

# **RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES**

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## Randomised trials in child health in developing countries 2017-18

### SEARCH STRATEGY

Pubmed Advanced strategy, search: “Clinical Queries”, ‘narrow’ search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Pacific) and (Child\* OR Adolescent OR Newborn or Neonat\*) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])). publication date between July 1<sup>st</sup> 2017 and June 30<sup>th</sup> 2018.

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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 developing 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. We 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 in most countries 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 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 345 trial publications were identified, a record number.** These were conducted in countries from all regions of the world. Several trials from 2017-18 will lead to significant changes in child health recommendations. This year 10 studies showed reductions in mortality, more than any other year. These studies are marked \*\*\* in the book. Where there were no trials this year under a certain sub-heading I have left the heading in the book, to highlight the lack of trials. Many trials could be listed under several sub-headings, and there is overlap in the sub-headings, so there may be fewer gaps than is first apparent.

The web-link for papers that are available in full-text on the Internet free of charge (**276 with free on-line access**) are included. Through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with publishers, the full-text versions of over 14,000 journal titles and 30,000 e-books 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 (2002-2017) are available at: [www.hospitalcareforchildren.org](http://www.hospitalcareforchildren.org)

### A brief summary of some of the important results in 2017-18

- Among 1 month to 5 years children in Niger, Malawi and Tanzania, childhood mortality was lower in communities randomly assigned to mass distribution of azithromycin than in those assigned to placebo, with the largest and only statistically significant effect seen in Niger, and the largest effect seen between 1-5 months (24.9% lower mortality than that with

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placebo; 95% CI, 10.6 to 37.0). In Malawi and Tanzania the effects did not reach statistical significance.

- In Botswana cotrimoxazole prophylaxis in HIV-exposed infants increased the risk of colonisation with cotrimoxazole resistant *E. coli* (80-90% resistant compared to 50%) and *Klebsiella* (60-70% resistance compared to 10-20%), compared to infants given placebo instead of cotrimoxazole.
- Neither zinc (in two trials) nor Vitamin D when used as adjunctive therapy for pneumonia reduced the duration of illness or improved markers of severity. In a very short-term study, nasal CPAP reduced the work of breathing in infants with bronchiolitis.
- Young women who attend more school days and stay in school have a lower risk of incident HIV and HSV-2 infection
- In Uganda delaying iron by 28 days in children with coexisting malaria and iron deficiency was associated with a reduced risk of subsequent all-cause illness
- In rural India a package of interventions addressing health knowledge and health seeking behaviour, supporting existing health services, and contracting out important areas of maternal and child healthcare led to a reduction in neonatal mortality of 24% (risk ratio 0.76, 95% CI 0.64 to 0.90) in small villages with high mortality rates
- In Burkina Faso economic strengthening combined with family coaching on child protection and child labour was effective in reducing children's exposures to hazardous work, compared with just single interventions such as economic strengthening or counselling of families.
- In several countries, including among Burmese refugee families in Thailand, and among HIV-exposed children and their families in Uganda, parenting skills programs improved child behaviour and development indices compared with controls.
- For children with diarrhoea and severe dehydration in India, rehydration with Ringers lactate improved clinical status and normalisation of pH ( $\geq 7.35$ ) at 6 hours greater than children rehydrated with normal saline.
- Rhubarb syrup (*Rheum ribes* L.) was effective as adjunctive therapy in reducing the duration of diarrhoea, fever and abdominal pain in children with suspected *Shigella*.
- To prevent cholera a one-week training course designed to develop habit formation for handwashing with soap was effective at 6 and 12 month follow-up, these habits were maintained by disgust at not washing hands, convenience (soap and water have to be available), and cholera awareness.
- Although Vitamin D deficiency was common in children with type 1 diabetes mellitus in Southern India, vitamin D supplementation did not improve Haemoglobin A1C levels or insulin requirements at 6 months compared with placebo.
- In a study of staff involved in randomised trials in Botswana, a country experiencing an increase in RCT, the following themes were highlighted: ethics board relationships (including delays in the process); research staff management (including staff attrition and career development); study recruitment and retention (including the use of reimbursements);

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resource availability (including challenges accessing laboratory equipment); and capacity-building (including issues of exporting locally sourced samples).

- In a single centre study in India children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better behaviour and quality of life scores than those who continued medical therapy alone at 12 months.
- In addition to cook stoves with chimneys to reduce indoor air pollution and acute respiratory disease, Rwandan children in households with cemented floors and ventilation holes in the cooking area were significantly less likely to experience symptoms of respiratory infection, illness with cough and difficulty breathing. In another study biomass cook stoves had no effect on school attendance in Malawi.
- A meta-analysis and 2 RCTs in Kenya and Bangladesh of WASH intervention trials showed a minimal beneficial effect on wasting, stunting and underweight. However in trials in 2017 WASH interventions were associated with lower risk of non-diarrheal morbidity (acute respiratory disease, influenza, fever), reduced parasitic infection (in another trial in Burkina Faso) and there was very low quality evidence from the meta-analysis to suggest some decrease to no change in mortality. WASH was effectively delivered in schools in Mali and reduced enteric infections. In Bangladesh and rural Kenya while nutrient supplementation and counselling modestly improved linear growth of children, there was no benefit to the integration of water, sanitation, and handwashing with nutrition on linear growth. In a large study in rural Tanzania, WASH uptake was limited, and no effect on child health outcomes were seen. So WASH is good for reducing diarrhoea, respiratory infections, and intestinal parasite infections, only if it is practiced consistently, but alone will not affect growth without improved nutritional intake.
- Among nearly 100,000 people involved in a trial of community-based case finding and treatment in Zambia, where populations move frequently, acceptance of HIV-testing through offering a door-to-door-based combination HIV prevention package was 72.2%. Active community-based case finding and treatment of HIV and tuberculosis works.
- In sub-Saharan Africa, children receiving first-line ART without viral load monitoring had good virological suppression and no difference in ART-resistance over 4 years of treatment, regardless of whether they had regular CD4 monitoring or not.
- Among 928 HIV infected children on second-line protease inhibitor based ART in 14 countries in Asia and sub-Saharan Africa, 16.4% of children experienced treatment failure (virus HIV RNA >1000 copies/mL) by 2 years of follow-up. Adolescents had much higher failure rates than younger children.
- In Johannesburg, among HIV infected children who were exposed to nevirapine as part of prevention of parent to child transmission, who were changed to Lopinavir boosted ritonavir, the probability of confirmed HIV RNA >1000 copies/mL (i.e. virological failure) by 48 months was 7% if changed to efavirenz at 3 years, compared to 12% if remained on Lopinavir-ritonavir.
- In Uganda, Zimbabwe, Malawi, and Kenya among HIV infected children and adults with advanced immunosuppression (CD4<100), use of enhanced antimicrobial prophylaxis: trimethoprim-sulfamethoxazole, plus 12 weeks of isoniazid-pyridoxine, 12 weeks of fluconazole, 5 days of azithromycin, and single dose of albendazole resulted in significantly

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lower rates of tuberculosis, cryptococcal infection, oral or oesophageal candidiasis, death of unknown cause, and hospitalization, compared with standard prophylaxis (trimethoprim-sulfamethoxazole alone).

- In Brazil, South Africa, Argentina, and USA, maternal CMV infection and particularly CMV in the urine was the strongest STI risk factor for maternal to child transmission of HIV (5 times increased risk than in the absence of maternal CMV infection), and also carried an increased risk of congenital CMV infection (30 times the risk).
- In Indian children with steroid-resistant nephrotic syndrome, overall, more than half of the patients showed initial response to oral cyclophosphamide, but only one-fourth patients had sustained remission on follow-up. Oral cyclophosphamide and IV cyclophosphamide were equally efficacious and safe. And in another trial mycophenolate was inferior to tacrolimus in maintaining remission in Indian children with steroid-resistant nephrotic syndrome.
- In Indian children with steroid responsive nephrotic syndrome who were off steroids, prescribing a short course of daily corticosteroids (0.5mg/kg prednisolone) during an upper respiratory tract infection significantly reduced the frequency of URTI-induced relapse of nephrotic syndrome.
- In Indian communities where lymphatic filariasis is endemic, annual treatment with diethylcarbamazine and albendazole reduced filarial antigenaemia and other markers of infection by 75% over 3 years.
- In Mali, to deliver seasonal malaria chemoprevention, directly-observed therapy by door-to-door delivery (active community treatment) to children aged 3-59 months during the malaria transmission season achieved a higher coverage rate than fixed-point delivery and non-directly observed treatment, but requires more time and resources.
- In Malawi, teachers are being trained to diagnose malaria based on rapid-diagnostic test results, and treat with artemisinin-based therapy.
- In Malaysia, artemether-lumefantrine was highly efficacious for treating uncomplicated Malaria knowlesi, which is increasingly reported in South East Asia. AL was more effective than chloroquine at achieving aparasitaemia at 48 hours.
- In a trial of 900 children with uncomplicated malaria in India and Africa, the once daily fixed-dose combination dispersible tablet of artemolane maleate (AM) 37.5 mg and piperaquine phosphate (PQP) 187.5 mg was as effective at clinical and parasitological cure as twice daily artemether-lumefantrine
- Among children in a high malaria transmission setting in Eastern Uganda, the number of days from to parasite clearance in severe malaria was significantly lower among participants who received intravenous Artesunate than those who received intravenous quinine, but high rates of re-infection were seen. In Republic of Congo, use of IV Artesunate was associated with lower rates of haemolytic anaemia than with quinine.
- In children with severe malaria neurocognitive abnormalities occurred in 35%, but in a trial of inhaled nitric oxide (NO) as adjunctive treatment or severe malaria, children receiving NO had a lower rate of fine motor skill abnormalities, but no difference in other neurodevelopmental measures.



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- In children in Afghanistan with vivax malaria, Primaquine 0.25 mg/kg/day for 14 days, in addition to chloroquine reduced the risk of relapse by 63% and was effective for 12 months, with the strongest protective effect in the first 6 months, and for 8 months after treatment in Papua New Guinea Primaquine reduced plasmodium vivax gametocytes by 73%.
- In a preliminary finding in a trial of severely malnourished children in Malawi, mortality was significantly lower in the intervention group treated with pancreatic enzymes than in those treated with placebo (18.6% vs 37.8%;  $p < 0.05$ ), as were rates of hospital discharge, although weight gain (the primary outcome of the trial) was no different.
- In rural India home visit by a community health worker a worker to mothers in the third trimester of pregnancy, then monthly visits to children younger than 2 years to support feeding, hygiene, care, and stimulation, as well as monthly women's group meetings to promote nutrition did not improve child's linear growth (the primary outcome) but was associated with lower infant mortality, and better health care prevention such as hand washing.
- In an observational study within a randomised trial, self-reported use of a herbal mixture to induce or hasten labour was associated with a 28% higher maternal mortality and 22% higher neonatal mortality, both significant.
- For mothers undergoing caesarean section, giving one dose of antibiotic pre-incision protected the mother from surgical site infections and febrile illness and decreased the hospital stay significantly, compared to if the single dose is given after incision.
- In Vietnam weekly preconception multiple micronutrient (MM) or iron and folic acid (IFA) supplementation improved offspring linear growth and fine motor development at 2 years of age as measured using the Bayley Scales for Infant Development.
- In Pakistan Lady-Health Workers trained in basic newborn resuscitation and in recognition and treatment of suspected neonatal respiratory infections linking with traditional birth attendants reduced neonatal mortality (42 deaths per 1000 livebirths in intervention clusters compared with 55 per 1000 in the control group, risk ratio 0.8; 95% CI 0.68-0.93) although only a small proportion of births (14%) were attended by the trained health workers, and home visits were only possible in 25% of births.
- In India, among preterm newborns 1-1.8kg, early initiation of Kangaroo Mother Care, even while they were on respiratory support and intravenous fluids, achieved significantly higher exclusive human milk feeding (86% vs. 45%,  $p < .001$ ) in hospital and almost exclusive human milk feeding (73% vs. 36%,  $p < .001$ ) until 1 month post-discharge compared to if KMC was only initiated after neonates were off respiratory support and IV fluids. In Taiwan a program of family-involved care for VLBW babies also lead to better growth nutrition and outcomes, and earlier hospital discharge.
- In a large cohort within a RCT in Ghana, babies born weighing  $< 1.50$  kg were 48-times more likely to die in the neonatal period than normal birth weight neonates, and about eight times more likely to die in late infancy (hazard ratio 8.42; 95% CI: 3.09-22.92). So the increased risk of mortality in the neonatal period persists in children long after they are discharged from hospital.
- In a trial in rural India involving over 4,500 infants over 2kg at birth and at least 35 weeks of gestation there was a significant reduction in the combination of sepsis and death (risk ratio

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0.60, 95% confidence interval 0.48-0.74) in infants treated with a synbiotic (*Lactobacillus plantarum* plus fructooligosaccharide), with few deaths (4 placebo, 6 synbiotic), compared to placebo. In another study analysing the effects of this symbiotic on the microbiome of rural Indian infants there was an increase in Gram positive bacteria and bacterial diversity, and a decrease in Gram negative bacteria.

- In a neonatal nursery in India, a single dose of clofibrate prior to starting phototherapy in term neonates with uncomplicated unconjugated hyperbilirubinemia lowered serum bilirubin more rapidly and reduced the duration of phototherapy significantly, compared to phototherapy alone.
- In a rural area in Peru lipid-based nutrient supplements given daily between 6 and 12 months of age increased haemoglobin concentration, reduced rates of anaemia and improved cognitive development in children compared to placebo, but showed no effects on anthropometric indicators, motor or language development.
- In an Ecuador indigenous community, the early introduction of eggs in the diet significantly improved growth in young children. The egg intervention increased length-for-age z score by 0.63 (95% confidence interval, 0.38-0.88) and weight-for-age z score by 0.61 (95% CI, 0.45-0.77), and reduced sugar-sweetened food consumption, compared with controls.
- In dose-response RCTs of Praziquantel in Côte d'Ivoire for the treatment of *Schistosoma mansoni* infection, maximum effect on parasite clearance was achieved with 40mg/kg for pre-school children, and 60mg/kg for school aged children. In northern Tanzania, among children treated for Schistosomiasis with Praziquantel 40mg/kg, the cure rate was higher on repeated dose (93.10%) compared to single dose (68.68%), ( $p < 0.001$ ) when stool was examined at 8 weeks after treatment. In Kenya, to achieve mass drug administration, annual or biennial administration of Praziquantel was provided by teachers. This decreased *S. mansoni* prevalence and infection intensity in 9-12 year old students to a similar degree whether the treatment was given annually or every second year.
- In Uganda, teaching primary school children to assess claims about the effects of health care treatments using the program "Informed Health Choices" improved children's ability to critically appraise health treatments. There was a positive effect, even in schools with large student to teacher ratios and few resources. In a related trial for parents, listening to the Informed Health Choices podcast led to a large improvement in their ability to assess claims about the effects of treatments.
- 100 children with severe sepsis in northern India were randomised to probiotics or standard treatment. Use of probiotics for 7 days (containing *Lactobacillus paracasei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Streptococcus salivarius*) resulted in a decrease in proinflammatory cytokines (IL-6, IL-12, IL-17, TNF-alpha) and an increase in anti-inflammatory cytokines (IL-10, TGF-Beta1). There was a lower organ failure score in the probiotic group, but no difference in mortality (11% overall).
- Among children with septic shock, if fluid bolus were given over 15-20 minutes each there was a significantly lower need for escalation of respiratory support (needing intubation, mechanical ventilation and increase in oxygenation index) in the first 24 hours after fluid resuscitation, compared to children who were given rapid fluid boluses over 5-10 minutes.

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- In Indonesia *Lactobacillus plantarum* IS-10506, a probiotic isolated from dadih, traditional fermented buffalo milk, given twice daily reduced atopic dermatitis severity, and markers of inflammation. In another trial in Egypt *L. rhamnosus*, given over 8 weeks, also reduced atopic dermatitis severity scores.
- In Vietnam, active community-based household-contact investigation plus standard passive case finding was 2.5 times more effective than standard passive case-finding alone for the detection, registration and treatment of tuberculosis in a high-prevalence setting.
- In an RCT of a new TB vaccine (infant MVA85A vaccination) some children also received Isoniazid-preventative therapy (IPT). IPT was highly effective: there were 23 (7.6%) TB cases among 304 IPT recipients vs. 305 (12.9%) among 2374 non-IPT recipients ( $P = 0.008$ ). In this trial IPT effectiveness was 85% (95%CI 76-91). There was no long-term effectiveness of infant MVA85A vaccination.
- In 2 meta-analyses of IPT trials in children living with HIV on ante-retroviral therapy, the protective effect against TB disease and death was uncertain: In one meta-analysis the pooled results showed a statistically nonsignificant reduction in TB incidence (RR: 0.70; 95% CI: 0.47-1.04;  $P = 0.07$ ) and mortality (RR: 0.94; 95% CI: 0.39-2.23;  $P = 0.88$ ) with the use of isoniazid compared with placebo. In the other meta-analysis the risk of TB disease among children on ITP and Ante-retroviral therapy was similar: risk ratio 0.76, 95% CI 0.50 to 1.14 and risk of death (RR 1.45, 95% CI 0.78 to 2.72).
- Among HIV infected children in Kenya, Gene Xpert MTB the pcr-based test for tuberculosis had similar performance on stool (sensitivity) as on sputum/gastric (60%) aspirate.
- In a meta-analysis of trials of the Dengue vaccine CYD-TDV, the vaccine was effective and immunogenic in children overall 54% (40-64). CYD-TDV had reduced efficacy against the dengue virus serotype 2 (DENV2) (34%), this serotype is known to cause severe dengue infections and dengue outbreaks.
- In a RCT in Nepal maternal influenza immunisation at 17-34 weeks gestation significantly reduced maternal influenza-like illness, influenza in infants, and low birthweight over 2 years.
- The Vero cell-derived inactivated JE virus vaccine IXIARO when given to children and adolescents 2 months and 17 years achieved very high seroconversion (>99%) of subjects, with, 4-fold increases in titre were reported for 77.4%-100% in different age groups, and seroconversion was maintained 7 months post-vaccination in 85.5%-100% of children.
- In Kenyan infants and children, hypo-responsiveness to pneumococcal conjugate vaccines (PCVs) occurred when the vaccine was given to infants and toddlers already having nasopharyngeal carriage of vaccine-type strains of pneumococcus.
- In an RCT modelling the global switch from trivalent OPV to bivalent OPV (1 and 3) plus one dose of IPV, there was an increased risk of faecal shedding of Sabin 2 (as identified by reverse transcriptase quantitative PCR) in household contact of infants challenged with monovalent OPV2, but not in the vaccinated infants. This suggests that there is decreased population immunity against Sabin 2 transmission within a short time after tOPV cessation.
- In a large field trial in Indonesia, the neonatal RV3-BB (Bishop-Barnes) was efficacious in preventing severe rotavirus gastroenteritis when administered according to a neonatal (75%

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efficacy) or an infant (51% efficacy) schedules, and 63% efficacious overall. In a RCT in India among infants 6-8 weeks of age, 3 doses of the bovine reassortant pentavalent rotavirus vaccine (BR-PV) had a vaccine efficacy of 36-41% against severe rotavirus diarrhoea.

- In Bangladesh, prenatal vitamin D supplementation 875 µg (35 000 IU)/week in the third trimester significantly reduced the prevalence of neonatal vitamin D deficiency, but did not affect the prevalence of vitamin D deficiency beyond 2 months of age.

Again this year some studies had small sample sizes, and many of the results should be seen as preliminary. The terms or phrases: ‘no difference’, non-inferiority, and equivalence were used in some papers with insufficient consideration to the possibility of a type II error. This can be misleading, and may result in the discarding of an effective intervention, or numerous inadequate trials of the same intervention.

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. Some papers are published RCT methodologies on planned studies, which I have put at the end of each topic section.

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...and other unknown factors. 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 **2763 trial publications** summarised in the 16 editions of this book. It is interesting to see the evolution of trials this year: the topics change over the years: this year more complex and nuanced trials on second-line therapy for treatment failure HIV, clarifications of the diverse effects of many interventions, trials on chronic conditions such as nephrotic syndrome and coeliac disease, trials of new interventions for old diseases (such as pancreatic enzymes or clofibrate), trials on reducing child abuse, child labour and domestic violence, and trials of health literacy in schools and communities.

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It is encouraging to see the evaluation of the developmental, psychological and mental health effects of interventions. Also encouraging is the increased number of trials that include adolescents, the recognition of maternal nutrition and physical and mental health to infant outcomes, and trials of various ways to improve education. Research gaps still exist in many areas, including on appropriate health care models for the management of common chronic childhood conditions such as epilepsy, asthma, and neurodevelopmental problems; and quality improvement research on how best to provide acute and chronic care for children in remote health care settings.

More support is needed for clinical research capacity in low income countries. More than ever a focus on understanding and reducing inequity is needed if child health is to improve, and clinical and public health researchers have a role to play in this.

Trevor Duke  
August 2018

## Acute respiratory infection

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

### Prevention of pneumonia

(see Vaccines – Pneumococcal)

### Treatment of pneumonia

[J Glob Health](#). 2018 Jun;8(1):010418. doi: 10.7189/jogh.08.010418.

#### **Zinc as an adjunct therapy in the management of severe pneumonia among Gambian children: randomized controlled trial.**

[Howie S](#), [Bottomley C](#), [Chimah O](#), [Ideh R](#), [Ebruke B](#), [Okomo U](#), [Onyeama C](#), [Donkor S](#), [Rodrigues O](#), [Tapgun M](#), [Janneh M](#), [Oluwalana C](#), [Kuti B](#), [Enwere G](#), [Esangbedo P](#), [Doherty C](#), [Mackenzie G](#), [Greenwood B](#), [Corrah T](#), [Prentice A](#), [Adegbola R](#), [Zaman S](#)

#### **BACKGROUND:**

The benefit of zinc as an adjunct therapy for severe pneumonia is not established. We assessed the benefit of adjunct zinc therapy for severe pneumonia in children and determined whether the study children were zinc deficient.

#### **METHODS:**

This was a randomized, parallel group, double-blind, placebo-controlled trial with an allocation ratio of 1:1 conducted in children with severe pneumonia to evaluate the efficacy of daily zinc as an adjunct treatment in preventing 'treatment failure' (presence of any sign of severe pneumonia) on day-5 and day-10 and in reducing the time to resolution of signs of severe pneumonia. Six hundred and four children 2-59 months of age presenting with severe pneumonia at six urban and rural health care facilities in The Gambia were individually randomised to receive placebo (n = 301) or zinc (n = 303) for seven days. To determine if the study children were zinc deficient, supplementation was continued in a randomly selected subgroup of 121 children from each arm for six months post-enrolment, and height-gain, nutritional status, plasma zinc concentrations, and immune competence were compared.

#### **RESULTS:**

Percentage of treatment failure were similar in placebo and zinc arms both on day 5 (14.0% vs 14.1%) and day 10 (5.2% vs 5.9%). The time to recovery from lower chest wall indrawing and sternal retraction was longer in the placebo compared to zinc arm (24.4 vs 23.0 hours;  $P = 0.011$  and 18.7 vs 11.0 hours;  $P = 0.006$  respectively). The time to resolution for all respiratory symptoms of severity was not significantly different between placebo and zinc arms (42.3 vs 30.9 hours respectively;  $P = 0.242$ ). In the six months follow-up sub-group, there was no significant difference in height gain, height-for-age and weight-for-height Z-scores, mid upper arm circumference, plasma zinc concentrations, and energy at six months post-enrolment.

#### **CONCLUSIONS:**

In this population, **zinc given as an adjunct treatment for severe pneumonia showed no benefit in treatment failure rates**, or clinically important benefit in time to recovery from respiratory symptoms and showed marginal benefit in rapidity of resolution of some signs of severity. This finding does not support routine use of zinc as an adjunct treatment in severe pneumonia in generally zinc replete children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5908397/pdf/jogh-08-010418.pdf>

[J Trop Pediatr](#). 2018 Apr 1;64(2):110-117. doi: 10.1093/tropej/fmx036.

**Efficacy of Oral Zinc Supplementation in Radiologically Confirmed Pneumonia: Secondary Analysis of a Randomized Controlled Trial.**

[Bagri NK](#), [Bagri N](#), [Jana M](#), [Gupta AK](#), [Wadhwa N](#), [Lodha R](#), [Kabra SK](#), [Chandran A](#), [Aneja S](#), [Chaturvedi MK](#), [Sodhi J](#), [Fitzwater SP](#), [Chandra J](#), [Rath B](#), [Kainth US](#), [Saini S](#), [Black RE](#), [Santosham M](#), [Bhatnagar S](#).

**OBJECTIVE:**

To evaluate the effect of zinc as an adjuvant therapy in radiologically confirmed pneumonia in children 2-24 months of age.

**PATIENTS AND METHODS:**

We analyzed data of 212 children with pneumonia for whom chest X-ray films were available at enrollment and at least two radiologists agreed on the diagnosis of pneumonia. We compared the time to recovery in the two groups (n = 121, zinc group and n = 91, placebo group) using a Cox proportional hazards regression model.

**RESULTS:**

Time to recovery was similar in both groups [median interquartile range: zinc, 84 h (64, 140 h); placebo, 85 h (65, 140 h)]. The absolute risk reduction for treatment failure was 5.2% (95% confidence interval: -4.8, 15.1) with zinc supplementation.

**CONCLUSION:**

**There was no significant beneficial effect of zinc on the duration of recovery or risk of treatment failure in children with radiologically confirmed pneumonia.**

[Clin Nutr ESPEN](#). 2017 Aug;20:24-28. doi: 10.1016/j.clnesp.2017.02.003. Epub 2017 May 3.

**Therapeutic effect of vitamin D in acute lower respiratory infection: A randomized controlled trial.**

[Somnath SH](#), [Biswal N](#), [Chandrasekaran V](#), [Jagadisan B](#), [Bobby Z](#).

**OBJECTIVES:**

To study the effect of vitamin D supplementation on the outcome of acute lower respiratory infection in hospitalized children.

**STUDY DESIGN:**

This is an open label parallel group randomized trial. Total of 154 children aged 2 mo-5 yrs (mean age 13 mo) admitted with **acute lower respiratory infection (ALRI)** were randomized to receive standard care therapy alone or standard care therapy for the respiratory infection along with a single oral dose of 100,000 IU of vitamin D3. Serum 25(OH)D levels were measured at admission in all the children and 72 h after administration of vitamin D in the supplemented group. Primary outcome measured was the duration of hospital stay. Secondary outcomes measured were mortality, incidence of complications, admission to PICU and recurrence of respiratory infections within 90 days of discharge. Primary outcome was compared using Mann Whitney U test and secondary outcomes were compared using chi-square or Fischer's exact test.

**RESULTS:**

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Baseline characteristics were comparable between the two groups. There was no statistically significant difference in the primary outcome (Median duration of hospital stay in both the groups) and also in secondary outcomes (mortality, PICU admission, complications and recurrence of respiratory infections within 90 days of discharge).

### CONCLUSION:

**Single oral dose of 100,000 IU of vitamin D<sub>3</sub> did not lead to reduction in duration of hospital stay, mortality, PICU admission or complications related to ALRI** when compared to standard therapy alone in under five children hospitalized with ALRI but was able to achieve serum vitamin D sufficiency within 72 h of administration. Registered under clinical trial Registry of India Identifier no: CTRI/2014/09/005032.

[Physiother Res Int](#). 2018 Jan;23(1). doi: 10.1002/pri.1690. Epub 2017 Jul 19.

### [Assisted autogenic drainage in infants and young children hospitalized with uncomplicated pneumonia, a pilot study.](#)

[Corten L](#), [Jelsma J](#), [Human A](#), [Rahim S](#), [Morrow BM](#).

### BACKGROUND AND PURPOSE:

Pneumonia is the most important respiratory problem in low-to-middle income countries. Airway clearance therapy continues to be used in children with pneumonia and secretion retention; however, there is lack of evidence to support or reject this treatment. This study aimed to investigate the feasibility of a randomized controlled trial (RCT) on the efficacy and safety of assisted autogenic drainage (AAD) compared to standard nursing care in children hospitalized with uncomplicated pneumonia.

### METHODS:

A single-blinded pilot RCT was conducted on 29 children (median age 3.5 months, IQR 1.5-9.4) hospitalized with uncomplicated pneumonia. The intervention group received standard nursing care with additional bi-daily AAD, for 10 to 30 min. The control group only received standard nursing care, unless otherwise deemed necessary by the physician or physiotherapist. The primary outcome measure was duration of hospitalization. The secondary outcome measures included days of fever and supplemental oxygen support; respiratory rate (RR) and heart rate adjusted for age; RR and oxygen saturation pre-, post-, and 1-hr post-treatment; oxygen saturation; adverse events; and mortality.

### RESULTS:

No difference was found for duration of hospitalization (median 7.5 and 7.0 days for the control and intervention groups, respectively); however, Kaplan-Meier analysis revealed a strong tendency towards a shorter time to discharge in the intervention group ( $p = .06$ ). No significant differences were found for the other outcome measures at time of discharge. No adverse events were reported. Within the intervention group, a significant reduction in RR adjusted for age was found.

### DISCUSSION:

As no adverse events were reported, and AAD did not prolong hospitalization; AAD might be considered as safe and effective in young children with uncomplicated pneumonia. However, a larger multicentred RCT is warranted to determine the efficacy of AAD compared to standard nursing care.

<https://onlinelibrary.wiley.com/doi/full/10.1002/pri.1690>



## Oxygen therapy

[Trials](#). 2017 Oct 27;18(1):502. doi: 10.1186/s13063-017-2241-8.

### **Improving oxygen therapy for children and neonates in secondary hospitals in Nigeria: study protocol for a stepped-wedge cluster randomised trial.**

[Graham HR](#), [Ayede AI](#), [Bakare AA](#), [Oyewole OB](#), [Peel D](#), [Gray A](#), [McPake B](#), [Neal E](#), [Qazi S](#), [Izadnegahdar R](#), [Falade AG](#), [Duke T](#).

#### **BACKGROUND:**

Oxygen is a life-saving, essential medicine that is important for the treatment of many common childhood conditions. Improved oxygen systems can reduce childhood pneumonia mortality substantially. However, providing oxygen to children is challenging, especially in small hospitals with weak infrastructure and low human resource capacity.

#### **METHODS/DESIGN:**

This trial will evaluate the implementation of improved oxygen systems at secondary-level hospitals in southwest Nigeria. The improved oxygen system includes: a standardised equipment package; training of clinical and technical staff; infrastructure support (including improved power supply); and quality improvement activities such as supportive supervision. Phase 1 will involve the introduction of pulse oximetry alone; phase 2 will involve the introduction of the full, improved oxygen system package. We have based the intervention design on a theory-based analysis of previous oxygen projects, and used quality improvement principles, evidence-based teaching methods, and behaviour-change strategies. We are using a stepped-wedge cluster randomised design with participating hospitals randomised to receive an improved oxygen system at 4-month steps (three hospitals per step). Our mixed-methods evaluation will evaluate effectiveness, impact, sustainability, process and fidelity. Our primary outcome measures are childhood pneumonia case fatality rate and inpatient neonatal mortality rate. Secondary outcome measures include a range of clinical, quality of care, technical, and health systems outcomes. The planned study duration is from 2015 to 2018.

#### **DISCUSSION:**

Our study will provide quality evidence on the effectiveness of improved oxygen systems, and how to better implement and scale-up oxygen systems in resource-limited settings. Our results should have important implications for policy-makers, hospital administrators, and child health organisations in Africa and globally.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5659007/>

## Bronchiolitis

[Indian Pediatr](#). 2018 Jan 15;55(1):27-30. Epub 2018 Sep 26.

### **Nasal Continuous Positive Airway Pressure in Bronchiolitis: A Randomized Controlled Trial.**

[Lal SN](#), [Kaur J](#), [Anthwal P](#), [Goyal K](#), [Bahl P](#), [Puliyel JM](#).

#### **OBJECTIVE:**

To evaluate the efficacy of nasal continuous positive airway pressure (nCPAP) in decreasing respiratory distress in bronchiolitis.

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### DESIGN:

Randomized controlled trial.

### SETTING:

Tertiary-care hospital in New Delhi, India. Participants: 72 infants (age <1y) hospitalized with a clinical diagnosis of bronchiolitis were randomized to receive standard care, or nCPAP in addition to standard care, in the first hour after admission. 23 parents refused to give consent for participation. 2 infants did not tolerate nCPAP.

### PARTICIPANTS:

72 infants (age <1y) hospitalized with a clinical diagnosis of bronchiolitis were randomized to receive standard care, or nCPAP in addition to standard care, in the first hour after admission. 23 parents refused to give consent for participation. 2 infants did not tolerate nCPAP.

### INTERVENTION:

The outcome was assessed after 60 minutes. If nCPAP was not tolerated or the distress increased, the infant was switched to standard care. Analysis was done on intention-to-treat basis.

### MAIN OUTCOME MEASURES:

Change in respiratory rate, Silverman-Anderson score and a Modified Pediatric Society of New Zealand Severity Score.

### RESULTS:

14 out of 32 in nCPAP group and 5 out of 35 in standard care group had change in respiratory rate  $\geq 10$  (P=0.008). The mean (SD) change in respiratory rate [8.0 (5.8) vs 5.1 (4.0), P=0.02] in Silverman-Anderson score [0.78 (0.87) vs 0.39 (0.73), P=0.029] and in Modified Pediatric Society of New Zealand Severity Score [2.5 (3.01) vs. 1.08 (1.3), P=0.012] were significantly different in the nCPAP and standard care groups, respectively.

### CONCLUSIONS:

nCPAP helped reduce respiratory distress significantly compared to standard care.

## Adolescent health

### Adolescents and HIV prevention and treatment

[Glob Pediatr Health](#). 2018 Jan 24;5:2333794X18754452. doi: 10.1177/2333794X18754452. eCollection 2018.

### [Preliminary Impacts of an HIV-Prevention Program Targeting Out-of-School Youth in Postconflict Liberia.](#)

[Kennedy SB](#), [Atwood K](#), [Harris AO](#), [Taylor CH](#), [Shamblen S](#), [Nagbe WM](#), [Gobeh ME](#), [Sosu F](#), [Tegli JK](#), [Morris CA](#).

Adolescents in Sub-Saharan Africa account for greater HIV/STI (human immuno deficiency virus/sexually transmitted infection) burdens and difficult-to-reach populations. This study implemented a community-based HIV/STI program to reach at-risk youth aged 15 to 17 years in postconflict Liberia. Using a randomized controlled trial, community youths were assigned to an adapted version of an effective HIV/STI program, Making Proud Choices, or attention-matched comparison curriculum, General Health Program. Both programs were of similar doses, reach and coverage, and administered in classroom settings by trained health educators. The findings suggest that the adapted HIV/STI program had positive effects on knowledge, sexual refusal and condom use self-efficacy, condom negotiation self-efficacy, positive condom attitudes, parental communication about sex, and negative condom attitudes over time. Culturally adapted

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community-based, behavioral-driven programs can positively affect mediators of sexual behaviors in at-risk adolescents in postconflict settings. This is the first published report of an evidence-based HIV/STI program on sexual risk-taking behaviors of community youths in Liberia.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5788126/>

[Prev Sci.](#) 2017 Nov;18(8):955-963. doi: 10.1007/s11121-017-0827-8.

### [Process Evaluation of a Clinical Trial to Test School Support as HIV Prevention Among Orphaned Adolescents in Western Kenya.](#)

[Hallfors DD](#), [Cho H](#), [Hartman S](#), [Mbai I](#), [Ouma CA](#), [Halpern CT](#).

Orphaned adolescents are a large and vulnerable population in sub-Saharan Africa, at higher risk for HIV than non-orphans. Yet prevention of new infection is critical for adolescents since they are less likely than adults to enter and remain in treatment and are the only age group with rising AIDS death rates. We report process evaluation for a randomized controlled trial (RCT) testing support to stay in school (tuition, uniform, nurse visits) as an HIV prevention strategy for orphaned Kenyan adolescents. The RCT found no intervention effect on HIV/HSV-2 biomarker outcomes. With process evaluation, we examined the extent to which intervention elements were implemented as intended among the intervention group (N = 412) over the 3-year study period (2012-2014), the implementation effects on school enrollment (0-9 terms), and whether more time in school impacted HIV/HSV-2. All analyses examined differences as a whole, and by gender. Findings indicate that school fees and uniforms were fully implemented in 94 and 96% of cases, respectively. On average, participants received 79% of the required nurse visits. Although better implementation of nurse visits predicted more terms in school, a number of terms did not predict the likelihood of HIV/HSV-2 infection. Attending boarding school also increased number of school terms, but reduced the odds of infection for boys only. Four previous RCTs have been conducted in sub-Saharan Africa, and only one found limited evidence of school impact on adolescent HIV/HSV-2 infection. Our findings add further indication that the association between school support and HIV/HSV-2 prevention appears to be weak or under-specified.

[Prev Sci.](#) 2017 Nov;18(8):943-954. doi: 10.1007/s11121-017-0817-x.

### [A School Support Intervention and Educational Outcomes Among Orphaned Adolescents: Results of a Cluster Randomized Controlled Trial in Kenya.](#)

[Cho H](#), [Catherine Ryberg R](#), [Hwang K](#), [Pearce LD](#), [Iritani BJ](#).

Globally, significant progress has been made in primary school enrollment. However, there are millions of adolescents-including orphans in sub-Saharan Africa-who still experience barriers to remaining in school. **We conducted a 4-year cluster randomized controlled trial (cRCT) (N = 835) in a high HIV prevalence area in western Kenya to test whether providing orphaned adolescents with a school support intervention improves their educational outcomes.** The school support intervention consisted of **directly paying tuition, exam fees, and uniform costs to primary and secondary schools for those students who remained enrolled.** In addition, research staff monitored intervention participants' school attendance and

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helped to address barriers to staying in school. This school support intervention had significant positive impacts on educational outcomes for orphaned adolescents. Over the course of the study, **school absence remained stable for intervention group participants** but increased in frequency for control group participants. Intervention group participants were less likely to drop out of school compared to the control group. Furthermore, the intervention participants were more likely to make age-appropriate progression in grade, matriculate into secondary school, and achieve higher levels of education by the end of the study. The intervention also increased students' expectations of graduating from college in the future. However, we found no significant intervention impact on primary and secondary school test scores. Results from this RCT suggest that **directly covering school-related expenses for male and female orphaned adolescents in western Kenya can improve their educational outcomes.**

[AIDS](#). 2017 Sep 24;31(15):2127-2134. doi: 10.1097/QAD.0000000000001584.

### **The effect of school attendance and school dropout on incident HIV and HSV-2 among young women in rural South Africa enrolled in HPTN 068.**

[Stoner MCD](#), [Pettifor A](#), [Edwards JK](#), [Aiello AE](#), [Halpern CT](#), [Julien A](#), [Selin A](#), [Twine R](#), [Hughes JP](#), [Wang J](#), [Agvei Y](#), [Gomez-Olive FX](#), [Wagner RG](#), [MacPhail C](#), [Kahn K](#).

#### **OBJECTIVE:**

To estimate the association between school attendance, school dropout, and risk of incident HIV and herpes simplex virus type 2 (HSV-2) infection among young women.

#### **DESIGN:**

We used **longitudinal data from a randomized controlled trial in rural Mpumalanga province**, South Africa, to assess the association between school days attended, school dropout, and incident HIV and HSV-2 in young women aged 13-23 years.

#### **METHODS:**

We examined inverse probability of exposure weighted survival curves and used them to calculate 1.5, 2.5, and 3.5-year risk differences and risk ratios for the effect of school attendance on incident HIV and HSV-2. A marginal structural Cox model was used to estimate hazard ratios for the effect of school attendance and school dropout on incident infection.

#### **RESULTS:**

**Risk of infection** increased over time as young women aged, and was **higher in young women with low school attendance (<80% school days) compared with high (≥80% school days). Young women with low attendance were more likely to acquire HIV [hazard ratio (HR): 2.97; 95% confidence interval (CI): 1.62, 5.45] and HSV-2 (HR: 2.47; 95% CI: 1.46, 4.17) over the follow-up period than young women with high attendance.** Similarly, young women who dropped out of school had a higher weighted hazard of both HIV (HR 3.25 95% CI: 1.67, 6.32) and HSV-2 (HR 2.70; 95% CI 1.59, 4.59).

#### **CONCLUSION:**

**Young women who attend more school days and stay in school have a lower risk of incident HIV and HSV-2 infection.** Interventions to increase frequency of school attendance and prevent dropout should be promoted to reduce risk of infection.

[AIDS](#). 2017 Jul 1;31 Suppl 3:S221-S232. doi: 10.1097/QAD.0000000000001530.

**Community intervention improves knowledge of HIV status of adolescents in Zambia: findings from HPTN 071-PopART for youth study.**

Shanaube K, Schaap A, Chaila MJ, Floyd S, Mackworth-Young C, Hoddinott G, Hayes R, Fidler S, Ayles H; HPTN 071 (PopART) Study Team.

**OBJECTIVE:**

To determine the uptake of home-based HIV counselling and testing (HCT) in four communities of the HPTN 071 (PopART) trial in Zambia among adolescents aged 15-19 years and explore factors associated with HCT uptake.

**DESIGN:**

The PopART for youth study is a three-arm community-randomized trial in 12 communities in Zambia and nine communities in South Africa which aims to evaluate the acceptability and uptake of a HIV prevention package, including universal HIV testing and treatment, among young people. The study is nested within the HPTN 071 (PopART) trial.

**METHODS:**

Using a door-to-door approach that includes systematically revisiting households, all adolescents enumerated were offered participation in the intervention and verbal consent was obtained. Data were analysed from October 2015 to September 2016.

**RESULTS:**

Among 15456 enumerated adolescents, 11 175 (72.3%) accepted the intervention. HCT uptake was 80.6% (8707/10809) and was similar by sex. Adolescents that knew their HIV-positive status increased almost three-fold, from 75 to 210. Following visits from community HIV care providers, knowledge of HIV status increased from 27.6% (3007/10884) to 88.5% (9636/10884). HCT uptake was associated with community, age, duration since previous HIV test; other household members accepting HCT, having an HIV-positive household member, circumcision, and being symptomatic for STIs.

**CONCLUSION:**

**Through a home-based approach of offering a combination HIV prevention package, the proportion of adolescents who knew their HIV status increased from ~28 to 89% among those that accepted the intervention.** Delivering a community-level door-to-door combination, HIV prevention package is acceptable to many adolescents and can be effective if done in combination with targeted testing.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5497780/>

J Acquir Immune Defic Syndr. 2018 May 22. doi: 10.1097/QAI.0000000000001766. [Epub ahead of print]

**Does partner selection mediate the relationship between school attendance and HIV/HSV-2 among adolescent girls and young women in South Africa: An analysis of HPTN 068 data.**

Stoner MC, Edwards JK, Miller WC, Aiello AE, Halpern CT, Julien A, Rucinski KB, Selin A, Twine R, Hughes JP, Wang J, Agyei Y, Gómez-Olivé FX, Wagner RG, Laeyendecker O, Macphail C, Kahn K, Pettifor A.

School attendance prevents HIV and HSV-2 in adolescent girls and young women (AGYW) but the mechanisms to explain this relationship remain unclear. Our study assesses the extent to

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which characteristics of sex partners, partner age and number, mediate the relationship between attendance and risk of infection in AGYW in South Africa.

### DESIGN:

We use longitudinal data from the HPTN 068 randomized controlled trial in rural South Africa where girls were enrolled in early adolescence and followed in the main trial for over three years. We examined older partners and number of partners as possible mediators.

### METHODS:

We use the parametric g-formula to estimate 4-year risk differences for the effect of school attendance on cumulative incidence of HIV/HSV-2 overall and the controlled direct effect (CDE) for mediation. We examined mediation separately and jointly for the mediators of interest.

### RESULTS:

**We found that young women with high attendance in school had a lower cumulative incidence of HIV compared to those with low attendance (risk difference=-1.6%).** Partner age difference (CDE=-1.2%) and number of partners (CDE=-0.4%) mediated a large portion of this effect. In fact, when we accounted for the mediators jointly, the effect of schooling on HIV was almost removed showing full mediation (CDE= -0.3%). The same patterns were observed for the relationship between school attendance and cumulative incidence of HSV-2 infection.

### CONCLUSION:

**Increasing school attendance reduces risk of acquiring HIV and HSV-2.** Our results indicate the importance of school attendance in reducing partner number and partner age difference in this relationship.

### Comment

Similar prior publications by the first author using the same data source include: Stoner M.C.D, Edwards J, Miller W, Aiello A, Halpern C, Selin A, Hughes J, Wang J, Laeyendecker O, Agyei Y, McPhail C, Kahn K, Pettifor A.(2017) The effect of schooling on incident HIV and HSV-2 infection in young South African women enrolled in HPTN 068. AIDS. 24;31(15):2127-213.

[Prev Sci.](#) 2018 May 16. doi: 10.1007/s11121-018-0902-9. [Epub ahead of print]

### [HIV Risk Among Displaced Adolescent Girls in Ethiopia: the Role of Gender Attitudes and Self-Esteem.](#)

[Bermudez LG](#), [Yu G](#), [Lu L](#), [Falb K](#), [Eoomkham J](#), [Abdella G](#), [Stark L](#).

Adolescent girls in sub-Saharan Africa have been deemed one of the most critical populations to address in the campaign for an HIV-free generation. Experiences of intimate partner violence (IPV), harmful gender norms, diminished personal agency, and age-disparate sex have been identified as factors in the increasing rate of new infections among this population. Using baseline data from a cluster-randomized controlled trial in three refugee camps in Benishangul-Gumuz Regional State in Ethiopia, our study quantitatively examined the associations between HIV risk factors, attitudes on gender inequality, IPV acceptability, and self-esteem for female adolescent refugees primarily from Sudan and South Sudan (n = 919). In multivariate models, adjusting for age and education, results showed girls who were more accepting of gender inequitable norms and IPV had greater odds of ever experiencing forced (OR 1.40, CI 1.15-1.70; OR 1.66, CI 1.42-1.94) or transactional sex (OR 1.28, CI 1.05-1.55; OR 1.59, CI 1.37-1.85) compared to girls who demonstrated less approval. Higher self-esteem was associated with increased odds of condom use (OR 1.13, CI 1.02-1.24) as well as decreased odds of adolescent marriage (OR 0.93, CI 0.90-0.95), age-disparate sex (OR 0.90, CI 0.86-0.94),

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and transactional sex (OR 0.96, CI 0.93-0.99). The findings suggest acceptance of inequitable gender norms (including those that perpetuate violence against women) and low self-esteem to be associated with common HIV risk factors among refugee adolescents living in Ethiopia. Greater attention towards the intersections of gender equality and self-valuation is needed when seeking to understand HIV risk among refugee adolescent girls in sub-Saharan Africa.

[BMC Public Health](#). 2018 Jan 10;18(1):120. doi: 10.1186/s12889-018-5027-3.

### [Cash transfer interventions for sexual health: meanings and experiences of adolescent males and females in inner-city Johannesburg.](#)

[Khoza N](#), [Stadler J](#), [MacPhail C](#), [Chikandiwa A](#), [Brahmbhatt H](#), [Delany-Moretlwe S](#).

#### **BACKGROUND:**

In sub-Saharan Africa, there is growing interest in the use of cash transfer (CT) programs for HIV treatment and prevention. However, there is limited evidence of the consequences related to CT provision to adolescents in low-resourced urban settings. We explored the experiences of adolescents receiving CTs to assess the acceptability and unintended consequences of CT strategies in urban Johannesburg, South Africa.

#### **METHODS:**

We collected qualitative data during a pilot randomized controlled trial of three CT strategies (monthly payments unconditional vs. conditional on school attendance vs. a once-off payment conditional on a clinic visit) involving 120 adolescents aged 16-18 years old in the inner city of Johannesburg. Interviews were conducted in isiZulu, Sesotho or English with a sub-sample of 49 participants who adhered to study conditions, 6 months after receiving CT (280 ZAR/ 20 USD) and up to 12 months after the program had ended. Interviews were transcribed and translated by three fieldworkers. Codes were generated using an inductive approach; transcripts were initially coded based on emerging issues and subsequently coded deductively using Atlas.ti 7.4.

#### **RESULTS:**

CTs promoted a sense of independence and an adult social identity amongst recipients. CTs were used to purchase personal and household items; however, there were gender differences in spending and saving behaviours. Male participants' spending reflected their preoccupation with maintaining a public social status through which they asserted an image of the responsible adult. In contrast, female participants' expenditure reflected assumption of domestic responsibilities and independence from older men, with the latter highlighting CTs' potential to reduce transactional sexual partnerships. Cash benefits were short-lived, as adolescents reverted to previous behavior after the program's cessation.

#### **CONCLUSION:**

CT programs offer adolescent males and females in low-income urban settings a sense of agency, which is vital for their transition to adulthood. However, gender differences in the expenditure of CTs and the effects of ending CT programs must be noted, as these may present potential unintended risks.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5761158/>

[J Adolesc](#). 2017 Dec;61:64-76. doi: 10.1016/j.adolescence.2017.09.007. Epub 2017 Sep 29.

**Correlates of school dropout and absenteeism among adolescent girls from marginalized community in north Karnataka, south India.**

Prakash R, Beattie T, Javalkar P, Bhattacharjee P, Ramananik S, Thalinja R, Murthy S, Davey C, Blanchard J, Watts C, Collumbien M, Moses S, Heise L, Isac S.

Secondary education among lower caste adolescent girls living in rural Karnataka, South India, is characterized by high rates of school drop-out and absenteeism. A cross-sectional baseline survey (N=2275) was conducted in 2014 as part of a cluster-randomized control trial among adolescent girls (13-14 year) and their families from marginalized communities in two districts of north Karnataka. Bivariate and multivariate logistic regression models were used. Overall, 8.7% girls reported secondary school dropout and 8.1% reported frequent absenteeism (past month). In adjusted analyses, economic factors (household poverty; girls' work-related migration), social norms and practices (child marriage; value of girls' education), and school-related factors (poor learning environment and bullying/harassment at school) were associated with an increased odds of school dropout and absenteeism. Interventions aiming to increase secondary school retention among marginalized girls may require a multi-level approach, with synergistic components that address social, structural and economic determinants of school absenteeism and dropout.

<https://www.sciencedirect.com/science/article/pii/S0140197117301483?via%3Dihub>

PLoS One. 2017 Aug 17;12(8):e0180833. doi: 10.1371/journal.pone.0180833. eCollection 2017.

**Peer violence perpetration and victimization: Prevalence, associated factors and pathways among 1752 sixth grade boys and girls in schools in Pakistan.**

Karmaliani R, Mcfarlane J, Somani R, Khuwaja HMA, Bhamani SS, Ali TS, Gulzar S, Somani Y, Chirwa ED, Jewkes R.

**BACKGROUND:**

Child peer violence is a global problem and seriously impacts health and education. There are few research studies available in Pakistan, or South Asia. We describe the prevalence of peer violence, associations, and pathways between socio-economic status, school performance, gender attitudes and violence at home.

**METHODS:**

1752 children were recruited into a cluster randomized controlled trial conducted on 40 fairly homogeneous public schools (20 for girls and 20 for boys), in Hyderabad, Pakistan. This was ranging from 20-65 children per school. All children were interviewed with questionnaires at baseline.

**RESULTS:**

Few children had no experience of peer violence in the previous 4 weeks (21.7% of girls vs.7% of boys). Some were victims (28.6%, of girls vs. 17.9% of boys), some only perpetrated (3.3% of girls vs. 2.5%) but mostly they perpetrated and were victims (46.4%.of girls vs 72.6%. of boys). The girls' multivariable models showed that missing the last school day due to work, witnessing her father fight a man in the last month and having more patriarchal gender attitudes were associated with both experiencing violence and perpetration, while, hunger was associated with perpetration only. For boys, missing two or more days of school in the last month, poorer school performance and more patriarchal attitudes were associated with both victimization and



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perpetration. Witnessing father fight, was associated with peer violence perpetration for boys. These findings are additionally confirmed with structural models.

### DISCUSSION:

**Peer violence in Pakistan is rooted in poverty and socialization of children, especially at home.** A critical question is whether a school-based intervention can empower children to reduce their violence engagement in the context of poverty and social norms supportive of violence. In the political context of Pakistan, reducing all violence is essential and understanding the potential of schools as a platform for intervention is key.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5560651/>

## Allergy

(See Vitamin D, skin disease)

## Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

[PLoS One](https://doi.org/10.1371/journal.pone.0183977). 2017 Aug 30;12(8):e0183977. doi: 10.1371/journal.pone.0183977. eCollection 2017.

### [Delaying the start of iron until 28 days after antimalarial treatment is associated with lower incidence of subsequent illness in children with malaria and iron deficiency.](https://doi.org/10.1371/journal.pone.0183977)

[Jaramillo EG](#), [Mupere E](#), [Opoka RO](#), [Hodges JS](#), [Lund TC](#), [Georgieff MK](#), [John CC](#), [Cusick SE](#).

We evaluated the incidence of all-cause and malaria-specific clinic visits during follow-up of a recent trial of iron therapy. In the main trial, Ugandan children 6-59 months with smear-confirmed malaria and iron deficiency [zinc protoporphyrin (ZPP)  $\geq 80$   $\mu\text{mol/mol}$  heme] were treated for malaria and **randomized to start a 27-day course of oral iron concurrently with (immediate group) or 28 days after (delayed group) antimalarial treatment.**

All children were followed for the same 56-day period starting at the time of antimalarial treatment (Day 0) and underwent passive and active surveillance for malaria and other morbidity for the entire follow-up period. All ill children were examined and treated by the study physician. In this secondary analysis of morbidity data from the main trial, we report that although the incidence of malaria-specific visits did not differ between the groups, **children in the immediate group had a higher incidence rate ratio of all-cause sick-child visits to the clinic during the follow-up period (Incidence Rate Ratio (IRR) immediate/delayed = 1.76; 95% CI: 1.05-3.03, p = 0.033).** Although these findings need to be tested in a larger trial powered for malaria-specific morbidity, these preliminary results suggest that **delaying iron by 28 days in children with coexisting malaria and iron deficiency is associated with a reduced risk of subsequent all-cause illness.**

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576757/>

[PLoS One](#). 2018 Jan 4;13(1):e0187663. doi: 10.1371/journal.pone.0187663. eCollection 2018.

**[An evaluation of hemoglobin measurement tools and their accuracy and reliability when screening for child anemia in Rwanda: A randomized study.](#)**

[Parker M](#), [Han Z](#), [Abu-Haydar E](#), [Matsiko E](#), [Iyakaremye D](#), [Tuyisenge L](#), [Magaret A](#), [Lyambabaje A](#).

Blood hemoglobin (Hb) is a common indicator for diagnosing anemia and is often determined through laboratory analysis of venous samples. One alternative to laboratory-based methods is the handheld HemoCue® Hb 201+ device, which requires a finger prick and wicking of blood into a pretreated cuvette for analysis. An alternative HemoCue® gravity method is being investigated for improved accuracy. Further, recent developments in noninvasive technologies could provide an accurate, rapid, safe, point-of-care option for hemoglobin estimation while addressing some limitations of current tools, but device performance must be assessed in low-resource settings. This study evaluated the performance of two HemoCue® Hb 201+ blood sampling methods and a noninvasive device (Pronto® with DCI-mini™ sensors) in a Rwandan pediatric clinic. **Reference hemoglobin values were determined in 132 children 6 to 59 months of age by using a standard hematology analyzer (Sysmex KN21™). Half were tested using the HemoCue® wicking method; half were tested using the HemoCue® gravity method; and 112 had successful hemoglobin readings with Pronto® DCI-mini™.** Statistical analysis was used to assess the level of bias generated by each method and the key drivers of bias. The HemoCue® gravity method was the least biased. The HemoCue® wicking and Pronto® methods biases were inversely related to the Sysmex KN21™ results. Both HemoCue® sampling methods correctly classified patients' anemic status in 80% or more of instances, whereas the Pronto® device had a correct classification rate of only 69%. The HemoCue® gravity method was more accurate than the traditional HemoCue® wicking method in this study, but its accuracy and operational feasibility should be confirmed by future studies. The Pronto® DCI-mini™ devices showed considerable promise but require further improvements in sensitivity and specificity before wider adoption.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754049/>

[BMJ Open](#). 2017 Nov 15;7(11):e018325. doi: 10.1136/bmjopen-2017-018325.

**[Benefits and risks of Iron interventions in children \(BRISC\): protocol for a three-arm parallel-group randomised controlled field trial in Bangladesh.](#)**

[Hasan MI](#), [Hossain SJ](#), [Baat S](#), [Dibley MJ](#), [Fisher J](#), [Grantham-McGregor S](#), [Tofail F](#), [Simpson JA](#), [Arifeen SE](#), [Hamadani J](#), [Biggs BA](#), [Pasricha SR](#).

**INTRODUCTION:**

Anaemia is a major global health problem affecting about 43% of preschool children globally and 60% of 6-24-month-old children in rural Bangladesh, half of which is attributed to iron deficiency (ID). Although WHO recommends universal supplementation with iron or home fortification with iron-containing multiple micronutrient powders (MMPs) to children under 2 years, evidence for benefits of these interventions on childhood development (a key rationale for these interventions) and harms (especially infection) remains limited. This study aims to evaluate the impact of iron or MMPs supplementation compared with placebo on

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(a) children's development, (b) growth, (c) morbidity from infections and (d) haematological and iron indices.

### METHODS AND ANALYSIS:

This study is a three-arm, blinded, double-dummy, parallel-group, placebo-controlled superiority trial using stratified individual block randomisation. The trial will randomise 3300 children aged 8-9 months equally to arm 1: iron syrup (12.5 mg elemental iron), placebo MMPs; arm 2: MMPs (including 12.5 mg elemental iron), placebo syrup; and arm 3: placebo syrup, placebo MNPs. Children will receive interventions for 3 months based on WHO recommendations and then be followed up for 9 months post intervention. The primary outcome is cognitive composite score measured by Bayley III. Secondary outcomes include motor and language composite score by Bayley III, behaviour rating using selected items from Wolke's rating scales and BSID-II behaviour ratings, temperament, growth, haemoglobin, anaemia and iron status, and infectious morbidity. Outcomes will be measured at baseline, at the end of 3-month intervention and after 9 months postintervention follow-up.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC29146650/>

[Nutrients](#). 2017 Jul 14;9(7). pii: E759. doi: 10.3390/nu9070759.

### [Iron Fortified Complementary Foods Containing a Mixture of Sodium Iron EDTA with Either Ferrous Fumarate or Ferric Pyrophosphate Reduce Iron Deficiency Anemia in 12- to 36-Month-Old Children in a Malaria Endemic Setting: A Secondary Analysis of a Cluster-Randomized Controlled Trial.](#)

[Glinz D](#), [Wegmüller R](#), [Ouattara M](#), [Diakitè VG](#), [Aaron GJ](#), [Hofer L](#), [Zimmermann MB](#), [Adiossan LG](#), [Utzinger J](#), [N'Goran EK](#), [Hurrell RF](#).

Iron deficiency anemia (IDA) is a major public health problem in sub-Saharan Africa. The efficacy of iron fortification against IDA is uncertain in malaria-endemic settings. **The objective of this study was to evaluate the efficacy of a complementary food (CF) fortified with sodium iron EDTA (NaFeEDTA) plus either ferrous fumarate (FeFum) or ferric pyrophosphate (FePP) to combat IDA in preschool-age children in a highly malaria endemic region.** This is a secondary analysis of a nine-month cluster-randomized controlled trial conducted in south-central Côte d'Ivoire. **378 children aged 12-36 months were randomly assigned to no food intervention ( $n = 125$ ; control group), CF fortified with 2 mg NaFeEDTA plus 3.8 mg FeFum for six days/week ( $n = 126$ ; FeFum group), and CF fortified with 2 mg NaFeEDTA and 3.8 mg FePP for six days/week ( $n = 127$ ; FePP group).** The outcome measures were hemoglobin (Hb), plasma ferritin (PF), iron deficiency (PF < 30 µg/L), and anemia (Hb < 11.0 g/dL). Data were analyzed with random-effect models and PF was adjusted for inflammation. The prevalence of *Plasmodium falciparum* infection and inflammation during the study were 44-66%, and 57-76%, respectively. There was a significant time by treatment interaction on IDA ( $p = 0.028$ ) and a borderline significant time by treatment interaction on iron deficiency with or without anemia ( $p = 0.068$ ). IDA prevalence sharply decreased in the FeFum (32.8% to 1.2%,  $p < 0.001$ ) and FePP group (23.6% to 3.4%,  $p < 0.001$ ). However, there was no significant time by treatment interaction on Hb or total anemia. These data indicate that, despite the high endemicity of malaria and elevated inflammation biomarkers (C-reactive protein or  $\alpha$ -1-acid-glycoprotein), **IDA was markedly reduced by provision of iron fortified CF to preschool-age children for 9 months, with no significant differences between a combination of NaFeEDTA with FeFum or NaFeEDTA with FePP.**

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However, there was no overall effect on anemia, suggesting most of the anemia in this setting is not due to ID.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC28708072/>

[Clin Nutr.](#) 2017 Aug;36(4):986-991. doi: 10.1016/j.clnu.2016.07.002. Epub 2016 Jul 18.

### **Supplementation of vitamin B12 or folic acid on hemoglobin concentration in children 6-36 months of age: A randomized placebo controlled trial.**

[Kumar T](#), [Taneja S](#), [Sachdev HPS](#), [Refsum H](#), [Yajnik CS](#), [Bhandari N](#), [Strand TA](#);

#### **BACKGROUND & AIMS:**

The main objective of this report is to **measure to what extent folate or vitamin B12 given daily for 6 months to young North Indian Children improves hemoglobin (Hb) concentration.**

#### **METHODS:**

In a randomized placebo controlled trial in low-to-middle income neighborhoods in New Delhi, India, children were randomized into four groups in a 1:1:1:1 ratio and supplemented daily for 6 months with 2 RDAs of vitamin B12, folic acid, both, or placebo. All children with anemia at baseline were given iron supplementation daily for 2 months. We measured the plasma concentrations of soluble transferrin receptor (sTfR), folate, vitamin B12, total homocysteine (tHcy) and Hb in 262 children.

#### **RESULTS:**

**Mean Hb concentration decreased in all four study groups during the six months of follow up and supplementation of either or both of the vitamins did not improve the Hb concentration. Iron supplements for the initial 2 mo had limited effect on anemia at 6 mo as almost 90% were still anemic at study end.**

#### **CONCLUSION:**

Supplementation of folic acid and/or vitamin B12 for 6 months does not improve Hb concentration in young children. Our findings do not argue for widespread vitamin B12 or folic acid supplementation to combat anemia. Our results also call for alternative strategies to improve iron status and treat iron deficiency anemia.

[MC Public Health.](#) 2017 Sep 25;17(1):738. doi: 10.1186/s12889-017-4755-0.

### **The effect of a micronutrient powder home fortification program on anemia and cognitive outcomes among young children in rural China: a cluster randomized trial.**

[Luo R](#), [Yue A](#), [Zhou H](#), [Shi Y](#), [Zhang L](#), [Martorell R](#), [Medina A](#), [Rozelle S](#), [Sylvia S](#).

#### **BACKGROUND:**

Anemia early in life has been associated with delayed cognitive and motor development. The WHO recommends home fortification using **multiple micronutrient powders (MNPs)** containing iron as a strategy to address anemia in children under two. We evaluated the effects of a program freely distributing MNP sachets to caregivers of infants in rural China.

#### **METHODS:**

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We conducted a cluster-randomized controlled trial in Shaanxi province, enrolling all children aged 6-11 months in target villages. Following a baseline survey, investigators randomly assigned each village/cluster to a control or treatment group. In the treatment group, caregivers were instructed to give MNPs daily. Follow-up was after 6, 12, and 18 months of intervention. Primary outcomes were hemoglobin concentrations and scores on the Bayley Scales of Infant Development.

### RESULTS:

One thousand, eight hundred and-two eligible children and their caregivers were enrolled. At baseline 48% (870) of children were anemic and 29% (529) were developmentally delayed. Six hundred and-ten children (117 villages) were assigned to the control group and 1192 children (234 villages) were assigned to the treatment group. **Assignment to the treatment group was associated with an improvement in hemoglobin levels (marginal effect 1.77 g/L, 95% CI 0.017-3.520, p-value = 0.048) and cognitive development (marginal effect 2.23 points, 95% CI 0.061-4.399, p-value = 0.044) after 6 months but not thereafter. There were no significant effects on motor development.** Zero effects after the first 6 months were not due to low compliance, low statistical power, or changes in feeding behavior. **Hemoglobin concentrations improved in both the treatment and control groups over the course of the study; however, 22% (325) of children remained anemic at endline, and 48% (721) were cognitively delayed.**

### CONCLUSIONS:

**Providing caregivers with MNP sachets modestly hastened improvement in hemoglobin levels** that was occurring absent intervention; however, this improvement did not translate into improved developmental outcomes at endline.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613507/>

[Nutrients](#). 2017 Sep 12;9(9). pii: E1002. doi: 10.3390/nu9091002.

### **A Micronutrient Fortified Beverage Given at Different Dosing Frequencies Had Limited Impact on Anemia and Micronutrient Status in Filipino Schoolchildren.**

[Angeles-Agdeppa I](#), [Magsadia CR](#), [Aaron GJ](#), [Lloyd BB](#), [Hilmers DC](#), [Bhutta ZA](#).

