target population. Strengthening immunization data quality and its use for improving immunization program performance are critical steps toward improving coverage and equity of immunization programs. The goal of this study was to determine the effectiveness of using community health workers (CHWs) to obtain quality and reliable data that can be used for planning and evidence-based response actions.
Methods: An implementation study in which 5 health facilities were stratified and randomized in two groups to (i) receive a package of interventions including monthly health unit immunization data audit meetings, and defaulter tracking and linkage and (ii) to serve as a control group was conducted between July and September 2020. Immunization coverage of infants in both arms was determined by a review of records three months before and after the study interventions. In addition, key informant and in-depth interviews were conducted among facility-based health workers and CHWs respectively, at the endline to explore the feasibility of the interventions.
Results: Overall, a total of 2,048 children under one year eligible for immunization were registered in Bukabooli sub-county by CHWs as compared to the estimated district population of 1,889 children representing a moderate variance of 8.4%. The study further

showed that it is feasible to use CHWs to track and link defaulters to points of immunization services as more than two-thirds (68%) of the children defaulting returned for catch-up immunization services. At the endline, immunization coverage for the Oral Polio Vaccine third dose; Rotavirus vaccine second dose; Pneumococcal Conjugate Vaccine third dose increased in both the intervention and control health facilities. There was a decrease in coverage for the Measles-Rubella vaccine decreased in the intervention health facilities and a decrease in Bacillus Calmette-Guérin vaccine coverage in the control facilities. Difference in difference analysis demonstrated that the intervention caused a significant 35.1% increase in coverage of Bacillus Calmette-Guérin vaccine (CI 9.00-61.19; p<0.05)). The intervention facilities had a 17.9% increase in DTP3 coverage compared to the control facilities (CI: 1.69-34.1) while for MR, OPV3, and Rota2 antigens, there was no significant effect of the intervention.

Conclusion: The use of CHWs to obtain reliable population estimates is feasible and can be useful in areas with consistently poor immunization coverage to estimate the target population. Facilitating monthly health unit immunization data audit meetings to identify, track, and link defaulters to immunization services is effective in increasing immunization coverage and equity.

Int J Infect Dis. 2023 Dec:137:9-15.
doi: 10.1016/j.ijid.2023.10.006. Epub 2023 Oct 11.

Immunogenicity and safety of concomitant administration of the sabin-strain-based inactivated poliovirus vaccine, the diphtheria-tetanus-acellular pertussis vaccine, and measles-mumps-rubella vaccine to healthy infants aged 18 months in China

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Abstract

Objectives: During the COVID-19 pandemic, there was a decline in vaccine coverage, and the implementation of combined vaccines and co-administration strategies emerged as potential solutions to alleviate this predicament. Our objective is to delve into the concurrent administration of the sabin-strain-based inactivated poliovirus vaccine (sIPV), the diphtheria-tetanus-acellular pertussis vaccine (DTaP), and measles-mumps-rubella vaccine (MMR), with the intention of bridging the evidentiary gap pertaining to vaccine co-administration in Chinese infants, and to ensure a safe and effective vaccination strategy, ultimately leading to an augmentation in immunization coverage.

Methods: This study was a follow-up trial of the "Immunogenicity and safety of concomitant administration of the sIPV with the DTaP vaccine in children: a multicenter, randomized, non-inferiority, controlled trial." Blood samples were collected on day 0 and day 30, and serum antibody levels were detected to measure antibody responses to each of the antigens. Local and systemic adverse events were monitored and compared among groups. This study is the first to fill the knowledge gap in China regarding the safe and effective combined vaccination of sIPV, DTaP, and MMR vaccines.

Results: The geometric mean titer of the poliovirus types I, II, and III neutralizing antibodies were 1060.22 (95% CI: 865.73-1298.39), 1537.06 (95% CI: 1324.27-1784.05), and 1539.10 (95%

CI: 1296.37-1827.29) in group I on day 30; geometric mean titer of antibodies against DTaP and MMR in the simultaneous vaccination group was non-inferior to those in the DTaP alone and MMR alone group. Reporting rates of local and systemic adverse reactions were similar between groups and no serious adverse events were reported throughout the clinical study period.
Conclusion: Co-administration of the sIPV, DTaP, and MMR was safe and did not impact immunogenicity, which would help to mitigate administrative costs and enhance vaccine coverage rates.

BMJ Glob Health. 2023 Oct;8(10):e012613.
doi: 10.1136/bmjgh-2023-012613.

Human-centred design bolsters vaccine confidence in the Philippines: results of a randomised controlled trial

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Abstract

Background: The public's confidence in vaccinations has eroded, and anti-vaccination movements have gained traction around the world, including in the Philippines. 'Salubong', a Filipino term, refers to welcoming someone back into one's life and elicits ideas about friendship and family relationships. We extended this concept to vaccines in efforts to design an intervention that would re-welcome vaccines into homes.
Methods: Using human-centred design, we developed and refined a story-based intervention that engages Filipino families, community leaders and community health workers. We conducted a randomised controlled trial among 719 caregivers of small children to test the developed intervention against a control video. We assessed the binary improvement (improvement vs no improvement) and the amount of improvement in vaccine attitudes and intentions after intervention exposure.
Results: Although the intervention group began with marginally higher baseline vaccine attitude scores, we found that 62% of the intervention group improved their vaccine attitude scores versus 37% of the control group (Fisher's exact, p<0.001). Among individuals whose scores improved after watching the assigned video, the intervention group saw higher mean attitude score improvements on the 5-point scale (Cohen's d=0.32 with 95% CI 0.10 to 0.54, two-sided t-test, p<0.01). We observed similar patterns among participants who stated that they had previously delayed or refused a vaccine for their child: 67% of 74 in the intervention group improved their vaccine attitude scores versus 42% of 54 in the control group (Fisher's exact, p<0.001). Among the subset of these individuals whose scores improved after watching the assigned video, the intervention group saw higher mean attitude score improvements on the 5-point scale that were marginally significant (Cohen's d=0.35 with 95% CI -0.01 to 0.70, two-sided t-test, p=0.06).
Conclusions: Our results provide solid evidence for the potential of co-designed vaccine confidence campaigns and regulations.

Vaccination demand and education

J Health Econ. 2024 May 18:96:102899.
doi: 10.1016/j.jhealeco.2024.102899. Online ahead of print.

Persistence and heterogeneity of the effects of educating mothers to improve child immunisation uptake: Experimental evidence from Uttar Pradesh in India

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Abstract

Childhood vaccinations are among the most cost-effective health interventions. Yet, in India, where immunisation services are widely available free of charge, a substantial proportion of children remain unvaccinated. We revisit households 30 months after a randomised experiment of a health information intervention designed to educate mothers on the benefits of child vaccination in Uttar Pradesh, India. We find that the large short-term effects on the uptake of diphtheria-pertussis-tetanus and measles vaccination were sustained at 30 months, suggesting the intervention did not simply bring forward vaccinations. We apply causal forests and find that the intervention increased vaccination uptake, but that there was substantial variation in the magnitude of the estimated effects. We conclude that characterising those who benefited most and conversely those who benefited least provides policy-makers with insights on how the intervention worked, and how the targeting of households could be improved.

SAGE Open Med. 2023 Oct 6:11:20503121231199857.
doi: 10.1177/20503121231199857. eCollection 2023.

Using behavioral insights to increase the demand for childhood vaccination in low resource settings: Evidence from a randomized controlled trial in Lebanon

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Abstract

Objective: Lebanon has historically maintained high immunization coverage rates for most routine vaccines. However, an increase in poverty rates coupled with an influx of over a million refugees posed significant challenges to the national immunization program. In response, an accelerated immunization activities (AIA) program, encompassing community-based outreach and referral activities, was launched to increase the demand for childhood vaccination through the public healthcare system. Despite this effort, uptake among refugee and host community households remained low, resulting in pockets of low immunization coverage rates. This study investigates the barriers that prevent households in low coverage areas from vaccinating their children, and evaluates a behavior change intervention designed to overcome the identified social, perceptual, and cognitive barriers.

Methods: Households with un- or under-vaccinated children were recruited from seven cadastres with low immunization coverage rates. A mixed methods approach, including stakeholder interviews and field observations, was employed to identify the main barriers to

vaccination. Thereafter, a cluster randomized trial was conducted to evaluate the impact of a visual planning aid comprising five behavior change techniques (nudges) on vaccine uptake. **Results:** A total of 12,332 un- or under-vaccinated children from 6160 households (3045 (49.4%) control households; 3115 (50.6%) treated households) were reached during the trial. The observed vaccination rates were 13.5% and 20.2% for control and treated households, respectively. This represents a 6.7 percentage points increase in the likelihood of a treated household to vaccinate at least one child, compared to the control group. At least 390 additional children benefited from life-saving vaccines due to the behavioral intervention. **Conclusions:** This study highlights the importance of integrating behavioral insights into vaccination campaigns and programs, especially in low resource settings, to ensure that more children can benefit from life-saving vaccines.

JMIR Public Health Surveill. 2024 Feb 27.
doi: 10.2196/49695. Online ahead of print.

Community engagement in vaccination promotion: A systematic review and meta-analysis

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Abstract

Background: Community engagement takes predominance in global immunization strategies with capacity to eliminate vaccination hesitancy and boost vaccination confidence. Despite strong support for community engagement in promoting health, evidence for community engagement in vaccination promotion emerges in fragments with uncertain qualities.

Objective: The current review aims to systematic examine the effectiveness of different contents and extents of community engagement for promoting vaccination rates.

Methods: This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive and exhaustive literature search was performed in four English databases (PubMed, Embase, Web of Science, and Cochrane Library) and Two Chinese databases (CNKI and Wan Fang) to locate all possible articles. Original research article with an experimental study design examined the effectiveness of community engagement in vaccination promotion was eligible for inclusion. Two reviewers independently performed the literature search, study selection, quality assessment and data extraction. Discrepancies were resolved through discussion, with the arbitration of a third reviewer where necessary.

Results: A total of 20 articles out of 11,404 records over the period of 2006 to 2021 were retrieved as the sample set to quantified the effectiveness of community engagement in vaccination promotion. These included studies were performed in various designs, 12 used single group pre-post study designs, 5 used cluster RCTs and 3 used non-randomized controlled trials. These included studies targeted multiple vaccine, 8 studies focused on children immunization, 8 studies focused on HPV vaccine, 3 studies focused on HBV vaccine, and 1 study focused on COVID-19 vaccine. Meta-analysis reported significant increases in vaccination rates in both pre-post comparation ((rate difference) RD:0.34; 95% CI: 0.21-0.47)

and between group comparation (RD: 0.18; 95% CI: 0.07-0.29). Meta-analysis about the contents of community engagement found that participant recruitment yielded the largest effect size (RD: 0.51; 95% CI: 0.37-0.67; I2=99.5%), followed by intervention development (RD: 0.36; 95% CI: 0.23-0.50; I2=99.7%), intervention implementation (RD: 0.35; 95% CI: 0.22-0.47; I2=99.8%), and data collection (RD: 0.34; 95% CI: 0.19-0.50; I2=99.8%). Meta-analysis about the extents of community engagement found that high community engagement extent yielded the largest effect size (RD: 0.49; 95% CI: 0.17-0.82; I2 = 99.5%), followed by moderate community engagement extent (RD: 0.45; 95% CI: 0.33-0.58; I2 = 99.4%), and low community engagement extent (RD: 0.15; 95% CI: 0.05-0.25; I2 = 98.6%). Meta-analysis about the types of intervention strategies found that "health service support" endorsed the largest effect sizes (RD: 0.45; 95% CI: 0.25-0.65; I2 = 99.9%), followed by "health education and discussion" (RD: 0.39; 95% CI: 0.20-0.58; I2 = 99.7%), "follow-up and reminder" (RD: 0.33; 95% CI: 0.23-0.42; I2 = 99.3%), and "social marketing campaign (SMC) and community mobilization (CM)" (RD: 0.24; 95% CI: 0.06-0.41; I2 = 99.9%).
Conclusions: The results of this meta-analysis supported the effectiveness of community engagement in vaccination promotion with variations in terms of engagement contents and extents. Community engagement required a "fit for purpose" approach rather than "one size fits all" approach to maximize the effectiveness of vaccine promotion.

Vaccine-related adverse effects

BCG and other tuberculosis vaccines

BMJ Glob Health. 2024 Feb 12;9(2):e014044.
doi: 10.1136/bmjgh-2023-014044.
Can earlier BCG-Japan and OPV vaccination reduce early infant mortality? A cluster-randomised trial in Guinea-Bissau
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Abstract
Objective: To assess the effect of providing BCG and oral polio vaccine (OPV) at an early home visit after delivery.
Design: Cluster-randomised trial, randomising 92 geographically defined clusters 1:1 to intervention/control arms.
Setting: Bandim Health Project Health and Demographic Surveillance System, Guinea-Bissau.
Participants: 2226 newborns enrolled between July 2016 and August 2019.
Interventions: In both arms, newborns received a home visit within 72 hours after birth. In intervention clusters (n=46), BCG and OPV were provided at the home visit.
Main outcome measure: Rates of non-accidental mortality were compared in Cox proportional hazards models from (last of) day 1 or enrolment, until (first of) day 60 or registration of non-trial vaccines.

Results: A total of 35 deaths (intervention: 7, control: 28) were registered during the trial. Providing BCG and OPV reduced non-accidental early infant mortality by 59% (8-82%). The intervention also reduced non-accidental hospital admissions. The intervention had little impact on growth and BCG scarring and tended to increase the risk of consultations.
Conclusions: The trial was stopped early due to lower-than-expected enrolment and event rates when 33% of the planned number of newborns had been enrolled. Despite the small size of the trial, the results support that early BCG and OPV vaccinations are beneficial and reduce early child mortality and morbidity.

Lancet Infect Dis. 2024 Mar;24(3):285-296.
doi: 10.1016/S1473-3099(23)00501-7. Epub 2023 Nov 25.

Safety and immunogenicity of ChAdOx1 85A prime followed by MVA85A boost compared with BCG revaccination among Ugandan adolescents who received BCG at birth: a randomised, open-label trial

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Abstract

Background: BCG confers reduced, variable protection against pulmonary tuberculosis. A more effective vaccine is needed. We evaluated the safety and immunogenicity of candidate regimen ChAdOx1 85A-MVA85A compared with BCG revaccination among Ugandan adolescents.

Methods: After ChAdOx1 85A dose escalation and age de-escalation, we did a randomised open-label phase 2a trial among healthy adolescents aged 12-17 years, who were BCG vaccinated at birth, without evident tuberculosis exposure, in Entebbe, Uganda. Participants were randomly assigned (1:1) using a block size of 6, to ChAdOx1 85A followed by MVA85A (on day 56) or BCG (Moscow strain). Laboratory staff were masked to group assignment. Primary outcomes were solicited and unsolicited adverse events (AEs) up to day 28 and serious adverse events (SAEs) throughout the trial; and IFN-γ ELISpot response to antigen 85A (day 63 [geometric mean] and days 0-224 [area under the curve; AUC).

Findings: Six adults (group 1, n=3; group 2, n=3) and six adolescents (group 3, n=3; group 4, n=3) were enrolled in the ChAdOx1 85A-only dose-escalation and age de-escalation studies (July to August, 2019). In the phase 2a trial, 60 adolescents were randomly assigned to ChAdOx1 85A-MVA85A (group 5, n=30) or BCG (group 6, n=30; December, 2019, to October, 2020). All 60 participants from groups 5 and 6 were included in the safety analysis, with 28 of 30 from group 5 (ChAdOx1 85A-MVA85A) and 29 of 30 from group 6 (BCG revaccination) analysed for immunogenicity outcomes. In the randomised trial, 60 AEs were reported among 23 (77%) of 30 participants following ChAdOx1 85A-MVA85A, 31 were systemic, with one severe event that occurred after the MVA85A boost that was rapidly self-limiting. All 30 participants in the BCG revaccination group reported at least one mild to moderate solicited AE; most were local reactions. There were no SAEs in either group. Ag85A-specific IFN-γ ELISpot responses peaked on day 63 in the ChAdOx1 85A-MVA85A group and were higher in

the ChAdOx1 85A-MVA85A group compared with the BCG revaccination group (geometric mean ratio 30·59 [95% CI 17·46-53·59], p<0·0001, day 63; AUC mean difference 57 091 [95% CI 40 524-73 658], p<0·0001, days 0-224).
Interpretation: The ChAdOx1 85A-MVA85A regimen was safe and induced stronger Ag85A-specific responses than BCG revaccination. Our findings support further development of booster tuberculosis vaccines.

Cholera vaccine

Cochrane Database Syst Rev. 2024 Jan 10;1(1):CD014573.
doi: 10.1002/14651858.CD014573.
Oral killed cholera vaccines for preventing cholera
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Abstract
Background: Cholera causes acute watery diarrhoea and death if not properly treated. Outbreaks occur in areas with poor sanitation, including refugee camps. Several vaccines have been developed and tested over the last 50 years. This is an update of a Cochrane review, originally published in 1998, which explored the effects of all vaccines for preventing cholera. This review examines oral vaccines made from killed bacteria.
Objectives: To assess the effectiveness and safety of the available World Health Organization (WHO)-prequalified oral killed cholera vaccines among children and adults.
Search methods: We searched the Cochrane Infectious Diseases Group Specialized Register; CENTRAL, MEDLINE; Embase; LILACS; and two trials registers (February 2023).
Selection criteria: We included randomized controlled trials (RCTs), including cluster-RCTs. There were no restrictions on the age and sex of the participants or the setting of the study. We considered any available WHO-prequalified oral killed cholera vaccine as an intervention. The control group was given a placebo, another vaccine, or no vaccine. The outcomes were related to vaccine effectiveness and safety. We included articles published in English only.
Data collection and analysis: Two review authors independently applied the inclusion criteria and extracted data from included studies. We assessed the risk of bias using the Cochrane ROB 1 assessment tool. We used the generic inverse variance and a random-effects model meta-analysis to estimate the pooled effect of the interventions. We assessed the certainty of the evidence using the GRADE approach. For vaccine effectiveness (VE), we converted the overall risk ratio (RR) to vaccine effectiveness using the formula: VE = (1 - RR) x 100%.
Main results: Five RCTs, reported in 12 records, with 462,754 participants, met the inclusion criteria. We identified trials on whole-cell plus recombinant vaccine (WC-rBS vaccine (Dukoral)) from Peru and trials on bivalent whole-cell vaccine (BivWC (Shanchol)) vaccine from India and Bangladesh. We did not identify any trials on other BivWC vaccines (Euvichol/Euvichol-Plus), or Hillchol. Two doses of Dukoral with or without a booster dose reduces cases of cholera at two-year follow-up in a general population of children and adults, and at five-month follow-up in an adult male population (overall VE 76%; RR 0.24, 95% confidence interval (CI) 0.08 to 0.65; 2 trials, 16,423 participants; high-certainty evidence). Two doses of Shanchol reduces cases of cholera at one-year follow-up (overall VE

37%; RR 0.63, 95% CI 0.47 to 0.85; 2 trials, 241,631 participants; high-certainty evidence), at two-year follow-up (overall VE 64%; RR 0.36, 95% CI 0.16 to 0.81; 2 trials, 168,540 participants; moderate-certainty evidence), and at five-year follow-up (overall VE 80%; RR 0.20, 95% CI 0.15 to 0.26; 1 trial, 54,519 participants; high-certainty evidence). A single dose of Shanchol reduces cases of cholera at six-month follow-up (overall VE 40%; RR 0.60, 95% CI 0.47 to 0.77; 1 trial, 204,700 participants; high-certainty evidence), and at two-year follow-up (overall VE 39%; RR 0.61, 95% CI 0.53 to 0.70; 1 trial, 204,700 participants; high-certainty evidence). A single dose of Shanchol also reduces cases of severe dehydrating cholera at six-month follow-up (overall VE 63%; RR 0.37, 95% CI 0.28 to 0.50; 1 trial, 204,700 participants; high-certainty evidence), and at two-year follow-up (overall VE 50%; RR 0.50, 95% CI 0.42 to 0.60; 1 trial, 204,700 participants; high-certainty evidence). We found no differences in the reporting of adverse events due to vaccination between the vaccine and control/placebo groups.

Authors' conclusions: Two doses of Dukoral reduces cases of cholera at two-year follow-up. Two doses of Shanchol reduces cases of cholera at five-year follow-up, and a single dose of Shanchol reduces cases of cholera at two-year follow-up. Overall, the vaccines were safe and well-tolerated. We found no trials on other BivWC vaccines (Euvichol/Euvichol-Plus). However, BivWC products (Shanchol, Euvichol/Euvichol-Plus) are considered to produce comparable vibriocidal responses. Therefore, it is reasonable to apply the results from Shanchol trials to the other BivWC products (Euvichol/Euvichol-Plus).

Lancet Glob Health. 2024 May;12(5):e826-e837.
doi: 10.1016/S2214-109X(24)00059-7.

Safety and immunogenicity of the Euvichol-S oral cholera vaccine for prevention of Vibrio cholerae O1 infection in Nepal: an observer-blind, active-controlled, randomised, non-inferiority, phase 3 trial

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Abstract

Background: In October, 2017, WHO launched a strategy to eliminate cholera by 2030. A primary challenge in meeting this goal is the limited global supply capacity of oral cholera vaccine and the worsening of cholera outbreaks since 2021. To help address the current shortage of oral cholera vaccine, a WHO prequalified oral cholera vaccine, Euvichol-Plus was reformulated by reducing the number of components and inactivation methods. We aimed to evaluate the immunogenicity and safety of Euvichol-S (EuBiologics, Seoul, South Korea) compared with an active control vaccine, Shanchol (Sanofi Healthcare India, Telangana, India) in participants of various ages in Nepal.

Methods: We did an observer-blind, active-controlled, randomised, non-inferiority, phase 3 trial at four hospitals in Nepal. Eligible participants were healthy individuals aged 1-40 years without a history of cholera vaccination. Individuals with a history of hypersensitivity reactions to other preventive vaccines, severe chronic disease, previous cholera vaccination,

receipt of blood or blood-derived products in the past 3 months or other vaccine within 4 weeks before enrolment, and pregnant or lactating women were excluded. Participants were randomly assigned (1:1:1:1) by block randomisation (block sizes of two, four, six, or eight) to one of four groups (groups A-D); groups C and D were stratified by age (1-5, 6-17, and 18-40 years). Participants in groups A-C were assigned to receive two 1·5 mL doses of Euvichol-S (three different lots) and participants in group D were assigned to receive the active control vaccine, Shanchol. All participants and site staff (with the exception of those who prepared and administered the study vaccines) were masked to group assignment. The primary immunogenicity endpoint was non-inferiority of immunogenicity of Euvichol-S (group C) versus Shanchol (group D) at 2 weeks after the second vaccine dose, measured by the seroconversion rate, defined as the proportion of participants who had achieved seroconversion (defined as ≥four-fold increase in V cholerae O1 Inaba and Ogawa titres compared with baseline). The primary immunogenicity endpoint was assessed in the per-protocol analysis set, which included all participants who received all their planned vaccine administrations, had no important protocol deviations, and who provided blood samples for all immunogenicity assessments. The primary safety endpoint was the number of solicited adverse events, unsolicited adverse events, and serious adverse events after each vaccine dose in all ages and each age stratum, assessed in all participants who received at least one dose of the Euvichol-S or Shanchol. Non-inferiority of Euvichol-S compared with Shanchol was shown if the lower limit of the 95% CI for the difference between the seroconversion rates in Euvichol-S group C versus Shanchol group D was above the predefined non-inferiority margin of -10%. The trial was registered at ClinicalTrials.gov, NCT04760236.
Findings: Between Oct 6, 2021, and Jan 19, 2022, 2529 healthy participants (1261 [49·9%] males; 1268 [50·1%] females), were randomly assigned to group A (n=330; Euvichol-S lot number ES-2002), group B (n=331; Euvichol-S ES-2003), group C (n=934; Euvichol-S ES-2004]), or group D (n=934; Shanchol). Non-inferiority of Euvichol-S versus Shanchol in seroconversion rate for both serotypes at 2 weeks after the second dose was confirmed in all ages (difference in seroconversion rate for V cholerae O1 Inaba -0·00 [95% CI -1·86 to 1·86]; for V cholerae O1 Ogawa -1·62 [-4·80 to 1·56]). Treatment-emergent adverse events were reported in 244 (9·7%) of 2529 participants in the safety analysis set, with a total of 403 events; 247 events were reported among 151 (9·5%) of 1595 Euvichol-S recipients and 156 events among 93 (10·0%) of 934 Shanchol recipients. Pyrexia was the most common adverse event in both groups (57 events among 56 [3·5%] of 1595 Euvichol-S recipients and 37 events among 35 [3·7%] of 934 Shanchol recipients). No serious adverse events were deemed to be vaccine-related.
Interpretation: A two-dose regimen of Euvichol-S vaccine was non-inferior to the active control vaccine, Shanchol, in terms of seroconversion rates 2 weeks after the second dose. The simplified formulation and production requirements of the Euvichol-S vaccine have the potential to increase the supply of oral cholera vaccine and reduce the gap between the current oral cholera vaccine supply and demand.

Covid-19 vaccines

Vaccine. 2023 Sep 15;41(40):5834-5840.
doi: 10.1016/j.vaccine.2023.08.021. Epub 2023 Aug 14.

Immunogenicity and reactogenicity of fractional, heterologous primary COVID-19 vaccination schedules with BNT162b2 boosters in 5-11-year-old Thai children: A multicenter, prospective, double-blind, randomized control trial

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Abstract

Objective: To evaluate immunogenicity and safety of heterologous COVID-19 primary vaccination regimens of CoronaVac with fractional and standard BNT162b2 dosages in 5-11-year-old Thai children.

Methods: This prospective, multicenter, double-blind, randomized control trial divided participants 1:1:1:1 to receive a second dose of either standard (10-μg) or half-dose (5-μg) BNT162b2 vaccines as follows: CoronaVac/10-μg-BNT162b2 (Group 1), CoronaVac/5-μg-BNT162b2 (Group 2), 10-μg-BNT162b2/10-μg-BNT162b2 (Group 3), or 10-μg-BNT162b2/5-μg-BNT162b2 (Group 4). A subset of participants from each arm received 10-μg-BNT162b2 booster (third) doses 16 weeks after their second vaccination. Humoral and cellular immunogenicity were assessed and adverse events (AEs) digitally self-reported.

Results: Of 553 enrolled participants, 50 % were male, the median (interquartile range) age was 8.65 (7.00, 10.00) years, and a majority (91 %) had normal weight-for-height. All participants exhibited similarly robust neutralizing antibodies (NAb) against the ancestral Wuhan strain two weeks after the second vaccination, with titers highest in Group 1 (737.60, 95% CI [654.80, 830.88]), followed by Groups 3 (630.42, 95% CI [555.50, 715.45]), 2 (593.98, 95% CI [506.02, 697.23]), and 4 (451.79, 95% CI [388.62, 525.23]), as well as 56.01 % and 49.68 % seroconversion for BA.1 and BA.5, respectively. Half-dose BNT162b2 as a second dose induced significantly lower NAb titers compared to their respective full-dose regimens ($p = 0.03$ for Groups 1 vs 2 and $p < 0.001$ for Groups 3 vs 4). 77.71 % of participants developed SARS-CoV-2 ancestral spike protein-specific T-cell responses two weeks after the second vaccination. This was similar across arms. Booster doses generated NAb titers 5.69-11.51-folds higher than the second vaccination against BA.1. AEs were similar across arms, all mild or moderate, and fully resolved 2-3 days thereafter.

Conclusion: Standard and fractional heterologous regimens of CoronaVac-BNT162b2 induced similar or higher humoral immunity than homologous BNT162b2 and represent alternative vaccine regimens for children. These findings are highly relevant in settings concurrently using both vaccines.

Ann Intern Med. 2024 Jan 9.
doi: 10.7326/M23-1754. Online ahead of print.

Real-World Effectiveness of BNT162b2 Against Infection and Severe Diseases in Children and Adolescents

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Christakis[5], Megan L Fitzgerald[6], Kathryn Hirabayashi[4], Ravi Jhaveri[7], Alka Khaitan[8], Tianchen Lyu[3], Suchitra Rao[9], Hanieh Razzaghi[4], Hayden T Schwenk[10], Fei Wang[11], Margot I Gage Witvliet[12], Eric J Tchetgen Tchetgen[13], Jeffrey S Morris[13], Christopher B Forrest[4], Yong Chen[14]

Abstract

Background: The efficacy of the BNT162b2 vaccine in pediatrics was assessed by randomized trials before the Omicron variant's emergence. The long-term durability of vaccine protection in this population during the Omicron period remains limited.

Objective: To assess the effectiveness of BNT162b2 in preventing infection and severe diseases with various strains of the SARS-CoV-2 virus in previously uninfected children and adolescents.

Design: Comparative effectiveness research accounting for underreported vaccination in 3 study cohorts: adolescents (12 to 20 years) during the Delta phase and children (5 to 11 years) and adolescents (12 to 20 years) during the Omicron phase.

Setting: A national collaboration of pediatric health systems (PEDSnet).

Participants: 77 392 adolescents (45 007 vaccinated) during the Delta phase and 111 539 children (50 398 vaccinated) and 56 080 adolescents (21 180 vaccinated) during the Omicron phase.

Intervention: First dose of the BNT162b2 vaccine versus no receipt of COVID-19 vaccine.

Measurements: Outcomes of interest include documented infection, COVID-19 illness severity, admission to an intensive care unit (ICU), and cardiac complications. The effectiveness was reported as (1-relative risk)*100, with confounders balanced via propensity score stratification.

Results: During the Delta period, the estimated effectiveness of the BNT162b2 vaccine was 98.4% (95% CI, 98.1% to 98.7%) against documented infection among adolescents, with no statistically significant waning after receipt of the first dose. An analysis of cardiac complications did not suggest a statistically significant difference between vaccinated and unvaccinated groups. During the Omicron period, the effectiveness against documented infection among children was estimated to be 74.3% (CI, 72.2% to 76.2%). Higher levels of effectiveness were seen against moderate or severe COVID-19 (75.5% [CI, 69.0% to 81.0%]) and ICU admission with COVID-19 (84.9% [CI, 64.8% to 93.5%]). Among adolescents, the effectiveness against documented Omicron infection was 85.5% (CI, 83.8% to 87.1%), with 84.8% (CI, 77.3% to 89.9%) against moderate or severe COVID-19, and 91.5% (CI, 69.5% to 97.6%) against ICU admission with COVID-19. The effectiveness of the BNT162b2 vaccine against the Omicron variant declined 4 months after the first dose and then stabilized. The analysis showed a lower risk for cardiac complications in the vaccinated group during the Omicron variant period.

PLOS Glob Public Health. 2023 Dec 4;3(12):e0002676.
doi: 10.1371/journal.pgph.0002676. eCollection 2023.

Effectiveness of the BNT162b2 vaccine in preventing morbidity and mortality associated with COVID-19 in children aged 5 to 11 years: A systematic review and meta-analysis

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Abstract

A rapid systematic review, based on Cochrane rapid review methodology was conducted to assess the effectiveness of two 10µg doses of BNT162b2 vaccine in preventing morbidity and mortality associated with COVID-19 in children aged 5 to 11 years. We searched the Cochrane Library COVID-19 study register, the COVID-NMA living review database and the McMaster University Living Evidence Synthesis for pre-appraised trials and observational studies up to 7 December 2022. Records were screened independently in duplicate. Where appraisal was not available, these were done in duplicate. Meta-analysis was conducted using RevMan 5.3 presenting risk ratios/odds ratios/inverse vaccine efficacy with 95% confidence intervals (CI). GRADE for assessing the overall certainty of the evidence was done in Gradepro. We screened 403 records and assessed 52 full-text articles for eligibility. One randomised controlled trial (RCT) and 24 observational studies were included. The RCT reported that BNT162b2 was likely safe and 91% efficacious, RR 0.09 (95% CI 0.03 to 0.32) against incident COVID-19 infection (moderate certainty evidence). In absolute terms, this is 19 fewer cases per 1,000 vaccines delivered (ranging from 15 to 21 fewer cases). Observational studies reported vaccine effectiveness (VE) against incident COVID-19 infection of 65% (OR 0.35, 95% CI 0.26 to 0.47) and 76% against hospitalisation (OR 0.24, 95% CI 0.13 to 0.42) (moderate certainty evidence). The absolute effect is 167 fewer cases per 1,000 vaccines given (ranging from 130 fewer to 196 fewer cases) and 4 fewer hospitalisations per 10,000 children (from 3 fewer to 5 fewer hospitalisations). Adverse events following vaccination with BNT162b2 were mild or moderate and transient. The evidence demonstrated a reduction in incident COVID-19 cases and small absolute reduction in hospitalisation if a two-dose BNT162b2 vaccine regimen is offered to children aged 5 to 11 years, compared to placebo. PROSPERO registration: CRD42021286710.

Int Immunopharmacol. 2024 Jan 25:127:111436.
doi: 10.1016/j.intimp.2023.111436. Epub 2023 Dec 25.

Comparative immunogenicity and safety of SpikoGen®, a recombinant SARS-CoV-2 spike protein vaccine in children and young adults: An immuno-bridging clinical trial

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Abstract

Background: SpikoGen® is a recombinant subunit spike protein ectodomain vaccine manufactured in insect cells and formulated with the novel polysaccharide-based Advax-CpG55.2 adjuvant. This study aimed to compare the immunogenicity and safety of SpikoGen® vaccine in children, adolescents and young adults.

Methods: This was a non-randomized, three-arm, open-label, parallel-group, immuno-bridging, non-inferiority trial to compare the immunogenicity and safety of a primary course of two intramuscular doses of SpikoGen® vaccine in children aged 5 to < 12 years, adolescents aged 12 to < 18 years and young adults aged 18 to 40 years. Children 5-12 years received a half dose of 12.5 µg spike protein, whereas the other groups received the full vaccine dose. Vaccine immunogenicity was evaluated via assessment of serum anti-spike

and neutralizing antibodies 14 days after the second dose. Solicited adverse events were recorded for 7 days after each vaccination. Safety assessments including serious adverse events were continued through six months after the second dose in children and adolescents.
Results: Two weeks after the second dose, seroconversion rates for neutralizing antibody levels were not significantly different for children (59.50 %), adolescents (52.06 %) and adults (56.01 %). The 95 % confidence interval of the difference in seroconversion rates between children and adults was within the prespecified non-inferiority margin of 10 % (-12 % to 5 %). SpikoGen® vaccine was well tolerated in all age groups with the most common solicited adverse events being injection site pain and fatigue which were generally transient and mild.
Conclusion: SpikoGen® vaccine was shown to be safe, well tolerated and immunogenic in children as young as 5 years of age, with non-inferior responses to those seen in adults. The Iranian FDA authorisation of SpikoGen® vaccine is now extended down to 5 years of age.

Dengue vaccine

Lancet Infect Dis. 2023 Sep 27:S1473-3099(23)00520-0.
doi: 10.1016/S1473-3099(23)00520-0. Online ahead of print.
Safety and durable immunogenicity of the TV005 tetravalent dengue vaccine, across serotypes and age groups, in dengue-endemic Bangladesh: a randomised, controlled trial
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Abstract
Background: Morbidity and mortality from dengue virus (DENV) is rapidly growing in the large populations of south Asia. Few formal evaluations of candidate dengue vaccine candidates have been undertaken in India, Pakistan, or Bangladesh. Tetravalent vaccines must be tested for safety and immunogenicity in all age groups and in those previously exposed and naive to DENV infections. TV005 is a live, attenuated tetravalent dengue vaccine. We evaluated the safety and immunogenicity of a single dose of TV005 across age groups in dengue-endemic Bangladesh.
Methods: We performed a randomised, placebo-controlled age de-escalating clinical trial of TV005 at a single clinical site in dengue-endemic Dhaka, Bangladesh, following a technology transfer from the USA. Healthy (as determined by history, clinical examination, and safety laboratory test results) volunteers aged 1-50 years were randomly assigned 3:1 (stratified by four age groups) to receive a single dose of TV005 vaccine or placebo. Participants were followed up for 3 years. The study was double blind and was unmasked at day 180; outcome assessors, clinic staff, and volunteers remained blind throughout. Primary outcomes were safety, evaluated per-protocol as proportion of volunteers with solicited related adverse events of any severity through 28 days post dosing, and post-vaccination seropositivity by day 180 using serotype-specific neutralising antibodies ($PRNT_{50}$ ≥10). Secondary outcomes

included viremia, impact of past dengue exposure, and durability of antibody responses. This study is registered with Clinicaltrials.gov, NCT02678455, and is complete.
Findings: Between March 13, 2016, and Feb 14, 2017, 192 volunteers were enrolled into four age groups (adults [18-50 years; 20 male and 28 female], adolescents [11-17 years; 27 male and 21 female], children [5-10 years; 15 male and 33 female], and young children [1-4 years; 29 male and 19 female]) with 48 participant per group. All participants were Bangladeshi. Vaccination was well tolerated and most adverse events were mild. Rash was the most common vaccine-associated solicited adverse event, in 37 (26%) of 144 vaccine recipients versus six (12%) of 48 placebo recipients; followed by fever in seven (5% of 144) and arthralgias in seven (6% of 108), which were only observed in vaccine recipients. Post-vaccine, volunteers of all ages (n=142) were seropositive to most serotypes with 118 (83%) seropositive to DENV 1, 141 (99%) to DENV 2, 137 (96%) to DENV 3, and 124 (87%) to DENV 4, overall by day 180. Post-vaccination, viraemia was not consistently found and antibody titres were higher (10-15-fold for DENV 1-3 and 1·6-fold for DENV 4) in individuals with past dengue exposure compared with the dengue-naive participants (DENV 1 mean 480 [SD 4·0] vs 32 [2·4], DENV 2 1042 [3·2] vs 105 [3·1], DENV 3 1406 [2·8] vs 129 [4·7], and DENV 4 105 [3·3] vs 65 [3·1], respectively). Antibody titres to all serotypes remained stable in most adults (63-86%) after 3 years of follow-up. However, as expected for individuals without past exposure to dengue, titres for DENV 1, 3, and 4 waned by 3 years in the youngest (1-4 year old) cohort (69% seropositive for DENV 2 and 22-28% seropositive for DENV 1, 3, and 4).
Interpretation: With 3 years of follow-up, the single-dose tetravalent dengue vaccine, TV005, was well tolerated and immunogenic for all four serotypes in young children to adults, including individuals with no previous dengue exposure.

N Engl J Med. 2024 Feb 1;390(5):397-408.
doi: 10.1056/NEJMoa2301790.

Live, Attenuated, Tetravalent Butantan-Dengue Vaccine in Children and Adults

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Abstract

Background: Butantan-Dengue Vaccine (Butantan-DV) is an investigational, single-dose, live, attenuated, tetravalent vaccine against dengue disease, but data on its overall efficacy are needed.
Methods: In an ongoing phase 3, double-blind trial in Brazil, we randomly assigned participants to receive Butantan-DV or placebo, with stratification according to age (2 to 6 years, 7 to 17 years, and 18 to 59 years); 5 years of follow-up is planned. The objectives of the trial were to evaluate overall vaccine efficacy against symptomatic, virologically confirmed

dengue of any serotype occurring more than 28 days after vaccination (the primary efficacy end point), regardless of serostatus at baseline, and to describe safety up to day 21 (the primary safety end point). Here, vaccine efficacy was assessed on the basis of 2 years of follow-up for each participant, and safety as solicited vaccine-related adverse events reported up to day 21 after injection. Key secondary objectives were to assess vaccine efficacy among participants according to dengue serostatus at baseline and according to the dengue viral serotype; efficacy according to age was also assessed.
Results: Over a 3-year enrollment period, 16,235 participants received either Butantan-DV (10,259 participants) or placebo (5976 participants). The overall 2-year vaccine efficacy was 79.6% (95% confidence interval [CI], 70.0 to 86.3) - 73.6% (95% CI, 57.6 to 83.7) among participants with no evidence of previous dengue exposure and 89.2% (95% CI, 77.6 to 95.6) among those with a history of exposure. Vaccine efficacy was 80.1% (95% CI, 66.0 to 88.4) among participants 2 to 6 years of age, 77.8% (95% CI, 55.6 to 89.6) among those 7 to 17 years of age, and 90.0% (95% CI, 68.2 to 97.5) among those 18 to 59 years of age. Efficacy against DENV-1 was 89.5% (95% CI, 78.7 to 95.0) and against DENV-2 was 69.6% (95% CI, 50.8 to 81.5). DENV-3 and DENV-4 were not detected during the follow-up period. Solicited systemic vaccine- or placebo-related adverse events within 21 days after injection were more common with Butantan-DV than with placebo (58.3% of participants, vs. 45.6%).
Conclusions: A single dose of Butantan-DV prevented symptomatic DENV-1 and DENV-2, regardless of dengue serostatus at baseline, through 2 years of follow-up.

Ebola vaccine

Lancet Glob Health. 2023 Nov;11(11):e1743-e1752.
doi: 10.1016/S2214-109X(23)00410-2.
Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in infants: a phase 2, randomised, double-blind, active-controlled trial in Guinea and Sierra Leone
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Abstract
Background: This study assessed the safety and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo Ebola virus (EBOV) vaccine regimen in infants aged 4-11 months in Guinea and Sierra Leone.
Methods: In this phase 2, randomised, double-blind, active-controlled trial, we randomly assigned healthy infants (1:1 in a sentinel cohort, 5:2 for the remaining infants via an

interactive web response system) to receive Ad26.ZEBOV followed by MVA-BN-Filo (Ebola vaccine group) or two doses of meningococcal quadrivalent conjugate vaccine (control group) administered 56 days apart. Infants were recruited at two sites in west Africa: Conakry, Guinea, and Kambia, Sierra Leone. All infants received the meningococcal vaccine 8 months after being randomly assigned. The primary objective was safety. The secondary objective was immunogenicity, measured as EBOV glycoprotein-binding antibody concentration 21 days post-dose 2, using the Filovirus Animal Non-Clinical Group ELISA. This study is registered with ClinicalTrials.gov (NCT03929757) and the Pan African Clinical Trials Registry (PACTR201905827924069).
Findings: From Aug 20 to Nov 29, 2019, 142 infants were screened and 108 were randomly assigned (Ebola vaccine n=75; control n=33). The most common solicited local adverse event was injection-site pain (Ebola vaccine 15 [20%] of 75; control four [12%] of 33). The most common solicited systemic adverse events with the Ebola vaccine were irritability (26 [35%] of 75), decreased appetite (18 [24%] of 75), pyrexia (16 [21%] of 75), and decreased activity (15 [20%] of 75). In the control group, ten (30%) of 33 had irritability, seven (21%) of 33 had decreased appetite, three (9%) of 33 had pyrexia, and five (15%) of 33 had decreased activity. The frequency of unsolicited adverse events was 83% (62 of 75 infants) in the Ebola vaccine group and 85% (28 of 33 infants) in the control group. No serious adverse events were vaccine-related. In the Ebola vaccine group, EBOV glycoprotein-binding antibody geometric mean concentrations (GMCs) at 21 days post-dose 2 were 27 700 ELISA units (EU)/mL (95% CI 20 477-37 470) in infants aged 4-8 months and 20 481 EU/mL (15 325-27 372) in infants aged 9-11 months. The responder rate was 100% (74 of 74 responded). In the control group, GMCs for both age groups were less than the lower limit of quantification and the responder rate was 3% (one of 33 responded).
Interpretation: Ad26.ZEBOV and MVA-BN-Filo was well tolerated and induced strong humoral responses in infants younger than 1 year. There were no safety concerns related to vaccination.

Enterovirus 71 vaccine

Haemophilus influenzae type b vaccine

Hum Vaccin Immunother. 2024 Dec 31;20(1):2342630.
doi: 10.1080/21645515.2024.2342630. Epub 2024 Apr 30.
Disparate kinetics in immune response of two different *Haemophilus influenzae* type b conjugate vaccines: Immunogenicity and safety observations from a randomized controlled phase IV study in healthy infants and toddlers using a 2+1 schedule
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Abstract
Since the introduction of *Haemophilus Influenzae* type b (Hib) conjugate vaccines, invasive Hib disease has strongly declined worldwide, yet continued control of Hib disease remains

important. In Europe, currently three different hexavalent combination vaccines containing Hib conjugates are marketed. In this phase IV, single-blind, randomized, controlled, multi-country study (NCT04535037), we aimed to compare, in a 2 + 1 vaccination schedule, the immunogenicity and safety and show non-inferiority, as well as superiority, of DTPa-HBV-IPV/Hib (Ih group) versus DTaP5-HB-IPV-Hib (Va group) in terms of anti-polyribosylribitol phosphate (PRP) antibody geometric mean concentrations (GMCs) and proportion of participants reaching anti-PRP antibody concentrations greater than or equal to a threshold of 5 µg/mL. One month after the booster vaccination, the anti-PRP antibody GMC ratio (Ih group/Va group) was 0.917 (95% CI: 0.710-1.185), meeting the non-inferiority criteria. The difference in percentage of participants (Ih group - Va group) reaching GMCs ≥5 µg/mL was -6.3% (95% CI: -14.1% to 1.5%), not reaching the predefined non-inferiority threshold. Interestingly, a slightly higher post-booster antibody avidity was observed in the Ih group versus the Va group. Both vaccines were well tolerated, and no safety concerns were raised. This study illustrates the different kinetics of the anti-PRP antibody response post-primary and post-booster using the two vaccines containing different Hib conjugates and indicates a potential differential impact of concomitant vaccinations on the anti-PRP responses. The clinical implications of these differences should be further studied.

Hepatitis A vaccine

Hum Vaccin Immunother. 2023 Aug 1;19(2):2227549.
doi: 10.1080/21645515.2023.2227549. Epub 2023 Jun 26.

Immunogenicity persistence of hepatitis A vaccines Healive® and Havrix® among children:15 years follow-up and long-term prediction

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Abstract

Healive® was the only Chinese WHO-prequalified inactivated vaccine for the hepatitis A virus, which has been widely used in national immunization programs in China. Long-term follow-up studies are needed to estimate the persistence of vaccine-induced antibody levels and the necessity for booster vaccines. During the trial, geometric mean concentrations (GMCs) and seroconversion rates (SRs) of anti-HAV antibodies were compared based on two different inactivated hepatitis A vaccines, Healive® and Havrix®. Four hundred children were randomly assigned to receive two doses of Healive® or Havrix® at 0 and 6 months. The current study assessed antibody persistence for both vaccines 15 years post-immunization. A mixed linear model was used to predict long-term antibody persistence. The GMCs were significantly higher for Healive® compared to Havrix® at 1, 6, 7, 66, 138 months ($P < .001$) and 186 months ($P = .004 < .05$) post-vaccination. Healive® and Havrix® reached a GMC of 164.8 mIU/ml and 105.7 mIU/ml post-15 years of vaccination, respectively. The seroconversion rates of both vaccines showed no statistically significant differences (97.9% for Healive® and 94.7% for Havrix®, $P = .20$). The prediction showed that Healive® would provide protection for a minimum of 30 years following immunization, with a lower limit of the 95% confidence intervals for GMCs greater than 20mIU/mL. Compared to Havrix®, the vaccine Healive® showed a stronger protective effect and better persistence among children at 15 years post-

full immunization. Prediction indicated at least 30 years of antibody persistence for Healive® and at least 25 years for Havrix®.

Vaccine. 2023 Oct 6;41(42):6215-6220.
doi: 10.1016/j.vaccine.2023.08.084. Epub 2023 Sep 1.

Immunogenicity and safety of Havisure™ vaccine developed by Human Biologicals Institute in healthy subjects of 12 months to 49 years of age: A phase II/III, randomized, single blind, non-inferiority study

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Abstract

Background: Hepatitis A is an inflammation of the liver caused by the hepatitis A virus (HAV). It is transmitted mainly because of poor personal hygiene via the faecal/oral route through ingestion of contaminated food or water or through the direct contact with an infectious person. Though most of the infected individuals recover from the infection, a few may develop fatal fulminant hepatitis. In this randomized, multicenter study, immunogenicity and safety of Havisure™ vaccine of Human Biologicals Institute was compared with Havrix® vaccine.

Methods: The study was carried out in 528 eligible healthy subjects, in two age groups across eight centres in India. Group A included subjects of 19-49 years and Group B subjects of 12 months to below 19 years of age. All subjects received two doses of either Havisure™ vaccine or Havrix® vaccine as per randomization at six months interval. Blood samples for antibody titre estimation were collected before vaccination and 4-6 weeks after 2nd dose of vaccination. Immunogenicity was assessed by estimating seroconversion rate, seroprotection rate, and geometric mean titres of antibodies. Safety was evaluated by collection and analysis of data on solicited and unsolicited adverse events.

Results: Of 528 enrolled subjects, 493 subjects completed the study. There was 100% seroconversion and seroprotection in both the vaccine arms. There was no statistical difference in the geometric mean titres between the two vaccine arms. Pain and swelling at the site of injection were the most common local adverse events whereas fever and headache were the most common systemic adverse events observed in both vaccine arms. No serious adverse event was reported in the study.

Conclusion: The study results indicate that the Havisure™ vaccine is immunogenic and safe when administered to healthy subjects of 12 months to 49 years of age, and is non-inferior to Havrix® Vaccine.

Hepatitis B vaccine

HIV vaccine

Hookworm vaccine

Lancet Infect Dis. 2024 Jul;24(7):760-774.
doi: 10.1016/S1473-3099(24)00104-X. Epub 2024 Mar 18.