This study evaluated the effects of a multi-micronutrient fortified juice drink given in different frequencies of consumption on hemoglobin (Hb) concentration of schoolchildren. Hb was measured in 2423 schoolchildren aged 6- to 9-years-old at baseline. **All anemic children (n = 246) were randomly allocated into groups: Daily dose (HD: high dose), 5X/week (MD: Moderate Dose), 3X/week (LD: Low Dose) and unfortified (Control).** Pre- and post-study measurements of micronutrients were collected from 228 children. At the endpoint, significant Hb increases were observed in all groups, but there was no significant difference between groups. **There was a significant reduction in anemia prevalence in all groups from 100% to 36% (Control), 30% (LD), 23% (MD) and 26% (HD).** No dose-response effect was observed in Hb in this population. Most likely, this resulted from better than expected micronutrient status and lower than expected severity of anemia and micronutrient deficiencies in this cohort. It is unlikely that the addition of a fortified beverage to school feeding programs in this population would have a positive impact. Whether such an intervention would be cost-effective as a preventative approach needs to be assessed. This study demonstrates the importance of targeting such interventions to appropriate populations.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622762/>

## Anaesthesia and intensive care

(see also Asthma)

### Intensive care

(See also: Treatment of severe malaria; Intravenous fluids)

[Paediatr Anaesth.](#) 2017 Aug;27(8):810-815. doi: 10.1111/pan.13179. Epub 2017 Jun 6.

### [Effects of intraoperative liberal fluid therapy on postoperative nausea and vomiting in children-A randomized controlled trial.](#)

[Ashok V](#), [Bala I](#), [Bharti N](#), [Jain D](#), [Samujh R](#).

#### **BACKGROUND:**

Postoperative nausea and vomiting (PONV) is one of the most distressing complications following surgery. Supplemental perioperative fluid therapy might be an effective strategy to reduce PONV in children.

#### **OBJECTIVES:**

The study was conducted to evaluate the effects of intraoperative liberal fluid therapy with crystalloids on PONV in children.

#### **METHODS:**

In this randomized trial, a total of 150 children of 3-7 years undergoing lower abdominal and penile surgery under general anesthesia were randomly assigned into two groups. "**Restricted group**" received 10 mL kg<sup>-1</sup> h<sup>-1</sup> and "**Liberal group**" received 30 mL kg<sup>-1</sup> h<sup>-1</sup> infusion of **Ringer's lactate solution intraoperatively**. All patients received a caudal block and intravenous paracetamol for analgesia. No opioids and muscle relaxants were used. All episodes of nausea-vomiting and the requirement of rescue antiemetic were assessed during 24 hours postoperatively.

#### **RESULTS:**

**The incidence of PONV was significantly less in the liberal group patients as compared to the restricted group; 33 (45.8%) patients in the restricted group had vomiting as compared to 20 (27.4%) patients in the liberal group (RR 0.59, 95% CI: 0.38-0.93, P=.021).**

The adjusted odds ratio of PONV for the liberal group vs restricted group was 2.24 (95% CI: 1.12-4.48, P=.022). The incidence of fluid intake during the first 6 postoperative hours was significantly higher in the restricted group patients; 60 (83%) children in the restricted group complained of thirst as compared to 12 (17%) children in the liberal group (RR 0.19, 95% CI: 0.18-0.33, P=.0001). The parents of the liberal group were more satisfied as compared to the restricted group (mean difference -0.9, 95% CI: -1.8, -0.1, P=.04). None of the children had any complication attributed to the liberal fluid therapy.

#### **CONCLUSION:**

Liberal intraoperative fluid therapy was found to be effective in reducing PONV in children undergoing lower abdominal surgery.

## Antibiotics

### Azithromycin mass drug administration

\*\*\* [N Engl J Med](#). 2018 Apr 26;378(17):1583-1592. doi: 10.1056/NEJMoa1715474.

#### [Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa.](#)

[Keenan JD](#), [Bailey RL](#), [West SK](#), [Arzika AM](#), [Hart J](#), [Weaver J](#), [Kalua K](#), [Mrango Z](#), [Ray KJ](#), [Cook C](#), [Lebas E](#), [O'Brien KS](#), [Emerson PM](#), [Porco TC](#), [Lietman TM](#); [MORDOR Study Group](#)

#### **BACKGROUND:**

We hypothesized that mass distribution of a broad-spectrum antibiotic agent to preschool children would reduce mortality in areas of sub-Saharan Africa that are currently far from meeting the Sustainable Development Goals of the United Nations.

#### **METHODS:**

In this cluster-randomized trial, we **assigned communities in Malawi, Niger, and Tanzania to four twice-yearly mass distributions of either oral azithromycin (approximately 20 mg per kilogram of body weight) or placebo**. Children 1 to 59 months of age were identified in twice-yearly censuses and were offered participation in the trial. Vital status was determined at subsequent censuses. The primary outcome was aggregate all-cause mortality; country-specific rates were assessed in prespecified subgroup analyses.

#### **RESULTS:**

A total of 1533 communities underwent randomization, 190,238 children were identified in the census at baseline, and 323,302 person-years were monitored. The mean ( $\pm$ SD) azithromycin and placebo coverage over the four twice-yearly distributions was  $90.4\pm 10.4\%$ . The overall annual mortality rate was 14.6 deaths per 1000 person-years in communities that received azithromycin (9.1 in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1000 person-years in communities that received placebo (9.6 in Malawi, 27.5 in Niger, and 5.5 in Tanzania). **Mortality was 13.5% lower overall (95% confidence interval [CI], 6.7 to 19.8) in communities that received azithromycin than in communities that received placebo ( $P<0.001$ ); the rate was 5.7% lower in Malawi (95% CI, -9.7 to 18.9), 18.1% lower in Niger (95% CI, 10.0 to 25.5), and 3.4% lower in Tanzania (95% CI, -21.2 to 23.0)**. Children in the age group of 1 to 5 months had the greatest effect from azithromycin (24.9% lower mortality than that with placebo; 95% CI, 10.6 to 37.0). Serious adverse events occurring within a week after administration of the trial drug or placebo were uncommon, and the rate did not differ significantly between the groups. Evaluation of selection for antibiotic resistance is ongoing.

#### **CONCLUSIONS:**

Among postneonatal, preschool children in sub-Saharan Africa, childhood mortality was lower in communities randomly assigned to mass distribution of azithromycin than in those assigned to placebo, with the largest effect seen in Niger. Any implementation of a policy of mass distribution would need to strongly consider the potential effect of such a strategy on antibiotic resistance

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5849140/>

[Am J Trop Med Hyg](#). 2017 Sep;97(3):696-701. doi: 10.4269/ajtmh.16-0487. Epub 2017 Jul 19.

**Mass Azithromycin and Malaria Parasitemia in Niger: Results from a Community-Randomized Trial.**

O'Brien KS, Cotter SY, Amza A, Kadri B, Nassirou B, Stoller NE, Zhou Z, Cotter C, West SK, Bailey RL, Rosenthal PJ, Gaynor BD, Porco TC, Lietman TM.

Studies designed to determine the effects of mass administration of azithromycin on trachoma have suggested that mass azithromycin distributions may also reduce the prevalence of malaria. These studies have typically examined the impact of a small number of treatments over short durations. In this prespecified substudy of a cluster-randomized trial for trachoma, we compared malaria parasitemia prevalence in 24 communities in Niger randomized to receive either annual or biannual mass azithromycin distributions over 3 years. The 12 communities randomized to annual azithromycin received three treatments during the high-transmission season, and the 12 communities randomized to biannual azithromycin received a total of six treatments: three during the high-transmission season and three during the low-transmission season. Blood samples were taken to assess malariometric indices among children in all study communities at a single time point during the high-transmission season after 3 years of the intervention. **No significant differences were identified in malaria parasitemia, parasite density, or hemoglobin concentration between the annual and biannual treatment arms.** When compared with annual mass azithromycin alone, additional mass azithromycin distributions given during the low-transmission season did not significantly reduce the subsequent prevalence of malaria parasitemia or parasite density after 3 years, as measured during the high-transmission season.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5590561/>

Antibiotic resistance and stewardship

J Int AIDS Soc. 2017 Nov;20(3). doi: 10.1002/jia2.25021.

**Cotrimoxazole prophylaxis was associated with enteric commensal bacterial resistance among HIV-exposed infants in a randomized controlled trial, Botswana.**

Powis KM, Souda S, Lockman S, Ajibola G, Bennett K, Leidner J, Hughes MD, Moyo S, van Widenfelt E, Jibril HB, Makhema J, Essex M, Shapiro RL.

**INTRODUCTION:**

Despite declining risk of vertical HIV transmission, prophylactic cotrimoxazole (CTX) remains widely used to reduce morbidity and mortality in the event of HIV infection among exposed infants, with an inherent risk of conferring commensal antimicrobial resistance. Using data from a randomized, placebo-controlled trial of infant CTX prophylaxis, we sought to quantify emergence of antibiotic resistance.

**METHODS:**

**HIV-exposed uninfected infants enrolled in the Botswana Mpepu study were randomized to prophylactic CTX or placebo between 14 and 34 days of life and continued through 15 months.** Stool samples were collected from a subset of participating infants at randomization, three, and six months, and stored at -70°C prior to culture. Specimens that grew *Escherichia coli* (*E. coli*) or *Klebsiella* species (*Klebsiella* spp.) underwent antibiotic susceptibility testing by Kirby Bauer method using CTX (CTX 1.25/23.75 µg) and Amoxicillin



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(10 µg) in Mueller Hinton agar. Fisher's exact testing was used to compare prevalence of resistance by randomization arm (CTX/placebo).

### RESULTS AND DISCUSSION:

A total of 381 stool samples from 220 infants were cultured: 118 at randomization, 151 at three months, and 112 at six-months. *E. coli* was isolated from 206 specimens and *Klebsiella* spp. from 138 specimens. Resistance to CTX was common in both *E. coli* and *Klebsiella* spp. at the randomization visit (52.2% and 37.7% respectively) and did not differ by study arm. ***E. Coli* isolates from CTX recipients at three and six months had 94.9% and 84.2% CTX resistance, as compared with 51.4% and 57.5% CTX resistance in isolates from placebo recipients (p=0.01). *Klebsiella* spp. isolates from CTX recipients had 79.0% and 68.8% CTX resistance at three and six months, as compared with 19.1% and 14.3% in isolates from placebo recipients (p<0.01).**

### CONCLUSIONS:

**HIV-exposed infants randomized to CTX prophylaxis had increased CTX-resistant commensal gastrointestinal bacteria compared with placebo recipients.** Additional research is needed to determine the longer-term clinical, microbiologic, and public health consequences of antimicrobial resistance selected by infant CTX prophylaxis.

[Indexed for MEDLINE]

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5810322/>

[Lancet Glob Health](#). 2017 Dec;5(12):e1258-e1267. doi: 10.1016/S2214-109X(17)30383-2. Epub 2017 Nov 5.

### [Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial.](#)

[Wei X](#), [Zhang Z](#), [Walley JD](#), [Hicks JP](#), [Zeng J](#), [Deng S](#), [Zhou Y](#), [Yin J](#), [Newell JN](#), [Sun Q](#), [Zou G](#), [Guo Y](#), [Upshur REG](#), [Lin M](#).

### BACKGROUND:

Inappropriate antibiotic prescribing contributes to the generation of drug resistance worldwide, and is particularly common in China. We assessed the effectiveness of an antimicrobial stewardship programme aiming to reduce inappropriate antibiotic prescribing in paediatric outpatients by targeting providers and caregivers in primary care hospitals in rural China.

### METHODS:

We did a pragmatic, cluster-randomised controlled trial with a 6-month intervention period. Clusters were primary care township hospitals in two counties of Guangxi province in China, which were randomly allocated to the intervention group or the control group (in a 1:1 ratio in Rong county and in a 5:6 ratio in Liujiang county). Randomisation was stratified by county. Eligible participants were children aged 2-14 years who attended a township hospital as an outpatient and were given a prescription following a primary diagnosis of an upper respiratory tract infection. The intervention included clinician guidelines and training on appropriate prescribing, monthly prescribing peer-review meetings, and brief caregiver education. In hospitals allocated to the control group, usual care was provided, with antibiotics prescribed at the individual clinician's discretion. Patients were masked to their allocated treatment group but doctors were not. The primary outcome was the antibiotic prescription rate in children attending

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the hospitals, defined as the cluster-level proportion of prescriptions for upper respiratory tract infections in 2-14-year-old outpatients, issued during the final 3 months of the 6-month intervention period (endline), that included one or more antibiotics. The outcome was based on prescription records and analysed by modified intention-to-treat. This study is registered with the ISRCTN registry, number ISRCTN14340536.

### FINDINGS:

We recruited all 25 eligible township hospitals in the two counties (14 hospitals in Rong county and 11 in Liujiang county), and randomly allocated 12 to the intervention group and 13 to the control group. We implemented the intervention in three internal pilot clusters between July 1, 2015, and Dec 31, 2015, and in the remaining nine intervention clusters between Oct 1, 2016 and March 31, 2016. Between baseline (the 3 months before implementation of the intervention) and endline (the final 3 months of the 6-month intervention period) the antibiotic prescription rate at the individual level decreased from 82% (1936/2349) to 40% (943/2351) in the intervention group, and from 75% (1922/2548) to 70% (1782/2552) in the control group. After adjusting for the baseline antibiotic prescription rate, stratum (county), and potentially confounding patient and prescribing doctor covariates, this endline difference between the groups represented an intervention effect (absolute risk reduction in antibiotic prescribing) of -29% (95% CI -42 to -16;  $p=0.0002$ ).

### INTERPRETATION:

In China's primary care setting, pragmatic interventions on antimicrobial stewardship targeting providers and caregivers substantially reduced prescribing of antibiotics for childhood upper respiratory tract infections.

[https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(17\)30383-2/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30383-2/fulltext)

## Asthma and chronic lung disease

[Pediatr Emerg Care](#). 2018 Mar;34(3):160-164. doi: 10.1097/PEC.0000000000001184.

### Montelukast Treatment of Acute Asthma Exacerbations in Children Aged 2 to 5 Years: A Randomized, Double-Blind, Placebo-Controlled Trial.

[Wang X](#), [Zhou J](#), [Zhao X](#), [Yi X](#).

### BACKGROUND:

Although montelukast has an established role in the management of chronic asthma in children, its efficacy in acute asthma exacerbations (AAEs) in children aged 2 to 5 years is not fully known. This study aimed to evaluate the effectiveness and safety of montelukast for treating AAE in children aged 2 to 5 years in China.

### METHODS:

In total, 120 Chinese children with AAE, aged 2 to 5 years, were randomly divided into 2 groups, each with 60 patients. All patients received either montelukast or placebo along with standard therapy for acute asthma between January 2011 and December 2015. The outcome measurements included the difference in peak expiratory flow and lung function improvements, as well as adverse events.

### RESULTS:

A total of 117 patients completed the study. **Montelukast showed no greater effectiveness than did placebo in increasing the peak expiratory flow during the period of hospital stay ( $P = 0.92$  at day 2,  $P = 0.86$  at day 3, and  $P = 0.82$  at day 4) and at discharge ( $P = 0.84$ ).**

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Similarly, the forced expiratory volume in 1 second at discharge also did not show significant difference between the 2 groups ( $P = 0.80$ ). In addition, no serious adverse events were found during the intervention period of the study.

### CONCLUSIONS:

The results of this study demonstrate no benefit of montelukast over placebo in the treatment of AAE in a cohort of 2- to 5-year-old children.

## Community health and health education

[Lancet Glob Health](#). 2018 Mar;6(3):e330-e341. doi: 10.1016/S2214-109X(18)30004-4.

### [Effect of a mass radio campaign on family behaviours and child survival in Burkina Faso: a repeated cross-sectional, cluster-randomised trial.](#)

[Sarrassat S](#), [Meda N](#), [Badolo H](#), [Ouedraogo M](#), [Some H](#), [Bambara R](#), [Murray J](#), [Remes P](#), [Lavoie M](#), [Cousens S](#), [Head R](#).

### BACKGROUND:

Media campaigns can potentially reach a large audience at relatively low cost but, to our knowledge, no randomised controlled trials have assessed their effect on a health outcome in a low-income country. We aimed to assess the effect of a radio campaign addressing family behaviours on all-cause post-neonatal under-5 child mortality in rural Burkina Faso.

### METHODS:

In this repeated cross-sectional, cluster randomised trial, clusters (distinct geographical areas in rural Burkina Faso with at least 40 000 inhabitants) were selected by Development Media International based on their high radio listenership (>60% of women listening to the radio in the past week) and minimum distances between radio stations to exclude population-level contamination. Clusters were randomly allocated to receive the intervention (a comprehensive radio campaign) or control group (no radio media campaign). Household surveys were performed at baseline (from December, 2011, to February, 2012), midline (in November, 2013, and after 20 months of campaigning), and endline (from November, 2014, to March, 2015, after 32 months of campaigning). Primary analyses were done on an intention-to-treat basis, based on cluster-level summaries and adjusted for imbalances between groups at baseline. The primary outcome was all-cause post-neonatal under-5 child mortality. The trial was designed to detect a 20% reduction in the primary outcome with a power of 80%. Routine data from health facilities were also analysed for evidence of changes in use and these data had high statistical power. The indicators measured were new antenatal care attendances, facility deliveries, and under-5 consultations. This trial is registered with ClinicalTrials.gov, number [NCT01517230](#).

### FINDINGS:

The intervention ran from March, 2012, to January, 2015. 14 clusters were selected and randomly assigned to the intervention group ( $n=7$ ) or the control group ( $n=7$ ). The average number of villages included per cluster was 34 in the control group and 29 in the intervention group. 2269 (82%) of 2784 women in the intervention group reported recognising the campaign's radio spots at endline. **Post-neonatal under-5 child mortality decreased from 93·3 to 58·5 per 1000 livebirths in the control group and from 125·1 to 85·1 per 1000 livebirths in the intervention group. There was no evidence of an intervention effect (risk ratio 1·00, 95% CI 0·82-1·22;  $p>0·999$ ).** In the first year of the intervention, under-5 consultations increased from 68 681 to 83 022 in the control group and from 79 852 to 111 758 in the intervention group. The intervention effect using interrupted time-series analysis was 35% (95%

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CI 20-51;  $p < 0.0001$ ). New antenatal care attendances decreased from 13 129 to 12 997 in the control group and increased from 19 658 to 20 202 in the intervention group in the first year (intervention effect 6%, 95% CI 2-10;  $p = 0.004$ ). Deliveries in health facilities decreased from 10 598 to 10 533 in the control group and increased from 12 155 to 12 902 in the intervention group in the first year (intervention effect 7%, 95% CI 2-11;  $p = 0.004$ ).

### INTERPRETATION:

A comprehensive radio campaign had no detectable effect on child mortality. Substantial decreases in child mortality were observed in both groups over the intervention period, reducing our ability to detect an effect. This, nevertheless, represents the first randomised controlled trial to show that mass media alone can change health-seeking behaviours.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817351/>

\*\*\* [PLoS Med.](#) 2017 Jul 5;14(7):e1002324. doi: 10.1371/journal.pmed.1002324. eCollection 2017 Jul.

### [Community health promotion and medical provision for neonatal health-CHAMPION cluster randomised trial in Nagarkurnool district, Telangana \(formerly Andhra Pradesh\), India.](#)

[Boone P](#), [Eble A](#), [Elbourne D](#), [Frost C](#), [Jayanty C](#), [Lakshminarayana R](#), [Mann V](#), [Mukherjee R](#), [Piaggio G](#), [Reddy P](#).

### BACKGROUND:

In the mid-2000s, neonatal mortality accounted for almost 40% of deaths of children under 5 years worldwide, and constituted 65% of infant deaths in India. The neonatal mortality rate in Andhra Pradesh was 44 per 1,000 live births, and was higher in the rural areas and tribal regions, such as the Nagarkurnool division of Mahabubnagar district (which became Nagarkurnool district in Telangana in 2014). The aim of the CHAMPION trial was to investigate whether a package of interventions comprising community health promotion and provision of health services (including outreach and facility-based care) could lead to a reduction of the order of 25% in neonatal mortality.

### METHODS AND FINDINGS:

The design was a trial in which villages (clusters) in Nagarkurnool with a population  $< 2,500$  were randomised to the CHAMPION package of health interventions or to the control arm (in which children aged 6-9 years were provided with educational interventions-the STRIPES trial). A woman was eligible for the CHAMPION package if she was married and  $< 50$  years old, neither she nor her husband had had a family planning operation, and she resided in a trial village at the time of a baseline survey before randomisation or married into the village after randomisation. **The CHAMPION intervention package comprised community health promotion (including health education via village health worker-led participatory discussion groups) and provision of health services (including outreach, with mobile teams providing antenatal check-ups, and facility-based care, with subsidised access to non-public health centres [NPHCs]).** Villages were stratified by travel time to the nearest NPHC and tribal status, and randomised (1:1) within strata. The primary outcome was neonatal mortality. Secondary outcomes included maternal mortality, causes of death, health knowledge, health practices including health service usage, satisfaction with care, and costs. The baseline survey (enumeration) was carried out between August and November 2007. After randomisation on 18 February 2008, participants, data collectors, and data analysts were not masked to

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allocation. The intervention was initiated on 1 August 2008. After an inception period, the assessment start date was 1 December 2008. The intervention ended on 31 May 2011, and data collection was completed on 30 November 2011. Primary analyses followed the intention to treat principle. In all, 14,137 women were enrolled in 232 control villages, and 15,532 in 232 intervention villages. Of these, 4,885 control women had 5,474 eligible pregnancies and gave birth to 4,998 eligible children. The corresponding numbers in intervention villages were 5,664 women, 6,351 pregnancies, and 5,798 children. **Of the live-born babies, 343 (6.9%) in the control arm and 303 (5.2%) in the intervention arm died in their first 28 days of life (risk ratio 0.76, 95% CI 0.64 to 0.90, p = 0.0018; risk difference -1.59%, 95% CI -2.63% to -0.54%), suggesting that there were 92 fewer deaths (95% CI 31 to 152) as a result of the intervention.** There were 9 (0.16%) maternal deaths in the control arm compared to 13 (0.20%) in the intervention arm (risk ratio 1.24, 95% CI 0.53 to 2.90, p = 0.6176; 1 death was reported as a serious adverse event). There was evidence of improved health knowledge and health practices including health service usage in the intervention arm compared to the control arm. Women in the intervention arm were more likely to rate their delivery and postnatal care as good or very good. The total cost of the CHAMPION interventions was US\$1,084,955 (\$11,769 per life saved, 95% CI \$7,115 to \$34,653). The main limitations of the study included that it could not be masked post-randomisation and that fetal losses were not divided into stillbirths and miscarriages because gestational age was not reliably reported.

### CONCLUSIONS:

The CHAMPION trial showed **that a package of interventions addressing health knowledge and health seeking behaviour, buttressing existing health services, and contracting out important areas of maternal and child healthcare led to a reduction in neonatal mortality of almost the hypothesized 25% in small villages in an Indian state with high mortality rates.** The intervention can be strongly justified in much of rural India, and is of potential use in other similar settings. Ongoing changes in maternal and child health programmes make it imperative that a similar intervention that establishes ties between the community and health facilities is tested in different settings.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5497957/>

## Child protection and family violence

[Child Abuse Negl.](#) 2017 Oct;72:338-351. doi: 10.1016/j.chiabu.2017.08.014. Epub 2017 Sep 4.

### [Randomized controlled trial of a parenting program to reduce the risk of child maltreatment in South Africa.](#)

[Lachman JM](#), [Cluver L](#), [Ward CL](#), [Hutchings J](#), [Mlotshwa S](#), [Wessels I](#), [Gardner F](#).

Parenting programs in high-income countries have been shown to reduce the risk of child maltreatment. However, there is limited evidence of their effectiveness in low- and middle-income countries. The objective of this study was to examine the initial effects of a parenting program in reducing the risk of child maltreatment in highly-deprived and vulnerable communities in Cape Town, South Africa. Low-income parents (N=68) with children aged three to eight years were randomly assigned to either a group-based parenting program or a wait-list control group. Observational and parent-report assessments were taken at baseline and at immediate post-test after the intervention was delivered. Primary outcomes were parent-report and observational assessments of harsh parenting, positive parenting, and child behavior problems. Secondary outcomes were parent-report assessments of parental depression, parenting

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stress, and social support. Results indicated moderate treatment effects for increased frequency of parent-report of positive parenting ( $d=0.63$ ) and observational assessments of parent-child play ( $d=0.57$ ). Observational assessments also found moderate negative treatment effects for less frequent positive child behavior ( $d=-0.56$ ). This study is the first randomized controlled trial design to rigorously test the effectiveness of a parenting program on reducing the risk of child maltreatment in sub-Saharan Africa using both observational and self-report assessments. Results provide preliminary evidence of effectiveness of reducing the risk of child maltreatment by improving positive parenting behavior. Further development is required to strengthen program components regarding child behavior management and nonviolent discipline strategies. Future research would benefit from a larger trial with sufficient power to determine program effectiveness.

[Public Health Nutr.](#) 2017 Oct;20(15):2810-2818. doi: 10.1017/S1368980017001136. Epub 2017 Jun 29.

### **Breast-feeding counselling mitigates the negative association of domestic violence on exclusive breast-feeding duration in rural Bangladesh. The MINIMat randomized trial.**

[Frith AL](#), [Ziaei S](#), [Naved RT](#), [Khan AI](#), [Kabir I](#), [Ekström EC](#).

#### **OBJECTIVE:**

To determine if exclusive breast-feeding counselling modifies the association of experience of any lifetime or specific forms of domestic violence (DV) on duration of exclusive breast-feeding (EBF).

#### **DESIGN:**

In the MINIMat trial pregnant women were randomized to receive either usual health messages (UHM) or usual health messages with breast-feeding counselling (BFC) in eight visits. During pregnancy (30 weeks), lifetime experience of any or specific forms of DV was measured. Infant feeding practice information was collected from 0 to 6 months at 15 d intervals.

#### **SETTING:**

Matlab, Bangladesh.

#### **SUBJECTS:**

Pregnant and postpartum women (n 3186) and their infants.

#### **RESULTS:**

Among women in the UHM group, those who had experienced any lifetime DV exclusively breast-fed for a shorter duration than women who did not experience any lifetime DV ( $P=0.02$ ). There was no difference, however, in duration of EBF among women in the BFC group based on their experience of any lifetime DV exposure ( $P=0.48$ ). Using Cox regression analysis, there was an interaction of exposure to any lifetime DV, sexual violence and controlling behaviour, and counselling group with duration of breast-feeding at or before 6 months ( $P$ -interaction $\leq 0.08$ ). Among the UHM group, experience of any lifetime DV, sexual violence or controlling behaviour was associated with fewer days of EBF ( $P<0.05$ ). In contrast, among the BFC group, experience of DV was not associated with duration of EBF.

#### **CONCLUSIONS:**

The experience of DV compromises EBF and the support of breast-feeding counselling programmes could assist this vulnerable group towards better infant feeding practices.

[J Adolesc Health](#). 2018 Jan;62(1S):S6-S14. doi: 10.1016/j.jadohealth.2017.07.007.

**[Integrating Economic Strengthening and Family Coaching to Reduce Work-Related Health Hazards Among Children of Poor Households: Burkina Faso.](#)**

[Karimli L](#), [Rost L](#), [Ismayilova L](#).

**PURPOSE:**

This is the first randomized controlled trial in Burkina Faso testing the effect of economic strengthening alone and in combination with family coaching on child's hazardous work and work-related health outcomes. The study also tests the association between different forms of hazardous work and child's health outcomes.

**METHODS:**

A total of 360 households from 12 villages participated in the study. Villages were randomly assigned to three study arms: **economic intervention alone, economic intervention integrated with family coaching, and control**. In each household, one female caregiver and one child aged 10-15 years were interviewed. Data were collected at baseline, 12 months, and 24 months. We ran multilevel mixed-effects models that account for both within-individual correlation over time and clustering of subjects within villages.

**RESULTS:**

Compared with the control group, **at 24 months, children in the integrated arm experienced significant reduction in exposure to hazardous work and some forms of hazards and abuse**. Results for children in the economic strengthening-only arm were more modest. In most cases, child's health was significantly associated not with specific forms of work per se, but with child's exposure to hazards and abuse while doing this form of work. We found no significant effect of intervention on child's work-related health.

**CONCLUSIONS:**

**Economic strengthening combined with family coaching on child protection issues, rather than implemented alone, may be more effective in reducing child's exposure to hazardous work**. Additional research is needed to understand gender differences and causal links between different forms of child work and health hazards.

[Glob Ment Health \(Camb\)](#). 2017 Oct 2;4:e18. doi: 10.1017/gmh.2017.10. eCollection 2017.

**[Testing the effectiveness of a transdiagnostic treatment approach in reducing violence and alcohol abuse among families in Zambia: study protocol of the Violence and Alcohol Treatment \(VATU\) trial.](#)**

[Kane JC](#), [Skavenski Van Wyk S](#), [Murray SM](#), [Bolton P](#), [Melendez F](#), [Danielson CK](#), [Chimponda P](#), [Munthali S](#), [Murray LK](#).

**BACKGROUND:**

Violence against women and girls (VAWG) is an urgent global health problem. Root causes for VAWG include the individual- and family-level factors of alcohol abuse, mental health problems, violence exposure, and related adverse experiences. Few studies in low- and middle-income countries (LMIC) have assessed the effectiveness of psychological interventions for reducing VAWG. This randomized controlled trial, part of the *What Works to Prevent Violence Against Women and Girls* consortium, examines the effectiveness of a common elements treatment approach (CETA) for reducing VAWG and comorbid alcohol abuse among families in Zambia.

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### **METHODS/DESIGN:**

Study participants are families consisting of three persons: an adult woman, her male husband or partner, and one of her children aged 8-17 (if available). Eligibility criteria include experience of moderate-to-severe intimate partner violence by the woman and hazardous alcohol use by her male partner. Family units are randomized to receive CETA or treatment as usual. The primary outcome is VAWG as measured by the Severity of Violence Against Women Scale, assessed along with secondary outcomes at 24 months post-baseline. Interim assessments are also conducted at 4-5 months (following CETA completion) and 12 months post-baseline.

### **CONCLUSIONS:**

This ongoing trial is one of the first in sub-Saharan Africa to evaluate the use of an evidence-based common elements approach for reducing VAWG by targeting a range of individual- and family-level factors, including alcohol abuse. Results of this trial will inform policy on what interventions work to prevent VAWG in LMIC with local perspectives on scale up and wider implementation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5719477/>

[Child Abuse Negl.](#) 2017 Sep;71:80-91. doi: 10.1016/j.chiabu.2017.04.019. Epub 2017 May 12.

### **[A randomized controlled trial of an intervention program to Brazilian mothers who use corporal punishment.](#)**

[Santini PM](#), [Williams LCA](#).

This study evaluated a positive parenting program to Brazilian mothers who used corporal punishment with their children. The intervention was conducted in four agencies serving vulnerable children, and at a home replica laboratory at the University. **Mothers who admitted using corporal punishment were randomly assigned between experimental (n=20) and control group (n=20).** The program consisted of 12 individual sessions using one unit from Projeto Parceria (Partnership Project), with specific guidelines and materials on positive parenting, followed by observational sessions of mother-child interaction with live coaching and a video feedback session in the lab. The study used an equivalent group experimental design with pre/post-test and follow-up, in randomized controlled trials. Measures involved: Initial Interview; Strengths and Difficulties Questionnaire (SDQ) - parent and child versions; Beck Depression Inventory (BDI); observational sessions with a protocol; and a Program Evaluation by participants. Analysis of mixed models for repeated measures revealed significant positive effects on the BDI and SDQ total scores, as well as less Conduct problems and Hyperactivity in SDQ measures from the experimental group mothers, comparing pre with post-test.

Observational data also indicated significant improvement in positive interaction from the experimental group mothers at post-test, in comparison with controls. No significant results were found, however, in children's observational measures. Limitations of the study involved using a restricted sample, among others. Implications for future research are suggested.

[Prev Sci.](#) 2017 Oct;18(7):865-878. doi: 10.1007/s11121-016-0727-3.

### **[The Effects of Musical Training on Child Development: a Randomized Trial of El Sistema in Venezuela.](#)**

[Alemán X](#), [Duryea S](#), [Guerra NG](#), [McEwan PJ](#), [Muñoz R](#), [Stampini M](#), [Williamson AA](#).



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Many studies have explored the links between music and children's outcomes; however, study designs have not been sufficiently rigorous to support causal findings. This study aims to assess the effects of a large-scale music program on children's developmental functioning in the context of high rates of exposure to violence. The paper describes the results of an experimental evaluation of Venezuela's National System of Youth and Children's Orchestras. The curriculum of the program, better known as "El Sistema," emphasizes social interactions through group instruction and group performances. The randomized control trial was conducted in 16 music centers between May 2012 and November 2013. In total, 2914 children ages 6-14 participated in the experiment, with approximately half receiving an offer of admission to the program in September 2012 and half in September 2013. **The treatment group children participated for one semester more than the control group children. After 1 year, full-sample ITT estimates indicate improved self-control (by 0.10 standard deviations) and reduced behavioral difficulties (by 0.08 standard deviations), both significant at 10% after controlling for multiple hypothesis testing.** There were no full-sample effects on other domains. Sub-sample effects are larger among (1) children with less-educated mothers and (2) boys, especially those exposed to violence at baseline. In the latter subgroup, we find lower levels of aggressive behavior. **We find that the program improved self-control and reduced behavioral difficulties, with the effects concentrated among subgroups of vulnerable children.** The results suggest the importance of devising mechanisms to target resources to the most vulnerable children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5602103/>

## Dengue

(see Vaccines - dengue)

## Development, cerebral palsy and mental health

(See also: School health programs; and Nutrition – micronutrients; Adolescent health)

[BMC Pediatr.](#) 2018 Feb 5;18(1):29. doi: 10.1186/s12887-018-1023-0.

### [Effects of home-based play-assisted stimulation on developmental performances of children living in extreme poverty: a randomized single-blind controlled trial.](#)

[Worku BN](#), [Abessa TG](#), [Wondafrash M](#), [Lemmens J](#), [Valy J](#), [Bruckers L](#), [Kolsteren P](#), [Granitzer M](#).

#### **BACKGROUND:**

Children living with foster families in a resource-limited setting such as Ethiopia are at risk of developmental problems. It is not yet clear whether intensive home-based developmental stimulation assisted by play can reduce these problems. The main objective of this study was to examine the effects of play-assisted intervention integrated into basic services on the developmental performance of children living with foster families in extreme poverty.

#### **METHODS:**

A randomized single-blind (investigator) controlled trial design was used. The study was conducted in Jimma, South West Ethiopia. Using computer-generated codes, eligible children of 3-59 months in age were randomly allocated to intervention (n = 39) and control (n = 39) groups at a 1:1 ratio. Children in the intervention group received home-based play-assisted stimulation

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in addition to the basic services provided to children in both groups. **The intervention consisted of an hour of play stimulation conducted during a weekly home visit over the course of six months.** Personal-social, language, fine and gross motor outcomes were assessed using Denver II-Jimma, and social-emotional outcome was obtained using an adapted Ages and Stages Questionnaire: Social-Emotional (ASQ: SE). Information about sociodemographic characteristics was collected using a structured questionnaire. Anthropometric methods were used to determine nutritional status. The effects of the intervention on the abovementioned outcomes over the study period and group differences in change over time were examined using Generalized Estimating Equations (GEE).

### RESULTS:

**Statistically significant intervention effects were found for language (P = 0.0014), personal-social (P = 0.0087) and social-emotional (P < 0.0001) performances.** At the midline of the study, language (effect size = 0.34) and social-emotional (effect size = - 0.603) benefits from the play-assisted stimulation had already been observed for the children in the intervention group. For language, the intervention effect depended on the child's sex (P = 0.0100) and for personal-social performance, on family income (P = 0.0300).

### CONCLUSIONS:

Intensive home-based play-assisted stimulation reduced the developmental problems of children in foster families in the context of extreme poverty. Longer follow-up may reveal further improvements in the developmental performance of the children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5800292/>

*Prev Sci.* 2017 Nov;18(8):964-975. doi: 10.1007/s11121-017-0822-0.

### [Transportability of an Evidence-Based Early Childhood Intervention in a Low-Income African Country: Results of a Cluster Randomized Controlled Study.](#)

[Huang KY](#), [Nakigudde J](#), [Rhule D](#), [Gumikiriza-Onoria JL](#), [Abura G](#), [Kolawole B](#), [Ndyabangi S](#), [Kim S](#), [Seidman E](#), [Ogedegbe G](#), [Brotman LM](#).

Children in Sub-Saharan Africa (SSA) are burdened by significant unmet mental health needs. Despite the successes of numerous school-based interventions for promoting child mental health, most evidence-based interventions (EBIs) are not available in SSA. This study investigated the implementation quality and effectiveness of one component of an EBI from a developed country (USA) in a SSA country (Uganda). The EBI component, Professional Development, was provided by trained Ugandan mental health professionals to Ugandan primary school teachers. It included large-group experiential training and small-group coaching to introduce and support a range of evidence-based practices (EBPs) to create nurturing and predictable classroom experiences. The study was guided by the Consolidated Framework for Implementation Research, the Teacher Training Implementation Model, and the RE-AIM evaluation framework. Effectiveness outcomes were studied using a cluster randomized design, in which 10 schools were randomized to intervention and wait-list control conditions. A total of 79 early childhood teachers participated. Teacher knowledge and the use of EBPs were assessed at baseline and immediately post-intervention (4-5 months later). A sample of 154 parents was randomly selected to report on child behavior at baseline and post-intervention. Linear mixed effect modeling was applied to examine effectiveness outcomes. Findings support the feasibility of training Ugandan mental health professionals to provide Professional Development for Ugandan teachers. Professional Development was delivered with high levels of fidelity and

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resulted in improved teacher EBP knowledge and the use of EBPs in the classroom, and child social competence.

[J Child Adolesc Ment Health](#). 2017 Sep;29(2):147-167. doi: 10.2989/17280583.2017.1372285.

### **Attention-training with children from socioeconomically disadvantaged backgrounds in Cape Town.**

[Schrieff-Elson LE](#), [Ockhuizen JH](#), [During G](#), [Thomas KGF](#).

#### **OBJECTIVE:**

Attention is a core process underlying competence in higher-order cognitive abilities. Previous research suggests that healthy children from low socioeconomic status (SES) backgrounds perform poorly, relative to those from higher SES backgrounds, on tasks assessing attentional abilities. In this pilot study, we investigated the effects of an attention-training intervention on task performance in low-SES children.

#### **METHOD:**

We conducted a quasi-controlled trial with stratified randomisation, using a pre-test/ post-test design. Participants were low-SES children aged 7-13 years. Each was assigned to either an intervention group, a play control group, or a test-only control group (n = 5 per group). We implemented a ten-week manualised cognitive rehabilitation program, Pay Attention!, administering standardised tests of attention, working memory, and inhibition before and after the intervention. Between- and within-group analyses and Reliable Change Index statistics evaluated differences in scores from pre- to post-intervention.

#### **RESULTS:**

Analyses detected no notable between-group differences at either pre- or post-intervention testing. However, on tests of selective attention, attentional control, and inhibition, there were significant within-group and positive individual reliable changes exclusive to the intervention-group participants.

#### **CONCLUSIONS:**

Given the variability in our findings, more research needs be conducted with a larger sample to determine, with greater rigour, the efficacy of the intervention within samples of healthy children from low-SES backgrounds.

[J Dev Behav Pediatr](#). 2017 Nov/Dec;38(9):753-764. doi: 10.1097/DBP.0000000000000510.

### **Effect of Caregiver Training on the Neurodevelopment of HIV-Exposed Uninfected Children and Caregiver Mental Health: A Ugandan Cluster-Randomized Controlled Trial.**

[Boivin MJ](#), [Nakasujja N](#), [Familiar-Lopez I](#), [Murray SM](#), [Sikorskii A](#), [Awadu J](#), [Shohet C](#), [Givon D](#), [Ruiseñor-Escudero H](#), [Schut EE](#), [Opoka RO](#), [Bass JK](#).

#### **OBJECTIVE:**

Early childhood development programs typically combine healthy nutrition and cognitive stimulation in an integrated model. We separately delivered these 2 components in a cluster-randomized controlled trial to evaluate their comparative effectiveness in promoting

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healthy child development and caregiver mental health. This is the first study to do so for HIV-affected children and their infected mothers.

### **METHODS:**

Two hundred twenty-one HIV-exposed but uninfected child (2-3 years old) and caregiver dyads in 18 geographic clusters in Eastern Uganda **were randomized by cluster to receive biweekly individualized sessions of either (1) Mediation Intervention for Sensitizing Caregivers (MISC) training emphasizing cognitive stimulation or (2) Uganda Community Based Association for Child Welfare (UCOBAC) program that delivered health and nutrition training.** Children were evaluated at baseline, 6 months, 1 year (training conclusion), and 1-year posttraining with the Mullen Scales of Early Learning (MSEL), the Color-Object Association Test for memory, the Early Childhood Vigilance Test of attention, and the Behavior Rating Inventory of Executive Function (BRIEF-parent). The Caldwell Home Observation for the Measurement of the Environment (HOME) was completed by observers to gauge caregiving quality after training. Caregiver depression/anxiety (Hopkins Symptom Checklist-25) and functionality (list of activities of daily living) were also evaluated. Data collectors were blinded to trial arm assignment.

### **RESULTS:**

Mediation Intervention for Sensitizing Caregivers resulted in significantly better quality of caregiving compared with UCOBAC midintervention with an adjusted mean difference (MadjDiff) of 2.34 (95% confidence interval [CI]: 1.54-3.15,  $p < .01$ ), postintervention (MadjDiff = 2.43, 95% CI: 1.61-3.25,  $p < .01$ ), and at 1-year follow-up (MadjDiff = 2.07, 95% CI: 1.23-2.90,  $p < .01$ ). MISC caregivers reported more problems on the BRIEF for their child at 1-year posttraining only ( $p < .01$ ). Caregiving quality (HOME) was significantly correlated with MSEL composite performance 1-year posttraining for both the MISC and the UCOBAC trial arms. Likewise, physical growth was significantly related to child development outcomes even though it did not differ between trial arms.

### **CONCLUSION:**

Even though MISC demonstrated an advantage of improving caregiving quality, it did not produce better child cognitive outcomes compared with health and nutrition training.

[Matern Child Nutr.](#) 2018 Jan;14(1). doi: 10.1111/mcn.12468. Epub 2017 Jun 6.

### **Influences of early child nutritional status and home learning environment on child development in Vietnam.**

[Nguyen PH](#), [DiGirolamo AM](#), [Gonzalez-Casanova I](#), [Young M](#), [Kim N](#), [Nguyen S](#), [Martorell R](#), [Ramakrishnan U](#).

Early childhood development plays a key role in a child's future health, educational success, and economic status. However, suboptimal early development remains a global challenge. This study examines the influences of quality of the home learning environment (HOME) and child stunting in the first year of life on child development. We used data collected from a randomized controlled trial of preconceptional micronutrient supplementation in Vietnam ( $n = 1,458$ ). The Bayley Scales of Infant Development-III were used to assess cognition, language, and motor development domains at 2 years. At 1 year, 14% of children were stunted, and 15%, 58%, and 28% of children lived in poor, medium, and high HOME environments, respectively. In multivariate generalized linear regression models, living in a high HOME environment was significantly associated with higher scores (0.10 to 0.13 SD) in each of the developmental domains. Stunted children scored significantly lower for cognitive, language, and

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motor development (-0.11 to -0.18), compared to nonstunted children. The negative associations between stunting on development were modified by HOME; the associations were strong among children living in homes with a poor learning environment whereas they were nonsignificant for those living in high-quality learning environments. In conclusion, child stunting the first year of life was negatively associated with child development at 2 years among children in Vietnam, but a high-quality HOME appeared to attenuate these associations. Early interventions aimed at improving early child growth as well as providing a stimulating home environment are critical to ensure optimal child development.

<https://onlinelibrary.wiley.com/doi/full/10.1111/mcn.12468>

[Prev Sci.](#) 2017 Oct;18(7):793-803. doi: 10.1007/s11121-016-0728-2.

### **Improving Mental Health Outcomes of Burmese Migrant and Displaced Children in Thailand: a Community-Based Randomized Controlled Trial of a Parenting and Family Skills Intervention.**

[Annan J](#), [Sim A](#), [Puffer ES](#), [Salhi C](#), [Betancourt TS](#).

The negative effects of displacement and poverty on child mental health are well-known, yet research on prevention interventions in low- and middle-income countries, especially fragile states, remains limited. We examined the **effectiveness of a parenting skills intervention on mental health outcomes among Burmese migrant and displaced children living in 20 communities in Thailand**. Participants were primary caregivers and children aged 7 to 15 years ( $n = 479$  families). **Families were randomly assigned to receive an adapted version of the Strengthening Families Program ( $n = 240$ ) or a wait-list control condition ( $n = 239$ ).** Assessments were conducted at baseline and 1-month post-intervention for both conditions and at 6 months for treatment group only. **One month after the program, children in the treatment condition showed significant reductions in externalizing problems (caregiver effect size (ES) -0.22,  $p = 0.02$ ; child report ES -0.11,  $p = 0.02$ ) and child attention problems compared with controls (caregiver report ES -0.23,  $p = 0.03$ ).** There was no significant treatment effect on children's internalizing problems (ES -0.06;  $p = 0.31$ ). Children reported a significant increase in prosocial protective factors relative to controls (ES 0.20,  $p < 0.01$ ). **Results suggest that an evidence-based parenting skills intervention adapted for a displaced and migrant Burmese population facing high levels of adversity can have positive effects on children's externalizing symptoms and protective psychosocial factors.**

[Prev Sci.](#) 2017 Oct;18(7):762-771. doi: 10.1007/s11121-016-0721-9.

### **Preliminary Effectiveness Study of Coping Power Program for Aggressive Children in Pakistan.**

[Mushtaq A](#), [Lochman JE](#), [Tariq PN](#), [Sabih F](#).

Aggression is a characteristic feature of many psychiatric disorders. To address the scarceness for evidence-based interventions for behavioral problems in Pakistan, we evaluated the effectiveness of culturally adapted version of Coping Power Program. The purpose of the study was to determine the extent to which Coping Power Program is capable of reducing aggressive behavior and improving competent behavior, when delivered in a different culture, i.e., Pakistan. With randomized control trial(RCT) of pre- and post-testing, 112 fourth grade boys were

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allocated to Coping Power intervention condition and waitlist control condition. The intervention group showed significant reduction in aggression at post assessment, in comparison to control group. Boys who received Coping Power intervention also showed improvements in behavior, social skills, and social cognitive processes, with better anger control and problem solving strategies, in comparison to the control group. The results of the study provide preliminary evidence, supporting the effectiveness of Coping Power Program for Pakistani children. Despite its limitations, the results of this study are promising and suggest that Coping Power is an effective intervention to reduce behavioral problems and promote healthy and positive behaviors in children, even when implemented in different contexts with greater potential for violence exposure.

[Res Rep Trop Med](#). 2018 May 24;9:89-93. doi: 10.2147/RRTM.S145209. eCollection 2018.

### **Nodding syndrome: recent insights into etiology, pathophysiology, and treatment.**

[Mwaka AD](#), [Semakula JR](#), [Abbo C](#), [Idro R](#).

Nodding syndrome is an enigmatic neuropsychiatric and epileptiform disorder associated with psychomotor, mental, and physical growth retardation. The disorder affects otherwise previously normal children aged 3-18 years, with a slight preponderance for the male child. Nodding syndrome has been described in rural regions of some low-income countries in sub-Saharan Africa including northern Uganda, South Sudan, and a mountainous region of southern Tanzania. The cause of the disorder has hitherto eluded scientists. Neuroimaging studies show involvement of the nervous system with associated severe cortical atrophy in the affected children. The affected communities have generated a number of perceived causes including some conspiracy theories related to intentional poisoning of water sources and foods, and causes related to fumes and chemicals from ammunitions used during civil wars in the affected regions. From biomedical perspectives, the treatment of the affected children is geared towards symptoms control and rehabilitation. There is evidence that seizures and behavioral problems including wandering and episodes of aggressions are controllable with anticonvulsants, especially sodium valproate and antipsychotics. No treatments have proven effective in reversing the course of the disorder, and cure remains a distant goal. Community members have used indigenous medicines, cleansing rituals, and prayer interventions, but have not perceived any reasonable improvements. A randomized controlled clinical trial is ongoing in northern Uganda to test the efficacy and effectiveness of doxycycline in the treatment of nodding syndrome. The hypothesis underlying the doxycycline trial underscores the role of antigenic mimicry: that antibodies generated against an antigen of a microorganism that resides inside the black fly-transmitted parasite, *Onchocerca volvulus* becomes directed against nervous tissue in the brain. This paper reviews some of the recent advances in researches on the etiologies, pathophysiology, and treatment of nodding syndrome.

[Alcohol Clin Exp Res](#). 2018 Jul;42(7):1327-1341. doi: 10.1111/acer.13769. Epub 2018 Jun 15.

### **Efficacy of Maternal Choline Supplementation During Pregnancy in Mitigating Adverse Effects of Prenatal Alcohol Exposure on Growth and Cognitive Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.**

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[Jacobson SW](#), [Carter RC](#), [Molteno CD](#), [Stanton ME](#), [Herbert JS](#), [Lindinger NM](#), [Lewis CE](#), [Dodge NC](#), [Hoyme HE](#), [Zeisel SH](#), [Meintjes EM](#), [Duggan CP](#), [Jacobson JL](#).

### BACKGROUND:

We recently demonstrated the acceptability and feasibility of a randomized, double-blind choline supplementation intervention for heavy drinking women during pregnancy. In this study, we report our results relating to the efficacy of this intervention in mitigating adverse effects of prenatal alcohol exposure (PAE) on infant growth and cognitive function.

### METHODS:

Sixty-nine Cape Coloured (mixed ancestry) heavy drinkers in Cape Town, South Africa, recruited in mid-pregnancy, were randomly assigned to receive a **daily oral dose of either 2 g of choline or placebo from time of enrollment until delivery**. Each dose consisted of an individually wrapped packet of powder that, when mixed with water, produced a sweet tasting grape-flavored drink. The primary outcome, eyeblink conditioning (EBC), was assessed at 6.5 months. Somatic growth was measured at birth, 6.5, and 12 months, recognition memory and processing speed on the Fagan Test of Infant Intelligence, at 6.5 and 12 months.

### RESULTS:

Infants born to choline-treated mothers were more likely to meet criterion for conditioning on EBC than the placebo group. Moreover, within the choline arm, degree of maternal adherence to the supplementation protocol strongly predicted EBC performance. Both groups were small at birth, but choline-treated infants showed considerable catch-up growth in weight and head circumference at 6.5 and 12 months. At 12 months, the infants in the choline treatment arm had higher novelty preference scores, indicating better visual recognition memory.

### CONCLUSIONS:

This exploratory study is the first to provide evidence that a high dose of choline administered early in pregnancy can mitigate adverse effects of heavy PAE on EBC, postnatal growth, and cognition in human infants. These findings are consistent with studies of alcohol-exposed animals that have demonstrated beneficial effects of choline supplementation on classical conditioning, learning, and memory.

[Alcohol Clin Exp Res](#). 2018 Jul;42(7):1315-1326. doi: 10.1111/acer.13768. Epub 2018 Jun 13.  
**[Feasibility and Acceptability of Maternal Choline Supplementation in Heavy Drinking Pregnant Women: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.](#)**

[Jacobson SW](#), [Carter RC](#), [Molteno CD](#), [Meintjes EM](#), [Senekal MS](#), [Lindinger NM](#), [Dodge NC](#), [Zeisel SH](#), [Duggan CP](#), [Jacobson JL](#).

### BACKGROUND:

Choline, an essential nutrient, serves as a methyl-group donor for DNA methylation and is a constituent of the neurotransmitter acetylcholine and a precursor to major components of cell membranes. Findings from animal studies suggest that choline supplementation during pregnancy can mitigate adverse effects of prenatal alcohol exposure on growth and neurocognitive function. We conducted a randomized, double-blind exploratory trial to examine feasibility and acceptability of a choline supplementation intervention during pregnancy.

### METHODS:

**Seventy heavy drinkers, recruited in mid-pregnancy, were randomly assigned to receive a daily oral dose of 2 g of choline or a placebo from time of enrollment until delivery.** Each dose consisted of an individually wrapped packet of powder that, when mixed with water, produced a sweet tasting grape-flavored drink. Adherence was assessed by collecting used and

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unused drink packets on a monthly basis and tabulating the number used. Side effects were assessed in monthly interviews. Blood samples obtained at enrollment and at 4 and 12 weeks after randomization were assayed for plasma choline concentration.

### RESULTS:

Adherence was good-to-excellent (median doses taken = 74.0%; interquartile range = 53.9 to 88.7%) and was not related to a range of sociodemographic characteristics or to alcohol consumption ascertained using a timeline follow-back interview. By 4 weeks, plasma choline concentrations were significantly higher in the choline supplementation than the placebo arm, and this group difference continued to be evident at 12 weeks. The only side effect was a small increase in nausea/dyspepsia. No effects were seen for diarrhea, vomiting, muscle stiffness, blood pressure, or body odor changes.

### CONCLUSIONS:

This study demonstrated that a choline supplementation program with very heavy drinkers during pregnancy is feasible even among highly disadvantaged, poorly educated women. The broad acceptability of this intervention is indicated by our finding that adherence was not related to maternal education, intellectual function, depression, nutritional status, or alcohol use

[Psychiatry Res.](#) 2017 Aug;254:151-157. doi: 10.1016/j.psychres.2017.04.033. Epub 2017 Apr 21.

### [Transgenerational trauma in a post-conflict setting: Effects on offspring PTSS/PTSD and offspring vulnerability in Cambodian families.](#)

[Burchert S](#), [Stammel N](#), [Knaevelsrud C](#).

We assessed transgenerational effects of maternal traumatic exposure, posttraumatic stress symptoms and posttraumatic stress disorder on trauma-related symptoms in Cambodian offspring born after the genocidal Khmer Rouge Regime. We conducted a randomized cross-sectional study. N=378 mothers from 4 provinces of the country and one of each of their grown-up children were interviewed. Lifetime traumatic exposure was determined using a context-adapted event list. Present posttraumatic stress symptoms and a potential posttraumatic stress disorder were assessed using the civilian version of the Posttraumatic Stress Disorder Checklist. We found no indication of transgenerational effects that were directly related to maternal traumatic exposure, posttraumatic stress symptoms or posttraumatic stress disorder. Instead, a gender-specific moderating effect was found. Individual traumatic exposure had a stronger effect on posttraumatic stress symptoms in daughters, the higher the mother's lifetime traumatic exposure. There is evidence of an interaction between lifetime traumatic exposure of mothers and their offspring that can be interpreted as an increased vulnerability to symptoms of posttraumatic stress in daughters. The mechanisms of transgenerational trauma in the Cambodian context require further research, as learning from previous conflicts will be instructive when addressing the pressing humanitarian needs of today's world.

[Matern Child Nutr.](#) 2018 May 17:e12621. doi: 10.1111/mcn.12621. [Epub ahead of print]



**Maternal depressive symptoms are negatively associated with child growth and development: Evidence from rural India.**

[Nguyen PH](#), [Friedman J](#), [Kak M](#), [Menon P](#), [Alderman H](#).

Maternal depression has been suggested as a risk factor for both poor child growth and development in many low- and middle-income countries, but the validity of many studies is hindered by small sample sizes, varying cut-offs used in depression diagnostics, and incomplete control of confounding factors. This study examines the association between maternal depressive symptoms (MDSs) and child physical growth and cognitive development in Madhya Pradesh, India, where poverty, malnutrition, and poor mental health coexist. Data were from a baseline household survey (n = 2,934) of a randomized controlled trial assessing an early childhood development programme. Multivariate linear and logistic regression analyses were conducted, adjusting for socio-economic factors to avoid confounding the association of mental health and child outcomes. MDS (measured using the Center for Epidemiologic Studies Short Depression Scale) was categorized as low, medium, and high in 47%, 42%, and 10% of mothers, respectively. The prevalence of child developmental delay ranged from 16% to 27% for various development domains. Compared with children of mothers with low MDS, those of high MDS mothers had lower height-for-age, weight-for-age, and weight-for-height z-scores (0.22, 0.21, and 0.15, respectively), a higher rate of stunting and underweight (~1.5 times), and higher rate of developmental delay (partial adjusted odds ratio ranged from 1.3-1.8 for different development domains and fully adjusted odds ratio = 1.4 for fine motor). Our results—that MDS is significantly associated with both child undernutrition and development delay—add to the call for practical interventions to address maternal depression to simultaneously address multiple outcomes for both women and children.

[Indian J Pediatr](#). 2018 Jul 25. doi: 10.1007/s12098-018-2747-4. [Epub ahead of print]

**Home-based Sensory Interventions in Children with Autism Spectrum Disorder: A Randomized Controlled Trial.**

[Padmanabha H](#), [Singhi P](#), [Sahu JK](#), [Malhi P](#).

**OBJECTIVES:**

To determine the feasibility and efficacy of home-based sensory interventions in children with Autism spectrum disorder (ASD) with sensory processing abnormalities.

**METHODS:**

This was a 12-wk, parallel group, pilot, randomized controlled trial. During the study-period, 185 children with ASD between 3-12 y of age, with sensory processing abnormalities were screened for eligibility. **Twenty-one children were randomly assigned to the sensory-intervention group and 19 to the standard-therapy group.** Sensory-intervention group received **home-based sensory interventions by the parents/caregivers plus standard therapy; standard-therapy group received speech therapy by the speech pathologists and applied behavior analysis by the child psychologist.**

**RESULTS:**

The mean change in scores at baseline and 12 wk into intervention showed that children in sensory-intervention group (Mean = 9.33, SD = 3.52) scored significantly better on Parent Rated 10-item Likert Scale (PRILS-10), as compared to standard-therapy group (Mean = 2.47, SD = 1.46),  $t(36) = 8.16$ ,  $p < 0.001$ ;  $d = 2.54$ . Marked improvement was noted especially in reduction of hyperactivity, motor-stereotypies and auditory sensitivity in those who underwent

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sensory interventions. The mean change in scores in sensory-intervention group on Children's Global Assessment Scale (CGAS) (Mean = -9.19, SD = 2.33,  $p < 0.011$ ;  $d = -1.75$ ) and Pediatric Quality of Life Inventory 4.0 (PedsQL™) (M = -10.53, SD = 5.34,  $p = 0.008$ ;  $d = -0.88$ ) showed significant difference in the sensory-intervention group as compared to standard-therapy group. Overall, there was 32.3%, 18.1% and 15.8% improvement on PRILS-10, CGAS and PedsQL™ respectively in sensory-intervention group.

### CONCLUSIONS:

The present findings suggest that home-based sensory interventions are feasible in a developing country and are suggested to have a beneficial role in ASD.

## Diarrhoea

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

### Treatment of diarrhoea

[J Pediatr Gastroenterol Nutr.](#) 2017 Dec;65(6):621-626. doi: 10.1097/MPG.0000000000001609.

### **Randomized Double-blind Trial of Ringer Lactate Versus Normal Saline in Pediatric Acute Severe Diarrheal Dehydration.**

[Karthi GB, Rameshkumar R, Mahadevan S.](#)

#### OBJECTIVE:

The aim of this study was to compare the effectiveness of Ringer lactate (RL) versus normal saline (NS) in the correction of pediatric acute severe diarrheal dehydration, as measured by improvement in clinical status and pH ( $\geq 7.35$ ).

#### METHODS:

A total of 68 children ages 1 month to 12 years with acute severe diarrheal dehydration (World Health Organization [WHO] classification) were randomized into RL (n=34) and NS groups (n=34) and received 100mL/kg of the assigned intravenous fluid according to WHO PLAN-C for the management of diarrheal dehydration. **The primary outcome was an improvement in clinical status and pH ( $\geq 7.35$ ) at the end of 6 hours.** Secondary outcomes were changes in serum electrolytes, renal and blood gas parameters, the volume of fluid required for dehydration correction excluding the first cycle, time to start oral feeding, hospital stay, and cost-effectiveness analysis.

#### RESULTS:

**Primary outcome was achieved in 38% versus 23% (relative risk=1.63, 95% confidence interval 0.80-3.40) in RL and NS groups, respectively.** No significant differences were observed in secondary outcomes in electrolytes, renal, and blood gas parameters. None required second cycle of dehydration correction. Median (interquartile range) time to start oral feeding (1.0 [0.19-2.0] vs 1.5 [0.5-2.0] hours) and hospital stay (2.0 [1.0-2.0] vs 2.0 [2.0-2.0] days) was similar. The median total cost was higher in RL than NS group ((Equation is included in full-text article.)120 [(Equation is included in full-text article.)120-(Equation is included in full-text article.)180] vs (Equation is included in full-text article.)55 [(Equation is included in full-text article.)55-(Equation is included in full-text article.)82],  $P \leq 0.001$ ).

#### CONCLUSION:

In pediatric acute severe diarrheal dehydration, resuscitation with RL and NS was associated with similar clinical improvement and biochemical resolution. Hence, NS is to be considered as the fluid of choice because of the clinical improvement, cost, and availability.

[PLoS One](#). 2018 Mar 27;13(3):e0193035. doi: 10.1371/journal.pone.0193035. eCollection 2018.

**Determinants of delay in timely treatment seeking for diarrheal diseases among mothers with under-five children in central Ethiopia: A case control study.**

[Degefa G](#), [Gebreslassie M](#), [Meles KG](#), [Jackson R](#).

**BACKGROUND:**

Delays in seeking timely appropriate care contributes to a large number of deaths from diarrhea in children. This study aimed to identify determinants of delays in seeking timely treatment by mothers/caregivers of under-five children with diarrheal diseases.

**METHODS:**

We used an unmatched case-control study from February-March 2017 among 316 children: 158 cases and 158 controls. Cases were mothers/caregivers with under-five children who had signs/symptoms of diarrhea and sought treatment after 24 hours onset of symptom. Controls sought treatment within 24 hours. Field workers collected data using a pre-tested standardized questionnaire. Multivariate logistic regression was conducted to identify determinants of delay in timely diarrhea treatment seeking. Statistical significance was declared by using a p-value < 0.05 and 95% of confidence interval (CI) for an adjusted-odds ratio (AOR).

**RESULTS:**

The determinants of delay in timely treatment seeking of mothers/caregivers of under-five children with diarrheal diseases were children < 24 months (AOR = 1.9, 95% CI: 1.1-3.4); fail to attend school (AOR = 2.4, 95% CI: 1.2-4.6); being female children (AOR = 1.7, 95% CI: 1.05-2.9); preferring government health facility for the treatment of children with diarrheal diseases (AOR = 2.9, 95% CI: 1.3-6.7); lack of past history taking children to health facility and lack of counseling (AOR = 4.8, 95% CI: 2.0-12.1); being in the 15-25 years age (AOR = 1.7, 95% CI: 1.1-3.0) and taking children to a health facility as a first response to diarrhea (AOR = 0.1, 95% CI: 0.01-0.8).

**CONCLUSIONS:**

Age of the child, maternal age, and disease related determinants were determinants for seeking timely treatment to diarrheal diseases. Providing skilled based health education and counseling to mothers/caregivers on seeking timely treatment and taking children with diarrheal diseases to a health facility as a first response to diarrhea is a paramount intervention to reduce morbidity and mortality of children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5870934/>

[J Integr Med](#). 2017 Sep;15(5):365-372. doi: 10.1016/S2095-4964(17)60344-3.

**Effects of rhubarb (*Rheum ribes* L.) syrup on dysenteric diarrhea in children: a randomized, double-blind, placebo-controlled trial.**

[Khiveh A](#), [Hashempur MH](#), [Shakiba M](#), [Lotfi MH](#), [Shakeri A](#), [Kazemeini S](#), [Mousavi Z](#), [Jabbari M](#), [Kamalinejad M](#), [Emtiazy M](#).

**BACKGROUND:**

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*Rheum ribes* L. is a plant native to China, Iran, Turkey, India, and a few other countries. Antidiarrheal activity is considered to be one of its important properties according to various systems of traditional medicine. An increasing rate of bacterial resistance to antibiotics has led to treatment failure in some cases of shigellosis in children, and underlines a need for safe, efficient and valid options.

### OBJECTIVE:

The purpose of this study is to **evaluate the efficacy of *R. ribes* syrup as a complementary medicine for treatment of shigellosis in children.**

### DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS:

This randomized, double-blind, placebo-controlled trial started with a group of **150 children aged between 12-72 months with suspected *Shigella* dysentery. *R. ribes* syrup or placebo syrup was administered to the intervention and control groups, respectively for 5 days.** In addition, the standard antibiotic treatment (ceftriaxone for the first 3 days and cefixime syrup for 2 further days) was administered to both groups.

### MAIN OUTCOME MEASURES:

Body temperature, abdominal pain, need for antipyretics, defecation frequency, stool volume and consistency and microscopic stool examination were recorded as outcome measures. Any observed adverse effects were also recorded.

### RESULTS:

**Mean duration of fever and diarrhea in the *R. ribes* group was significantly lower than that in the placebo group (P = 0.016 and 0.001, respectively).** In addition, patients in the *R. ribes* group showed shorter duration of need for antipyretics and shorter duration of abdominal pain (P = 0.012 and 0.001, respectively). However, there were no significant differences between the two groups regarding the microscopic stool analyses. Furthermore, no adverse effect was reported.

### CONCLUSION:

***R. ribes* syrup can be recommended as a complementary treatment for children with *Shigella* dysentery.**

[Pediatr Infect Dis J. 2018 Jan;37\(1\):35-42. doi: 10.1097/INF.0000000000001712.](#)

### [\*\*A Double-blind, Randomized, Placebo-controlled Trial of \*Lactobacillus acidophilus\* for the Treatment of Acute Watery Diarrhea in Vietnamese Children.\*\*](#)

[Hong Chau TT](#), [Minh Chau NN](#), [Hoang Le NT](#), [Chung The H](#), [Voong Vinh P](#), [Nguyen To NT](#), [Ngoc NM](#), [Tuan HM](#), [Chau Ngoc TL](#), [Kolader ME](#), [Farrar JJ](#), [Wolbers M](#), [Thwaites GE](#), [Baker S](#); [Oxford-Vietnam Probiotics Study Group](#).