Safety and immunogenicity of the co-administered Na-APR-1 and Na-GST-1 hookworm vaccines in school-aged children in Gabon: a randomised, controlled, observer-blind, phase 1, dose-escalation trial

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Abstract

Background: A human hookworm vaccine is being developed to protect children against iron deficiency and anaemia associated with chronic infection with hookworms. Necator americanus aspartic protease-1 (Na-APR-1) and N americanus glutathione S-transferase-1 (Na-GST-1) are components of the blood digestion pathway critical to hookworm survival in the host. Recombinant Na-GST-1 and catalytically inactive Na-APR-1 (Na-APR-1[M74]) adsorbed to Alhydrogel were safe and immunogenic when delivered separately or co-administered to adults in phase 1 trials in non-endemic and endemic areas. We aimed to investigate the safety and immunogenicity of these antigens in healthy children in a hookworm-endemic area.

Methods: This was a randomised, controlled, observer-blind, phase 1, dose-escalation trial, conducted in a clinical research centre, in 60 children aged six to ten years in Lambaréné, a hookworm-endemic region of Gabon. Healthy children (determined by clinical examination and safety laboratory testing) were randomised 4:1 to receive co-administered Na-GST-1 on Alhydrogel plus Na-APR-1(M74) on Alhydrogel and glucopyranosyl lipid A in aqueous formulation (GLA-AF), or co-administered ENGERIX-B hepatitis B vaccine (HBV) and saline placebo, injected into the deltoid of each arm. Allocation to vaccine groups was observer-masked. In each vaccine group, children were randomised 1:1 to receive intramuscular injections into each deltoid on two vaccine schedules, one at months 0, 2, and 4 or at months 0, 2, and 6. 10 µg, 30 µg, and 100 µg of each antigen were administered in the first, second, and third cohorts, respectively. The intention-to-treat population was used for safety analyses; while for immunogenicity analyses, the per-protocol population was used (children who received all scheduled vaccinations). The primary outcome was to evaluate the vaccines' safety and reactogenicity in healthy children aged between six and ten years. The secondary outcome was to measure antigen-specific serum IgG antibody levels at pre-vaccination and post-vaccination timepoints by qualified ELISAs. The trial is registered with ClinicalTrials.gov, NCT02839161, and is completed.

Findings: Between Jan 23 and Oct 3, 2017, 137 children were screened, of whom 76 were eligible for this trial. 60 children were recruited, and allocated to either 10 µg of the co-administered antigens (n=8 for each injection schedule), 30 µg (n=8 for each schedule), 100 µg (n=8 for each schedule), or HBV and placebo (n=6 for each schedule) in three sequential cohorts. Co-administration of the vaccines was well tolerated; the most frequent solicited adverse events were mild-to-moderate injection-site pain, observed in up to 12 (75%) of 16 participants per vaccine group, and mild headache (12 [25%] of 48) and fever (11 [23%] of 48). No vaccine-related serious adverse events were observed. Significant anti-Na-APR-1(M74) and anti-Na-GST-1 IgG levels were induced in a dose-dependent manner, with peaks seen 14 days after the third vaccinations, regardless of dose (for Na-APR-1[M74], geometric

mean levels [GML]=2295·97 arbitrary units [AU] and 726·89 AU, while for Na-GST-1, GMLs=331·2 AU and 21·4 AU for the month 0, 2, and 6 and month 0, 2, and 4 schedules, respectively). The month 0, 2, and 6 schedule induced significantly higher IgG responses to both antigens (p=0·01 and p=0·04 for Na-APR-1[M74] and Na-GST-1, respectively).
Interpretation: Co-administration of recombinant Na-APR-1(M74) and Na-GST-1 to school-aged Gabonese children was well tolerated and induced significant IgG responses. These results justify further evaluation of this antigen combination in proof-of-concept controlled-infection and efficacy studies in hookworm-endemic areas.

HPV vaccine

Lancet Glob Health. 2024 Mar;12(3):e491-e499.
doi: 10.1016/S2214-109X(23)00586-7.

Comparing one dose of HPV vaccine in girls aged 9-14 years in Tanzania (DoRIS) with one dose in young women aged 15-20 years in Kenya (KEN SHE): an immunobridging analysis of randomised controlled trials

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Abstract

Background: The first randomised controlled trial of single-dose human papillomavirus (HPV) vaccine efficacy, the Kenya single-dose HPV-vaccine efficacy (KEN SHE) trial, showed greater than 97% efficacy against persistent HPV16 and HPV18 infection at 36 months among women in Kenya. We compared antibody responses after one dose of HPV vaccine in the Dose Reduction Immunobridging and Safety Study (DoRIS), the first randomised trial of the single- dose regimen in girls aged 9-14 years, the target age range for vaccination, with those after one dose of the same vaccine in KEN SHE.
Methods: In the DoRIS trial, 930 girls aged 9-14 years in Tanzania were randomly assigned to one, two, or three doses of the 2-valent vaccine (Cervarix) or the 9-valent vaccine (Gardasil-9). The proportion seroconverting and geometric mean concentrations (GMCs) at month 24 after one dose were compared with those in women aged 15-20 years who were randomly assigned to one dose of the same vaccines at the same timepoint in KEN SHE. Batched samples were tested together by virus-like particle ELISA for HPV16 and HPV18 IgG antibodies. Non-inferiority of GMC ratios (DoRIS trial:KEN SHE) was predefined as a lower bound of the 95% CI less than 0·50.
Findings: Month 24 HPV16 and HPV18 antibody GMCs in DoRIS were similar or higher than those in KEN SHE. 2-valent GMC ratios were 0·90 (95% CI 0·72-1·14) for HPV16 and 1·02 (0·78-1·33) for HPV18. 9-valent GMC ratios were 1·44 (95% CI 1·14-1·82) and 1·47 (1·13-1·90), respectively. Non-inferiority of antibody GMCs and seropositivity was met for HPV16 and HPV18 for both vaccines.
Interpretation: HPV16 and HPV18 immune responses in young girls 24 months after a single dose of 2-valent or 9-valent HPV vaccine were comparable to those in young women who were randomly assigned to a single dose of the same vaccines and in whom efficacy had been shown. A single dose of HPV vaccine, when given to girls in the target age range for

vaccination, induces immune responses that could be effective against persistent HPV16 and HPV18 infection at least two years after vaccination.

Sci Bull (Beijing). 2023 Oct 30;68(20):2448-2455.
doi: 10.1016/j.scib.2023.09.020. Epub 2023 Sep 19.

Immunogenicity and safety of an Escherichia coli-produced human papillomavirus (types 6/11/16/18/31/33/45/52/58) L1 virus-like-particle vaccine: a phase 2 double-blind, randomized, controlled trial

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Abstract

The Escherichia coli-produced human papillomavirus (HPV) 16/18 bivalent vaccine (Cecolin) has received prequalification by the World Health Organization based on its high efficacy and good safety profile. We aimed to evaluate the immunogenicity and safety of the second-generation nonavalent HPV 6/11/16/18/31/33/45/52/58 vaccine (Cecolin 9) through the randomized, blinded phase 2 clinical trial. Eligible healthy women aged 18-45 years were randomly (1:1) allocated to receive three doses of 1.0 mL (270 μg) of Cecolin 9 or placebo with a 0-1-6-month schedule. The primary endpoint was the seroconversion rate and geometric mean titer of neutralizing antibodies (nAbs) one month after the full vaccination course (month 7). The secondary endpoint was the safety profile including solicited adverse reactions occurring within 7 d, adverse events (AEs) occurring within 30 d after each dose, and serious adverse events (SAEs) occurring during the 7-month follow-up period. In total, 627 volunteers were enrolled and randomly assigned to Cecolin 9 (n = 313) or placebo (n = 314) group in Jiangsu Province, China. Almost all participants in the per-protocol set for immunogenicity (PPS-I) seroconverted for nAbs against all the nine HPV types at month 7, while two failed to seroconvert for HPV 11 and one did not seroconvert for HPV 52. The incidence rates of total AEs in the Cecolin 9 and placebo groups were 80.8% and 72.9%, respectively, with the majority of them being mild and recovering shortly. None of the SAEs were considered related to vaccination. In conclusion, the E. coli-produced 9-valent HPV (9vHPV) vaccine candidate was well tolerated and immunogenic, which warrants further efficacy studies in larger populations.

Infect Chemother. 2023 Nov 20.
doi: 10.3947/ic.2023.0064. Online ahead of print.

Comparative Effects of Bivalent, Quadrivalent, and Nonavalent Human Papillomavirus Vaccines in The Prevention of Genotype-Specific Infection: A Systematic Review and Network Meta-Analysis

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Abstract

Background: Human papillomavirus (HPV) infection is a major global disease burden and the main cause of cervical cancer. Certain HPV genotypes, with are the most common etiologic pathogens and cause a significant disease burden, are being targeted for vaccine development. However, few studies have focused on the comparative effectiveness of the bivalent HPV (2v-HPV), quadrivalent HPV (4v-HPV), and nonavalent HPV (9v-HPV) vaccines against HPV strain-specific infection. This study investigated the comparative effects of these vaccines against genotype-specific infection.
Materials and methods: We conducted a pairwise and network meta-analysis of published randomized clinical trials of HPV vaccines according to sex and HPV infection status for nine HPV genotypes (HPV 6/11/16/18/31/33/45/52/58).
Results: Overall, 10 randomized controlled trials (12 articles) were included in this study. In the network meta-analysis, no statistically significant differences were observed in the prevention of carcinogenic HPV strains (16/18/31/33/45/52/58) between the 2v-HPV and 4v-HPV vaccines in female HPV infection-naïve populations. However, the 9v-HPV vaccine showed a significantly superior effect compared with 2v-HPV and 4v-HPV vaccines in preventing HPV 31/33/45/52/58 infections. Although 2v-HPV and 4v-HPV vaccines provided some cross-protection against HPV 31/33/45/52/58 infections, the effect was significant only on HPV 31 infection. For HPV 16 and 18, neither statistically significant nor small differences were found in the prevention of HPV infection among the 2v-HPV, 4v-HPV, and 9v-HPV vaccines.
Conclusion: Our study complements previous understanding of how the effect of HPV vaccines differs according to the HPV genotype. This is important because HPV genotype prevalence varies among countries. We advocate for continued efforts in vaccinating against HPV, while public health agencies should consider the difference in the vaccine effect and HPV genotype prevalence when implementing HPV vaccination in public vaccination programs.

Lancet Oncol. 2023 Dec;24(12):1321-1333.
doi: 10.1016/S1470-2045(23)00480-1. Epub 2023 Nov 7.

Immunogenicity and safety of a new quadrivalent HPV vaccine in girls and boys aged 9-14 years versus an established quadrivalent HPV vaccine in women aged 15-26 years in India: a randomised, active-controlled, multicentre, phase 2/3 trial

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Abstract
Background: To meet global cervical cancer elimination efforts, a wider range of affordable and accessible vaccines against human papillomavirus (HPV) are needed. We aimed to evaluate the immunogenicity and safety of a quadrivalent HPV vaccine (targeting HPV types 6, 11, 16, and 18), developed and manufactured by the Serum Institute of India (SIIPL). Here we report outcomes in the 9-14 years cohort.

Methods: This randomised, active-controlled, phase 2/3 trial was conducted at 12 tertiary care hospitals across India. Healthy participants aged 9-14 years or 15-26 years with no history of HPV vaccination were eligible for enrolment. Female participants were randomly assigned (1:1) with an interactive web response system, by use of a central computer-generated schedule and block randomisation (block sizes of 2, 4, 6, and 8), to receive the SIIPL quadrivalent HPV vaccine (Cervavac; SIIPL, Pune, India) or the comparator quadrivalent HPV vaccine (Gardasil; Merck Sharp & Dohme, Harleem, the Netherlands). Participants, investigators, laboratory technicians, and sponsors were masked to treatment allocation of female participants. Male participants were given the SIIPL quadrivalent HPV vaccine in an open-label manner. Study vaccines were administered intramuscularly with a two-dose schedule (at day 0 and 6 months) in the cohort aged 9-14 years, and with a three-dose schedule (at day 0, month 2, and month 6) in the cohort aged 15-26-years. Immunogenicity was assessed 30 days after the last dose by use of multiplexed ELISA. The primary outcome was the non-inferiority of immune response in terms of the geometric mean titre (GMT) of antibodies against HPV types 6, 11, 16, and 18 generated by the SIIPL quadrivalent HPV vaccine in girls and boys (aged 9-14 years) compared with the GMT generated by the comparator quadrivalent HPV vaccine in women aged 15-26 years at month 7 in the modified per-protocol population (ie, all participants who received all doses of study vaccines per assigned treatment group and had both day 0 and 1-month immunogenicity measurements after the last dose following protocol-defined window periods with no major protocol deviations). Non-inferiority was established if the lower bound of the 98·75% CI of the GMT ratio was 0·67 or higher. The co-primary outcome of occurrence of solicited adverse events (within 7 days of each dose) and unsolicited adverse events (up to 30 days after the last dose) was assessed in all participants who were enrolled and received at least one dose of study vaccine. The trial is registered with the Clinical Trials Registry - India (CTRI/2018/06/014601), and long-term follow-up is ongoing.

Findings: Between Sept 20, 2018, and Feb 9, 2021, 2341 individuals were screened, of whom 2307 eligible individuals were enrolled and vaccinated: 1107 (738 girls and 369 boys) in the cohort aged 9-14 years and 1200 (819 women and 381 men) in the cohort aged 15-26 years. No race or ethnicity data were collected. 350 girls and 349 boys in the SIIPL quadrivalent HPV vaccine group and 338 women in the comparator vaccine group were included in the modified per-protocol population for the primary endpoint analysis. The median follow-up for the analyses was 221 days (IQR 215-231) for girls and 222 days (217-230) for boys in the SIIPL quadrivalent HPV vaccine group, 223 days (216-232) for girls in the comparator vaccine group, and 222 days (216-230) for women in the comparator vaccine group. GMT ratios were non-inferior in girls and boys receiving the SIIPL quadrivalent HPV vaccine compared with women receiving the comparator vaccine: GMT ratios for girls were 1·97 (98·75% CI 1·67-2·32) for HPV type 6, 1·63 (1·38-1·91) for HPV type 11, 1·90 (1·60-2·25) for HPV type 16, and 2·16 (1·79-2·61) for HPV type 18. For boys the GMT ratios were 1·86 (1·57-2·21) for HPV type 6, 1·46 (1·23-1·73) for HPV type 11, 1·62 (1·36-1·94) for HPV type 16, and 1·80 (1·48-2·18) for HPV type 18. The safety population comprised all 1107 participants (369 girls and 369 boys in the SIIPL quadrivalent HPV vaccine group, and 369 girls in the comparator group). Solicited adverse events occurred in 176 (48%) of 369 girls and 124 (34%) of 369 boys in the SIIPL vaccine group and 179 (49%) of 369 girls in the comparator vaccine group. No grade 3-4 solicited adverse events occurred within 7 days of each dose. Unsolicited adverse events occurred in 143 (39%) girls and 147 (40%) boys in the SIIPL vaccine group, and 143 (39%) girls in the comparator vaccine group. The most common grade 3 unsolicited adverse event was dengue fever, in

one (<1%) girl in the SIIPL vaccine group and three (1%) girls in the comparator group. There were no grade 4 or 5 adverse events. Serious adverse events occurred in three (1%) girls and three (1%) boys in the SIIPL vaccine group, and five (1%) girls in the comparator vaccine group. No vaccine-related serious adverse events were reported. There were no treatment-related deaths.

Interpretation: We observed a non-inferior immune response with the SIIPL quadrivalent HPV vaccine in girls and boys aged 9-14 years and an acceptable safety profile compared with the comparator vaccine. These findings support extrapolation of efficacy from the comparator vaccine to the SIIPL quadrivalent HPV vaccine in the younger population. The availability of the SIIPL quadrivalent HPV vaccine could help meet the global demand for HPV vaccines, and boost coverage for both girls and boys globally.

Nat Med. 2023 Dec 4.
doi: 10.1038/s41591-023-02658-0. Online ahead of print.

Durability of single-dose HPV vaccination in young Kenyan women: randomized controlled trial 3-year results

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Abstract

Cervical cancer burden is high where prophylactic vaccination and screening coverage are low. We demonstrated in a multicenter randomized, double-blind, controlled trial that single-dose human papillomavirus (HPV) vaccination had high vaccine efficacy (VE) against persistent infection at 18 months in Kenyan women. Here, we report findings of this trial through 3 years of follow-up. Overall, 2,275 healthy women aged 15-20 years were recruited and randomly assigned to receive bivalent (n = 760), nonavalent (n = 758) or control (n = 757) vaccine. The primary outcome was incident-persistent vaccine type-specific cervical HPV infection. The primary evaluation was superiority analysis in the modified intention-to-treat (mITT) HPV 16/18 and HPV 16/18/31/33/45/52/58 cohorts. The trial met its prespecified end points of vaccine type-specific persistent HPV infection. A total of 75 incident-persistent infections were detected in the HPV 16/18 mITT cohort: 2 in the bivalent group, 1 in the nonavalent group and 72 in the control group. Nonavalent VE was 98.8% (95% CI 91.3-99.8%, P < 0.0001) and bivalent VE was 97.5% (95% CI 90.0-99.4%, P < 0.0001). Overall, 89 persistent infections were detected in the HPV 16/18/31/33/45/52/58 mITT cohort: 5 in the nonavalent group and 84 in the control group; nonavalent VE was 95.5% (95% CI 89.0-98.2%, P < 0.0001). There were no vaccine-related severe adverse events. Three years after vaccination, single-dose HPV vaccination was highly efficacious, safe and conferred durable protection

Vaccine. 2024 Apr 2;42(9):2290-2298.
doi: 10.1016/j.vaccine.2024.02.077. Epub 2024 Mar 1.

Safety and immunogenicity of Innovax bivalent human papillomavirus vaccine in girls 9-14 years of age: Interim analysis from a phase 3 clinical trial

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Abstract

Background: World Health Organization human papillomavirus (HPV) vaccination recommendations include a single- or two-dose schedule in individuals 9-20 years old and advice for generating data on single-dose efficacy or immunobridging. The ongoing Phase 3 trial of Innovax's bivalent (types 16 and 18) HPV vaccine (Cecolin®) assesses in low- and middle-income countries alternative dosing schedules and generates data following one dose in girls 9-14 years old. Interim data for the 6-month dosing groups are presented.

Methods: In Bangladesh and Ghana, 1,025 girls were randomized to receive either two doses of Cecolin at 6-, 12-, or 24-month intervals; one dose of Gardasil® followed by one dose of Cecolin at month 24; or two doses of Gardasil 6 months apart (referent). Serology was measured by enzyme-linked immunosorbent assay (ELISA) and, in a subset, by neutralization assays. Primary objectives include immunological non-inferiority of the Cecolin schedules to referent one month after the second dose. Safety endpoints include reactogenicity and unsolicited adverse events for 7 and 30 days post-vaccination, respectively, as well as serious adverse events throughout the study.

Results: Interim analyses included data from the two groups on a 0, 6-month schedule with 205 participants per group. One month after Dose 2, 100% of participants were seropositive by ELISA and had seroconverted for both antigens. Non-inferiority of Cecolin to Gardasil was demonstrated. Six months following one dose, over 96% of participants were seropositive by ELISA for both HPV antigens, with a trend for higher geometric mean concentration following Cecolin administration. Reactogenicity and safety were comparable between both vaccines.

Conclusions: Cecolin in a 0, 6-month schedule elicits robust immunogenicity. Non-inferiority to Gardasil was demonstrated one month after a 0, 6-month schedule. Immunogenicity following one dose was comparable to Gardasil up to six months. Both vaccines were safe and well tolerated

Vaccine X. 2024 Apr 16:19:100486.
doi: 10.1016/j.jvacx.2024.100486. eCollection 2024 Aug.

Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to multidose vaccination regimens or no vaccination: An updated systematic review of evidence from clinical trials

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Abstract

Objectives: This study systematically reviewed the published literature from clinical trials on the efficacy and immunogenicity of single-dose HPV vaccination compared to multidose schedules or no HPV vaccination.

Methods: Four databases were searched for relevant articles published from Jan-1999 to Feb-2023. Articles were assessed for eligibility for inclusion using pre-defined criteria. Relevant data were extracted from eligible articles and a descriptive quality assessment was performed for each study. A narrative data synthesis was conducted, examining HPV infection, other clinical outcomes and immunogenicity responses by dose schedule.

Results: Fifteen articles reporting data from six studies (all in healthy young females) were included. One article was included from each of three studies that prospectively randomised participants to receive a single HPV vaccine dose versus one or more comparator schedule(s). The other 12 articles reported data from three studies that randomised participants to receive multidose HPV vaccine (or control vaccine) schedules; in those studies, some participants failed to complete their allocated schedule, and evaluations were conducted to compare participants who actually received one, two or three doses. Across all efficacy studies, the incidence or prevalence of HPV16/18 infection was very low among HPV-vaccinated participants, regardless of the number of doses received; with no evidence for a difference between dose groups. In immunogenicity studies, HPV16/18 antibody seropositivity rates were high among all HPV-vaccinated participants. Antibody levels were significantly lower with one dose compared to two or three doses, but levels with one dose were stable and sustained to 11 years post-vaccination.
Conclusions: Results from this review support recent World Health Organization recommendations allowing either one- or two-dose HPV vaccination in healthy young females. Longer-term efficacy and immunogenicity data from ongoing studies are awaited. Randomised trials of single-dose HPV-vaccination are urgently needed in other populations, e.g. boys, older females and people with HIV.

Influenza vaccine

J Infect Dis. 2023 Oct 3;228(7):957-965.
doi: 10.1093/infdis/jiad153.

Streptococcus pyogenes Colonization in Children Aged 24-59 Months in the Gambia: Impact of Live Attenuated Influenza Vaccine and Associated Serological Responses

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Abstract
Background: Immunity to Streptococcus pyogenes in high burden settings is poorly understood. We explored S. pyogenes nasopharyngeal colonization after intranasal live attenuated influenza vaccine (LAIV) among Gambian children aged 24-59 months, and resulting serological response to 7 antigens.
Methods: A post hoc analysis was performed in 320 children randomized to receive LAIV at baseline (LAIV group) or not (control). S. pyogenes colonization was determined by quantitative polymerase chain reaction (qPCR) on nasopharyngeal swabs from baseline (day 0), day 7, and day 21. Anti-streptococcal IgG was quantified, including a subset with paired serum before/after S. pyogenes acquisition.
Results: The point prevalence of S. pyogenes colonization was 7%-13%. In children negative at day 0, S. pyogenes was detected at day 7 or 21 in 18% of LAIV group and 11% of control group participants (P = .12). The odds ratio (OR) for colonization over time was significantly

increased in the LAIV group (day 21 vs day 0 OR, 3.18; P = .003) but not in the control group (OR, 0.86; P = .79). The highest IgG increases following asymptomatic colonization were seen for M1 and SpyCEP proteins.
Conclusions: Asymptomatic S. pyogenes colonization appears modestly increased by LAIV, and may be immunologically significant. LAIV could be used to study influenza-S. pyogenes interactions.

Japanese encephalitis virus vaccine

Malaria vaccine

Lancet. 2024 Feb 10;403(10426):533-544.
doi: 10.1016/S0140-6736(23)02511-4. Epub 2024 Feb 1.
Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial
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Abstract
Background: Recently, we found that a new malaria vaccine, R21/Matrix-M, had over 75% efficacy against clinical malaria with seasonal administration in a phase 2b trial in Burkina Faso. Here, we report on safety and efficacy of the vaccine in a phase 3 trial enrolling over 4800 children across four countries followed for up to 18 months at seasonal sites and 12 months at standard sites.
Methods: We did a double-blind, randomised, phase 3 trial of the R21/Matrix-M malaria vaccine across five sites in four African countries with differing malaria transmission intensities and seasonality. Children (aged 5-36 months) were enrolled and randomly assigned (2:1) to receive 5 µg R21 plus 50 µg Matrix-M or a control vaccine (licensed rabies vaccine [Abhayrab]). Participants, their families, investigators, laboratory teams, and the local study team were masked to treatment. Vaccines were administered as three doses, 4 weeks apart, with a booster administered 12 months after the third dose. Half of the children were recruited at two sites with seasonal malaria transmission and the remainder at standard sites with perennial malaria transmission using age-based immunisation. The primary objective was protective efficacy of R21/Matrix-M from 14 days after third vaccination to 12 months after completion of the primary series at seasonal and standard sites separately as co-primary endpoints. Vaccine efficacy against multiple malaria episodes and severe malaria, as well as safety and immunogenicity, were also assessed. This trial is registered on ClinicalTrials.gov, NCT04704830, and is ongoing.

Findings: From April 26, 2021, to Jan 12, 2022, 5477 children consented to be screened, of whom 1705 were randomly assigned to control vaccine and 3434 to R21/Matrix-M; 4878 participants received the first dose of vaccine. 3103 participants in the R21/Matrix-M group and 1541 participants in the control group were included in the modified per-protocol analysis (2412 [51·9%] male and 2232 [48·1%] female). R21/Matrix-M vaccine was well tolerated, with injection site pain (301 [18·6%] of 1615 participants) and fever (754 [46·7%] of 1615 participants) as the most frequent adverse events. Number of adverse events of special interest and serious adverse events did not significantly differ between the vaccine groups. There were no treatment-related deaths. 12-month vaccine efficacy was 75% (95% CI 71-79; p<0·0001) at the seasonal sites and 68% (61-74; p<0·0001) at the standard sites for time to first clinical malaria episode. Similarly, vaccine efficacy against multiple clinical malaria episodes was 75% (71-78; p<0·0001) at the seasonal sites and 67% (59-73; p<0·0001) at standard sites. A modest reduction in vaccine efficacy was observed over the first 12 months of follow-up, of similar size at seasonal and standard sites. A rate reduction of 868 (95% CI 762-974) cases per 1000 children-years at seasonal sites and 296 (231-362) at standard sites occurred over 12 months. Vaccine-induced antibodies against the conserved central Asn-Ala-Asn-Pro (NANP) repeat sequence of circumsporozoite protein correlated with vaccine efficacy. Higher NANP-specific antibody titres were observed in the 5-17 month age group compared with 18-36 month age group, and the younger age group had the highest 12-month vaccine efficacy on time to first clinical malaria episode at seasonal (79% [95% CI 73-84]; p<0·001) and standard (75% [65-83]; p<0·001) sites.
Interpretation: R21/Matrix-M was well tolerated and offered high efficacy against clinical malaria in African children. This low-cost, high-efficacy vaccine is already licensed by several African countries, and recently received a WHO policy recommendation and prequalification, offering large-scale supply to help reduce the great burden of malaria in sub-Saharan Africa.

Med. 2023 Aug 7;S2666-6340(23)00226-X.
doi: 10.1016/j.medj.2023.07.003. Online ahead of print.

Superior antibody immunogenicity of a viral-vectored RH5 blood-stage malaria vaccine in Tanzanian infants as compared to adults

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Abstract

Background: RH5 is a leading blood-stage candidate antigen for a Plasmodium falciparum vaccine; however, its safety and immunogenicity in malaria-endemic populations are unknown.
Methods: A phase 1b, single-center, dose-escalation, age-de-escalation, double-blind, randomized, controlled trial was conducted in Bagamoyo, Tanzania (NCT03435874). Between 12th April and 25th October 2018, 63 healthy adults (18-35 years), young children (1-6 years), and infants (6-11 months) received a priming dose of viral-vectored ChAd63 RH5 or

rabies control vaccine. Sixty participants were boosted with modified vaccinia virus Ankara (MVA) RH5 or rabies control vaccine 8 weeks later and completed 6 months of follow-up post priming. Primary outcomes were the number of solicited and unsolicited adverse events post vaccination and the number of serious adverse events over the study period. Secondary outcomes included measures of the anti-RH5 immune response.
Findings: Vaccinations were well tolerated, with profiles comparable across groups. No serious adverse events were reported. Vaccination induced RH5-specific cellular and humoral responses. Higher anti-RH5 serum immunoglobulin G (IgG) responses were observed post boost in young children and infants compared to adults. Vaccine-induced antibodies showed growth inhibition activity (GIA) in vitro against P. falciparum blood-stage parasites; their highest levels were observed in infants.
Conclusions: The ChAd63-MVA RH5 vaccine shows acceptable safety and reactogenicity and encouraging immunogenicity in children and infants residing in a malaria-endemic area. The levels of functional GIA observed in RH5-vaccinated infants are the highest reported to date following human vaccination. These data support onward clinical development of RH5-based blood-stage vaccines to protect against clinical malaria in young African infants.

Front Immunol. 2023 Oct 16:14:1267372.
doi: 10.3389/fimmu.2023.1267372. eCollection 2023.

Safety and immunogenicity of BK-SE36/CpG malaria vaccine in healthy Burkinabe adults and children: a phase 1b randomised, controlled, double-blinded, age de-escalation trial

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Abstract
Background: BK-SE36/CpG is a recombinant blood-stage malaria vaccine candidate based on the N-terminal *Plasmodium falciparum* serine repeat antigen5 (SE36), adsorbed to aluminium hydroxide gel and reconstituted, prior to administration, with synthetic oligodeoxynucleotides bearing CpG motifs. In healthy Japanese adult males, BK-SE36/CpG was well tolerated. This study assessed its safety and immunogenicity in healthy malaria-exposed African adults and children.
Methods: A double-blind, randomised, controlled, age de-escalating clinical trial was conducted in an urban area of Ouagadougou, Burkina Faso. Healthy participants (n=135) aged 21-45 years (Cohort 1), 5-10 years (Cohort 2) and 12-24 months (Cohort 3) were randomised to receive three vaccine doses (Day 0, 28 and 112) of BK-SE36/CpG or rabies vaccine by intramuscular injection.
Results: One hundred thirty-four of 135 (99.2%) subjects received all three scheduled vaccine doses. Vaccinations were well tolerated with no related Grade 3 (severe) adverse events (AEs). Pain/limitation of limb movement, headache in adults and fever in younger children (all mild to moderate in intensity) were the most frequently observed local and systemic AEs. Eighty-three of BK-SE36/CpG (91%) recipients and 37 of control subjects (84%) had Grade 1/2 events within 28 days post vaccination. Events considered by the investigator to be vaccine related were experienced by 38% and 14% of subjects in BK-SE36/CpG and

control arms, respectively. Throughout the trial, six Grade 3 events (in 4 subjects), not related to vaccination, were recorded in the BK-SE36/CpG arm: 5 events (in 3 subjects) within 28 days of vaccination. All serious adverse events (SAEs) (n=5) were due to severe malaria (52-226 days post vaccination) and not related to vaccination. In all cohorts, BK-SE36/CpG arm had higher antibody titres after Dose 3 than after Dose 2. Younger cohorts had stronger immune responses (12-24-month-old > 5-10 years-old > 21-45 years-old). Sera predominantly reacted to peptides that lie in intrinsically unstructured regions of SE36. In the control arm, there were no marked fold changes in antibody titres and participants' sera reacted poorly to all peptides spanning SE36.
Conclusion: BK-SE36/CpG was well-tolerated and immunogenic. These results pave the way for further proof-of-concept studies to demonstrate vaccine efficacy.

Lancet. 2024 Apr 27;403(10437):1660-1670.
doi: 10.1016/S0140-6736(24)00004-7. Epub 2024 Apr 4.

Feasibility, safety, and impact of the RTS,S/AS01$_E$ malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomised introduction of the vaccine in Ghana, Kenya, and Malawi

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Abstract
Background: The RTS,S/AS01$_E$ malaria vaccine (RTS,S) was introduced by national immunisation programmes in Ghana, Kenya, and Malawi in 2019 in large-scale pilot schemes. We aimed to address questions about feasibility and impact, and to assess safety signals that had been observed in the phase 3 trial that included an excess of meningitis and cerebral malaria cases in RTS,S recipients, and the possibility of an excess of deaths among girls who received RTS,S than in controls, to inform decisions about wider use.
Methods: In this prospective evaluation, 158 geographical clusters (66 districts in Ghana; 46 sub-counties in Kenya; and 46 groups of immunisation clinic catchment areas in Malawi) were randomly assigned to early or delayed introduction of RTS,S, with three doses to be administered between the ages of 5 months and 9 months and a fourth dose at the age of approximately 2 years. Primary outcomes of the evaluation, planned over 4 years, were mortality from all causes except injury (impact), hospital admission with severe malaria (impact), hospital admission with meningitis or cerebral malaria (safety), deaths in girls compared with boys (safety), and vaccination coverage (feasibility). Mortality was monitored in children aged 1-59 months throughout the pilot areas. Surveillance for meningitis and severe malaria was established in eight sentinel hospitals in Ghana, six in Kenya, and four in Malawi. Vaccine uptake was measured in surveys of children aged 12-23 months about 18 months after vaccine introduction. We estimated that sufficient data would have accrued after 24 months to evaluate each of the safety signals and the impact on severe malaria in a pooled analysis of the data from the three countries. We estimated incidence rate ratios

(IRRs) by comparing the ratio of the number of events in children age-eligible to have received at least one dose of the vaccine (for safety outcomes), or age-eligible to have received three doses (for impact outcomes), to that in non-eligible age groups in implementation areas with the equivalent ratio in comparison areas. To establish whether there was evidence of a difference between girls and boys in the vaccine's impact on mortality, the female-to-male mortality ratio in age groups eligible to receive the vaccine (relative to the ratio in non-eligible children) was compared between implementation and comparison areas. Preliminary findings contributed to WHO's recommendation in 2021 for widespread use of RTS,S in areas of moderate-to-high malaria transmission.

Findings: By April 30, 2021, 652 673 children had received at least one dose of RTS,S and 494 745 children had received three doses. Coverage of the first dose was 76% in Ghana, 79% in Kenya, and 73% in Malawi, and coverage of the third dose was 66% in Ghana, 62% in Kenya, and 62% in Malawi. 26 285 children aged 1-59 months were admitted to sentinel hospitals and 13 198 deaths were reported through mortality surveillance. Among children eligible to have received at least one dose of RTS,S, there was no evidence of an excess of meningitis or cerebral malaria cases in implementation areas compared with comparison areas (hospital admission with meningitis: IRR 0·63 [95% CI 0·22-1·79]; hospital admission with cerebral malaria: IRR 1·03 [95% CI 0·61-1·74]). The impact of RTS,S introduction on mortality was similar for girls and boys (relative mortality ratio 1·03 [95% CI 0·88-1·21]). Among children eligible for three vaccine doses, RTS,S introduction was associated with a 32% reduction (95% CI 5-51%) in hospital admission with severe malaria, and a 9% reduction (95% CI 0-18%) in all-cause mortality (excluding injury).

Interpretation: In the first 2 years of implementation of RTS,S, the three primary doses were effectively deployed through national immunisation programmes. There was no evidence of the safety signals that had been observed in the phase 3 trial, and introduction of the vaccine was associated with substantial reductions in hospital admission with severe malaria. Evaluation continues to assess the impact of four doses of RTS,S.

Lancet Infect Dis. 2024 May 6:S1473-3099(24)00179-8.
doi: 10.1016/S1473-3099(24)00179-8. Online ahead of print.

Genotypic analysis of RTS,S/AS01$_E$ malaria vaccine efficacy against parasite infection as a function of dosage regimen and baseline malaria infection status in children aged 5-17 months in Ghana and Kenya: a longitudinal phase 2b randomised controlled trial

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Abstract

Background: The first licensed malaria vaccine, RTS,S/AS01$_E$, confers moderate protection against symptomatic disease. Because many malaria infections are asymptomatic, we conducted a large-scale longitudinal parasite genotyping study of samples from a clinical trial exploring how vaccine dosing regimen affects vaccine efficacy.

Methods: Between Sept 28, 2017, and Sept 25, 2018, 1500 children aged 5-17 months were randomly assigned (1:1:1:1:1) to receive four different RTS,S/AS01$_E$ regimens or a rabies control vaccine in a phase 2b open-label clinical trial in Ghana and Kenya. Participants in the four RTS,S groups received two full doses at month 0 and month 1 and either full doses at month 2 and month 20 (group R012-20); full doses at month 2, month 14, month 26, and month 38 (group R012-14); fractional doses at month 2, month 14, month 26, and month 38 (group Fx012-14; early fourth dose); or fractional doses at month 7, month 20, and month 32 (group Fx017-20; delayed third dose). We evaluated the time to the first new genotypically detected infection and the total number of new infections during two follow-up periods (12 months and 20 months) in more than 36 000 dried blood spot specimens from 1500 participants. To study vaccine effects on time to the first new infection, we defined vaccine efficacy as one minus the hazard ratio (HR; RTS,S vs control) of the first new infection. We performed a post-hoc analysis of vaccine efficacy based on malaria infection status at first vaccination and force of infection by month 2. This trial (MAL-095) is registered with ClinicalTrials.gov, NCT03281291.

Findings: We observed significant and similar vaccine efficacy (25-43%; 95% CI union 9-53) against first new infection for all four RTS,S/AS01$_E$ regimens across both follow-up periods (12 months and 20 months). Each RTS,S/AS01$_E$ regimen significantly reduced the mean number of new infections in the 20-month follow-up period by 1·1-1·6 infections (95% CI union 0·6-2·1). Vaccine efficacy against first new infection was significantly higher in participants who were infected with malaria (68%; 95% CI 50-80) than in those who were uninfected (37%; 23-48) at the first vaccination (p=0·0053).

Interpretation: All tested dosing regimens blocked some infections to a similar degree. Improved vaccine efficacy in participants infected during vaccination could suggest new strategies for highly efficacious malaria vaccine development and implementation.

Lancet Infect Dis. 2024 Jan;24(1):75-86.
doi: 10.1016/S1473-3099(23)00368-7. Epub 2023 Aug 22.

Seasonal vaccination with RTS,S/AS01$_E$ vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial

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Abstract

Background: Seasonal vaccination with the RTS,S/AS01$_E$ vaccine combined with seasonal malaria chemoprevention (SMC) prevented malaria in young children more effectively than either intervention given alone over a 3 year period. The objective of this study was to establish whether the added protection provided by the combination could be sustained for a further 2 years.

Methods: This was a double-blind, individually randomised, controlled, non-inferiority and superiority, phase 3 trial done at two sites: the Bougouni district and neighbouring areas in Mali and Houndé district, Burkina Faso. Children who had been enrolled in the initial 3-year trial when aged 5-17 months were initially randomly assigned individually to receive SMC with sulphadoxine-pyrimethamine and amodiaquine plus control vaccines, RTS,S/AS01$_E$ plus placebo SMC, or SMC plus RTS,S/AS01$_E$. They continued to receive the same interventions until the age of 5 years. The primary trial endpoint was the incidence of clinical malaria over the 5-year trial period in both the modified intention-to-treat and per-protocol populations. Over the 5-year period, non-inferiority was defined as a 20% increase in clinical malaria in the RTS,S/AS01$_E$-alone group compared with the SMC alone group. Superiority was defined as a 12% difference in the incidence of clinical malaria between the combined and single intervention groups. The study is registered with ClinicalTrials.gov, NCT04319380, and is complete.

Findings: In April, 2020, of 6861 children originally recruited, 5098 (94%) of the 5433 children who completed the initial 3-year follow-up were re-enrolled in the extension study. Over 5 years, the incidence of clinical malaria per 1000 person-years at risk was 313 in the SMC alone group, 320 in the RTS,S/AS01$_E$-alone group, and 133 in the combined group. The combination of RTS,S/AS01$_E$ and SMC was superior to SMC (protective efficacy 57·7%, 95% CI 53·3 to 61·7) and to RTS,S/AS01$_E$ (protective efficacy 59·0%, 54·7 to 62·8) in preventing clinical malaria. RTS,S/AS01$_E$ was non-inferior to SMC (hazard ratio 1·03 [95% CI 0·95 to 1·12]). The protective efficacy of the combination versus SMC over the 5-year period of the study was very similar to that seen in the first 3 years with the protective efficacy of the combination versus SMC being 57·7% (53·3 to 61·7) and versus RTS/AS01$_E$-alone being 59·0% (54·7 to 62·8). The comparable figures for the first 3 years of the study were 62·8% (58·4 to 66·8) and 59·6% (54·7 to 64·0%), respectively. Hospital admissions for WHO-defined severe malaria were reduced by 66·8% (95% CI 40·3 to 81·5), for malarial anaemia by 65·9% (34·1 to 82·4), for blood transfusion by 68·1% (32·6 to 84·9), for all-cause deaths by 44·5% (2·8 to 68·3), for deaths excluding external causes or surgery by 41·1% (-9·2 to 68·3), and for deaths from malaria by 66·8% (-2·7 to 89·3) in the combined group compared with the SMC alone group. No safety signals were detected.

Interpretation: Substantial protection against malaria was sustained over 5 years by combining seasonal malaria vaccination with seasonal chemoprevention, offering a potential new approach to malaria control in areas with seasonal malaria transmission.

Maternal immunization

BMC Public Health. 2024 May 2;24(1):1213.
doi: 10.1186/s12889-024-18486-x.

Effect of maternal vaccination on infant morbidity in Bangladesh

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Abstract

Background: Risk factors of infant mortality in Africa and south Asian countries have been broadly discussed. However, infant morbidity is largely underestimated. We analyzed the

data from a randomized vaccine trial in Bangladesh to identify and assess the effect of risk factors on infant morbidity.
Methods: Pregnant women were randomly assigned to receive either inactivated influenza vaccine or pneumococcal polysaccharide vaccine and the infants were randomly assigned to receive 7-valent pneumococcal conjugate vaccine or Hib conjugate vaccine at week 6, 10 and 14. The data were collected from August 2004 through December 2005. Each pair of infant and mother were followed for 24 weeks after birth with weekly visits. Generalized estimating equations (GEE) for repeated measurements and Poisson regression models were used to identify the risk factors and evaluate their effect on the longitudinal incidence and total number of episodes of respiratory illness with fever (RIF), diarrhea disease, ear problem and pneumonia.
Results: A total of 340 pregnant women were randomized with mean age of 25 years. The baseline mother and infant characteristics were similar between two treatment groups. Exclusive breastfeeding and higher paternal education level were common factors associated with lower infant morbidity of RIF (adjusted OR = 0.40 and 0.94 with $p < 0.01$ and $p = 0.02$, respectively), diarrhea disease (adjusted OR = 0.39 and 0.95 with $p < 0.01$ and $p = 0.04$, respectively), and ear problem (adjusted OR = 0.20 and 0.76 with $p < 0.01$ and $p < 0.01$, respectively). Maternal influenza vaccine significantly reduced the incidence of RIF (adjusted OR = 0.54; $p < 0.01$) but not diarrhea disease or ear problem ($p > 0.05$). Female infants had lower incidence of diarrhea disease (adjusted OR = 0.67; $p = 0.01$) and ear problem (adjusted OR = 0.12; $p = 0.01$).
Conclusions: Maternal influenza vaccination, exclusive breastfeeding, female children, and higher paternal education level significantly reduced the infant morbidity within the 24 weeks after birth in Bangladesh.

Emerg Microbes Infect. 2023 Dec;12(1):2204146.
doi: 10.1080/22221751.2023.2204146.
Effect of immunization during pregnancy and pre-existing immunity on diphtheria-tetanus-acellular pertussis vaccine responses in infants
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Abstract
Immunization during pregnancy (IP) against pertussis is recommended in many countries to protect infants. Although maternal antibodies can influence the infants' antibody responses to primary vaccinations, their effect on the development of functional antibodies and B cells remain poorly studied. We investigated the maternal immune response to IP and the effect of IP and pre-existing antibodies on infants' primary vaccine responses in an open-label, non-randomized trial. Forty-seven mothers received tetanus-diphtheria-acellular pertussis (Tdap) vaccine during pregnancy, and 22 mothers were included as controls. Sixty-nine infants received primary doses of DTaP at three and five months of age. Geometric mean concentrations of antibodies to pertussis toxin, filamentous haemagglutinin, pertactin, diphtheria, and tetanus toxins, pertussis toxin neutralizing antibodies (PTNAs), and plasma and memory B-cell frequencies were studied at delivery, and at three, five and six months. Levels of antibodies, PTNAs, and frequencies of memory B-cells were significantly increased

at delivery and up to six months after in mothers with IP compared to those without IP (all $p < 0.05$, except for PT-specific memory B-cells). In vaccinated pregnant women, high pre-existing antibody levels were positively correlated with higher antibody responses after IP. IP blunted the infants' antibody and plasma B-cell responses to all vaccine antigens, except for tetanus toxin. This blunting effect was the strongest in infants with high concentrations of maternal antibodies. In conclusion, IP resulted in significantly higher concentrations of antibodies in infants up to three months of age (all $p < 0.05$); but was associated with blunting of various infants' vaccine responses.

BMJ Glob Health. 2023 Oct;8(10):e012376.
doi: 10.1136/bmjgh-2023-012376.

Are maternal vaccines effective and safe for mothers and infants? A systematic review and meta-analysis of randomised controlled trials

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Abstract

Introduction: Maternal vaccination is a promising strategy to reduce the burden of vaccine-preventable diseases for mothers and infants. We aimed to provide an up-to-date overview of the efficacy and safety of all available maternal vaccines.

Methods: We searched PubMed, Embase, CENTRAL and ClinicalTrials.gov on 1 February 2022, for phase III and IV randomised controlled trials (RCTs) that compared maternal vaccination against any pathogen with placebo or no vaccination. Primary outcomes were laboratory-confirmed or clinically confirmed disease in mothers and infants. Secondary safety outcomes included intrauterine growth restriction, stillbirth, maternal death, preterm birth, congenital malformations and infant death. Random effects meta-analysis were used to calculate pooled risk ratio's (RR). Quality appraisal was performed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Six RCTs on four maternal vaccines, influenza, tetanus, diphtheria and pertussis (Tdap), pneumococcal and respiratory syncytial virus (RSV) were eligible. The overall risk of bias and certainty of evidence varied from low to high. Maternal influenza vaccination significantly reduced the number of laboratory-confirmed influenza cases (RR 0.58, 95% CI 0.42 to 0.79, event rate 57 vs 98, 2 RCTs, n=6003, I^2=0%), and clinically confirmed influenza cases in mothers (RR 0.88, 95% CI 0.78 to 0.99, event rate 418 vs 472, 2 RCTs, n=6003, I^2=0%), and laboratory-confirmed influenza in infants (RR 0.66, 95% CI 0.52 to 0.85, event rate 98 vs 148, 2 RCTs, n=5883, I^2=0%), although this was not significant for clinically confirmed influenza in infants (RR 0.99, 95% CI 0.94 to 1.05, event rate 1371 vs 1378, 2 RCTs, n=5883, I^2=0%). No efficacy data were available on maternal Tdap vaccination. Maternal pneumococcal vaccination did not reduce laboratory-confirmed and clinically confirmed middle ear disease (RR 0.49, 95% CI 0.24 to 1.02, event rate 9 vs 18, 1 RCT, n=133 and RR 0.88 95% CI 0.69 to 1.12, event rate 42 vs 47, 1 RCT, n=133, respectively), and clinically confirmed lower-respiratory tract infection (LRTI) (RR 1.08, 95% CI 0.82 to 1.43, event rate 18 vs 34, 1 RCT, n=70) in infants. Maternal RSV vaccination did not reduce laboratory-confirmed RSV LRTI in infants (RR 0.75, 95% CI 0.56 to 1.01, event rate 103 vs 71, 1 RCT, n=4527). There was no evidence of a significant effect of any of the maternal vaccines on the reported safety outcomes.

Conclusions: The few RCTs with low event rates suggest that, depending on the type of maternal vaccine, the vaccine might effectively prevent disease and within its size does not show safety concerns in mothers and infants.

Emerg Microbes Infect. 2023 Dec;12(1):2185456.
doi: 10.1080/22221751.2023.2185456.

Safety of hepatitis E vaccination for pregnancy: a post-hoc analysis of a randomized, double-blind, controlled phase 3 clinical trial

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Abstract

Special attention has been paid to Hepatitis E (HE) prophylaxis for pregnant women due to poor prognosis of HE in this population. We conducted a post-hoc analysis based on the randomized, double-blind, HE vaccine (Hecolin)-controlled phase 3 clinical trial of human papillomavirus (HPV) vaccine (Cecolin) conducted in China. Eligible healthy women aged 18-45 years were randomly assigned to receive three doses of Cecolin or Hecolin and were followed up for 66 months. All the pregnancy-related events throughout the study period were closely followed up. The incidences of adverse events, pregnancy complications, and adverse pregnancy outcomes were analysed based on the vaccine group, maternal age, and interval between vaccination and pregnancy onset. During the study period, 1263 Hecolin receivers and 1260 Cecolin receivers reported 1684 and 1660 pregnancies, respectively. The participants in the two vaccine groups showed similar maternal and neonatal safety profiles, regardless of maternal age. Among the 140 women who were inadvertently vaccinated during pregnancy, the incidences of adverse reactions had no statistical difference between the two groups (31.8% vs 35.1%, $p = 0.6782$). The proximal exposure to HE vaccination was not associated with a significantly higher risk of abnormal foetal loss (OR 0.80, 95% CI 0.38-1.70) or neonatal abnormality (OR 2.46, 95% CI 0.74-8.18) than that to HPV vaccination, as did distal exposure. Significant difference was not noted between pregnancies with proximal and distal exposure to HE vaccination. Conclusively, HE vaccination during or shortly before pregnancy is not associated with increased risks for both the pregnant women and pregnancy outcomes.