### BACKGROUND:

Probiotics are the most frequently prescribed treatment for children hospitalized with diarrhea in Vietnam. We were uncertain of the benefits of probiotics for the treatment of acute watery diarrhea in Vietnamese children.

### METHODS:

We conducted a double-blind, placebo-controlled, randomized trial of children hospitalized with acute watery diarrhea in Vietnam. **Children meeting the inclusion criteria (acute watery diarrhea) were randomized to receive either 2 daily oral doses of  $2 \times 10$  CFUs of a local probiotic containing *Lactobacillus acidophilus* or placebo for 5 days as an adjunct to standard of care.** The primary end point was time from the first dose of study medication to the start of the first 24-hour period without diarrhea. Secondary outcomes included the total

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duration of diarrhea and hospitalization, daily stool frequency, treatment failure, daily fecal concentrations of rotavirus and norovirus, and *Lactobacillus* colonization.

### RESULTS:

One hundred and fifty children were randomized into each study group. **The median time from the first dose of study medication to the start of the first 24-hour diarrhea-free period was 43 hours (interquartile range, 15-66 hours) in the placebo group and 35 hours (interquartile range, 20-68 hours) in the probiotic group (acceleration factor 1.09 [95% confidence interval, 0.78-1.51]; P = 0.62).** There was also no evidence that probiotic treatment was efficacious in any of the predefined subgroups nor significantly associated with any secondary end point.

### CONCLUSIONS:

This was a large double-blind, placebo-controlled trial in which the probiotic underwent longitudinal quality control. We found under these conditions that *L. acidophilus* was not beneficial in treating children with acute watery diarrhea.

[Nutrients](#). 2017 Aug 16;9(8). pii: E887. doi: 10.3390/nu9080887.

### [The Efficacy of \*Bifidobacterium longum\* BORI and \*Lactobacillus acidophilus\* AD031 Probiotic Treatment in Infants with Rotavirus Infection.](#)

[Park MS](#), [Kwon B](#), [Ku S](#), [Ji GE](#).

A total of 57 infants hospitalized with rotavirus disease were included in this study.

**The children were randomly divided into the study's two treatment groups: three days of the oral administration of (i) a probiotics formula containing both *Bifidobacterium longum* BORI and *Lactobacillus acidophilus* AD031 ( $N = 28$ ); or (ii) a placebo (probiotic-free skim milk,  $N = 29$ ) and the standard therapy for diarrhea.** There were no differences in age, sex, or blood characteristics between the two groups. **When the 57 cases completed the protocol, the duration of the patients' diarrhea was significantly shorter in the probiotics group ( $4.38 \pm 1.29$ ,  $N = 28$ ) than the placebo group ( $5.61 \pm 1.23$ ,  $N = 29$ ), with a  $p$ -value of 0.001.** Symptoms such as duration of fever ( $p = 0.119$ ), frequency of diarrhea ( $p = 0.119$ ), and frequency of vomiting ( $p = 0.331$ ) tended to be ameliorated by the probiotic treatment; however, differences were not statistically significant between the two groups. There were no serious, adverse events and no differences in the frequency of adverse events in both groups.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5579680/>

[Asia Pac J Clin Nutr](#). 2018;27(3):512-518. doi: 10.6133/apjcn.082017.05.

### [Pancreatic enzyme replacement therapy \(PERT\) in children with persistent diarrhea: avoidance of elemental diet need, accessibility and costs.](#)

[Widodo AD](#), [Setiabudy R](#), [Timan IS](#), [Bardosono S](#), [Winarta W](#), [Firmansyah A](#).

### BACKGROUND AND OBJECTIVES:

Persistent diarrhea has been proven to cause pancreatic exocrine insufficiency, due to decreased stimulation to the pancreas caused by prolonged mucosal injury. Pancreatic enzyme replacement therapy (PERT) given in conjunction to regular treatment is thought to be beneficial in replacing

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this pancreatic enzyme deficiency, avoiding the need of elemental diet. This study aims to evaluate the benefit of PERT in children with persistent diarrhea.

### **METHODS AND STUDY DESIGN:**

This is a randomized, **two double-blind parallel group, placebo-controlled clinical trial to evaluate the effects of pancreatic enzyme supplementation in persistent diarrhea**. Children age 6-60 months were recruited from pediatric inpatient and outpatient units of five hospitals in Jakarta. Subjects were randomly assigned to either pancreatic enzyme 8371 USP unit of lipase or placebo, 3 times daily for 1 month, as an adjunctive therapy to standard treatment. Subjects were then reevaluated at 2 weeks and 4 weeks interval after administration of enzyme or placebo. Variables observed were length of diarrhea after the start of intervention, change in serum prealbumin, and change in FE-1 between week 0 and week 4.

### **RESULTS:**

**Pan-creatic enzyme supplementation shortens the length of diarrhea by 7 days in the intervention group compared to placebo (p=0.019)**. Serum prealbumin and FE-1 shows trend that favors the intervention group, although not statistically significant (p>0.05).

### **CONCLUSION:**

PERT is clinically effective in reducing the length of diarrhea, thus minimizing the need, accessibility and costs of an elemental diet.

<http://apjcn.nhri.org.tw/server/APJCN/27/3/512.pdf>

[PLoS One. 2017 Oct 9;12\(10\):e0185177. doi: 10.1371/journal.pone.0185177. eCollection 2017.](https://doi.org/10.1371/journal.pone.0185177)

### **Rapid enteric testing to permit targeted antimicrobial therapy, with and without Lactobacillus reuteri probiotics, for paediatric acute diarrhoeal disease in Botswana: A pilot, randomized, factorial, controlled trial.**

[Pernica JM](#), [Steenhoff AP](#), [Mokomane M](#), [Moorad B](#), [Lechiile K](#), [Smieja M](#), [Mazhani L](#), [Cheng J](#), [Kelly MS](#), [Loeb M](#), [Stordal K](#), [Goldfarb DM](#).

### **INTRODUCTION:**

Diarrhoeal disease is the second-leading cause of death in young children. Current guidelines recommend treating children with acute non-bloody diarrhea with oral rehydration solutions and zinc, but not antimicrobials. However, in many resource-limited settings, infections with treatable enteric bacterial and protozoan pathogens are common. Probiotics have shown promise as an adjunct treatment for diarrhoea but have not been studied in sub-Saharan Africa.

### **METHODS:**

We conducted a pilot, factorial, randomized, placebo-controlled trial of children aged 2-60 months hospitalized in Botswana for acute non-bloody diarrhoea. A rapid test-and-treat intervention, consisting of multiplex PCR testing of rectal swabs taken at enrolment, accompanied by targeted antimicrobial therapy if treatable pathogens were detected, was compared to the reference standard of no stool testing. Additionally, Lactobacillus reuteri DSM 17938 x 60 days was compared to placebo treatment. The main objective of this pilot study was to assess feasibility. The primary clinical outcome was the increase in age-standardized height (HAZ) at 60 days adjusted for baseline HAZ.

### **RESULTS:**

Seventy-six patients were enrolled over a seven-month study period. We judged that the recruitment rate, lab processing times, communication protocols, provision of specific antimicrobials, and follow-up rates were acceptable. Compared to the reference arm (no stool testing and placebo treatment), the combination of the rapid test-and-treat strategy plus L. reuteri DSM 17938 was associated with an increase of 0.61 HAZ (95% CI 0.09-1.13) and 93% lower odds of recurrent diarrhoea (OR 0.07, 95% CI 0.01-0.61) at 60 days.

### DISCUSSION:

We demonstrated that it was feasible to evaluate the study interventions in Botswana. Despite the small sample size, we observed a statistically significant increase in HAZ at 60 days and significantly lower odds of recurrent diarrhoea in children receiving both rapid test-and-treat and *L. reuteri*. There is sufficient evidence to warrant proceeding with a larger follow-up trial in a similar setting.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5633142/>

### Diarrhoea prevention

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

[Lancet Glob Health](#). 2017 Jul;5(7):e699-e709. doi: 10.1016/S2214-109X(17)30217-6.

### **Effect of community health clubs on child diarrhoea in western Rwanda: cluster-randomised controlled trial.**

[Sinharoy SS](#), [Schmidt WP](#), [Wendt R](#), [Mfura L](#), [Crossett E](#), [Grépin KA](#), [Jack W](#), [Rwabufigiri BN](#), [Habyarimana J](#), [Clasen T](#).

### BACKGROUND:

Community health clubs are multi-session village-level gatherings led by trained facilitators and designed to promote healthy behaviours mainly related to water, sanitation, and hygiene. They have been implemented in several African and Asian countries but have never been evaluated rigorously. We aimed to evaluate the effect of two versions of the community health club model on child health and nutrition outcomes.

### METHODS:

We did a cluster-randomised trial in Rusizi district, western Rwanda. We defined villages as clusters. **We assessed villages for eligibility then randomly selected 150 for the study** using a simple random sampling routine in Stata. We stratified villages by wealth index and by the proportion of children younger than 2 years with caregiver-reported diarrhoea within the past 7 days. **We randomly allocated these villages to three study groups: no intervention (control; n=50), eight community health club sessions (Lite intervention; n=50), or 20 community health club sessions (Classic intervention; n=50).** Households in these villages were enrolled in 2013 for a baseline survey, then re-enrolled in 2015 for an endline survey. The primary outcome was caregiver-reported diarrhoea within the previous 7 days in children younger than 5 years. Analysis was by intention to treat and per protocol. This trial is registered with ClinicalTrials.gov, number [NCT01836731](#).

### FINDINGS:

At the baseline survey undertaken between May, 2013, and August, 2013, 8734 households with children younger than 5 years of age were enrolled. At the endline survey undertaken between Sept 21, 2015, and Dec 22, 2015, 7934 (91%) of the households were re-enrolled. **Among children younger than 5 years, the prevalence of caregiver-reported diarrhoea in the previous 7 days was 514 (14%) of 3616 assigned the control, 453 (14%) of 3196 allocated the Lite intervention (prevalence ratio compared with control 0·97, 95% CI 0·81-1·16; p=0·74), and 495 (14%) of 3464 assigned the Classic intervention (prevalence ratio compared with control 0·99, 0·85-1·15; p=0·87).**

### INTERPRETATION:

Community health clubs, in this setting in western Rwanda, had no effect on caregiver-reported diarrhoea among children younger than 5 years. Our results question the value of implementing this intervention at scale for the aim of achieving health gains.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5561270/>

## Cholera

[Health Educ Behav](#). 2017 Aug;44(4):613-625. doi: 10.1177/1090198116683141. Epub 2017 Jan 10.

### **Psychosocial Factors Mediating the Effect of the CHoBI7 Intervention on Handwashing With Soap: A Randomized Controlled Trial.**

[George CM](#), [Biswas S](#), [Jung D](#), [Perin J](#), [Parvin T](#), [Monira S](#), [Saif-Ur-Rahman KM](#), [Rashid MU](#), [Bhuyian SI](#), [Thomas ED](#), [Dreibelbis R](#), [Begum F](#), [Zohura F](#), [Zhang X](#), [Sack DA](#), [Alam M](#), [Sack RB](#), [Leontsini E](#), [Winch PJ](#).

Inadequate hand hygiene is estimated to result in nearly 300,000 deaths annually, with the majority of deaths being among children younger than 5 years. In an effort to promote handwashing with soap and water treatment behaviors among highly susceptible household members of cholera patients, we recently developed the **Cholera-Hospital-Based Intervention-for-7-Days (CHoBI7)**; chobi means picture in Bengali. This 1-week handwashing with soap and water treatment intervention is delivered by a promoter in the hospital and the home to cholera patients and their household members. **In our randomized controlled trial of this intervention, we observed a significant reduction in symptomatic cholera infections during the 1-week intervention period compared to the control arm and sustained high uptake of observed handwashing with soap behaviors up to 12 months postintervention.** The aim of the present study was to assess the underlying mechanism of change that led to the high handwashing with soap behavior observed among participants who received the CHoBI7 intervention. Handwashing with soap was measured using 5-hour structured observation, and psychosocial factors were assessed using a structured questionnaire among 170 intervention and 174 control household members enrolled in the CHoBI7 trial. To investigate potential mediators of the CHoBI7 intervention effect, mediation models were performed. **Response efficacy was found to mediate the intervention's effect on habit formation for handwashing with soap at the 1-week follow-up, and disgust, convenience, and cholera awareness were mediators of habit maintenance at the 6- to 12-month follow-up.** These results support the use of theory-driven approaches for the development and implementation of handwashing with soap interventions.

[Vaccine](#). 2017 Sep 5;35(37):5043-5049. doi: 10.1016/j.vaccine.2017.07.021. Epub 2017 Jul 29.

### **Socioeconomic risk factors for cholera in different transmission settings: An analysis of the data of a cluster randomized trial in Bangladesh.**

[Saha A](#), [Hayen A](#), [Ali M](#), [Rosewell A](#), [Clemens JD](#), [Raina MacIntyre C](#), [Qadri F](#).

#### **BACKGROUND:**

Cholera remains a threat globally, and socioeconomic factors play an important role in transmission of the disease. We assessed socioeconomic risk factors for cholera in vaccinated



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and non-vaccinated communities to understand whether the socioeconomic risk factors differ by transmission patterns for cholera.

### **METHODS:**

We used data from a cluster randomized control trial conducted in Dhaka, Bangladesh. There were 90 geographic clusters; 30 in each of the three arms of the study: vaccine (VAC), vaccine plus behavioural change (VBC), and non-intervention. The data were analysed for the three populations: (1) vaccinees in the vaccinated communities (VAC and VBC arms), (2) non-vaccinated individuals in the vaccinated communities and (3) all individuals in the non-vaccinated communities (non-intervention arm). A generalized estimating equation with logit link function was used to evaluate the risk factors for cholera among these different populations adjusting for household level correlation in the data.

### **RESULTS:**

A total of 528 cholera and 226 cholera with severe dehydration (CSD) in 268,896 persons were observed during the two-year follow-up. For population 1, the cholera risk was not associated with any socioeconomic factors; however CSD was less likely to occur among individuals living in a household having  $\leq 4$  members (aOR=0.55, 95% CI=0.32-0.96). Among population 2, younger participants and individuals reporting diarrhoea during registration were more likely to have cholera. Females and individuals reporting diarrhoea during registration were at increased risk of CSD. Among population 3, individuals living in a household without a concrete floor, in an area with high population density, closer to the study hospital, or not treating drinking water were at significantly higher risk for both cholera and CSD.

### **CONCLUSION:**

The profile of socioeconomic factors associated with cholera varies by individuals' vaccination status as well as the transmission setting. In a vaccinated community where transmission would be expected to be lower, socioeconomic factors may not increase the risk of the disease.

## Water quality and purification

[Am J Trop Med Hyg.](#) 2017 Dec;97(6):1867-1871. doi: 10.4269/ajtmh.17-0387. Epub 2017 Oct 12.

### **Effectiveness of the Hydrogen Sulfide Test as a Water Quality Indicator for Diarrhea Risk in Rural Bangladesh.**

[Islam M](#), [Ercumen A](#), [Naser AM](#), [Unicomb L](#), [Rahman M](#), [Arnold BF](#), [Colford JM Jr](#), [Luby SP](#).

Microbiological water quality is usually assessed by the identification of *Escherichia coli* (*E. coli*), a fecal indicator. **The hydrogen sulfide (H<sub>2</sub>S) test is an inexpensive, easy-to-use, and portable alternative field-based water quality test. Our study evaluated the H<sub>2</sub>S test's effectiveness as a water quality indicator for diarrhea risk.** Field workers collected stored drinking water samples for H<sub>2</sub>S analysis and detection of *E. coli* by membrane filtration and measured caregiver-reported diarrhea among children < 5 years in the same households 1 month later. We assessed the association between the H<sub>2</sub>S test (incubated for 24 hours and 48 hours) and diarrhea prevalence, with 2-day and 7-day symptom recall periods ( $N = 1,348$ ). We determined the sensitivity, specificity, and positive and negative predictive value (PPV, NPV) of the H<sub>2</sub>S test compared with *E. coli* ( $N = 525$ ). Controlling for potentially confounding covariates, H<sub>2</sub>S-positive water (at 24 or 48 hours) was not associated with 2-day diarrhea prevalence (24-hour prevalence ratio [PR] = 1.03, 95% confidence interval [CI]: 0.63-1.69; 48-hour PR = 0.89, 95% CI: 0.58-1.38) or 7-day diarrhea prevalence (24-hour PR = 1.17, 95% CI:

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0.76-1.78; 48-hour PR = 1.21, 95% CI: 0.81-1.80). The sensitivity, PPV, and NPV of the H<sub>2</sub>S test was significantly higher when the H<sub>2</sub>S test was incubated for 48 versus 24 hours whereas specificity showed the opposite trend. H<sub>2</sub>S test sensitivity, PPV, and NPV increased with increasing *E. coli* levels, consistent with previous evidence that the H<sub>2</sub>S test is a useful water quality tool in high-contamination settings. However, our results suggest that the H<sub>2</sub>S test is not an effective indicator for waterborne diarrhea.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805062/>

## Ear disease and hearing loss

[BMJ Open](#). 2017 Oct 11;7(10):e016457. doi: 10.1136/bmjopen-2017-016457.

### [Feasibility and acceptability of training community health workers in ear and hearing care in Malawi: a cluster randomised controlled trial.](#)

[Mulwafu W](#), [Kuper H](#), [Viste A](#), [Goplen FK](#).

#### **OBJECTIVE:**

To assess the feasibility and acceptability of training community health workers (CHWs) in ear and hearing care, and their ability to identify patients with ear and hearing disorders.

#### **DESIGN:**

Cluster randomised controlled trial (RCT).

#### **SETTING:**

Health centres in Thyolo district, Malawi.

#### **PARTICIPANTS:**

Ten health centres participated, 5 intervention (29 CHWs) and 5 control (28 CHWs).

#### **INTERVENTION:**

Intervention CHWs received 3 days of training in primary ear and hearing care, while among control CHWs, training was delayed for 6 months. Both groups were given a pretest that assessed knowledge about ear and hearing care, only the intervention group was given the posttest on the third day of training. The intervention group was given 1 month to identify patients with ear and hearing disorders in their communities, and these people were screened for hearing disorders by ear, nose and throat clinical specialists.

#### **OUTCOME MEASURES:**

Primary outcome measure was improvement in knowledge of ear and hearing care among CHWs after the training. Secondary outcome measures were number of patients with ear or hearing disorders identified by CHWs and number recorded at health centres during routine activities, and the perceived feasibility and acceptability of the intervention.

#### **RESULTS:**

The average overall correct answers increased from 55% to 68% (95% CI 65 to 71) in the intervention group ( $p < 0.001$ ). A total of 1739 patients with potential ear and hearing disorders were identified by CHWs and 860 patients attended the screening camps, of whom 400 had hearing loss (73 patients determined through bilateral fail on otoacoustic emissions, 327 patients through audiometry). Where cause could be determined, the most common cause of ear and hearing disorders was chronic suppurative otitis media followed by impacted wax. The intervention was perceived as feasible and acceptable to implement.

#### **CONCLUSIONS:**

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Training was effective in improving the knowledge of CHW in ear and hearing care in Malawi and allowing them to identify patients with ear and hearing disorders. This intervention could be scaled up to other CHWs in low-income and middle-income countries.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652500/>

## Ebola and viral haemorrhagic fever

(See Vaccines - Ebola vaccine)

## Endocrine disorders and bone health

### Diabetes

[J Clin Diagn Res.](#) 2017 Sep;11(9):SC15-SC17. doi: 10.7860/JCDR/2017/27321.10645. Epub 2017 Sep 1.

### [Does Vitamin D Supplementation Improve Glycaemic Control In Children With Type 1 Diabetes Mellitus? - A Randomized Controlled Trial.](#)

[Sharma S](#), [Biswal N](#), [Bethou A](#), [Rajappa M](#), [Kumar S](#), [Vinayagam V](#).

#### **INTRODUCTION:**

Vitamin D endocrine system is a potential immune system modulator and has been implicated in the pathogenesis of several autoimmune diseases including Type 1 Diabetes Mellitus (T1DM). Studies have demonstrated an inverse risk relationship between T1DM and Vitamin D levels and also, shown a reduced risk of the disease with its supplementation.

#### **AIM:**

To evaluate the role of Vitamin D as an adjuvant in improving glycaemic control and residual pancreatic beta-cell function. Primary outcome was the mean change in HbA1c levels over a period of six months.

#### **MATERIALS AND METHODS:**

This double-blinded randomized controlled trial was done in a tertiary care hospital, Southern India and included 52 children aged 1-18 years with T1DM, with 26 participants each in the intervention and standard of care arm. **Oral Vitamin D therapy was administered once a month for six months in addition to insulin in intervention arm while only insulin was continued for other arm.** Plasma HbA1c, serum 25-Hydroxy vitamin D (25OHD), insulin dose and C-peptide were measured at baseline and repeated after 6 months.

#### **RESULTS:**

**Prevalence of Vitamin D deficiency was as high as 63.5% i.e., 33 of total 52 children with T1DM.** The mean C-peptide levels were significantly high in intervention arm as compared to standard of care after six months. However, there was no significant difference in HbA1c, and insulin requirement at six months between the two groups. No adverse events due to Vitamin D therapy were noted.

#### **CONCLUSION:**

Oral Vitamin D may serve as an adjuvant to insulin therapy for children with T1DM by augmenting residual beta-cell function and improving insulin secretion. However, a significant decrease in HbA1c level and requirement for exogenous insulin was not achieved in our study.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5713820/>

*J Diet Suppl.* 2018 Jun 29;1-11. doi: 10.1080/19390211.2018.1470123. [Epub ahead of print]

**Effect of Antioxidant Supplementation on Total Antioxidant Status in Indian Children with Type 1 Diabetes.**

Parthasarathy L, Khadilkar V, Chiplonkar S, Khadilkar A.

Hyperglycemia results in the overproduction of free oxygen radicals that impair the endogenous antioxidant defenses. A randomized controlled trial was conducted to compare the **effect of 3 months of antioxidant supplementation in the form of foods rich in micronutrients with pharmacological supplement on total antioxidant status of Indian children with type 1 diabetes.** Ninety children with diabetes (mean age  $11.5 \pm 3.6$  yrs, 37 boys) were randomly allocated to three groups: **Group 1 (n = 31) = DM controls; Group 2 (n = 30) = multimicronutrient syrup; and Group 3 (n = 29) = dietary supplements (nine snack recipes rich in micronutrients).** They received intervention for 3 months. Healthy controls were enrolled from local schools. Fasting blood was tested for total antioxidant status (TAS) and glycosylated hemoglobin (HbA1C). Children with diabetes had lower TAS ( $0.70 \pm 0.2$  vs.  $1 \pm 0.24$  mmol/l,  $p = .0001$ ) compared to healthy controls. Anthropometric and biochemical parameters were similar at baseline for all groups of diabetic children. Group 1 showed significant deterioration in TAS at endline ( $0.72 \pm 0.16$  vs.  $0.60 \pm 0.17$  mmol/l,  $p = .008$ ). Increase in TAS recorded in Group 2 was from  $0.66 \pm 0.21$  to  $0.70 \pm 0.16$  mmol/l and in Group 3 was from  $0.68$  to  $0.73$  mmol/l. There was a significant difference between Group 1 and Group 3 for percentage change in TAS ( $-13\%$  vs.  $16\%$ ,  $p = .035$ ). Postsupplementation there was an increase in TAS values in children with diabetes, but they were still lower than in healthy controls. Indian diabetic children have compromised antioxidant status, which may be improved by incorporation of multimicronutrient-rich recipes in their diets.

*J Crit Care.* 2018 Feb;43:340-345. doi: 10.1016/j.jcrc.2017.09.175. Epub 2017 Sep 22.

**A randomized controlled trial of one bag vs. two bag system of fluid delivery in children with diabetic ketoacidosis: Experience from a developing country.**

Dhochak N, Jayashree M, Singhi S.

**PURPOSE:**

To compare one vs. two bag system with respect to blood glucose variability (BGV), time for resolution of acidosis and incidence of hypoglycemia, hypokalemia, and cerebral edema in children with diabetic ketoacidosis (DKA).

**MATERIAL AND METHODS:**

In an open labelled randomized controlled trial, thirty consecutive patients  $\leq 12$  years with DKA were randomized to either one (n=15) or two bag (n=15) system of intravenous fluid delivery. The two bags had similar electrolyte but differing dextrose concentration (none vs. 12.5%) and changing the rate of fluid, delivered different dextrose concentrations. BGV was primary outcome while hypoglycemia (blood glucose,  $BG < 50$  mg/dL), hypokalemia (serum potassium  $< 3.5$  mEq/L), time to resolution of acidosis and cerebral edema were secondary outcomes.

**RESULTS:**

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The one and two bag systems had similar BGV parameters; median hourly absolute BG change (mg/dL) [44 (30-74.5) vs. 36 (31-49);  $p=0.54$ ], mean of standard deviation of BG measurements [65.1 (25.1) vs. 65.5 (26.8);  $p=0.96$ ] and median number of undesirable events (hourly blood sugar change  $\geq 50$ mg/dL) [4.5 (1.75-6.0) vs. 5.0 (3.0-8.0);  $p=0.31$ ]. The incidence of hypoglycemia [42.9% (n=6) vs. 26.7% (n=4);  $p=0.45$ ] and hypokalemia [64% (n=9) vs. 67% (n=10);  $p=0.23$ ], and mean (SD) time to resolution of acidosis [20.3 (14.8) and 20.3 (7.0);  $p=0.59$ ] were similar in both the groups. None had cerebral edema.

### CONCLUSIONS:

The one and two bag systems were similar to each other with respect to BGV, incidence of complications and time to resolution of acidosis.

## Bone health

[Indian Pediatr.](#) 2018 Feb 15;55(2):115-120. Epub 2017 Dec 14.

### Assisted Physical Exercise for Improving Bone Strength in Preterm Infants Less than 35 Weeks Gestation: A Randomized Controlled Trial.

[Shaw SC](#), [Sankar MJ](#), [Thukral A](#), [Natarajan CK](#), [Deorari AK](#), [Paul VK](#), [Agarwal R](#).

### OBJECTIVE:

To compare the efficacy of daily assisted physical exercise (starting from one week of postnatal age) on bone strength at 40 weeks of post menstrual age to no intervention in infants born between 27 and 34 weeks of gestation.

### DESIGN:

Open-label randomized controlled trial.

### SETTING:

Tertiary-care teaching hospital in northern India from 16 May, 2013 to 21 November, 2013.

### PARTICIPANTS:

50 preterm neonates randomized to Exercise group (n=26) or Control group (n=24).

### INTERVENTION:

Neonates in Exercise group underwent one session of physical exercise daily from one week of age, which included range-of-motion exercises with gentle compression, flexion and extension of all the extremities with movements at each joint done five times, for a total of 10-15 min. Infants in Control group underwent routine care and were not subjected to any massage or exercise.

### MAIN OUTCOME MEASURES:

Primary: Bone speed of sound of left tibia measured by quantitative ultrasound at 40 weeks post menstrual age. Secondary: Anthropometry (weight length and head circumference) and biochemical parameters (calcium, phosphorus, alkaline phosphatase) at 40 weeks post menstrual age.

### RESULTS:

The tibial bone speed of sound was comparable between the two groups [2858 (142) m/s vs. 2791 (122) m/s; mean difference 67.6 m/s; 95% CI - 11 to 146 m/s;  $P=0.38$ ]. There was no difference in anthropometry or biochemical parameters.

### CONCLUSIONS:

Daily assisted physical exercise does not affect the bone strength, anthropometry or biochemical parameters in preterm (27 to 34 weeks) infants.

<https://www.indianpediatrics.net/feb2018/115.pdf>

## Ethics

[Trials](#). 2017 Oct 27;18(1):503. doi: 10.1186/s13063-017-2237-4.

### [Lessons from the field: the conduct of randomized controlled trials in Botswana.](#)

[Bonsu JM](#), [Frasso R](#), [Curry AE](#).

#### **BACKGROUND:**

The conduct of randomized controlled trials (RCTs) in low-resource settings may present unique financial, logistic, and process-related challenges. Middle-income countries that have comparable disease burdens to low-income countries, but greater availability of resources, may be conducive settings for RCTs. Indeed, the country of Botswana is experiencing a rapid increase in the conduct of RCTs. Our objective was to explore the experiences of individuals conducting RCTs in Botswana to gain an understanding of the challenges and adaptive strategies to their work.

#### **METHODS:**

We conducted in-depth interviews with 14 national and international individuals working on RCTs in Botswana. Participants included principal investigators, research coordinators, lab technicians, research assistants, and other healthcare professionals. Interviews were audiotaped, transcribed verbatim, and coded for thematic analysis.

#### **RESULTS:**

Five primary themes were identified: ethics board relationships (including delays in the process); research staff management (including staff attrition and career development); study recruitment and retention (including the use of reimbursements); resource availability (including challenges accessing laboratory equipment); and capacity-building (including issues of exporting locally sourced samples). These themes were explored to discuss key challenges and adaptive strategies.

#### **CONCLUSIONS:**

This study offers a first-hand account of individuals engaged in conducting RCTs in Botswana, a nation that is experiencing a rapid increase in research activities. Findings provide a foundational understanding for researchers in Botswana and trial managers in similar settings when planning RCTs so that the conduct of research does not outpace the ability to manage, support, and regulate it.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5658937/>

[Hum Vaccin Immunother](#). 2017 Sep 2;13(9):2185-2191. doi: 10.1080/21645515.2017.1320624. Epub 2017 Jun 9.

### [Recall and decay of consent information among parents of infants participating in a randomized controlled clinical trial using an audio-visual tool in The Gambia.](#)

[Mboizi RB](#), [Afolabi MO](#), [Okoye M](#), [Kampmann B](#), [Roca A](#), [Idoko OT](#).

#### [Author information](#)

#### **Abstract**

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Communicating essential research information to low literacy research participants in Africa is highly challenging, since this population is vulnerable to poor comprehension of consent information. Several supportive materials have been developed to aid participant comprehension in these settings. Within the framework of a pneumococcal vaccine trial in The Gambia, we **evaluated the recall and decay of consent information during the trial which used an audio-visual tool called 'Speaking Book', to foster comprehension among parents of participating infants.** The Speaking Book was developed in the 2 most widely spoken local languages. Four-hundred and 9 parents of trial infants gave consent to participate in this nested study and were included in the baseline assessment of their knowledge about trial participation. An additional assessment was conducted approximately 90 d later, following completion of the clinical trial protocol. All parents received a Speaking Book at the start of the trial. Trial knowledge was already high at the baseline assessment with no differences related to socio-economic status or education. Knowledge of key trial information was retained at the completion of the study follow-up. The Speaking Book (SB) was well received by the study participants. We hypothesize that the SB may have contributed to the retention of information over the trial follow-up. Further studies evaluating the impact of this innovative tool are thus warranted.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612460/>

## Epilepsy and acute seizures

[Neurol India](#). 2018 Mar-Apr;66(2):385-390. doi: 10.4103/0028-3886.227281.

### **Addition of pyridoxine to prednisolone in the treatment of infantile spasms: A pilot, randomized controlled trial.**

[Kunnanayaka V](#), [Jain P](#), [Sharma S](#), [Seth A](#), [Aneja S](#).

#### **BACKGROUND:**

West syndrome is a catastrophic epilepsy syndrome characterized by infantile spasms, hypsarrhythmia, and developmental arrest or regression.

#### **AIM:**

The aim of this study was to explore the role of pyridoxine in the management of infantile spasms.

#### **SETTING AND DESIGN:**

This was a pilot, randomized, open-label trial conducted at a tertiary level hospital from November 2012 to March 2014.

#### **MATERIALS AND METHODS:**

Children aged 3 months to 3 years presenting with infantile spasms in clusters (at least 1 cluster/day) with hypsarrhythmia or its variants on electroencephalogram (EEG) were enrolled. The study participants were randomized to receive either oral prednisolone (4 mg/kg/day) alone or 30 mg/kg/day of pyridoxine with oral prednisolone. The primary outcome measure was the proportion of children who achieved spasm freedom for 48 h on day-14 after treatment initiation, as per parental reports, in both the groups. The adverse effects were also monitored. The study was registered with clinicaltrials.gov (ClinicalTrials.gov Identifier: [NCT01828437](#)).

#### **RESULTS:**

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Sixty-two children were randomized into the two groups with comparable baseline characteristics. The proportion of children with spasm cessation on day-14 was similar in the two groups (39 vs. 37%,  $P = 0.98$ ). The adverse effects were comparable in both the groups.

### CONCLUSIONS:

The combination of pyridoxine with oral prednisolone was not found to be a beneficial therapy as compared to prednisolone alone in the treatment of infantile spasms in this pilot study. However, high dose pyridoxine may be safe in children with infantile spasms.

[Epilepsy Res.](#) 2017 Dec;138:5-10. doi: 10.1016/j.eplepsyres.2017.10.003. Epub 2017 Oct 6.

### [Effect of carbamazepine and oxcarbazepine on serum neuron-specific enolase in focal seizures: A randomized controlled trial.](#)

[Maiti R](#), [Mishra BR](#), [Sanyal S](#), [Mohapatra D](#), [Parida S](#), [Mishra A](#).

Neuron-specific enolase (NSE) is the most investigated biomarker in the context of epilepsy and brain damage. The present study was conducted to investigate the change in serum NSE in patients with focal seizure and the effect of carbamazepine and oxcarbazepine on serum NSE. The present study is a randomized, open-label, parallel design clinical trial (ClinicalTrials.gov Identifier: [NCT02705768](#)) conducted on 60 patients of focal seizure. After recruitment, detailed history, clinical evaluations including Chalfont-National Hospital seizure severity scale (NHS3), Quality of Life in Epilepsy Inventory (QOLIE-31) and serum NSE estimation were done at baseline. Thirty healthy volunteers were recruited for a baseline evaluation of serum NSE. **After randomization, one group received tablet oxcarbazepine and another group received tablet carbamazepine.** At 4 weeks follow-up, all the parameter were reassessed. Serum NSE level was found to be significantly increased in patients with focal seizure in comparison to healthy volunteers. In both drug groups, serum NSE decreased significantly but the reduction in carbamazepine group (1.43; 95%CI: 0.18-2.67;  $p=0.025$ ) was significantly higher than oxcarbazepine group. NHS3 score, score in all seven domains of QOLIE-31 and final QOLIE-31 score improved significantly in both the groups. In conclusion, serum NSE increases in the patients with focal seizure within 48h of a seizure episode. Therapy with carbamazepine and oxcarbazepine can decrease serum NSE level but the reduction is significantly higher with carbamazepine. Therapy with both the drugs can decrease the severity of epilepsy and improve the quality of life but adverse events were more with carbamazepine.

[Epilepsy Behav.](#) 2017 Nov;76:110-113. doi: 10.1016/j.yebeh.2017.07.005. Epub 2017 Sep 15.

### [Comparison of lacosamide versus sodium valproate in status epilepticus: A pilot study.](#)

[Misra UK](#), [Dubey D](#), [Kalita J](#).

### PURPOSE:

The purpose of this study was to compare the efficacy and safety of lacosamide (LCM) and sodium valproate (SVA) in lorazepam (LOR)-resistant SE.

### METHODS:

Patients with LOR-resistant SE were randomized to intravenous LCM 400mg at the rate of 60mg/kg/min or SVA 30mg/kg at the rate of 100mg/min. The SE severity score (STESS),



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duration of SE and its etiology, and MRI findings were noted. Primary outcome was seizure cessation for 1h, and secondary outcomes were 24h seizure remission, in-hospital death, and severe adverse events (SAE).

### RESULTS:

Sixty-six patients were included, and their median age was 40 (range 18-90) years. **Thirty-three patients each received LCM and SVA.** Their demographic, clinical, STESS, etiology, and MRI findings were not significantly different. One-hour seizure remission was not significantly different between LCM and SVA groups (66.7% vs 69.7%;  $P=0.79$ ). **Twenty-four-hour seizure freedom was insignificantly higher in SVA (20, 66.6%) compared with LCM group (15, 45.5%).** Death (10 vs 12) and composite side effects (4 vs 6) were also not significantly different in LCM and SVA groups. LCM was associated with hypotension and bradycardia (1 patient), and SVA with liver dysfunction (6).

### CONCLUSION:

In patients with LOR-resistant SE, both LCM and SVA have comparable efficacy and safety.

### Comment

*High possibility of a type II error in this study, given the small numbers. The study has not proven lacosamide and sodium valproate are comparable, and larger studies would be needed in order to clarify this.*

[N Engl J Med.](#) 2017 Oct 26;377(17):1639-1647. doi: 10.1056/NEJMoa1615335.

### Surgery for Drug-Resistant Epilepsy in Children.

[Dwivedi R](#), [Ramanujam B](#), [Chandra PS](#), [Sapra S](#), [Gulati S](#), [Kalaivani M](#), [Garg A](#), [Bal CS](#), [Tripathi M](#), [Dwivedi SN](#), [Sagar R](#), [Sarkar C](#), [Tripathi M](#).

### BACKGROUND:

Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials.

### METHODS:

In this single-center trial, we randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). The patients in the medical-therapy group were assigned to a waiting list for surgery. The primary outcome was freedom from seizures at 12 months. Secondary outcomes were the score on the Hague Seizure Severity scale, the Binet-Kamat intelligence quotient, the social quotient on the Vineland Social Maturity Scale, and scores on the Child Behavior Checklist and the Pediatric Quality of Life Inventory.

### RESULTS:

At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group ( $P<0.001$ ). Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to the score on the Hague Seizure Severity scale (difference, 19.4; 95% confidence interval [CI], 15.8 to 23.1;  $P<0.001$ ), on the Child Behavior Checklist (difference, 13.1; 95% CI, 10.7 to 15.6;  $P<0.001$ ), on the Pediatric Quality of Life Inventory (difference, 21.9; 95% CI, 16.4 to 27.6;  $P<0.001$ ), and on the Vineland Social Maturity Scale (difference, 4.7; 95% CI, 0.4 to 9.1;  $P=0.03$ ), but not on the Binet-Kamat intelligence quotient (difference, 2.5; 95% CI, -0.1 to 5.1;  $P=0.06$ ). Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%).

### CONCLUSIONS:

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In this **single-center trial, children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months.** Surgery resulted in anticipated neurologic deficits related to the region of brain resection. (Funded by the Indian Council of Medical Research and others; Clinical Trial Registry-India number, CTRI/2010/091/000525 .).

[https://www.nejm.org/doi/10.1056/NEJMoa1615335?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub%3dwww.ncbi.nlm.nih.gov](https://www.nejm.org/doi/10.1056/NEJMoa1615335?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)

[Seizure](#). 2017 Dec;53:55-61. doi: 10.1016/j.seizure.2017.11.003. Epub 2017 Nov 7.

### **Telephonic review for outpatients with epilepsy-A prospective randomized, parallel group study.**

[Bahrani K](#), [Singh MB](#), [Bhatia R](#), [Prasad K](#), [Vibha D](#), [Shukla G](#), [Vishnubhatla S](#), [Patterson V](#).

#### **PURPOSE:**

Our objective was to assess how telephonic review of outpatients with stable epilepsy compared with conventional face-to-face clinic management.

#### **METHODS:**

We constructed a randomized parallel group study of suitable patients attending our Epilepsy Clinic and compared telephonic review with conventional clinic visit based management. Primary outcomes were the percentage of patients with breakthrough seizures and total number of breakthrough seizures. We also compared cost, patient satisfaction and numbers defaulting.

#### **RESULTS:**

**A total of 465 patients were randomized and 429 were included in the final analysis. There was no significant difference in breakthrough seizures between the two groups.** Mean time spent in the consultation was 10min in the telephone group (FT) and 22h in the face-to-face group (FC) and cost was INR 865 more expensive on an average in the FC group. Satisfaction was over 90% in the FT group. Significantly more people in the FC group were lost to follow-up.

#### **CONCLUSION:**

This study provides Class I evidence that the number of stable epilepsy patients who have breakthrough seizures and the total number of breakthrough seizures remain the same irrespective of whether patients are reviewed telephonically or face-to-face in the clinic. Clinicians managing epilepsy patients should consider using telephonic review for selected patients. Telephonic reviews have the potential of effectively reducing the secondary treatment gap in millions of patients who do not have easy access to doctors.

## Hygiene, sanitation and environmental health

(See also Environmental enteropathy)

## Indoor air pollution

[Environ Res Lett.](#) 2018;13(4). pii: 045011. doi: 10.1088/1748-9326/aab047. Epub 2018 Apr 17.

### **Household air pollution (HAP), microenvironment and child health: Strategies for mitigating HAP exposure in urban Rwanda.**

[Das I](#), [Pedit J](#), [Handa S](#), [Jagger P](#).

Exposure to household air pollution (HAP) from cooking and heating with solid fuels is major risk factor for morbidity and mortality in sub-Saharan Africa. Children under five are particularly at risk for acute lower respiratory infection. We use baseline data from randomized controlled trial evaluating a household energy intervention in Gisenyi, Rwanda to investigate the role of the microenvironment as a determinant of children's HAP-related health symptoms. Our sample includes 529 households, with 694 children under five. We examine the association between likelihood of HAP-related health symptom prevalence and characteristics of the microenvironment including: dwelling and cooking area structure; distance to nearest road; and tree cover. **We find that children residing in groups of enclosed dwellings, in households that cook indoors, and in households proximate to tree cover, are significantly more likely to experience symptoms of respiratory infection, illness with cough and difficulty breathing.** On the other hand, children in households with cemented floors and ventilation holes in the cooking area, are significantly less likely to experience the same symptoms. Our findings suggest that in addition to promoting increased access to clean cooking technologies, there are important infrastructure and micro-environment related interventions that mitigate HAP exposure.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5909824/>

[PloS One.](#) 2018 Apr 12;13(4):e0193376. doi: 10.1371/journal.pone.0193376. eCollection 2018.

### **From kitchen to classroom: Assessing the impact of cleaner burning biomass-fuelled cookstoves on primary school attendance in Karonga district, northern Malawi.**

[Kelly CA](#), [Crampin AC](#), [Mortimer K](#), [Dube A](#), [Malava J](#), [Johnston D](#), [Unterhalter E](#), [Glynn JR](#).

Household air pollution from burning solid fuels is responsible for an estimated 2.9 million premature deaths worldwide each year and 4.5% of global disability-adjusted life years, while cooking and fuel collection pose a considerable time burden, particularly for women and children. Cleaner burning biomass-fuelled cookstoves have the potential to lower exposure to household air pollution as well as reduce fuelwood demand by increasing the combustion efficiency of cooking fires, which may in turn yield ancillary benefits in other domains. The present paper capitalises on opportunities offered by the Cooking and Pneumonia Study (CAPS), the largest randomised trial of biomass-fuelled cookstoves on health outcomes conducted to date, the design of which allows for the evaluation of additional outcomes at scale. This mixed methods study assesses the impact of cookstoves on primary school absenteeism in Karonga district, northern Malawi, in particular by conferring health and time and resource gains on young people aged 5-18. The analysis combines quantitative data from 6168 primary school students with in-depth interviews and focus group discussions carried out among 48 students in the same catchment area in 2016. Negative binomial regression models find no evidence that the cookstoves affected primary school absenteeism overall [IRR 0.92 (0.71-1.18),  $p = 0.51$ ]. **Qualitative analysis suggests that the cookstoves did not sufficiently improve household health to influence school attendance, while the time and resource burdens**

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associated with cooking activities-although reduced in intervention households-were considered to be compatible with school attendance in both trial arms. More research is needed to assess whether the cookstoves influenced educational outcomes not captured by the attendance measure available, such as timely arrival to school or hours spent on homework.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896910/>

## Water, Sanitation and Hygiene

[Lancet Glob Health](#). 2018 Mar;6(3):e316-e329. doi: 10.1016/S2214-109X(18)30005-6. Epub 2018 Jan 29.

### Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Kenya: a cluster-randomised controlled trial.

[Null C](#), [Stewart CP](#), [Pickering AJ](#), [Dentz HN](#), [Arnold BF](#), [Arnold CD](#), [Benjamin-Chung J](#), [Clasen T](#), [Dewey KG](#), [Fernald LCH](#), [Hubbard AE](#), [Kariger P](#), [Lin A](#), [Luby SP](#), [Mertens A](#), [Njenga SM](#), [Nyambane G](#), [Ram PK](#), [Colford JM Jr](#).

#### **BACKGROUND:**

Poor nutrition and exposure to faecal contamination are associated with diarrhoea and growth faltering, both of which have long-term consequences for child health. We aimed to assess whether water, sanitation, handwashing, and nutrition interventions reduced diarrhoea or growth faltering.

#### **METHODS:**

The WASH Benefits cluster-randomised trial enrolled pregnant women from villages in rural Kenya and evaluated outcomes at 1 year and 2 years of follow-up. Geographically-adjacent clusters were block-randomised to active control (household visits to measure mid-upper-arm circumference), passive control (data collection only), or compound-level interventions including household visits to promote target behaviours: drinking chlorinated water (water); safe sanitation consisting of disposing faeces in an improved latrine (sanitation); handwashing with soap (handwashing); combined water, sanitation, and handwashing; counselling on appropriate maternal, infant, and young child feeding plus small-quantity lipid-based nutrient supplements from 6-24 months (nutrition); and combined water, sanitation, handwashing, and nutrition. Primary outcomes were caregiver-reported diarrhoea in the past 7 days and length-for-age Z score at year 2 in index children born to the enrolled pregnant women. Masking was not possible for data collection, but analyses were masked. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number [NCT01704105](#).

#### **FINDINGS:**

Between Nov 27, 2012, and May 21, 2014, 8246 women in 702 clusters were enrolled and randomly assigned an intervention or control group. 1919 women were assigned to the active control group; 938 to passive control; 904 to water; 892 to sanitation; 917 to handwashing; 912 to combined water, sanitation, and handwashing; 843 to nutrition; and 921 to combined water, sanitation, handwashing, and nutrition. Data on diarrhoea at year 1 or year 2 were available for 6494 children and data on length-for-age Z score in year 2 were available for 6583 children (86% of living children were measured at year 2). Adherence indicators for sanitation, handwashing, and nutrition were more than 70% at year 1, handwashing fell to less than 25% at year 2, and for water was less than 45% at year 1 and less than 25% at year 2; combined groups were comparable to single groups. None of the interventions reduced

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diarrhoea prevalence compared with the active control. Compared with active control (length-for-age Z score  $-1.54$ ) children in nutrition and combined water, sanitation, handwashing, and nutrition were taller by year 2 (mean difference  $0.13$  [95% CI  $0.01-0.25$ ] in the nutrition group;  $0.16$  [ $0.05-0.27$ ] in the combined water, sanitation, handwashing, and nutrition group). The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.

### INTERPRETATION:

**Behaviour change messaging combined with technologically simple interventions such as water treatment, household sanitation upgrades from unimproved to improved latrines, and handwashing stations did not reduce childhood diarrhoea or improve growth, even when adherence was at least as high as has been achieved by other programmes.**

Counselling and supplementation in the nutrition group and combined water, sanitation, handwashing, and nutrition interventions led to small growth benefits, but there was no advantage to integrating water, sanitation, and handwashing with nutrition. The interventions might have been more efficacious with higher adherence or in an environment with lower baseline sanitation coverage, especially in this context of high diarrhoea prevalence.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5809717/>

[Lancet Glob Health](#). 2018 Mar;6(3):e302-e315. doi: 10.1016/S2214-109X(17)30490-4. Epub 2018 Jan 29.

### **Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial.**

[Luby SP](#), [Rahman M](#), [Arnold BF](#), [Unicomb L](#), [Ashraf S](#), [Winch PJ](#), [Stewart CP](#), [Begum F](#), [Hussain F](#), [Benjamin-Chung J](#), [Leontsini E](#), [Naser AM](#), [Parvez SM](#), [Hubbard AE](#), [Lin A](#), [Nizame FA](#), [Jannat K](#), [Ercumen A](#), [Ram PK](#), [Das KK](#), [Abedin J](#), [Clasen TF](#), [Dewey KG](#), [Fernald LC](#), [Null C](#), [Ahmed T](#), [Colford JM Jr](#).

### BACKGROUND:

Diarrhoea and growth faltering in early childhood are associated with subsequent adverse outcomes. We aimed to assess whether water quality, sanitation, and handwashing interventions alone or combined with nutrition interventions reduced diarrhoea or growth faltering.

### METHODS:

The WASH Benefits Bangladesh cluster-randomised trial enrolled pregnant women from villages in rural Bangladesh and evaluated outcomes at 1-year and 2-years' follow-up. Pregnant women in geographically adjacent clusters were block-randomised to one of seven clusters: chlorinated drinking water (water); upgraded sanitation (sanitation); promotion of handwashing with soap (handwashing); combined water, sanitation, and handwashing; counselling on appropriate child nutrition plus lipid-based nutrient supplements (nutrition); combined water, sanitation, handwashing, and nutrition; and control (data collection only). Primary outcomes were caregiver-reported diarrhoea in the past 7 days among children who were in utero or younger than 3 years at enrolment and length-for-age Z score among children born to enrolled pregnant women. Masking was not possible for data collection, but analyses were masked. Analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, number NCC01590095.

### FINDINGS:

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Between May 31, 2012, and July 7, 2013, 5551 pregnant women in 720 clusters were randomly allocated to one of seven groups. 1382 women were assigned to the control group; 698 to water; 696 to sanitation; 688 to handwashing; 702 to water, sanitation, and handwashing; 699 to nutrition; and 686 to water, sanitation, handwashing, and nutrition. 331 (6%) women were lost to follow-up. Data on diarrhoea at year 1 or year 2 (combined) were available for 14 425 children (7331 in year 1, 7094 in year 2) and data on length-for-age Z score in year 2 were available for 4584 children (92% of living children were measured at year 2). All interventions had high adherence. Compared with a prevalence of 5.7% (200 of 3517 child weeks) in the control group, 7-day diarrhoea prevalence was lower among index children and children under 3 years at enrolment who received sanitation (61 [3.5%] of 1760; prevalence ratio 0.61, 95% CI 0.46-0.81), handwashing (62 [3.5%] of 1795; 0.60, 0.45-0.80), combined water, sanitation, and handwashing (74 [3.9%] of 1902; 0.69, 0.53-0.90), nutrition (62 [3.5%] of 1766; 0.64, 0.49-0.85), and combined water, sanitation, handwashing, and nutrition (66 [3.5%] of 1861; 0.62, 0.47-0.81); diarrhoea prevalence was not significantly lower in children receiving water treatment (90 [4.9%] of 1824; 0.89, 0.70-1.13). Compared with control (mean length-for-age Z score -1.79), children were taller by year 2 in the nutrition group (mean difference 0.25 [95% CI 0.15-0.36]) and in the combined water, sanitation, handwashing, and nutrition group (0.13 [0.02-0.24]). The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.

### INTERPRETATION:

Nutrient supplementation and counselling modestly improved linear growth, but there was no benefit to the integration of water, sanitation, and handwashing with nutrition. Adherence was high in all groups and diarrhoea prevalence was reduced in all intervention groups except water treatment. Combined water, sanitation, and handwashing interventions provided no additive benefit over single interventions.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5809718/>

\*\*\* [Indian Pediatr.](#) 2018 May 15;55(5):381-393. Epub 2018 Feb 9.

### [Impact of Water, Sanitation and Hygiene Interventions on Growth, Non-diarrheal Morbidity and Mortality in Children Residing in Low- and Middle-income Countries: A Systematic Review.](#)

[Gera T, Shah D, Sachdev HS.](#)

### OBJECTIVE:

To evaluate the impact of water, sanitation and hygiene (WASH) interventions in children (age <18 y) on growth, non-diarrheal morbidity and mortality in children.

### DESIGN:

Systematic review of randomized controlled trials, non-randomized controlled trials and controlled before-after studies.

### SETTING:

Low- and middle-income countries.

### PARTICIPANTS:

41 trials with WASH intervention, incorporating data on 113055 children.

### INTERVENTION:

Hygiene promotion and education (15 trials), water intervention (10 trials), sanitation improvement (7 trials), all three components of WASH (4 trials), combined water and sanitation (1 trial), and sanitation and hygiene (1 trial).

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### OUTCOME MEASURES:

(i) Anthropometry: weight, height, weight-for-height, mid-arm circumference; (ii) Prevalence of malnutrition; (iii) Non-diarrheal morbidity; and (iv) mortality.

### RESULTS:

There may be little or no effect of hygiene intervention on most anthropometric parameters (low- to very-low quality evidence). Hygiene intervention reduced the risk of developing Acute respiratory infections by 24% (RR 0.76; 95% CI 0.59, 0.98; moderate quality evidence), cough by 10% (RR 0.90; 95% CI 0.83, 0.97; moderate quality evidence), laboratory-confirmed influenza by 50% (RR 0.5; 95% CI 0.41, 0.62; very low quality evidence), fever by 13% (RR 0.87; 95% CI 0.74, 1.02; moderate quality evidence), and conjunctivitis by 51% (RR 0.49; 95% CI 0.45, 0.55; low quality evidence). There was low quality evidence to suggest no impact of hygiene intervention on mortality (RR 0.65; 95% CI 0.25, 1.7). Improvement in water supply and quality was associated with slightly higher weight-for-age Z-score (MD 0.03; 95% CI 0, 0.06; low quality evidence), but no significant impact on other anthropometric parameters or infectious morbidity (low to very low quality evidence). There was very low quality evidence to suggest reduction in mortality (RR 0.45; 95% CI 0.25, 0.81). Improvement in sanitation had a variable effect on the anthropometry and infectious morbidity. Combined water, sanitation and hygiene intervention improved height-for-age Z scores (MD 0.22; 95% CI 0.12, 0.32) and decreased the risk of stunting by 13% (RR 0.87; 95% CI 0.81, 0.94) (very low quality of evidence). There was no evidence of significant effect of combined WASH interventions on non-diarrheal morbidity (fever, respiratory infections, intestinal helminth infection and school absenteeism) (low- to very-low quality of evidence). Any WASH intervention (considered together) resulted in lower risk of underweight (RR 0.81; 95% CI 0.69, 0.96), stunting (RR 0.77; 95% CI 0.68, 0.86) and wasting (RR 0.12, 0.85) (low- to very-low quality of evidence).

### CONCLUSIONS:

Available evidence suggests that there **may be little or no effect of WASH interventions on the anthropometric indices in children from low- and middle-income countries**. There is low- to very-low quality of evidence to suggest decrease in prevalence of wasting, stunting and underweight. **WASH interventions (especially hygiene intervention) were associated with lower risk of non-diarrheal morbidity (very low to moderate quality evidence). There was very low quality evidence to suggest some decrease to no change in mortality.** These potential health benefits lend support to the ongoing efforts for provision of safe and adequate water supply, sanitation and hygiene.

<https://www.indianpediatrics.net/may2018/381.pdf>

[Am J Trop Med Hyg. 2017 Sep;97\(3\):904-913. doi: 10.4269/ajtmh.16-0964. Epub 2017 Jul 19. School Children's Intestinal Parasite and Nutritional Status One Year after Complementary School Garden, Nutrition, Water, Sanitation, and Hygiene Interventions in Burkina Faso.](#)

[Erismann S, Diagbouga S, Schindler C, Odermatt P, Knoblauch AM, Gerold J, Leuenberger A, Shrestha A, Tarnagda G, Utzinger J, Cissé G.](#)

The potential health benefits of combined agricultural, nutrition, water, sanitation, and hygiene (WASH) interventions are poorly understood. We aimed to determine whether complementary school garden, nutrition, and WASH interventions reduce intestinal parasites and improve school children's nutritional status in two regions of Burkina Faso. A cluster-randomized controlled trial was conducted in the Plateau Central and Center-Ouest regions of Burkina Faso. A total of 360 randomly selected children, aged 8-15 years, had complete baseline and end-line

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survey data. Mixed regression models were used to assess the impact of the interventions, controlling for baseline characteristics. **The prevalence of intestinal parasitic infections decreased both in intervention and control schools, but the decrease was significantly higher in the intervention schools related to the control schools (odds ratio [OR] of the intervention effect = 0.2, 95% confidence interval [CI] = 0.1-0.5).** Indices of undernutrition did not decrease at end-line in intervention schools. Safe handwashing practices before eating and the use of latrines at schools were significantly higher in the intervention schools than in the control schools at end-line (OR = 6.9, 95% CI = 1.4-34.4, and OR = 14.9, 95% CI = 1.4-153.9, respectively). Parameters of water quality remained unchanged. **A combination of agricultural, nutritional, and WASH-related interventions embedded in the social-ecological systems and delivered through the school platform improved several child health outcomes, including intestinal parasitic infections and some WASH-related behaviors.** Sustained interventions with stronger household and community-based components are, however, needed to improve school children's health in the long-term.

[Am J Trop Med Hyg.](#) 2017 Sep;97(3):876-887. doi: 10.4269/ajtmh.16-1006. Epub 2017 Jul 27.  
**[Use of Serologic Responses against Enteropathogens to Assess the Impact of a Point-of-Use Water Filter: A Randomized Controlled Trial in Western Province, Rwanda.](#)**

[Zambrano LD](#), [Priest JW](#), [Ivan E](#), [Rusine J](#), [Nagel C](#), [Kirby M](#), [Rosa G](#), [Clasen TF](#).

Diarrhea is a leading contributor to childhood morbidity and mortality in sub-Saharan Africa. Given the challenge of blinding most water, sanitation, and hygiene (WASH) interventions, diarrheal disease outcome measures in WASH intervention trials are subject to potential bias and misclassification. Using the platform of a cluster-randomized controlled trial of a household-based drinking water filter in western province, Rwanda, we assessed the impact of the drinking water filter on enteric seroconversion in young children as a health outcome and examined the association between serologic responses and caregiver-reported diarrhea. Among the 2,179 children enrolled in the trial, 189 children 6-12 months of age were enrolled in a nested serology study. These children had their blood drawn at baseline and 6-12 months after the intervention was distributed. Multiplex serologic assays for *Giardia*, *Cryptosporidium*, *Entamoeba histolytica*, norovirus, *Campylobacter*, enterotoxigenic *Escherichia coli* and *Vibrio cholerae* were performed. **Despite imperfect uptake, receipt of the water filter was associated with a significant decrease in seroprevalence of IgG directed against *Cryptosporidium parvum* Cp17 and Cp23 (relative risk [RR]: 0.62, 95% confidence interval [CI]: 0.44-0.89).** Serologic responses were positively associated with reported diarrhea in the previous 7 days for both *Giardia intestinalis* (RR: 1.94, 95% CI: 1.04-3.63) and *C. parvum* (RR: 2.21, 95% CI: 1.09-4.50). Serologic responses for all antigens generally increased in the follow-up round, rising sharply after 12 months of age. The water filter is associated with reduced serologic responses against *C. parvum*, a proxy for exposure and infection; therefore, serologic responses against protozoa may be a suitable health outcome measure for WASH trials among children with diarrhea.

[BMC Public Health.](#) 2018 Feb 1;18(1):208. doi: 10.1186/s12889-018-5092-7.



**Interventions to reduce post-acute consequences of diarrheal disease in children: a systematic review.**

Pavlinac PB, Brander RL, Atlas HE, John-Stewart GC, Denno DM, Walson JL.

**BACKGROUND:**

Although acute diarrhea often leads to acute dehydration and electrolyte imbalance, children with diarrhea also suffer long term morbidity, including recurrent or prolonged diarrhea, loss of weight, and linear growth faltering. They are also at increased risk of post-acute mortality. **The objective of this systematic review was to identify interventions that address these longer term consequences of diarrhea.**

**METHODS:**

We searched Medline for randomized controlled trials (RCTs) of interventions conducted in low- and middle-income countries, published between 1980 and 2016 that included children under 15 years of age with diarrhea and follow-up of at least 7 days. Effect measures were summarized by intervention. PRISMA guidelines were followed.

**RESULTS:**

Among 314 otherwise eligible RCTs, 65% were excluded because follow-up did not extend beyond 7 days. Forty-six trials were included, the majority of which (59%) were conducted in Southeast Asia (41% in Bangladesh alone). Most studies were small, 76% included less than 200 participants. **Interventions included: therapeutic zinc alone (28.3%) or in combination with vitamin A (4.3%), high protein diets (19.6%), probiotics (10.9%), lactose free diets (10.9%), oral rehydration solution (ORS) formulations (8.7%), dietary supplements (6.5%), other dietary interventions (6.5%), and antimicrobials (4.3%).** Prolonged or recurrent diarrhea was the most commonly reported outcome, and was assessed in ORS, probiotic, vitamin A, and zinc trials with no consistent benefit observed. **Seven trials evaluated mortality, with follow-up times ranging from 8 days to 2 years. Only a single trial found a mortality benefit (therapeutic zinc).** There were mixed results for dietary interventions affecting growth and diarrhea outcomes in the post-acute period.

**CONCLUSION:**

Despite the significant post-acute mortality and morbidity associated with diarrheal episodes, there is sparse evidence evaluating the effects of interventions to decrease these sequelae. Adequately powered trials with extended follow-up are needed to identify effective interventions to prevent post-acute diarrhea outcomes.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5796301/>

Infect Dis Poverty. 2017 Sep 19;6(1):137. doi: 10.1186/s40249-017-0351-x.

**Effects of improved sanitation on diarrheal reduction for children under five in Idiofa, DR Congo: a cluster randomized trial.**

Cha S, Lee J, Seo D, Park BM, Mansiangi P, Bernard K, Mulakub-Yazho GJN, Famasulu HM.

**BACKGROUND:**

The lack of safe water and sanitation contributes to the rampancy of diarrhea in many developing countries.

**METHODS:**

This study describes the design of a cluster-randomized trial in Idiofa, the Democratic Republic of the Congo, seeking evidence of the impact of improved sanitation on diarrhea for children

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under four. Of the 276 quarters, 18 quarters were randomly allocated to the intervention or control arm. Seven hundred and twenty households were sampled and the youngest under-four child in each household was registered for this study. The primary endpoint of the study is diarrheal incidence, prevalence and duration in children under five.

### DISCUSSION:

Material subsidies will be provided only to the households who complete pit digging plus superstructure and roof construction, regardless of their income level. This study employs a Sanitation Calendar so that the mother of each household can record the diarrheal episodes of her under-four children on a daily basis. The diary enables examination of the effect of the sanitation intervention on diarrhea duration and also resolves the limitation of the small number of clusters in the trial. In addition, the project will be monitored through the 'Sanitation Map', on which all households in the study area, including both the control and intervention arms, are registered. To avoid information bias or courtesy bias, photos will be taken of the latrine during the household visit, and a supervisor will determine well-equipped latrine uptake based on the photos. This reduces the possibility of recall bias and under- or over-estimation of diarrhea, which was the main limitation of previous studies.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604412/>

[Global Health](#). 2017 Oct 17;13(1):78. doi: 10.1186/s12992-017-0302-0.

### [Disentangling the effects of a multiple behaviour change intervention for diarrhoea control in Zambia: a theory-based process evaluation.](#)

[Greenland K](#), [Chipungu J](#), [Chilekwa J](#), [Chilengi R](#), [Curtis V](#).

### BACKGROUND:

Diarrhoea is a leading cause of child death in Zambia. As elsewhere, the disease burden could be greatly reduced through caregiver uptake of existing prevention and treatment strategies. We recently reported the results of the **Komboni Housewives intervention which tested a novel strategy employing motives including affiliation and disgust to improve caregiver practice of four diarrhoea control behaviours: exclusive breastfeeding; handwashing with soap; and correct preparation and use of oral rehydration salts (ORS) and zinc**. The intervention was delivered via community events (women's forums and road shows), at health clinics (group session) and via radio. A cluster randomised trial revealed that the intervention resulted in a small improvement in exclusive breastfeeding practices, but was only associated with small changes in the other behaviours in areas with greater intervention exposure. This paper reports the findings of the process evaluation that was conducted alongside the trial to investigate how factors associated with intervention delivery and receipt influenced caregiver uptake of the target behaviours.

### METHODS:

Process data were collected from the eight peri-urban and rural intervention areas throughout the six-month implementation period and in all 16 clusters 4-6 weeks afterwards. Intervention implementation (fidelity, reach, dose delivered and recruitment strategies) and receipt (participant engagement and responses, and mediators) were explored through review of intervention activity logs, unannounced observation of intervention events, semi-structured interviews, focus groups with implementers and intervention recipients, and household surveys. Evaluation methods and analyses were guided by the intervention's theory of change and the evaluation framework of Linnan and Steckler.

### RESULTS:

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Intervention reach was lower than intended: 39% of the surveyed population reported attending one or more face-to-face intervention event, of whom only 11% attended two or more intervention events. The intervention was not equally feasible to deliver in all settings: fewer events took place in remote rural areas, and the intervention did not adequately penetrate communities in several peri-urban sites where the population density was high, the population was slightly higher socio-economic status, recruitment was challenging, and numerous alternative sources of entertainment existed. Adaptations made by the implementers affected the fidelity of implementation of messages for all target behaviours. Incorrect messages were consequently recalled by intervention recipients. **Participants were most receptive to the novel disgust and skills-based interactive demonstrations targeting exclusive breastfeeding and ORS preparation respectively. However, initial disgust elicitation was not followed by a change in associated psychological mediators, and social norms were not measurably changed.**

### CONCLUSIONS:

The lack of measured behaviour change was likely due to issues with both the intervention's content and its delivery. Achieving high reach and intensity in community interventions delivered in diverse settings is challenging. Achieving high fidelity is also challenging when multiple behaviours are targeted for change. Further work using improved tools is needed to explore the use of subconscious motives in behaviour change interventions. To better uncover how and why interventions achieve their measured effects, process evaluations of complex interventions should develop and employ frameworks for investigation and interpretation that are structured around the intervention's theory of change and the local context.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5645837/>

[Soc Sci Med.](#) 2018 Jan;196:66-76. doi: 10.1016/j.socscimed.2017.10.025. Epub 2017 Nov 4.  
**[Enhancing handwashing frequency and technique of primary caregivers in Harare, Zimbabwe: A cluster-randomized controlled trial using behavioral and microbial outcomes.](#)**

[Friedrich MND](#), [Kappler A](#), [Mosler HJ](#).

### RATIONALE:

Consistent hand hygiene prevents diarrheal and respiratory diseases, but it is often not practiced. The disease burden is highest in low-income settings, which need effective interventions to promote domestic handwashing. To date, most handwashing campaigns have focused on promoting frequent handwashing at key times, whereas specifically promoting handwashing techniques proven to be effective in removing microbes has been confined to healthcare settings.

### METHODS:

We used a cluster-randomized, factorial, controlled trial to test the effects of two handwashing interventions on the behavior of primary caregivers in Harare, Zimbabwe. One intervention targeted caregivers directly, and the other targeted them through their children. Outcome measures were surveyed at baseline and six weeks' follow-up and included observed handwashing frequency and technique and fecal hand contamination before and after handwashing.

### RESULTS:

Combining the direct and indirect interventions resulted in observed handwashing with soap at 28% of critical handwashing times, while the corresponding figure for the non-intervention control was 5%. Observed handwashing technique, measured as the number of correctly

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performed handwashing steps, increased to an average of 4.2, while the control averaged 3.4 steps. Demonstrated handwashing technique increased to a mean of 6.8 steps; the control averaged 5.2 steps. No statistically significant group differences in fecal hand contamination before or after handwashing were detected.

### CONCLUSIONS:

The results provide strong evidence that the campaign successfully improved handwashing frequency and technique. It shows that the population-tailored design, based on social-cognitive theory, provides effective means for developing powerful interventions for handwashing behavior change. We did not find evidence that children acted as strong agents of handwashing behavior change. The fact that the microbial effectiveness of handwashing did not improve despite strong improvements in handwashing technique calls for critical evaluation of existing handwashing recommendations. The aim of future handwashing campaigns should be to promote both frequent and effective handwashing.

[PLoS Negl Trop Dis](#). 2018 Apr 16;12(4):e0006418. doi: 10.1371/journal.pntd.0006418. eCollection 2018 Apr.

### [The impact of school water, sanitation, and hygiene improvements on infectious disease using serum antibody detection.](#)

[Chard AN](#), [Trinies V](#), [Moss DM](#), [Chang HH](#), [Doumbia S](#), Lammie PJ, [Freeman MC](#).

### BACKGROUND:

Evidence from recent studies assessing the impact of school water, sanitation and hygiene (WASH) interventions on child health has been mixed. Self-reports of disease are subject to bias, and few WASH impact evaluations employ objective health measures to assess reductions in disease and exposure to pathogens. We utilized antibody responses from dried blood spots (DBS) to measure the impact of a school WASH intervention on infectious disease among pupils in Mali.

### METHODOLOGY/PRINCIPAL FINDINGS:

We randomly selected 21 beneficiary primary schools and their 21 matched comparison schools participating in a matched-control trial of a comprehensive school-based WASH intervention in Mali. DBS were collected from 20 randomly selected pupils in each school (n = 807). We analyzed eluted IgG from the DBS using a Luminex multiplex bead assay to 28 antigens from 17 different pathogens. Factor analysis identified three distinct latent variables representing vector-transmitted disease (driven primarily by dengue), food/water-transmitted enteric disease (driven primarily by *Escherichia coli* and *Vibrio cholerae*), and person-to-person transmitted enteric disease (driven primarily by norovirus). Data were analyzed using a linear latent variable model. Antibody evidence of food/water-transmitted enteric disease (change in latent variable mean ( $\beta$ ) = -0.24; 95% CI: -0.53, -0.13) and person-to-person transmitted enteric disease ( $\beta$  = -0.17; 95% CI: -0.42, -0.04) was lower among pupils attending beneficiary schools. There was no difference in antibody evidence of vector-transmitted disease ( $\beta$  = 0.11; 95% CI: -0.05, 0.33).

### CONCLUSIONS/SIGNIFICANCE:

**Evidence of enteric disease was lower among pupils attending schools benefitting from school WASH improvements than students attending comparison schools.** These findings support results from the parent study, which also found reduced incidence of self-reported diarrhea among pupils of beneficiary schools. DBS collection was feasible in this resource-poor field setting and provided objective evidence of disease at a low cost per antigen analyzed, making it an effective measurement tool for the WASH field.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5919668/>

[PLoS One](#). 2017 Nov 1;12(11):e0186228. doi: 10.1371/journal.pone.0186228. eCollection 2017.

**[Are there synergies from combining hygiene and sanitation promotion campaigns: Evidence from a large-scale cluster-randomized trial in rural Tanzania.](#)**

[Briceño B](#), [Coville A](#), [Gertler P](#), [Martinez S](#).

**SUMMARY:**

The current evidence on handwashing and sanitation programs suggests limited impacts on health when at-scale interventions have been tested in isolation. However, no published experimental evidence currently exists that tests the interaction effects between sanitation and handwashing. We present the results of two large-scale, government-led handwashing and sanitation promotion campaigns in rural Tanzania, with the objective of tracing the causal chain from hygiene and sanitation promotion to changes in child health outcomes and specifically testing for potential interaction effects of combining handwashing and sanitation interventions.

**METHODS:**

The study is a factorial cluster-randomized control trial where 181 rural wards from 10 districts in Tanzania were randomly assigned to receive sanitation promotion, handwashing promotion, both interventions together or neither (control). Interventions were rolled out from February 2009 to June 2011 and the endline survey was conducted from May to November 2012, approximately one year after program completion. The sample was composed of households with children under 5 years old in the two largest villages in each ward. Masking was not possible due to the nature of the intervention, but enumerators played no part in the intervention and were blinded to treatment status. **The primary outcome of interest was 7-day diarrhea prevalence for children under five.** Intermediate outcomes of behavior change including improved latrine construction, levels of open defecation and handwashing with soap were also analyzed. Secondary health outcomes included anemia, height-for-age and weight-for-age of children under 5. An intention-to-treat analysis was used to assess the relationship between the interventions and outcomes of interest.

**FINDINGS:**

One year after the end of the program, ownership of improved latrines increased from 49.7% to 64.8% (95% CI 57.9%-71.7%) and regular open defecation decreased from 23.1% to 11.1% (95% CI 3.5%-18.7%) in sanitation promotion-only wards. Households in handwashing promotion-only wards showed marginal improvements in handwashing behavior related to food preparation but not at other critical junctures. There were no detectable interaction effects for the combined intervention. The associated cost-per-household gaining access to improved sanitation is estimated to be USD \$194. **Final effects on child health measured through diarrhea, anemia, stunting and wasting were absent in all treatment groups.**

**INTERPRETATION:**

Although statistically significant, the changes in intermediate outcomes achieved through each intervention in isolation were not large enough to generate meaningful health impacts. With no observable signs of interaction, the combined intervention produced similar results. The study highlights the importance of focusing on intermediate outcomes of take up and behavior change as a critical first step in large-scale programs before realizing the changes in health that sanitation and hygiene interventions aim to deliver.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5665426/>

[Elife](#). 2017 Oct 5;6. pii: e29365. doi: 10.7554/eLife.29365.

**[Effects of water, sanitation, handwashing, and nutritional interventions on telomere length among children in a cluster-randomized controlled trial in rural Bangladesh.](#)**

[Lin A](#), [Arnold BF](#), [Mertens AN](#), [Lin J](#), [Benjamin-Chung J](#), [Ali S](#), [Hubbard AE](#), [Stewart CP](#), [Shoab AK](#), [Rahman MZ](#), [Hossen MS](#), [Mutsuddi P](#), [Famida SL](#), [Akther S](#), [Rahman M](#), [Unicomb L](#), [Dhabhar FS](#), [Fernald LCH](#), [Colford JM Jr](#), [Luby SP](#).

**Background:** Shorter childhood telomere length (TL) and more rapid TL attrition are widely regarded as manifestations of stress. However, the potential effects of health interventions on child TL are unknown. We hypothesized that a water, sanitation, handwashing (WSH), and nutritional intervention would slow TL attrition during the first two years of life. **Methods:** In a trial in rural Bangladesh (ClinicalTrials.gov, [NCT01590095](#)), we randomized geographical clusters of pregnant women into individual water treatment, sanitation, handwashing, nutrition, combined WSH, combined nutrition plus WSH (N + WSH), or control arms. We conducted a substudy enrolling children from the control arm and the N + WSH intervention arm. Participants and outcome assessors were not masked; analyses were masked. Relative TL was measured at 1 and 2 years after intervention, and the change in relative TL was reported. Analysis was intention-to-treat. **Findings:** Between May 2012 and July 2013, in the overall trial, we randomized 720 geographical clusters of 5551 pregnant women to a control or an intervention arm. In this substudy, after 1 year of intervention, we assessed a total of 662 children (341 intervention and 321 control) and 713 children after 2 years of intervention (383 intervention and 330 control). **Children in the intervention arm had significantly shorter relative TL compared with controls after 1 year of intervention (difference -163 base pairs (bp), p=0.001).** Between years 1 and 2, TL increased in the intervention arm (+76 bp) and decreased in the controls (-23 bp) (p=0.050). After 2 years, there was no difference between the arms (p=0.305). **Interpretation:** Our unexpected finding of increased telomere attrition during the first year of life in the intervention group suggests that rapid telomere attrition during this critical period could reflect the improved growth in the intervention group, rather than accumulated stress. **Funding:** The Bill and Melinda Gates Foundation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5675593/>

## Haematological disorders

(See also Anaemia and iron deficiency, Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

[Blood](#). 2017 Dec 14;130(24):2585-2593. doi: 10.1182/blood-2017-06-788935. Epub 2017 Oct 19.

**[Novel use Of Hydroxyurea in an African Region with Malaria \(NOHARM\): a trial for children with sickle cell anemia.](#)**

[Opoka RO](#), [Ndugwa CM](#), [Latham TS](#), [Lane A](#), [Hume HA](#), [Kasirye P](#), [Hodges JS](#), [Ware RE](#), [John CC](#).

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Hydroxyurea treatment is recommended for children with sickle cell anemia (SCA) living in high-resource malaria-free regions, but its safety and efficacy in malaria-endemic sub-Saharan Africa, where the greatest sickle-cell burden exists, remain unknown. **In vitro studies suggest hydroxyurea could increase malaria severity, and hydroxyurea-associated neutropenia could worsen infections.** NOHARM (Novel use Of Hydroxyurea in an African Region with Malaria) was a randomized, double-blinded, placebo-controlled trial conducted in malaria-endemic Uganda, comparing hydroxyurea to placebo at  $20 \pm 2.5$  mg/kg per day for 12 months. The primary outcome was incidence of clinical malaria. Secondary outcomes included SCA-related adverse events (AEs), clinical and laboratory effects, and hematological toxicities. **Children received either hydroxyurea (N = 104) or placebo (N = 103). Malaria incidence did not differ between children on hydroxyurea (0.05 episodes per child per year; 95% confidence interval [0.02, 0.13]) vs placebo (0.07 episodes per child per year [0.03, 0.16]); the hydroxyurea/placebo malaria incidence rate ratio was 0.7 ([0.2, 2.7];  $P = .61$ ).** Time to infection also did not differ significantly between treatment arms. A composite SCA-related clinical outcome (vaso-occlusive painful crisis, dactylitis, acute chest syndrome, splenic sequestration, or blood transfusion) was less frequent with hydroxyurea (45%) than placebo (69%;  $P = .001$ ). **Children receiving hydroxyurea had significantly increased hemoglobin concentration and fetal hemoglobin, with decreased leukocytes and reticulocytes.** Serious AEs, sepsis episodes, and dose-limiting toxicities were similar between treatment arms. Three deaths occurred (2 hydroxyurea, 1 placebo, and none from malaria). Hydroxyurea treatment appears safe for children with SCA living in malaria-endemic sub-Saharan Africa, without increased severe malaria, infections, or AEs. Hydroxyurea provides SCA-related laboratory and clinical efficacy, but optimal dosing and monitoring regimens for Africa remain undefined.

[J Hematol.](#) 2017 Aug;92(8):780-788. doi: 10.1002/ajh.24770. Epub 2017 Jun 15.

### [Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria \(SPIN trial\).](#)

[Galadanci NA](#), Umar Abdullahi S, [Vance LD](#), [Musa Tabari A](#), [Ali S](#), [Belonwu R](#), [Salihu A](#), [Amal Galadanci A](#), [Wudil Jibir B](#), [Bello-Manga H](#), [Neville K](#), [Kirkham FJ](#), [Shyr Y](#), [Phillips S](#), [Covert BV](#), Kassim AA, [Jordan LC](#), [Aliyu MH](#), DeBaun MR.

The vast majority of children with sickle cell anemia (SCA) live in Africa, where evidence-based guidelines for primary stroke prevention are lacking. In Kano, Nigeria, we conducted a feasibility trial to determine the acceptability of hydroxyurea therapy for primary stroke prevention in children with abnormal transcranial Doppler (TCD) measurements. Children with SCA and abnormal non-imaging TCD measurements ( $\geq 200$  cm/s) received moderate fixed-dose hydroxyurea therapy ( $\sim 20$  mg/kg/day). A comparison group of children with TCD measurements  $< 200$  cm/s was followed prospectively. Approximately 88% (330 of 375) of families agreed to be screened, while 87% (29 of 33) of those with abnormal TCD measurements, enrolled in the trial. No participant elected to withdraw from the trial. The average mean corpuscular volume increased from 85.7 fl at baseline to 95.5 fl at 24 months (not all of the children who crossed over had a 24 month visit), demonstrating adherence to hydroxyurea. The comparison group consisted of initially 210 children, of which four developed abnormal TCD measurements, and were started on hydroxyurea. None of the monthly research visits were missed ( $n =$  total 603 visits). Two and 10 deaths occurred in the treatment and comparison groups, with mortality rates of 2.69 and 1.81 per 100 patient-years,

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respectively ( $P = .67$ ). Our results provide strong evidence, for high family recruitment, retention, and adherence rates, to undertake the first randomized controlled trial with hydroxyurea therapy for primary stroke prevention in children with SCA living in Africa.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5523858/>

*BMJ Open*. 2017 Jul 10;7(7):e017190. doi: 10.1136/bmjopen-2017-017190.

### **Subdissociative intranasal ketamine plus standard pain therapy versus standard pain therapy in the treatment of paediatric sickle cell disease vaso-occlusive crises in resource-limited settings: study protocol for a randomised controlled trial.**

[Young JR](#), [Sawe HR](#), [Mfinanga JA](#), [Nshom E](#), [Helm E](#), [Moore CG](#), [Runyon MS](#), [Reynolds SL](#).

#### **INTRODUCTION:**

Pediatric sickle cell disease, highly prevalent in sub-Saharan Africa, carries great morbidity and mortality risk. Limited resources and monitoring make management of acute vaso-occlusive crises challenging. This study aims to evaluate the efficacy and safety of subdissociative intranasal ketamine as a cheap, readily available and easily administered adjunct to standard pain therapy. We hypothesise that subdissociative, intranasal ketamine may significantly augment current approaches to pain management in resource-limited settings in a safe and cost-effective manner.

#### **METHODS AND ANALYSIS:**

This is a multicentred, randomised, double-blind, placebo-controlled trial enrolling children 4-16 years of age with sickle cell disease and painful vaso-occlusive pain crises. Study sites include two sub-Saharan teaching and referral hospitals with acute intake areas. All patients receive standard analgesic therapy during evaluation. Patients randomised to the treatment arm receive 1 mg/kg intranasal ketamine at onset of therapy, while placebo arm participants receive volume-matched intranasal normal saline. All participants and clinical staff are blinded to the treatment allocation. Data will be analysed on an intention-to-treat basis. Primary endpoints are changes in self-report pain scales (Faces Pain Scale-Revised) at 30, 60 and 120 minutes and rates of adverse events. Secondary endpoints include hospital length of stay, total analgesia use and quality of life assessment 2-3 weeks postintervention.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541700/>

## HIV / AIDS

*J Int AIDS Soc*. 2018 Jul;21 Suppl 4:e25135. doi: 10.1002/jia2.25135.

### **Households, fluidity, and HIV service delivery in Zambia and South Africa - an exploratory analysis of longitudinal qualitative data from the HPTN 071 (PopART) trial.**

[Hoddinott G](#), [Myburgh H](#), [de Villiers L](#), [Ndubani R](#), [Mantantana J](#), [Thomas A](#), [Mbewe M](#), [Ayles H](#), [Bock P](#), [Seeley J](#), [Shanaube K](#), [Hargreaves J](#), [Bond V](#), [Reynolds L](#); [HPTN 071 \(PopART\) Study Team](#).



### INTRODUCTION:

Population distributions, family and household compositions, and people's sense of belonging and social stability in southern Africa have been shaped by tumultuous, continuing large-scale historical disruptions. As a result, many people experience high levels of geographic and social fluidity, which intersect with individual and population-level migration patterns. We describe the complexities of household fluidity and HIV service access in South Africa and Zambia to explore implications for health systems and service delivery in contexts of high household fluidity.

### METHODS:

**HPTN 071 (PopART) is a three-arm cluster randomized controlled trial implemented in 21 peri-urban study communities in Zambia and South Africa between 2013 and 2018.** A qualitative cohort nested in the trial included 148 purposively sampled households. Data collection was informed by ethnographic and participatory research principles. The analysis process was reflexive and findings are descriptive narrative summaries of emergent ideas.

### RESULTS:

Households in southern Africa are extremely fluid, with people having a tenuous sense of security in their social networks. This fluidity intersects with high individual and population mobility. To characterize fluidity, we describe thematic patterns of household membership and residence. We also identify reasons people give for moving around and shifting social ties, including economic survival, fostering interpersonal relationships, participating in cultural, traditional, religious, or familial gatherings, being institutionalized, and maintaining patterns of substance use. **High fluidity disrupted HIV service access for some participants.** Despite these challenges, many participants were able to regularly access HIV testing services and participants living with HIV were especially resourceful in maintaining continuity of antiretroviral therapy (ART). **We identify three key features of health service interactions that facilitated care continuity: disclosure to family members, understanding attitudes among health services staff including flexibility to accommodate clients' transient pressures, and participants' agency in ART-related decisions.**

### CONCLUSIONS:

Choices made to manage one's experiential sense of household fluidity are intentional responses to livelihood and social support constraints. To enhance retention in care for people living with HIV, policy makers and service providers should focus on creating responsive, flexible health service delivery systems designed to accommodate many shifts in client circumstances.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6053477/>

[AIDS](#). 2017 Jul 17;31(11):1555-1564. doi: 10.1097/QAD.0000000000001514.

### **What works - reaching universal HIV testing: lessons from HPTN 071 (PopART) trial in Zambia.**

[Shanaube K](#), [Schaap A](#), [Floyd S](#), [Phiri M](#), [Griffith S](#), [Chaila J](#), [Bock P](#), [Hayes R](#), [Fidler S](#), [Ayles H](#); [HPTN 071 \(PopART\) Study Team](#).

### OBJECTIVE:

**To determine the uptake of home-based HIV counselling and testing (HCT) in four HPTN 071 (PopART) trial communities (implementing a 'full' combination HIV prevention package that includes universal HIV testing and treatment) in Zambia.** We also explore factors associated with uptake of HCT in these communities.

### DESIGN:

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HPTN 071 (PopART) is a three-arm community-randomized trial in 12 communities in Zambia and nine communities in South Africa evaluating the impact of a combination HIV prevention package, including universal HIV testing and treatment, on HIV incidence.

### **METHODS:**

Using a door-to-door approach that includes systematically revisiting households, individuals were offered participation in the intervention, and verbal consent was obtained. Data were analysed for the first 18 months of the intervention, December 2013 to June 2015 for individuals 18 years and older.

### **RESULTS:**

Among 121 130 enumerated household members, 101 102 (83.5%) accepted the intervention. HCT uptake was 72.2% (66 894/92 612), similar by sex but varied across communities. HCT uptake was associated with younger age, sex, community, being symptomatic for TB and sexually transmitted infections and longer time since previous HIV test. Knowledge of HIV status due to the intervention increased by 36% overall and by 66% among HIV positive participants; the highest impact was among 18-24 years old.

### **CONCLUSION:**

Overall acceptance of HIV-testing through offering a **door-to-door-based combination HIV prevention package was 72.2%**. The intervention increased knowledge of HIV status from ~50 to ~90%. However, challenges still remain and a one-off intervention is unlikely to be successful but will require repeated visits and multiple strategies.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5491236/>

## Ante-retroviral therapy (ART)

*PLoS Med.* 2017 Nov 14;14(11):e1002432. doi: 10.1371/journal.pmed.1002432. eCollection 2017 Nov.

### **[Virological response and resistance among HIV-infected children receiving long-term antiretroviral therapy without virological monitoring in Uganda and Zimbabwe: Observational analyses within the randomised ARROW trial.](#)**

[Szubert AJ](#), [Prendergast AJ](#), [Spyer MJ](#), [Musiiime V](#), [Musoke P](#), [Bwakura-Dangarembizi M](#), [Nahirya-Ntege P](#), [Thomason MJ](#), [Ndashimye E](#), [Nkanya I](#), [Senfuma O](#), [Mudenge B](#), [Klein N](#), [Gibb DM](#), [Walker AS](#); [ARROW Trial Team](#).

### **BACKGROUND:**

Although WHO recommends viral load (VL) monitoring for those on antiretroviral therapy (ART), availability in low-income countries remains limited. We investigated long-term VL and resistance in HIV-infected children managed without real-time VL monitoring.

### **METHODS AND FINDINGS:**

In the ARROW factorial trial, **1,206 children initiating ART in Uganda and Zimbabwe between 15 March 2007 and 18 November 2008, aged a median 6 years old, with median CD4% of 12%, were randomised to monitoring with or without 12-weekly CD4 counts and to receive 2 nucleoside reverse transcriptase inhibitors (2NRTI, mainly abacavir+lamivudine) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or 3 NRTIs as long-term ART.** All children had VL assayed retrospectively after a median of 4 years on ART; those with >1,000 copies/ml were genotyped. Three hundred and sixteen children had VL and genotypes assayed longitudinally (at least every 24 weeks).

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Overall, 67 (6%) switched to second-line ART and 54 (4%) died. **In children randomised to WHO-recommended 2NRTI+NNRTI long-term ART, 308/378 (81%) monitored with CD4 counts versus 297/375 (79%) without had VL <1,000 copies/ml at 4 years (difference = +2.3% [95% CI -3.4% to +8.0%]; P = 0.43), with no evidence of differences in intermediate/high-level resistance to 11 drugs.** Among children with longitudinal VLs, only 5% of child-time post-week 24 was spent with persistent low-level viraemia (80-5,000 copies/ml) and 10% with VL rebound  $\geq 5,000$  copies/ml. No child resuppressed <80 copies/ml after confirmed VL rebound  $\geq 5,000$  copies/ml. A median of 1.0 (IQR 0.0,1.5) additional NRTI mutation accumulated over 2 years' rebound. Nineteen out of 48 (40%) VLs 1,000-5,000 copies/ml were immediately followed by resuppression <1,000 copies/ml, but only 17/155 (11%) VLs  $\geq 5,000$  copies/ml resuppressed (P < 0.0001). Main study limitations are that analyses were exploratory and treatment initiation used 2006 criteria, without pre-ART genotypes.

### CONCLUSIONS:

In this study, **children receiving first-line ART in sub-Saharan Africa without real-time VL monitoring had good virological and resistance outcomes over 4 years, regardless of CD4 monitoring strategy.** Many children with detectable low-level viraemia spontaneously resuppressed, highlighting the importance of confirming virological failure before switching to second-line therapy. Children experiencing rebound  $\geq 5,000$  copies/ml were much less likely to resuppress, but NRTI resistance increased only slowly. These results are relevant to the increasing numbers of HIV-infected children receiving first-line ART in sub-Saharan Africa with limited access to virological monitoring.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5685482/>

[J Int AIDS Soc.](#) 2017 Sep 15;20(1):21930. doi: 10.7448/IAS.20.1.21930.

### **Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: adolescents at high risk of failure.**

[Boerma RS](#), [Bunupuradah T](#), Dow D, [Fokam J](#), Kariminia A, [Lehman D](#), [Kityo C](#), [Musiime V](#), [Palumbo P](#), [Schoffelen A](#), [Sophan S](#), Zandoni B, [Rinke de Wit TF](#), [Calis JCJ](#), [Sigaloff KCE](#); Paediatric Second-line Study Group.

### INTRODUCTION:

The number of HIV-infected children and adolescents requiring second-line antiretroviral treatment (ART) is increasing in low- and middle-income countries (LMIC). However, the effectiveness of paediatric second-line ART and potential risk factors for virologic failure are poorly characterized. We performed an aggregate analysis of second-line ART outcomes for children and assessed the need for paediatric third-line ART.

### METHODS:

We performed a multicentre analysis by systematically reviewing the literature to identify cohorts of children and adolescents receiving second-line ART in LMIC, contacting the corresponding study groups and including patient-level data on virologic and clinical outcomes. Kaplan-Meier survival estimates and Cox proportional hazard models were used to describe cumulative rates and predictors of virologic failure. **Virologic failure was defined as two consecutive viral load measurements >1000 copies/ml after at least six months of second-line treatment.**

### RESULTS:

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We included 12 cohorts representing 928 children on second-line protease inhibitor (PI)-based ART in 14 countries in Asia and sub-Saharan Africa. **After 24 months, 16.4% (95% confidence interval (CI): 13.9-19.4) of children experienced virologic failure. Adolescents (10-18 years) had failure rates of 14.5 (95% CI 11.9-17.6) per 100 person-years compared to 4.5 (95% CI 3.4-5.8) for younger children (3-9 years).** Risk factors for virologic failure were adolescence (adjusted hazard ratio [aHR] 3.93,  $p < 0.001$ ) and short duration of first-line ART before treatment switch (aHR 0.64 and 0.53,  $p = 0.008$ , for 24-48 months and >48 months, respectively, compared to <24 months).

### CONCLUSIONS:

In LMIC, paediatric PI-based second-line ART was associated with relatively low virologic failure rates. **However, adolescents showed exceptionally poor virologic outcomes in LMIC, and optimizing their HIV care requires urgent attention.** In addition, 16% of children and adolescents failed PI-based treatment and will require integrase inhibitors to construct salvage regimens. These drugs are currently not available in LMIC.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5640308/>

[Lancet HIV](#). 2017 Aug;4(8):e341-e348. doi: 10.1016/S2352-3018(17)30065-6. Epub 2017 May 8.

### [Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial.](#)

[Paton NI](#), [Kityo C](#), [Thompson J](#), [Nankya I](#), [Bagenda L](#), [Hoppe A](#), [Hakim J](#), [Kambugu A](#), [van Oosterhout JJ](#), [Kiconco M](#), [Bertagnolio S](#), [Easterbrook PJ](#), [Mugenyi P](#), [Walker AS](#); [Europe Africa Research Network for Evaluation of Second-line Therapy \(EARNEST\) Trial Team](#).

### [Collaborators \(277\)](#)

### BACKGROUND:

Cross-resistance after first-line antiretroviral therapy (ART) failure is expected to impair activity of nucleoside reverse-transcriptase inhibitors (NRTIs) in second-line therapy for patients with HIV, but evidence for the effect of cross-resistance on virological outcomes is limited. We aimed to assess the association between the activity, predicted by resistance testing, of the NRTIs used in second-line therapy and treatment outcomes for patients infected with HIV.

### METHODS:

We did an observational analysis of additional data from a published open-label, randomised trial of second-line ART (EARNEST) in sub-Saharan Africa. **1277 adults or adolescents infected with HIV in whom first-line ART had failed (assessed by WHO criteria with virological confirmation) were randomly assigned to a boosted protease inhibitor (standardised to ritonavir-boosted lopinavir) with two to three NRTIs (clinician-selected, without resistance testing); or with raltegravir; or alone as protease inhibitor monotherapy (discontinued after week 96).** We tested genotypic resistance on stored baseline samples in patients in the protease inhibitor and NRTI group and calculated the predicted activity of prescribed second-line NRTIs. We measured viral load in stored samples for all patients obtained every 12-16 weeks. This trial is registered with Controlled-Trials.com (number ISRCTN 37737787) and ClinicalTrials.gov (number [NCT00988039](#)).

### FINDINGS:

Baseline genotypes were available in 391 (92%) of 426 patients in the protease inhibitor and NRTI group. **176 (89%) of 198 patients prescribed a protease inhibitor with no predicted-**

active NRTIs had viral suppression (viral load <400 copies per mL) at week 144, compared with 312 (81%) of 383 patients in the protease inhibitor and raltegravir group at week 144 ( $p=0.02$ ) and 233 (61%) of 280 patients in the protease inhibitor monotherapy group at week 96 ( $p<0.0001$ ). Compared with results with no active NRTIs, 95 (85%) of 112 patients with one predicted-active NRTI had viral suppression ( $p=0.3$ ) and 20 (77%) of 26 patients with two or three active NRTIs had viral suppression ( $p=0.08$ ). Over all follow-up, greater predicted NRTI activity was associated with worse viral load suppression (global  $p=0.0004$ ).

**INTERPRETATION:**

Genotypic resistance testing might not accurately predict NRTI activity in protease inhibitor-based second-line ART. Our results do not support the introduction of routine resistance testing in ART programmes in low-income settings for the purpose of selecting second-line NRTIs.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5555436/>

*Clin Infect Dis.* 2017 Aug 1;65(3):477-485. doi: 10.1093/cid/cix335.

**Switching to Efavirenz Versus Remaining on Ritonavir-boosted Lopinavir in Human Immunodeficiency Virus-infected Children Exposed to Nevirapine: Long-term Outcomes of a Randomized Trial.**

Murnane PM, Strehlau R, Shiau S, Patel F, Mbete N, Hunt G, Abrams EJ, Coovadia A, Kuhn L.

**BACKGROUND:**

We previously demonstrated the noninferiority of switching to efavirenz (EFV) versus remaining on ritonavir-boosted lopinavir (LPV/r) for virologic control in children infected with human immunodeficiency virus (HIV) and exposed to nevirapine (NVP) for prevention of mother-to-child transmission. Here we assess outcomes up to 4 years post-randomization.

**METHODS:**

From 2010-2013, 298 NVP-exposed HIV-infected children  $\geq 3$  years of age were randomized to switch to EFV or remain on LPV/r in

Johannesburg, South Africa (Clinicaltrials.gov [NCT01146873](https://clinicaltrials.gov/ct2/show/study/NCT01146873)). After trial completion, participants were invited to enroll into observational follow-up. We compared HIV RNA levels, CD4 counts and percentages, lipids, and growth across groups through four years post-randomization.

**RESULTS:**

HIV RNA levels 51-1000 copies/mL were less frequently observed in the EFV group than the LPV/r group (odds ratio [OR] 0.67, 95% confidence interval [CI]: 0.51-0.88,  $P = .004$ ), as was HIV RNA >1000 copies/mL (OR 0.52 95% CI: 0.28-0.98,  $P = .04$ ). **The probability of confirmed HIV RNA >1000 copies/mL by 48 months was 0.07 and 0.12 in the EFV and LPV/r groups, respectively ( $P = .21$ ).** Children randomized to EFV had a reduced risk of elevated total cholesterol (OR 0.45 95% CI: 0.27-0.75,  $P = .002$ ) and a reduced risk of abnormal triglycerides (OR 0.42, 95% CI 0.29-0.62,  $P < .001$ ).

**CONCLUSIONS:**

Our results indicate that the benefits of switching virologically suppressed NVP-exposed HIV-infected children  $\geq 3$  years of age from LPV/r to EFV are sustained long-term. This approach has several advantages, including improved palatability, reduced metabolic toxicity, simplified cotreatment for tuberculosis, and preservation of second line options.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5849095/>

[J Acquir Immune Defic Syndr](#). 2017 Sep 1;76(1):55-59. doi: 10.1097/QAI.0000000000001452.

**Defining a Cutoff for Atazanavir in Hair Samples Associated With Virological Failure Among Adolescents Failing Second-Line Antiretroviral Treatment.**

[Chawana TD](#), [Gandhi M](#), [Nathoo K](#), [Ngara B](#), [Louie A](#), [Horng H](#), [Katzenstein D](#), [Metcalf J](#), [Nhachi CFB](#); [AdolescentTreatment Failure \(ATF\) study team](#).

**BACKGROUND:**

Adequate antiretroviral exposure is crucial to virological suppression. We assessed the relationship between atazanavir hair levels with self-reported adherence, virological outcomes, and the effect of a home-based adherence intervention in HIV-infected adolescents failing second-line antiretroviral treatment in Zimbabwe.

**METHODS:**

HIV-infected adolescents on atazanavir/ritonavir-based second-line treatment for  $\geq 6$  months with viral load (VL)  $> 1000$  copies/mL were randomized to either standard care (control) or standard care plus modified directly administered antiretroviral therapy (intervention). Questionnaires were administered; VL and hair samples were collected at baseline and after 90 days in each group. Viral suppression was defined as  $< 1000$  copies/mL after follow-up.

**RESULTS:**

Fifty adolescents (10-18 years) were enrolled; 23 (46%) were randomized to intervention and 27 (54%) to control. Atazanavir hair concentration  $< 2.35$  ng/mg (lower interquartile range for those with virological suppression) defined a cutoff below which most participants experienced virological failure. Male sex ( $P = 0.03$ ), virological suppression at follow-up ( $P = 0.013$ ), greater reduction in VL ( $P = 0.006$ ), and change in average self-reported adherence over the previous month ( $P = 0.031$ ) were associated with adequate ( $> 2.35$  ng/mg) hair concentrations. Participants with virological failure were more likely to have suboptimal atazanavir hair concentrations (RR = 7.2, 95% CI: 1 to 51,  $P = 0.049$ ). There were no differences in atazanavir hair concentration between the arms after follow-up.

**CONCLUSIONS:**

A threshold of atazanavir concentrations in hair (2.35 ng/mg), above which virological suppression was likely, was defined for adolescents failing second-line atazanavir/ritonavir-based ART in Zimbabwe. Male sex and better self-reported adherence were associated with adequate atazanavir hair concentrations. Antiretroviral hair concentrations may serve as a useful clinical tool among adolescents.

[J Int AIDS Soc](#). 2017 Jul 21;20(Suppl 4):21673. doi: 10.7448/IAS.20.5.21673.

**High rates of viral suppression in adults and children with high CD4+ counts using a streamlined ART delivery model in the SEARCH trial in rural Uganda and Kenya.**

[Kwarisiima D](#), [Kamya MR](#), [Owaraganise A](#), [Mwangwa F](#), [Byonanebye DM](#), [Ayieko J](#), [Plenty A](#), [Black D](#), [Clark TD](#), [Nzarubara B](#), [Snyman K](#), [Brown L](#), [Bukusi E](#), [Cohen CR](#), [Geng EH](#), [Charlebois ED](#), [Ruel TD](#), [Petersen ML](#), [Havlrir D](#), [Jain V](#).

**INTRODUCTION:**

The 2015 WHO recommendation of antiretroviral therapy (ART) for all HIV-positive persons calls for treatment initiation in millions of persons newly eligible with high CD4+ counts.

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Efficient and effective care models are urgently needed for this population. We evaluated clinical outcomes of asymptomatic HIV-positive adults and children starting ART with high CD4+ counts using a novel streamlined care model in rural Uganda and Kenya.

### **METHODS:**

In the 16 intervention communities of the HIV test-and-treat Sustainable East Africa Research for Community Health Study ([NCT01864603](https://www.clinicaltrials.gov/ct2/show/study/NCT01864603)), all HIV-positive individuals irrespective of CD4 were offered ART (efavirenz [EFV]/tenofovir disoproxil fumarate + emtricitabine (FTC) or lamivudine (3TC). We studied adults ( $\geq$  fifteen years) with  $CD4 \geq 350/\mu L$  and children (two to fourteen years) with  $CD4 > 500/\mu L$  otherwise ineligible for ART by country guidelines. Clinics implemented a patient-centred streamlined care model designed to reduce patient-level barriers and maximize health system efficiency. It included (1) nurse-conducted visits with physician referral of complex cases, (2) multi-disease chronic care (including for hypertension/diabetes), (3) patient-centred, friendly staff, (4) viral load (VL) testing and counselling, (5) three-month return visits and ART refills, (6) appointment reminders, (7) tiered tracking for missed appointments, (8) flexible clinic hours (outside routine schedule) and (9) telephone access to clinicians. Primary outcomes were 48-week retention in care, viral suppression (% with measured week 48  $VL \leq 500$  copies/mL) and adverse events.

**Results** Overall, 972 HIV-positive adults with  $CD4+ \geq 350/\mu L$  initiated ART with streamlined care. Patients were 66% female and had median age thirty-four years (IQR, 28-42),  $CD4+ 608/\mu L$  (IQR, 487-788/ $\mu L$ ) and VL 6775 copies/mL (IQR, <500-37,003 c/mL). At week 48, retention was 92% (897/972; 2 died/40 moved/8 withdrew/4 transferred care/21/964 [2%] were lost to follow-up). Viral suppression occurred in 778/838 (93%) and 800/972 (82%) in intention-to-treat analysis. Grade III/IV clinical/laboratory adverse events were rare: 95 occurred in 74/972 patients (7.6%). Only 8/972 adults (0.8%) switched ART from EFV to lopinavir (LPV) ( $n = 2$  for dizziness,  $n = 2$  for gynaecomastia,  $n = 4$  for other reasons). Among 83 children, week 48 retention was 89% (74/83), viral suppression was 92% (65/71) and grade III/IV adverse events occurred in 4/83 (4.8%).

### **CONCLUSIONS:**

Using a streamlined care model, viral suppression, retention and ART safety were high among asymptomatic East African adults and children with high CD4+ counts initiating treatment.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5577724/>

\*\*\* [N Engl J Med.](https://doi.org/10.1056/NEJMoa1615822) 2017 Jul 20;377(3):233-245. doi: 10.1056/NEJMoa1615822.

### **Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa.**

[Hakim J](#), [Musiime V](#), [Szubert AJ](#), [Mallewa J](#), [Siika A](#), [Agutu C](#), [Walker S](#), [Pett SL](#), [Bwakura-Dangarembizi M](#), [Lugemwa A](#), [Kaunda S](#), [Karoney M](#), [Musoro G](#), [Kabahenda S](#), [Nathoo K](#), [Maitland K](#), [Griffiths A](#), [Thomason MJ](#), [Kityo C](#), [Mugenyi P](#), [Prendergast AJ](#), [Walker AS](#), [Gibb DM](#); [REALITY Trial Team](#).

### **Collaborators (196)**

### **BACKGROUND:**

In sub-Saharan Africa, among patients with advanced human immunodeficiency virus (HIV) infection, the rate of death from infection (including tuberculosis and cryptococcus) shortly after the initiation of antiretroviral therapy (ART) is approximately 10%.

### **METHODS:**

In this factorial open-label trial conducted in Uganda, Zimbabwe, Malawi, and Kenya, we enrolled HIV-infected adults and children 5 years of age or older who had not received previous

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ART and were starting ART with a CD4+ count of fewer than 100 cells per cubic millimeter. They underwent simultaneous randomization to receive enhanced antimicrobial prophylaxis or standard prophylaxis, adjunctive raltegravir or no raltegravir, and supplementary food or no supplementary food. Here, we report on **the effects of enhanced antimicrobial prophylaxis, which consisted of continuous trimethoprim-sulfamethoxazole plus at least 12 weeks of isoniazid-pyridoxine (coformulated with trimethoprim-sulfamethoxazole in a single fixed-dose combination tablet), 12 weeks of fluconazole, 5 days of azithromycin, and a single dose of albendazole, as compared with standard prophylaxis (trimethoprim-sulfamethoxazole alone)**. The primary end point was 24-week mortality.

### RESULTS:

A total of 1805 patients (1733 adults and 72 children or adolescents) underwent randomization to receive either enhanced prophylaxis (906 patients) or standard prophylaxis (899 patients) and were followed for 48 weeks (loss to follow-up, 3.1%). The median baseline CD4+ count was 37 cells per cubic millimeter, but 854 patients (47.3%) were asymptomatic or mildly symptomatic. In the Kaplan-Meier analysis at 24 weeks, the rate of death with enhanced prophylaxis was lower than that with standard prophylaxis (80 patients [8.9% vs. 108 [12.2%]; hazard ratio, 0.73; 95% confidence interval [CI], 0.55 to 0.98;  $P=0.03$ ); 98 patients (11.0%) and 127 (14.4%), respectively, had died by 48 weeks (hazard ratio, 0.76; 95% CI, 0.58 to 0.99;  $P=0.04$ ). **Patients in the enhanced-prophylaxis group had significantly lower rates of tuberculosis ( $P=0.02$ ), cryptococcal infection ( $P=0.01$ ), oral or esophageal candidiasis ( $P=0.02$ ), death of unknown cause ( $P=0.03$ ), and new hospitalization ( $P=0.03$ ).** However, there was no significant between-group difference in the rate of severe bacterial infection ( $P=0.32$ ). There were nonsignificantly lower rates of serious adverse events and grade 4 adverse events in the enhanced-prophylaxis group ( $P=0.08$  and  $P=0.09$ , respectively). Rates of HIV viral suppression and adherence to ART were similar in the two groups.

### CONCLUSIONS:

Among HIV-infected patients with advanced immunosuppression, enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death at both 24 weeks and 48 weeks without compromising viral suppression or increasing toxic effects.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5603269/>

*Pediatr Infect Dis J.* 2017 Aug;36(8):761-767. doi: 10.1097/INF.0000000000001544.

### **Insulin Resistance and Markers of Inflammation in HIV-infected Ugandan Children in the CHAPAS-3 Trial.**

Dirajlal-Fargo S, Musiime V, Cook A, Mirembe G, Kenny J, Jiang Y, Debanne S, Klein N, McComsey GA.

### BACKGROUND:

Few studies have investigated metabolic complications in HIV-infected African children and their relation with inflammation.

### METHODS:

We compared baseline and changes in insulin resistance [homeostatic model assessment of insulin resistance (HOMA-IR)] and in markers of inflammation over 48 weeks, in a subset of antiretroviral therapy (ART)-naive Ugandan children from the Children with HIV in Africa-Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens trial randomized to zidovudine-, stavudine- or abacavir (ABC)-based regimen.



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Nonparametric methods were used to explore between-group and within-group differences, and multivariable analysis to assess associations of HOMA-IR.

### RESULTS:

One-hundred eighteen children were enrolled, and median age (interquartile range) was 2.8 years (1.7-4.3). Baseline median HOMA-IR (interquartile range) was 0.49 (0.38-1.07) and similar between the arms. At week 48, median relative changes in HOMA-IR were 14% (-29% to 97%) in the zidovudine arm, -1% (-30% to 69%) in the stavudine arm and 6% (-34% to 124%) in the ABC arm ( $P \leq 0.03$  for all the arms compared with baseline, but  $P = 0.90$  for between-group differences). Several inflammation markers significantly decreased in all study arms; soluble CD14 increased on ABC and did not change in the other 2 arms. In multivariate analysis, only changes in soluble CD163 were positively associated with HOMA-IR changes.

### CONCLUSIONS:

In ART-naive Ugandan children, HOMA-IR changed significantly after 48 weeks of ART and correlated with monocyte activation.

[PLoS One](https://doi.org/10.1371/journal.pone.0192068). 2018 Mar 9;13(3):e0192068. doi: 10.1371/journal.pone.0192068. eCollection 2018.

### [Impact of a Family Clinic Day intervention on paediatric and adolescent appointment adherence and retention in antiretroviral therapy: A cluster randomized controlled trial in Uganda.](#)

[Graves JC](#), [Elyanu P](#), [Schellack CJ](#), [Asire B](#), [Prust ML](#), [Prescott MR](#), [Mirembe E](#), [Lukabwe I](#), [Mirembe B](#), [Musinguzi J](#), [Moberley SA](#).

### BACKGROUND:

In 2013, Uganda adopted a test-and-treat policy for HIV patients 15 years or younger. Low retention rates among paediatric and adolescent antiretroviral therapy (ART) initiates could severely limit the impact of this new policy. This evaluation tested the impact of a differentiated care model called Family Clinic Day (FCD), a family-centered appointment scheduling and health education intervention on patient retention and adherence to monthly appointment scheduling.

### METHODS:

We conducted a cluster randomized controlled trial, from October 2014 to March 2015. Forty-six facilities were stratified by implementing partner and facility type and randomly assigned to the control or intervention arm. Primary outcomes included the proportion of patients retained in care at 6 months and the proportion adherent to their appointment schedule at last study period scheduled visit. Data collection occurred retrospectively in May 2015. Six patient focus group discussions and 17 health workers interviews were conducted to understand perspectives on FCD successes and challenges.

### RESULTS:

A total of 4,715 paediatric and adolescent patient records were collected, of which 2,679 ( $n = 1,319$  from 23 control facilities and 1,360 from 23 intervention facilities) were eligible for inclusion. The FCD did not improve retention (aOR 1.11; 90% CI 0.63-1.97,  $p = 0.75$ ), but was associated with improved adherence to last appointment schedule (aOR 1.64; 90% CI 1.27-2.11,  $p < 0.001$ ). Qualitative findings suggested that FCD patients benefited from health education and increased psychosocial support.

### CONCLUSION:

FCD scale-up in Uganda may be an effective differentiated care model to ensure patient adherence to ART clinic appointment schedules, a key aspect necessary for viral load suppression. Patient health outcomes may also benefit following an increase in knowledge based

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on health education, and peer support. Broad challenges facing ART clinics, such as under-staffing and poor filing systems, should be addressed in order to improve patient care.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844531/>

[Trials](#). 2017 Oct 20;18(1):478. doi: 10.1186/s13063-017-2198-7.

### [Evaluating a multi-component, community-based program to improve adherence and retention in care among adolescents living with HIV in Zimbabwe: study protocol for a cluster randomized controlled trial.](#)

[Mavhu W](#), [Willis N](#), [Mufuka J](#), [Mangenah C](#), [Mvududu K](#), [Bernays S](#), [Mangezi W](#), [Apollo T](#), [Araya R](#), [Weiss HA](#), [Cowan FM](#).

#### **BACKGROUND:**

World Health Organization (WHO) adolescent HIV-testing and treatment guidelines recommend community-based interventions to support antiretroviral therapy (ART) adherence and retention in care, while acknowledging that the evidence to support this recommendation is weak. This cluster randomized controlled trial aims to evaluate the effectiveness and cost-effectiveness of a psychosocial, community-based intervention on HIV-related and psychosocial outcomes.

#### **METHODS/DESIGN:**

We are conducting the trial in two districts. Sixteen clinics were randomized to either enhanced ART-adherence support or standard of care. Eligible individuals (HIV-positive adolescents aged 13-19 years and eligible for ART) in both arms receive ART and adherence support provided by adult counselors and nursing staff. Adolescents in the intervention arm additionally attend a monthly support group, are allocated to a designated community adolescent treatment supporter, and followed up through a short message service (SMS) and calls plus home visits. The type and frequency of contact is determined by whether the adolescent is "stable" or in need of enhanced support. Stable adolescents receive a monthly home visit plus a weekly, individualized SMS. An additional home visit is conducted if participants miss a scheduled clinic appointment or support-group meeting. Participants in need of further, enhanced, support receive bi-weekly home visits, weekly phone calls and daily SMS. Caregivers of adolescents in the intervention arm attend a caregiver support group. Trial outcomes are assessed through a clinical, behavioral and psychological assessment conducted at baseline and after 48 and 96 weeks. The primary outcome is the proportion who have died or have virological failure (viral load  $\geq 1000$  copies/ml) at 96 weeks. Secondary outcomes include virological failure at 48 weeks, retention in care (proportion of missed visits) and psychosocial outcomes at both time points. Statistical analyses will be conducted and reported in line with CONSORT guidelines for cluster randomized trials, including a flowchart.

#### **DISCUSSION:**

This study provides a unique opportunity to generate evidence of the impact of the on-going Zvandiri program, for adolescents living with HIV, on virological failure and psychosocial outcomes as delivered in a real-world setting. If found to reduce rates of treatment failure, this would strengthen support for further scale-up across Zimbabwe and likely the region more widely.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649065/>

## Early infant diagnosis

(See also: Vaccines – BCG vaccine and delayed administration in HIV exposed infants)

## Management of HIV-related conditions

[Cochrane Database Syst Rev](#). 2018 Jul 24;7:CD009012. doi: 10.1002/14651858.CD009012.pub3. [Epub ahead of print]

### **Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis.**

[Eshun-Wilson I](#), [Okwen MP](#), [Richardson M](#), [Bicanic T](#).

#### **BACKGROUND:**

There remains uncertainty about the optimum timing of antiretroviral therapy (ART) initiation in HIV-positive people with cryptococcal meningitis. This uncertainty is the result of conflicting data on the mortality risk and occurrence of immune reconstitution inflammatory syndrome (IRIS) when ART is initiated less than four weeks after cryptococcal meningitis treatment is commenced.

#### **OBJECTIVES:**

To compare the outcomes of early initiation of ART (less than four weeks after starting antifungal treatment) versus delayed initiation of ART (four weeks or more after starting antifungal treatment) in HIV-positive people with concurrent cryptococcal meningitis.

#### **SEARCH METHODS:**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase for trials published between 1 January 1980 and 7 August 2017. We additionally searched international trial registries, including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), and conference abstracts from the International AIDS Society (IAS) and the Conference on Retroviruses and Opportunistic Infections (CROI) for ongoing or unpublished studies between 2015 and 2017. We reviewed reference lists of included studies to identify additional studies.

#### **SELECTION CRITERIA:**

We included randomized controlled trials (RCTs) that compared early versus delayed ART initiation in HIV-positive people with cryptococcal meningitis. Children, adults, and adolescents from any setting were eligible for inclusion.

#### **DATA COLLECTION AND ANALYSIS:**

Two review authors independently applied the inclusion criteria and extracted data. We presented dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CIs). We presented time-to-death data as hazard ratios with 95% CIs. We assessed the certainty of the evidence using the GRADE approach.

#### **MAIN RESULTS:**

Four trials including 294 adult participants met the inclusion criteria of this review. Participants were predominantly from low- and middle-income countries. Two trials treated cryptococcal meningitis with amphotericin B and fluconazole; a third trial used fluconazole monotherapy; and the fourth trial did not specify the antifungal used. Early ART initiation may increase all-cause mortality compared to delayed ART initiation (RR 1.42, 95% CI 1.02 to 1.97; 294 participants, 4 trials; low-certainty evidence). Early ART initiation may reduce relapse of cryptococcal meningitis compared to delayed ART initiation (RR 0.27, 95% CI 0.07 to 1.04; 205 participants, 2 trials, low-certainty evidence). We are uncertain whether early ART initiation increases or reduces cryptococcal IRIS events compared to delayed ART initiation (RR 3.56, 95% CI 0.51 to 25.02; 205 participants, 2 trials;  $I^2 = 54%$ ; very low-certainty evidence). We are uncertain if early ART initiation increases or reduces virological suppression

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at six months compared to delayed ART initiation (RR 0.93, 95% CI 0.72 to 1.22; 205 participants, 2 trials;  $I^2$  statistic = 0%; very low-certainty evidence). We were unable to pool results related to rate of fungal clearance for the two trials that reported this outcome; individual trial results indicated that there was no difference in cerebrospinal fluid fungal clearance between trial arms. Similarly, we were unable to pool results on adverse events for the trials reporting on this outcome; individual trial results indicated no difference in the occurrence of grade 3 to 5 adverse events between trial arms. Three of the four included trials had an overall low or unclear risk of bias related to the primary outcome of all-cause mortality. However, we assessed one trial as at high risk of bias due to selective outcome reporting and other bias. This, in addition to the few clinical events and imprecision of effect estimates, led to downgrading of the evidence to low or very low certainty.

### **AUTHORS' CONCLUSIONS:**

The results of this review are relevant to HIV-positive adults with cryptococcal meningitis in low- and middle-income countries. **These data suggest a higher risk of mortality among people who initiate ART within four weeks of cryptococcal meningitis diagnosis. However, it is unclear if this higher mortality risk is related to cryptococcal meningitis-IRIS.**

DOI: [10.1002/14651858.CD009012.pub3](https://doi.org/10.1002/14651858.CD009012.pub3)

## Nutrition, growth and development of children with HIV

[BMC Pediatr.](https://doi.org/10.1186/s12887-018-1201-0) 2018 Jul 9;18(1):222. doi: 10.1186/s12887-018-1201-0.

### **Evaluating the effectiveness of a multi-component intervention on early childhood development in paediatric HIV care and treatment programmes: a randomised controlled trial.**

[Chingono R](#), [Mebrahtu H](#), [Mupambireyi Z](#), [Simms V](#), [Weiss HA](#), [Ndlovu P](#), [Charasika F](#), [Tomlinson M](#), [Cluver LD](#), [Cowan FM](#), [Sherr L](#).

### **BACKGROUND:**

HIV infection in a family may affect optimum child development. Our hypothesis is that child development outcomes among HIV-exposed infants will be improved through a complex early childhood stimulation (ECS) programme, and income and loans saving programme for HIV positive parents.

### **METHODS:**

The study was a cluster-randomized controlled trial in 30 clinic sites in two districts in Zimbabwe. Clinics were randomised in a 1:1 allocation ratio to the Child Health Intervention for Development Outcomes (CHIDO) intervention or Ministry of Health standard care. The CHIDO intervention comprises three elements: a group ECS parenting programme, an internal savings and lending scheme (ISALS) and case-management home visits by village health workers. The intervention was aimed at caregiver-child dyads (child aged 0-24 months) where the infant was HIV exposed or infected. The primary outcomes were cognitive development (assessed by the Mullen Scales of Early Learning) and retention of the child in HIV care, at 12 months after enrolment. A comprehensive process evaluation was conducted.

### **DISCUSSION:**

The results of this cluster-randomised trial will provide important information regarding the effects of multi-component interventions in mitigating developmental delays in HIV-exposed infants living in resource-limited environments.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6038232/>

*J Int AIDS Soc.* 2017 Oct;20(2). doi: 10.1002/jia2.25015.

**[Absence of neurocognitive disadvantage associated with paediatric HIV subtype A infection in children on antiretroviral therapy.](#)**

[Bangirana P, Ruel TD, Boivin MJ, Pillai SK, Giron LB, Sikorskii A, Banik A, Achan J.](#)

**INTRODUCTION:**

Infection with HIV subtype A has been associated with poorer neurocognitive outcomes compared to HIV subtype D in Ugandan children not eligible for antiretroviral therapy (ART). In this study, we sought to determine whether subtype-specific differences are also observed among children receiving ART.

**MATERIALS AND METHODS:**

Children were recruited from a clinical trial in which they were randomized to receive either lopinavir (LPV)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)- based ART ([NCT00978068](#)). Age at initiation of ART ranged from six months to six years. HIV subtype was determined by PCR amplification and population sequencing of the pol region derived from peripheral blood mononuclear cell DNA, followed by application of the REGA and Recombinant Identification Programme algorithms. General cognition was assessed using the Kaufman Assessment Battery for Children (Second Edition), attention using the Test of Variables of Attention, and motor skills using the Bruininks-Oseretsky Test of Motor Proficiency (Second Edition). Home environment was assessed using the Home Observation for the Measurement of the Environment (HOME). Age-adjusted test z-scores were entered into a regression model that adjusted for sex, socio-economic status score, HOME score, years of schooling, and ART treatment type.

**RESULTS:**

One hundred and five children were tested; median (interquartile range) age was 7.05 years (6.30 to 8.44), CD4 count was 867.7 cells/mm<sup>3</sup> (416.0 to 1203.5), and duration on ART was 4.03 years (3.55 to 4.23). Seventy-eight children had HIV subtype A and 27 had subtype D; the groups had comparable home and socio-economic status, except that there were more males among children infected with subtype A than D (64.7% vs. 35.3%,  $p = 0.02$ ). There were no differences between the subtypes in general cognition (estimated mean difference: 0.20; 95% CI: -0.11 to 0.50);  $p = 0.21$ ), attention (-0.18, 95% CI: -0.60 to 0.24,  $p = 0.41$ ) and motor skills (1.60, 95% CI: -0.84 to 4.04,  $p = 0.20$ ).

**CONCLUSIONS:**

Our results imply that ART may diminish the neurocognitive disadvantage seen in treatment-naïve HIV-infected children with subtype A.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5810341/>

*Soc Sci Med.* 2017 Oct;190:256-264. doi: 10.1016/j.socscimed.2017.02.007. Epub 2017 Feb 13.

**[A randomized controlled trial of a resilience-based intervention on psychosocial well-being of children affected by HIV/AIDS: Effects at 6- and 12-month follow-up.](#)**

[Li X, Harrison SE, Fairchild AJ, Chi P, Zhao J, Zhao G.](#)

### **BACKGROUND:**

Global literature suggests that resilience-based interventions may yield improvements in psychosocial well-being for vulnerable children, but limited data are available regarding the efficacy of such interventions among children affected by parental HIV/AIDS.

### **OBJECTIVE:**

To evaluate initial efficacy of a multi-level resilience-based intervention among children affected by parental HIV/AIDS in China in improving children's psychosocial well-being and resilience-related outcomes.

### **METHOD:**

Seven hundred-ninety children, 6-17 years of age, were recruited from rural China. Children were either AIDS orphans or were living with one or two parents infected with HIV/AIDS. Children and primary caregivers were randomly assigned to participate in a 4-arm trial to evaluate the Child-Caregiver-Advocacy Resilience (ChildCARE) intervention. This resilience-based psychosocial intervention provides programming at three levels (child, caregiver, community). Survey data were collected at baseline, 6-months, and 12-months in order to examine efficacy of the child-only and child + caregiver arms in improving children's psychological resilience.

### **RESULTS:**

Intervention groups displayed improvements in several resilience-related outcomes at 6- and 12-month follow-ups, including self-reported coping, hopefulness, emotional regulation, and self-control. The child-only intervention arm showed some fading of intervention effects by 12-months.

### **CONCLUSION:**

Preliminary findings suggest that the ChildCARE intervention is efficacious in promoting psychosocial well-being of children affected by parental HIV/AIDS in rural China. Targeting both children and caregivers for psychosocial intervention may be effective in improving children's resilience. Additional evaluation and modifications, including the inclusion of booster sessions, should be considered to further strengthen the program.

[Matern Child Nutr.](#) 2018 Apr;14(2):e12503. doi: 10.1111/mcn.12503. Epub 2017 Aug 29.

### **[The effects of a lipid-based nutrient supplement and antiretroviral therapy in a randomized controlled trial on iron, copper, and zinc in milk from HIV-infected Malawian mothers and associations with maternal and infant biomarkers.](#)**

[Hampel D](#), [Shahab-Ferdows S](#), [Gertz E](#), [Flax VL](#), [Adair LS](#), [Bentley ME](#), [Jamieson DJ](#), [Tegha G](#), [Chasela CS](#), [Kamwendo D](#), [van der Horst CM](#), [Allen LH](#).

We evaluated effects of antiretroviral (ARV) therapy and lipid-based nutrient supplements (LNSs) on iron, copper, and zinc in milk of exclusively breastfeeding HIV-infected Malawian mothers and their correlations with maternal and infant biomarkers. Human milk and blood at 2, 6, and 24 weeks post-partum and blood during pregnancy ( $\leq 30$  weeks gestation) were collected from 535 mothers/infant-pairs in the Breastfeeding, Antiretrovirals, and Nutrition study. The participants received ARV, LNS, ARV and LNS, or no intervention from 0 to 28 weeks post-partum. ARVs negatively affected copper and zinc milk concentrations, but only at 2 weeks, whereas LNS had no effect. Among all treatment groups, approximately 80-90% of copper and zinc and <50% of iron concentrations met the current adequate intake for infants at 2 weeks and

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only 1-19% at 24 weeks. Pregnancy haemoglobin was negatively correlated with milk iron at 2 and 6 weeks ( $r = -.18$ ,  $p < .02$  for both). The associations of the milk minerals with each other were the strongest correlations observed ( $r = .11-.47$ ,  $p < .05$  for all); none were found with infant biomarkers. At 2 weeks, moderately anaemic women produced milk higher in iron when ferritin was higher or TfR lower. At 6 weeks, higher maternal  $\alpha$ -1-acid glycoprotein and C-reactive protein were associated with higher milk minerals in mildly anaemic women. Infant TfR was lower when milk mineral concentrations were higher at 6 weeks and when mothers were moderately anaemic during pregnancy. ARV affects copper and zinc milk concentrations in early lactation, and maternal haemoglobin during pregnancy and lactation could influence the association between milk minerals and maternal and infant iron status and biomarkers of inflammation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5832511/>

## Prevention of parent to child transmission of HIV and maternal HIV care

[IDS Res Ther.](#) 2017 Dec 16;14(1):61. doi: 10.1186/s12981-017-0187-2.

### [A cluster randomized controlled trial of lay health worker support for prevention of mother to child transmission of HIV \(PMTCT\) in South Africa.](#)

[Peltzer K](#), [Weiss SM](#), [Soni M](#), [Lee TK](#), [Rodriguez VJ](#), [Cook R](#), [Alcaide ML](#), [Setswe G](#), [Jones DL](#).

#### **BACKGROUND:**

We evaluate the impact of clinic-based PMTCT community support by trained lay health workers in addition to standard clinical care on PMTCT infant outcomes.

#### **METHODS:**

In a cluster randomized controlled trial, twelve community health centers (CHCs) in Mpumalanga Province, South Africa, were randomized to have pregnant women living with HIV receive either: a standard care (SC) condition plus time-equivalent attention-control on disease prevention (SC; 6 CHCs;  $n = 357$ ), or an enhanced intervention (EI) condition of SC PMTCT plus the "Protect Your Family" intervention (EI; 6 CHCs;  $n = 342$ ). HIV-infected pregnant women in the SC attended four antenatal and two postnatal video sessions and those in the EI, four antenatal and two postnatal PMTCT plus "Protect Your Family" sessions led by trained lay health workers. Maternal PMTCT and HIV knowledge were assessed. Infant HIV status at 6 weeks postnatal was drawn from clinic PCR records; at 12 months, HIV status was assessed by study administered DNA PCR. Maternal adherence was assessed by dried blood spot at 32 weeks, and infant adherence was assessed by maternal report at 6 weeks. The impact of the EI was ascertained on primary outcomes (infant HIV status at 6 weeks and 12 months and ART adherence for mothers and infants), and secondary outcomes (HIV and PMTCT knowledge and HIV transmission related behaviours). A series of logistic regression and latent growth curve models were developed to test the impact of the intervention on study outcomes.

#### **RESULTS:**

In all, 699 women living with HIV were recruited during pregnancy (8-24 weeks), and assessments were completed at baseline, at 32 weeks pregnant (61.7%), and at 6 weeks (47.6%), 6 months (50.6%) and 12 months (59.5%) postnatally. Infants were tested for HIV at 6 weeks and 12 months, 73.5% living infants were tested at 6 weeks and 56.7% at 12 months. There were

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no significant differences between SC and EI on infant HIV status at 6 weeks and at 12 months, and no differences in maternal adherence at 32 weeks, reported infant adherence at 6 weeks, or PMTCT and HIV knowledge by study condition over time.

### CONCLUSION:

The enhanced intervention administered by trained lay health workers did not have any salutary impact on HIV infant status, ART adherence, HIV and PMTCT knowledge. Trial registration [clinicaltrials.gov](https://clinicaltrials.gov): number [NCT02085356](https://clinicaltrials.gov/ct2/show/study/NCT02085356).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732507/>

[Afr J AIDS Res.](#) 2017 Sep;16(3):215-223. doi: 10.2989/16085906.2017.1362017.

### **"We have heard it together": a qualitative analysis of couple HIV testing and counselling recruitment in Malawi's Option B+ programme.**

[Rosenberg NE](#), [Gross R](#), [Mtande T](#), [Maman S](#), [Golin CE](#), [Saidi F](#), [Manthalu O](#), [Hoffman I](#), [Hosseinipour MC](#), [Miller WC](#).

Encouraging HIV-infected pregnant women to recruit male partners for couple HIV testing and counselling (CHTC) is promoted by the World Health Organization, but remains challenging. Formal strategies for recruiting the male partners of pregnant women have not been explored within an Option B+ programme. Our objective was to learn about experiences surrounding CHTC recruitment within a formal CHTC recruitment study. A

randomised controlled trial comparing two CHTC recruitment strategies was conducted among HIV-infected pregnant women presenting to Bwaila Antenatal Unit in 2014. **Women were randomised to receive an invitation to attend the clinic as a couple or this invitation plus clinic-led phone and community tracing.** A qualitative study was conducted with a subset of participants to learn about recruitment. This paper describes experiences of a subset of HIV-infected pregnant women (N = 20) and male partners (N = 17). One on one in-depth interviews were audio-recorded, transcribed, translated, and coded using content analysis. **Nearly all women presented the invitation and disclosed their HIV-positive status to their partners on the day of HIV diagnosis, often to facilitate pill-taking. Men and women in both arms perceived the messages to be more compelling since they came from the clinic, rather than the woman herself.** Couples who attended CHTC displayed greater care for one another and mutual support for HIV-related behaviours. Facilitating CHTC with invitations and tracing can support CHTC uptake and support for HIV-affected couples. In an Option B+ context, inviting partners for CHTC can facilitate male involvement and have important benefits for families.