Measles vaccine

Int J Infect Dis. 2023 Sep;134:23-30.
doi: 10.1016/j.ijid.2023.05.011. Epub 2023 May 12.

Overall effect of a campaign with measles vaccine on the composite outcome mortality or hospital admission: A cluster-randomized trial among children aged 9-59 months in rural Guinea-Bissau

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Abstract
Objectives: Campaigns with measles vaccine (C-MV) are conducted to eradicate measles, but prior studies indicate that MV reduces non-measles mortality and hospital admissions too. We hypothesized that C-MV reduces death/hospital admission by 30%.
Methods: Between 2016-2019, we conducted a non-blinded cluster-randomized trial randomizing village clusters in rural Guinea-Bissau to a C-MV targeting children aged 9-59 months. In Cox proportional hazards models, we assessed the effect of C-MV, obtaining hazard ratios (HR) for the composite outcome (death/hospital admission). We also examined potential effect modifiers.
Results: Among 18,411 children (9636 in 111 intervention clusters/8775 in 110 control clusters), 379 events occurred (208 intervention/171 control) during a median follow-up period of 22 months. C-MV did not reduce the composite outcome (HR 1.12, 95% confidence interval 0.88-1.41). Mortality among enrolled children (5.3 intervention and 4.6 control, per 1000 person-years) was approximately half the pre-trial mortality rate (11.1 intervention and 8.9 control, per 1000 person-years). Neither planned nor explorative analyses of potential effect modifiers explained the contrasting results to prior studies.
Conclusion: C-MV did not reduce overall mortality or hospital admission. This might be explained by changes in disease patterns, baseline differences in health status, and/or modifying effects of other campaigns during follow-up.

Measles, mumps, rubella combination vaccines

Lancet. 2024 May 11;403(10439):1879-1892.
doi: 10.1016/S0140-6736(24)00532-4. Epub 2024 Apr 29.
A measles and rubella vaccine microneedle patch in The Gambia: a phase 1/2, double-blind, double-dummy, randomised, active-controlled, age de-escalation trial
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Abstract
Background: Microneedle patches (MNPs) have been ranked as the highest global priority innovation for overcoming immunisation barriers in low-income and middle-income countries. This trial aimed to provide the first data on the tolerability, safety, and immunogenicity of a measles and rubella vaccine (MRV)-MNP in children.
Methods: This single-centre, phase 1/2, double-blind, double-dummy, randomised, active-controlled, age de-escalation trial was conducted in The Gambia. To be eligible, all participants had to be healthy according to prespecified criteria, aged 18-40 years for the adult cohort, 15-18 months for toddlers, or 9-10 months for infants, and to be available for visits throughout the follow-up period. The three age cohorts were randomly assigned in a 2:1 ratio (adults) or 1:1 ratio (toddlers and infants) to receive either an MRV-MNP (Micron Biomedical, Atlanta, GA, USA) and a placebo (0·9% sodium chloride) subcutaneous injection, or a placebo-MNP and an MRV subcutaneous injection (MRV-SC; Serum Institute of India,

Pune, India). Unmasked staff ransomly assigned the participants using an online application, and they prepared visually identical preparations of the MRV-MNP or placebo-MNP and MRV-SC or placebo-SC, but were not involved in collecting endpoint data. Staff administering the study interventions, participants, parents, and study staff assessing trial endpoints were masked to treatment allocation. The safety population consists of all vaccinated participants, and analysis was conducted according to route of MRV administration, irrespective of subsequent protocol deviations. The immunogenicity population consisted of all vaccinated participants who had a baseline and day 42 visit result available, and who had no protocol deviations considered to substantially affect the immunogenicity endpoints. Solicited local and systemic adverse events were collected for 14 days following vaccination. Unsolicited adverse events were collected to day 180. Age de-escalation between cohorts was based on the review of the safety data to day 14 by an independent data monitoring committee. Serum neutralising antibodies to measles and rubella were measured at baseline, day 42, and day 180. Analysis was descriptive and included safety events, seroprotection and seroconversion rates, and geometric mean antibody concentrations. The trial was registered with the Pan African Clinical Trials Registry PACTR202008836432905, and is complete.

Findings: Recruitment took place between May 18, 2021, and May 27, 2022. 45 adults, 120 toddlers, and 120 infants were randomly allocated and vaccinated. There were no safety concerns in the first 14 days following vaccination in either adults or toddlers, and age de-escalation proceeded accordingly. In infants, 93% (52/56; 95% CI 83·0-97·2) seroconverted to measles and 100% (58/58; 93·8-100) seroconverted to rubella following MRV-MNP administration, while 90% (52/58; 79·2-95·2) and 100% (59/59; 93·9-100) seroconverted to measles and rubella respectively, following MRV-SC. Induration at the MRV-MNP application site was the most frequent local reaction occurring in 46 (77%) of 60 toddlers and 39 (65%) of 60 infants. Related unsolicited adverse events, most commonly discolouration at the application site, were reported in 35 (58%) of 60 toddlers and 57 (95%) of 60 infants that had received the MRV-MNP. All local reactions were mild. There were no related severe or serious adverse events.

Interpretation: The safety and immunogenicity data support the accelerated development of the MRV-MNP.

Meningococcal vaccine

Norovirus vaccine

Hum Vaccin Immunother. 2023 Dec 31;19(1):2204787.
doi: 10.1080/21645515.2023.2204787. Epub 2023 May 4.

Immunogenicity and tolerability of a bivalent virus-like particle norovirus vaccine candidate in children from 6 months up to 4 years of age: A phase 2 randomized, double-blind trial

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Abstract

We conducted a dose-finding phase 2 study of the HilleVax bivalent virus-like particle (VLP) vaccine candidate (HIL-214) in two cohorts of children, 6-≤12 months and 1-≤4 years of age (N = 120 per cohort), in Panama and Colombia (ClinicalTrials.gov, identifier NCT02153112). On Day 1, children randomized to one of the four equal groups received intramuscular injections of four different HIL-214 formulations containing 15/15, 15/50, 50/50, or 50/150 μg of GI.1/GII.4c genotype VLPs and 0.5 mg $Al(OH)_3$. On Day 29, half the children in each group received a second vaccination (N = 60), while the other half received saline placebo injections to maintain the blind. VLP-specific ELISA Pan-Ig and histo-blood group binding antigen-blocking antibodies (HBGA) were measured on Days 1, 29, 57 and 210. On Day 29, after one dose, there were large Pan-Ig and HBGA responses in both age cohorts with some indication of dose-dependence, and higher geometric mean titers (GMT) in the older children. A further increase in titers was observed 28 days after a second dose in the 6-≤12-month-old groups, but less so in the 1-≤4-year-old groups; GMTs at Day 57 were broadly similar across doses and in both age groups. GMTs of Pan-Ig and HBGA persisted above baseline up to Day 210. All formulations were well tolerated with mostly mild-to-moderate transient solicited adverse events reported by parents/guardians, and no vaccine-related serious adverse events occurred. Further development of HIL-214 is warranted to protect the most susceptible young children against norovirus.

Prentavalent vaccine (DTP-HepB-Hib)

Pediatr Infect Dis J. 2023 Aug 1;42(8):711-718.
doi: 10.1097/INF.0000000000003975. Epub 2023 Apr 27.

Immunogenicity and Safety of a Hexavalent DTwP-IPV-HB-PRP~T Vaccine Versus Separate DTwP-HB-PRP~T, bOPV, and IPV Vaccines Administered at 2, 4, 6 Months of Age Concomitantly With Rotavirus and Pneumococcal Conjugate Vaccines in Healthy Infants in Thailand

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Abstract

Background: This study investigated the immunogenicity and safety of a fully liquid, hexavalent, diphtheria (D)-tetanus (T)-whole-cell pertussis (wP)-inactivated poliovirus (IPV)-hepatitis B (HB)- Haemophilus influenzae b (PRP-T) vaccine compared to licensed DTwP-HB-PRP~T, IPV, and bivalent oral poliovirus (bOPV) vaccines following co-administration with other pediatric vaccines [pneumococcal conjugate vaccine (PCV13) and rotavirus vaccine].

Methods: Phase III, randomized, open-label study in Thailand. Healthy infants received DTwP-IPV-HB-PRP~T at 2, 4 and 6 months of age (N = 228), or DTwP-HB-PRP~T and bOPV (2, 4 and 6 months of age) and IPV (4 months of age) (N = 231). All participants received PCV13 (2, 4 and 6 months of age) and rotavirus vaccine (2 and 4 months of age). Immunogenicity for all antigens was assessed using validated assays, and noninferiority post-third dose was evaluated for anti-D, anti-T, anti-pertussis [anti-pertussis toxin (anti-PT) and anti-fimbriae

2/3 (anti-FIM)], anti-polio 1, 2, 3, anti-HB, and anti-PRP~T. Safety was assessed using parental reports.
Results: Noninferiority was demonstrated for each antigen, and overall noninferiority of DTwP-IPV-HB-PRP~T versus DTwP-HB-PRP~T+bOPV+IPV was concluded. Similarity in each group was observed for the GMC ratio for antirotavirus antibodies (20.9 and 17.3, respectively) and anti-PCV13 antibodies (range: 8.46-32.6 and 7.53-33.1, respectively). Two serious adverse events were related to DTwP-IPV-HB-PRP~T (febrile convulsion and acute febrile illness) and 1 was related to DTwP-HB-PRP~T+bOPV+IPV (febrile seizure), but overall there were no safety concerns with similar rates of participants experiencing solicited (99.1% and 98.3%) and unsolicited (19.3% and 19.5%) adverse events in each group.
Conclusions: This study confirmed the suitability of DTwP-IPV-HB-PRP~T primary series vaccination in combination with rotavirus and PCV13 vaccines.

PLoS One. 2023 Aug 15;18(8):e0284898.
doi: 10.1371/journal.pone.0284898. eCollection 2023.

Safety and immunogenicity of a new formulation of a pentavalent DTwP-HepB-Hib vaccine in healthy Indian infants-A randomized study

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Abstract
Background: Pentavalent vaccines (DTP-HepB-Hib) have been introduced in many countries in their routine public immunization programmes to protect against diphtheria (D), tetanus (T), pertussis (P), hepatitis B (Hep B) and Hemophilus influenzae type b (Hib) diseases. This study compared the safety and immunogenicity of a new formulation of a whole-cell Bordetella pertussis (wP) based pentavalent vaccine (DTwP-HepB-Hib). The new formulation was developed using well-characterized hepatitis B and pertussis whole cell vaccine components.
Methods: This was a phase III, observer-blind, randomized, non-inferiority, multi-center study conducted in India among 460 infants who were followed up for safety and immunogenicity for 28 days after administration of three doses of either investigational or licensed comparator formulations at 6-8, 10-12 and 14-16 weeks of age.
Results: The investigational formulation of DTwP-HepB-Hib vaccine was non-inferior to the licensed formulation in terms of hepatitis B seroprotection rate (% of subjects with HepB antibodies ≥10mIU/mL were 99.1% versus 99.0%, respectively, corresponding to a difference of 0.1% (95% CI, -2.47 to 2.68)) and pertussis immune responses (adjusted geometric mean concentrations of antibodies for anti-PT were 76.7 EU/mL versus 63.3 EU/mL, with a ratio of aGMTs of 1.21 (95% CI, 0.89-1.64), and for anti-FIM were 1079 EU/mL versus 1129 EU/mL, with a ratio of aGMTs of 0.95 (95% CI, 0.73-1.24), respectively). The immune responses to other valences (D, T, and Hib) in the two formulations were also similar. The safety profile of both formulations was found to be similar and were well tolerated.
Conclusions: The investigational DTwP-HepB-Hib vaccine formulation was immunogenic and well-tolerated when administered as three dose primary series in infants.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2352909.
doi: 10.1080/21645515.2024.2352909. Epub 2024 May 16.

Antibody persistence to diphtheria toxoid, tetanus toxoid, *Bordetella pertussis* antigens, and *Haemophilus influenzae* type b following primary and first booster with pentavalent versus hexavalent vaccines

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Abstract

Thailand has incorporated the whole-cell (wP) pertussis vaccine into the expanded program on immunization since 1977 and has offered the acellular pertussis (aP) vaccine as an optional vaccine for infants since 2001. We followed healthy children from a clinical trial (ClinicalTrials.gov NCT02408926) in which children were randomly assigned to receive either pentavalent (DTwP-HB-Hib) or hexavalent (DTaP-IPV-HB-Hib) vaccines for their primary series (administered at 2, 4, and 6 months) and first booster vaccination (18 months). Both groups received Tdap-IPV as a second booster at the age of 4 y. Blood samples were collected for evaluation of antibody persistence to diphtheria toxoid (DT), tetanus toxoid (TT), and *Bordetella pertussis* (*B. pertussis*) between 2 and 6 y of age annually, and for the immunogenicity study of Tdap-IPV at 1 month after the second booster. Antibody persistence to *Haemophilus influenzae* type b (Hib) was followed until 3 y of age. A total of 105 hexavalent-vaccinated children and 91 pentavalent-vaccinated children completed this study. Both pentavalent and hexavalent groups demonstrated increased antibody levels against DT, TT, and *B. pertussis* antigens following the second booster with Tdap-IPV. All children achieved a seroprotective concentration for anti-DT and anti-TT IgG at 1 month post booster. The hexavalent group possessed significantly higher anti-pertactin IgG (adjusted $p = .023$), whereas the pentavalent group possessed significantly higher anti-pertussis toxin IgG (adjusted $p < .001$) after the second booster. Despite declining levels post-second booster, a greater number of children sustained protective levels of anti-DT and anti-TT IgG compared to those after the first booster.

Pneumococcal vaccine

Vaccine. 2023 Aug 23;41(37):5392-5399.
doi: 10.1016/j.vaccine.2023.07.026. Epub 2023 Jul 20.

Pneumococcal carriage, serotype distribution, and antimicrobial susceptibility in Papua New Guinean children vaccinated with PCV10 or PCV13 in a head-to-head trial

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Abstract

Background: Children in Papua New Guinea (PNG) are at high risk of pneumococcal infections. We investigated pneumococcal carriage rates, serotype distribution, and

antimicrobial susceptibility in PNG children after vaccination with 10-valent or 13-valent pneumococcal conjugate vaccines (PCV10; PCV13).
Methods: Infants (N = 262) were randomized to receive 3 doses of PCV10 or PCV13 at 1-2-3 months of age, followed by pneumococcal polysaccharide vaccination (PPV) or no PPV at 9 months of age. Nasopharyngeal swabs (NPS) collected at ages 1, 4, 9, 10, 23 and 24 months were cultured using standard bacteriological procedures. Morphologically distinct Streptococcus pneumoniae colonies were serotyped by the Quellung reaction. Antimicrobial susceptibility was determined by Kirby-Bauer disc diffusion and minimum inhibitory concentration (MIC).
Results: S. pneumoniae was isolated from 883/1063 NPS collected at 1-23 months of age, including 820 serotypeable (64 different serotypes) and 144 non-serotypeable isolates. At age 23 months, 93.6% (95%CI 86.6-97.6%) of PCV10 recipients and 88.6% (95%CI 80.1-94.4%) of PCV13 recipients were pneumococcal carriers, with higher carriage of PCV10 serotypes by PCV10 recipients (19.8%, 95%CI 12.2-29.5) than PCV13 recipients (9.3%, 95%CI 4.1-17.3) (p = 0.049). There were no other statistically significant differences between PCV10 and PCV13 recipients and children receiving PPV or no PPV. Nearly half (45.6%) of carried pneumococci were non-susceptible to penicillin based on the meningitis breakpoint (MIC ≥ 0.12 µg/mL), but resistance was rare (1.1%) using the non-meningitis cut-off (MIC ≥ 8 µg/mL). Non-susceptibility to trimethoprim-sulfamethoxazole (SXT) was common: 23.2% of isolates showed intermediate resistance (MIC 1/19-2/38 µg/mL) and 16.9% full resistance (MIC ≥ 4/76 µg/mL). PCV serotypes 14 and 19A were commonly non-susceptible to both penicillin (14, 97%; 19A, 70%) and SXT (14, 97%; 19A, 87%).
Conclusion: Even after PCV10 or PCV13 vaccination, children living in a high-risk setting such as PNG continue to experience high levels of pneumococcal colonization, including carriage of highly antimicrobial-resistant PCV serotypes.

Lancet Infect Dis. 2023 Aug;23(8):933-944.
doi: 10.1016/S1473-3099(23)00061-0. Epub 2023 Apr 14.

Efficacy against pneumococcal carriage and the immunogenicity of reduced-dose (0 + 1 and 1 + 1) PCV10 and PCV13 schedules in Ho Chi Minh City, Viet Nam: a parallel, single-blind, randomised controlled trial

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Abstract
Background: Interest in reduced-dose pneumococcal conjugate vaccine (PCV) schedules is growing, but data on their ability to provide direct and indirect protection are scarce. We evaluated 1 + 1 (at 2 months and 12 months) and 0 + 1 (at 12 months) schedules of PCV10 or PCV13 in a predominately unvaccinated population.
Methods: In this parallel, single-blind, randomised controlled trial, healthy infants aged 2 months were recruited from birth records in three districts in Ho Chi Minh City, Vietnam, and assigned (4:4:4:4:9) to one of five groups: PCV10 at 12 months of age (0 + 1 PCV10), PCV13 at 12 months of age (0 + 1 PCV13), PCV10 at 2 months and 12 months of age (1 + 1 PCV10), PCV13 at 2 months and 12 months of age (1 + 1 PCV13), and unvaccinated control. Outcome assessors were masked to group allocation, and the infants' caregivers and those administering vaccines were not. Nasopharyngeal swabs collected at 6 months, 12 months,

18 months, and 24 months were analysed for pneumococcal carriage. Blood samples collected from a subset of participants (200 per group) at various timepoints were analysed by ELISA and opsonophagocytic assay. The primary outcome was the efficacy of each schedule against vaccine-type carriage at 24 months, analysed by intention to treat for all those with a nasopharyngeal swab available. This trial is registered at ClinicalTrials.gov, NCT03098628.
Findings: 2501 infants were enrolled between March 8, 2017, and July 24, 2018 and randomly assigned to study groups (400 to 0 + 1 PCV10, 400 to 0 + 1 PCV13, 402 to 1 + 1 PCV10, 401 to 1 + 1 PCV13, and 898 to control). Analysis of the primary endpoint included 341 participants for 0 + 1 PCV10, 356 0 + 1 PCV13, 358 1 + 1 PCV10, 350 1 + 1 PCV13, and 758 control. At 24 months, a 1 + 1 PCV10 schedule reduced PCV10-type carriage by 58% (95% CI 25 to 77), a 1 + 1 PCV13 schedule reduced PCV13-type carriage by 65% (42 to 79), a 0 + 1 PCV10 schedule reduced PCV10-type carriage by 53% (17 to 73), and a 0 + 1 PCV13 schedule non-significantly reduced PCV13-type carriage by 25% (-7 to 48) compared with the unvaccinated control group. Reactogenicity and serious adverse events were similar across groups.
Interpretation: A 1 + 1 PCV schedule greatly reduces vaccine-type carriage and is likely to generate substantial herd protection and provide some degree of individual protection during the first year of life. Such a schedule is suitable for mature PCV programmes or for introduction in conjunction with a comprehensive catch-up campaign, and potentially could be most effective given as a mixed regimen (PCV10 then PCV13). A 0 + 1 PCV schedule has some effect on carriage along with a reasonable immune response and could be considered for use in humanitarian crises or remote settings.

Vaccine. 2024 May 10;42(13):3157-3165.
doi: 10.1016/j.vaccine.2024.03.056. Epub 2024 Apr 17.

Immunogenicity and safety of a 14-valent pneumococcal polysaccharide conjugate vaccine (PNEUBEVAX 14™) administered to 6-8 weeks old healthy Indian Infants: A single blind, randomized, active-controlled, Phase-III study

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Abstract
Background: Introduction of pneumococcal conjugate vaccines (PCVs) reduced the number of cases of pneumococcal disease (PD). However, there is an increase in clinical and economic burden of PD from serotypes that are not part of the existing pneumococcal vaccines, particularly impacting pediatric and elder population. In addition, the regions where the PCV is not available, the disease burden remains high. In this study, immunogenicity and safety of the BE's 14-valent PCV (PNEUBEVAX 14™; BE-PCV-14) containing two additional epidemiologically important serotypes (22F and 33F) was evaluated in infants in comparison to licensed vaccine, Prevenar-13 (PCV-13).
Methods: This is a pivotal phase-3 single blind randomized active-controlled study conducted at 12 sites across India in 6-8 weeks old healthy infants at 6-10-14 weeks dosing schedule to assess immunogenic non-inferiority and safety of a candidate BE-PCV-14. In total, 1290 infants were equally randomized to receive either BE-PCV-14 or PCV-13. Solicited local reactions and systemic events, adverse events (AEs), serious AEs (SAEs), and medically attended AEs (MAAEs) were recorded. Immunogenicity was assessed by measuring anti-

PnCPS (anti-pneumococcal capsular polysaccharide) IgG concentration and functional antibody titers through opsonophagocytic activity (OPA), one month after completing three dose schedule. Cross protection to serotype 6A offered by serotype 6B was also assessed in this study.
Findings: The safety profile of BE-PCV-14 was comparable to PCV-13 vaccine. Majority of reported AEs were mild in nature. No severe or serious AEs were reported in both the treatment groups. For the twelve common serotypes and for the additional serotypes (22F and 33F) in BE-PCV-14, NI criteria was demonstrated as defined by WHO TRS-977. Primary immunogenicity endpoint was met in terms of IgG immune responses for all 14 serotypesof BE-PCV-14. Moreover, a significant proportion of subjects (69%) seroconverted against serotype 6A, even though this antigen was not present in BE-PCV-14. This indicates that serotype 6B of BE-PCV-14 cross protects serotype 6A. BE-PCV-14 also elicited comparable serotype specific functional OPA immune responses to all the serotypes common to PCV-13.
Interpretations: BE-PCV-14 was found to be safe and induced robust and functional serotype specific immune responses to all 14 serotypes. It also elicited cross protective immune response against serotype 6B.These findings suggest that BE-PCV-14 can be safely administered to infants and achieve protection against pneumococcal disease caused by serotypes covered in the vaccine.

EClinicalMedicine. 2023 Jul 1;61:102073.
doi: 10.1016/j.eclinm.2023.102073. eCollection 2023 Jul.

Immunogenicity and seroefficacy of 10-valent and 13-valent pneumococcal conjugate vaccines: a systematic review and network meta-analysis of individual participant data

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Abstract

Background: Vaccination of infants with pneumococcal conjugate vaccines (PCV) is recommended by the World Health Organization. Evidence is mixed regarding the differences in immunogenicity and efficacy of the different pneumococcal vaccines.
Methods: In this systematic-review and network meta-analysis, we searched the Cochrane Library, Embase, Global Health, Medline, clinicaltrials.gov and trialsearch.who.int up to February 17, 2023 with no language restrictions. Studies were eligible if they presented data comparing the immunogenicity of either PCV7, PCV10 or PCV13 in head-to-head randomised trials of young children under 2 years of age, and provided immunogenicity data for at least one time point after the primary vaccination series or the booster dose. Publication bias was assessed via Cochrane's Risk Of Bias due to Missing Evidence tool and comparison-adjusted funnel plots with Egger's test. Individual participant level data were requested from publication authors and/or relevant vaccine manufacturers. Outcomes included the geometric mean ratio (GMR) of serotype-specific IgG and the relative risk (RR) of seroinfection. Seroinfection was defined for each individual as a rise in antibody between the post-primary vaccination series time point and the booster dose, evidence of presumed subclinical infection. Seroefficacy was defined as the RR of seroinfection. We also estimated

the relationship between the GMR of IgG one month after priming and the RR of seroinfection by the time of the booster dose. The protocol is registered with PROSPERO, ID CRD42019124580.
Findings: 47 studies were eligible from 38 countries across six continents. 28 and 12 studies with data available were included in immunogenicity and seroefficacy analyses, respectively. GMRs comparing PCV13 vs PCV10 favoured PCV13 for serotypes 4, 9V, and 23F at 1 month after primary vaccination series, with 1.14- to 1.54- fold significantly higher IgG responses with PCV13. Risk of seroinfection prior to the time of booster dose was lower for PCV13 for serotype 4, 6B, 9V, 18C and 23F than for PCV10. Significant heterogeneity and inconsistency were present for most serotypes and for both outcomes. Two-fold higher antibody after primary vaccination was associated with a 54% decrease in risk of seroinfection (RR 0.46, 95% CI 0.23-0.96).
Interpretation: Serotype-specific differences were found in immunogenicity and seroefficacy between PCV13 and PCV10. Higher antibody response after vaccination was associated with a lower risk of subsequent infection. These findings could be used to compare PCVs and optimise vaccination strategies.