<https://www.tandfonline.com/doi/abs/10.2989/16085906.2017.1362017>

[J Acquir Immune Defic Syndr.](#) 2017 Nov 1;76(3):273-280. doi: 10.1097/QAI.0000000000001515.

### **Stepped-Wedge Cluster Randomized Controlled Trial to Promote Option B+ Retention in Central Mozambique.**

[Pfeiffer JT](#), [Napúa M](#), [Wagenaar BH](#), [Chale F](#), [Hoek R](#), [Micek M](#), [Manuel J](#), [Michel C](#), [Cowan JG](#), [Cowan JF](#), [Gimbel S](#), [Sherr K](#), [Gloyd S](#), [Chapman RR](#).

### BACKGROUND:



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This randomized trial studied performance of Option B+ in Mozambique and evaluated an enhanced retention package in public clinics.

### SETTING:

The study was conducted at 6 clinics in Manica and Sofala Provinces in central Mozambique.

### METHODS:

Seven hundred sixty-one pregnant women tested HIV+, immediately initiated antiretroviral (ARV) therapy, and were followed to track retention at 6 clinics from May 2014 to May 2015. Clinics were randomly allocated within a stepped-wedge fashion to intervention and control periods. The intervention included (1) workflow modifications and (2) active patient tracking. Retention was defined as percentage of patients returning for 30-, 60-, and 90-day medication refills within 25-35 days of previous refills.

### RESULTS:

During control periods, 52.3% of women returned for 30-day refills vs. 70.8% in intervention periods [odds ratio (OR): 1.80; 95% confidence interval (CI): 1.05 to 3.08]. At 60 days, 46.1% control vs. 57.9% intervention were retained (OR: 1.82; CI: 1.06 to 3.11), and at 90 days, 38.3% control vs. 41.0% intervention (OR: 1.04; CI: 0.60 to 1.82). In prespecified subanalyses, birth before pickups was strongly associated with failure—women giving birth before ARV pickup were 33.3 times (CI: 4.4 to 250.3), 7.5 times (CI: 3.6 to 15.9), and 3.7 times (CI: 2.2 to 6.0) as likely to not return for ARV pickups at 30, 60, and 90 days, respectively.

### CONCLUSIONS:

The intervention was effective at 30 and 60 days, but not at 90 days. Combined 90-day retention (40%) and adherence (22.5%) were low. Efforts to improve retention are particularly important for women giving birth before ARV refills.

[Clin Infect Dis.](#) 2017 Aug 1;65(3):405-413. doi: 10.1093/cid/cix222.

## [Cytomegalovirus Urinary Shedding in HIV-infected Pregnant Women and Congenital Cytomegalovirus Infection.](#)

[Adachi K](#), [Xu J](#), [Ank B](#), [Watts DH](#), [Mofenson LM](#), [Pilotto JH](#), [Joao E](#), [Santos B](#), [Fonseca R](#), [Kreitchmann R](#), [Pinto J](#), [Mussi-Pinhata MM](#), [Gray G](#), [Theron G](#), [Morgado MG](#), [Bryson YJ](#), [Veloso VG](#), [Klausner JD](#), [Moye J](#), [Nielsen-Saines K](#); [NICHD HPTN 040 Study Team.](#)  
[Collaborators \(83\)](#)

### BACKGROUND:

Cytomegalovirus (CMV) urinary shedding in pregnant women infected with human immunodeficiency virus (HIV) was evaluated to determine whether it poses an increased risk for congenital CMV infection (cCMV).

### METHODS:

A subset of mother-infant pairs enrolled in the perinatal NICHD HPTN 040 study (distinguished by no antiretroviral use before labor) was evaluated. Maternal and infant urines were tested by qualitative real-time polymerase chain reaction (RT-PCR) for CMV DNA with quantitative RT-PCR performed on positive specimens.

### RESULTS:

Urine specimens were available for 260 women with 85.4% from the Americas and 14.6% from South Africa. Twenty-four women (9.2%) had detectable CMV viraemia by qualitative PCR. Maternal CMV viraemia was not associated with mean CD4 cell counts or HIV viral load but was associated with younger maternal age ( $P = .02$ ). Overall, 10 of 260 infants (3.8%) had cCMV. Women with detectable peripartum CMV viraemia were more likely to have infants with cCMV than those without: 20.8% (5/24) versus 2.1% (5/236), ( $P = .0001$ ). Women with CMV viraemia had significantly higher rates of HIV perinatal transmission (29.2% vs. 8.1%,  $P = .002$ ). They

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were 5 times (adjusted odds ratio [aOR] = 5.6, 95% confidence interval [CI] 1.9-16.8) and nearly 30 times (aOR, 29.7; 95% CI, 5.4-164.2) more likely to transmit HIV and CMV to their infants, respectively. Maternal gonorrhoea (aOR, 19.5; 95% CI, 2.5-151.3) and higher maternal HIV log<sub>10</sub> viral load (OR, 2.8; 95% CI, 1.3-6.3) were also significant risk factors for cCMV.

### CONCLUSION:

In this cohort of HIV-infected pregnant women not on antiretrovirals, urinary CMV shedding was a significant risk factor for CMV and HIV transmission to infants.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850431/>

*PLoS One.* 2018 Jan 5;13(1):e0189851. doi: 10.1371/journal.pone.0189851. eCollection 2018.

### **Combined evaluation of sexually transmitted infections in HIV-infected pregnant women and infant HIV transmission.**

[Adachi K](#), [Xu J](#), [Yeganeh N](#), [Camarca M](#), [Morgado MG](#), [Watts DH](#), [Mofenson LM](#), [Veloso VG](#), [Pilotto JH](#), [Joao E](#), [Gray G](#), [Theron G](#), [Santos B](#), [Fonseca R](#), [Kreitchmann R](#), [Pinto J](#), [Mussi-Pinhata MM](#), [Ceriotta M](#), [Machado DM](#), [Bryson YJ](#), [Grinsztejn B](#), [Moye J](#), [Klausner JD](#), [Bristow CC](#), [Dickover R](#), [Mirochnick M](#), [Nielsen-Saines K](#); [NICHD HPTN 040 Study Team](#).

### BACKGROUND:

Sexually transmitted infections (STIs) including *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Treponema pallidum* (TP), and cytomegalovirus (CMV) may lead to adverse pregnancy and infant outcomes. The role of combined maternal STIs in HIV mother-to-child transmission (MTCT) was evaluated in mother-infant pairs from NICHD HPTN 040.

### METHODOLOGY:

Urine samples from HIV-infected pregnant women during labor were tested by polymerase chain reaction (PCR) for CT, NG, and CMV. Infant HIV infection was determined by serial HIV DNA PCR testing. Maternal syphilis was tested by VDRL and confirmatory treponemal antibodies.

### RESULTS:

A total of 899 mother-infant pairs were evaluated. Over 30% had at least one of the following infections (TP, CT, NG, and/or CMV) detected at the time of delivery. High rates of TP (8.7%), CT (17.8%), NG (4%), and CMV (6.3%) were observed. HIV MTCT was 9.1% (n = 82 infants). HIV MTCT was 12.5%, 10.3%, 11.1%, and 26.3% among infants born to women with CT, TP, NG or CMV respectively. Forty-two percent of HIV-infected infants were born to women with at least one of these 4 infections. Women with these infections were nearly twice as likely to have an HIV-infected infant (aOR 1.9, 95% CI 1.1-3.0), particularly those with 2 STIs (aOR 3.4, 95% CI 1.5-7.7). **Individually, maternal CMV (aOR 4.4 1.5-13.0) and infant congenital CMV (OR 4.1, 95% CI 2.2-7.8) but not other STIs (TP, CT, or NG) were associated with an increased risk of HIV MTCT.**

### CONCLUSION:

HIV-infected pregnant women identified during labor are at high risk for STIs. Co-infection with STIs including CMV nearly doubles HIV MTCT risk. CMV infection appears to confer the largest risk of HIV MTCT.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5755782/>

## HIV vaccine

(see Vaccine – HIV vaccine)

## Helminth and other gastrointestinal disorders

(See also Anaemia, Diarrhoea, Micronutrients and food fortification, Malaria and HIV)

[PLoS Negl Trop Dis](https://doi.org/10.1371/journal.pntd.0006562). 2018 Jun 4;12(6):e0006562. doi: 10.1371/journal.pntd.0006562. eCollection 2018 Jun.

### [Diagnostic comparison between FECPAKG2 and the Kato-Katz method for analyzing soil-transmitted helminth eggs in stool.](#)

[Moser W](#), [Bärenbold O](#), [Mirams GJ](#), [Cools P](#), [Vlaminck J](#), [Ali SM](#), [Ame SM](#), [Hattendorf J](#), [Vounatsou P](#), [Levecke B](#), [Keiser J](#).

#### **BACKGROUND:**

Over one billion people are infected with soil-transmitted helminths (STH), i.e. *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*. For estimating drug efficacy and monitoring anthelmintic drug resistance, accurate diagnostic methods are critical. **FECPAKG2 is a new remote-diagnostic tool used in veterinary medicine, which produces an image of the stool sample that can be stored on an internet cloud.** We compared for the first time FECPAKG2 with the recommended **Kato-Katz method**.

#### **METHODOLOGY/PRINCIPAL FINDINGS:**

Two stool samples were collected from adolescent participants (age 15-18 years) at baseline and 14 to 21 days after treatment in the framework of a randomized clinical trial on Pemba Island, Tanzania. Stool samples were analyzed with different diagnostic efforts: i) one or ii) two Kato-Katz thick smears from the first sample, iii) two Kato-Katz thick smears from two samples and iv) FECPAKG2 from the first sample. Parameters were calculated based on a hierarchical Bayesian egg count model. Complete data for all diagnostic efforts were available from 615 participants at baseline and 231 hookworm-positive participants at follow-up. At baseline **FECPAKG2 revealed a sensitivity of 75.6% (72.0-77.7) for detecting *A. lumbricoides*, 71.5% (67.4-95.3) for hookworm and 65.8% (64.9-66.2) for *T. trichiura*, which was significantly lower (all  $p < 0.05$ ) than any of the Kato-Katz methods and highly dependent on infection intensity.** Despite that the egg counts based on FECPAKG2 were relatively lower compared to Kato-Katz by a ratio of 0.38 (0.32-0.43) for *A. lumbricoides*, 0.36 (0.33-0.40) for hookworm and 0.08 (0.07-0.09) for *T. trichiura*, the egg reduction rates (ERR) were correctly estimated with FECPAKG2.

#### **CONCLUSIONS/SIGNIFICANCE:**

The sensitivity to identify any STH infection was considerably lower for FECPAKG2 compared to Kato-Katz. Following rigorous development, FECPAKG2 might be an interesting tool with unique features for epidemiological and clinical studies.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002127/>

#### **Comment**

*The Kato-Katz method, referred to above, is recommended by WHO to semi-quantify intestinal helminthic infestations caused by *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm and *Schistosoma* spp. In the technique faeces are sieved through a mesh screen to remove large*

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particles. A portion of sieved sample is then transferred through the hole of a template on a slide. After filling the hole, the template is removed and the remaining sample is covered with a piece of cellophane soaked in glycerol. The glycerol clears the faecal material from around the eggs. The eggs are then counted and the number calculated per gram of faeces.

<https://microbeonline.com/kato-katz-technique-principle-procedure-results/>

[Lancet Infect Dis.](#) 2017 Nov;17(11):1162-1171. doi: 10.1016/S1473-3099(17)30487-5. Epub 2017 Aug 29.

### **Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Côte d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial.**

[Moser W](#), [Coulibaly JT](#), [Ali SM](#), [Ame SM](#), [Amour AK](#), [Yapi RB](#), [Albonico M](#), [Puchkov M](#), [Huwlyer J](#), [Hattendorf J](#), [Keiser J](#).

#### **BACKGROUND:**

Preventive chemotherapy is the current strategy to control soil-transmitted helminth infections (caused by *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*). But, to improve efficacy and avoid emerging resistance, new drugs are warranted. Tribendimidine has shown good anthelmintic efficacy and is therefore a frontrunner for monotherapy and combination chemotherapy.

#### **METHODS:**

We did a randomised, controlled, single-blinded, non-inferiority trial on Pemba Island, Tanzania, and in Côte d'Ivoire. We recruited adolescents aged 15-18 years from four primary schools on Pemba, and school attendees and non-schoolers from two districts in Côte d'Ivoire. Only hookworm-positive participants were randomly assigned (1:1:1:1) to single, oral doses of tribendimidine 400 mg plus placebo (tribendimidine monotherapy), tribendimidine 400 mg plus ivermectin 200 µg/kg, tribendimidine 400 mg plus oxantel pamoate 25 mg/kg, or albendazole 400 mg plus oxantel pamoate 25 mg/kg. Randomisation was done via a computer-generated list in block sizes of four or eight. Participants were asked to provide two stool samples on 2 consecutive days at baseline and again 14-21 days at follow-up. The primary outcome was the difference in egg-reduction rates (ERRs; ie, the geometric mean reduction) in hookworm egg counts between treatment groups, measured by the Kato-Katz technique. Differences in coadministered treatment groups were assessed for non-inferiority with a margin of -3% to albendazole plus oxantel pamoate based on the available-case population, analysed by intention to treat. Safety was assessed 3 h and 24 h after treatment. This study is registered with ISRCTN (number 14373201).

#### **FINDINGS:**

Between July 26, and Dec 23, 2016, we treated 636 hookworm-positive participants, and outcome data were available for 601 participants (151 assigned to tribendimidine monotherapy, 154 to tribendimidine plus ivermectin, 148 to tribendimidine plus oxantel pamoate, and 148 to albendazole plus oxantel pamoate). **Tribendimidine plus ivermectin was non-inferior to albendazole plus oxantel pamoate** (ERRs 99.5% [95% CI 99.2-99.7] vs 96.0% [93.9-97.4]; difference 3.52 percentage points [2.05-5.65]). Likewise, **tribendimidine plus oxantel pamoate was non-inferior to albendazole plus oxantel pamoate** (ERRs 96.5% [95% CI 94.9 to 97.6] vs 96.0% [93.9 to 97.4]; difference 0.48 percentage points [-1.61 to 2.88]). 3 h after

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treatment, headache (n=50 [8%]) and vertigo (n=37 [6%]) were the most widely reported symptoms; 24 h after treatment, 50 (8%) patients reported vertigo and 41 (7%) reported headache. Mainly mild adverse events were reported with peak numbers (n=111 [18%]) at 24 h after treatment. Three participants had moderate adverse events 3 h after treatment: two (<1%) had vertigo and one (<1%) had headache, and two had moderate adverse events 24 h after treatment: one (<1%) had vomiting and one (<1%) had vomiting plus diarrhoea.

### INTERPRETATION:

**Tribendimidine in combination with either ivermectin or oxantel pamoate had a similar, non-inferior efficacy profile as albendazole plus oxantel pamoate, hence tribendimidine will be a useful addition to the depleted anthelmintic drug armamentarium**

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S1473309917304875?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1473309917304875%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Am J Trop Med Hyg.](#) 2017 Dec;97(6):1851-1856. doi: 10.4269/ajtmh.17-0108. Epub 2017 Aug 31.

### **Efficacy and Safety of a Single-Dose Mebendazole 500 mg Chewable, Rapidly-Disintegrating Tablet for *Ascaris lumbricoides* and *Trichuris trichiura* Infection Treatment in Pediatric Patients: A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study.**

[Silber SA](#), [Diro E](#), [Workneh N](#), [Mekonnen Z](#), [Levecke B](#), [Steinmann P](#), [Umulisa I](#), [Alemu H](#), [Baeten B](#), [Engelen M](#), [Hu P](#), [Friedman A](#), [Baseman A](#), [Mrus J](#).

This randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of a newchewable, rapidly-disintegrating mebendazole (MBZ) 500 mg tablet for *Ascaris lumbricoides* and *Trichuris trichiura* infection treatment. Pediatric patients (1-15 years;  $N = 295$ ; from Ethiopia and Rwanda) excreting *A. lumbricoides* and/or *T. trichiura* eggs were enrolled. The study had a screening phase (3 days), a double-blind treatment phase (DBP, 19 days), and an open-label phase (OLP, 7 days). Patients received MBZ or placebo on day 1 of DBP and open-label MBZ on day  $19 \pm 2$  after stool sample collection. **Cure rates (primary endpoint), defined as species-specific egg count of 0 at the end of DBP, were significantly higher in the MBZ group than placebo for *A. lumbricoides* (83.7% [72/86; 95% CI: 74.2%; 90.8%] versus 11.1% [9/81; 95% CI: 5.2%; 20.1%],  $P < 0.001$ ) and for *T. trichiura* (33.9% [42/124; 95% CI: 25.6%; 42.9%] versus 7.6% [9/119; 95% CI: 3.5%; 13.9%],  $P < 0.001$ ).** Egg reduction rates (secondary endpoint) were significantly higher in the MBZ group than placebo for *A. lumbricoides* (97.9% [95% CI: 94.4; 99.9] versus 19.2% [95% CI: -5.9; 41.5];  $P < 0.001$ ) and *T. trichiura* (59.7% [95% CI: 33.9; 78.8] versus 10.5% [95% CI: -16.8; 32.9];  $P = 0.003$ ). Treatment-emergent adverse events (TEAEs) in MBZ group occurred in 6.3% (9/144) of patients during DBP and 2.5% (7/278) during OLP. No deaths, serious TEAEs, or TEAEs leading to discontinuations were reported. A 500 mg chewable MBZ tablet was more efficacious than placebo for the treatment of *A. lumbricoides* and *T. trichiura* infections in pediatric patients, and no safety concerns were identified.

<https://www.ncbi.nlm.nih.gov/pubmed/29016336>

[Pediatr Allergy Immunol.](#) 2017 Dec;28(8):784-792. doi: 10.1111/pai.12804. Epub 2017 Oct 5.

**Effects of treating helminths during pregnancy and early childhood on risk of allergy-related outcomes: Follow-up of a randomized controlled trial.**

[Namara B](#), [Nash S](#), [Lule SA](#), [Akurut H](#), [Mpairwe H](#), [Akello F](#), [Tumusiime J](#), [Kizza M](#), [Kabagenyi J](#), [Nkurunungi G](#), [Muhangi L](#), [Webb EL](#), [Muwanga M](#), [Elliott AM](#).

**BACKGROUND:**

Helminth infections, common in low-income countries, may protect against allergy-related disease. Early exposure may be a key. In the Entebbe Mother and Baby Study, treating helminths during pregnancy resulted in increased eczema rates in early childhood. We followed the cohort to determine whether this translated to increased asthma rates at school age.

**METHODS:**

This randomized, double-blind, placebo-controlled trial, conducted in Entebbe, Uganda, had three interventions. During pregnancy, women were randomized, simultaneously, to albendazole vs placebo and to praziquantel vs placebo. Their children were independently randomized to quarterly albendazole vs placebo from age 15 months to 5 years. We here report follow-up to age 9 years. Primary outcomes at 9 years were recent reported wheeze, skin prick test positivity (SPT) to common allergens and allergen-specific IgE positivity to dust mite or cockroach. Secondary outcomes were doctor-diagnosed asthma and eczema rates between 5 and 9 years, recent eczema, rhinitis and urticaria at 9 years, and SPT and IgE responses to individual allergens.

**RESULTS:**

2507 pregnant women were enrolled; 1215 children were seen at age nine, of whom 1188 are included in this analysis. Reported wheeze was rare at 9 years (3.7%) while SPT positivity (25.0%) and IgE positivity (44.1%) were common. There was no evidence of a treatment effect for any of the three interventions on any of the primary outcomes.

**CONCLUSIONS:**

Prenatal and early-life treatment of helminths, in the absence of change in other exposures, is unlikely to increase the risk of atopic diseases later in childhood in this tropical, low-income setting.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765453/>

[Cureus.](#) 2018 Jan 28;10(1):e2118. doi: 10.7759/cureus.2118.

**Addition of a Short Course of Prednisolone to a Gluten-Free Diet vs. Gluten-Free Diet Alone in Recovery of Celiac Disease: A Pilot Randomized Controlled Trial.**

[Abbas A](#), [Shahab T](#), [Sherwani RK](#), [Alam S](#).

**BACKGROUND:** A gluten-free diet (GFD) is the standard of care in the management of patients with celiac disease, but clinical and histological recovery are often delayed. In newly diagnosed patients, strict compliance to GFD is difficult to achieve; this is especially true in developing countries where gluten-free food is often difficult to obtain. Steroids, when used alone, can be effective in inducing recovery in patients with celiac disease. We performed a randomized controlled trial to study the effect of a short course of prednisolone combined with a GFD on the recovery of celiac disease. Materials and methods This study was a single-center,

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randomised, open-label trial. This investigation was done in a pediatric gastroenterology unit of a tertiary teaching hospital in north India. **Twenty-eight newly diagnosed celiac disease patients were enrolled in the study.** Prednisolone was given at 1 mg/kg for four weeks; duodenal biopsies and IgA anti-tissue transglutaminase (tTg) levels were assessed at eight weeks, six months, and 12 months from the start of the study. Outcome measures The primary outcome measures used to indicate clinical, histological, and immunological recovery of celiac disease were clinical improvement at eight weeks and the proportion of patients with improved histology by at least one grade and who were tissue transglutaminase (tTg) seronegative at eight weeks. The secondary measures were the proportion of patients showing normalization of histological features and the proportions of patients becoming seronegative at six months and one year of GFD. Results **Patients were randomized into the GFD only (n = 14) or GFD with prednisolone (GFD+P) (n = 14) groups.** No significant differences were detected in clinical recovery at eight weeks; none of the patients became seronegative at eight weeks, six months, or 12 months. The proportion of patients with improvement in histology by at least one grade was higher in the GFD+P group at eight weeks, and there was no difference in overall histological improvement at 12 months after starting treatment. Conclusion **The addition of a short course of prednisolone to a GFD does not affect clinical and serological recovery** but might result in rapid histological recovery compared to a GFD alone in patients newly diagnosed with celiac disease.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873829/>

[Trop Doct.](#) 2018 Apr;48(2):112-116. doi: 10.1177/0049475517740312. Epub 2017 Nov 15.

### **Serum zinc, copper and iron status of children with coeliac disease on three months of gluten-free diet with or without four weeks of zinc supplements: a randomised controlled trial.**

[Negi K](#), [Kumar R](#), [Sharma L](#), [Datta SP](#), [Choudhury M](#), [Kumar P](#).

Data about the effect of zinc supplementation with gluten-free diet on normalisation of plasma zinc, copper and iron in patients with coeliac disease are scanty. We evaluated the effect of zinc supplementation on serum zinc, copper and iron levels in patients with coeliac disease, by randomising 71 children newly diagnosed with coeliac disease into two groups: Group A = gluten-free diet (GFD); and Group B = gluten-free diet with zinc supplements (GFD +Zn). The rise in iron and zinc was significantly higher in the latter, but the mean rise of copper levels was slightly higher in the former, but the difference was not significant.

## Hepatitis

## Injury prevention

## Integrated management of Childhood Illness (IMCI)

## Iodine deficiency

## Kidney disease

[Indian J Nephrol](#). 2017 Nov-Dec;27(6):430-434. doi: 10.4103/ijn.IJN\_201\_16.

### [A Randomized Controlled Trial of Intravenous versus Oral Cyclophosphamide in Steroid-resistant Nephrotic Syndrome in Children.](#)

[Shah KM](#), [Ohri AJ](#), [Ali US](#).

**BACKGROUND:** This is a randomized, parallel group, active-controlled trial to compare the efficacy of intravenous cyclophosphamide (IVCP) with oral cyclophosphamide (OCP) in patients with steroid-resistant nephrotic syndrome (SRNS) in children. **Fifty consecutive children with idiopathic SRNS were biopsied and then randomized to receive either OCP at a dose of 2 mg/kg/day for 12 weeks or IVCP at a dose of 500 mg/m<sup>2</sup>/month for 6 months.** Both groups received tapering doses of oral steroids. The response was evaluated in terms of induction of complete remission (CR) or partial remission (PR), time to remit, and side effects. The groups were followed up to determine the duration of remission, percentage of patients who remain in sustained remission for more than 1 year after completion of therapy, change in steroid response status, progression to chronic kidney disease stage 3 or more. Of the fifty patients, OCP was given to 25 children and IVCP to 25 children. The demographic data, histopathology, biochemical profile, and duration of follow-up in the two groups were comparable. **The rates of induction of CR were 52% versus 44% and of PR were 8% versus 8% in the intravenous (IV) and oral group, respectively.** Time to remit was shorter with OCP than IVCP (53 days vs. 84.4 days). Incidence of side effects (both major and minor) was 36% in IVCP versus 20% in OCP group. The actuarial cumulative sustained remission in our study was 12% in IVCP compared with 16% in OCP at 1 year after completion of therapy. Twelve percent children in both the groups exhibited restoration of steroid sensitivity. **Thus, in our study, overall, more than half of SRNS patients showed initial response to cyclophosphamide, but only one-fourth patients had sustained remission on follow-up. OCP and IVCP were equally efficacious and safe in idiopathic SRNS in children.**

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5704406/>

[Kidney Int](#). 2018 Feb;93(2):510-518. doi: 10.1016/j.kint.2017.08.011. Epub 2017 Oct 18.

### [A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome.](#)



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[Gruppen MP](#), [Bouts AH](#), [Jansen-van der Weide MC](#), [Merkus MP](#), [Zurowska A](#), [Maternik M](#), [Massella L](#), [Emma F](#), [Niaudet P](#), [Cornelissen EAM](#), [Schurmans T](#), [Raes A](#), [van de Walle J](#), [van Dyck M](#), [Gulati A](#), [Bagga A](#), [Davin JC](#); [all members of the Levamisole Study Group](#).

**BACKGROUND:** Levamisole has been considered the least toxic and least expensive steroid-sparing drug for preventing relapses of steroid-sensitive idiopathic nephrotic syndrome (SSINS). However, evidence for this is limited as previous randomized clinical trials were found to have methodological limitations. Therefore, we conducted an international multicenter, placebo-controlled, double-blind, randomized clinical trial to reassess its usefulness in prevention of relapses in children with SSINS. The efficacy and safety of one year of levamisole treatment in children with SSINS and frequent relapses were evaluated. The primary analysis cohort consisted of 99 patients from 6 countries. **Between 100 days and 12 months after the start of study medication, the time to relapse (primary endpoint) was significantly increased in the levamisole compared to the placebo group (hazard ratio 0.22 [95% confidence interval 0.11-0.43]).** Significantly, after 12 months of treatment, six percent of placebo patients versus 26 percent of levamisole patients were still in remission. During this period, the most frequent serious adverse event (four of 50 patients) possibly related to levamisole was asymptomatic moderate neutropenia, which was reversible spontaneously or after treatment discontinuation. Thus, in children with SSINS and frequent relapses, levamisole prolonged the time to relapse and also prevented recurrence during one year of treatment compared to prednisone alone. However, regular blood controls are necessary for safety issues.

<https://www.sciencedirect.com/science/article/pii/S0085253817306075?via%3Dihub>

[Pediatr Nephrol](#). 2017 Nov;32(11):2063-2070. doi: 10.1007/s00467-017-3716-2. Epub 2017 Jul 19.

### **The effect of vitamin D and calcium supplementation in pediatric steroid-sensitive nephrotic syndrome.**

[Banerjee S](#), [Basu S](#), [Sen A](#), [Sengupta J](#).

#### **BACKGROUND:**

Low serum levels of total 25-hydroxycholecalciferol (25(OH)D) occur in nephrotic syndrome (NS). We aimed to assess the effects of vitamin D3 and calcium supplementation on 25(OH)D levels, bone mineralization, and NS relapse rate in children with steroid-sensitive NS.

#### **METHODS:**

A randomized controlled trial (RCT) was performed in children with steroid-sensitive NS. The treatment group received vitamin D3 (60,000 IU orally, weekly for 4 weeks) and calcium supplements (500 to 1,000 mg/day for 3 months) after achieving NS remission. Blood samples for bone biochemistry were taken during relapse (T0), after 6 weeks (T1) and 6 months (T2) of randomization, whereas a lumbar DXA scan was performed at T0 and T2. Renal ultrasound was performed after study completion in the treatment group and in all patients with hypercalciuria.

#### **RESULTS:**

Of the 48 initial recruits, 43 patients completed the study. Post-intervention, 25(OH)D levels showed significant improvements in the treatment group compared with controls at T1 ( $p < 0.001$ ) and T2 ( $p < 0.001$ ). However, this was not associated with differences in bone mineral content (BMC) ( $p = 0.44$ ) or bone mineral density (BMD) ( $p = 0.64$ ) between the groups. Additionally, there was no reduction in relapse number in treated patients ( $p = 0.54$ ). Documented hypercalciuria occurred in 52% of patients in the treatment group, but was not associated with nephrocalcinosis.

**CONCLUSIONS:**

Although supplementation with calcium and vitamin D improved 25(OH)D levels significantly, there was no effect on BMC, BMD or relapse rate over a 6-month follow-up. Occurrence of hypercalciuria mandates caution and appropriate monitoring if using such therapy. Appropriate dosage of vitamin D3 remains uncertain and studies examining biologically active vitamin D may provide answers.

<https://link.springer.com/article/10.1007%2Fs00467-017-3716-2>

*Pediatr Nephrol.* 2017 Aug;32(8):1377-1382. doi: 10.1007/s00467-017-3640-5. Epub 2017 Mar 24.

**Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome.**

[Abeyagunawardena AS](#), [Thalgahagoda RS](#), [Dissanayake PV](#), [Abeyagunawardena S](#), [Illangasekera YA](#), [Karunadasa UI](#), [Trompeter RS](#).

**BACKGROUND:**

Relapses of childhood nephrotic syndrome (NS) are frequently precipitated by viral upper respiratory tract infections (URTIs). A review of the literature reveals that in patients with steroid-dependent NS on alternate day corticosteroids, a short course of daily corticosteroid therapy during the course of an URTI may reduce relapse frequency.

**OBJECTIVE:**

To assess the effect of a short course of low-dose corticosteroid therapy during the course of an URTI on relapse frequency in patients with steroid-sensitive NS who have not been taking any treatment for a minimum period of 3 months.

**METHODS:**

A double-blind placebo-controlled crossover trial was conducted on 48 patients with idiopathic NS who had not been receiving corticosteroid therapy for a minimum of 3 months. Patients were randomized into two groups. **Group A received 5 days of daily prednisolone at 0.5 mg/kg at the onset of an URTI while group B received 5 days of placebo. Both groups were followed up for 1 year and the URTI-induced relapse frequency was noted. A crossover was performed during the next year, with group A receiving placebo and group B receiving prednisolone.**

**RESULTS:**

Thirty-three patients completed the study. In the treatment group, 115 episodes of URTI led to 11 relapses while in the control group 101 episodes of URTI led to 25 relapses. There was no significant difference between the mean number of URTIs between the treatment and control groups. **The treatment group had significantly less relapses compared to the control group ( $p = 0.014$ ). Within the treatment group, 65.6% did not relapse, while the remainder had a single relapse. In contrast, only 40.6% of the control group remained in remission while 40.6% suffered a single relapse and 18.8% had two or more relapses.**

**CONCLUSIONS:**

**Prescribing a short course of daily corticosteroids during an URTI significantly reduces the frequency of URTI-induced relapse in patients with steroid-responsive NS who are off corticosteroid therapy.**

<https://link.springer.com/content/pdf/10.1007%2Fs00467-017-3640-5.pdf>

[Kidney Int.](#) 2017 Jul;92(1):248-257. doi: 10.1016/j.kint.2017.01.019. Epub 2017 Mar 18.

**[Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome.](#)**

[Sinha A](#), [Gupta A](#), [Kalaivani M](#), [Hari P](#), [Dinda AK](#), [Bagga A](#).

Studies of nephrotic syndrome show that substitution of calcineurin inhibitors by mycophenolate mofetil (MMF) enables sustained remission and corticosteroid sparing and avoids therapy associated adverse effects. However, controlled studies in patients with steroid resistance are lacking. Here we examined the effect of switching from therapy with tacrolimus to MMF on disease course in an open-label, one-to-one randomized, controlled trial on children (one to 18 years old), recently diagnosed with steroid-resistant nephrotic syndrome, at a referral center in India. **Following six months of therapy with tacrolimus, patients with complete or partial remission were randomly assigned such that 29 received MMF while 31 received tacrolimus along with tapering prednisolone on alternate days for 12 months.** On intention-to-treat analyses, the proportion of patients with a favorable outcome (sustained remission, infrequent relapses) at one year was significantly lower (44.8%) in the MMF group than in the tacrolimus group (90.3%). **The incidence of relapses was significantly higher for patients treated with MMF than tacrolimus** (mean difference: 1.05 relapses per person-year). While there was no difference in the proportion of patients with sustained remission, the risk of recurrence of steroid resistance was significantly higher for patients receiving MMF compared to tacrolimus (mean difference: 20.7%). Compared to tacrolimus, patients receiving MMF had a significantly (71%) lower likelihood of a favorable outcome and significantly increased risk of treatment failure (frequent relapses, steroid resistance). Thus, replacing tacrolimus with MMF after six months of tacrolimus therapy for steroid-resistant nephrotic syndrome in children is associated with significant risk of frequent relapses or recurrence of resistance. These findings have implications for guiding the duration of therapy with tacrolimus for steroid-resistant nephrotic syndrome.

<https://www.sciencedirect.com/science/article/pii/S0085253817300704?via%3Dihub>

## Leishmaniasis

[J Antimicrob Chemother.](#) 2017 Nov 1;72(11):3131-3140. doi: 10.1093/jac/dkx283.

**[Visceral leishmaniasis relapse hazard is linked to reduced miltefosine exposure in patients from Eastern Africa: a population pharmacokinetic/pharmacodynamic study.](#)**

[Dorlo TPC](#), [Kip AE](#), [Younis BM](#), [Ellis SJ](#), [Alves F](#), [Beijnen JH](#), [Njenga S](#), [Kirigi G](#), [Hailu A](#), [Olobo J](#), [Musa AM](#), [Balasegaram M](#), [Wasunna M](#), [Karlsson MO](#), [Khalil EAG](#).

### BACKGROUND:

Low efficacy of miltefosine in the treatment of visceral leishmaniasis was recently observed in Eastern Africa.

### OBJECTIVES:

To describe the pharmacokinetics and establish a pharmacokinetic/pharmacodynamic relationship for miltefosine in Eastern African patients with visceral leishmaniasis, using a time-to-event approach to model relapse of disease.

### METHODS:

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Miltefosine plasma concentrations from 95 patients (48 monotherapy versus 47 combination therapy) were included in the population pharmacokinetic model using non-linear mixed effects modelling. Subsequently a time-to-event model was developed to model the time of clinical relapse. Various summary pharmacokinetic parameters (various AUCs, Time > EC50, Time > EC90), normalized within each treatment arm to allow simultaneous analysis, were evaluated as relapse hazard-changing covariates.

### RESULTS:

A two-compartment population model with first-order absorption fitted the miltefosine pharmacokinetic data adequately. Relative bioavailability was reduced (-74%, relative standard error 4.7%) during the first week of treatment of the monotherapy arm but only the first day of the shorter combination regimen. Time to the relapse of infection could be described using a constant baseline hazard (baseline 1.8 relapses/year, relative standard error 72.7%). Miltefosine Time > EC90 improved the model significantly when added in a maximum effect function on the baseline hazard (half maximal effect with Time > EC90 6.97 days for monotherapy).

### CONCLUSIONS:

Miltefosine drug exposure was found to be decreased in Eastern African patients with visceral leishmaniasis, due to a (transient) initial lower bioavailability. Relapse hazard was inversely linked to miltefosine exposure. Significantly lower miltefosine exposure was observed in children compared with adults, further urging the need for implementation of dose adaptations for children.

<https://academic.oup.com/jac/article/72/11/3131/4106324>

*PLoS Negl Trop Dis.* 2017 Sep 5;11(9):e0005890. doi: 10.1371/journal.pntd.0005890. eCollection 2017 Sep.

### **Control of *Phlebotomus argentipes* (Diptera: Psychodidae) sand fly in Bangladesh: A cluster randomized controlled trial.**

[Chowdhury R](#), [Faria S](#), [Huda MM](#), [Chowdhury V](#), [Maheswary NP](#), [Mondal D](#), [Akhter S](#), [Akter S](#), [Khan RK](#), [Nabi SG](#), [Kroeger A](#), [Argaw D](#), [Alvar J](#), [Dash AP](#), [Banu Q](#).

### BACKGROUND:

A number of studies on visceral leishmaniasis (VL) vector control have been conducted during the past decade, sometimes came to very different conclusion. The present study on a large sample investigated different options which are partially unexplored including: (1) **indoor residual spraying (IRS) with alpha cypermethrin 5WP**; (2) **long lasting insecticide impregnated bed-net (LLIN)**; (3) **impregnation of local bed-nets with slow release insecticide K-O TAB 1-2-3 (KOTAB)**; (4) **insecticide spraying in potential breeding sites outside of house using chlorpyrifos 20EC (OUT) and different combinations of the above.**

### METHODS:

The study was a cluster randomized controlled trial where 3089 houses from 11 villages were divided into 10 sections, each section with 6 clusters and each cluster having approximately 50 houses. Based on vector density (males plus females) during baseline survey, the 60 clusters were categorized into 3 groups: (1) high, (2) medium and (3) low. Each group had 20 clusters. From these three groups, 6 clusters (about 300 households) were randomly selected for each type of intervention and control arms. Vector density was measured before and 2, 4, 5, 7, 11, 14, 15, 18 and 22 months after intervention using CDC light traps. The impact of interventions was measured by using the difference-in-differences regression model.

### RESULTS:

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A total of 17,434 sand flies were collected at baseline and during the surveys conducted over 9 months following the baseline measurements. At baseline, the average *P. argentipes* density per household was 10.6 (SD = 11.5) in the control arm and 7.3 (SD = 8.46) to 11.5 (SD = 20.2) in intervention arms. The intervention results presented as the range of percent reductions of sand flies (males plus females) and rate ratios in 9 measurements over 22 months. Among single type interventions, the effect of IRS with 2 rounds of spraying (applied by the research team) ranged from 13% to 75% reduction of *P. argentipes* density compared to the control arm (rate-ratio [RR] ranged from 0.25 to 0.87). LLINs caused a vector reduction of 9% to 78% (RR, 0.22 to 0.91). KOTAB reduced vectors by 4% to 73% (RR, 0.27 to 0.96). The combination of LLIN and OUT led to a vector reduction of 26% to 86% (RR, 0.14 to 0.74). The reduction for the combination of IRS and OUT was 8% to 88% (RR, 0.12 to 0.92). IRS and LLIN combined resulted in a vector reduction of 13% to 85% (RR, 0.15 to 0.77). The IRS and KOTAB combination reduced vector densities by 16% to 86% (RR, 0.14 to 0.84). Some intermediate measurements for KOTAB alone and for IRS plus LLIN; and IRS plus KOTAB were not statistically significant. The bioassays on sprayed surfaces or netting materials showed favourable results (>80% mortality) for 22 months (IRS tested for 12 months). In the KOTAB, a gradual decline was observed after 6 months.

### CONCLUSIONS:

**LLIN and OUT was the best combination to reduce VL vector densities for 22 months or longer.** Operationally, this is much easier to apply than IRS. A cost analysis of the preferred tools will follow. The relationship between vector density (males plus females) and leishmaniasis incidence should be investigated, and this will require estimates of the Entomological Inoculation Rate.

<http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0005890&type=printable>

## Lymphatic filariasis

[PLoS Negl Trop Dis.](#) 2017 Oct 23;11(10):e0005631. doi: 10.1371/journal.pntd.0005631. eCollection 2017 Oct.

### [Lymphatic pathology in asymptomatic and symptomatic children with \*Wuchereria bancrofti\* infection in children from Odisha, India and its reversal with DEC and albendazole treatment.](#)

[Kar SK](#), [Dwivedi B](#), [Das BK](#), [Agrawala BK](#), [Ramachandran CP](#), [Horton J](#).

### BACKGROUND:

Once interruption of transmission of lymphatic filariasis is achieved, morbidity prevention and management becomes more important. A study in *Brugia malayi* filariasis from India has shown sub-clinical lymphatic pathology with potential reversibility. We studied a *Wuchereria bancrofti* infected population, the major contributor to LF globally.

### METHODS:

Children aged 5-18 years from Odisha, India were screened for *W. bancrofti* infection and disease. 102 infected children, 50 with filarial disease and 52 without symptoms were investigated by lymphoscintigraphy and then **randomized to receive a supervised single oral dose of DEC and albendazole which was repeated either annually or semi-annually.** The lymphatic pathology was evaluated six monthly for two years.

### FINDINGS:

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Baseline lymphoscintigraphy showed abnormality in lower limb lymphatics in 80% of symptomatic (40/50) and 63.5% (33/52) of asymptomatic children. Progressive improvement in baseline pathology was seen in 70.8, 87.3, 98.6, and 98.6% of cases at 6, 12, 18, and 24 months follow up, while in 4.2, 22.5, 47.9 and 64.8%, pathology reverted to normal. This was independent of age ( $p = 0.27$ ), symptomatic status ( $p = 0.57$ ) and semi-annual/bi-annual dosing ( $p = 0.46$ ). Six of eleven cases showed clinical reduction in lymphedema of legs.

### INTERPRETATION:

A significant proportion of a young *W. bancrofti* infected population exhibited lymphatic pathology which was reversible with annual dosage of DEC and albendazole. This provides evidence for morbidity prevention & treatment of early lymphedema. It can also be used as a tool to improve community compliance during mass drug administration.

<http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0005631&type=printable>

**Parasitol Res.** 2017 Oct;116(10):2683-2694. doi: 10.1007/s00436-017-5577-9. Epub 2017 Aug 7.

### **Efficacy and tolerability of treatment with single doses of diethylcarbamazine (DEC) and DEC plus albendazole (ABZ) for three consecutive years in lymphatic filariasis: a field study in India.**

[Kshirsagar NA](#), [Gogtay NJ](#), [Garg BS](#), [Deshmukh PR](#), [Rajgor DD](#), [Kadam VS](#), [Thakur PA](#), [Gupta A](#), [Ingole NS](#), [Lazdins-Helds JK](#).

Lymphatic filariasis (LF) affects 73 countries, causes morbidity and impedes socioeconomic development. We had found no difference in safety and micro (Mf) and macro filarial action of single-dose diethylcarbamazine (DEC) and DEC + albendazole (ABZ) in an F01 study done in India (year 2000). There was a programmatic need to evaluate safety and efficacy of multiple annual treatments (F02). **Subjects (155) from the F01 study, meeting inclusion-exclusion criteria, were enrolled in F02 and treated with further two annual doses of DEC or DEC + ABZ.** Efficacy was evaluated for Mf positivity by peripheral smear (PS) and nucleopore (NP) filter, circulating filarial antigen (CFA) and filarial dance sign (FDS) positivity and Mf count at yearly follow-up. Safety was assessed for 5 days after drug administration. Total of 139 subjects evaluated for efficacy (69 DEC and 70 DEC + ABZ group). Mf positivity prevalence declined progressively by 95% (PS), 66% (NP), and 95% (PS) and 86% (NP); **CFA positivity prevalence declined by 15% and 9%; FDS by 100% each; Mf count declined by 75.5 and 76.9% with three annual treatment of DEC and DEC + ABZ, respectively.** Addition of ABZ did not show any advantage over DEC given as three annual rounds for LF. DEC and DEC + ABZ were well tolerated. There was no correlation between result of CFA and FDS, (both claimed to be indicative of adult worm). **Analysis of published studies and our data indicate that macrofilaricidal effect of DEC/DEC + ABZ may be seen in children and not adults, with three or more annual dosing.**

<https://link.springer.com/content/pdf/10.1007%2Fs00436-017-5577-9.pdf>

## Leprosy

**PLoS Negl Trop Dis.** 2017 Oct 4;11(10):e0005952. doi: 10.1371/journal.pntd.0005952. eCollection 2017 Oct.

**Effectiveness of 32 versus 20 weeks of prednisolone in leprosy patients with recent nerve function impairment: A randomized controlled trial.**

[Wagenaar I](#), [Post E](#), [Brandsma W](#), [Bowers B](#), [Alam K](#), [Shetty V](#), [Pai V](#), [Husain S](#), [Sigit Prakoeswa CR](#), [Astari L](#), [Hagge D](#), [Shah M](#), [Neupane K](#), [Tamang KB](#); [TENLEP study group](#), [Nicholls P](#), [Richardus JH](#).

**BACKGROUND:**

While prednisolone is commonly used to treat recent nerve function impairment (NFI) in leprosy patients, the optimal treatment duration has not yet been established. In this "Treatment of Early Neuropathy in Leprosy" (TENLEP) trial, we evaluated whether a **32-week prednisolone course is more effective than a 20-week course in restoring and improving nerve function.**

**METHODS:**

In this multi-centre, triple-blind, randomized controlled trial, leprosy patients who had recently developed clinical NFI (<6 months) were allocated to a prednisolone treatment regimen of either 20 weeks or 32 weeks. Prednisolone was started at either 45 or 60 mg/day, depending on the patient's body weight, and was then tapered. Throughout follow up, NFI was assessed by voluntary muscle testing and monofilament testing. The primary outcome was the proportion of patients with improved or restored nerve function at week 78. As secondary outcomes, we analysed improvements between baseline and week 78 on the Reaction Severity Scale, the SALSA Scale and the Participation Scale. Serious Adverse Events and the need for additional prednisolone treatment were monitored and reported.

**RESULTS:**

We included 868 patients in the study, 429 in the 20-week arm and 439 in the 32-week arm. At 78 weeks, the proportion of patients with improved or restored nerve function did not differ significantly between the groups: 78.1% in the 20-week arm and 77.5% in the 32-week arm ( $p = 0.821$ ). Nor were there any differences in secondary outcomes, except for a significant higher proportion of Serious Adverse Events in the longer treatment arm.

**CONCLUSION:**

In our study, a **20-week course of prednisolone was as effective as a 32-week course in improving and restoring recent clinical NFI in leprosy patients.** Twenty weeks is therefore the preferred initial treatment duration for leprosy neuropathy, after which likely only a minority of patients require further individualized treatment.

<http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0005952&type=printable>

[PLoS Negl Trop Dis](#). 2017 Jul 13;11(7):e0005725. doi: 10.1371/journal.pntd.0005725. eCollection 2017 Jul.

**Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients.**

[Penna GO](#), [Bührer-Sékula S](#), [Kerr LRS](#), [Stefani MMA](#), [Rodrigues LC](#), [de Araújo MG](#), [Ramos AMC](#), [de Andrade ARC](#), [Costa MB](#), [Rosa PS](#), [Gonçalves HS](#), [Cruz R](#), [Barreto ML](#), [Pontes MAA](#), [Penna MLF](#).

**BACKGROUND:**

Leprosy control is based on early diagnosis and multidrug therapy. For treatment purposes, leprosy patients can be classified as paucibacillary (PB) or multibacillary (MB), according to the

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number of skin lesions. Studies regarding a uniform treatment regimen (U-MDT) for all leprosy patients have been encouraged by the WHO, rendering disease classification unnecessary.

### METHODOLOGY AND FINDINGS:

An independent, randomized, controlled clinical trial conducted from 2007 to 2015 in Brazil, compared main outcomes (frequency of reactions, bacilloscopic index trend, disability progression and relapse rates) among **MB patients treated with a uniform regimen/U-MDT (dapsone+rifampicin+clofazimine for six months) versus WHO regular-MDT/R-MDT (dapsone+rifampicin+clofazimine for 12 months)**. A total of 613 newly diagnosed, untreated MB patients with high bacterial load were included. There was no statistically significant difference in Kaplan-Meier survival function regarding reaction or disability progression among patients in the U-MDT and R-MDT groups, with more than 25% disability progression in both groups. The full mixed effects model adjusted for the bacilloscopic index average trend in time showed no statistically significant difference for the regression coefficient in both groups and for interaction variables that included treatment group. **During active follow up, four patients in U-MDT group relapsed representing a relapse rate of 2.6 per 1000 patients per year of active follow up (95% CI [0.81, 6.2] per 1000). During passive follow up three patients relapsed in U-MDT and one in R-MTD.** As this period corresponds to passive follow up, sensitivity analysis estimated the relapse rate for the entire follow up period between 2.9- and 4.5 per 1000 people per year.

### CONCLUSION:

Our results on the first randomized and controlled study on U-MDT together with the results from three previous studies performed in China, India and Bangladesh, support the hypothesis that UMDT is an acceptable option to be adopted in endemic countries to treat leprosy patients in the field worldwide.

<http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0005725&type=printable>

## Malaria

(See also Maternal health, Anaemia)

### Malaria diagnosis

[BMC Med.](#) 2017 Jul 7;15(1):124. doi: 10.1186/s12916-017-0891-8.

### [Use of malaria rapid diagnostic tests by community health workers in Afghanistan: cluster randomised trial.](#)

[Leslie T](#), [Rowland M](#), [Mikhail A](#), [Cundill B](#), [Willey B](#), [Alokozai A](#), [Mayan I](#), [Hasanzai A](#), [Baktash SH](#), [Mohammed N](#), [Wood M](#), [Rahimi HU](#), [Laurent B](#), [Buhler C](#), [Whitty CJM](#).

### BACKGROUND:

The World Health Organisation (WHO) recommends parasitological diagnosis of malaria before treatment, but use of malaria rapid diagnostic tests (mRDTs) by community health workers (CHWs) has not been fully tested within health services in south and central Asia. mRDTs could allow CHWs to diagnose malaria accurately, improving treatment of febrile illness.

### METHODS:

A cluster randomised trial in community health services was undertaken in Afghanistan. The primary outcome was the proportion of suspected malaria cases correctly treated for polymerase chain reaction (PCR)-confirmed malaria and PCR negative cases receiving no antimalarial drugs measured at the level of the patient. CHWs from 22 clusters (clinics) received standard training on clinical diagnosis and treatment of malaria; 11 clusters randomised to the intervention arm



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received additional training and were provided with mRDTs. CHWs enrolled cases of suspected malaria, and the mRDT results and treatments were compared to blind-read PCR diagnosis.

### RESULTS:

In total, 256 CHWs enrolled 2400 patients with 2154 (89.8%) evaluated. **In the intervention arm, 75.3% (828/1099) were treated appropriately vs. 17.5% (185/1055) in the control arm (cluster adjusted risk ratio: 3.72, 95% confidence interval 2.40-5.77;  $p < 0.001$ ). In the control arm, 85.9% (164/191) with confirmed *Plasmodium vivax* received chloroquine compared to 45.1% (70/155) in the intervention arm ( $p < 0.001$ ).** Overuse of chloroquine in the control arm resulted in 87.6% (813/928) of those with no malaria (PCR negative) being treated vs. 10.0% (95/947) in the intervention arm,  $p < 0.001$ . **In the intervention arm, 71.4% (30/42) of patients with *P. falciparum* did not receive artemisinin-based combination therapy, partly because operational sensitivity of the RDTs was low (53.2%, 38.1-67.9).** There was high concordance between recorded RDT result and CHW prescription decisions: 826/950 (87.0%) with a negative test were not prescribed an antimalarial. Co-trimoxazole was prescribed to 62.7% of malaria negative patients in the intervention arm and 15.0% in the control arm.

### CONCLUSIONS:

**While introducing mRDT reduced overuse of antimalarials, this action came with risks that need to be considered before use at scale: an appreciable proportion of malaria cases will be missed by those using current mRDTs.** Higher sensitivity tests could be used to detect all cases. Overtreatment with antimalarial drugs in the control arm was replaced with increased antibiotic prescription in the intervention arm, resulting in a probable overuse of antibiotics.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5501368/>

## Insecticide-treated bed nets

### Other preventative interventions

(See also: Vaccines – malaria vaccine)

[MC Public Health](#). 2018 Jul 18;18(1):894. doi: 10.1186/s12889-018-5746-5.

### [Evaluating the impact of screening plus eave tubes on malaria transmission compared to current best practice in central Côte d'Ivoire: a two armed cluster randomized controlled trial.](#)

[Sternberg ED](#), [Cook J](#), [Ahoua Alou LP](#), [Aoura CJ](#), [Assi SB](#), [Doudou DT](#), [Koffi AA](#), [N'Guessan R](#), [Oumbouke WA](#), [Smith RA](#), [Worrall E](#), [Kleinschmidt I](#), [Thomas MB](#).

### BACKGROUND:

Access to long-lasting insecticidal nets (LLINs) has increased and malaria has decreased globally, but malaria transmission remains high in parts of sub-Saharan Africa and insecticide resistance threatens current progress. Eave tubes are a new tool for the targeted delivery of insecticides against mosquitoes attempting to enter houses. The primary objective of this trial is to test whether screening plus eave tubes (SET) provides protection against malaria, on top of universal coverage with LLINs in an area of intense pyrethroid resistance. The trial will also assess acceptability and cost-effectiveness of the intervention.

### METHODS/DESIGN:

A two-armed, cluster randomized controlled trial will be conducted to evaluate the effect of SET on clinical malaria incidence in children living in central Côte d'Ivoire. Forty villages will be

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selected based on population size and the proportion of houses suitable for modification with SET. Using restricted randomization, half the villages will be assigned to the treatment arm (SET + LLINs) and the remainder will be assigned to the control arm (LLINs only). In both arms, LLINs will be distributed and in the treatment arm, householders will be offered SET. Fifty children aged six months to eight years old will be enrolled from randomly selected households in each of the 40 villages. Cohorts will be cleared of malaria parasites at the start of the study and one year after recruitment, and will be monitored for clinical malaria case incidence by active case detection over two years. Mosquito densities will be assessed using CDC light traps and human landing catches and a subset of Anopheles mosquitoes will be examined for parity status and tested for sporozoite infection. Acceptability of SET will be monitored using surveys and focus groups. Cost-effectiveness analysis will measure the incremental cost per case averted and per disability-adjusted life year (DALY) averted of adding SET to LLINs. Economic and financial costs will be estimated from societal and provider perspective using standard economic evaluation methods.

### DISCUSSION:

This study will be the first evaluation of the epidemiological impact of SET. Trial findings will show whether SET is a viable, cost-effective technology for malaria control in Côte d'Ivoire and possibly elsewhere.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052618/>

[PLoS One](#). 2018 Mar 5;13(3):e0193296. doi: 10.1371/journal.pone.0193296. eCollection 2018.

### [Optimal mode for delivery of seasonal malaria chemoprevention in](#)

### [Ouelessebouyou, Mali: A cluster randomized trial.](#)

[Barry A](#), [Issiaka D](#), [Traore T](#), [Mahamar A](#), [Diarra B](#), [Sagara I](#), [Kone D](#), [Doumbo OK](#), [Duffy P](#), [Fried M](#), [Dicko A](#).

### BACKGROUND:

Seasonal malaria chemoprevention (SMC), the administration of complete therapeutic courses of antimalarials to children aged 3-59 months during the malaria transmission season, is a new strategy recommended by the World Health Organization (WHO) for malaria control in Sahelian countries such as Mali with seasonal transmission. The strategy is a highly cost-effective approach to reduce malaria burden in these areas. Despite the substantial benefits of SMC on malaria infection and disease, the optimal approach to deliver SMC remains to be determined. While fixed-point delivery (FPD) and non-directly observed treatment (NDOT) by community health workers are logistically attractive, these need to be evaluated and compared to other modes of delivery for maximal coverage.

### METHODS:

To determine the optimal mode fixed-point (FPD) vs door-to-door delivery (DDD); directly observed treatment (DOT) vs. non- directly observed treatment (NDOT)), 31 villages in four health sub-districts were randomized to receive three rounds of SMC with Sulfadoxine-pyrimethamine plus Amodiaquine (SP+AQ) at monthly intervals using one of the following methods: FPD+DOT; FPD+NDOT; DDD+DOT; DDD+NDOT. The primary endpoint was SMC coverage assessed by cross-sectional survey of 2,035 children at the end of intervention period.

### RESULTS:

Coverage defined as the proportion of children who received all three days of SMC treatment during the three monthly rounds based information collected by interview (primary endpoint) was significantly higher in children who received SMC using DDD 74% (95% CI 69% - 80%) compared to FPD 60% (95% CI 50% - 70%);  $p = 0.009$ . It was similar in children who received

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SMC using DOT or NDOT 65%, (95% CI 55% - 76%) versus 68% (95% CI 57% - 79%);  $p = 0.72$ .

### CONCLUSIONS:

**In summary, door-to-door delivery of SMC provides better coverage than FPD.** Directly observed therapy, which requires more time and resources, did not improve coverage with SMC.

<http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0193296&type=printable>

[Malar J.](#) 2017 Aug 7;16(1):318. doi: 10.1186/s12936-017-1964-z.

### **School-based diagnosis and treatment of malaria by teachers using rapid diagnostic tests and artemisinin-based combination therapy: experiences and perceptions of users and implementers of the Learner Treatment Kit, southern Malawi.**

[Mphwatiwa T](#), [Witek-McManus S](#), [Mtali A](#), [Okello G](#), [Nguluwe P](#), [Chatsika H](#), [Roschnik N](#), [Halliday KE](#), [Brooker SJ](#), [Mathanga DP](#).

### BACKGROUND:

**Training teachers to diagnose uncomplicated malaria using malaria rapid diagnostic tests and treat with artemisinin-based combination therapy has the potential to improve the access of primary school children (6-14 years) to prompt and efficient treatment for malaria, but little is known about the acceptability of such an intervention.** This qualitative study explored experiences and perceptions of users and implementers of a programme of school-based malaria case management via a first-aid kit-the Learner Treatment Kit (LTK)-implemented as part of a cluster-randomized controlled trial in Zomba district, Malawi.

### METHODS:

From 29 primary schools where teachers were trained to test and treat school children for malaria using the LTK, six schools were purposively selected on the basis of relative intervention usage (low, medium or high); school size and geographical location. In total eight focus group discussions were held with school children, parents and guardians, and teachers; and 20 in-depth interviews were conducted with key stakeholders at the school, district and national levels. Interviews were recorded, transcribed, and analysed using a thematic analysis approach.

### RESULTS:

The LTK was widely perceived by respondents to be a worthwhile intervention, with the opinion that trained teachers were trusted providers of malaria testing and treatment to school children. Benefits of the programme included a perception of improved access to malaria treatment for school children; decreased school absenteeism; and that the programme supported broader national health and education policies. Potential barriers to successful implementation expressed included increased teacher workloads, a feeling of inadequate supervision from health workers, lack of incentives and concerns for the sustainability of the programme regarding the supply of drugs and commodities.

### CONCLUSION:

**Training teachers to test for and treat uncomplicated malaria in schools was well received by both users and implementers alike, and was perceived by the majority of stakeholders to be a valuable programme.** Factors raised as critical to the success of such a programme included ensuring an effective supervisory system, a reliable supply chain, and the training of greater numbers of teachers per school to manage high consultation numbers, especially during the peak malaria transmission season.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5547577/>

[Cochrane Database Syst Rev.](#) 2018 Mar 21;3:CD011444. doi: 10.1002/14651858.CD011444.pub2.

**[Mefloquine for preventing malaria in pregnant women.](#)**

[González R](#), [Pons-Duran C](#), [Piqueras M](#), [Aponte JJ](#), [Ter Kuile FO](#), [Menéndez C](#).

**BACKGROUND:**

The World Health Organization recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine for malaria for all women who live in moderate to high malaria transmission areas in Africa. However, parasite resistance to sulfadoxine-pyrimethamine has been increasing steadily in some areas of the region. Moreover, HIV-infected women on cotrimoxazole prophylaxis cannot receive sulfadoxine-pyrimethamine because of potential drug interactions. Thus, there is an urgent need to identify alternative drugs for prevention of malaria in pregnancy. One such candidate is mefloquine.

**OBJECTIVES:**

To assess the effects of mefloquine for preventing malaria in pregnant women, specifically, to evaluate: the efficacy, safety, and tolerability of mefloquine for preventing malaria in pregnant women; and the impact of HIV status, gravidity, and use of insecticide-treated nets on the effects of mefloquine.

**SEARCH METHODS:**

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, Latin American Caribbean Health Sciences Literature (LILACS), the Malaria in Pregnancy Library, and two trial registers up to 31 January 2018. In addition, we checked references and contacted study authors to identify additional studies, unpublished data, confidential reports, and raw data from published trials.

**SELECTION CRITERIA:**

Randomized and quasi-randomized controlled trials comparing mefloquine IPT or mefloquine prophylaxis against placebo, no treatment, or an alternative drug regimen.

**DATA COLLECTION AND ANALYSIS:**

Two review authors independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias, and extracted data. We contacted trial authors to ask for additional information when required. Dichotomous outcomes were compared using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes using mean differences (MDs). We have presented all measures of effect with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach for the following main outcomes of analysis: maternal peripheral parasitaemia at delivery, clinical malaria episodes during pregnancy, placental malaria, maternal anaemia at delivery, low birth weight, spontaneous abortions and stillbirths, dizziness, and vomiting.

**MAIN RESULTS:**

Six trials conducted between 1987 and 2013 from Thailand (1), Benin (3), Gabon (1), Tanzania (1), Mozambique (2), and Kenya (1) that included 8192 pregnant women met our inclusion criteria. **Two trials (with 6350 HIV-uninfected pregnant women) compared two IPTp doses of mefloquine with two IPTp doses of sulfadoxine-pyrimethamine. Two other trials involving 1363 HIV-infected women compared three IPTp doses of mefloquine plus cotrimoxazole with cotrimoxazole. One trial in 140 HIV-infected women compared three doses of IPTp-mefloquine with cotrimoxazole. Finally, one trial enrolling 339 of unknown HIV status compared mefloquine prophylaxis with placebo.** Study participants included

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women of all gravidities and of all ages (four trials) or > 18 years (two trials). Gestational age at recruitment was > 20 weeks (one trial), between 16 and 28 weeks (three trials), or ≤ 28 weeks (two trials). Two of the six trials blinded participants and personnel, and only one had low risk of detection bias for safety outcomes. **When compared with sulfadoxine-pyrimethamine, IPTp-mefloquine results in a 35% reduction in maternal peripheral parasitaemia at delivery (RR 0.65, 95% CI 0.48 to 0.86; 5455 participants, 2 studies; high-certainty evidence) but may have little or no effect on placental malaria infections (RR 1.04, 95% CI 0.58 to 1.86; 4668 participants, 2 studies; low-certainty evidence). Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy (incidence rate ratio (IRR) 0.83, 95% CI 0.65 to 1.05, 2 studies; high-certainty evidence). Mefloquine decreased maternal anaemia at delivery (RR 0.84, 95% CI 0.76 to 0.94; 5469 participants, 2 studies; moderate-certainty evidence). Data show little or no difference in the proportions of low birth weight infants (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; high-certainty evidence) and in stillbirth and spontaneous abortion rates (RR 1.20, 95% CI 0.91 to 1.58; 6219 participants, 2 studies; I<sup>2</sup> statistic = 0%; high-certainty evidence). IPTp-mefloquine increased drug-related vomiting (RR 4.76, 95% CI 4.13 to 5.49; 6272 participants, 2 studies; high-certainty evidence) and dizziness (RR 4.21, 95% CI 3.36 to 5.27; participants = 6272, 2 studies; high-certainty evidence). When compared with cotrimoxazole, IPTp-mefloquine plus cotrimoxazole probably results in a 48% reduction in maternal peripheral parasitaemia at delivery (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 studies; moderate-certainty evidence) and a 72% reduction in placental malaria (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 studies; high-certainty evidence) but has little or no effect on the incidence of clinical malaria episodes during pregnancy (IRR 0.76, 95% CI 0.33 to 1.76, 1 study; high-certainty evidence) and probably no effect on maternal anaemia at delivery (RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; moderate-certainty evidence), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; moderate-certainty evidence), and rates of spontaneous abortion and stillbirth (RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 studies; very low-certainty evidence). Mefloquine was associated with higher risks of drug-related vomiting (RR 7.95, 95% CI 4.79 to 13.18; 1055 participants, one study; high-certainty evidence) and dizziness (RR 3.94, 95% CI 2.85 to 5.46; 1055 participants, 1 study; high-certainty evidence).**

### **AUTHORS' CONCLUSIONS:**

**Mefloquine was more efficacious than sulfadoxine-pyrimethamine in HIV-uninfected women or daily cotrimoxazole prophylaxis in HIV-infected pregnant women for prevention of malaria infection and was associated with lower risk of maternal anaemia, no adverse effects on pregnancy outcomes (such as stillbirths and abortions), and no effects on low birth weight and prematurity. However, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.**

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011444.pub2/full#0>

*Trials*. 2017 Nov 2;18(1):511. doi: 10.1186/s13063-017-2249-0.

**[Community-led Responses for Elimination \(CoRE\): a study protocol for a community randomized controlled trial assessing the effectiveness of community-level, reactive focal drug administration for reducing Plasmodium falciparum infection prevalence and incidence in Southern Province, Zambia.](#)**

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[Bridges DJ](#), [Miller JM](#), [Chalwe V](#), [Moonga H](#), [Hamainza B](#), [Steketee R](#), [Silumbe K](#), [Nyangu J](#), [Larsen DA](#).

### BACKGROUND:

Zambia is pushing for, and has made great strides towards, the elimination of malaria transmission in Southern Province. **Reactive focal test and treat (RFTAT) using rapid diagnostic tests and artemether-lumefantrine (AL) has been key in making this progress.** Reactive focal drug administration (RFDA) using dihydroartemisinin-piperazine (DHAP), may be superior in accelerating clearance of the parasite reservoir in humans due to the provision of enhanced chemoprophylactic protection of at-risk populations against new infections. The primary aim of this study is to quantify the relative effectiveness of RFDA with DHAP against RFTAT with AL (standard of care) for reducing *Plasmodium falciparum* prevalence and incidence.

### METHODS/DESIGN:

The study will be conducted in four districts in Southern Province, Zambia; an area of low malaria transmission and high coverage of vector control. A community randomized controlled trial of 16 health facility catchment areas will be used to evaluate the impact of sustained year-round routine RFDA for 2 years, relative to a control of year-round routine RFTAT. Reactive case detection will be triggered by a confirmed malaria case, e.g., by microscopy or rapid diagnostic test at any government health facility. Reactive responses will be performed by community health workers (CHW) within 7 days of the index case confirmation date. Responses will be performed out to a radius of 140 m from the index case household. A subset of responses will be followed longitudinally for 90 days to examine reinfection rates. Primary outcomes include a post-intervention survey of malaria seropositivity (n = 4800 children aged 1 month to under 5 years old) and a difference-in-differences analysis of malaria parasite incidence, as measured through routine passive case detection at health facilities enrolled in the study. The study is powered to detect approximately a 65% relative reduction in these outcomes between the intervention versus the control.

### DISCUSSION:

Strengths of this trial include a robust study design and an endline cross-sectional parasite survey as well as a longitudinal sample. Primary limitations include statistical power to detect only a 65% reduction in primary outcomes, and the potential for contamination to dilute the effects of the intervention.

<https://trialsjournal.biomedcentral.com/track/pdf/10.1186/s13063-017-2249-0>

## Treatment of uncomplicated malaria

[Ann Parasitol.](#) 2018;64(1):49–57. doi: 10.17420/ap6401.132.

### **Efficacy and tolerability of artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria at two sentinel sites across Côte d’Ivoire**

[Konaté A](#), [Barro-Kiki PCM](#), [Angora KE](#), [Bédia-Tanoh AV](#), [Djohan V](#), [Kassi KF](#), [Vanga-Bosson H](#), [Miézan AJS](#), [Assi SB](#), [Menan EIH](#), [Yavo W](#).

Malaria remains a major public health problem in Côte d’Ivoire. The aim of this study is to **compare the efficacy and tolerability of artesunate-amodiaquine (ASAQ) versus artemether-lumefantrine (AL) for the treatment of uncomplicated malaria**, at two malaria

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surveillance sites in Côte d'Ivoire. The World Health Organization 2003 protocol was used for this multicenter open randomized clinical trial with a 42-day follow-up. We recruited 240 patients (120 per arm), of whom 114 (ASAQ group) and 112 (AL group) were fully followed-up. **According to intention-to-treat statistical analysis, PCR-corrected cure rates for ASAQ and AL treatments were 95.8% and 92.5% on day 28, and 95% and 92.5% on day 42, respectively.** Based on per-protocol statistical analysis, ASAQ and AL treatment rates reached 100% and 99.1%, respectively, on day 28 and remained the same on day 42. Overall, both drugs were well-tolerated at the clinical and biological level. This study shows that ASAQ and AL are still effective and well-tolerated. Accordingly, they can continue being used to treat uncomplicated malaria in Côte d'Ivoire. However, monitoring of their efficacy should remain a priority for health authorities.

<https://www.ncbi.nlm.nih.gov/pubmed/29717574>

*Clin Infect Dis.* 2018 Jan 6;66(2):229-236. doi: 10.1093/cid/cix779.

### **Artemether-Lumefantrine Versus Chloroquine for the Treatment of Uncomplicated Plasmodium knowlesi Malaria: An Open-Label Randomized Controlled Trial CAN KNOW.**

[Grigg MJ](#), [William T](#), [Barber BE](#), [Rajahram GS](#), [Menon J](#), [Schimann E](#), [Wilkes CS](#), [Patel K](#), [Chandna A](#), [Price RN](#), [Yeo TW](#), [Anstey NM](#).

#### **BACKGROUND:**

*Plasmodium knowlesi* is reported increasingly across Southeast Asia and is the most common cause of malaria in Malaysia. No randomized trials have assessed the comparative efficacy of artemether-lumefantrine (AL) for knowlesi malaria.

#### **METHODS:**

A randomized controlled trial was conducted in 3 district hospitals in Sabah, Malaysia to compare the efficacy of AL against chloroquine (CQ) for uncomplicated knowlesi malaria. Participants were included if they weighed >10 kg, had a parasitemia count <20000/μL, and had a negative rapid diagnostic test result for *Plasmodium falciparum* histidine-rich protein 2. Diagnosis was confirmed by means of polymerase chain reaction. Patients were block randomized to AL (total target dose, 12 mg/kg for artemether and 60 mg/kg for lumefantrine) or CQ (25 mg/kg). The primary outcome was parasite clearance at 24 hours in a modified intention-to-treat analysis.

#### **RESULTS:**

From November 2014 to January 2016, a total of 123 patients (including 18 children) were enrolled. **At 24 hours after treatment 76% of patients administered AL (95% confidence interval [CI], 63%-86%; 44 of 58) were aparasitemic, compared with 60% administered CQ (47%-72%; 39 of 65; risk ratio, 1.3 [95% CI, 1.0-1.6]; P = .06).** Overall parasite clearance was shorter after AL than after CQ (median, 18 vs 24 hours, respectively; P = .02), with all patients aparasitemic by 48 hours. By day 42 there were no treatment failures. The risk of anemia during follow-up was similar between arms. Patients treated with AL would require lower bed occupancy than those treated with CQ (2414 vs 2800 days per 1000 patients; incidence rate ratio, 0.86 [95% CI, .82-.91]; P < .001). There were no serious adverse events.

#### **CONCLUSIONS:**

AL is highly efficacious for treating uncomplicated knowlesi malaria; its excellent tolerability and rapid therapeutic response allow earlier hospital discharge, and support its use as a first-line artemisinin-combination treatment policy for all *Plasmodium* species in Malaysia.

<https://academic.oup.com/cid/article/66/2/229/4103230>

*BMC Med.* 2017 Oct 9;15(1):181. doi: 10.1186/s12916-017-0940-3.

**A randomised, double-blind clinical phase II trial of the efficacy, safety, tolerability and pharmacokinetics of a single dose combination treatment with artefenomel and piperazine in adults and children with uncomplicated *Plasmodium falciparum* malaria.**

Macintyre F, Adoke Y, Tiono AB, Duong TT, Mombo-Ngoma G, Bouyou-Akotet M, Tinto H, Bassat Q, Issifou S, Adamy M, Demarest H, Duparc S, Leroy D, Laurijssens BE, Biguenet S, Kibuuka A, Tshefu AK, Smith M, Foster C, Leipoldt I, Kreamsner PG, Phuc BQ, Ouedraogo A, Ramharter M; OZ-Piperazine Study Group.

**Collaborators (22)**

**BACKGROUND:**

The clinical development of a single encounter treatment for uncomplicated malaria has the potential to significantly improve the effectiveness of antimalarials. Exploratory data suggested that the combination of artefenomel and piperazine phosphate (PQP) has the potential to achieve satisfactory cure rates as a single dose therapy. The primary objective of the study was to determine whether **a single dose of artefenomel (800 mg) plus PQP in ascending doses is an efficacious treatment for uncomplicated *Plasmodium falciparum* malaria in the 'target' population of children  $\leq 5$  years of age in Africa as well as Asian patients of all ages.**

**METHODS:**

**Patients in six African countries and in Vietnam were randomised to treatment with follow-up for 42-63 days.** Efficacy, tolerability, safety and pharmacokinetics were assessed. Additional key objectives were to characterise the exposure-response relationship for polymerase chain reaction (PCR)-adjusted **adequate clinical and parasitological response at day 28 post-dose (ACPR28)** and to further investigate Kelch13 mutations. Patients in Africa (n = 355) and Vietnam (n = 82) were included, with 85% of the total population being children < 5 years of age.

**RESULTS:**

**ACPR28 in the per protocol population (95% confidence interval) was 70.8% (61.13-79.19), 68.4% (59.13-76.66) and 78.6% (70.09-85.67) for doses of 800 mg artefenomel with 640 mg, 960 mg and 1440 mg of PQP respectively.** ACPR28 was lower in Vietnamese than in African patients (66.2%; 54.55-76.62 and 74.5%; 68.81-79.68) respectively. Within the African population, efficacy was lowest in the youngest age group of  $\geq 0.5$  to  $\leq 2$  years, 52.7% (38.80-66.35). Initial parasite clearance was twice as long in Vietnam than in Africa. Within Vietnam, the frequency of the Kelch13 mutation was 70.1% and was clearly associated with parasite clearance half-life (PCt<sub>1/2</sub>). The most significant tolerability finding was vomiting (28.8%).

**CONCLUSIONS:**

In this first clinical trial evaluating a single encounter antimalarial therapy, **none of the treatment arms reached the target efficacy of > 95% PCR-adjusted ACPR at day 28.** Achieving very high efficacy following single dose treatment is challenging, since > 95% of the population must have sufficient concentrations to achieve cure across a range of parasite sensitivities and baseline parasitaemia levels. While challenging, the development of tools suitable for deployment as single encounter curative treatments for adults and children in Africa and to support elimination strategies remains a key development goal.

<https://bmcmecicine.biomedcentral.com/articles/10.1186/s12916-017-0940-3>



[Clin Infect Dis.](#) 2017 Oct 30;65(10):1711-1720. doi: 10.1093/cid/cix617.

**Assessment of Efficacy and Safety of Arterolane Maleate-Piperaquine Phosphate Dispersible Tablets in Comparison With Artemether-Lumefantrine Dispersible Tablets in Pediatric Patients With Acute Uncomplicated Plasmodium falciparum Malaria: A Phase 3, Randomized, Multicenter Trial in India and Africa.**

[Toure OA](#), [Mwapasa V](#), [Sagara I](#), [Gaye O](#), [Thompson R](#), [Maheshwar AV](#), [Mishra P](#), [Behra N](#), [Tshefu AK](#), [Das RR](#), [Anvikar AR](#), [Sharma P](#), [Roy A](#), [Sharma SK](#), [Nasa A](#), [Jalali RK](#), [Valecha N](#); [Arterolane Maleate-Piperaquine Phosphate \(AM-PQP\) Study Team. Collaborators \(28\)](#)

**BACKGROUND:**

Administration of artemisinin-based combination therapy (ACT) to infant and young children can be challenging. A formulation with accurate dose and ease of administration will improve adherence and compliance in children. **The fixed-dose combination dispersible tablet of arterolane maleate (AM) 37.5 mg and piperaquine phosphate (PQP) 187.5 mg can make dosing convenient in children.**

**METHODS:**

This multicenter (India and Africa), comparative, parallel-group trial enrolled 859 patients aged 6 months to 12 years with Plasmodium falciparum malaria. **Patients were randomized in a ratio of 2:1 to AM-PQP (571 patients) once daily and artemether-lumefantrine (AL) (288 patients) twice daily for 3 days and followed for 42 days.**

**RESULTS:**

**The cure rate (ie, polymerase chain reaction-corrected adequate clinical and parasitological response) in the per-protocol population at day 28 was 100.0% and 98.5% (difference, 1.48% [95% confidence interval {CI}, .04%-2.91%]) in the AM-PQP and AL arms, respectively, and 96.0% and 95.8% (difference, 0.14% [95% CI, -2.68% to 2.95%]) in the intention-to-treat (ITT) population. The cure rate was comparable at day 42 in the ITT population (AM-PQP, 94.4% vs AL, 93.1%). The median parasite clearance time was 24 hours in both the arms. The median fever clearance time was 6 hours in AM-PQP and 12 hours in the AL arm. Both the treatments were found to be safe and well tolerated. Overall, safety profile of both the treatments was similar.**

**CONCLUSIONS:**

The efficacy and safety of fixed-dose combination of AM and PQP was comparable to AL for the treatment of uncomplicated P. falciparum malaria in pediatric patients.

<https://academic.oup.com/cid/article/65/10/1711/4096624>

## Treatment of severe or complicated malaria

[BMC Infect Dis.](#) 2017 Dec 28;17(1):794. doi: 10.1186/s12879-017-2924-5.

**Intravenous artesunate plus Artemisinin based Combination Therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children: a randomized controlled clinical trial.**

[Byakika-Kibwika P](#), [Achan J](#), [Lamorde M](#), [Karera-Gonahasa C](#), [Kiragga AN](#), [Mayanja-Kizza H](#), [Kiwanuka N](#), [Nsobyia S](#), [Talisuna AO](#), [Merry C](#).

## Randomised trials in child health in developing countries 2017-18

### BACKGROUND:

Severe malaria is a medical emergency associated with high mortality. Adequate treatment requires initial parenteral therapy for fast parasite clearance followed by longer acting oral antimalarial drugs for cure and prevention of recrudescence.

### METHODS:

In a randomized controlled clinical trial, we evaluated the **42-day parasitological outcomes of severe malaria treatment with intravenous artesunate (AS) or intravenous quinine (QNN) followed by oral artemisinin based combination therapy (ACT) in children living in a high malaria transmission setting in Eastern Uganda.**

### RESULTS:

We enrolled 300 participants and all were included in the intention to treat analysis. Baseline characteristics were similar across treatment arms. **The median and interquartile range for number of days from baseline to parasite clearance was significantly lower among participants who received intravenous AS (2 (1-2) vs 3 (2-3),  $P < 0.001$ ).** Overall, 63.3% (178/281) of the participants had unadjusted parasitological treatment failure over the 42-day follow-up period. Molecular genotyping to distinguish re-infection from recrudescence was performed in a sample of 127 of the 178 participants, of whom majority 93 (73.2%) had re-infection and 34 (26.8%) had recrudescence. The 42 day risk of recrudescence did not differ with ACT administered. Adverse events were of mild to moderate severity and consistent with malaria symptoms.

### CONCLUSION:

**In this high transmission setting, we observed adequate initial treatment outcomes followed by very high rates of malaria re-infection post severe malaria treatment.** The impact of recurrent antimalarial treatment on the long term efficacy of antimalarial regimens needs to be investigated and surveillance mechanisms for resistance markers established since recurrent malaria infections are likely to be exposed to sub-therapeutic drug concentrations. More strategies for prevention of recurrent malaria infections in the most at risk populations are needed.

<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2924-5>

[BMC Infect Dis.](#) 2017 Aug 17;17(1):575. doi: 10.1186/s12879-017-2678-0.

### **Post-treatment haemolysis in African children with hyperparasitaemic falciparum malaria; a randomized comparison of artesunate and quinine.**

[Fanello C](#), [Onyamboko M](#), [Lee SJ](#), [Woodrow C](#), [Setaphan S](#), [Chotivanich K](#), [Buffet P](#), [Jauréguiberry S](#), [Rockett K](#), [Stepniewska K](#), [Day NPJ](#), [White NJ](#), [Dondorp AM](#).

### BACKGROUND:

Parenteral artesunate is the treatment of choice for severe malaria. Recently, haemolytic anaemia occurring 1 to 3 weeks after artesunate treatment of falciparum malaria has been reported in returning travellers in temperate countries.

### METHODS:

To assess these potential safety concerns in African children, in whom most deaths from malaria occur, an open-labelled, randomized controlled trial was conducted in Kinshasa, Democratic Republic of Congo. 217 children aged between 6 months and 14 years with acute uncomplicated falciparum malaria and parasite densities over 100,000/ $\mu$ L were randomly allocated to intravenous artesunate or quinine, hospitalized for 3 days and then followed for 42 days.

### RESULTS:

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The immediate reduction in haemoglobin was less with artesunate than with quinine: median (IQR) fall at 72 h 1.4 g/dL (0.90-1.95) vs. 1.7 g/dL (1.10-2.40) ( $p = 0.009$ ). This was explained by greater pitting then recirculation of once infected erythrocytes. Only 5% of patients (in both groups) had a  $\geq 10\%$  reduction in haemoglobin after day 7 ( $p = 0.1$ ). One artesunate treated patient with suspected concomitant sepsis had a protracted clinical course and required a blood transfusion on day 14.

### CONCLUSIONS:

Clinically significant delayed haemolysis following parenteral artesunate is uncommon in African children hospitalised with acute falciparum malaria and high parasitaemias.

<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2678-0>

[PLoS One](#). 2018 Jan 25;13(1):e0191550. doi: 10.1371/journal.pone.0191550. eCollection 2018.

### **Inhaled nitric oxide and cognition in pediatric severe malaria: A randomized double-blind placebo controlled trial.**

[Bangirana P](#), [Conroy AL](#), [Opoka RO](#), [Hawkes MT](#), [Hermann L](#), [Miller C](#), [Namasopo S](#), [Liles WC](#), [John CC](#), [Kain KC](#).

### BACKGROUND:

Severe malaria is a leading cause of acquired neurodisability in Africa and is associated with reduced nitric oxide (NO) bioavailability. A neuroprotective role for inhaled NO has been reported in animal studies, and administration of inhaled NO in preterm neonates with respiratory distress syndrome is associated with a 47% reduced risk of cognitive impairment at two years of age.

### METHODS:

A randomized double-blind placebo-controlled trial of inhaled NO versus placebo as an adjunctive therapy for severe malaria was conducted in Uganda between 2011 and 2013. Children received study gas for a maximum 72 hours (inhaled NO, 80 parts per million; room air placebo). Neurocognitive testing was performed on children <5 years at 6 month follow-up. The neurocognitive outcomes assessed were overall cognition (a composite of fine motor, visual reception, receptive language, and expressive language), attention, associative memory, and the global executive composite. Main outcomes were attention, associative memory, and overall cognitive ability.

### RESULTS:

**Sixty-one children receiving iNO and 59 children receiving placebo were evaluated.** Forty-two children (35.0%) were impaired in at least one neurocognitive domain. By intention-to-treat analysis, there were no differences in unadjusted or unadjusted age-adjusted z-scores for overall cognition ( $\beta$  (95% CI): 0.26 (-0.19, 0.72),  $p = 0.260$ ), attention (0.18 (-0.14, 0.51),  $p = 0.267$ ), or memory (0.14 (-0.02, 0.30),  $p = 0.094$ ) between groups by linear regression. Children receiving inhaled NO had a 64% reduced relative risk of fine motor impairment than children receiving placebo (relative risk, 95% CI: 0.36, 0.14-0.96) by log binomial regression following adjustment for anticonvulsant use.

### CONCLUSIONS:

**Severe malaria is associated with high rates of neurocognitive impairment.** Treatment with inhaled NO was associated with reduced risk of fine motor impairment. These results need to be prospectively validated in a larger study powered to assess cognitive outcomes in order to evaluate whether strategies to increase bioavailable NO are neuroprotective in children with severe malaria.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0191550>

## Treatment of vivax malaria

*Am J Trop Med Hyg.* 2017 Dec;97(6):1782-1787. doi: 10.4269/ajtmh.17-0290. Epub 2017 Oct 26.

### **Chloroquine-Primaquine versus Chloroquine Alone to Treat Vivax Malaria in Afghanistan: An Open Randomized Superiority Trial.**

[Awab GR](#), [Imwong M](#), [Bancone G](#), [Jeeyapant A](#), [Day NPJ](#), [White NJ](#), [Woodrow CJ](#).

Afghanistan's national guidelines recommend primaquine (PQ) for radical treatment of *Plasmodium vivax* malaria, but this is rarely implemented because of concerns over potential hemolysis in patients who have G6PD deficiency. Between August 2009 and February 2014, we conducted an **open-label, randomized controlled trial of chloroquine (CQ) alone versus chloroquine plus primaquine (0.25 mg base/kg/day for 14 days) (CQ+PQ) in patients aged 6 months and older with microscopy confirmed *P. vivax* infection. In the CQ+PQ group, G6PD deficiency was excluded by fluorescent spot testing.** The primary outcome was *P. vivax* recurrence assessed by survival analysis over one year follow-up. Of 593 patients enrolled, 570 attended at or after 14 days of follow-up. ***Plasmodium vivax* recurrences occurred in 37 (13.1%) of 282 patients in the CQ+PQ arm versus 86 (29.9%) of 288 in the CQ arm (Cox proportional hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.25-0.54) (intention-to-treat analysis).** Protection against recurrence was greater in the first 6 months of follow-up (HR 0.082; 95% CI 0.029-0.23) than later (HR 0.65, 95% CI 0.41-1.03). **Five of seven patients requiring hospital admission were considered possible cases of PQ-related hemolysis, and PQ was stopped in a further six; however, in none of these cases did hemoglobin fall by  $\geq 2$  g/dL or to below 7 g/dL, and genotyping did not detect any cases of Mediterranean variant G6PD deficiency. PQ 0.25 mg/kg/day for 14 days prevents relapse of *P. vivax* in Afghanistan.** Patient visits during the first week may improve adherence. Implementation will require deployment of point-of-care phenotypic tests for G6PD deficiency.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805052/>

*PLoS Negl Trop Dis.* 2017 Jul 21;11(7):e0005753. doi: 10.1371/journal.pntd.0005753. eCollection 2017 Jul.

### **Effects of liver-stage clearance by Primaquine on gametocyte carriage of Plasmodium vivax and P. falciparum.**

[Wampfler R](#), [Hofmann NE](#), [Karl S](#), [Betuela I](#), [Kinboro B](#), [Lorry L](#), [Silkey M](#), [Robinson LJ](#), [Mueller I](#), [Felger I](#).

#### **BACKGROUND:**

**Primaquine (PQ) is the only currently licensed antimalarial that prevents *Plasmodium vivax* (Pv) relapses. It also clears mature *P. falciparum* (Pf) gametocytes, thereby reducing post-treatment transmission.** Randomized PQ treatment in a treatment-to-reinfection cohort in Papua New Guinean children permitted the study of Pv and Pf gametocyte carriage after radical cure and to investigate the contribution of Pv relapses.

#### **METHODS:**

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**Children received radical cure with Chloroquine, Artemether-Lumefantrine plus either PQ or placebo.** Blood samples were subsequently collected in 2-to 4-weekly intervals over 8 months. Gametocytes were detected by quantitative reverse transcription-PCR targeting pvs25 and pfs25.

### RESULTS:

**PQ treatment reduced the incidence of Pv gametocytes by 73%**, which was comparable to the effect of PQ on incidence of blood-stage infections. 92% of Pv and 79% of Pf gametocyte-positive infections were asymptomatic. Pv and to a lesser extent Pf gametocyte positivity and density were associated with high blood-stage parasite densities. Multivariate analysis revealed that the odds of gametocytes were significantly reduced in mixed-species infections compared to single-species infections for both species (ORPv = 0.39 [95% CI 0.25-0.62], ORPf = 0.33 [95% CI 0.18-0.60], p<0.001). No difference between the PQ and placebo treatment arms was observed in density of Pv gametocytes or in the proportion of Pv infections that carried gametocytes. First infections after blood-stage and placebo treatment, likely caused by a relapsing hypnozoite, were equally likely to carry gametocytes than first infections after PQ treatment, likely caused by an infective mosquito bite.

### CONCLUSION:

Pv relapses and new infections are associated with similar levels of gametocytaemia. Relapses thus contribute considerably to the Pv reservoir highlighting the importance of effective anti-hypnozoite treatment for efficient control of Pv.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005753>

## 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)

[Am J Clin Nutr.](#) 2017 Aug;106(2):657-666. doi: 10.3945/ajcn.116.149799. Epub 2017 Jun 14.

### **Effect of a package of health and nutrition services on sustained recovery in children after moderate acute malnutrition and factors related to sustaining recovery: a cluster-randomized trial.**

[Stobaugh HC](#), [Bollinger LB](#), [Adams SE](#), [Crocker AH](#), [Grise JB](#), [Kennedy JA](#), [Thakwalakwa C](#), [Maleta KM](#), [Dietzen DJ](#), [Manary MJ](#), [Trehan I](#).

**Background:** Children who recover from moderate acute malnutrition (MAM) have high rates of relapse in the year after nutritional recovery. Interventions to decrease these adverse outcomes are needed to maximize the overall effectiveness of supplemental feeding programs (SFPs). **Objective:** We evaluated the effectiveness of a package of health and nutrition interventions on improving the proportion of children who sustained recovery for 1 y after MAM treatment. We further explored factors related to sustained recovery. **Design:** We conducted a cluster-randomized clinical effectiveness trial involving rural Malawian children aged 6-62 mo who were enrolled on discharge from an SFP for MAM. We enrolled 718 children at 10 control sites and 769 children at 11 intervention sites. In addition to routine health and nutrition counseling, the intervention group received a package of health and nutrition interventions that consisted of a lipid nutrient supplement,

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### **deworming medication, zinc supplementation, a bed net, and malaria chemoprophylaxis.**

A survival analysis was used to determine the effectiveness of the intervention as well as to identify factors associated with sustained recovery. **Results: Of 1383 children who returned for the full 12-mo follow-up period, 407 children (56%) and 347 children (53%) sustained recovery in the intervention and control groups, respectively.** There was no significant difference in relapse-free survival curves between the treatment and control groups ( $P = 0.380$ ; log-rank test). **The risk factors for relapse or death after initial recovery were a smaller midupper arm circumference on SFP admission ( $P = 0.01$ ) and discharge ( $P < 0.001$ ), a lower weight-for-height zscore on discharge ( $P < 0.01$ ), and the receipt of ready-to-use supplementary food as opposed to ready-to-use therapeutic food during treatment ( $P < 0.05$ ).** **Conclusion:** The provision of a package of health and nutrition services in addition to traditional SFP treatment has no significant effect on improving sustained recovery in children after treatment of MAM. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT02351687](https://doi.org/10.1186/1745-7244-2-1687).

<https://academic.oup.com/ajcn/article/106/2/657/4557624>

\*\*\* [Pediatr.](https://doi.org/10.1016/j.jpeds.2017.07.013) 2017 Nov;190:85-92.e2. doi: 10.1016/j.jpeds.2017.07.013. Epub 2017 Sep 11.

### **Pancreatic Enzyme Replacement Therapy in Children with Severe Acute Malnutrition: A Randomized Controlled Trial.**

[Bartels RH](#), [Bourdon C](#), [Potani I](#), [Mhango B](#), [van den Brink DA](#), [Mponda JS](#), [Muller Kobold AC](#), [Bandsma RH](#), [Boele van Hensbroek M](#), [Voskuijl WP](#).

#### **OBJECTIVE:**

To assess the benefits of pancreatic enzyme replacement therapy (PERT) in children with complicated severe acute malnutrition.

#### **STUDY DESIGN:**

We conducted a randomized, controlled trial in 90 children aged 6-60 months with complicated severe acute malnutrition at the Queen Elizabeth Central Hospital in Malawi. All children received standard care; the intervention group also received PERT for 28 days.

#### **RESULTS:**

Children treated with PERT for 28 days did not gain more weight than controls ( $13.7 \pm 9.0\%$  in controls vs  $15.3 \pm 11.3\%$  in PERT;  $P = .56$ ). Exocrine pancreatic insufficiency was present in 83.1% of patients on admission and fecal elastase-1 levels increased during hospitalization mostly seen in children with nonedematous severe acute malnutrition ( $P < .01$ ). **Although the study was not powered to detect differences in mortality, mortality was significantly lower in the intervention group treated with pancreatic enzymes (18.6% vs 37.8%;**

**$P < .05$ ).** Children who died had low fecal fatty acid split ratios at admission. Exocrine pancreatic insufficiency was not improved by PERT, but children receiving PERT were more likely to be discharged with every passing day ( $P = .02$ ) compared with controls.

#### **CONCLUSIONS:**

PERT does not improve weight gain in severely malnourished children but does increase the rate of hospital discharge. **Mortality was lower in patients on PERT, a finding that needs to be investigated in a larger cohort with stratification for edematous and nonedematous malnutrition.** Mortality in severe acute malnutrition is associated with markers of poor digestive function.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0022347617309472?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0022347617309472%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

*Am J Clin Nutr.* 2017 Oct;106(4):1100-1112. doi: 10.3945/ajcn.117.156653. Epub 2017 Aug 16.

**Soya, maize, and sorghum-based ready-to-use therapeutic food with amino acid is as efficacious as the standard milk and peanut paste-based formulation for the treatment of severe acute malnutrition in children: a noninferiority individually randomized controlled efficacy clinical trial in Malawi.**

Bahwere P, Akomo P, Mwale M, Murakami H, Banda C, Kathumba S, Banda C, Jere S, Sadler K, Collins S.

**Background:** Development of more cost-effective **ready-to-use therapeutic food (RUTF)** is a global public health priority. To date, previous lower-cost recipes have been less effective than the standard **peanut and milk (PM)-based RUTF**, particularly in children aged <24 mo.

**Objective:** We aimed to **compare the efficacy of the PM-RUTF to a milk-free soya, maize, and sorghum (FSMS)-RUTF enriched with crystalline amino acids without cow milk powder and a milk, soya, maize, and sorghum (MSMS)-RUTF containing 9.3% skim cow milk powder.**

**Design:** This nonblinded, 3-arm, parallel-group, simple randomized controlled trial enrolled Malawian children with severe acute malnutrition.

**Results:** In intention-to-treat analyses, FSMS-RUTF showed noninferiority for recovery rates in children aged 24-59 mo ( $\Delta$ : -1.9%; 95% CI: -9.5%, 5.6%) and 6-23 mo ( $\Delta$ : -0.2%; 95% CI: -7.5%, 7.1%) compared with PM-RUTF. MSMS-RUTF also showed noninferiority for recovery rates in children aged 24-59 mo ( $\Delta$ : 0.0%; 95% CI: -7.3%, 7.4%) and 6-23 mo ( $\Delta$ : 0.6%; 95% CI: -4.3%, 5.5%). Noninferiority in recovery rates was also observed in per-protocol analyses. For length of stay in the program (time to cure), both FSMS-RUTF in children aged 24-59 mo ( $\Delta$ : 2.8 d; 95% CI: -0.8, 6.5 d) and 6-23 mo ( $\Delta$ : 3.4 d; 95% CI: -1.2, 8.0 d) and MSMS-RUTF in children aged 24-59 mo ( $\Delta$ : 0.2 d; 95% CI: -3.1, 3.6 d) and 6-23 mo ( $\Delta$ : 1.2 d; 95% CI: -3.4, 5.8 d) were not inferior to PM-RUTF. FSMS-RUTF was also significantly better than PM-RUTF at increasing hemoglobin and body iron stores in anemic children, with mean hemoglobin increases of 2.1 (95% CI: 1.6, 2.6) and 1.3 (95% CI: 0.9, 1.8) and mean body iron store increases of 2.0 (95% CI: 0.8, 3.3) and 0.1 (95% CI: -1.1, 1.3) for FSMS-RUTF and PM-RUTF, respectively.

**Conclusions:** Milk-free soya, maize, and sorghum (FSMS)-RUTF enriched with crystalline amino acids without cow milk powder is efficacious in the treatment of severe acute malnutrition in children aged 6-23 and 24-59 mo. It is also better at correcting iron deficiency anemia than PM-RUTF.

<https://academic.oup.com/ajcn/article/106/4/1100/4652044>

*Food Nutr Bull.* 2017 Sep;38(3):275-290. doi: 10.1177/0379572117700754. Epub 2017 Apr 4.  
**A Randomized Controlled Trial of Two Ready-to-Use Supplementary Foods Demonstrates Benefit of the Higher Dairy Supplement for Reduced Wasting**

**in Mothers, and Differential Impact in Infants and Children Associated With Maternal Supplement Response.**

[Schlossman N](#), [Brown C](#), [Batra P](#), [de Sa AB](#), [Balan I](#), [Balan A](#), [Gamache MG](#), [Wood L](#), [Pruzensky W](#), [Saltzman E](#), [Roberts SB](#), [Balé C](#).

**BACKGROUND:**

There is no consensus over best approaches to reliably prevent malnutrition in rural communities in low-income countries.

**OBJECTIVE:**

We compared the effectiveness of 2 lipid-based ready-to-use supplementary foods (RUSFs) differing in dairy protein content to improve the nutritional status of mothers and at-risk infants and young children in rural Guinea-Bissau.

**METHODS:**

A 3-month cluster-randomized controlled pilot trial of 2 RUSFs was conducted with 692 mothers and 580 mildly or moderately malnourished infants (6-23 months) and children (24-59 months) from 13 villages. The RUSFs contained either 478 (mothers, children) or 239 kcal/d (infants) with 15% or 33% of protein from dairy and were distributed at community health centers 5 d/wk. Controls were wait-listed to receive RUSF. Primary outcomes were mid-upper arm circumference (MUAC) in mothers, and weight-for-age and height-for-age z-scores (WAZ and HAZ) in infants and children.

**RESULTS:**

There was a significant effect of the RUSF-33% on MUAC in mothers (  $P = .03$ ). The WAZ and HAZ increased substantially, by  $\approx 1$  z-score, in infants and children (  $P < .01$ ) independent of group randomization. In children, but not infants, baseline WAZ and change in maternal MUAC were associated with change in WAZ ( $\beta = .07$ ,  $P = .02$ ).

**CONCLUSION:**

**Ready-to-use supplementary foods with higher dairy protein content had a significant benefit in village mothers, supporting a comparable recent finding in preschool children.**

In addition, supplementation of children <2 years resulted in improved growth independent of family nutritional status, whereas success in older children was associated with change in maternal nutrition, suggesting the need for community-level education about preventing malnutrition in older, as well as younger, children.

[PLoS Med.](#) 2017 Sep 11;14(9):e1002387. doi: 10.1371/journal.pmed.1002387. eCollection 2017 Sep.

**Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: A randomised 2 × 2 × 3 factorial trial in Burkina Faso.**

[Fabiansen C](#), [Yaméogo CW](#), [Iuel-Brockdorf AS](#), [Cichon B](#), [Rytter MJH](#), [Kurpad A](#), [Wells JC](#), [Ritz C](#), [Ashorn P](#), [Filteau S](#), [Briend A](#), [Shepherd S](#), [Christensen VB](#), [Michaelsen KF](#), [Friis H](#).

**BACKGROUND:**

Children with moderate acute malnutrition (MAM) are treated with lipid-based nutrient supplement (LNS) or corn-soy blend (CSB). We assessed the effectiveness of (a) matrix, i.e., LNS or CSB, (b) soy quality, i.e., soy isolate (SI) or dehulled soy (DS), and (c) percentage of



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total protein from dry skimmed milk, i.e., 0%, 20%, or 50%, in increasing fat-free tissue accretion.

### METHODS AND FINDINGS:

Between September 9, 2013, and August 29, 2014, a randomised  $2 \times 2 \times 3$  factorial trial recruited 6- to 23-month-old children with MAM in Burkina Faso. The intervention comprised **12 weeks of food supplementation providing 500 kcal/day as LNS or CSB, each containing SI or DS, and 0%, 20%, or 50% of protein from milk**. Fat-free mass (FFM) was assessed by deuterium dilution technique. By dividing FFM by length squared, the primary outcome was expressed independent of length as FFM index (FFMI) accretion over 12 weeks. Other outcomes comprised recovery rate and additional anthropometric measures. Of 1,609 children, 4 died, 61 were lost to follow-up, and 119 were transferred out due to supplementation being switched to non-experimental products. No children developed allergic reaction. At inclusion, 95% were breastfed, mean (SD) weight was 6.91 kg (0.93), with 83.5% (5.5) FFM. In the whole cohort, weight increased 0.90 kg (95% CI 0.88, 0.93;  $p < 0.01$ ) comprising 93.5% (95% CI 89.5, 97.3) FFM. As compared to children who received CSB, FFMI accretion was increased by 0.083 kg/m<sup>2</sup> (95% CI 0.003, 0.163;  $p = 0.042$ ) in those who received LNS. In contrast, SI did not increase FFMI compared to DS (mean difference 0.038 kg/m<sup>2</sup>; 95% CI -0.041, 0.118;  $p = 0.35$ ), irrespective of matrix. Having 20% milk protein was associated with 0.097 kg/m<sup>2</sup> (95% CI -0.002, 0.196) greater FFMI accretion than having 0% milk protein, although this difference was not significant ( $p = 0.055$ ), and there was no effect of 50% milk protein (0.049 kg/m<sup>2</sup>; 95% CI -0.047, 0.146;  $p = 0.32$ ). There was no effect modification by season, admission criteria, or baseline FFMI, stunting, inflammation, or breastfeeding ( $p > 0.05$ ). LNS compared to CSB resulted in 128 g (95% CI 67, 190;  $p < 0.01$ ) greater weight gain if both contained SI, but there was no difference between LNS and CSB if both contained DS (mean difference 22 g; 95% CI -40, 84;  $p = 0.49$ ) (interaction  $p = 0.017$ ). Accordingly, SI compared to DS increased weight by 89 g (95% CI 27, 150;  $p = 0.005$ ) when combined with LNS, but not when combined with CSB. A limitation of this and other food supplementation trials is that it is not possible to collect reliable data on individual adherence.

### CONCLUSIONS:

Based on this study, children with MAM mainly gain fat-free tissue when rehabilitated. **Nevertheless, LNS yields more fat-free tissue and higher recovery rates than CSB.** Moreover, current LNSs with DS may be improved by shifting to SI. The role of milk relative to soy merits further research.

<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002387>

\*\*\* [Lancet Glob Health](#). 2017 Oct;5(10):e1004-e1016. doi: 10.1016/S2214-109X(17)30339-X.

### **Effect of participatory women's groups and counselling through home visits on children's linear growth in rural eastern India (CARING trial): a cluster-randomised controlled trial.**

[Nair N](#), [Tripathy P](#), [Sachdev HS](#), [Pradhan H](#), [Bhattacharyya S](#), [Gope R](#), [Gagrai S](#), [Rath S](#), [Rath S](#), [Sinha R](#), [Roy SS](#), [Shewale S](#), [Singh V](#), [Srivastava A](#), [Costello A](#), [Copas A](#), [Skordis-Worrall J](#), [Haghpast-Bidgoli H](#), [Saville N](#), [Prost A](#).

### BACKGROUND:

Around 30% of the world's stunted children live in India. The Government of India has proposed a new cadre of community-based workers to improve nutrition in 200 districts. We aimed to find out the effect of such a worker carrying out home visits and participatory group meetings on children's linear growth.

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### METHODS:

We did a cluster-randomised controlled trial in two adjoining districts of Jharkhand and Odisha, India. 120 clusters (around 1000 people each) were randomly allocated to intervention or control using a lottery. Randomisation took place in July, 2013, and was stratified by district and number of hamlets per cluster (0, 1-2, or  $\geq 3$ ), resulting in six strata. In each intervention cluster, **a worker carried out one home visit in the third trimester of pregnancy, monthly visits to children younger than 2 years to support feeding, hygiene, care, and stimulation, as well as monthly women's group meetings to promote individual and community action for nutrition.** Participants were pregnant women identified and recruited in the study clusters and their children. We excluded stillbirths and neonatal deaths, infants whose mothers died, those with congenital abnormalities, multiple births, and mother and infant pairs who migrated out of the study area permanently during the trial period. Data collectors visited each woman in pregnancy, within 72 h of her baby's birth, and at 3, 6, 9, 12, and 18 months after birth. The primary outcome was children's length-for-age Z score at 18 months of age. Analyses were by intention to treat. Due to the nature of the intervention, participants and the intervention team were not masked to allocation. Data collectors and the data manager were masked to allocation. The trial is registered as ISCRTN (51505201) and with the Clinical Trials Registry of India (number 2014/06/004664).

### RESULTS:

Between Oct 1, 2013, and Dec 31, 2015, **we recruited 5781 pregnant women. 3001 infants were born to pregnant women recruited between Oct 1, 2013, and Feb 10, 2015, and were therefore eligible for follow-up (1460 assigned to intervention; 1541 assigned to control).** Three groups of children could not be included in the final analysis: 147 migrated out of the study area (67 in intervention clusters; 80 in control clusters), 77 died after the neonatal period and before 18 months (31 in intervention clusters; 46 in control clusters), and seven had implausible length-for-age Z scores ( $< -5$  SD; one in intervention cluster; six in control clusters). We measured 1253 (92%) of 1362 eligible children at 18 months in intervention clusters, and 1308 (92%) of 1415 eligible children in control clusters. **Mean length-for-age Z score at 18 months was -2.31 (SD 1.12) in intervention clusters and -2.40 (SD 1.10) in control clusters (adjusted difference 0.107, 95% CI -0.011 to 0.226,  $p=0.08$ ).** The intervention did not significantly affect exclusive breastfeeding, timely introduction of complementary foods, morbidity, appropriate home care or care-seeking during childhood illnesses. In intervention clusters, more pregnant women and children attained minimum dietary diversity (adjusted odds ratio [aOR] for women 1.39, 95% CI 1.03-1.90; for children 1.47, 1.07-2.02), more mothers washed their hands before feeding children (5.23, 2.61-10.5), fewer children were underweight at 18 months (0.81, 0.66-0.99), and **fewer infants died (0.63, 0.39-1.00).**

### INTERPRETATION:

Introduction of a new worker in areas with a high burden of undernutrition in rural eastern India did not significantly increase children's length. **However, certain secondary outcomes such as self-reported dietary diversity and handwashing, as well as infant survival were improved.** The interventions tested in this trial can be further optimised for use at scale, but substantial improvements in growth will require investment in nutrition-sensitive interventions, including clean water, sanitation, family planning, girls' education, and social safety nets.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S2214109X1730339X?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2214109X1730339X%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## Maternal health

(see also Malaria)

[BMC Complement Altern Med.](https://doi.org/10.1186/s12906-018-2203-z) 2018 May 25;18(1):166. doi: 10.1186/s12906-018-2203-z.  
[Associations between the use of herbal medicines and adverse pregnancy outcomes in rural Malawi: a secondary analysis of randomised controlled trial data.](#)  
[Zamawe C<sup>1</sup>, King C<sup>2</sup>, Jennings HM<sup>2</sup>, Fottrell E<sup>2</sup>.](#)

### BACKGROUND:

The use of herbal medicines during pregnancy is very high globally and previous studies have pointed out possible associations with adverse pregnancy outcomes. Nevertheless, the safety of herbal medicines in pregnancy is under-explored in low-income countries experiencing high maternal and neonatal complications. **We investigated the associations between self-reported use of Mwanamphepo (a group of herbal medicines commonly used to induce or hasten labour) and adverse maternal and neonatal outcomes in rural Malawi.**

### METHODS:

We conducted a cross-sectional analysis of secondary household data relating to 8219 births that occurred between 2005 and 2010 in Mchinji district, Malawi. The data were collected as part of a cluster-randomised controlled trial (RCT) that evaluated community interventions designed to reduce maternal and neonatal mortality. Data were gathered on maternity history, demographic characteristics, pregnancy outcomes and exposure to Mwanamphepo. Associations between self-reported use of Mwanamphepo and maternal morbidity as well as neonatal death or morbidity were examined using mixed-effects models, adjusted for relevant covariates. All analyses were also adjusted for the clustered nature of the survey.

### RESULTS:

Of the 8219 births, Mwanamphepo was used in 2113 pregnancies, representing an estimated prevalence of 25.7%. **The self-reported use of Mwanamphepo was significantly associated with increased occurrence of maternal morbidity and neonatal death or morbidity.** Specifically, the odds of maternal morbidity were 28% higher among self-reported users than non-users of Mwanamphepo (AOR = 1.28; 95% CI = 1.09-1.50) and the probabilities of neonatal death or morbidity were 22% higher (AOR = 1.22; 95% CI = 1.06-1.40) among neonates whose mother reportedly used Mwanamphepo than those who did not.

### CONCLUSION:

The use of Mwanamphepo was associated with adverse pregnancy outcomes in rural Malawi. Thus, herbal medicines may not be safe in pregnancy. Where possible, pregnant women should be discouraged from using herbal medicines of unconfirmed safety and those who report to have used should be closely monitored by health professionals. The study was limited by the self-report of exposure and unavailability of data relating to some possible confounders.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5970448/>

[Malar J.](https://doi.org/10.1186/s12936-017-2040-4) 2017 Oct 5;16(1):400. doi: 10.1186/s12936-017-2040-4.

[Relationships between infection with Plasmodium falciparum during pregnancy, measures of placental malaria, and adverse birth outcomes.](#)

## Randomised trials in child health in developing countries 2017-18

[Kapisi J](#), [Kakuru A](#), [Jagannathan P](#), [Muhindo MK](#), [Natureeba P](#), [Aworu P](#), [Nakalembe M](#), [Ssekitolesko R](#), [Olwoch P](#), [Ategeka J](#), [Nayebare P](#), [Clark TD](#), [Rizzuto G](#), [Muehlenbachs A](#), [Havlir DV](#), [Kamya MR](#), [Dorsey G](#), [Gaw SL](#).

### BACKGROUND:

Malaria in pregnancy has been associated with maternal morbidity, placental malaria, and adverse birth outcomes. However, data are limited on the relationships between longitudinal measures of malaria during pregnancy, measures of placental malaria, and birth outcomes.

### METHODS:

This is a nested observational study of data from a randomized controlled trial of intermittent preventive therapy during pregnancy among 282 participants with assessment of placental malaria and delivery outcomes. HIV-uninfected pregnant women were enrolled at 12-20 weeks of gestation. Symptomatic malaria during pregnancy was measured using passive surveillance and monthly detection of asymptomatic parasitaemia using loop-mediated isothermal amplification (LAMP). Placental malaria was defined as either the presence of parasites in placental blood by microscopy, detection of parasites in placental blood by LAMP, or histopathologic evidence of parasites or pigment. Adverse birth outcomes assessed included low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA) infants.

### RESULTS:

The 282 women were divided into three groups representing increasing malaria burden during pregnancy. Fifty-two (18.4%) had no episodes of symptomatic malaria or asymptomatic parasitaemia during the pregnancy, 157 (55.7%) had low malaria burden (0-1 episodes of symptomatic malaria and < 50% of samples LAMP+), and 73 (25.9%) had high malaria burden during pregnancy ( $\geq 2$  episodes of symptomatic malaria or  $\geq 50\%$  of samples LAMP+). Women with high malaria burden had increased risks of placental malaria by blood microscopy and LAMP [aRR 14.2 (1.80-111.6) and 4.06 (1.73-9.51), respectively], compared to the other two groups combined. Compared with women with no malaria exposure during pregnancy, the risk of placental malaria by histopathology was higher among low and high burden groups [aRR = 3.27 (1.32-8.12) and aRR = 7.07 (2.84-17.6), respectively]. Detection of placental parasites by any method was significantly associated with PTB [aRR 5.64 (1.46-21.8)], and with a trend towards increased risk for LBW and SGA irrespective of the level of malaria burden during pregnancy.

### CONCLUSION:

Higher malaria burden during pregnancy was associated with placental malaria and together with the detection of parasites in the placenta were associated with increased risk for adverse birth outcomes.

<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-017-2040-4>

## Antenatal care

\*\*\* [Lancet Glob Health](#). 2018 Jan;6(1):e57-e65. doi: 10.1016/S2214-109X(17)30421-7.

### [Provision of medical supply kits to improve quality of antenatal care in Mozambique: a stepped-wedge cluster randomised trial.](#)

[Betrán AP](#), [Bergel E](#), [Griffin S](#), [Melo A](#), [Nguyen MH](#), [Carbonell A](#), [Mondlane S](#), [Meriadi M](#), [Temmerman M](#), [Gülmezoglu AM](#); [WHO Antenatal Care Trial in Mozambique Research Group](#).

### [Collaborators \(16\)](#)

## Randomised trials in child health in developing countries 2017-18

### BACKGROUND:

High levels of maternal and newborn mortality and morbidity remain a daunting reality in many low-income countries. Several interventions delivered during antenatal care have been shown to improve maternal and newborn outcomes, but stockouts of medical supplies at point of care can prevent implementation of these services. We aimed to evaluate whether a supply chain strategy based on the provision of kits could improve quality of care.

### METHODS:

We did a pragmatic, stepped-wedge, cluster-randomised controlled trial at ten antenatal care clinics in Mozambique. Clinics were eligible if they were not already implementing the proposed antenatal care package; they served at least 200 new pregnant women per year; they had Maternal and Child Health (MCH) nurses; and they were willing to participate. All women attending antenatal care visits at the participating clinics were included in the trial. Participating clinics were randomly assigned to shift from control to intervention on prespecified start dates.

**The intervention involved four components (kits with medical supplies, a cupboard to store these supplies, a tracking sheet to monitor stocks, and a one-day training session).**

The primary outcomes were the proportion of women screened for anaemia and proteinuria, and the proportion of women who received mebendazole in the first antenatal care visit. The intervention was delivered under routine care conditions, and analyses were done according to the intention-to-treat principle. This trial is registered with the Pan African Clinical Trial Registry, number PACTR201306000550192.

### FINDINGS:

Between March, 2014, and January, 2016, 218 277 antenatal care visits were registered, with 68 598 first and 149 679 follow-up visits. We found significant improvements in all three primary outcomes. In first visits, 5519 (14·6%) of 37 826 women were screened for anaemia in the control period, compared with 30 057 (97·7%) of 30 772 in the intervention period (adjusted odds ratio 832·40; 99% CI 666·81-1039·11;  $p < 0·0001$ ); 3739 (9·9%) of 37 826 women were screened for proteinuria in the control period, compared with 29 874 (97·1%) of 30 772 in the intervention period (1875·18; 1447·56-2429·11;  $p < 0·0001$ ); and 17 926 (51·4%) of 34 842 received mebendazole in the control period, compared with 24 960 (88·2%) of 28 294 in the intervention period (1·88; 1·70-2·09;  $p < 0·0001$ ). The effect was immediate and sustained over time, with negligible heterogeneity between sites.

### INTERPRETATION:

A supply chain strategy that resolves stockouts at point of care can result in a vast improvement in quality during antenatal care visits, when compared with the routine national process for procurement and distribution of supplies.

[https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(17\)30421-7/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30421-7/fulltext)

[BMJ Open](#). 2017 Oct 22;7(10):e014348. doi: 10.1136/bmjopen-2016-014348.

[\*\*The effects of a household conditional cash transfer programme on coverage and quality of antenatal care: a secondary analysis of Indonesia's pilot programme.\*\*](#)

[Triyana M, Shankar AH.](#)

### OBJECTIVE:

To analyse the effectiveness of a household conditional cash transfer programme (CCT) on antenatal care (ANC) coverage reported by women and ANC quality reported by midwives.

### DESIGN:

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The CCT was piloted as a cluster randomised control trial in 2007. Intent-to-treat parameters were estimated using linear regression and logistic regression.

### SETTING:

Secondary analysis of the longitudinal CCT impact evaluation survey, conducted in 2007 and 2009. This included 6869 pregnancies and 1407 midwives in 180 control subdistricts and 180 treated subdistricts in Indonesia.

### OUTCOME MEASURES:

ANC component coverage index, a composite measure of each ANC service component as self-reported by women, and ANC provider quality index, a composite measure of ANC service provided as self-reported by midwives. Each index was created by principal component analysis (PCA). Specific ANC component items were also assessed.

### RESULTS:

The CCT was associated with improved ANC component coverage index by 0.07 SD (95% CI 0.002 to 0.141). Women were more likely to receive the following assessments: weight (OR 1.56 (95% CI 1.25 to 1.95)), height (OR 1.41 (95% CI 1.247 to 1.947)), blood pressure (OR 1.36 (95% CI 1.045 to 1.761)), fundal height measurements (OR 1.65 (95% CI 1.372 to 1.992)), fetal heart beat monitoring (OR 1.29 (95% CI 1.006 to 1.653)), external pelvic examination (OR 1.28 (95% CI 1.086 to 1.505)), iron-folic acid pills (OR 1.42 (95% CI 1.081 to 1.859)) and information on pregnancy complications (OR 2.09 (95% CI 1.724 to 2.551)). On the supply side, the CCT had no significant effect on the ANC provider quality index based on reports from midwives.

### CONCLUSIONS:

The CCT programme improved ANC coverage for women, but midwives did not improve ANC quality. The results suggest that enhanced ANC utilisation may not be sufficient to improve health outcomes, and steps to improve ANC quality are essential for programme impact.

<https://bmjopen.bmj.com/content/7/10/e014348>

[BMC Pregnancy Childbirth](#). 2017 Nov 8;17(Suppl 2):336. doi: 10.1186/s12884-017-1493-3.

### [Randomized controlled pilot of a group antenatal care model and the sociodemographic factors associated with pregnancy-related empowerment in sub-Saharan Africa.](#)

[Patil CL](#), [Klima CS](#), [Leshabari SC](#), [Steffen AD](#), [Pauls H](#), [McGown M](#), [Norr KF](#).

### BACKGROUND:

The links between empowerment and a number of health-related outcomes in sub-Saharan Africa have been documented, but empowerment related to pregnancy is under-investigated. Antenatal care (ANC) is the entry point into the healthcare system for most women, so it is important to understand how ANC affects aspects of women's sense of control over their pregnancy. We compare pregnancy-related empowerment for women randomly assigned to the standard of care versus CenteringPregnancy-based group ANC (intervention) in two sub-Saharan countries, Malawi and Tanzania.

### METHODS:

Pregnant women in Malawi (n = 112) and Tanzania (n = 110) were recruited into a pilot study and randomized to individual ANC or group ANC. Retention at late pregnancy was 81% in Malawi and 95% in Tanzania. In both countries, individual ANC, termed focused antenatal care (FANC), is the standard of care. FANC recommends four ANC visits plus a 6-week post-birth visit and is implemented following the country's standard of care. In group ANC, each contact

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included self- and midwife-assessments in group space and 90 minutes of interactive health promotion. The number of contacts was the same for both study conditions. We measured pregnancy-related empowerment in late pregnancy using the Pregnancy-Related Empowerment Scale (PRES). Independent samples t-tests and multiple linear regressions were employed to assess whether group ANC led to higher PRES scores than individual ANC and to investigate other sociodemographic factors related to pregnancy-related empowerment.

### RESULTS:

In Malawi, women in group ANC had higher PRES scores than those in individual ANC. Type of care was a significant predictor of PRES and explained 67% of the variation. This was not so in Tanzania; PRES scores were similar for both types of care. Predictive models including sociodemographic variables showed religion as a potential moderator of treatment effect in Tanzania. Muslim women in group ANC had a higher mean PRES score than those in individual ANC; a difference not observed among Christian women.

### CONCLUSIONS:

Group ANC empowers pregnant women in some contexts. More research is needed to identify the ways that models of ANC can affect pregnancy-related empowerment in addition to perinatal outcomes globally.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5688418/>

[Health Aff \(Millwood\)](#). 2017 Nov;36(11):1956-1964. doi: 10.1377/hlthaff.2017.0537.

### [Measuring The Impact Of Cash Transfers And Behavioral 'Nudges' On Maternity Care In Nairobi, Kenya.](#)

[Cohen J](#), [Rothschild C](#), [Golub G](#), [Omondi GN](#), [Kruk ME](#), [McConnell M](#).

Many patients in low-income countries express preferences for high-quality health care but often end up with low-quality providers. We conducted a randomized controlled trial with pregnant women in Nairobi, Kenya, to analyze whether cash transfers, enhanced with behavioral "nudges," can help women deliver in facilities that are consistent with their preferences and are of higher quality. We tested two interventions. The first was a labeled cash transfer (LCT), which explained that the cash was to help women deliver where they wanted. The second was a cash transfer that combined labeling and a commitment by the recipient to deliver in a prespecified desired facility as a condition of receiving the final payment (L-CCT). The L-CCT improved patient-perceived quality of interpersonal care but not perceived technical quality of care. It also increased women's likelihood of delivering in facilities that met standards for routine and emergency newborn care but not the likelihood of delivering in facilities that met standards for obstetric care. The LCT had fewer measured benefits. Women preferred facilities with high technical and interpersonal care quality, but these quality measures were often negatively correlated within facilities. Even with cash transfers, many women still used poor-quality facilities. A larger study is warranted to determine whether the L-CCT can improve maternal and newborn outcomes.

[https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2017.0537?url\\_ver=Z39.88-2003&rfr\\_id=ori%3Arid%3Acrossref.org&rfr\\_dat=cr\\_pub%3Dpubmed](https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2017.0537?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed)

[Health Policy Plan](#). 2017 Oct 1;32(suppl\_1):i42-i52. doi: 10.1093/heapol/czw092.

**[Uganda Newborn Study \(UNEST\) trial: Community-based maternal and newborn care economic analysis.](#)**

[Ekirapa-Kiracho E](#), [Barger D](#), [Mayora C](#), [Waiswa P](#), [Lawn JE](#), [Kalungi J](#), [Namazzi G](#), [Kerber K](#), [Owen H](#), [Daviaud E](#).

The Uganda Newborn Study (UNEST) was a two-arm cluster Randomized Control Trial to study the effect of pregnancy and postnatal home visits by local community health workers called 'Village Health Teams' (VHT) coupled with health systems strengthening. To inform programme planning and decision making, additional economic and financial costs of community and facility components were estimated from the perspective of the provider using the Excel-based Cost of Integrating Newborn Care Tool. Additional costs excluded costs already paid by the government for the routine health system and covered design, set-up, and 1-year implementation phases. Improved efficiency was modelled by reducing the number of VHT per village from two to one and varying the number of home visits/mother, the programme's financial cost at scale was projected (population of 100 000). 92% of expectant mothers (n = 1584) in the intervention area were attended by VHTs who performed an average of three home visits per mother. The annualized additional financial cost of the programme was \$83 360 of which 4% (\$3266) was for design, 24% (\$20 026) for set-up and 72% (\$60 068) for implementation. 56% (\$47 030) went towards health facility strengthening, whereas 44% (\$36 330) was spent at the community level. The average cost/mother for the community programme, excluding one-off design costs, amounted to \$22.70 and the average cost per home visit was \$7.50. The additional cost of the preventive home visit programme staffed by volunteer VHTs represents \$1.04 per capita, 1.8% of Uganda's public health expenditure per capita (\$59.00). If VHTs were to spend an average of 6 h a week on the programme, costs per mother would drop to \$13.00 and cost per home visit to \$3.20, in a population of 100 000 at 95% coverage. Additional resources are needed to rollout the government's VHT strategy nationally, maintaining high quality and linkages to quality facility-based care.

[https://academic.oup.com/heapol/article/32/suppl\\_1/i42/4283075](https://academic.oup.com/heapol/article/32/suppl_1/i42/4283075)

## Obstetric care and delivery

[N Engl J Med](#). 2017 Dec 14;377(24):2313-2324. doi: 10.1056/NEJMoa1701075.

**[Outcomes of a Coaching-Based WHO Safe Childbirth Checklist Program in India.](#)**

[Semrau KEA](#), [Hirschhorn LR](#), [Marx Delaney M](#), [Singh VP](#), [Saurastri R](#), [Sharma N](#), [Tuller DE](#), [Firestone R](#), [Lipsitz S](#), [Dhingra-Kumar N](#), [Kodkany BS](#), [Kumar V](#), [Gawande AA](#); [BetterBirth Trial Group](#).

**[Collaborators \(21\)](#)**

**BACKGROUND:**

The prevalence of facility-based childbirth in low-resource settings has increased dramatically during the past two decades, yet gaps in the quality of care persist and mortality remains high. The World Health Organization (WHO) Safe Childbirth Checklist, a quality-improvement tool, promotes systematic adherence to practices that have been associated with improved child birth outcomes.

**METHODS:**



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We conducted a matched-pair, cluster-randomized, controlled trial in 60 pairs of facilities across 24 districts of Uttar Pradesh, India, testing the effect of the BetterBirth program, an 8-month coaching-based implementation of the Safe Childbirth Checklist, on a composite outcome of perinatal death, maternal death, or maternal severe complications within 7 days after delivery. Outcomes - assessed 8 to 42 days after delivery - were compared between the intervention group and the control group with adjustment for clustering and matching. We also compared birth attendants' adherence to 18 essential birth practices in 15 matched pairs of facilities at 2 and 12 months after the initiation of the intervention.

### RESULTS:

Of 161,107 eligible women, we enrolled 157,689 (97.9%) and determined 7-day outcomes for 157,145 (99.7%) mother-newborn dyads. Among 4888 observed births, birth attendants' mean practice adherence was significantly higher in the intervention group than in the control group (72.8% vs. 41.7% at 2 months; 61.7% vs. 43.9% at 12 months;  $P < 0.001$  for both comparisons).

**However, there was no significant difference between the trial groups either in the composite primary outcome (15.1% in the intervention group and 15.3% in the control group; relative risk, 0.99; 95% confidence interval, 0.83 to 1.18;  $P = 0.90$ ) or in secondary maternal or perinatal adverse outcomes.**

### CONCLUSIONS:

Birth attendants' adherence to essential birth practices was higher in facilities that used the coaching-based WHO Safe Childbirth Checklist program than in those that did not, but maternal and perinatal mortality and maternal morbidity did not differ significantly between the two groups.

<https://www.nejm.org/doi/full/10.1056/NEJMoa1701075>

[Int J Qual Health Care](#). 2018 Apr 30. doi: 10.1093/intqhc/mzy086. [Epub ahead of print]

### **Effectiveness of a WHO Safe Childbirth Checklist Coaching-based intervention on the availability of Essential Birth Supplies in Uttar Pradesh, India.**

[Maisonneuve JJ](#), [Semrau KEA](#), [Maji P](#), [Pratap Singh V](#), [Miller KA](#), [Solsky I](#), [Dixit N](#), [Sharma J](#), [Lagoo J](#), [Panariello N](#), [Neal B](#), [Kalita T](#), [Kara N](#), [Kumar V](#), [Hirschhorn LR](#).

### OBJECTIVE:

Evaluate the impact of a World Health Organization Safe Childbirth Checklist coaching-based intervention (BetterBirth Program) on availability and procurement of essential childbirth-related supplies.

### DESIGN:

Matched pair, cluster-randomized controlled trial.

### SETTING:

Uttar Pradesh, India.

### PARTICIPANTS:

120 government-sector health facilities (60 interventions, 60 controls). Supply-availability surveys were conducted quarterly in all sites. Coaches collected supply procurement sources from intervention sites.

### INTERVENTIONS:

Coaching targeting implementation of Checklist with data feedback and action planning.

### MAIN OUTCOME MEASURES:

Mean supply availability by study arm; change in procurement sources for intervention sites.

### RESULTS:

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At baseline, 6 and 12 months, the intervention sites had a mean of 20.9 (95% confidence interval (CI): 20.2-21.5); 22.4 (95% CI: 21.8-22.9) and 22.1 (95% CI:21.4-22.8) items, respectively. Control sites had 20.8 (95% CI: 20.3-21.3); 20.9 (95% CI: 20.3-21.5) and 21.7 (95% CI: 20.8-22.6) items at the same time-points. There was a small but statistically significant higher availability in intervention sites at 6 months (difference-in-difference (DID) = 1.43,  $P < 0.001$ ), which was not seen by 12 months (DID = 0.37,  $P = 0.53$ ). Greater difference between intervention and control sites starting in the bottom quartile of supply availability was seen at 6 months (DID = 4.0,  $P = 0.0002$ ), with no significant difference by 12 months (DID = 1.5,  $P = 0.154$ ). No change was seen in procurement sources with ~5% procured by patients with some rates as high as 29% (oxytocin).

### CONCLUSIONS:

Implementation of the BetterBirth Program, incorporating supply availability, resulted in modest improvements with catch-up by control facilities by 12 months. Supply-chain coaching may be most beneficial in sites starting with lower supply availability. Efforts are needed to reduce reliance on patient-funding for some critical medications.

<https://academic.oup.com/intqhc/advance-article/doi/10.1093/intqhc/mzy086/4990396>

[Health Policy Plan.](#) 2017 Oct 1;32(8):1092-1101. doi: 10.1093/heapol/czx045.

### **A cluster-randomized evaluation of an intervention to increase skilled birth attendant utilization in mid- and far-western Nepal.**

[Choulagai BP](#), [Onta S](#), [Subedi N](#), [Bhatta DN](#), [Shrestha B](#), [Petzold M](#), [Krettek A](#)

Skilled birth attendant (SBA) utilization is low in remote and rural areas of Nepal. We designed and implemented an evaluation to assess the effectiveness of a five-component intervention that addressed previously identified barriers to SBA services in mid- and far-western Nepal. We randomly and equally allocated 36 village development committees with low SBA utilization among 1-year intervention and control groups. The eligible participants for the survey were women that had delivered a baby within the past 12 months preceding the survey.

Implementation was administered by trained health volunteers, youth groups, mothers' groups and health facility management committee members. Post-intervention, we used difference-in-differences and mixed-effects regression models to assess and analyse any increase in the utilization of skilled birth care and antenatal care (ANC) services. All analyses were done by intention to treat. Interviewees included 1746 and 2098 eligible women in the intervention and control groups, respectively. The 1-year intervention was effective in increasing the use of skilled birth care services (OR = 1.57; CI 1.19-2.08); however, the intervention had no effect on the utilization of ANC services. Expanding the intervention with modifications, e.g. mobilizing more active and stable community groups, ensuring adequate human resources and improving quality of services as well as longer or repeated interventions will help achieve greater effect in increasing the utilization of SBA.

<https://academic.oup.com/heapol/article/32/8/1092/3798544>

[BMC Pregnancy Childbirth.](#) 2017 Oct 3;17(1):340. doi: 10.1186/s12884-017-1526-y.

**[A randomized controlled double blind trial comparing the effects of the prophylactic antibiotic, Cefazolin, administered at caesarean delivery at two different timings \(before skin incision and after cord clamping\) on both the mother and newborn.](#)**

[Jyothirmayi CA](#), [Halder A](#), [Yadav B](#), [Samuel ST](#), [Kuruville A](#), [Jose R](#).

**BACKGROUND:**

Caesarean delivery (CD) increases the risk of postpartum infection by 5 to 20 fold. Prevention of surgical site infection (SSI) is the goal of antibiotic prophylaxis. This study was carried out to assess the optimum timing for prophylactic antibiotic administration and to assess the amount of the antibiotic crossing the placental barrier.