Vaccine. 2024 Mar 28:S0264-410X(24)00371-2.
doi: 10.1016/j.vaccine.2024.03.065. Online ahead of print.

Effects of PCV10 and PCV13 on pneumococcal serotype 6C disease, carriage, and antimicrobial resistance

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Abstract
Background: The cross-protection of pneumococcal conjugate vaccines (PCV) against serotype 6C is not clearly documented, although 6C represents a substantial burden of pneumococcal disease in recent years. A systematic review by the World Health Organization that covered studies through 2016 concluded that available data were insufficient to determine if either PCV10 (which contains serotype 6B but not 6A) or PCV13 (containing serotype 6A and 6B) conferred protection against 6C.
Methods: We performed a systematic review of randomized controlled trials and observational studies published between January 2010 - August 2022 (Medline/Embase), covering the direct, indirect, and overall effect of PCV10 and PCV13 against 6C invasive pneumococcal disease (IPD), non-IPD, nasopharyngeal carriage (NPC), and antimicrobial resistance (AMR).
Results: Of 2548 publications identified, 112 were included. Direct vaccine effectiveness against 6C IPD in children ranged between 70 and 85 % for ≥ 1 dose PCV13 (n = 3 studies), was 94 % in fully PCV13 vaccinated children (n = 2), and -14 % for ≥ 1 dose of PCV10 (n = 1). Compared to PCV7, PCV13 efficacy against 6C NPC in children was 66 % (n = 1). Serotype 6C IPD rates or NPC prevalence declined post-PCV13 in most studies in children (n = 5/6) and almost half of studies in adults (n = 5/11), while it increased post-PCV10 for IPD and non-IPD in all studies (n = 6/6). Changes in AMR prevalence were inconsistent.
Conclusions: In contrast to PCV10, PCV13 vaccination consistently protected against 6C IPD and NPC in children, and provided some level of indirect protection to adults, supporting that serotype 6A but not 6B provides cross-protection to 6C. Vaccine policy makers and

regulators should consider the effects of serotype 6A-containing PCVs against serotype 6C disease in their decisions.

Lancet Microbe. 2023 Sep;4(9):e683-e691.
doi: 10.1016/S2666-5247(23)00178-7.

Effect of 13-valent pneumococcal conjugate vaccine on experimental carriage of Streptococcus pneumoniae serotype 6B in Blantyre, Malawi: a randomised controlled trial and controlled human infection study

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Abstract

Background: The effect of childhood pneumococcal conjugate vaccine implementation in Malawi is threatened by absence of herd effect. There is persistent vaccine-type pneumococcal carriage in both vaccinated children and the wider community. We aimed to use a human infection study to measure 13-valent pneumococcal conjugate vaccine (PCV13) efficacy against pneumococcal carriage.

Methods: We did a double-blind, parallel-arm, randomised controlled trial investigating the efficacy of PCV13 or placebo against experimental pneumococcal carriage of Streptococcus pneumoniae serotype 6B (strain BHN418) among healthy adults (aged 18-40 years) from Blantyre, Malawi. We randomly assigned participants (1:1) to receive PCV13 or placebo. PCV13 and placebo doses were prepared by an unmasked pharmacist to maintain research team and participant masking with identification only by a randomisation identification number and barcode. 4 weeks after receiving either PCV13 or placebo, participants were challenged with 20 000 colony forming units (CFUs) per naris, 80 000 CFUs per naris, or 160 000 CFUs per naris by intranasal inoculation. The primary endpoint was experimental pneumococcal carriage, established by culture of nasal wash at 2, 7, and 14 days. Vaccine efficacy was estimated per protocol by means of a log-binomial model adjusting for inoculation dose. The trial is registered with the Pan African Clinical Trials Registry, PACTR202008503507113, and is now closed.

Findings: Recruitment commenced on April 27, 2021 and the final visit was completed on Sept 12, 2022. 204 participants completed the study protocol (98 PCV13, 106 placebo). There were lower carriage rates in the vaccine group at all three inoculation doses (0 of 21 vs two [11%] of 19 at 20 000 CFUs per naris; six [18%] of 33 vs 12 [29%] of 41 at 80 000 CFUs per naris, and four [9%] of 44 vs 16 [35%] of 46 at 160 000 CFUs per naris). The overall carriage rate was lower in the vaccine group compared with the placebo group (ten [10%] of 98 vs 30 [28%] of 106; Fisher's p value=0·0013) and the vaccine efficacy against carriage was estimated at 62·4% (95% CI 27·7-80·4). There were no severe adverse events related to vaccination or inoculation of pneumococci.

Interpretation: This is, to our knowledge, the first human challenge study to test the efficacy of a pneumococcal vaccine against pneumococcal carriage in Africa, which can now be used to establish vaccine-induced correlates of protection and compare alternative strategies to prevent pneumococcal carriage. This powerful tool could lead to new means to enhance reduction in pneumococcal carriage after vaccination.

Polio vaccine

Lancet Infect Dis. 2023 Sep;23(9):1062-1071.
doi: 10.1016/S1473-3099(23)00139-1. Epub 2023 May 10.

Immunogenicity of novel oral poliovirus vaccine type 2 administered concomitantly with bivalent oral poliovirus vaccine: an open-label, non-inferiority, randomised, controlled trial

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Abstract

Background: Novel oral poliovirus vaccine type 2 (nOPV2) was developed by modifying the Sabin strain to increase genetic stability and reduce risk of seeding new circulating vaccine-derived poliovirus type 2 outbreaks. Bivalent oral poliovirus vaccine (bOPV; containing Sabin types 1 and 3) is the vaccine of choice for type 1 and type 3 outbreak responses. We aimed to assess immunological interference between nOPV2 and bOPV when administered concomitantly.

Methods: We conducted an open-label, non-inferiority, randomised, controlled trial at two clinical trial sites in Dhaka, Bangladesh. Healthy infants aged 6 weeks were randomly assigned (1:1:1) using block randomisation, stratified by site, to receive nOPV2 only, nOPV2 plus bOPV, or bOPV only, at the ages of 6 weeks, 10 weeks, and 14 weeks. Eligibility criteria included singleton and full term (≥37 weeks' gestation) birth and parents intending to remain in the study area for the duration of study follow-up activities. Poliovirus neutralising antibody titres were measured at the ages of 6 weeks, 10 weeks, 14 weeks, and 18 weeks. The primary outcome was cumulative immune response for all three poliovirus types at the age of 14 weeks (after two doses) and was assessed in the modified intention-to-treat population, which was restricted to participants with adequate blood specimens from all study visits. Safety was assessed in all participants who received at least one dose of study product. A non-inferiority margin of 10% was used to compare single and concomitant administration. This trial is registered with ClinicalTrials.gov, NCT04579510.

Findings: Between Feb 8 and Sept 26, 2021, 736 participants (244 in the nOPV2 only group, 246 in the nOPV2 plus bOPV group, and 246 in the bOPV only group) were enrolled and included in the modified intention-to-treat analysis. After two doses, 209 (86%; 95% CI 81-90) participants in the nOPV2 only group and 159 (65%; 58-70) participants in the nOPV2 plus bOPV group had a type 2 poliovirus immune response; 227 (92%; 88-95) participants in the

nOPV2 plus bOPV group and 229 (93%; 89-96) participants in the bOPV only group had a type 1 response; and 216 (88%; 83-91) participants in the nOPV2 plus bOPV group and 212 (86%; 81-90) participants in the bOPV only group had a type 3 response. Co-administration was non-inferior to single administration for types 1 and 3, but not for type 2. There were 15 serious adverse events (including three deaths, one in each group, all attributable to sudden infant death syndrome); none were attributed to vaccination.
Interpretation: Co-administration of nOPV2 and bOPV interfered with immunogenicity for poliovirus type 2, but not for types 1 and 3. The blunted nOPV2 immunogenicity we observed would be a major drawback of using co-administration as a vaccination strategy.

Lancet. 2024 Feb 22:S0140-6736(23)02844-1.
doi: 10.1016/S0140-6736(23)02844-1. Online ahead of print.
Safety of the novel oral poliovirus vaccine type 2 (nOPV2) in infants and young children aged 1 to <5 years and lot-to-lot consistency of the immune response to nOPV2 in infants in The Gambia: a phase 3, double-blind, randomised controlled trial
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Abstract
Background: Novel oral poliovirus vaccine type 2 (nOPV2) has been engineered to improve the genetic stability of Sabin oral poliovirus vaccine (OPV) and reduce the emergence of circulating vaccine-derived polioviruses. This trial aimed to provide key safety and immunogenicity data required for nOPV2 licensure and WHO prequalification.
Methods: This phase 3 trial recruited infants aged 18 to <52 weeks and young children aged 1 to <5 years in The Gambia. Infants randomly assigned to receive one or two doses of one of three lots of nOPV2 or one lot of bivalent OPV (bOPV). Young children were randomised to receive two doses of nOPV2 lot 1 or bOPV. The primary immunogenicity objective was to assess lot-to-lot equivalence of the three nOPV2 lots based on one-dose type 2 poliovirus neutralising antibody seroconversion rates in infants. Equivalence was declared if the 95% CI for the three pairwise rate differences was within the -10% to 10% equivalence margin. Tolerability and safety were assessed based on the rates of solicited adverse events to 7 days, unsolicited adverse events to 28 days, and serious adverse events to 3 months post-dose. Stool poliovirus excretion was examined. The trial was registered as PACTR202010705577776 and is completed.
Findings: Between February and October, 2021, 2345 infants and 600 young children were vaccinated. 2272 (96·9%) were eligible for inclusion in the post-dose one per-protocol population. Seroconversion rates ranged from 48·9% to 49·2% across the three lots. The minimum lower bound of the 95% CIs for the pairwise differences in seroconversion rates between lots was -5·8%. The maximum upper bound was 5·4%. Equivalence was therefore shown. Of those seronegative at baseline, 143 (85·6%) of 167 (95% CI 79·4-90·6) infants and 54 (83·1%) of 65 (71·7-91·2) young children seroconverted over the two-dose nOPV2 schedule. The post-two-dose seroprotection rates, including participants who were both seronegative and seropositive at baseline, were 604 (92·9%) of 650 (95% CI 90·7-94·8) in infants and 276 (95·5%) of 289 (92·4-97·6) in young children. No safety concerns were

identified. 7 days post-dose one, 78 (41·7%) of 187 (95% CI 34·6-49·1) infants were excreting the type 2 poliovirus.
Interpretation: nOPV2 was immunogenic and safe in infants and young children in The Gambia. The data support the licensure and WHO prequalification of nOPV2.

Lancet Infect Dis. 2024 Mar;24(3):275-284.
doi: 10.1016/S1473-3099(23)00519-4. Epub 2023 Dec 15.

Safety and immunogenicity of shorter interval schedules of the novel oral poliovirus vaccine type 2 in infants: a phase 3, randomised, controlled, non-inferiority study in the Dominican Republic

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Abstract

Background: The novel oral poliovirus vaccine type 2 (nOPV2) is now authorised by a WHO emergency use listing and widely distributed to interrupt outbreaks of circulating vaccine-derived poliovirus type 2. As protection of vulnerable populations, particularly young infants, could be facilitated by shorter intervals between the two recommended doses, we aimed to assess safety and non-inferiority of immunogenicity of nOPV2 in 1-week, 2-week, and 4-week schedules.

Methods: In this phase 3, open-label, randomised trial, healthy, full-term, infants aged 6-8 weeks from a hospital or a clinic in the Dominican Republic were randomly allocated (1:1:1 ratio) using a pre-prepared, computer-generated randomisation schedule to three groups to receive two doses of nOPV2 immunisations with a 1-week interval (group A), 2-week interval (group B), or 4-week interval (group C). The nOPV2 vaccine was given at a 0·1 mL dose and contained at least 10^5 50% cell culture infective dose. Neutralising antibodies against poliovirus types 1, 2, and 3 were measured before each immunisation and 4 weeks after the second dose. The primary outcome was the type 2 seroconversion rate 28 days after the second dose, and the non-inferiority margin was defined as a lower bound 95% CI of greater than -10%. Safety and reactogenicity were assessed through diary cards completed by the parent or guardian. The trial is registered with ClinicalTrials.gov, NCT05033561.

Findings: We enrolled 905 infants between Dec 16, 2021, and March 28, 2022. 872 infants were included in the per-protocol analyses: 289 in group A, 293 in group B, and 290 in group C. Type 2 seroconversion rates were 87·5% (95% CI 83·2 to 91·1) in group A (253 of 289 participants), 91·8% (88·1 to 94·7) in group B (269 of 293 participants), and 95·5% (92·5 to 97·6) in group C (277 of 290 participants). Non-inferiority was shown for group B compared with group C (difference in rates -3·7; 95% CI -7·9 to 0·3), but not for group A compared with group C (-8·0; -12·7 to -3·6). 4 weeks after the second nOPV2 dose, type 2 neutralising antibodies increased in all three groups such that over 95% of each group was seroprotected against polio type 2, although final geometric mean titres tended to be highest with longer intervals between doses. Immunisation with nOPV2 was well tolerated with no causal association to vaccination of any severe or serious adverse event; one death from septic shock during the study was unrelated to the vaccine.

Interpretation: Two nOPV2 doses administered 1 week or 2 weeks apart from age 6 weeks to 8 weeks were safe and immunogenic. Immune responses after a 2-week interval were non-

inferior to those after the standard 4-week interval, but marked responses after a 1-week interval suggest that schedules with an over 1-week interval can be used to provide flexibility to campaigns to improve coverage and hasten protection during circulating vaccine-derived poliovirus type 2 outbreaks.

Vaccine. 2024 Mar 19;42(8):1973-1979.
doi: 10.1016/j.vaccine.2024.02.042. Epub 2024 Feb 21.

Immunogenicity and lot-to-lot consistency of booster shot with Sabin inactivated poliomyelitis vaccine in Chinese children aged 18-24 Months: A phase Ⅳ clinical trial

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Abstract

Background: There has been no data on the immunogenicity and safety of the 4th booster dose of the sIPV immunization in 18-24 months old children in post-marketing studies of large cohort providing with robust results.

Method: In a phase Ⅳ randomized, double-blinded clinical trial, 1200 participants aged 2 months were immunized with three consecutive doses of sIPV at 2, 3, and 4 months old to complete primary immunization. Out of the 1200 participants, 1129 received the 4th dose of sIPV as booster immunization. Immunogenicity was evaluated in 1100 participants.

Results: Seropositive rates of the anti-poliovirus type 1, 2, and 3 neutralizing antibodies were 99.9 %, 98.0 %, 98.2 %, respectively, with GMTs of 557.0, 146.1, 362.0 one year after primary vaccination. After booster vaccination between 18 and 24 months old, the seropositive rates for 3 types all reached 100.0 %, with GMTs of 8343.6, 5039.6, 5492.0, respectively. Particularly for the anti-poliovirus type 2 antibody, the GMT was 230.4 after primary immunization, maintained to 146.1 one year after primary immunization, and increased to as high as 5039.6 after booster vaccination. The GMT ratios between each batch groups after booster immunization were between 0.67 and 1.50, meeting the immunological equivalence criteria. The incidence rate of adverse reaction was 23.0 %, which was comparable to those in the phase Ⅲ trial but had a lower incidence. Furthermore, no SUSAR was reported in this study.

Interpretation: In conclusion, as the anti-poliovirus antibodies gradually waned one year post sIPV primary vaccination, especially the type 2 antibody waned to a very low level, suggesting the importance of the booster immunization for children at the age of 18-24 months old. The booster shot can greatly enhance the antibody level and protect children from the potential risk of infection with WPV and VDPV by supplementing the anti-poliovirus type 2 immunity gap in the current real world

Vaccine. 2023 Sep 22;41(41):6083-6092.
doi: 10.1016/j.vaccine.2023.08.055. Epub 2023 Aug 29.

Poliovirus type 1 systemic humoral and intestinal mucosal immunity induced by monovalent oral poliovirus vaccine, fractional inactivated poliovirus vaccine, and bivalent oral poliovirus vaccine: A randomized controlled trial

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Abstract

Background: To inform response strategies, we examined type 1 humoral and intestinal immunity induced by 1) one fractional inactivated poliovirus vaccine (fIPV) dose given with monovalent oral poliovirus vaccine (mOPV1), and 2) mOPV1 versus bivalent OPV (bOPV).

Methods: We conducted a randomized, controlled, open-label trial in Dhaka, Bangladesh. Healthy infants aged 5 weeks were block randomized to one of four arms: mOPV1 at age 6-10-14 weeks/fIPV at 6 weeks (A); mOPV1 at 6-10-14 weeks/fIPV at 10 weeks (B); mOPV1 at 6-10-14 weeks (C); and bOPV at 6-10-14 weeks (D). Immune response at 10 weeks and cumulative response at 14 weeks was assessed among the modified intention-to-treat population, defined as seroconversion from seronegative (<1:8 titers) to seropositive (≥1:8) or a four-fold titer rise among seropositive participants sustained to age 18 weeks. We examined virus shedding after two doses of mOPV1 with and without fIPV, and after the first mOPV1 or bOPV dose. The trial is registered at ClinicalTrials.gov (NCT03722004).

Findings: During 18 December 2018 - 23 November 2019, 1,192 infants were enrolled (arms A:301; B:295; C:298; D:298). Immune responses at 14 weeks did not differ after two mOPV1 doses alone (94% [95% CI: 91-97%]) versus two mOPV1 doses with fIPV at 6 weeks (96% [93-98%]) or 10 weeks (96% [93-98%]). Participants who received mOPV1 and fIPV at 10 weeks had significantly lower shedding ($p < 0{\cdot}001$) one- and two-weeks later compared with mOPV1 alone. Response to one mOPV1 dose was significantly higher than one bOPV dose (79% versus 67%; $p < 0{\cdot}001$) and shedding two-weeks later was significantly higher after mOPV1 (76% versus 56%; $p < 0{\cdot}001$) indicating improved vaccine replication. Ninety-nine adverse events were reported, 29 serious including two deaths; none were attributed to study vaccines.

Interpretation: Given with the second mOPV1 dose, fIPV improved intestinal immunity but not humoral immunity. One mOPV1 dose induced higher humoral and intestinal immunity than bOPV.

Vaccines (Basel). 2024 Apr 17;12(4):424.
doi: 10.3390/vaccines12040424.

The Immunogenicity of Monovalent Oral Poliovirus Vaccine Type 1 (mOPV1) and Inactivated Poliovirus Vaccine (IPV) in the EPI Schedule of India

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Abstract

Background: In 2016, the Global Polio Eradication Initiative (GPEI) recommended the cessation of using type 2 oral poliovirus vaccine (OPV) and OPV, with countries having to switch from the trivalent to bivalent OPV (bOPV) with the addition of inactivated poliovirus vaccine (IPV) in their routine immunization schedule. The current GPEI strategy 2022-2026 includes a bOPV cessation plan and a switch to IPV alone or a combination of vaccine schedules in the future. The focus of our study was to evaluate the immunogenicity of monovalent OPV type 1 (mOPV1) with IPV and IPV-only schedules.

Methods: This was a three-arm, multi-center randomized-controlled trial conducted in 2016-2017 in India. Participants, at birth, were randomly assigned to the bOPV-IPV (Arm A) or mOPV1-IPV (Arm B) or IPV (Arm C) schedules. Serum specimens collected at birth and at 14,

18, and 22 weeks old were analyzed with a standard microneutralization assay for all the three poliovirus serotypes.
Results: The results of 598 participants were analyzed. The type 1 cumulative seroconversion rates four weeks after the completion of the schedule at 18 weeks were 99.5% (97.0-99.9), 100.0% (97.9-100.0), and 96.0% (92.0-98.1) in Arms A (4bOPV + IPV), B (4mOPV1 + IPV), and C (3IPV), respectively. Type 2 and type 3 seroconversions at 18 weeks were 80.0% (73.7-85.1), 76.9% (70.3-82.4); 93.2% (88.5-96.1), 100.0% (98.0-100.0); and 81.9% (75.6-86.8), 99.4% (96.9-99.9), respectively, in the three arms.
Conclusions: This study shows the high efficacy of different polio vaccines for serotype 1 in all three schedules. The type 1 seroconversion rate of mOPV1 is non-inferior to bOPV. All the vaccines provide high type-specific immunogenicity. The program can adopt the use of different vaccines or schedules depending on the epidemiology from time to time.

Rabies vaccine

Hum Vaccin Immunother. 2023 Dec 31;19(1):2211896.
doi: 10.1080/21645515.2023.2211896. Epub 2023 May 30.
Safety and immunogenicity of rabies vaccine (PVRV-WIBP) in healthy Chinese aged 10-50 years old: Randomized, blinded, parallel controlled phase III clinical study
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Abstract
This phase III clinical trial aimed to assess the safety and demonstrate the immunogenicity of a candidate freeze-dried purified Vero cell-based rabies vaccine (PVRV-WIBP) developed for human use. A cohort of 40 participants in stage 1 and 1956 subjects in stage 2 with an age range of 10-50 years were recruited for the phase III clinical trial. For safety analysis in stage 1, 20 participants received either 4-dose or 5-dose regimen of PVRV-WIBP. In stage 2, 1956 subjects were randomly divided into the 5-dose PVRV-WIBP, 5-dose PVRV-LNCD, and 4-dose PVRV-WIBP groups. The serum neutralizing antibody titer against rabies was determined on day 7 or 14 and day 35 or 42. Adverse reactions were recorded for more than 6 months. Most adverse reactions, which were mild and moderate in severity, occurred and resolved within 1 week after each injection in the PVRV-WIBP (4 and 5 doses) and PVRV-LNCD (5 doses) groups. All three groups achieved complete seroconversion 14 days after the initial dose and 14 days after completing the full vaccination schedule, the susceptible subjects in the PVRV-WIBP group (4-dose or 5-dose regimen) displayed higher neutralizing antibody titers against the rabies virus compared to those in the PVRV-LNCD group (5-dose regimen). PVRV-WIBP induced non-inferior immune responses versus PVRV-LNCD as assessed by seroconversion rate. PVRV-WIBP was well tolerated and non-inferior to PVRV-LNCD in healthy individuals aged 10-50 years. The results indicated that PVRV-WIBP (both 4- and 5-dose schedules) could be an alternative to rabies post-exposure prophylaxis.

Rotavirus vaccine

Hum Vaccin Immunother. 2023 Dec 15;19(3):2278346.
doi: 10.1080/21645515.2023.2278346. Epub 2023 Nov 15.

Phase III randomized clinical studies to evaluate the immunogenicity, lot-to-lot consistency, and safety of ROTAVAC® liquid formulations (ROTAVAC 5C & 5D) and non-inferiority comparisons with licensed ROTAVAC® (frozen formulation) in healthy infants

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Abstract

The WHO pre-qualified rotavirus vaccine, ROTAVAC®, is derived naturally from the neonatal 116E rotavirus strain, and stored at -20°C. As refrigerator storage is preferable, immunogenicity and safety of liquid formulations kept at 2-8°C, having excipients to stabilize the rotavirus, with or without buffers, were compared with ROTAVAC® in different clinical studies. Study-1, the pivotal trial for this entire product development work, was a randomized, single-blind trial with two operationally seamless phases: (i) an exploratory phase involving 675 infants in which two formulations, ROTAVAC 5C (LnHRV-1.5 mL and LnHRV-2.0 mL) containing buffer and excipients to stabilize the virus against gastric acidity and temperature, were compared with ROTAVAC®. As the immune response of ROTAVAC 5C (LnHRV-2.0 mL) was non-inferior to ROTAVAC®, it was selected for (ii) confirmatory phase, involving 1,302 infants randomized 1:1:1:1 to receive three lots of LnHRV-2.0 mL, or ROTAVAC®. Primary objectives were the evaluation of non-inferiority and lot-to-lot consistency. The secondary objectives were to assess the safety and interference with the concomitant pentavalent vaccine. As it was separately established that buffers are not required for ROTAVAC®, in Study-2, the safety and immunogenicity of ROTAVAC 5D® (with excipients) were compared with ROTAVAC® and lot-to-lot consistency was assessed in another study. All lots elicited consistent immune responses, did not interfere with UIP vaccines, and had reactogenicity similar to ROTAVAC®. ROTAVAC 5C and ROTAVAC 5D® were immunogenic and well tolerated as ROTAVAC®. ROTAVAC 5D® had comparable immunogenicity and safety profiles with ROTAVAC® and can be stored at 2-8°C, leading to WHO pre-qualification.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2324538.
doi: 10.1080/21645515.2024.2324538. Epub 2024 Mar 20.