**METHODS:**

**Eligible mothers were recruited, after informed consent, once the decision for CD was made. Each mother received two injections, one prior to skin incision and one after cord clamping, (one being the study drug Cefazolin, and the other, a placebo) based on the randomization code. Demographic, maternal and neonatal monitoring data until discharge from hospital, and at the 6 weeks postpartum visit were collected. Levels of the prophylactic antibiotic were measured from the cord blood in every 8th neonate. The objective of the study was to compare the effects of the prophylactic antibiotic, intravenous Cefazolin 1 g, administered at Caesarean delivery (CD) at two different timings (before skin incision and after cord clamping) on both the mother and newborn. The secondary outcomes that were followed up were the number of maternal and neonatal readmissions. An appropriate test for significance, Fisher's exact test was used to find the association between risk variables and outcome.**

**RESULTS:**

**The total numbers of mothers enrolled were 1106, of whom 553 mothers received antibiotic prior to skin incision (pre-incision) and 543 mothers received antibiotic after cord clamping (post-incision). The pre-incision group had significantly less febrile illness (RR = 0.48, 95% CI: 0.29 - 0.80) and SSI (RR = 0.14, 95% CI: 0.04 - 0.53) when compared with the post- incision group. The post-incision group significantly had >7 days hospital stay when compared to the 4-7 days stay of the pre-incision group (p = 0.005). There were no differences in any of the neonatal outcomes. The quantity of the antibiotic in the cord blood was only 2-3%.**

**CONCLUSIONS:**

Pre incision prophylactic antibiotic protected the mother from SSI and febrile illness and decreased the hospital stay significantly.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5627463/>

[Glob Health Res Policy](#). 2018 Apr 4;3:12. doi: 10.1186/s41256-018-0066-y. eCollection 2018.

**[Increasing women's access to skilled pregnancy care to reduce maternal and perinatal mortality in rural Edo State, Nigeria: a randomized controlled trial.](#)**

[Yaya S](#), [Okonofua F](#), [Ntoimo L](#), [Kadio B](#), [Deuboue R](#), [Imongan W](#), [Balami W](#).

**BACKGROUND:**

Nigeria presently has the second highest absolute number of maternal deaths and perinatal deaths (stillbirth and neonatal deaths) in the world. The country accounts for up to 14% of global maternal deaths and is second only to India in the number of women who die

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during childbirth. Although all parts of the country are worsened by these staggering statistics, several lines of evidence show that most maternal, and perinatal deaths occur in the north-east and north-west geo-political zones where women have limited access to evidence-based maternal and neonatal health services. The proposed project intends to identify the demand and supply factors that prevent women from using PHCs for maternal and early new-born care in Nigeria, and to test innovative and community relevant interventions for improving women's access to PHC services, and thus, ultimately, to prevent maternal and perinatal deaths.

### **METHODS:**

An open-labelled, randomized controlled trial will be carried out in two local government areas selected based on three criteria (i) maternal mortality rates (ii) PHC utilization rates and (iii) geographic localization. The study will be conducted over 54-months in six communities, with PHCs in six communities of similar status serving as control sites. Surveys about quality of care and maternal health services utilization will be carried out at baseline, at midterm and at end of the project to test the effectiveness of the intervention, alongside conventional epidemiological measures of maternal and perinatal mortality. Ethical approval for the study has been granted (reference no. NHREC/01/01/2007). The findings will be published in compliance with reporting guidelines for randomized controlled trials.

### **DISCUSSION:**

The current Federal Government in Nigeria has identified PHC as its main strategy for increasing access to health in Nigeria. However, despite numerous efforts, there are persisting concerns that there is currently no scientific evidence on which to base the improvement of PHCs. The results of this study will identify barriers in the use of PHCs and will provide scientific evidence for effective and innovative interventions for improving PHCs that can be rolled out throughout the country.

<https://link.springer.com/article/10.1186/s41256-018-0066-y>

## Maternal nutrition and micronutrient supplementation

[Matern Child Health J.](#) 2018 Jul 12. doi: 10.1007/s10995-018-2605-z. [Epub ahead of print] **[Effect of Maternal Vitamin B12 Supplementation on Cognitive Outcomes in South Indian Children: A Randomized Controlled Clinical Trial.](#)**

[Thomas S](#), [Thomas T](#), [Bosch RJ](#), [Ramthal A](#), [Bellinger DC](#), [Kurpad AV](#), [Duggan CP](#), [Srinivasan K](#).

**OBJECTIVES:** To examine the effects of oral maternal vitamin B12 supplementation during pregnancy and early lactation on cognitive development in children. **Method** We studied 218 children born to mothers enrolled in a placebo-controlled, randomized trial of vitamin B12 supplementation during pregnancy through 6 weeks post-partum. Cognitive functions were assessed at 30 months using the Bayley Scales of Infant Development- 3rd edition (BSID III). The association of maternal sociodemographic characteristics, maternal biochemical status during pregnancy, birth weight and home environment with each sub-domain of BSID-III was examined using linear regression analysis. Separate multiple linear regression analyses for each of the BSID-III sub-domains with maternal trimester specific nutritional biomarker status was conducted. **Results** Children of mothers who received oral vitamin B12 supplementation had significantly higher scores on expressive language compared to children of mothers who

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received placebo ( $\beta = 0.14$ ,  $P = 0.03$ ). Children of mothers with elevated serum total homocysteine (tHcy) in the second and third trimesters of pregnancy had significantly lower scores on expressive language ( $\beta = -0.18$ ,  $P = 0.03$  and  $\beta = -0.19$ ,  $P = 0.02$ , respectively) and gross motor domains ( $\beta = -0.23$ ,  $P = 0.008$  and  $\beta = -0.30$ ,  $P = 0.001$ , respectively) of BSID-III adjusted for treatment arm and multiple confounders, compared with children whose mothers did not have elevated tHcy. Conclusions for practice **Maternal B12 supplementation during pregnancy was associated with higher expressive language scores in children at 30 months.** Elevated maternal tHcy levels during pregnancy had negative associations with expressive language and gross motor domains of BSID-III. Larger trials of maternal B12 supplementation are needed to confirm these findings.

<https://link.springer.com/article/10.1007%2Fs10995-018-2605-z>

[Eur J Clin Nutr.](#) 2017 Sep;71(9):1046-1053. doi: 10.1038/ejcn.2017.29. Epub 2017 Apr 12.  
**[Vitamin B<sub>12</sub> status in pregnant women and their infants in South India.](#)**  
[Finkelstein JL](#), [Kurpad AV](#), [Thomas T](#), [Srinivasan K](#), [Duggan C](#)

### BACKGROUND/OBJECTIVES:

Vitamin B<sub>12</sub> deficiency during pregnancy has been associated with increased risk of adverse perinatal outcomes. However, few studies have investigated the burden and determinants of vitamin B<sub>12</sub> status in young infants. This study was conducted to determine the associations between maternal and infant vitamin B<sub>12</sub> status.

### SUBJECTS/METHODS:

Pregnant women participating in a vitamin B<sub>12</sub> supplementation trial in Bangalore, India, were randomized to receive vitamin B<sub>12</sub> (50  $\mu\text{g}$ ) or placebo supplementation daily during pregnancy through 6 weeks postpartum. All women received 60 mg of iron and 500  $\mu\text{g}$  of folic acid daily during pregnancy, as per standard of care. This prospective analysis was conducted to determine the associations between maternal vitamin B<sub>12</sub> biomarkers (that is, plasma vitamin B<sub>12</sub>, methylmalonic acid (MMA) and tHcy) during each trimester with infant vitamin B<sub>12</sub> status ( $n=77$ ) at 6 weeks of age.

### RESULTS:

At baseline ( $\leq 14$  weeks of gestation), 51% of mothers were vitamin B<sub>12</sub> deficient (vitamin B<sub>12</sub>  $< 150$  pmol/l) and 43% had impaired vitamin B<sub>12</sub> status (vitamin B<sub>12</sub>  $< 150$  pmol/l and MMA  $> 0.26$   $\mu\text{mol/l}$ ); 44% of infants were vitamin B<sub>12</sub> deficient at 6 weeks of age. After adjusting for vitamin B<sub>12</sub> supplementation, higher vitamin B<sub>12</sub> concentrations in each trimester were associated with increased infant vitamin B<sub>12</sub> concentrations and lower risk of vitamin B<sub>12</sub> deficiency in infants ( $P < 0.05$ ). After adjusting for vitamin B<sub>12</sub> supplementation, infants born to women with vitamin B<sub>12</sub> deficiency had a twofold greater risk of vitamin B<sub>12</sub> deficiency ( $P < 0.01$ ). Higher maternal folate concentrations also predicted lower risk of vitamin B<sub>12</sub> deficiency in infants ( $P < 0.05$ ). Impaired maternal vitamin B<sub>12</sub> status, which combined both circulating and functional biomarkers, was the single best predictor of infant vitamin B<sub>12</sub> status.

### CONCLUSIONS:

Impaired maternal vitamin B<sub>12</sub> status throughout pregnancy predicted higher risk of vitamin B<sub>12</sub> deficiency in infants, after adjusting for vitamin B<sub>12</sub> supplementation. Future interventions are needed to improve vitamin B<sub>12</sub> status preconceptionally, and to ensure optimal vitamin B<sub>12</sub> status and health outcomes in pregnant women and their children.

<https://www.nature.com/articles/ejcn201729>

[J Nutr.](#) 2017 Dec;147(12):2326-2337. doi: 10.3945/jn.117.257303. Epub 2017 Oct 11.

**[Integrating Nutrition Interventions into an Existing Maternal, Neonatal, and Child Health Program Increased Maternal Dietary Diversity, Micronutrient Intake, and Exclusive Breastfeeding Practices in Bangladesh: Results of a Cluster-Randomized Program Evaluation.](#)**

[Nguyen PH](#), [Kim SS](#), [Sanghvi T](#), [Mahmud Z](#), [Tran LM](#), [Shabnam S](#), [Aktar B](#), [Haque R](#), [Afsana K](#), [Frongillo EA](#), [Ruel MT](#), [Menon P](#).

**Background:** Maternal undernutrition is a major concern globally, contributing to poor birth outcomes. Limited evidence exists on delivering multiple interventions for maternal nutrition simultaneously. Alive & Thrive addressed this gap by integrating nutrition-focused interpersonal counseling, community mobilization, distribution of free micronutrient supplements, and weight-gain monitoring through an existing Maternal, Neonatal, and Child Health (MNCH) program in Bangladesh.

**Objectives:** We evaluated the effect of providing nutrition-focused MNCH compared with standard MNCH (antenatal care with standard nutrition counseling) on coverage of nutrition interventions, maternal dietary diversity, micronutrient supplement intake, and early breastfeeding practices.

**Methods:** We used a cluster-randomized design with cross-sectional surveys at baseline (2015) and endline (2016) ( $n \sim 300$  and 1000 pregnant or recently delivered women, respectively, per survey round). We derived difference-in-difference effect estimates, adjusted for geographic clustering and infant age and sex.

**Results:** Coverage of interpersonal counseling was high; >90% of women in the nutrition-focused MNCH group were visited at home by health workers for maternal nutrition and breastfeeding counseling. The coverage of community mobilization activities was ~50%. Improvements were significantly greater in the nutrition-focused MNCH group than in the standard MNCH group for consumption of iron and folic acid [effect: 9.8 percentage points (pp); 46 tablets] and calcium supplements (effect: 12.8 pp; 50 tablets). Significant impacts were observed for the number of food groups consumed (effect: 1.6 food groups), percentage of women who consumed  $\geq 5$  food groups/d (effect: 30.0 pp), and daily intakes of several micronutrients. A significant impact was also observed for exclusive breastfeeding (EBF; effect: 31 pp) but not for early initiation of breastfeeding.

**Conclusions:** Addressing nutrition during pregnancy by delivering interpersonal counseling and community mobilization, providing free supplements, and ensuring weight-gain monitoring through an existing MNCH program improved maternal dietary diversity, micronutrient supplement consumption, and EBF practices.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5697969/>

[Matern Child Nutr.](#) 2018 Jan;14(1). doi: 10.1111/mcn.12441. Epub 2017 Mar 2.

**[Effect of a micronutrient-rich snack taken preconceptionally and throughout pregnancy on ultrasound measures of fetal growth: The Mumbai Maternal Nutrition Project \(MMNP\).](#)**

[Lawande A](#), [Di Gravio C](#), [Potdar RD](#), [Sahariah SA](#), [Gandhi M](#), [Chopra H](#), [Sane H](#), [Kehoe SH](#), [Marley-Zagar E](#), [Margetts BM](#), [Jackson AA](#), [Fall CHD](#).

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Improving micronutrient intakes of under-nourished mothers in low- and middle-income countries increases birth weight, but there is little data on the nature and timing during gestation of any effects on fetal growth. Ultrasound measures of fetal size were used to determine whether and when a food-based supplement affected fetal growth. Non-pregnant women living in Mumbai slums, India (N = 6,513), were randomly assigned to receive either a daily micronutrient-rich snack containing green leafy vegetables, fruit, and milk (treatment) or a snack made from lower-micronutrient vegetables (control) in addition to their usual diet from before pregnancy until delivery. From 2,291 pregnancies, the analysis sample comprised 1,677 fetuses (1,335 fetuses of women supplemented for  $\geq 3$  months before conception). First-trimester (median: 10 weeks, interquartile range: 9-12 weeks) fetal crown-rump length was measured. Fetal head circumference, biparietal diameter, femur length, and abdominal circumference were measured during the second (19, 19-20 weeks) and third trimesters (29, 28-30 weeks). The intervention had no effect on fetal size or growth at any stage of pregnancy. In the second trimester, there were interactions between parity and allocation group for biparietal diameter ( $p = .02$ ) and femur length ( $p = .04$ ) with both being smaller among fetuses of primiparous women and larger among those of multiparous women, in the treatment group compared with the controls. Overall, a micronutrient-rich supplement did not increase standard ultrasound measures of fetal size and growth at any stage of pregnancy. Additional ultrasound measures of fetal soft tissues (fat and muscle) may be informative.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5482394/>

*J Perinatol.* 2017 Jul;37(7):782-786. doi: 10.1038/jp.2017.43. Epub 2017 Apr 6.

### **Iron supplementation in singleton pregnancy: Is there a benefit to doubling the dose of elemental iron in iron-deficient pregnant women? a randomized controlled trial.**

Shinar S, Skornick-Rapaport A, Maslovitz S.

#### **OBJECTIVE:**

To assess the efficacy of doubling the 30 mg dose of iron in women with iron deficiency anemia (IDA) in singleton pregnancies.

#### **STUDY DESIGN:**

Prospective randomized controlled trial. Iron-deficient women were randomized during the second trimester to receive one or two capsules of daily iron supplement, containing 34 mg of ferrous sulfate, from 17 weeks until 6 weeks postpartum. The primary outcome was hemoglobin (Hgb) at 35 weeks. Secondary outcomes included ferritin at 35 weeks, Hgb during pregnancy and postpartum, birth weights, preterm birth rate, gastrointestinal side effects, intravenous iron administration and compliance.

#### **RESULTS:**

In all, 160 women were randomized to receive one capsule and 164 received two capsules. Both groups had similar Hgb ( $10.1 \text{ g dl}^{-1}$ ) and ferritin ( $9.3$  and  $9.4 \text{ ng l}^{-1}$ ) at allocation. Hgb concentration in both groups was similar at 35 weeks ( $10.8 \text{ g dl}^{-1}$ ). There were no significant differences in any of the secondary outcomes.

#### **CONCLUSION:**

In IDA pregnant women, a single dose of iron is as effective as a double dose.

<https://www.nature.com/articles/jp201743>

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*J Nutr.* 2017 Aug;147(8):1586-1592. doi: 10.3945/jn.117.248963. Epub 2017 Jun 14.

### **Daily Consumption of Lipid-Based Nutrient Supplements Containing 250 µg Iodine Does Not Increase Urinary Iodine Concentrations in Pregnant and Postpartum Women in Bangladesh.**

[Mridha MK](#), [Matias SL](#), [Paul RR](#), [Hussain S](#), [Khan MSA](#), [Siddiqui Z](#), [Ullah B](#), [Sarker M](#), [Hossain M](#), [Young RT](#), [Arnold CD](#), [Dewey KG](#).

**Background:** Maternal iodine deficiency during pregnancy and lactation is common in Bangladesh.

**Objective:** We evaluated the effect of lipid-based nutrient supplements for pregnant and lactating women (LNS-PL) on urinary iodine concentration (UIC).

**Methods:** We conducted a cluster-randomized controlled effectiveness trial in which we enrolled 4011 pregnant women at  $\leq 20$  gestational weeks. Women in 48 clusters received iron and folic acid (IFA; 60 mg Fe/d + 400 µg folic acid/d) and women in 16 clusters received LNS-PL (20 g/d, 118 kcal) containing 22 vitamins and minerals (including 250 µg I). We randomly selected a subsample of 1159 women for repeated urine sample collection, i.e., at enrollment, at 36 wk of gestation, and at 6 mo postpartum, for UIC analysis, a secondary outcome of the trial.

**Results:** The geometric mean UIC at 36 wk of gestation and at 6 mo postpartum did not differ significantly between the IFA and LNS-PL groups. The median (quartile 1, quartile 3) UIC at 36 wk was 27.4 µg/L (16.9, 52.7 µg/L) in the IFA group and 30.2 µg/L (17.7, 56.6 µg/L) in the LNS-PL group; at 6 mo, these were 23.0 µg/L (10.0, 45.9 µg/L) in the IFA group and 22.2 µg/L (9.1, 50.4 µg/L) in the LNS-PL group.

**Conclusion:** Daily consumption of LNS-PL containing 250 µg I did not increase the UICs of pregnant and lactating women in Bangladesh. Iodine from lipid-based nutrient supplements may have been stored in the thyroid gland or secreted in breast milk instead of being excreted in urine. Additional research that uses other biomarkers of iodine status is needed to determine how to meet the iodine requirements of pregnant and lactating women in Bangladesh and similar settings. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT01715038](https://clinicaltrials.gov/ct2/show/study/NCT01715038).

<https://academic.oup.com/jn/article/147/8/1586/4584658>

*Acta Paediatr.* 2017 Dec;106(12):1979-1986. doi: 10.1111/apa.14009. Epub 2017 Aug 29.

### **Prenatal early food and multiple micronutrient supplementation trial reduced infant mortality in Bangladesh, but did not influence morbidity.**

[Kallioinen M](#), [Ekström EC](#), [Khan AI](#), [Lindström E](#), [Persson LÅ](#), [Rahman A](#), [Selling KE](#).

#### **AIM:**

A previous maternal and infant nutrition intervention in rural Matlab, Bangladesh, showed that prenatal nutrient supplements improved child survival, but had no effect on size at birth. This secondary analysis examined whether prenatal multiple micronutrient supplements (MMS), on their own or combined with an early invitation to receive prenatal food supplements, affected child morbidity.

#### **METHODS:**

This randomised trial enrolled 4436 pregnant women from November 2001 to October 2003 and allocated them to early or standard invitations to food supplements, in the ninth and 20th weeks of pregnancy, respectively, and supplements of either the standard 60 mg iron with 400 µg folic



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acid, 30 mg iron with 400 µg folic acid or MMS. Quasi-Poisson regression was used to analyse morbidity.

### RESULTS:

There were 3560 single live births and 3516 had morbidity data. The incidence rates of fever, diarrhoea and acute lower respiratory tract infection were 15.3, 3.6 and 2.3 episodes per person-year, respectively. The separate or combined interventions had no effect on morbidity up to 24 months.

### CONCLUSION:

Early invitations to prenatal food supplements or prenatal MMS had no effect on common infections in rural Bangladesh, suggesting that earlier findings on improved child survival were not mediated by an effect on child morbidity.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/apa.14009>

*J Nutr.* 2017 Aug;147(8):1593-1601. doi: 10.3945/jn.117.250597. Epub 2017 Jun 14.

### **Preconception Micronutrient Supplementation with Iron and Folic Acid Compared with Folic Acid Alone Affects Linear Growth and Fine Motor Development at 2 Years of Age: A Randomized Controlled Trial in Vietnam.**

[Nguyen PH](#), [Gonzalez-Casanova I](#), [Young MF](#), [Truong TV](#), [Hoang H](#), [Nguyen H](#), [Nguyen S](#), [DiGirolamo AM](#), [Martorell R](#), [Ramakrishnan U](#).

**Background:** Maternal health and nutrition play a crucial role in early child growth and development. However, little is known about the benefits of preconception micronutrient interventions beyond the role of folic acid (FA) and neural tube defects. **Objective:** We evaluated the impact of weekly preconception multiple micronutrient (MM) or iron and folic acid (IFA) supplementation on child growth and development through the age of 2 y compared with FA alone.

**Methods:** We followed 1599 offspring born to women who participated in a randomized controlled trial of preconception supplementation in Vietnam. Women received weekly supplements that contained either 2800 µg FA, 60 mg Fe and 2800 µg FA, or 15 MMs including IFA, from baseline until conception followed by daily prenatal IFA supplements until delivery. Child anthropometry was measured at birth and at 3, 6, 12, 18, and 24 mo. Child development was measured with the use of the Bayley Scales for Infant Development III at 24 mo.

**Results:** The groups were similar for baseline maternal and offspring birth characteristics. At 24 mo of age, the offspring in the IFA group had significantly higher length-for-age z scores (LAZs) (0.14; 95% CI: 0.03, 0.26), reduced risk of being stunted (0.87; 95% CI: 0.76, 0.99), and smaller yearly decline in LAZs (0.10; 95% CI: 0.04, 0.15) than the offspring in the FA group. Similar trends were found for the offspring in the MM group compared with the FA group for LAZs (0.10; 95% CI: -0.02, 0.22) and the risk of being stunted (0.88; 95% CI: 0.77, 1.01). Offspring in the IFA group had improved motor development ( $P = 0.03$ ), especially fine motor development (0.41; 95% CI: 0.05, 0.77), at the age of 24 mo, but there were no differences for measures of cognition or language.

**Conclusions:** Preconception supplementation with IFA improved linear growth and fine motor development at 2 y of age compared with FA. Future studies should examine whether these effects persist and improve child health and schooling. The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT01665378](https://clinicaltrials.gov/ct2/show/study/NCT01665378).

<https://academic.oup.com/jn/article/147/8/1593/4584665>

[J Nutr.](#) 2017 Sep;147(9):1776-1784. doi: 10.3945/jn.117.248880. Epub 2017 Jul 19.

**[Prenatal Lipid-Based Nutrient Supplements Do Not Affect Pregnancy or Childbirth Complications or Cesarean Delivery in Bangladesh: A Cluster-Randomized Controlled Effectiveness Trial.](#)**

[Mridha MK](#), [Matias SL](#), [Paul RR](#), [Hussain S](#), [Sarker M](#), [Hossain M](#), [Peerson JM](#), [Vosti SA](#), [Dewey KG](#).

**Background:** Pregnancy and childbirth complications and cesarean delivery are common in Bangladesh.

**Objective:** We evaluated the effect of lipid-based nutrient supplements for pregnant and lactating women (LNS-PL) on pregnancy and childbirth complications and cesarean delivery.

**Methods:** We conducted the Rang-Din Nutrition Study, a cluster-randomized controlled effectiveness trial within a community health program in rural Bangladesh. We enrolled 4011 pregnant women in early pregnancy. Women in 48 clusters received iron and folic acid (IFA; 60 mg Fe + 400 µg folic acid/d) and women in 16 clusters received LNS-PL (20 g/d, 118 kcal) containing essential fatty acids and 22 vitamins and minerals. Pregnancy and childbirth complications and the cesarean delivery rate were secondary outcomes of the study.

**Results:** Women in the LNS-PL group did not differ significantly from the IFA group with respect to mean systolic blood pressure at 36 wk gestation (113 and 112 mm Hg;  $P = 0.17$ ), diastolic blood pressure at 36 wk gestation (68.9 and 68.7 mmHg;  $P = 0.88$ ), or mean total number of pregnancy and childbirth complications (0.32 and 0.31;  $P = 0.86$ ). They also did not differ significantly with respect to the prevalence of high blood pressure at 36 wk (1.74% and 2.03%;  $P = 0.62$ ), antepartum hemorrhage (0.83% and 1.39%;  $P = 0.21$ ), prolonged labor (8.34% and 8.79%;  $P = 0.68$ ), early rupture of membranes (9.30% and 8.45%;  $P = 0.43$ ), convulsions (1.57% and 1.08%;  $P = 0.24$ ), high blood pressure in labor (1.54% and 1.19%;  $P = 0.46$ ), obstructed labor (2.83% and 2.91%;  $P = 0.90$ ), any complications during pregnancy or childbirth (35.9% and 37.1%;  $P = 0.64$ ), episiotomy (6.31% and 6.44%;  $P = 0.90$ ), or cesarean delivery (15.6% and 14.2%;  $P = 0.48$ ).

**Conclusion:** Compared with IFA, antenatal LNS-PL did not increase or decrease pregnancy and child birth complications or cesarean delivery among women in rural Bangladesh

<https://academic.oup.com/jn/article/147/9/1776/4743534>

[Am J Epidemiol.](#) 2017 Sep 1;186(5):603-611. doi: 10.1093/aje/kwx080.

**[Maternal Dietary L-Arginine and Adverse Birth Outcomes in Dar es Salaam, Tanzania.](#)**

[Darling AM](#), [McDonald CR](#), [Urassa WS](#), [Kain KC](#), [Mwiru RS](#), [Fawzi WW](#).

The amino acid arginine is a physiological precursor to nitric oxide, which is a key mediator of embryonic survival, fetal growth, and pregnancy maintenance. We evaluated the association between consumption of the amino acid arginine and the rate of adverse birth outcomes using data from a double-blind, randomized, placebo-controlled micronutrient supplementation trial among pregnant women in Dar es Salaam, Tanzania (2001-2004). Dietary intakes of arginine were assessed using repeated 24-hour recalls that were administered throughout pregnancy. Participants ( $n = 7,591$ ) were monitored by research midwives

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throughout follow-up to assess pregnancy outcomes. Cubic-restricted splines and multivariable log-Poisson regression with empirical standard errors were used to estimate the continuous and categorical associations between arginine intake and adverse birth outcomes. Compared with women within the lowest quintile of arginine intake, those within the highest quintile had 0.79 times the risk of preterm birth before 37 weeks (95% confidence interval: 0.63, 1.00;  $P = 0.03$ ). The continuous associations of arginine intake with preterm birth before 37 weeks and with preterm birth before 34 weeks were characterized by an initial rapid decrease in risk with increasing intake ( $P$  for nonlinearity  $< 0.01$ ). Arginine intake was not associated with fetal loss or giving birth to infants who were born small for their gestational ages. This data suggest that the association between dietary arginine intake and preterm birth warrants further investigation.

<https://academic.oup.com/aje/article/186/5/603/3813219>

[BMJ Open](#). 2017 Aug 21;7(8):e015393. doi: 10.1136/bmjopen-2016-015393.

### **Making a balanced plate for pregnant women to improve birthweight of infants: a study protocol for a cluster randomised controlled trial in rural Bangladesh.**

[Chowdhury M](#), [Raynes-Greenow C](#), [Alam A](#), [Dibley MJ](#).

#### **OBJECTIVES:**

Low birthweight significantly contributes to neonatal mortality, morbidities and psychosocial debilities throughout the course of life. A large proportion of infants (36-55%) in Bangladesh is born with low birthweight. Nutritional status of women during pregnancy is critical for optimal growth and development of the fetus. Nutrition education has been found to improve maternal nutritional status. Our study aims to determine whether nutrition education with a practical demonstration during pregnancy is an effective intervention for improving the birthweight of infants compared with standard nutrition education only.

#### **METHODS AND ANALYSIS:**

We will conduct a community-based cluster randomised controlled trial in one rural district of Bangladesh. Treatments will be allocated evenly between the study clusters ( $n=36$ ). Participants in the intervention clusters receive 'balanced plate nutrition education' with a practical demonstration from community health workers 4-7 times throughout their entire pregnancy, starting from the first trimester. The control clusters will receive standard nutrition education delivered by public and other healthcare providers as per ongoing antenatal care protocol. Our sample size would be 900 pregnant women to determine 100 g differences in mean birthweight, considering 5% type 1 error, 80% power and an intra-cluster correlation coefficient of 0.03. The primary outcome of the trial is birthweight of the infants and the secondary outcomes include daily caloric intake and dietary diversity score among the pregnant women. Outcomes will be measured at enrolment, third to ninth month of gestation (monthly) and at delivery. Community health workers blinded to the study hypothesis will collect all data.

#### **ETHICS AND DISSEMINATION:**

The study was approved by the James P Grant School of Public Health, BRAC University Ethical Review Committee, Dhaka, Bangladesh. We will communicate the final results to relevant research and public health groups and publish research papers in peer-reviewed journals.

<https://bmjopen.bmj.com/content/7/8/e015393>

[Am J Clin Nutr.](#) 2017 Oct 1;106(4):1062-1069. doi: 10.3945/ajcn.117.157198.

**Trial of ready-to-use supplemental food and corn-soy blend in pregnant Malawian women with moderate malnutrition: a randomized controlled clinical trial.**

[Callaghan-Gillespie M](#), [Schaffner AA](#), [Garcia P](#), [Fry J](#), [Eckert R](#), [Malek S](#), [Trehan I](#), [Thakwalakwa C](#), [Maleta KM](#), [Manary MJ](#), [Papathakis PC](#).

**BACKGROUND:**

Malnutrition during pregnancy in sub-Saharan Africa is associated with poor birth outcomes.

**OBJECTIVE:**

This study compared maternal and offspring anthropometry for moderately malnourished pregnant women receiving ready-to-use supplemental food (RUSF), a fortified corn-soy blend (CSB+) with a daily multiple micronutrient antenatal supplement [United Nations International Multiple Micronutrient Preparation (UNIMMAP)], or standard of care comprising CSB+ and iron and folic acid (IFA).

**DESIGN:**

A single-blind randomized controlled clinical trial was conducted in southern Malawi among 1828 pregnant women with moderate malnutrition, defined as a midupper arm circumference (MUAC)  $\geq 20.6$  and  $\leq 23.0$  cm. Women received 1 of 3 dietary treatment regimens that provided  $\sim 900$  kcal/d and 33-36 g protein/d. Maternal and infant anthropometry were followed until the child was 3 mo old.

**RESULTS:**

Newborns had a mean length-for-age z score of  $-1.3 \pm 1.2$  and 22% were stunted at birth. Mothers receiving RUSF had the highest weight gain during supplementation ( $3.4 \pm 2.6$ ,  $3.0 \pm 2.2$ , and  $3.2 \pm 2.4$  kg for the RUSF, CSB+ with UNIMMAP, and CSB+ with IFA groups, respectively;  $P = 0.03$ ). Newborn birth weights and lengths were similar across intervention groups, but the incidence of newborns with a birth weight  $< 2.4$  kg (weight-for-age z score  $< -2$ ) was higher in the CSB+ with UNIMMAP group than the other groups (17%, 18%, and 24% for the CSB+ with IFA, RUSF, and CSB+ with UNIMMAP groups, respectively;  $P = 0.02$ ). At birth, HIV-exposed newborns had a similar length and weight as newborns without HIV exposure, but their head circumference was smaller ( $34.0 \pm 1.5$  and  $34.3 \pm 1.6$  cm, respectively;  $P = 0.02$ ). At 3 mo of age, HIV-exposed infants had smaller weights, lengths, and head and arm circumferences than infants without HIV exposure.

**CONCLUSIONS:**

RUSF improved maternal weight gain compared with CSB+ with UNIMMAP. The large amount of food given and the modest effect on linear growth in newborns suggests that stunting in utero is unlikely to be reduced by supplemental food alone. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT02120599](#).

<https://academic.oup.com/ajcn/article/106/4/1062/4652046>

## **Meningitis and encephalitis**

\*\*\* [Homeopathy.](#) 2018 Jun 5. doi: 10.1055/s-0038-1656715. [Epub ahead of print]

**Effectiveness of Homeopathic Medicines as Add-on to Institutional Management Protocol for Acute Encephalitis Syndrome in Children: An Open-Label Randomized Placebo-Controlled Trial.**

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[Oberai P<sup>1</sup>](#), [Varanasi R<sup>1</sup>](#), [Padmanabhan M<sup>2</sup>](#), [Upadhyaya A<sup>3</sup>](#), [Singh S<sup>3</sup>](#), [Singh SP<sup>3</sup>](#), [Vikram D<sup>3</sup>](#), [Khan T<sup>3</sup>](#), [Prasad R<sup>3</sup>](#), [Gupta AK<sup>3</sup>](#), [Singh JR<sup>3</sup>](#), [Manchanda RK<sup>1</sup>](#).

### BACKGROUND:

Acute encephalitis syndrome (AES) is endemic to certain parts of India, with limited treatment options. In our initial exploratory comparative observational study of 151 patients with AES, there was significantly reduced mortality with adjunctive homeopathy compared to institutional management protocol (IMP). The present randomized placebo-controlled trial brings more statistical rigor to this research program.

### METHODS:

This study was conducted at a pediatric unit from 2013 to 2015. Children aged > 6 months and ≤ 18 years and receiving IMP were randomized to receive adjunctive homeopathy ( $n = 325$ ) or placebo as control ( $n = 323$ ). The primary effectiveness analysis was based on Glasgow Outcome Scale (GOS). Morbidity was assessed using the Liverpool Outcome Score for Assessing Children at Follow-up. Analysis was by intention to treat.

### RESULTS:

A total of 612 children were analyzed (Homeopathy [H] = 304; Control [C] = 308). The primary outcome, GOS, differed significantly between H and C groups. There was 14.8% death/neuro-vegetative state in the H group compared to 29.8% in the C group. Relative risk was 0.49 (95% confidence interval [CI]: 0.36 to 0.68), with absolute risk reduction of 15.0% (95% CI: 8.6 to 21.6%). Number needed to treat to prevent one additional death/neuro-vegetative state was 6.6 (95% CI: 4.6 to 11.6). Proportional-odds analysis also revealed a greater effect in the H group: odds ratio, 0.40 (95% CI: 0.27 to 0.60). **The most frequently used medicines were *Belladonna* ( $n = 116$ ), *Stramonium* ( $n = 33$ ), *Arsenicum album* ( $n = 25$ ), *Sulfur* ( $n = 18$ ), *Opium* ( $n = 17$ ), and *Nux vomica* ( $n = 10$ ).**

### CONCLUSION:

Adjunctive homeopathic medicines may improve clinical outcomes associated with AES. Further randomized and controlled studies, using double-blinded trial design, are recommended to discover if the current findings may be corroborated.

## Mobile phone technology

[Reprod Health](#). 2017 Nov 7;14(1):146. doi: 10.1186/s12978-017-0407-1.

### [PRENACEL - a mHealth messaging system to complement antenatal care: a cluster randomized trial.](#)

[Oliveira-Ciabati L](#), [Vieira CS](#), [Franzon ACA](#), [Alves D](#), [Zaratini FS](#), [Braga GC](#), [Sanchez JAC](#), [Bonifácio LP](#), [Andrade MS](#), [Fernandes M](#), [Quintana SM](#), [Fabio SV](#), [Pileggi VN](#), [Vieira EM](#), [Souza JP](#).

### BACKGROUND:

The aim of this study was to determine whether PRENACEL (a bi-directional, mobile-phone based, short text message service (SMS)) increases the coverage of recommended antenatal care (ANC) practices.

### METHODS:

A parallel, cluster-randomized trial in which 20 public primary Health Care Units (PHCUs) were randomly allocated to the intervention (10 PHCUs) or control (10 PHCUs) group. The study population included pregnant women aged 18 or above with a gestational age of 20 weeks or less. Pregnant women receiving ANC in intervention PHCUs were invited through leaflets and posters to register in PRENACEL. Women who registered in PRENACEL received a

## Randomised trials in child health in developing countries 2017-18

weekly set of short text messages with health education and health promotion content related to pregnancy and childbirth and were also able to clarify ANC queries through SMS. All women received routine ANC. The primary outcome was the proportion of women with high ANC Score, a composite measure of coverage of recommended ANC practices. Chi-square or Fisher's exact tests and multivariate log-binomial regression were used to analyze the outcomes.

### RESULTS:

A total of 1210 eligible women received ANC in the participating PHCUs and took part of this study (770 in the intervention group and 440 in the control group). 20.4% (157/770) of intervention-group women registered in PRENACEL, but only 116 read all messages (73.9% of women who registered in PRENACEL, 116/157). The adjusted intention-to-treat analysis suggested no difference between intervention and control groups in the primary outcome (Adjusted Relative Risk (AdjRR): 1.05 (95% Confidence Interval (CI): 1.00-1.09). Both crude and adjusted per-protocol analysis suggested a positive effect of PRENACEL (Crude RR (95% CI): 1.14 (1.06-1.22), AdjRR (95% CI): 1.12 (1.05-1.21). The multivariate analysis also suggests that the PRENACEL group (women who read all SMS) had higher mean ANC score [48.5 ( $\pm$ 4.2) vs 45.2 ( $\pm$ 8.7),  $p < 0.01$ ], higher proportion of women with  $\geq 6$  ANC visits (96.9% vs. 84.8%,  $p = 0.01$ ), and higher rates of syphilis testing (40.5% vs. 24.8%,  $p = 0.03$ ) and HIV testing (46.6% vs. 25.7%,  $p < 0.01$ ) during ANC.

### CONCLUSIONS:

A bi-directional, mobile-phone based, short text message service is potentially useful to improve the coverage of recommended ANC practices, including syphilis and HIV testing.

<https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-017-0407-1>

[Am J Public Health](#). 2017 Dec;107(12):1944-1950. doi: 10.2105/AJPH.2017.304089. Epub 2017 Oct 19.

### [Text Messaging for Improving Antiretroviral Therapy Adherence: No Effects After 1 Year in a Randomized Controlled Trial Among Adolescents and Young Adults.](#)

[Linnemayr S](#), [Huang H](#), [Luoto J](#), [Kambugu A](#), [Thirumurthy H](#), [Haberer JE](#), [Wagner G](#), [Mukasa B](#).

### OBJECTIVES:

To assess the effectiveness of Short Message Service (SMS) reminder messages on antiretroviral and cotrimoxazole prophylaxis adherence among HIV-positive youths as well as the relative effectiveness of SMS with and without a response option.

### METHODS:

Eligible HIV-positive patients aged 15 to 22 years at 2 HIV clinics in Kampala, Uganda, participated in a year-long parallel individual-randomized controlled trial and were assigned in a 1-to-1-to-1 ratio to a weekly SMS message group, weekly SMS message with response option group, or a usual-care control group.

### RESULTS:

We enrolled 332 participants. Electronically measured mean adherence was 67% in the control group, 64% in the 1-way SMS group (95% confidence interval [CI] = 0.77, 1.14), and 61% in the 2-way SMS group (95% CI = 0.75, 1.12) in an intent-to-treat analysis. Results for secondary outcomes and complete-case analysis were similarly statistically insignificant across groups.

### CONCLUSIONS:

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Despite previous evidence that interventions using SMS reminders can promote antiretroviral therapy adherence, this study shows that they are not always effective in achieving behavior change. More research is needed to find out for whom, and under what conditions, they can be beneficial.

[Trials](#). 2017 Oct 11;18(1):475. doi: 10.1186/s13063-017-2213-z.

### [The added value of a mobile application of Community Case Management on referral, re-consultation and hospitalization rates of children aged under 5 years in two districts in Northern Malawi: study protocol for a pragmatic, stepped-wedge cluster-randomized controlled trial.](#)

[Hardy V](#), [O'Connor Y](#), [Heavin C](#), [Mastellos N](#), [Tran T](#), [O'Donoghue J](#), [Fitzpatrick AL](#), [Ide N](#), [Wu TJ](#), [Chirambo GB](#), [Muula AS](#), [Nyirenda M](#), [Carlsson S](#), [Andersson B](#), [Thompson M](#).

#### **BACKGROUND:**

There is evidence to suggest that frontline community health workers in Malawi are under-referring children to higher-level facilities. Integrating a digitized version of paper-based methods of Community Case Management (CCM) could strengthen delivery, increasing urgent referral rates and preventing unnecessary re-consultations and hospital admissions.

This trial aims to evaluate the added value of the Supporting LIFE electronic Community Case Management Application (SL eCCM App) compared to paper-based CCM on urgent referral, re-consultation and hospitalization rates, in two districts in Northern Malawi.

#### **METHODS/DESIGN:**

This is a pragmatic, stepped-wedge cluster-randomized trial assessing the added value of the SL eCCM App on urgent referral, re-consultation and hospitalization rates of children aged 2 months and older to up to 5 years, within 7 days of the index visit. One hundred and two health surveillance assistants (HSAs) were stratified into six clusters based on geographical location, and clusters randomized to the timing of crossover to the intervention using simple, computer-generated randomization. Training workshops were conducted prior to the control (paper-CCM) and intervention (paper-CCM + SL eCCM App) in assigned clusters. Neither participants nor study personnel were blinded to allocation. Outcome measures were determined by abstraction of clinical data from patient records 2 weeks after recruitment. A nested qualitative study explored perceptions of adherence to urgent referral recommendations and a cost evaluation determined the financial and time-related costs to caregivers of subsequent health care utilization. The trial was conducted between July 2016 and February 2017.

#### **DISCUSSION:**

This is the first large-scale trial evaluating the value of adding a mobile application of CCM to the assessment of children aged under 5 years. The trial will generate evidence on the potential use of mobile health for CCM in Malawi, and more widely in other low- and middle-income countries.

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2213-z>

## Newborn care

## Community-based newborn care

[Health Policy Plan](#). 2017 Oct 1;32(suppl\_1):i21-i32. doi: 10.1093/heapol/czx054.

### **Community-Based Interventions for Newborns in Ethiopia (COMBINE): Cost-effectiveness analysis.**

[Mathewos B](#), [Owen H](#), [Sitrin D](#), [Cousens S](#), [Degeffie T](#), [Wall S](#), [Bekele A](#), [Lawn JE](#), [Daviaud E](#).

About 87 000 neonates die annually in Ethiopia, with slower progress than for child deaths and 85% of births are at home. As part of a multi-country, standardized economic evaluation, we examine the incremental benefit and costs of providing management of possible serious bacterial infection (PSBI) for newborns at health posts in Ethiopia by Health Extension Workers (HEWs), linked to improved implementation of existing policy for community-based newborn care (Health Extension Programme). The government, with Save the Children/Saving Newborn Lives and John Snow, Inc., undertook a cluster randomized trial. Both trial arms involved improved implementation of the Health Extension Programme. **The intervention arm received additional equipment, support and supervision for HEWs to identify and treat PSBI.** In 2012, ~95% of mothers in the study area received at least one pregnancy or postnatal visit in each arm, an average of 5.2 contacts per mother in the intervention arm (4.9 in control). Of all visits, 79% were conducted by volunteer community health workers. HEWs spent around 9% of their time on the programme. The financial cost per mother and newborn was \$34 (in 2015 USD) in the intervention arm (\$27 in control), economic costs of \$37 and \$30, respectively. Adding PSBI management at community level was estimated to reduce neonatal mortality after day 1 by 17%, translating to a cost per DALY averted of \$223 or 47% of the GDP per capita, a highly cost-effective intervention by WHO thresholds. In a routine situation, the intervention programme cost would represent 0.3% of public health expenditure per capita and 0.5% with additional monthly supervision meetings. A platform wide approach to improved supervision including a dedicated transport budget may be more sustainable than a programme-specific approach. In this context, strengthening the existing HEW package is cost-effective and also avoids costly transfers to health centres/hospitals.

[https://academic.oup.com/heapol/article/32/suppl\\_1/i21/4061543](https://academic.oup.com/heapol/article/32/suppl_1/i21/4061543)

\*\*\* [Lancet Glob Health](#). 2017 Aug;5(8):e796-e806. doi: 10.1016/S2214-109X(17)30248-6.

### **Effect of provision of home-based curative health services by public sector health-care providers on neonatal survival: a community-based cluster-randomised trial in rural Pakistan.**

[Soofi S](#), [Cousens S](#), [Turab A](#), [Wasan Y](#), [Mohammed S](#), [Ariff S](#), [Bhatti Z](#), [Ahmed I](#), [Wall S](#), [Bhutta ZA](#).

#### **BACKGROUND:**

Although the effectiveness of community mobilisation and promotive care delivered by community health workers in reducing perinatal and neonatal mortality is well established, evidence in support of home-based neonatal resuscitation and infection management is mixed. We assessed the effectiveness of adding training in neonatal bag and mask resuscitation and oral antibiotic therapy for suspected neonatal infections to a basic preventive and promotive interventions package delivered by public sector community-based lady health workers (LHWs) in rural Pakistan.

#### **METHODS:**



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We did a cluster-randomised controlled trial in two subdistricts of Naushahro Feroze in rural Sindh, Pakistan, between April 15, 2009, and Dec 10, 2012. LHWs, trained in basic newborn resuscitation and in recognition and treatment (with oral amoxicillin) of suspected neonatal respiratory infections, were linked with traditional birth attendants and encouraged to attend home births. Control clusters received routine care through the existing national programme. The primary outcome was all-cause neonatal mortality. Independent data collection teams recorded data for all pregnancies and their outcomes, morbidity, mortality, and household practices related to maternal and newborn care.

### FINDINGS:

Of the 27 randomised clusters with functional LHW programmes, 13 were allocated to the intervention group (n=242 749) and 14 to the control group (n=256 985). **In the intervention group, LHWs did 80% of the planned community mobilisation sessions, but were able to attend only 1184 (14%) of 8425 deliveries and 4318 (25%) of 17 288 neonatal visits within 72 h of birth (p<0.0001 for both variables compared with the control group). The neonatal mortality rate was 42 deaths per 1000 livebirths in intervention clusters compared with 55 per 1000 in the control group (risk ratio 0.80, 95% CI 0.68-0.93; p=0.005).**

### INTERPRETATION:

The reduction in neonatal mortality in intervention clusters occurred against a background of improvements in domiciliary practices for maternal and newborn care. However, the poor reach of LHWs in accessing newborn infants at birth and in the early postnatal period underscores the limitations of tasking community health workers in public sector programmes working in similar circumstances with such complex interventions. Such community-based interventions in health systems should be accompanied by concerted efforts to improve quality of care in facilities and referral systems.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S2214109X17302486?returnurl=https%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2214109X17302486%3Fshowall%3Dtrue&referrer=https%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Health Aff \(Millwood\)](#). 2017 Nov;36(11):1947-1955. doi: 10.1377/hlthaff.2017.0553.

### **Mentor Mothers Program Improved Child Health Outcomes At A Relatively Low Cost In South Africa.**

[Wynn A](#), [Rotheram-Borus MJ](#), [Leibowitz AA](#), [Weichle T](#), [Roux IL](#), [Tomlinson M](#).

In light of South Africa's high prenatal HIV prevalence and infant mortality rate, a cluster randomized controlled trial was conducted to evaluate an intervention called Philani+, which used community health workers (known as Mentor Mothers) to deliver pre- and postnatal home visits in Cape Town, South Africa, to improve maternal and child health. We assessed the costs and benefits of this intervention and made comparisons with other scenarios that depicted increased capacity and provision of nurse-delivered care. The recurrent cost of the twenty-four-month intervention was US\$80,001. The major health outcomes analyzed were differences in the proportion of infants who were low birthweight, stunted, and suboptimally breastfed between intervention and control groups. Each case of low birthweight averted cost US\$2,397; of stunted growth, US\$2,454; and of suboptimal breastfeeding, US\$1,618. Employment of community health workers was cost saving compared to that of nurses. Philani+ improved child health at a relatively low cost, considering the health system costs associated with low birthweight and undernutrition. The model could be suitable for replication in low-resource settings to improve child health in other countries.

[PLoS One](#). 2017 Dec 20;12(12):e0189677. doi: 10.1371/journal.pone.0189677. eCollection 2017.

**[Identifying maternal and infant factors associated with newborn size in rural Bangladesh by partial least squares \(PLS\) regression analysis.](#)**

[Kabir A](#), [Rahman MJ](#), [Shamim AA](#), [Klemm RDW](#), [Labrique AB](#), [Rashid M](#), [Christian P](#), [West KP Jr.](#)

Birth weight, length and circumferences of the head, chest and arm are key measures of newborn size and health in developing countries. We assessed maternal socio-demographic factors associated with multiple measures of newborn size in a large rural population in Bangladesh using partial least squares (PLS) regression method. PLS regression, combining features from principal component analysis and multiple linear regression, is a multivariate technique with an ability to handle multicollinearity while simultaneously handling multiple dependent variables. We analyzed maternal and infant data from singletons (n = 14,506) born during a double-masked, cluster-randomized, placebo-controlled maternal vitamin A or  $\beta$ -carotene supplementation trial in rural northwest Bangladesh. PLS regression results identified numerous maternal factors (parity, age, early pregnancy MUAC, living standard index, years of education, number of antenatal care visits, preterm delivery and infant sex) significantly ( $p < 0.001$ ) associated with newborn size. Among them, preterm delivery had the largest negative influence on newborn size (Standardized  $\beta = -0.29 - -0.19$ ;  $p < 0.001$ ). Scatter plots of the scores of first two PLS components also revealed an interaction between newborn sex and preterm delivery on birth size. PLS regression was found to be more parsimonious than both ordinary least squares regression and principal component regression. It also provided more stable estimates than the ordinary least squares regression and provided the effect measure of the covariates with greater accuracy as it accounts for the correlation among the covariates and outcomes. Therefore, PLS regression is recommended when either there are multiple outcome measurements in the same study, or the covariates are correlated, or both situations exist in a dataset.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0189677>

[Health Policy Plan](#). 2017 Oct 1;32(suppl\_1):i53-i63. doi: 10.1093/heapol/czw112.

**[South-Africa \(Goodstart III\) trial: community-based maternal and newborn care economic analysis.](#)**

[Daviaud E](#), [Nkonki L](#), [Ijumba P](#), [Doherty T](#), [Lawn JE](#), [Owen H](#), [Jackson D](#), [Tomlinson M.](#)

In light of South Africa's generalized HIV/AIDS epidemic coupled with high infant mortality, we undertook a cluster Randomized Control Trial (2008-10) assessing the effect of Community Health Worker (CHW) antenatal and postnatal home visits on, amongst other indicators, levels of HIV-free survival, and exclusive and appropriate infant feeding at 12 weeks. Cost and time implications were calculated, by assessing the 15 participating CHWs, using financial records, mHealth and interviews. Sustainability and scalability were assessed, enabling identification of health system issues. The majority (96%) of women in the community received an average of 4.1 visits (target seven). The paid, single purpose CHWs spent 13 h/week on the programme. The financial cost per mother amounted to \$94 (\$23 per home visit). Modelling target coverage (95% mothers, seven visits) and increased efficiency showed that if CHWs spent 25 h/week on

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the programme, the number of CHWs required would decrease from 15 to 12. The intervention almost doubled exclusive breastfeeding (EBF) at 12 weeks and showed a 6% relative increase in EBF with each additional CHW visit. Home visit programmes improve access and prevention but are not an inexpensive alternative: the observed cost per home visit is twice that of a clinic visit and in target/efficiency scenario decreases to 70% of the cost of a clinic visit. Ensuring sustainability requires optimizing the design of programmes and deployment of human resources, whilst maintaining impact. However, low remuneration of CHWs leads to shorter working hours, low motivation and sub-optimal coverage even in a situation with well-resourced supervision. The community-based care programme in South-Africa is based on multi-purpose CHWs, its cost and impact should be compared with results from this study. Quality of support for multi-purpose CHWs may be the biggest challenge to address to achieving higher efficiency of community-based services.

[https://academic.oup.com/heapol/article/32/suppl\\_1/i53/4283076](https://academic.oup.com/heapol/article/32/suppl_1/i53/4283076)

[Trials](#). 2017 Jul 12;18(1):322. doi: 10.1186/s13063-017-2050-0.

### [Efficacy of umbilical cord cleansing with a single application of 4% chlorhexidine for the prevention of newborn infections in Uganda: study protocol for a randomized controlled trial.](#)

[Nankabirwa V](#), [Tylleskär T](#), [Tumuhamyé J](#), [Tumwine JK](#), [Ndeezi G](#), [Martines JC](#), [Sommerfelt H](#).

#### **BACKGROUND:**

Yearly, nearly all the estimated worldwide 2.7 million neonatal deaths occur in low- and middle-income countries. Infections, including those affecting the umbilical cord (omphalitis), are a significant factor in approximately a third of these deaths. In fact, the odds of all-cause mortality are 46% higher among neonates with omphalitis than in those without. **Five large randomized controlled trials in Asia and Sub-Saharan Africa (SSA) have examined the effect of multiple cord stump applications with 4% chlorhexidine (CHX) for at least 7 days on the risk of omphalitis and neonatal death.** These studies, all community-based, show that multiple CHX applications reduced the risk of omphalitis. Of these trials, only one study from South Asia (the Bangladeshi study) and none from Africa examined the effect of a single application of CHX as soon as possible after birth. In this Bangladeshi trial, CHX led to a reduction in the risk of mild-moderate omphalitis and neonatal death. It is important, in an African setting, to explore the effect of a single application among health-facility births. **A single application is programmatically much simpler to implement than daily applications for 7 days.** Therefore, our study compares umbilical cord cleansing with a single application of 4% CHX at birth with dry cord care among Ugandan babies born in health facilities, on the risk of omphalitis and severe neonatal illness.

#### **METHODS:**

The CHX study is a facility-based, individually randomized controlled trial that will be conducted among 4760 newborns in Uganda. The primary outcomes are severe illness and omphalitis during the neonatal period. Analysis will be by intention-to-treat.

#### **DISCUSSION:**

This study will provide novel evidence, from a Sub-Saharan African setting, of the effect of umbilical cord cleansing with a single application of 4% CHX at birth and identify modifiable risk factors for omphalitis.

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2050-0>

## Neonatal intensive care – general

[J Trop Pediatr](#). 2017 Oct 1;63(5):374-379. doi: 10.1093/tropej/fmw099.

### **Umbilical Venous Catheter Versus Peripherally Inserted Central Catheter in Neonates: A Randomized Controlled Trial.**

[Dongara AR](#), [Patel DV](#), [Nimbalkar SM](#), [Potana N](#), [Nimbalkar AS](#).

Peripherally inserted central catheter (PICC) and umbilical venous catheter (UVC) in terms of success rate, complications, cost and time of insertion in neonatal intensive care were compared. Neonates requiring vascular access for minimum 7 days were included. Sample size of 72 per group was determined. Trial was registered at Clinical Trials Registry of India (CTRI/2015/02/005529). Success rates of the UVC and PICC were 68.1% and 65.3%, respectively ( $p = 0.724$ ). Mean (SD) time needed for PICC and UVC insertion was 34.13 (34.69) and 28.31 (17.19) min, respectively ( $p = 0.205$ ). Mean (SD) cost of PICC insertion vs. UVC insertion was 60.9 (8.6) vs. 11.9 (8.7) US dollars ( $p < 0.0001$ ). Commonest cause for failure of UVC was displacement [6 (8.3%)] and that for PICC was blockage [9 (12.5%)].

#### **CONCLUSIONS:**

UVC is a cheaper alternative to PICC, with similar success rate, short-term complications and time needed for insertion.

<https://academic.oup.com/tropej/article/63/5/374/2888426>

## Low birth weight and prematurity

[J Hum Lact](#). 2017 Aug;33(3):533-539. doi: 10.1177/0890334416685072. Epub 2017 Feb 2.

### **Randomized Controlled Trial on Effect of Intermittent Early Versus Late Kangaroo Mother Care on Human Milk Feeding in Low-Birth-Weight Neonates.**

[Jayaraman D](#)<sup>1</sup>, [Mukhopadhyay K](#)<sup>1</sup>, [Bhalla AK](#)<sup>1</sup>, [Dhaliwal LK](#)<sup>2</sup>.

#### **BACKGROUND:**

Breastfeeding at discharge among sick low-birth-weight (LBW) infants is low despite counseling and intervention like kangaroo mother care (KMC). Research aim: The aim was to study the effects of early initiation of KMC on exclusive human milk feeding, growth, mortality, and morbidities in LBW neonates compared with late initiation of KMC during the hospital stay and postdischarge.

#### **METHODS:**

A randomized controlled trial was conducted in level 2 and 3 areas of a tertiary care neonatal unit over 15 months. **Inborn neonates weighing 1 to 1.8 kg and hemodynamically stable were randomized to receive either early KMC, initiated within the first 4 days of life, or late KMC (off respiratory support and intravenous fluids).** Follow-up was until 1 month postdischarge. Outcomes were proportion of infants achieving exclusive human milk feeding and direct breastfeeding, growth, mortality and morbidities during hospital stay, and postdischarge feeding and KMC practices until 1 month.

#### **RESULTS:**

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The early KMC group ( n = 80) achieved significantly higher exclusive human milk feeding (86% vs. 45%, p < .001) and direct breastfeeding (49% vs. 30%, p = .021) in hospital and almost exclusive human milk feeding (73% vs. 36%, p < .001) until 1 month postdischarge than the late KMC group ( n = 80). The incidence of apnea (11.9% vs. 20%, p = .027) and recurrent apnea requiring ventilation (8.8% vs. 15%, p = .02) were significantly reduced in the early KMC group. There was no significant difference in mortality, morbidities, and growth during the hospital stay and postdischarge.

### CONCLUSION:

Early KMC significantly increased exclusive human milk feeding and direct breastfeeding in LBW infants.

<http://journals.sagepub.com/doi/pdf/10.1177/0890334416685072>

[J Matern Fetal Neonatal Med.](#) 2017 Jul;30(14):1659-1665. doi: 10.1080/14767058.2016.1220531. Epub 2016 Aug 30.

### To compare growth outcomes and cost-effectiveness of "Kangaroo ward care" with "intermediate intensive care" in stable extremely low birth weight infants: randomized control trial.

[Sharma D](#), [Murki S](#), [Pratap OT](#).

### AIMS:

To compare growth outcome and cost-effectiveness of "Kangaroo ward care" (KWC) with "Intermediate intensive care" (IIC) in stable extremely low birth weight (ELBW) infants.

### MATERIALS AND METHODS:

This is secondary analysis of the study and we analyzed 62 ELBW infants, 33 were randomized to KWC and 29 to IIC once the infant reached a weight of 1150 g. Infants in the KWC group were shifted to the Kangaroo ward immediately after randomization and in the IIC group received IIC care till they attain a weight of 1250 g before shifting to Kangaroo ward.

### RESULTS:

The gain in weight (g/day), length (cm/week), and head circumference (cm/week) were comparable between the two groups. The mean weight, length, and head circumference were comparable at term gestational age. The infants in KWC group were shifted five days earlier to Kangaroo ward when compared to IIC group. The cost-effective analysis using "top-down" and "bottom-up" accounting method showed that there was significant reduction of hospital and parents expenditure in KWC group (p < 0.001) with approximate saving of 452 USD for each patient in the KWC group.

### CONCLUSION:

Early shifting of ELBW infants for KWC is very efficacious and cost-effective intervention when compared to IIC. (CTRI/2014/05/004625).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944513/>

[J Matern Fetal Neonatal Med.](#) 2017 Nov;30(21):2572-2577. doi: 10.1080/14767058.2016.1256992. Epub 2016 Nov 29.

**In resource limited areas complete enteral feed in stable very low birth weight infants (1000-1500 g) started within 24 h of life can improve nutritional outcome.**

Bora R, Murthy NB.

**OBJECTIVE:**

To evaluate feasibility of complete enteral feed (CEF) in stable very low birth weight neonates weighing 1000-1500 g.

**SUBJECTS AND INTERVENTIONS:**

**One hundred and three stable very low birth weight (vlbw) neonates (1000-1500 g) irrespective of gestational age (GA) were randomized to receive either CEF with expressed breast milk (EBM) (n = 51) or minimal enteral feed (MEF) supplemented with intravenous fluid (IVF). (MEF) (n = 52).** Feed volume was increased progressively. Primary outcome measures were feed intolerance (FI) and necrotizing enterocolitis (NEC) in first 21 days of life or discharge from NICU, whichever was earlier. Secondary outcome measures were the time taken to reach calorie intake of 110 kcal/kg/D and regain of birthweight.

**RESULTS:**

FI was observed in n = 12 (23.53%) in CEF group versus n = 6 (11.53%) in MEF group (p = 0.1264). NEC was observed in 4 (7.8%) in CEF group versus 1(1.9%) in MEF group (p = 0.16) and results were comparable in both groups. Birthweight regain (10.6 ± 1.6 days versus 11.8 ± 1.6 days, p = 0.038), NICU discharge (11.7 ± 2.6 days versus 13.0 ± 3.45 days, p = 0.038) and time to reach 110 kcal/kg/day (9.571 ± 1.458 days versus 10.833 ± 1.655 days, p = 0.001) were significantly earlier in CEF compared to MEF group.

**CONCLUSION:**

Complete enteral feeds started within 24 h of life is feasible in vlbw neonates.

J Perinat Med. 2017 Nov 27;45(8):953-957. doi: 10.1515/jpm-2015-0375.

**Is early breast milk fortification more effective in preterm infants?: a clinical trial.**

Alizadeh Taheri P, Sajjadian N, Asgharyan Fargi M, Shariat M.

**OBJECTIVE:**

Breast feeding alone does not provide adequate nutrition for growth in preterm infants; therefore, fortifiers are added when over 70-80 cc/kg/day of breast milk is tolerated. As there are few studies comparing early and late breast milk fortification, the following study was conducted.

**STUDY DESIGN:**

This double-blind clinical trial was performed on 80 preterm infants (gestational age of 28-34 weeks, birth weight <2 kg). The newborns were randomly divided into two groups to receive either early or late fortification. The primary and secondary outcomes were the difference in growth indices and complications (including feeding intolerance, necrotizing enterocolitis (NEC), and septicemia) between the two groups, respectively.

**RESULTS:**

Both groups showed increases in growth indices; however, there was no statistically significant difference in increments of growth indices and complications between the two groups.

**CONCLUSION:**

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Our findings suggest that early fortification from the first feeding in neonates with exclusive breast feeding did not improve growth in the first 4 weeks in preterm neonates in comparison with late fortification; so early fortification may not be cost effective.

<https://www.researchgate.net/publication/308699367> Is early breast milk fortification more effective in preterm infants a clinical trial

[J Matern Fetal Neonatal Med.](#) 2017 Aug 31:1-9. doi: 10.1080/14767058.2017.1370704. [Epub ahead of print]

### [Role of delayed cord clamping in prevention of necrotizing enterocolitis in preterm neonates: a systematic review.](#)

[Garg BD](#), [Kabra NS](#), [Bansal A](#).

#### **BACKGROUND:**

Necrotizing enterocolitis (NEC) is one of the leading causes of neonatal mortality and morbidity particularly in very-low-birth-weight (VLBW) neonates. The incidence of NEC varies across countries and neonatal centers in between 7% and 14%.

#### **AIMS:**

**The aim of this study is to evaluate the role of delayed cord clamping (DCC) for prevention of NEC in preterm neonates.**

#### **METHOD:**

The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, ongoing clinical trials, and abstract of conferences.

#### **RESULTS:**

This review included six RCTs that fulfilled inclusion criteria. **There was statistically significant reduction in the incidence of NEC in DCC group (12.2% versus 20.6%; risk ratio (RR) 0.59; 95% CI 0.37-0.94; p = .02; number needed to treat (NNT) 12). However, mortality due to any cause before hospital discharge was not statistically significant (RR 0.80; 95% CI 0.33-2.00; p = .64).**

#### **CONCLUSION:**

The role of DCC in the prevention of NEC is supported by the current evidences. However, given the small sample sizes and other limitations of these studies, current evidences are not sufficient. We need large high-quality trials, with sufficient power to reliably assess clinically relevant differences in important outcomes.

[Indian J Pediatr.](#) 2018 Mar;85(3):172-178. doi: 10.1007/s12098-017-2490-2. Epub 2017 Nov 4.

### [Effect of Placental Transfusion on Iron Stores in Moderately Preterm Neonates of 30-33 weeks Gestation.](#)

[Das B](#), [Sundaram V](#), [Kumar P](#), [Mordi WT](#), [Dhaliwal LK](#), [Das R](#).

#### **OBJECTIVE:**

To assess the effect of placental transfusion by delayed cord clamping (DCC) of 60 s or cord milking (CM) on serum ferritin levels at hospital discharge and 3 mo of postmenstrual age

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(PMA) in preterm neonates of 30 to 33 wk gestation in comparison to early cord clamping (ECC) within 10 s.

### **METHODS:**

This mixed longitudinal study was conducted in moderately preterm neonates of 30 to 33 wk gestation born in a level III unit in Northern India with the study sample nested within a randomized controlled trial on placental transfusion. **Intervention was delayed cord clamping for 60 s or cord milking compared with early cord clamping (within 10 s). Primary outcome measure was serum ferritin levels at discharge.** Secondary outcome measures were serum ferritin levels at 3 mo PMA, incidence of anemia, need for blood transfusion and incidence of iron deficiency by 3 mo PMA.

### **RESULTS:**

Out of the 215 randomly chosen infants, serum ferritin levels were estimated at least at one time point (at discharge or at 3 mo PMA) in 197 neonates [placental transfusion - 107; early cord clamping - 90]. Amongst them, ferritin level was estimated at discharge in 141 neonates, at 3 mo PMA in 76 neonates and at both time points in 20 neonates. Median (IQR) serum ferritin ( $\mu\text{g/L}$ ) at discharge was significantly higher in placental transfusion group in comparison to the ECC group [399 (309,600) ( $n = 79$ ) vs. 254 (190,311) ( $n = 62$ );  $p < 0.001$ ]. Median (IQR) ferritin level at 3 mo PMA was not different between the study groups [20 (14,57) ( $n = 39$ ) vs. 24 (8,52) ( $n = 37$ );  $p = 0.2$ ]. **The incidence of anemia by 3 mo PMA was significantly lesser in the placental transfusion group.** No difference was observed in anemia requiring blood transfusion and iron deficiency by 3 mo PMA between the groups.