A phase 3 randomized, open-label study evaluating the immunogenicity and safety of concomitant and staggered administration of a live, pentavalent rotavirus vaccine and an inactivated poliomyelitis vaccine in healthy infants in China

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Abstract
This open-label, randomized, phase 3 study in China (V260-074; NCT04481191) evaluated the immunogenicity and safety of concomitant and staggered administration of three doses of an oral, live, pentavalent rotavirus vaccine (RV5) and three doses of an intramuscular, inactivated poliomyelitis vaccine (IPV) in 400 healthy infants. The primary objective was the non-inferiority of neutralizing antibody (nAb) responses in the concomitant- versus the staggered-use groups. Antibody responses were measured at baseline and 1-month post-dose 3 (PD3). Parents/legal guardians recorded adverse events for 30 or 15 d after study vaccinations in the concomitant-use or staggered-use groups, respectively. At PD3, >98% of participants seroconverted to all three poliovirus types, and the primary objective was met as lower bounds of the two-sided 95% CI for between-group difference in nAb seroconversion percentages ranged from - 4.3% to - 1.6%, for all poliovirus types, $p < .001$. At PD3, geometric mean titers (GMTs) of nAb responses to poliovirus types 1, 2, and 3 in the concomitant-use group and the staggered-use group were comparable; 100% of participants had nAb titers ≥1:8 and ≥1:64 for all poliovirus types. Anti-rotavirus serotype-specific IgA GMTs and participants with ≥3-fold rise in postvaccination titers from baseline were comparable between groups. Administration of RV5 and IPV was well tolerated with comparable safety profiles in both groups. The immunogenicity of IPV in the concomitant-use group was non-inferior to the staggered-use group and RV5 was immunogenic in both groups. No safety concerns were identified. These data support the concomitant use of RV5 and IPV in healthy Chinese infants.

Am J Trop Med Hyg. 2024 Apr 16;110(6):1201-1209.
doi: 10.4269/ajtmh.23-0348. Print 2024 Jun 5.

Effect of Non-Rotavirus Enteric Infections on Vaccine Efficacy in a ROTASIIL Clinical Trial

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Abstract
This study examined the relative proportion of enteric pathogens associated with severe gastroenteritis (GE) among children younger than 2 years in a phase III efficacy trial of the ROTASIIL® vaccine in India, evaluated the impact of co-infections on vaccine efficacy (VE), and characterized the association between specific pathogens and the clinical profile of severe GE. Stored stool samples collected from cases of severe GE in the phase III trial were tested by quantitative polymerase chain reaction using TaqMan™ Array Cards. Etiology was attributed by calculating the adjusted attributable fraction (AF) for each pathogen. A test-negative design was used to estimate VE. The pathogens with the highest AFs for severe diarrhea were rotavirus (23.5%), adenovirus 40/41 (17.0%), Shigella spp./enteroinvasive Escherichia coli, norovirus GII, enterotoxigenic E. coli, and Cryptosporidium spp. A considerable proportion of the disease in these children could not be explained by the pathogens tested. Severe GE cases associated with rotavirus and Shigella spp. were more likely to have a longer duration of vomiting and diarrhea, respectively. Cases attributed to Cryptosporidium spp. were more severe and required hospitalization. In the intention-to-treat population, VE was estimated to be 43.9% before and 46.5% after adjustment for co-infections; in the per-protocol population, VE was 46.7% before and 49.1% after adjustments. Rotavirus continued to be the leading cause of severe GE in this age group. The adjusted VE

estimates obtained did not support co-infections as a major cause of lower vaccine performance in low- and middle-income countries.

RSV vaccine

J Infect Dis. 2024 Jan 12;229(1):95-107.
doi: 10.1093/infdis/jiad271.

Safety and Immunogenicity of a ChAd155-Vectored Respiratory Syncytial Virus Vaccine in Infants 6-7 Months of age: A Phase 1/2 Randomized Trial

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Abstract

Background: Respiratory syncytial virus (RSV) is a common cause of lower respiratory tract infections in infants. This phase 1/2, observer-blind, randomized, controlled study assessed the safety and immunogenicity of an investigational chimpanzee-derived adenoviral vector RSV vaccine (ChAd155-RSV, expressing RSV F, N, and M2-1) in infants.

Methods: Healthy 6- to 7-month-olds were 1:1:1-randomized to receive 1 low ChAd155-RSV dose (1.5 × 1010 viral particles) followed by placebo (RSV_1D); 2 high ChAd155-RSV doses (5 × 1010 viral particles) (RSV_2D); or active comparator vaccines/placebo (comparator) on days 1 and 31. Follow-up lasted approximately 2 years.

Results: Two hundred one infants were vaccinated (RSV_1D: 65; RSV_2D: 71; comparator: 65); 159 were RSV-seronaive at baseline. Most solicited and unsolicited adverse events after ChAd155-RSV occurred at similar or lower rates than after active comparators. In infants who developed RSV infection, there was no evidence of vaccine-associated enhanced respiratory disease (VAERD). RSV-A neutralizing titers and RSV F-binding antibody concentrations were higher post-ChAd155-RSV than postcomparator at days 31, 61, and end of RSV season 1 (mean follow-up, 7 months). High-dose ChAd155-RSV induced stronger responses than low-dose, with further increases post-dose 2.

Conclusions: ChAd155-RSV administered to 6- to 7-month-olds had a reactogenicity/safety profile like other childhood vaccines, showed no evidence of VAERD, and induced a humoral immune response.

Influenza Other Respir Viruses. 2023 Jul 25;17(7):e13176.

doi: 10.1111/irv.13176. eCollection 2023 Jul.

Safety and efficacy of AK0529 in respiratory syncytial virus-infected infant patients: A phase 2 proof-of-concept trial

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Abstract

Background: Respiratory syncytial virus (RSV) infection is a cause of substantial morbidity and mortality in young children. There is currently no effective therapy available.

Methods: This was a Phase 2 study of the oral RSV fusion protein inhibitor AK0529 in infants aged 1-24 months, hospitalized with RSV infection. In Part 1, patients ($n = 24$) were randomized 2:1 to receive a single dose of AK0529 up to 4 mg/kg or placebo. In Part 2, patients ($n = 48$) were randomized 2:1 to receive AK0529 at 0.5, 1, or 2 mg/kg bid or placebo for 5 days. Sparse pharmacokinetic samples were assessed using population pharmacokinetics modelling. Safety, tolerability, viral load, and respiratory signs and symptoms were assessed daily during treatment.

Results: No safety or tolerability signals were detected for AK0529: grade ≥3 treatment-emergent adverse events occurring in 4.1% of patients in AK0529 and 4.2% in placebo groups, respectively, and none led to death or withdrawal from the study. In Part 2, targeted drug exposure was reached with 2 mg/kg bid. A numerically greater reduction in median viral load with 2 mg/kg bid AK0529 than with placebo at 96 h was observed. A -4.0 (95% CI: -4.51, -2.03) median reduction in Wang Respiratory Score from baseline to 96 h was observed in the 2 mg/kg group compared with -2.0 (95% CI: -3.42, -1.82) in the placebo group.

Conclusions: AK0529 was well tolerated in hospitalized RSV-infected infant patients. Treatment with AK0529 2 mg/kg bid was observed to reduce viral load and Wang Respiratory Score.

Salmonella typhi vaccine

Schistosomiasis vaccine

Typhoid vaccine

Clin Infect Dis. 2023 Jul 5;77(1):138-144.
doi: 10.1093/cid/ciad132.

Programmatic Effectiveness of a Pediatric Typhoid Conjugate Vaccine Campaign in Navi Mumbai, India

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Warrier[12], Shalini Yadav[13], Debjit Chakraborty[14], Sunil Bahl[15], Arun Katkar[4], Abhishek Kunwar[4], Vijay Yewale[6], Jason R Andrews[1], Pankaj Bhatnagar[4], Shanta Dutta[14], Stephen P Luby[1]

Abstract

Background: The World Health Organization recommends vaccines for prevention and control of typhoid fever, especially where antimicrobial-resistant typhoid circulates. In 2018, the Navi Mumbai Municipal Corporation (NMMC) implemented a typhoid conjugate vaccine (TCV) campaign. The campaign targeted all children aged 9 months through 14 years within NMMC boundaries (approximately 320 000 children) over 2 vaccination phases. The phase 1 campaign occurred from 14 July 2018 through 25 August 2018 (71% coverage, approximately 113 420 children). We evaluated the phase 1 campaign's programmatic effectiveness in reducing typhoid cases at the community level.

Methods: We established prospective, blood culture-based surveillance at 6 hospitals in Navi Mumbai and offered blood cultures to children who presented with fever ≥3 days. We used a cluster-randomized (by administrative boundary) test-negative design to estimate the effectiveness of the vaccination campaign on pediatric typhoid cases. We matched test-positive, culture-confirmed typhoid cases with up to 3 test-negative, culture-negative controls by age and date of blood culture and assessed community vaccine campaign phase as an exposure using conditional logistic regression.

Results: Between 1 September 2018 and 31 March 2021, we identified 81 typhoid cases and matched these with 238 controls. Cases were 0.44 times as likely to live in vaccine campaign communities (programmatic effectiveness, 56%; 95% confidence interval [CI], 25% to 74%; P = .002). Cases aged ≥5 years were 0.37 times as likely (95% CI, .19 to .70; P = .002) and cases during the first year of surveillance were 0.30 times as likely (95% CI, .14 to .64; P = .002) to live in vaccine campaign communities.

Conclusions: Our findings support the use of TCV mass vaccination campaigns as effective population-based tools to combat typhoid fever.

Hum Vaccin Immunother. 2023 Dec 31;19(1):2203634.
doi: 10.1080/21645515.2023.2203634.

A randomized, observer-blind, controlled phase III clinical trial assessing safety and immunological non-inferiority of Vi-diphtheria toxoid versus Vi-tetanus toxoid typhoid conjugate vaccine in healthy volunteers in eastern Nepal

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Abstract

Typhoid remains one of the major serious health concerns for children in developing countries. With extremely drug-resistant cases emerging, preventative measures like sanitation and vaccination, including typhoid conjugate vaccines (TCV) remain the mainstay in its prevention and control. Different types of TCVs are being developed to meet the global demand. This report outlines the results from a study done to assess the immunogenicity and safety of Vi-Diphtheria toxoid (Vi-DT) TCV in Nepal. The study was a randomized, active-controlled, immunological non-inferiority and safety study. Eligible participants from Sunsari

and Morang districts of eastern Nepal were randomized into 4 study groups (A-D) within 3 age strata (6 months to <2 years, 2 to <18 years, and 18 to 45 years). Groups A to C received a single dose (25 µg) of Vi-DT test vaccine from any of the 3 lots, while group D received the comparator, Typbar-TCV®, Vi-tetanus toxoid (Vi-TT) vaccine (25 µg) in 1:1:1:1 ratio and evaluated at 4 weeks postvaccination with 6 months follow-up. Amongst 400 randomized participants, anti-Vi-IgG seroconversion rates for all age strata in Vi-DT pooled groups (A+B+C) were 100.00% (97.5% CI 98.34-100.00) vs 98.99% (97.5% CI 93.99-99.85) in Vi-TT group (D) at 4 weeks. Comparable safety events were reported between the groups. Three serious adverse events (1 in Vi-DT; 2 in Vi-TT group) were reported during the 6 months follow-up, none being related to the investigational product. Thus, Vi-DT vaccine is safe, immunogenic, and immunologically non-inferior to Vi-TT when analyzed at 4 weeks postvaccination.

J Pediatric Infect Dis Soc. 2023 Sep 27;12(9):513-518.
doi: 10.1093/jpids/piad058.

Durable Anti-Vi IgG and IgA Antibody Responses in 15-Month-Old Children Vaccinated With Typhoid Conjugate Vaccine in Burkina Faso

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Abstract

We assessed anti-Vi IgG/IgA responses to typhoid conjugate vaccine (TCV) in children enrolled in a double-blind randomized controlled, phase 2 trial in Burkina Faso. Anti-Vi IgG seroconversion and anti-Vi IgA titers were higher in TCV than control recipients at 30-35 months post-vaccination. TCV induces durable immunity in Burkinabe children vaccinated at 15 months.

Lancet. 2024 Feb 3;403(10425):459-468.
doi: 10.1016/S0140-6736(23)02031-7. Epub 2024 Jan 25.

Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children

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Abstract

Background: Randomised controlled trials of typhoid conjugate vaccines among children in Africa and Asia have shown high short-term efficacy. Data on the durability of protection beyond 2 years are sparse. We present the final analysis of a randomised controlled trial in Malawi, encompassing more than 4 years of follow-up, with the aim of investigating vaccine efficacy over time and by age group.

Methods: In this phase 3, double-blind, randomised controlled efficacy trial in Blantyre, Malawi, healthy children aged 9 months to 12 years were randomly assigned (1:1) by an unmasked statistician to receive a single dose of Vi polysaccharide conjugated to tetanus toxoid vaccine (Vi-TT) or meningococcal capsular group A conjugate (MenA) vaccine. Children had to have no previous history of typhoid vaccination and reside in the study areas for inclusion and were recruited from government schools and health centres. Participants, their parents or guardians, and the study team were masked to vaccine allocation. Nurses administering vaccines were unmasked. We did surveillance for febrile illness from vaccination until follow-up completion. The primary outcome was first occurrence of blood culture-confirmed typhoid fever. Eligible children who were randomly assigned and vaccinated were included in the intention-to-treat analyses. This trial is registered at ClinicalTrials.gov, NCT03299426.
Findings: Between Feb 21, 2018, and Sept 27, 2018, 28 130 children were vaccinated; 14 069 were assigned to receive Vi-TT and 14 061 to receive MenA. After a median follow-up of 4·3 years (IQR 4·2-4·5), 24 (39·7 cases per 100 000 person-years) children in the Vi-TT group and 110 (182·7 cases per 100 000 person-years) children in the MenA group were diagnosed with a first episode of blood culture-confirmed typhoid fever. In the intention-to-treat population, efficacy of Vi-TT was 78·3% (95% CI 66·3-86·1), and 163 (129-222) children needed to be vaccinated to prevent one case. Efficacies by age group were 70·6% (6·4-93·0) for children aged 9 months to 2 years; 79·6% (45·8-93·9) for children aged 2-4 years; and 79·3% (63·5-89·0) for children aged 5-12 years.
Interpretation: A single dose of Vi-TT is durably efficacious for at least 4 years among children aged 9 months to 12 years and shows efficacy in all age groups, including children younger than 2 years. These results support current WHO recommendations in typhoid-endemic areas for mass campaigns among children aged 9 months to 15 years, followed by routine introduction in the first 2 years of life.

Lancet Glob Health. 2024 Apr;12(4):e589-e598.
doi: 10.1016/S2214-109X(23)00606-X.

Efficacy of typhoid vaccines against culture-confirmed Salmonella Typhi in typhoid endemic countries: a systematic review and meta-analysis

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Abstract
Background: Typhoid is a serious public health threat in many low-income and middle-income countries. Several vaccines for typhoid have been recommended by WHO for typhoid prevention in endemic countries. This study aimed to review the efficacy of typhoid vaccines against culture-confirmed Salmonella enterica serovar Typhi.
Methods: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase for studies published in English between Jan 1, 1986 and Nov 2, 2023. We included randomised controlled trials (RCTs) comparing typhoid vaccines with a placebo or another vaccine. This meta-analysis evaluated the efficacy and safety of several typhoid vaccines, including live attenuated oral Ty21a vaccine, Vi capsular polysaccharide (Vi-PS), Vi polysaccharide conjugated to recombinant Pseudomonas aeruginosa exotoxin A vaccine (Vi-rEPA), and Vi-tetanus toxoid conjugate vaccine (TCV). The certainty of evidence for key

outcomes was evaluated using Grading of Recommendations, Assessment, Development, and Evaluations methodology. The outcome of interest was typhoid fever confirmed by the isolation of Salmonella enterica serovar Typhi in blood and adverse events following immunisation. This study is registered with PROSPERO (CRD42021241043).
Findings: We included 14 RCTs assessing four different vaccines (Ty21a: four trials; Vi-PS: five trials; Vi-rEPA: one trial; TCV: four trials) involving 585 253 participants. All trials were conducted in typhoid endemic countries and the age of participants ranged from 6 months to 50 years. The pooled efficacy against typhoid fever was 45% (95% CI 33-55%; four trials; 247 649 participants; I^2 59%; moderate certainty) for Ty21a and 58% (44-69%; five trials; 214 456 participants; I^2 34%; moderate certainty) for polysaccharide Vi-PS. The cumulative efficacy of two doses of Vi-rEPA vaccine at 2 years was 91% (88-96%; one trial; 12 008 participants; moderate certainty). The pooled efficacy of a single shot of TCV at 2 years post-immunisation was 83% (77-87%; four trials; 111 130 participants; I^2 0%; moderate certainty). All vaccines were safe, with no serious adverse effects reported in the trials.
Interpretation: The existing data from included trials provide promising results regarding the efficacy and safety of the four recommended typhoid vaccines. TCV and Vi-rEPA were found to have the highest efficacy at 2 years post-immunisation. However, follow-up data for Vi-rEPA are scarce and only TCV is pre-qualified by WHO. Therefore, roll-out of TCV into routine immunisation programmes in typhoid endemic settings is highly recommended.

Varicella vaccine

Yellow fever vaccine

Lancet Infect Dis. 2023 Aug;23(8):965-973.
doi: 10.1016/S1473-3099(23)00131-7. Epub 2023 Apr 28.
Immunogenicity and safety of fractional doses of 17D-213 yellow fever vaccine in children (YEFE): a randomised, double-blind, non-inferiority substudy of a phase 4 trial
Aitana Juan-Giner[1], Maria L Namulwana[2], Derick Kimathi[3], Kyra H Grantz[4], Gamou Fall[5], Moussa Dia[5], Ndeye S Bob[5], Amadou Alpha Sall[5], Caroline Nerima[2], Mateus Kambale Sahani[2], Edgar M Mulogo[6], Immaculate Ampeire[7], Joachim Hombach[8], Deborah Nanjebe[2], Juliet Mwanga-Amumpaire[2], Derek A T Cummings[9], Philip Bejon[3], George M Warimwe[3], Rebecca F Grais[10]
Abstract
Background: Current supply shortages constrain yellow fever vaccination activities, particularly outbreak response. Although fractional doses of all WHO-prequalified yellow fever vaccines have been shown to be safe and immunogenic in a randomised controlled trial in adults, they have not been evaluated in a randomised controlled trial in young children (9-59 months old). We aimed to assess the immunogenicity and safety of fractional doses compared with standard doses of the WHO-prequalified 17D-213 vaccine in young children.
Methods: This substudy of the YEFE phase 4 study was conducted at the Epicentre Mbarara Research Centre (Mbarara, Uganda). Eligible children were aged 9-59 months without contraindications for vaccination, without history of previous yellow fever vaccination or infection and not requiring yellow fever vaccination for travelling. Participants were

randomly assigned, using block randomisation, 1:1 to standard or fractional (one-fifth) dose of yellow fever vaccine. Investigators, participants, and laboratory personnel were blinded to group allocation. Participants were followed for immunogenicity and safety at 10 days, 28 days, and 1 year after vaccination. The primary outcome was non-inferiority in seroconversion (-10 percentage point margin) 28 days after vaccination measured by 50% plaque reduction neutralisation test ($PRNT_{50}$) in the per-protocol population. Safety and seroconversion at 10 days and 12-16 months after vaccination (given COVID-19 resctrictions) were secondary outcomes. This study is registered with ClinicalTrials.gov, NCT02991495.
Findings: Between Feb 20, 2019, and Sept 9, 2019, 433 children were assessed, and 420 were randomly assigned to fractional dose (n=210) and to standard dose (n=210) 17D-213 vaccination. 28 days after vaccination, 202 (97%, 95% CI 95-99) of 207 participants in the fractional dose group and 191 (100%, 98-100) of 191 in the standard dose group seroconverted. The absolute difference in seroconversion between the study groups in the per-protocol population was -2 percentage points (95% CI -5 to 1). 154 (73%) of 210 participants in the fractional dose group and 168 (80%) of 210 in the standard dose group reported at least one adverse event 28 days after vaccination. At 10 days follow-up, seroconversion was lower in the fractional dose group than in the standard dose group. The most common adverse events were upper respiratory tract infections (n=221 [53%]), diarrhoea (n=68 [16%]), rhinorrhoea (n=49 [12%]), and conjunctivitis (n=28 [7%]). No difference was observed in incidence of adverse events and serious adverse events between study groups.
Conclusions: Fractional doses of the 17D-213 vaccine were non-inferior to standard doses in inducing seroconversion 28 days after vaccination in children aged 9-59 months when assessed with $PRNT_{50}$, but we found fewer children seroconverted at 10 days. The results support consideration of the use of fractional dose of yellow fever vaccines in WHO recommendations for outbreak response in the event of a yellow fever vaccine shortage to include children.

Vitamin A

(also see Retinopathy of Prematurity)

Eur J Nutr. 2024 Apr;63(3):905-918.
doi: 10.1007/s00394-023-03314-6. Epub 2024 Jan 19.
Supplementation of red palm olein-enriched biscuits improves levels of provitamin A carotenes, iron, and erythropoiesis in vitamin A-deficient primary schoolchildren: a double-blinded randomised controlled trial
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Abstract
Purpose: Vitamin A deficiency (VAD) remains a significant contributor to childhood morbidity and mortality in developing countries; therefore, the implementation of sustainable and cost-effective approaches to control VAD is of utmost pertinence. This study aims to investigate the efficacy of red palm olein (RPO)-enriched biscuit supplementation in

improving vitamin A, haematological, iron, and inflammatory status among vitamin A-deficient schoolchildren.
Methods: We conducted a double-blinded, randomised controlled trial involving 651 rural primary schoolchildren (8-12 years) with VAD in Malaysia. The schoolchildren were randomised to receive either RPO-enriched biscuits (experimental group, n = 334) or palm olein-enriched biscuits (control group, n = 317) for 6-month duration.
Results: Significant improvements in retinol and retinol-binding protein 4 levels were observed in both groups after supplementation ($P < 0.001$). The improvement in retinol levels were similar across groups among subjects with confirmed VAD ($P = 0.40$). Among those with marginal VAD, greater improvement in retinol levels was recorded in the control group ($P < 0.001$) but lacked clinical significance. The levels of α- and β-carotenes, haematological parameters (haemoglobin, packed cell volume, mean corpuscular volume and mean corpuscular haemoglobin) and iron enhanced more significantly in the experimental group ($P < 0.05$). The significant reduction in the prevalence of microcytic anaemia (- 21.8%) and high inflammation (- 8.1%) was only observed in the experimental group.
Conclusion: The supplementation of RPO-enriched biscuits enhanced levels of provitamin A carotenes, iron, and erythropoiesis, and exhibited anti-inflammatory effects. Therefore, the incorporation of RPO into National Nutritional Intervention Programs may be a potential measure to improve the health status of vitamin A-deficient children, among various other interventions.

Vitamin D

(See also Neonates – preterm and low birth weight, and Endocrine diseases and bone health)

Nutrients. 2024 Jun 11;16(12):1828.
doi: 10.3390/nu16121828.
Does Vitamin D3 Supplementation Improve Depression Scores among Rural Adolescents? A Randomized Controlled Trial
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Abstract
Background: Contemporary evidence has been established demonstrating that stunted vitamin D levels are associated with depression, poor mood, and other mental disorders. Individuals with normal vitamin D levels have a much lower probability of developing depression. Improving vitamin D levels by supplementation has shown betterment in depressive patients among different age groups. The objective of this study was to assess the effect of vitamin D supplementation on depression scores among rural adolescents.
Material and methods: This study was a cluster randomized controlled trial carried out for a period of 3 years among adolescents from rural Kolar. The sample size was calculated based on previous research and was determined to be 150 for each group. The intervention arm received 2250 IU of vitamin D, and the control arm received a lower dose of 250 IU of vitamin D for 9 weeks. To assess sociodemographic status, a pretested, semi-structured questionnaire was used, and, to assess depression, the Beck Depression Inventory (BDI-II)

was used. A baseline assessment was carried out for vitamin D status and depression status, followed by a post-intervention assessment. From the start of the trial, the participants were contacted every week by the pediatric team to investigate any side effects.
Results: Out of 235 school students in the vitamin D supplementation arm, 129 (54.9%) belonged to the 15 years age group, 124 (52.8%) were boys, and 187 (79.6%) belonged to a nuclear family. Out of 216 school students in the calcium supplementation arm, 143 (66.2%) belonged to the 15 years age group, 116 (53.7%) were girls, and 136 (63%) belonged to a nuclear family. By comparing Beck depression scores before and after the intervention, it was found that the vitamin D intervention arm showed a statistically significant reduction in Beck depression scores.
Conclusions: The present study showed that vitamin D supplementation reduced depression scores, showing some evidence that nutritional interventions for mental health issues such as depression are an excellent option. Vitamin D supplementation in schools can have numerous beneficiary effects on health while mutually benefiting mental health.

BMJ Paediatr Open. 2024 Apr 10;8(1):e002495.
doi: 10.1136/bmjpo-2024-002495.

Influence of vitamin D supplementation on growth, body composition, pubertal development and spirometry in South African schoolchildren: a randomised controlled trial (ViDiKids)

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Abstract
Objective: To determine whether weekly oral vitamin D supplementation influences growth, body composition, pubertal development or spirometric outcomes in South African schoolchildren.
Design: Phase 3 double-blind randomised placebo-controlled trial.
Setting: Socioeconomically disadvantaged peri-urban district of Cape Town, South Africa.
Participants: 1682 children of black African ancestry attending government primary schools and aged 6-11 years at baseline.
Interventions: Oral vitamin D_3 (10 000 IU/week) versus placebo for 3 years.
Main outcome measures: Height-for-age and body mass index-for-age, measured in all participants; Tanner scores for pubertal development, spirometric lung volumes and body composition, measured in a subset of 450 children who additionally took part in a nested substudy.
Results: Mean serum 25-hydroxyvitamin D_3 concentration at 3-year follow-up was higher among children randomised to receive vitamin D versus placebo (104.3 vs 64.7 nmol/L, respectively; mean difference (MD) 39.7 nmol/L, 95% CI 37.6 to 41.9 nmol/L). No statistically significant differences in height-for-age z-score (adjusted MD (aMD) -0.08, 95% CI -0.19 to 0.03) or body mass index-for-age z-score (aMD -0.04, 95% CI -0.16 to 0.07) were seen between vitamin D versus placebo groups at follow-up. Among substudy participants, allocation to vitamin D versus placebo did not influence pubertal development scores, % predicted forced

expiratory volume in 1 s (FEV1), % predicted forced vital capacity (FVC), % predicted FEV1/FVC, fat mass or fat-free mass.
Conclusions: Weekly oral administration of 10 000 IU vitamin D_3 boosted vitamin D status but did not influence growth, body composition, pubertal development or spirometric outcomes in South African schoolchildren.

Indian Pediatr. 2024 Jun 15;61(6):533-539.
Epub 2024 Apr 5.
Effect of Antenatal Oral Vitamin D Supplementation on Serum 25(OH)D Concentration in Exclusively Breastfed Infants at 6 Months of age - A Randomized Double-Blind Placebo-Controlled Trial
Prashant Prabhakar[1], M M A Faridi[2], Anju Aggarwal[1], Rachna Aggarwal[3], S V Madhu[4], Rajeev Malhotra[5]
Abstract
Objective: To compare the proportion of exclusively breastfed (EBF) infants having severe vitamin D deficiency (25(OH)D concentration <11 ng/mL) at 6 months of age when mothers were supplemented with 300,000 IU vitamin D3 or placebo during the third trimester of pregnancy.
Methods: In this randomized double-blind placebo-controlled trial, we recruited 100 pregnant women (who were willing to exclu-sively breastfeed their babies for 6 months) at 30-32 weeks gestation and the infants born to them. Pregnant women were randomized to receive either oral vitamin D3 60,000 IU or placebo, given weekly for 5 weeks during the third trimester. Serum 25(OH)D, calcium, phosphorus and alkaline phosphatase concentration were measured in all participants at recruitment, in the cord blood at delivery, and in infants at 6 months of age. The proportion of infants developing severe vitamin D deficiency and rickets at 6 months was assessed.
Results: A total 72 mother-infant dyads were followed-up till 6 months. At enrollment, the mean (SD) serum 25(OH)D concentration (ng/mL) were comparable in mothers in the intervention and control groups [12.9 (5.8) vs 12.8 (5.9), P = 0.96]. The mean (SD) 25(OH)D concentration (ng/mL) in the cord blood was significantly higher in the intervention group compared to the control group [42.1 (17.1) vs 12.7 (6.3); P = 0.002]. Serum 25(OH)D levels (ng/mL) in the infants at 6 months age were higher in the intervention group compared to the control group [31.8 (10.9) vs 12.5 (5.7); P < 0.001]. No infant in the intervention group had severe vitamin D deficiency at 6 months age compared to 54.3% infants in the control group (P < 0.001). No infant in the intervention group developed rickets.
Conclusion: Oral supplementation of vitamin D3 to pregnant women in the third trimester prevents severe hypovitaminosis D in the EBF infants at 6 months of age.

Nutr Rev. 2023 Jul 10;nuad082.
doi: 10.1093/nutrit/nuad082. Online ahead of print.
High-dose oral vitamin D supplementation for prevention of infections in children aged 0 to 59 months: a systematic review and meta-analysis

Janet Adede Carboo [1], Robin Claire Dolman-Macleod [1], Linda Malan [1], Martani Johanni Lombard [1]

Abstract

Context: Vitamin D plays an important role in immune function, and the deficiency thereof has been associated with several infections, most notably respiratory tract infections. However, data from intervention studies investigating the effect of high-dose vitamin D supplementation on infections have been inconclusive.

Objective: The aim of this study was to evaluate the level of evidence regarding the efficacy of vitamin D supplementation above the standard dose (400 IU) in preventing infections in apparently healthy children < 5 years of age.

Data sources: PubMed, Scopus, Science Direct, Web of Science, Google Scholar, CINAHL, and MEDLINE electronic databases were searched between August 2022 and November 2022. Seven studies met the inclusion criteria.

Data extraction: Meta-analyses of outcomes in more than one study were performed using Review Manager software. Heterogeneity was evaluated using the I2 statistic. Randomized controlled trials in which vitamin D was supplemented at > 400 IU compared with placebo, no treatment, or standard dose were included.

Data analysis: Seven trials that enrolled a total of 5748 children were included. Odds ratios (ORs) with 95%CIs were calculated using random- and fixed-effects models. There was no significant effect of high-dose vitamin D supplementation on the incidence of upper respiratory tract infection (OR, 0.83; 95%CI, 0.62-1.10). There was a 57% (95%CI, 0.30-0.61), 56% (95%CI, 0.27-0.07), and 59% (95%CI, 0.26-0.65) reduction in the odds of influenza/cold, cough, and fever incidence, respectively, with daily supplementation of vitamin D > 1000 IU. No effect was found on bronchitis, otitis media, diarrhea/gastroenteritis, primary care visits for infections, hospitalizations, or mortality.

Conclusion: High-dose vitamin D supplementation provided no benefit in preventing upper respiratory tract infections (moderate certainty of evidence) but reduced the incidence influenza/cold (moderate certainty of evidence), cough, and fever (low certainty of evidence). These findings are based on a limited number of trials and should be interpreted with caution. Further research is needed.

J Steroid Biochem Mol Biol. 2023 Dec:235:106411.
doi: 10.1016/j.jsbmb.2023.106411. Epub 2023 Oct 21.

Maternal vitamin D intakes during pregnancy and child health outcome

Erdenebileg Nasantogtokh [1], Davaasambuu Ganmaa [2], Shirchinjav Altantuya [1], Bayarsaikhan Amgalan [3], Davaasambuu Enkhmaa [4]

Abstract

We conducted a follow up of the children in Mongolia whose mothers received one of the three doses of vitamin D (600, 2000, or 4000 IU daily) during pregnancy as part of the randomized, double-blind, clinical trial of vitamin D supplementation to determine their impact on child health to two years. In the parental trial, 119 pregnant women were assigned to 600 IU/day, 121 were assigned 2000 IU/day, and 120 were assigned 4000 IU/day starting at 12-16 weeks' gestation and continuing throughout pregnancy. At baseline, maternal serum 25(OH)D concentrations were similar across arms; 91 % were 50 nmol/l. As expected, there was a dose-response association between the amount of vitamin D consumed (600, 2000, or

4000 IU daily) and maternal 25(OH)D levels at the end of the intervention. Total 311 children of 311 mothers were followed for 2 years to evaluate health outcomes. We determined the child's health outcomes (rickets, respiratory disease [pneumonia, asthma], and diarrhea/vomiting) using a questionnaire and physical examination (3, 6, and 24 months of age). Low levels of mothers' serum 25(OH)D during pregnancy increased the risk of developing rickets, respiratory illness, and other diseases in children during the early childhood period. Rickets was diagnosed in 15.6 % of children of women who received 600 IU of vitamin D during pregnancy, which was higher than in other vitamin D groups. Children in the group whose mothers received low doses of vitamin D (600 IU/day) had a greater probability of developing respiratory diseases compared to the other groups: pneumonia was diagnosed in n = 36 (35.0 %) which was significantly higher than the group receiving vitamin D 4000 IU/day (n = 34 (31.5 %) p = 0.048). In the group whose pregnant mother consumed 600 IU/day of vitamin D, the risk of child pneumonia was ~ 2 times higher than in the group who consumed 4000 IU/day (OR=1.99, 95 % CI: 1.01-3.90). The incidence of diarrhea and vomiting in children was 12.1 % lower in the 2000 IU/day group and 13.1 % lower in the 4000 IU/day group compared with the 600 IU/day group (p = 0.051). The offspring of pregnant women who regularly used vitamin D at doses above 600 IU/day had lower respiratory disease, rickets, and diarrheal risks at 2 years.

Pediatrics. 2024 Jun 1;153(6):e2023063263.
doi: 10.1542/peds.2023-063263.

Maternal Vitamin D Supplementation and Infantile Rickets: Secondary Analysis of a Randomized Trial

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Abstract

Background: The role of maternal vitamin D supplementation in the prevention of infantile rickets is unknown, particularly in low- and middle-income countries without routine infant vitamin D supplementation. Through secondary analysis of a randomized, placebo-controlled trial in Bangladesh, we examined the dose-ranging effects of maternal vitamin D supplementation on the risk of biochemical rickets at 6 to 12 months of age.

Methods: Pregnant women (n = 1300) were randomized into 5 groups: placebo, or vitamin D 4200 IU/week, 16 800 IU/week, or 28 000 IU/week from second trimester to delivery and placebo until 6 months postpartum; or 28 000 IU/week prenatally and until 6 months postpartum. Infants underwent biochemical rickets screening from 6 to 12 months of age (n = 790). Relative risks (RR) and 95% confidence intervals (95% CI) of biochemical rickets were estimated for each group versus placebo.

Results: Overall, 39/790 (4.9%) infants had biochemical rickets. Prevalence was highest in the placebo group (7.8%), and the risk was significantly lower among infants whose mothers received combined prenatal and postpartum vitamin D at 28 000 IU/week (1.3%; RR, 0.16; 95% CI, 0.03-0.72). Risks among infants whose mothers received only prenatal supplementation (4200 IU, 16 800 IU, 28 000 IU weekly) were not significantly different from placebo: 3.8% (RR, 0.48; 95% CI, 0.19-1.22), 5.8% (RR, 0.74; 95% CI, 0.33-1.69), and 5.7% (RR, 0.73; 95% CI, 0.32-1.65), respectively.

Conclusions: Maternal vitamin D supplementation (28 000 IU/week) during the third trimester of pregnancy until 6 months postpartum reduced the risk of infantile biochemical rickets. Further research is needed to define optimal postpartum supplementation dosing during lactation.

J Pediatr Endocrinol Metab. 2023 May 18;36(7):683-691.
doi: 10.1515/jpem-2023-0146. Print 2023 Jul 26.

Daily vs. monthly oral vitamin D_3 for treatment of symptomatic vitamin D deficiency in infants: a randomized controlled trial

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Abstract

Objectives: Compare the efficacy and safety of daily vs. monthly oral vitamin D_3 in treating symptomatic vitamin D deficiency in infants.

Methods: 90 infants with symptomatic vitamin D deficiency were randomized into Daily (D) [46 infants] and Bolus (B) [44 infants] groups to receive oral vitamin D_3, daily (2000 IU/day) and bolus (60,000 IU/month) for three months respectively. Both groups received daily oral calcium @50 mg/kg/day. Serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), 25-hydroxy cholecalciferol [25(OH)D], parathyroid hormone (PTH) levels, urine calcium: creatinine ratio and radiological score were assessed at baseline, 4 and 12 weeks. At the end of 12 weeks, 78 infants were available for evaluation of efficacy and safety of both regimens.

Results: Both regimens led to a statistically significant increase in Ca and P levels and fall in ALP and PTH levels from baseline to 4 and 12 weeks of therapy, with no inter-group difference. Infants in group D had statistically significant higher mean 25(OH)D levels as compared to group B at 4 weeks (group D 130.89 ± 43.43 nmol/L, group B - 108.25 ± 32.40 nmol/L; p - 0.012) and 12 weeks (group D - 193.69 ± 32.47 nmol/L, group B - 153.85 ± 33.60 nmol/L; p<0.001). Eight infants [group D - 6/41 (14.6 %); group B - 2/37 (5.4 %), p=0.268] developed mild asymptomatic hypercalcemia without hypercalciuria at 12 weeks that corrected spontaneously within a week.

Conclusions: Both daily and monthly oral vitamin D_3 in equivalent doses are efficacious and safe for treating symptomatic vitamin D deficiency in infants.

Lancet Diabetes Endocrinol. 2024 Jan;12(1):29-38.
doi: 10.1016/S2213-8587(23)00317-0. Epub 2023 Dec 1.

Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a multicentre, double-blind, randomised, placebo-controlled trial

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Abstract

Background: Vitamin D supplementation has been shown to increase total hip areal bone mineral density in healthy children and adolescents. We aimed to investigate whether

supplementing schoolchildren living in Mongolia with weekly vitamin D_3 for 3 years affected fracture risk.
Methods: We did a multicentre, double-blind, randomised, placebo-controlled trial across 18 public schools in Ulaanbaatar, Mongolia. Schoolchildren were eligible if they were aged 6-13 years at screening, had a negative QuantiFERON-TB Gold In-tube assay (QFT) result, were not hypersensitive to vitamin D or immunocompromised, did not use vitamin D supplements, did not have clinical signs of rickets, and had no intention of leaving Ulaanbaatar within 3 years. Participants were randomly assigned (1:1) to receive either vitamin D (oral dose of 14 000 international units [IU] vitamin D_3, once per week) or placebo for 3 years using permuted block randomisation stratified by school of attendance. Participants, care providers, and all trial staff were masked to group assignment during the intervention. Prespecified secondary outcomes were incidence of fractures and adverse events, ascertained using questionnaires. The fracture and safety analyses included participants who completed at least one follow-up fracture questionnaire. We estimated adjusted risk ratios (RRs) and 95% CIs using generalised linear models with binomial distribution and a log link function with adjustment for school of attendance. The trial is registered with ClinicalTrials.gov, NCT02276755, and the intervention ended in May, 2019.
Findings: Between Sept 2, 2015, and March 20, 2017, 11 475 children were invited to participate in the study and 8851 were recruited and randomly assigned to receive either vitamin D (n=4418) or placebo (n=4433). 8348 participants were included in the fracture and safety analyses (4176 [94·5%] in the vitamin D group and 4172 [94·1%] in the placebo group). Of these, 4125 (49·4%) were female, 4223 (50·6%) were male, and 7701 (92·2%) were of Khalkh ancestry. Median age was 9·2 years (IQR 8·0-10·7) and 7975 (95·5%) participants had baseline serum 25-hydroxyvitamin D concentrations less than 50 nmol/L. During a median follow-up of 3·0 years (IQR 2·9-3·1), 268 (6·4%) participants in the vitamin D group and 253 (6·1%) in the placebo group reported one or more fractures (adjusted RR 1·10, 95% CI 0·93-1·29; p=0·27). Incidence of adverse events did not differ between study groups.
Interpretation: Oral vitamin D supplementation at a dose of 14 000 IU/week for 3 years was safe, but did not influence fracture risk in schoolchildren living in Mongolia who had a high baseline prevalence of vitamin D deficiency.

J Nutr. 2024 Apr 27:S0022-3166(24)00234-7.
doi: 10.1016/j.tjnut.2024.04.031. Online ahead of print.
The relationship between vitamin D intake and serum 25-hydroxyvitamin D in young children: a meta-regression to inform WHO/FAO vitamin D intake recommendations
Magali Rios-Leyvraz[1], Laura Martino[2], Kevin D Cashman[3]
Abstract
Background: This work was commissioned by the WHO and FAO to inform their update of the vitamin D requirements for children below 4 years old.
Objective: The objective of this work was to undertake multi-level and multivariable dose-response modelling of serum 25OHD to total vitamin D intake in children below 4 years of age and to derive updated vitamin D requirements for young children.
Methods: Systematically identified randomized controlled trials among healthy children from 2 weeks up to 3.9 years of age provided with daily vitamin D supplements or vitamin D-fortified foods were included. Linear and non-linear random effects multi-level meta-regression models with and without covariates were fitted and compared. Inter-individual

variability was included by simulating the individual serum 25OHD responses. The percentage of individuals reaching set minimal and maximal serum 25OHD thresholds were calculated and used to derive vitamin D requirements.
Results: A total of 31 trials with 186 data points, from North America, Europe, Asia and Australasia/Oceania, with latitudes ranging from 38°S to 61°N, and with participants of likely mostly light or medium skin pigmentation, were included; in 29 studies the children received vitamin D supplements and in two studies the children received vitamin D fortified milks with or without supplements. The dose-response relationship between vitamin D intake and serum 25OHD was best fitted with the unadjusted quadratic model; adding additional covariates, such as age, did not significantly improve the model. At a vitamin D intake of 10 µg/d, 97.3% of the individuals were predicted to achieve a minimal serum 25OHD threshold of 28 nmol/L. At a vitamin D intake of 35 µg/d, 1.4% of the individuals predicted to reach a maximal serum 25OHD threshold of 200 nmol/L.
Conclusions: In conclusion, this paper details the methodological steps taken to derive vitamin D requirements in children below 4 years of age, including the addition of an inter-individual variability component.
Keywords: 25OHD; Serum 25-hydroxyvitamin D; children; meta-analysis; meta-regression; nutrient requirements; vitamin D intake.

Indian J Ophthalmol. 2024 Jul 1;72(Suppl 4):S634-S638.
doi: 10.4103/IJO.IJO_773_23. Epub 2024 May 20.
Serum vitamin D levels in children with vernal keratoconjunctivitis - A study from a tertiary care pediatric hospital of North India
Meenakshi Wadhwani[1], Shikha Sharma[2], Rahul Singh[3]
Abstract
Background: To study the levels of vitamin D serum levels in children with vernal keratoconjuctivits (VKC) and comparing vitamin D levels in after giving vitamin D supplements between intervention and control group.
Methods: The study was conducted in population between 1 to 12 years in tertiary care hospital in North India. Amongst children with VKC, full ocular examination along with Boninis clinical grading of VKC and serum vitamin D levels were assessed. Whole study group was randomly divided into two groups. Intervention group had received vitamin D powder while control group kept under observation.
Results: A total of 88 children received vitamin D supplementation and 39 kept in control group.
Conclusion: Our study suggests that children in intervention group showed improvement in serum vitamin D levels with the clinical improvement in VKC grading too.

Yaws

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

Nutr. 2023 Oct;153(10):3092-3100.
doi: 10.1016/j.tjnut.2023.08.013. Epub 2023 Aug 25.

The Effect of Zinc Biofortified Wheat Produced via Foliar Application on Zinc Status: A Randomized, Controlled Trial in Indian Children

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Abstract

Background: Agronomic zinc biofortification of wheat by foliar application increases wheat zinc content and total zinc absorption in humans.

Objectives: To assess the effect of agronomically biofortified whole wheat flour (BFW) on plasma zinc (PZC) compared with a postharvest fortified wheat (PHFW) and unfortified control wheat (CW) when integrated in a midday school meal scheme.

Methods: We conducted a 20-wk double-blind intervention trial in children (4-12 y, n = 273) individually randomly assigned to 3 groups to receive a daily school lunch consisting of 3 chapattis prepared with the 3 different wheat flour types. Measurements of anthropometry, blood biochemistry, and leukocyte DNA strand breaks were conducted. We applied sparse serial sampling to monitor PZC over time, and analysis was performed using linear mixed-effects models.

Results: Mean zinc content in BFW, PHFW, and CW were 48.0, 45.1, and 21.2 ppm, respectively ($P < 0.001$). Mean (standard deviation) daily zinc intakes in the study intervention in BFW, PHFW, and CW groups were 4.4 (1.6), 5.9 (1.9) and 2.6 (0.6) mg Zn/d, respectively, with intake in groups PHFW and BFW differing from CW ($P < 0.001$) but no difference between BFW and PHFW. There were no time effect, group difference, or group × time interaction in PZC. Prevalence of zinc deficiency decreased in the BFW (from 14.1%-11.2%), PHFW (from 8.9%-2.3%), and CW (9.8%-8.8%) groups, but there was no time × treatment interaction in the prevalence of zinc deficiency ($P = 0.191$). Compliance with consuming the study school meals was associated with PZC ($P = 0.006$). DNA strand breaks were not significantly associated with PZC ($n = 51$; $r = 0.004$, $P = 0.945$).

Conclusions: Consumption of either PHFW or BFW provided an additional ~1.8 to 3.3 mg Zn/d, but it did not affect PZC or zinc deficiency, growth, or DNA strand breaks.

Am J Perinatol. 2023 Nov 8.
doi: 10.1055/s-0043-1776762. Online ahead of print.

Zinc Supplementation in Very Low Birth Weight Infants: A Randomized Controlled Trial

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Abstract

Objective: Preterm infants have high zinc (Zn) requirements and are generally believed to be in a negative Zn balance in the early period of life. In this study, we aimed to investigate the effect of high-dose Zn supplementation in very low birth weight (VLBW: infants with birth weight < 1.5 kg) infants on feeding intolerance and development of mortality and/or morbidities including necrotizing enterocolitis (NEC) and late-onset sepsis (LOS).
Study design: This is a prospective randomized trial. VLBW preterm infants with gestational age of <32 weeks were randomly allocated on the seventh day of life to receive extra amount of supplemental Zn along with the enteral feedings (9 + 3 mg), besides regular low-dose supplementation (3 mg), from enrollment until discharge. Outcome measures were feeding intolerance, NEC (stage ≥ 2), LOS, and mortality.
Results: A total of 195 infants (97 from study group and 98 from control group) were analyzed. A total of 46 (47.4%) infants in the study group and 64 (65.3%) infants in the control group ended up with feeding intolerance ($p = 0.012$). NEC was observed in 11 infants (11.2%) in the control group and only 1 infant (1%) in the study group ($p = 0.003$). There was a negative correlation between high-dose Zn supplementation and number of culture-proven LOS episodes ($p = 0.041$). This significance was also present for clinical sepsis, being higher in the control group ($p = 0.029$). No relationship between high-dose Zn supplementation and mortality and other morbidities (hemodynamically significant patent ductus arteriosus, bronchopulmonary dysplasia, retinopathy of prematurity, and severe intraventricular hemorrhage) was observed.
Conclusion: Zn supplementation for VLBW infants is found to be effective to decrease feeding intolerance, NEC, and LOS episodes in this vulnerable population. Current data support the supplementation of VLBW infants with higher than regular dose of Zn.

J Nutr. 2024 Feb;154(2):403-411.
doi: 10.1016/j.tjnut.2023.12.011. Epub 2023 Dec 11.

Effects of Zinc Supplementation on Metabolomic Profiles in Tanzanian Infants: A Randomized Trial

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Abstract

Background: Provision of zinc supplementation to young children has been associated with reduced infectious morbidity and better growth outcomes. However, the metabolic pathways underlying these outcomes are unclear, and metabolomic data from humans undergoing zinc supplementation, particularly infants, are generally lacking.
Objectives: This study aimed to examine the effect of zinc supplementation on metabolic profiles in Tanzanian infants aged 6 wk and 6 mo.
Methods: Blood samples were collected at age 6 wk and 6 mo from 50 Tanzanian infants who were enrolled in a randomized placebo-controlled trial of zinc supplementation (5 mg oral daily). Metabolomic analysis using an ultrahigh-performance liquid chromatography/tandem mass spectroscopy platform was performed to identify potential metabolomic profiles and biomarkers associated with zinc supplementation. Principal component analysis (PCA) was used to summarize metabolomic data from all samples. Two-way repeated measures analysis of variance with compound symmetry covariance structures

were used to compare metabolome levels over time between infants in the 2 treatment arms.
Results: In PCA, the samples tended to be more separated by child age (6 wk compared with 6 mo) than by zinc supplementation status. We found that zinc supplementation affected a variety of metabolites associated with amino acid, lipid, nucleotide, and xenobiotic metabolism, including indoleacetate in the tryptophan metabolism pathway; 3-methoxytrosine and 4-hydrxoyphenylphruvate in the tyrosine pathway; eicosanedioate, 2-aminooctanoate, and N-acetyl-2-aminooctanoate in the fatty acid pathway; and N6-succinyladenosine in the purine metabolism pathway. Compared to the relatively small number of metabolites associated with zinc supplements, many infant metabolites changed significantly from age 6 wk to 6 mo.
Conclusions: Zinc supplementation, despite having overall clinical benefits, appears to induce limited metabolomic changes in blood metabolites in young infants. Future larger studies may be warranted to further examine metabolic pathways associated with zinc supplementation. The parent trial was registered at clinicaltrials.gov as NCT00421668.