### **CONCLUSIONS:**

In 30 to 33 wk preterm neonates, placental transfusion resulted in significantly higher serum ferritin at discharge in comparison to early cord clamping. However, this benefit did not persist till 3 mo PMA.

<https://link.springer.com/content/pdf/10.1007%2Fs12098-017-2490-2.pdf>

[J Perinatol](#). 2018 May;38(5):496-504. doi: 10.1038/s41372-018-0064-4. Epub 2018 Feb 6.

### **Placental transfusion in preterm neonates of 30-33 weeks' gestation: a randomized controlled trial.**

[Das B](#), [Sundaram V](#), [Tarnow-Mordi W](#), [Ghadge A](#), [Dhaliwal LK](#), [Kumar P](#).

### **OBJECTIVES:**

To compare effect of placental transfusion by delayed cord clamping (DCC) or cord milking (CM) with early cord clamping (ECC) on a composite of mortality or abnormal neurological status at 40 weeks' post-menstrual age (PMA) and 24-30 months' chronological age in neonates of 30-33 weeks' gestation.

### **STUDY DESIGN:**

Randomized, controlled trial.

### **OUTCOMES:**

A composite of mortality or abnormal neurological status at 40 weeks PMA and survival free of neurodevelopmental abnormalities at 24-30 months' chronological age.

### **RESULTS:**

A total of 461 neonates were randomized to placental transfusion ( $n = 233$ ) or to ECC ( $n = 228$ ). Among those assigned to placental transfusion group, 173 underwent DCC while in the remaining 60, CM was done. Incidence of mortality or abnormal neurological status at 40 weeks PMA (43 (18%) vs 35 (15%), RR (95% CI) 1.2 (0.8, 1.8),  $p = 0.4$ ) and survival free of



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neurodevelopmental impairment at 24-30 months of chronological age (99 (47%) vs. 100 (50%); RR (95% CI): 0.9 (0.8, 1.2); P = 0.9) was similar between the study groups. The placental transfusion group showed a trend towards lower incidence of necrotizing enterocolitis.

### CONCLUSION:

In 30-33 weeks' gestation preterm neonates, placental transfusion as compared to early cord clamping resulted in similar mortality or abnormal neurological status at 40 weeks PMA and at 24-30 months of chronological age.

<https://www.nature.com/articles/s41372-018-0064-4>

*J Trop Pediatr.* 2018 Jan 22. doi: 10.1093/tropej/fmy001. [Epub ahead of print]

### Effect of Antenatal Steroids on Respiratory Morbidity of Late Preterm Newborns: A Randomized Controlled Trial.

Ontela V<sup>1</sup>, Dorairajan G<sup>1</sup>, Bhat VB<sup>2</sup>, Chinnakali P<sup>3</sup>.

### OBJECTIVE:

The objective of this article was to study the effect of antenatal dexamethasone on the respiratory morbidity of late preterm newborns.

### STUDY DESIGN:

A randomized controlled trial, conducted in Obstetrics and Gynecology Department in collaboration with Neonatology department at JIPMER, India. In total, 155 women were studied in each group. Intention to treat analysis and per protocol analysis were done.

### RESULTS:

Overall 31 (10%) newborns were admitted to intensive care unit. The composite respiratory morbidity (defined as respiratory distress syndrome and/or transient tachypnea of newborn) was observed in 64 (41.6%) infants in the study and 56 (36.2%) infants in the control group. On multivariable-adjusted analysis, use of steroids was not found to be associated with decrease in composite respiratory morbidity [adjusted relative risk 0.91 (95% confidence interval: 0.7-1.2)].

### CONCLUSIONS:

Antenatal dexamethasone does not reduce the composite respiratory morbidity of babies born vaginally or by emergency cesarean to women with late preterm labor.

<https://academic.oup.com/tropej/advance-article/doi/10.1093/tropej/fmy001/4819249>

*J Pediatr.* 2018 Jun 1. pii: S0022-3476(18)30626-7. doi: 10.1016/j.jpeds.2018.04.072. [Epub ahead of print]

### Gastric Residual Volume in Feeding Advancement in Preterm Infants (GRIP Study): A Randomized Trial.

Singh B, Rochow N, Chessell L, Wilson J, Cunningham K, Fusch C, Dutta S, Thomas S.

### OBJECTIVE:

To evaluate the effect of not relying on prefeeding gastric residual volumes to guide feeding advancement on the time to reach full feeding volumes in preterm infants, compared with

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routine measurement of gastric residual volumes. We hypothesized that not measuring prefeeding gastric residual volumes can shorten the time to reach full feeds.

### STUDY DESIGN:

In this single-center, randomized, controlled trial, we included gavage fed preterm infants with birth weights (BW) 1500-2000 g who were enrolled within 48 hours of birth. Exclusion criteria were major congenital malformations, asphyxia, and BW below the third percentile. In the study group, the gastric residual volume was measured only in the presence of bloody aspirates, vomiting, or an abnormal abdominal examination. In the control group, gastric residual volume was assessed routinely, and feeding advancement was based on the gastric residual volume. The primary outcome was the time to reach feeding volumes of 120 mL/kg per day. Secondary outcomes were time to regain BW, episodes of feeding interruptions, sepsis, and necrotizing enterocolitis.

### RESULTS:

Eighty-seven infants were enrolled. There were no differences between the study and control groups with respect to time to reach full feeds (6 days [95% CI, 5.5-6.5] vs 5 days [95% CI, 4.5-5.5];  $P = .82$ ), time to regain BW, episodes of feeding interruptions, or sepsis. Two infants in the control group developed necrotizing enterocolitis.

### CONCLUSIONS:

Avoiding routine assessment of gastric residual volume before feeding advancement did not shorten the time to reach full feeds in preterm infants with BW between 1500 and 2000 g.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0022347618306267?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0022347618306267%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

*Neonatology*. 2017;112(4):347-353. doi: 10.1159/000477999. Epub 2017 Aug 3.

### Saline Enemas versus Glycerin Suppositories to Promote Enteral Feeding in Premature Infants: A Pilot Randomized Controlled Trial.

Ibrahim T, Li Wei C, Bautista D, Sriram B, Xiangzhen Fay L, Rajadurai VS.

### BACKGROUND:

Meconium retention is associated with feeding intolerance. Trials using glycerol and Gastrografin to expedite the evacuation of meconium have failed to generate clinically valid results for efficacy and safety.

### OBJECTIVE:

We assessed the feasibility of aggressive meconium evacuation with saline rectal washout (RW) in very-low-birth-weight infants to reduce the time it took them to reach full enteral feeds.

### METHODS:

We conducted an open-label, pilot, randomized controlled trial (RCT) (birth weight stratified, i.e., to 750-999 g and 1,000-1,500 g) of early aggressive meconium evacuation with twice-daily normal saline RW compared to conventional management with glycerin suppositories (GS), until full enteral feeds (110 mL/kg/day) were reached. Primary outcome was time to reach full enteral feeds. Safety, process, and secondary efficacy outcomes were also evaluated.

### RESULTS:

Sixty-one infants were randomized, 28 to RW and 33 to GS. The process and feasibility outcomes were met. RW was found to be safe; none of the RW-randomized infants developed necrotizing enterocolitis ( $\geq$  stage II) or complications secondary to RW. Evidence of efficacy was supported: in the 750-999 g stratum ( $n = 15$ ), the median time to full enteral feeds was

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shorter with RW (11.0 days, 95% CI: 10.4-11.6) than with GS (15.6 days, 95% CI: 13.0-18.2) by a reduction of 4.6 days ( $p = 0.027$ ). In the 1,000-1,500 g stratum ( $n = 46$ ), there was no evidence of benefit: RW 10.2 days (95% CI 8.3-12.1) and GS 10.1 days (95% CI 9.3-10.9,  $p = 0.304$ ).

### CONCLUSION:

Our protocol was feasible and an adequately powered RCT is required to confirm the findings of this trial.

[J Trop Pediatr.](#) 2018 Mar 23. doi: 10.1093/tropej/fmy012. [Epub ahead of print]

### [An Open-label Randomized Controlled Trial to Compare Weight Gain of Very Low Birth Weight Babies with or without Addition of Coconut Oil to Breast Milk.](#)

[Arun S](#), [Kumar M](#), [Paul T](#), [Thomas N](#), [Mathai S](#), [Rebekah G](#), [Thomas N](#).

### BACKGROUND:

Nutritional guidelines involving the feeding of very low birth weight babies (VLBW) recommend addition of Human Milk Fortifiers to breast milk. Owing to financial constraints, it is a practice in low- and middle-income countries (LMIC) to add coconut oil to aid better weight gain. There are inadequate data on improvement of growth parameters with oral coconut oil supplementation of breast milk.

### METHODS:

In this randomized controlled trial, we measured growth parameters and body composition of 60 babies who received either breast milk with coconut oil or breast milk alone. Randomization was stratified according to intrauterine growth appropriate for gestational age ( $n = 30$ ) and small for gestational age ( $n = 30$ ).

### RESULTS:

There was no difference in weight gain between the two groups. **The weight gain velocity was  $15 \pm 3.6$  and  $14.4 \pm 3.4$  g/kg/day ( $p$  value = 0.49) in the breast milk alone and in the breast milk with coconut oil group, respectively.** There was no difference in increase in head circumference and length. Triceps skinfold thickness ( $n = 56$ ) was similar in both groups, but subscapular skinfold thickness was significantly more in the coconut oil group. Total body fat percentage did not differ between the groups ( $25.2 \pm 4.3$  vs.  $25.5 \pm 4.3\%$ ,  $p = 0.79$ ).

### CONCLUSION:

Oral supplementation of coconut oil along with breast milk did not increase growth parameters or result in change in body composition in very low birth weight (VLBW) babies.

<https://academic.oup.com/tropej/advance-article/doi/10.1093/tropej/fmy012/4951827>

[J Matern Fetal Neonatal Med.](#) 2018 Sep;31(17):2349-2366. doi: 10.1080/14767058.2017.1342797. Epub 2017 Jun 30.

### [Role of amino acid supplementation in the prevention of necrotizing enterocolitis in preterm neonates - a review of current evidences.](#)

[Garg BD](#), [Kabra NS](#).

### BACKGROUND:

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Necrotizing enterocolitis (NEC) is one of the most common acute and fatal gastrointestinal emergency in very low birth weight (VLBW) preterm neonates with mortality range from 15 to 30%. NEC is likely due to multifactorial process such as oxidative injury, ischemic necrosis, and over-reactive inflammatory response to intestinal microbes.

### AIMS:

To evaluate the role of amino acid supplementation for reduction of neonatal NEC in preterm neonates.

### METHOD:

The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Web of Science, Scopus, Index Copernicus, African Index Medicus (AIM), Thomson Reuters (ESCI), Chemical Abstracts Service (CAS) and other database.

### RESULTS:

This review included 15 RCTs that fulfilled inclusion criteria. The total neonates enrolled in these different RCT are 3424 (amino acid group 1711 and control 1713). Almost all participating neonates were of VLBW or extremely low birth weight (ELBW). In two trials, birth weight was between 1500-2000 grams. The intervention was started within first few days after birth and continued up to 30th day of postnatal age in most of the trials. In two trials, intervention was continued up to 120th day of postnatal age. Arginine, glutamine and N-acetyl cysteine (NAC) were used at the dose of 1.5 mol/kg/day (261 mg/kg/day), 0.3 grams/kg/day and 16-32 mg/kg/day, respectively.

### CONCLUSION:

**Role of amino acid in the prevention of neonatal NEC is not exclusively supported by the current evidence.** Only three studies were able to show reduction in the incidence of NEC with amino acid supplementation (arginine, glutamine), and the remaining studies did not report any positive effect. Amino acid supplementation was not associated with significant reduction in mortality due to any causes. However, arginine supplementation was associated with significant reduction in mortality due to NEC. Two studies on glutamine were reported significant reduction in the incidence of invasive infection. Only one study reported significant positive effects on growth parameters and less time to reach full enteral feeds. None of the studies showed any effect on the duration of hospital stay.

[Arch Dis Child Fetal Neonatal Ed.](#) 2017 Sep;102(5):F389-F394. doi: 10.1136/archdischild-2016-311548. Epub 2017 Jan 13.

### **Prophylactic propranolol for prevention of ROP and visual outcome at 1 year (PreROP trial).**

[Sanghvi KP<sup>1</sup>](#), [Kabra NS<sup>2</sup>](#), [Padhi P<sup>2</sup>](#), [Singh U<sup>1</sup>](#), [Dash SK<sup>2</sup>](#), [Avasthi BS<sup>2</sup>](#).

### OBJECTIVE:

To evaluate the role of prophylactic propranolol in the prevention of retinopathy of prematurity (ROP) in infants  $\leq 32$  weeks of gestational age and their visual outcome at 1 year of corrected gestational age.

### DESIGN:

Randomised double blind placebo controlled trial, parallel group enrolment with allocation ratio of 1:1.

### SETTINGS:

Two level III neonatal intensive care units.

### PARTICIPANTS:

109 preterm neonates of  $\leq 32$  weeks of gestation with postnatal age  $\leq 8$  days old.

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### **INTERVENTION:**

*Study group:* Infants with gestational age between 26 and 32 weeks were started on propranolol prophylaxis (0.5 mg/kg/dose every 12 hours) on seventh completed day of life, till a corrected gestational age of 37 weeks or complete vascularisation of retina whichever was later. *Control group* infants received a placebo.

### **OUTCOME MEASURES:**

*Primary:* ROP of all grades; *Secondary:* evaluation of complications due to propranolol, ROP needing treatment with laser and/or antivascular endothelial growth factor (anti-VEGF) and visual outcome at 12 months corrected age.

### **RESULTS:**

Prophylactic propranolol in the prescribed dose of 1 mg/kg/day showed a decreasing trend in the incidence of ROP (56.8% vs 68.6%;  $p=0.39$ ), need for laser therapy (21.56% vs 31.37%;  $p=0.37$ ), treatment with anti-VEGF (3.92% vs 15.68%;  $p=0.09$ ) or visual outcomes at 1 year in the study and control groups, respectively, though these reductions were not statistically significant. Decreasing trends favouring propranolol in all other ROP-related outcomes were also noted in the study group.

### **CONCLUSIONS:**

Prophylactic propranolol in the prescribed dose of 1 mg/kg/day showed a decreasing trend in all outcomes of ROP though statistically not significant.

<https://fn.bmj.com/content/fetalneonatal/102/5/F389.full.pdf>

[Indian Pediatr.](#) 2018 Apr 15;55(4):292-296. Epub 2018 Feb 9.

### **Pain Control Interventions in Preterm Neonates: A Randomized Controlled Trial.**

[Shukla VV](#), [Bansal S](#), [Nimbalkar A](#), [Chapla A](#), [Phatak A](#), [Patel D](#), [Nimbalkar S](#).

### **OBJECTIVE:**

To compare individual efficacy and additive effects of pain control interventions in preterm neonates.

### **DESIGN:**

Randomized controlled trial.

### **SETTING:**

Level-3 University affiliated neonatal intensive care unit.

### **PARTICIPANTS:**

200 neonates (26-36 wk gestational age) requiring heel-prick for bedside glucose assessment. Exclusion criteria were neurologic impairment and critical illness precluding study interventions.

### **INTERVENTION:**

Neonates were randomly assigned to Kangaroo mother care with Music therapy, Music therapy, Kangaroo Mother care or Control (no additional intervention) groups. All groups received expressed breast milk with cup and spoon as a baseline pain control intervention.

### **MAIN OUTCOME MEASURES:**

Assessment of pain using Premature Infant Pain Profile (PIPP) score on recorded videos.

### **RESULTS:**

The mean (SD) birth weight and gestational age of the neonates was 1.9 (0.3) kg and 34 (2.3) wk, respectively. Analysis of variance showed significant difference in total PIPP score across groups ( $P<0.001$ ). Post-hoc comparisons using Sheffe's test revealed that the mean (SD) total PIPP score was significantly lower in Kangaroo mother care group [7.7 (3.9) vs. 11.5 (3.4), 95% CI(-5.9, -1.7),  $P<0.001$ ] as well as Kangaroo mother care with Music therapy group [8.5 (3.2)

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vs. 11.5 (3.4), 95%CI (-5.1, -0.9), P=0.001] as compared to Control group. PIPP score was not significantly different between Control group and Music therapy group.

### CONCLUSIONS:

Kangaroo mother care with and without Music therapy (with expressed breast milk) significantly reduces pain on heel-prick as compared to expressed breast milk alone. Kangaroo mother care with expressed breast milk should be the first choice as a method for pain control in preterm neonates.

<https://www.indianpediatrics.net/apr2018/292.pdf>

[Matern Child Nutr.](#) 2018 Jan;14(1). doi: 10.1111/mcn.12504. Epub 2017 Aug 25.

### **Low-birthweight infants born to short-stature mothers are at additional risk of stunting and poor growth velocity: Evidence from secondary data analyses.**

[Sinha B](#), [Taneja S](#), [Chowdhury R](#), [Mazumder S](#), [Rongsen-Chandola T](#), [Upadhyay RP](#), [Martines J](#), [Bhandari N](#), [Bhan MK](#).

Low-birthweight (LBW) infants are at an increased risk of stunting and poor linear growth. The risk might be additionally higher in these infants when born to short mothers. However, this hypothesis has been less explored. The objective of this secondary data analysis was to determine the risk of linear growth faltering and difference in linear growth velocity in LBW infants born to short mothers (<150 cm) compared to those born to mothers with height  $\geq 150$  cm during the first year of life. This analysis uses data from a community-based randomized controlled trial of 2,052 hospital-born term infants with birthweight  $\leq 2,500$ g from urban low-middle socioeconomic neighbourhoods in Delhi, India. Data on maternal height and infant birth length were available from 1,858 (90.5%) of the infants. Infant anthropometry outcomes were measured at birth, 3, 6, 9, and 12 months of age. We found that infants born to short mothers had around twofold higher odds of stunting and lower attained length-for-age Z scores compared to infants of mothers with height  $\geq 150$  cm, at all ages of assessment. Linear growth velocity was significantly lower in infants of short mothers particularly in the first 6 months of life. **We conclude that LBW infants born to short mothers are at a higher risk of stunting and have slower postnatal growth velocity resulting in lower attained length-for-age Z scores in infancy.** Evidence-based strategies need to be tested to optimize growth velocity in LBW infants especially those born to short mothers.

<https://onlinelibrary.wiley.com/doi/epdf/10.1111/mcn.12504>

[Phys Ther.](#) 2017 Dec 1;97(12):1158-1168. doi: 10.1093/ptj/pzx089.

### **Family-centered Care Improved Neonatal Medical and Neurobehavioral Outcomes in Preterm Infants: Randomized Controlled Trial.**

[Yu YT](#), [Hsieh WS](#), [Hsu CH](#), [Lin YJ](#), [Lin CH](#), [Hsieh S](#), [Lu L](#), [Cherng RJ](#), [Chang YJ](#), [Fan PC](#), [Yao NJ](#), [Chen WJ](#), [Jeng SF](#).

### BACKGROUND:

Family-centered care for preterm infants in Western societies has yielded short- to medium-term benefits. However, the intervention effects have rarely been validated in Eastern societies.

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### **OBJECTIVE:**

The aim of this study was to examine whether a family-centered intervention program (FCIP) could improve the short-term medical and neurobehavioral outcomes in preterm infants with very low birth weight (VLBW; a birth weight of <1,500 g) in Taiwan over the outcomes seen with a usual care program (UCP).

### **DESIGN:**

This was a multicenter, single-blind, randomized controlled trial study.

### **SETTING:**

Three medical centers in northern and southern Taiwan were the locations for the study.

### **PARTICIPANTS:**

The participants were 251 VLBW preterm infants without severe perinatal complications.

### **INTERVENTION:**

The infants were randomly assigned to receive the FCIP or the UCP during hospitalization.

### **MEASUREMENTS:**

Infant morbidities, feeding, growth, and neurobehavioral performance were evaluated during the neonatal period. Parental adherence to interventions was measured in the FCIP group.

### **RESULTS:**

The FCIP promoted earlier full enteral feeding ( $\beta = -1.1$  weeks; 95% CI = -1.9 to -0.2 weeks) and hospital discharge ( $\beta = -0.6$  week; 95% CI = -1.1 to -0.1 weeks), greater weight gain ( $\beta = 3.3$  g/d; 95% CI = 0.1 to 6.6 g/d), and better neurobehavioral performance than the UCP ( $\beta = 1.2$  points; 95% CI = 0.2 to 2.3 points). Furthermore, a higher degree of parental motivation in interventions, goal attainment, and comprehensiveness of home activities was significantly associated with greater effects in infants' neurobehavioral performance and weight gain ( $r = .20-.31$ ; all  $P_s < .05$ ).

### **LIMITATIONS:**

The findings may not be generalized to preterm infants with severe perinatal diseases and parents with a low level of interest in interventions.

### **CONCLUSIONS:**

Family-centered care facilitated short-term medical and neurobehavioral outcomes in VLBW preterm infants in Taiwan; the effects were likely achieved through parental adherence to interventions. The designated strategies may be considered in a future launch of family-centered care in Taiwan.

<https://academic.oup.com/ptj/article/97/12/1158/4101240>

[Am J Perinatol.](#) 2017 Oct;34(12):1185-1189. doi: 10.1055/s-0037-1601564. Epub 2017 Apr 10.

### **Neurodevelopmental Outcomes of Preterm Infants Treated with Oral Paracetamol Versus Ibuprofen for Patent Ductus Arteriosus.**

[Oncel MY](#), [Eras Z](#), [Uras N](#), [Canpolat FE](#), [Erdeve O](#), [Oguz SS](#).

**Objective:** This study aims to determine the effects of paracetamol versus ibuprofen treatment given to preterm infants for the pharmacological closure of patent ductus arteriosus (PDA) on neurodevelopmental outcomes at 18 to 24 months' corrected age. **Method:** A follow-up study was conducted to evaluate the neurodevelopmental outcomes of preterm infants (gestational age  $\leq 30$  weeks) enrolled in a randomized controlled trial comparing oral paracetamol versus oral ibuprofen for the closure of PDA. The developmental assessment was done by using "Bayley Scales of Infant Development, Second Edition" at 18 to 24 months' corrected age. **Results:** A total of 80 infants completed the trial protocol. Of the 75 infants eligible for

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follow-up, 61 infants (30 in the paracetamol group and 31 in the ibuprofen group) were evaluated. There was no significant difference in neurodevelopmental outcomes between the two groups. **Conclusion:** The neurodevelopmental outcomes did not differ among the preterm infants who receive either paracetamol or ibuprofen at 18 to 24 months' corrected age.

[Bull World Health Organ.](#) 2017 Aug 1;95(8):574-583. doi: 10.2471/BLT.16.180273. Epub 2017 May 26.

### [A cohort study of low birth weight and health outcomes in the first year of life, Ghana.](#)

[O'Leary M](#), [Edmond K](#), [Floyd S](#), [Newton S](#), [Thomas G](#), [Thomas SL](#).

#### **OBJECTIVE:**

To investigate the effect of birth weight on infant mortality, illness and care seeking in rural Ghana.

#### **METHODS:**

Using randomized controlled trial data, we compared infants weighing 2.00-2.49, 1.50-1.99 and < 1.50 kg with non-low-birth-weight infants. We generated adjusted mortality hazard ratios (aHR), adjusted illness rate ratios (aRR) and adjusted odds ratios (aOR) for health-facility admissions and absence of care seeking for four time periods: infancy, the neonatal period, early infancy and late infancy - represented by ages of 0-364, 0-27, 28-182 and 183-364 days, respectively.

#### **FINDINGS:**

Among 22 906 infants, compared with non-low-birth-weight infants: (i) infants weighing 2.00-2.49, 1.50-1.99 and < 1.50 kg were about two (aHR: 2.13; 95% confidence interval, CI: 1.76-2.59), eight (aHR: 8.21; 95% CI: 6.26-10.76) and 25 (aHR: 25.38; 95% CI: 18.36-35.10) times more likely to die in infancy, respectively; (ii) those born weighing < 1.50 kg were about 48 (aHR: 48.45; 95% CI: 32.81-71.55) and eight (aHR: 8.42; 95% CI: 3.09-22.92) times more likely to die in the neonatal period and late infancy, respectively; (iii) those born weighing 1.50-1.99 kg (aRR: 1.57; 95% CI: 1.27-1.95) or < 1.50 kg (aRR: 1.58; 95% CI: 1.13-2.21) had higher neonatal illness rates; and (iv) for those born weighing 1.50-1.99 kg, care was less likely to be sought in the neonatal period (aOR: 3.30; 95% CI: 1.98-5.48) and early infancy (aOR: 1.74; 95% CI: 1.26-2.39).

#### **CONCLUSION:**

For low-birth-weight infants in Ghana, strategies to minimize mortality and improve care seeking are needed.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537746/>

[J Glob Health.](#) 2017 Dec;7(2):020415. doi: 10.7189/jogh.07.020415.

### [Immunization practices in low birth weight infants from rural Haryana, India: Findings from secondary data analysis.](#)

[Upadhyay RP](#), [Chowdhury R](#), [Mazumder S](#), [Taneja S](#), [Sinha B](#), [Martines J](#), [Bahl R](#), [Bhandari N](#), [Bhan MK](#).

#### **BACKGROUND:**



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Low birth weight (LBW) infants constitute a vulnerable subset of infants with impaired immunity in early life. In India, there is scarcity of studies that focus on immunization practices in such infants. This analysis aimed to examine immunization practices in LBW infants with the intention to identify areas requiring intervention.

### **METHODS:**

Data on immunization status of LBW infants enrolled in an individually randomized, double-masked, placebo-controlled trial of neonatal vitamin A supplementation were analysed. Study outcomes were full immunization by one year of age and delayed vaccination with DPT1 and DPT3. Multivariable logistic regression was performed to identify factors associated with the outcome(s).

### **FINDINGS:**

Out of 10 644 LBW infants enrolled in trial, immunization data were available for 10 517 (98.8%). Less than one-third (29.7%) were fully immunized by one year of age. Lowest wealth quintile (adjusted odds ratio (AOR) 0.39, 95% confidence interval (CI) 0.32-0.47), Muslim religion (AOR 0.41, 95% CI 0.35-0.48) and age of mother <20 years (AOR 0.62, 95% CI 0.52-0.73) were associated with decreased odds of full immunization. Proportion of infants with delayed vaccination for DPT1 and DPT3 were 52% and 81% respectively. Lowest wealth quintiles (AOR 1.51, 95% CI 1.25-1.82), Muslim religion (AOR 1.41, 95% CI 1.21-1.65), mother aged <20 years (AOR 1.31, 95% CI 1.11-1.53) and birth weight <2000 g (AOR 1.20, 95% CI 1.03-1.40) were associated with higher odds of delayed vaccination for DPT-1. Maternal education ( $\geq 12$  years of schooling) was associated with high odds of full immunization (AOR 2.39, 95% CI 1.97-2.91) and low odds of delayed vaccination for both DPT-1 (AOR 0.59, 95% CI 0.49-0.73) and DPT-3 (AOR 0.57, 95% CI 0.43-0.76).

### **CONCLUSION:**

In this population, LBW infants are at a risk of delayed and incomplete immunization and therefore need attention. The risks are even higher in identified subgroups that should specifically be targeted.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5804036/>

## Perinatal asphyxia

[Resuscitation](#). 2017 Jul;116:66-72. doi: 10.1016/j.resuscitation.2017.04.012. Epub 2017 Apr 17.

### **Born not breathing: A randomised trial comparing two self-inflating bag-masks during newborn resuscitation in Tanzania.**

[Thallinger M](#), [Ersdal HL](#), [Francis F](#), [Yeconia A](#), [Mduma E](#), [Kidanto H](#), [Linde JE](#), [Eilevstjønn J](#), [Gunnæs N](#), [Størdal K](#).

### **AIMS:**

Effective ventilation is crucial to save non-breathing newborns. We compared standard equipment for newborn resuscitation to a new Upright bag, in an area with high neonatal mortality.

### **METHODS:**

Newborns requiring resuscitation at Haydom Lutheran Hospital, Tanzania, were ventilated with 230ml standard or 320ml Upright bag-mask by weekly non-blinded block randomisation. A Laerdal Newborn Resuscitation Monitor collected ventilation data through a flow sensor

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between mask and bag and heart rate with electrocardiography electrodes. Primary outcome was expiratory tidal volume per birth weight.

### RESULTS:

Of 6110 babies born, 136 randomised to standard bag-mask and 192 to Upright, both groups had similar birth weight, gestational age, Apgar scores, gender, and mode of delivery. Compared to standard bag-mask, Upright gave higher median expiratory tidal volume (8.6ml/kg (IQR: 3.5-13.8) vs. 10.0ml/kg (IQR: 4.3-16.8) difference ratio 1.29, 95% CI 1.05, 1.58,  $p=0.014$ ), increased mean airway and peak inspiratory pressures, and higher early expired CO<sub>2</sub> (median at 20s 4.2% vs. 3.2%,  $p=0.0099$ ). Clinical outcome 30min post-delivery was normal in 44% with standard versus 57% with Upright ( $p=0.016$ ), but similar at 24h.

### CONCLUSION AND RELEVANCE:

Upright provided higher expired tidal volume, MAP, PIP and early ECO<sub>2</sub> than the standard bag. Clinical outcome differed at 30min, but not at 24h. Larger volume of Upright than standard bag can be an important factor. The results are relevant for low- and high-income settings as ventilatory and heart rate parameters during resuscitation of newborns are rarely reported.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S030095721730165X?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS030095721730165X%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[J Perinatol.](#) 2018 Jul 5. doi: 10.1038/s41372-018-0161-4. [Epub ahead of print]

### **Umbilical cord milking for neonates who are depressed at birth: a randomized trial of feasibility.**

[Girish M](#), [Jain V](#), [Dhokane R](#), [Gondhali SB](#), [Vaidya A](#), [Aghai ZH](#).

### OBJECTIVE:

To evaluate the feasibility and safety of umbilical cord milking (UCM) in neonates who are depressed at birth.

### STUDY DESIGN:

This is a quasi-randomized, non-blinded, controlled trial on infants ( $\geq 35$  weeks) who were depressed at birth. UCM (cord milked three times) was performed during the even months and the neonates born during the odd months were in the control group. Primary outcome was feasibility and safety.

### RESULTS:

A total of 101 infants were enrolled (50 UCM group and 51 control group) between January 2015 and October 2016. UCM was performed in 95% of infants (59/62) who qualified to receive UCM. There were no significant differences in resuscitation delay, resuscitation efforts, and short-term outcomes between the two groups.

### CONCLUSIONS:

UCM is feasible for term and late preterm infants who are depressed at birth. A larger clinical trial is needed to evaluate long-term benefits of UCM in neonates with HIE.

<https://www.nature.com/articles/s41372-018-0161-4>

[Indian Pediatr.](#) 2018 Mar 15;55(3):206-210.

**Effect of Gastric Lavage on Meconium Aspiration Syndrome and Feed Intolerance in Vigorous Infants Born with Meconium Stained Amniotic Fluid - A Randomized Control Trial.**

Gidaganti S, Faridi MM, Narang M, Batra P.

**OBJECTIVE:**

To compare the incidence of meconium aspiration syndrome and feed intolerance in infants born through meconium stained amniotic fluid with or without gastric lavage performed at birth.

**SETTING:**

Neonatal unit of a teaching hospital in New Delhi, India.

**DESIGN:**

Parallel group unmasked randomized controlled trial.

**PARTICIPANTS:**

700 vigorous infants of gestational age  $\geq 34$  weeks from through meconium stained amniotic fluid.

**INTERVENTION:**

Gastric lavage in the labor room with normal saline at 10 mL per kg body weight (n=350) or no gastric lavage (n=350). Meconiumcrit was measured and expressed as  $\leq 30\%$  and  $>30\%$ .

**OUTCOME MEASURES:**

Meconium aspiration syndrome, feed intolerance and procedure-related complications during 72 h of observation.

**RESULTS:**

5 (1.4%) infants in lavage group and 8 (2.2%) in no lavage group developed meconium aspiration syndrome (RR 0.63, 95% CI 0.21, 1.89). Feed intolerance was observed in 37 (10.5%) and 53 infants (15.1%) in lavage and no lavage groups, respectively (RR 0.70, 95% CI 0.47, 1.03). None of the infants in either group developed apnea, bradycardia or cyanosis during the procedure.

**CONCLUSIONS:**

Gastric lavage performed in the labor room does not seem to reduce either meconium aspiration syndrome or feed intolerance in vigorous infants born through meconium stained amniotic fluid.

<https://link.springer.com/content/pdf/10.1007%2Fs13312-018-1318-0.pdf>

Trials. 2017 Sep 18;18(1):432. doi: 10.1186/s13063-017-2165-3.

**Hypothermia for encephalopathy in low and middle-income countries(HELIX): study protocol for a randomised controlled trial.**

Thayyil S, Oliveira V, Lally PJ, Swamy R, Bassett P, Chandrasekaran M, Mondkar J, Mangalabharathi S, Benkappa N, Seeralar A, Shahidullah M, Montaldo P, Herberg J, Manerkar S, Kumaraswami K, Kamalaratnam C, Prakash V, Chandramohan R, Bandya P, Mannan MA, Rodrigo R, Nair M, Ramji S, Shankaran S; HELIX Trial group.

**BACKGROUND:**

Therapeutic hypothermia reduces death and disability after moderate or severe neonatal encephalopathy in high-income countries and is used as standard therapy in these settings. However, the safety and efficacy of cooling therapy in low- and middle-income countries (LMICs), where 99% of the disease burden occurs, remains unclear. We will examine whether whole body cooling reduces death or neurodisability at 18-22 months after neonatal encephalopathy, in LMICs.

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### METHODS:

We will randomly allocate 408 term or near-term babies (aged  $\leq 6$  h) with moderate or severe neonatal encephalopathy admitted to public sector neonatal units in LMIC countries (India, Bangladesh or Sri Lanka), to either usual care alone or whole-body cooling with usual care. Babies allocated to the cooling arm will have core body temperature maintained at 33.5 °C using a servo-controlled cooling device for 72 h, followed by re-warming at 0.5 °C per hour. All babies will have detailed infection screening at the time of recruitment and 3 Tesla cerebral magnetic resonance imaging and spectroscopy at 1-2 weeks after birth. Our primary endpoint is death or moderate or severe disability at the age of 18 months.

### DISCUSSION:

Upon completion, HELIX will be the largest cooling trial in neonatal encephalopathy and will provide a definitive answer regarding the safety and efficacy of cooling therapy for neonatal encephalopathy in LMICs. The trial will also provide important data about the influence of co-existent perinatal infection on the efficacy of hypothermic neuroprotection.

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2165-3>

## Neonatal infection

[diatr Infect Dis J. 2017 Dec;36\(12\):e328-e333. doi: 10.1097/INF.0000000000001576.](#)

**[The Treatment of Possible Severe Infection in Infants: An Open Randomized Safety Trial of Parenteral Benzylpenicillin and Gentamicin Versus Ceftriaxone in Infants <60 days of Age in Malawi.](#)**  
[Molyneux EM](#), [Dube Q](#), [Banda FM](#), [Chiume M](#), [Singini I](#), [Mallewa M](#), [Schwalbe EC](#), [Heyderman RS](#).

### BACKGROUND:

The World Health Organization recommends benzylpenicillin and gentamicin as antimicrobial treatment for infants with sepsis in low-income settings, and ceftriaxone or cefotaxime as an alternative. In a meta-analysis from 13 low-income settings, *Staphylococcus aureus*, *Klebsiella* spp. and *Escherichia coli* accounted for 55% of infants with sepsis. In a review of bacterial meningitis, resistance to third generation cephalosporins was >50% of all isolates, and 44% of Gram-negative isolates were gentamicin resistant. However, ceftriaxone may cause neonatal jaundice, and gentamicin may cause deafness. Therefore, **we compared parenteral benzylpenicillin plus gentamicin with ceftriaxone as first-line treatment, assessing outcome and adverse events.**

### METHODS:

This was an open randomized trial carried out in the Queen Elizabeth Central Hospital, Blantyre, Malawi, from 2010 to 2013. Infants <60 days of age with possible severe sepsis received either benzylpenicillin and gentamicin or ceftriaxone. Adverse events and outcomes were recorded until 6 months post discharge.

### RESULTS:

Three-hundred forty-eight infants were included in analyses. **Outcome in the benzylpenicillin and gentamicin and ceftriaxone groups was similar; deaths were 13.7% and 16.5% and sequelae were 14.5% and 11.2%, respectively.** More infants in the penicillin/gentamicin group required phototherapy: 15% versus 5%,  $P = 0.03$ . Thirteen (6%) survivors had bilateral

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hearing loss. There was no difference between the treatment groups. By 6 months post discharge, 11 more infants had died, and 17 more children were found to have sequelae.

### CONCLUSIONS:

**Ceftriaxone and gentamicin are safe for infants in our setting. Infants should receive long-term follow-up as many poor outcomes occurred after hospital discharge.**

<https://insights.ovid.com/pubmed?pmid=28263245>

\*\*\* [Nature](#). 2017 Aug 24;548(7668):407-412. doi: 10.1038/nature23480. Epub 2017 Aug 16.

### **[A randomized synbiotic trial to prevent sepsis among infants in rural India.](#)**

[Panigrahi P](#), [Parida S](#), [Nanda NC](#), [Satpathy R](#), [Pradhan L](#), [Chandel DS](#), [Baccaglini L](#), [Mohapatra A](#), [Mohapatra SS](#), [Misra PR](#), [Chaudhry R](#), [Chen HH](#), [Johnson JA](#), [Morris JG](#), [Paneth N](#), [Gewolb IH](#)

Sepsis in early infancy results in one million annual deaths worldwide, most of them in developing countries. No efficient means of prevention is currently available. Here we report on a randomized, double-blind, placebo-controlled trial of an oral synbiotic preparation (*Lactobacillus plantarum* plus fructooligosaccharide) in rural Indian newborns. **We enrolled 4,556 infants that were at least 2,000 g at birth, at least 35 weeks of gestation, and with no signs of sepsis or other morbidity, and monitored them for 60 days. We show a significant reduction in the primary outcome (combination of sepsis and death) in the treatment arm (risk ratio 0.60, 95% confidence interval 0.48-0.74), with few deaths (4 placebo, 6 synbiotic).** Significant reductions were also observed for culture-positive and culture-negative sepsis and lower respiratory tract infections. These findings suggest that a large proportion of neonatal sepsis in developing countries could be effectively prevented using a synbiotic containing *L. plantarum* ATCC-202195.

- [Global health: Probiotic prevents infections in newborns.](#) [Nature. 2017]

<https://www.nature.com/articles/nature23480>

### Comment

*Synbiotics refer to food ingredients or supplements combining probiotics and prebiotics in some form of synergism. Synbiotic were conceived as mixtures of probiotics and prebiotics that beneficially affect the host by increasing microbial diversity in the gastrointestinal tract, by selectively stimulating the growth or by activating the metabolism of health-promoting bacteria, and reducing pathogenic bacteria.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648921/>

[J Pediatr Gastroenterol Nutr](#). 2017 Aug;65(2):218-224. doi: 10.1097/MPG.0000000000001522.

### **[Changes in the Gut Microbiota After Early Administration of Oral Synbiotics to Young Infants in India.](#)**

[Chandel DS](#), [Perez-Munoz ME](#), [Yu F](#), [Boissy R](#), [Satpathy R](#), [Misra PR](#), [Sharma N](#), [Chaudhry R](#), [Parida S](#), [Peterson DA](#), [Gewolb IH](#), [Panigrahi P](#).

### OBJECTIVES:

The authors examined the changes in the developing gut microbiota of Indian infants enrolled in a colonization study of an oral synbiotic (*Lactobacillus plantarum* and fructo-oligosaccharides) preparation.

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### **METHODS:**

Frozen stool samples were available from a previously published clinical study of the synbiotic preparation administered daily for 7 days to full-term Indian infants delivered by C-section. 16S rRNA gene sequencing of fecal bacterial community-DNA was done in 11 infants sampled on day 7 and day 60 of life.

### **RESULTS:**

All infants showed changes in bacterial diversity with age. While Firmicutes and Proteobacteria were predominant in all, Actinobacteria and Bacteroidetes were initially low on day 7. In control infants, we observed a significant increase ( $P=0.012$ ) in the proportions of Actinobacteria on day 60. In the treated group, during the 60-day period, there was a 10-fold increase in Bacteroidetes, a somewhat smaller increase in Firmicutes, and a reduction in Proteobacteria. Compared to controls, treated infants were increasingly colonized by different Gram-positive genera including Enterococcus, Lactobacillus, and Bifidobacterium. Relatively less known taxa and some unassigned sequence reads added to enriched diversity observed in the treated group.

### **CONCLUSIONS:**

There was a high level of bacterial diversity among infants examined in the present study. Synbiotic treatment induced an increase in overall taxa and Gram-positive diversity, especially in the first week of life. Changes in the microbiota during early infancy should be used as a rationale for selecting probiotics in diverse clinical settings.

<https://insights.ovid.com/pubmed?pmid=28121648>

[J Matern Fetal Neonatal Med.](#) 2017 Jul;30(13):1627-1631. doi: 10.1080/14767058.2016.1220524. Epub 2016 Aug 25.

### **Efficacy of zinc supplementation on serum calprotectin, inflammatory cytokines and outcome in neonatal sepsis - a randomized controlled trial.**

[Banupriya N](#), [Vishnu Bhat B](#), [Benet BD](#), [Sridhar MG](#), [Parija SC](#).

### **OBJECTIVE:**

To find out the efficacy of zinc supplementation in decreasing the levels of serum calprotectin and inflammatory cytokines with improvement in outcome in neonatal sepsis.

### **METHODS:**

Neonates with clinical signs suggestive of sepsis and at least two screening tests positive were randomized into two groups - zinc group and control group. The zinc group received 3 mg/kg of zinc sulfate monohydrate twice a day orally for 10 days along with antibiotics. The control group received antibiotics and supportive care. Serum zinc, calprotectin, TNF- $\alpha$  and IL-6 were estimated in serum at recruitment and 10 days later after completion of antibiotics. The babies were monitored daily till discharge and mortality rate was compared between the groups.

### **RESULTS:**

Baseline characteristics were similar between the groups. Serum zinc levels were considerably increased in the zinc group after supplementation. There was significant decline in concentrations of serum calprotectin, TNF- $\alpha$  and IL-6 ( $p < 0.05$ ) in the zinc group. In the control group also, serum calprotectin and IL-6 levels were found to be decreased significantly after antibiotic treatment ( $p < 0.05$ ), while TNF- $\alpha$  showed insignificant reduction. Kaplan-Meier analysis was performed to assess the survival time between the groups. The mortality was lower in the zinc group compared to the control group 5 versus 11,  $p=0.12$ .

### **CONCLUSION:**

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Neonates with sepsis who received zinc in addition to antibiotics showed significant reduction in serum calprotectin and inflammatory cytokines. Although mortality was lower in zinc group, it was not statistically significant.

### Jaundice

[Indian J Pediatr](#). 2017 Oct;84(10):763-767. doi: 10.1007/s12098-017-2360-y. Epub 2017 May 17.

#### [Clofibrate as an Adjunct to Phototherapy for Unconjugated Hyperbilirubinemia in Term Neonates.](#)

[Kumar P](#), [Adhisivam B](#), [Vishnu Bhat B](#).

#### **OBJECTIVE:**

To evaluate the efficacy of oral clofibrate as an adjunct to phototherapy for unconjugated hyperbilirubinemia in term neonates.

#### **METHODS:**

This randomized controlled trial was done in the level III neonatal intensive care unit (NICU) of a tertiary care hospital. Ninety term neonates with unconjugated hyperbilirubinemia with serum bilirubin 15-25 mg/dl were randomized to either intervention group (single dose of clofibrate in a dose of 50 mg/kg prior to starting phototherapy) or standard care group (only phototherapy). Primary outcome was absolute fall in bilirubin by 48 h. Secondary outcomes were duration of phototherapy, absolute fall in bilirubin levels at 12, 24, 36, 48 h, need for exchange transfusion and incidence of side-effects.

#### **RESULTS:**

After 48 h of intervention, significantly lower bilirubin levels were noted in the intervention group compared to standard care group with a mean difference of 7 mg/dl (95% CI 6.7 mg/dl to 7.2 mg/dl). Duration of phototherapy required was less in the intervention group compared to standard care group with mean difference of 23.82 h (95% CI 30.46 h to 17.18 h). Exchange transfusion was needed for 4 neonates in the standard care group and none in the intervention group. No side-effects were noted with clofibrate.

#### **CONCLUSIONS:**

Single dose clofibrate prior to starting phototherapy in term neonates with uncomplicated unconjugated hyperbilirubinemia reduces the duration of phototherapy significantly.

<https://link.springer.com/article/10.1007%2Fs12098-017-2360-y>

#### **Comment**

*Clofibrate is a glucuronosyl transferase inducer, and is a lipid-lowering agent used for controlling high cholesterol and triacylglyceride levels in the blood. It increases lipoprotein lipase activity to promote the conversion of VLDL to LDL, and hence reduce the level of VLDL. An effect on neonatal hyperbilirubinaemia was shown in a previous study:*

<https://www.ncbi.nlm.nih.gov/pubmed/22267374>

## Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

## Growth monitoring

[Am J Clin Nutr.](#) 2017 Oct;106(4):1070-1077. doi: 10.3945/ajcn.117.157545. Epub 2017 Aug 23.

### [Home- and community-based growth monitoring to reduce early life growth faltering: an open-label, cluster-randomized controlled trial.](#)

[Fink G](#), [Levenson R](#), [Tembo S](#), [Rockers PC](#).

**Background:** Despite the continued high prevalence of faltering growth, height monitoring remains limited in many low- and middle-income countries. **Objective:** The objective of this study was to test whether providing parents with information on their child's height can improve children's height and developmental outcomes.

**Design: Villages in Chipata District, Zambia ( $n = 127$ ), were randomly assigned with equal probability to 1 of 3 groups: home-based growth monitoring (HBGM), community-based growth monitoring including nutritional supplementation for children with stunted growth (CBGM+NS), and control.** Primary study outcomes were individual height-for-age  $z$  score (HAZ) and overall child development assessed with the International Fetal and Newborn Growth Consortium for the 21st Century Neurodevelopment Assessment tool. Secondary outcomes were weight-for-age  $z$  score (WAZ), protein consumption, breastfeeding, and general dietary diversity.

**Results:** We enrolled a total of 547 children with a median age of 13 mo at baseline. **Estimated mean difference ( $\beta$ ) in HAZ was 0.127 (95% CI: -0.107, 0.361) for HBGM and -0.152 (95% CI: -0.341, 0.036) for CBGM+NS.** HBGM had no impact on child development [ $\beta$ : -0.017 (95% CI: -0.133, 0.098)]; CBGM+NS reduced overall child development scores by -0.118 SD (95% CI: -0.230, -0.006 SD). Both interventions had larger positive effects among children with stunted growth at baseline, with estimated interaction effects of 0.503 (95% CI: 0.160, 0.846) and 0.582 (95% CI: 0.134, 1.030) for CBGM+NS and HBGM, respectively. **HBGM increased mean WAZ [ $\beta = 0.183$  (95% CI: 0.037, 0.328)].** Both interventions improved parental reports of children's protein intake.

**Conclusions:** The results from this trial suggest that growth monitoring has a limited effect on children's height and development, despite improvements in self-reported feeding practices. **HBGM had modest positive effects on children with stunted growth.** Given its relatively low cost, this intervention may be a cost-effective tool for increasing parental efforts toward reducing children's physical growth deficits.

<https://academic.oup.com/ajcn/article/106/4/1070/4652048>

## Micronutrients, multivitamins, and food fortification

(See also Vitamin A)

[BMC Public Health.](#) 2018 Feb 1;18(1):205. doi: 10.1186/s12889-018-5097-2.

### [Adherence to home fortification with micronutrient powders in Kenyan pre-school children: self-reporting and sachet counts compared to an electronic monitoring device.](#)

[Teshome EM](#), [Oriaro VS](#), [Andango PEA](#), [Prentice AM](#), [Verhoef H](#)



### BACKGROUND:

The efficacy of home fortification with iron-containing micronutrient powders varies between trials, perhaps in part due to population differences in adherence. We aimed to assess to what extent adherence measured by sachet count or self-reporting forms is in agreement with adherence measured by electronic device. In addition, we explored how each method of adherence assessment (electronic device, sachet count, self-reporting forms) is associated with haemoglobin concentration measured at the end of intervention; and to what extent baseline factors were associated with adherence as measured by electronic device.

### METHODS:

**Three hundred thirty-eight rural Kenyan children aged 12-36 months were randomly allocated to three treatment arms (home fortification with two different iron formulations or placebo).** Home fortificants were administered daily by parents or guardians over a 30 day-intervention period. We assessed adherence using an electronic device that stores and provides information of the time and day of opening of the container that was used to store the fortificants sachets in each child's residence. In addition, we assessed adherence by self-reporting and sachet counts. We also measured haemoglobin concentration at the end of intervention.

### RESULTS:

Adherence, defined as having received at least 24 sachets ( $\geq 80\%$ ), during the 30-day intervention period was attained by only 60.6% of children as assessed by the electronic device. The corresponding values were higher when adherence was assessed by self-report (83.9%; difference: 23.3%, 95% CI: 18.8% to 27.8%) or sachet count (86.3%; difference: 25.7%, 95% CI: 21.0% to 30.4%). Among children who received iron, each 10 openings of the electronic cap of the sachet storage container were associated with an increase in haemoglobin concentration at the end of intervention by 1.2 g/L (95% CI: 0.0 to 1.9 g/L). Adherence was associated with the age of the parent but not with intervention group; with age, sex or anthropometric indices of the child; or with age or sex of the parent or guardian.

### CONCLUSIONS:

The use of self-reporting and sachet count may lead to overestimates of adherence to home fortification.

<https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-018-5097-2>

[BMJ Open](#). 2017 Nov 14;7(11):e017631. doi: 10.1136/bmjopen-2017-017631.

### [Effect of iron and zinc-biofortified pearl millet consumption on growth and immune competence in children aged 12-18 months in India: study protocol for a randomised controlled trial.](#)

[Mehta S](#), [Finkelstein JL](#), [Venkatramanan S](#), [Huey SL](#), [Udipi SA](#), [Ghugre P](#), [Ruth C](#), [Canfield RL](#), [Kurpad AV](#), [Potdar RD](#), [Haas JD](#).

### INTRODUCTION:

Biofortified crops represent a sustainable agricultural solution for the widespread micronutrient malnutrition in India and other resource-limited settings. This study aims to investigate the effect of the consumption of foods prepared with iron- and zinc-biofortified pearl millet (FeZn-PM) by children on biomarkers of iron and zinc status, growth, and immune function.

### METHODS AND ANALYSIS:

We will conduct a randomised controlled feeding trial in identified slums of Mumbai, India among 200 children aged between 12 and 18 months. Children will be

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randomised to receive foods prepared with the biofortified PM (FeZn-PM, ICTP8203-Fe) or non-biofortified PM. Anthropometric and morbidity data will be gathered every month for 9 months. Biological samples will be collected at baseline, midline and endline to assess iron and zinc status, including haemoglobin, serum ferritin, serum transferrin receptor, serum zinc, C-reactive protein and alpha-1 acid glycoprotein. Biological samples will be archived for future analyses. The midline measurement will be a random serial sample between baseline and endline. Immune function will be assessed at each time point by the measurement of T cell counts and vaccine responses in a subset, respectively.

### **ETHICS AND DISSEMINATION:**

This study has obtained clearance from the Health Ministry Screening Committee of the Indian Council of Medical Research. Ethical clearance has been obtained from Cornell University's Institutional Review Board, the Inter System Biomedica Ethics Committee and St John's Research Institute's Institutional Ethics Review Board. The results of this study will be disseminated at several research conferences and as published articles in peer-reviewed journals.

### **TRIAL REGISTRATION NUMBER:**

Clinical trial registration number [NCT02233764](https://clinicaltrials.gov/ct2/show/study/NCT02233764). CTRI registration number REF/2014/10/007731.

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### **KEYWORDS:**

biofortification; children; growth; iron; pearl millet; zinc

<https://bmjopen.bmj.com/content/7/11/e017631>

[Matern Child Nutr.](#) 2017 Oct;13(4). doi: 10.1111/mcn.12403. Epub 2016 Dec 7.

### **[The impact of home fortification with multiple micronutrient powder on vitamin A status in young children: A multicenter pragmatic controlled trial in Brazil.](#)**

[Silva LLS](#), [Augusto RA](#), [Tietzmann DC](#), [Sequeira LAS](#), [Hadler MCCM](#), [Muniz PT](#), [de Lira PIC](#), [Cardoso MA](#); [ENFAC Working Group](#).

Home fortification with multiple micronutrient powder (MNP) is effective in the prevention of anemia in young children. However, the impact on their vitamin A status remains controversial. This study aimed to evaluate the effect of MNP on vitamin A status in young Brazilian children. A multicenter pragmatic, controlled trial was carried out in primary health centers in four Brazilian cities. In the beginning of the study, the control group (CG) consisted of children 11-14 months old ( $n = 395$ ) attending in routine pediatric health care. In parallel, the intervention group (IG) was composed of children 6-8 months old ( $n = 399$ ), in the same health centers, who followed the intervention with MNP for 2-3 months. The analysis of the effect of MNP on vitamin A status was performed by comparing the IG with the CG after a 4- to 6-month follow-up when IG children had reached the age of the controls. The prevalence of vitamin A deficiency (VAD; serum retinol  $<0.70 \mu\text{mol/L}$ ) in the CG was 16.2%, while in the IG was 7.5%—a 55% reduction in the VAD [prevalence ratio (95% confidence interval) = 0.45 (0.28; 0.72)]. This reduction was also significant when stratifying the study centers by coverage of the Brazilian Vitamin A Supplementation Program. The adjusted mean of vitamin A serum concentrations improved in the IG compared with CG children, with a shift to the right in the vitamin A distribution. Home fortification with MNP was effective in reducing VAD among young Brazilian children.

## Lipid-based nutrition supplements

[J Nutr.](#) 2017 Dec;147(12):2309-2318. doi: 10.3945/jn.117.257386. Epub 2017 Oct 4.

### [Maternal and Child Supplementation with Lipid-Based Nutrient Supplements, but Not Child Supplementation Alone, Decreases Self-Reported Household Food Insecurity in Some Settings.](#)

[Adams KP](#), [Ayifah E](#), [Phiri TE](#), [Mridha MK](#), [Adu-Afarwuah S](#), [Arimond M](#), [Arnold CD](#), [Cummins J](#), [Hussain S](#), [Kumwenda C](#), [Matias SL](#), [Ashorn U](#), [Lartey A](#), [Maleta KM](#), [Vosti SA](#), [Dewey KG](#).

**Background:** It is unknown whether self-reported measures of household food insecurity change in response to food-based nutrient supplementation.

**Objective:** We assessed the impacts of **providing lipid-based nutrient supplements (LNSs) to women during pregnancy and postpartum and/or to their children on self-reported household food insecurity in Malawi** [DOSE and DYAD trial in Malawi (DYAD-M)], Ghana [DYAD trial in Ghana (DYAD-G)], and Bangladesh [Rang-Din Nutrition Study (RDNS) trial].

**Methods:** Longitudinal household food-insecurity data were collected during 3 individually randomized trials and 1 cluster-randomized trial testing the efficacy or effectiveness of LNSs (generally 118 kcal/d). Seasonally adjusted Household Food Insecurity Access Scale (HFIAS) scores were constructed for 1127 DOSE households, 732 DYAD-M households, 1109 DYAD-G households, and 3671 RDNS households. The impact of providing LNSs to women during pregnancy and the first 6 mo postpartum and/or to their children from 6 to 18-24 mo on seasonally adjusted HFIAS scores was assessed by using negative binomial models (DOSE, DYAD-M, and DYAD-G trials) and mixed-effect negative binomial models (RDNS trial).

**Results:** In the DOSE and DYAD-G trials, seasonally adjusted HFIAS scores were not different between the LNS and non-LNS groups. In the DYAD-M trial, the average household food-insecurity scores were 14% lower ( $P = 0.01$ ) in LNS households than in non-LNS households. In the RDNS trial, compared with non-LNS households, food-insecurity scores were 17% lower ( $P = 0.02$ ) during pregnancy and the first 6 mo postpartum and 15% lower ( $P = 0.02$ ) at 6-24 mo postpartum in LNS households.

**Conclusions:** The daily provision of LNSs to mothers and their children throughout much of the "first 1000 d" may improve household food security in some settings, which could be viewed as an additional benefit that may accrue in households should policy makers choose to invest in LNSs to promote child growth and development.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5697970/>

[PLoS Med.](#) 2017 Aug 15;14(8):e1002377. doi: 10.1371/journal.pmed.1002377. eCollection 2017 Aug.

### [Impact of fortified versus unfortified lipid-based supplements on morbidity and nutritional status: A randomised double-blind placebo-controlled trial in ill Gambian children.](#)

[Unger SA](#), [Drammeh S](#), [Hasan J](#), [Ceesay K](#), [Sinjanka E](#), [Beyai S](#), [Sonko B](#), [Dondoh BL](#), [Fulford AJ](#), [Moore SE](#), [Prentice AM](#)

#### **BACKGROUND:**

Multiple micronutrients (MMN) are commonly prescribed in pediatric primary healthcare in sub-Saharan Africa to improve nutritional status and appetite without evidence for their

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effectiveness or international clinical guidelines. Community-wide MMN supplementation has shown limited and heterogeneous impact on growth and morbidity. Short-term ready-to-use therapeutic foods in acutely sick children in a hospital setting also had limited efficacy regarding subsequent growth. The effectiveness of MMN in improving morbidity or growth in sick children presenting for primary care has not been assessed.

### **METHODS AND FINDINGS:**

We undertook a **double-blind randomised controlled trial of small-quantity lipid-based nutrient supplements (SQ-LNS) fortified with 23 micronutrients in children aged 6 months (mo) to 5 years (y) presenting with an illness at a rural primary healthcare centre in The Gambia. Primary outcomes were repeat clinic presentations and growth over 24 wk.**

Participants were randomly assigned to receive 1 of 3 interventions: **(1) supplementation with micronutrient-fortified SQ-LNS for 12 wk (MMN-12), (2) supplementation with micronutrient-fortified SQ-LNS for 6 wk followed by unfortified SQ-LNS for 6 wk (MMN-6), or (3) supplementation with unfortified SQ-LNS for 12 wk (MMN-0) to be consumed in daily portions.** Treatment masking used 16 letters per 6-wk block in the randomisation process. Blinded intention-to-treat analysis based on a prespecified statistical analysis plan included all participants eligible and correctly enrolled. Between December 2009 and June 2011, 1,101 children (age 6-60 mo, mean 25.5 mo) were enrolled, and 1,085 were assessed (MMN-0 = 361, MMN-6 = 362, MMN-12 = 362). MMN supplementation was associated with a small increase in height-for-age z-scores 24 wk after recruitment (effect size for MMN groups combined: 0.084 SD/24 wk, 95% CI: 0.005, 0.168;  $p = 0.037$ ; equivalent to 2-5 mm depending on age). No significant difference in frequency of morbidity measured by the number of visits to the clinic within 24 wk follow-up was detected with 0.09 presentations per wk for all groups (MMN-0 versus MMN-6: adjusted incidence rate ratio [IRR] 1.03, 95% CI: 0.92, 1.16; MMN-0 versus MMN-12: 1.05, 95% CI: 0.93, 1.18). In post hoc analysis, clinic visits significantly increased by 43% over the first 3 wk of fortified versus unfortified SQ-LNS (adjusted IRR 1.43; 95% CI: 1.07, 1.92;  $p = 0.016$ ), with respiratory presentations increasing by 52% with fortified SQ-LNS (adjusted IRR 1.52; 95% CI: 1.01, 2.30;  $p = 0.046$ ). The number of severe adverse events during supplementation were similar between groups (MMN-0 = 20 [1 death]; MMN-6 = 21 [1 death]; MMN-12 = 20 [0 death]). No participant withdrew due to adverse effects. Study limitations included the lack of supervision of daily supplementation.

### **CONCLUSION:**

**Prescribing micronutrient-fortified SQ-LNS to ill children presenting for primary care in rural Gambia had a very small effect on linear growth and did not reduce morbidity compared to unfortified SQ-LNS.** An early increase in repeat visits indicates a need for the establishment of evidence-based guidelines and caution with systematic prescribing of MMN. Future research should be directed at understanding the mechanisms behind the lack of effect of MMN supplementation on morbidity measures and limited effect on growth.

<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002377>

[Matern Child Nutr.](#) 2017 Jul;13(3). doi: 10.1111/mcn.12377. Epub 2016 Dec 2.

### **[Impact of small quantity lipid-based nutrient supplements on infant and young child feeding practices at 18 months of age: results from four randomized controlled trials in Africa.](#)**

[Arimond M](#), [Abbeddou S](#), [Kumwenda C](#), [Okronipa H](#), [Hemsworth J](#), [Jimenez EY](#), [Ocansey E](#), [Lartey A](#), [Ashorn U](#), [Adu-Afarwuah S](#), [Vosti SA](#), [Hess SY](#), [Dewey KG](#).

Optimal infant and young child feeding (IYCF) practices can help ensure nutrient adequacy and support healthy growth and development. Small-quantity lipid-based nutrient supplements (SQ-

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LNS) have been proposed to help fill nutrient gaps, but little is known about the impact of provision of SQ-LNS on breastfeeding or complementary feeding practices. In the context of four coordinated randomized controlled nutrient supplementation trials in diverse sites in Africa, we compared IYCF practices at infant age 18 months (after 9-12 months of supplementation) between those receiving and not receiving SQ-LNS. Practices were assessed by caregiver recall. Continued breastfeeding ranged from 74% (Ghana site) to 97% (Burkina Faso site) and did not differ between groups in any site; prevalence of frequent breastfeeding also did not differ. In two sites (Burkina Faso and Malawi), infants receiving SQ-LNS were more likely to meet the World Health Organization recommendations for frequency of feeding (percentage point differences of 12-14%,  $P < 0.0001$  and  $P = 0.005$ , respectively; the remaining two sites did not have data for this indicator). Most indicators of infant dietary diversity did not differ between groups in any site, but in the same two sites where frequency of feeding differed, infants receiving SQ-LNS were less likely to have low frequency of consumption of animal-source foods in the previous week (percentage point differences of 9-19% for lowest tertile,  $P = .02$  and  $P = 0.04$ , respectively). We conclude that provision of SQ-LNS did not negatively impact self-reported IYCF practices and may have positively impacted frequency of feeding.

<https://onlinelibrary.wiley.com/doi/full/10.1111/mcn.12377>

[Public Health Nutr.](#) 2017 Nov;20(16):2998-3007. doi: 10.1017/S1368980017001811. Epub 2017 Aug 9.

### **Effects of lipid-based nutrient supplements v. micronutrient powders on nutritional and developmental outcomes among Peruvian infants.**

[Matias SL](#), [Vargas-Vásquez A](#), [Bado Pérez R](#), [Alcázar Valdivia L](#), [Aquino Vivanco O](#), [Rodríguez Martín A](#), [Novalbos Ruiz JP](#).

#### **OBJECTIVE:**

To determine the effects of lipid-based nutrient supplements (LNS) on children's Hb, linear growth and development, compared with supplementation with micronutrient powder (MNP).

#### **DESIGN:**

The study was a two-arm parallel-group randomized controlled trial, where participants received either LNS or MNP for daily consumption during 6 months. Supplements were delivered by staff at government-run health centres. Hb, anthropometric, motor development, language development and problem-solving indicators were measured by trained research assistants when children were 12 months of age.

#### **SETTING:**

The study was conducted in five rural districts in the Province of Ambo in the Department of Huánuco, Peru.

#### **SUBJECTS:**

We enrolled 6-month-old children (n 422) at nineteen health centres.

#### **RESULTS:**

**Children who received LNS had a higher mean Hb concentration and lower odds of anaemia than those who received MNP.** No significant differences in height-for-age, weight-for-height or weight-for-age Z-score, or stunting and underweight prevalence, were observed. Provision of LNS was associated with a higher pre-verbal language (gestures) score, but such effect lost significance after adjustment for covariates. Children in the LNS group had higher problem-solving task scores and increased odds of achieving this cognitive task than children in the MNP group. No significant differences were observed on receptive language or gross motor development.

**CONCLUSIONS:**

**LNS between 6 and 12 months of age increased Hb concentration, reduced anaemia and improved cognitive development in children**, but showed no effects on anthropometric indicators, motor or language development.

[https://www.cambridge.org/core/services/aop-cambridge-core/content/view/44F0C301A3D13654E908B924BC342D32/S1368980017001811a.pdf/effect\\_s\\_of\\_lipidbased\\_nutrient\\_supplements\\_v\\_micronutrient\\_powders\\_on\\_nutritional\\_and\\_develop\\_mental\\_outcomes\\_among\\_peruvian\\_infants.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/44F0C301A3D13654E908B924BC342D32/S1368980017001811a.pdf/effect_s_of_lipidbased_nutrient_supplements_v_micronutrient_powders_on_nutritional_and_develop_mental_outcomes_among_peruvian_infants.pdf)

*PLoS One.* 2017 Aug 3;12(8):e0181770. doi: 10.1371/journal.pone.0181770. eCollection 2017.

**Differing growth responses to nutritional supplements in neighboring health districts of Burkina Faso are likely due to benefits of small-quantity lipid-based nutrient supplements (LNS).**

Hess SY, Peerson JM, Becquey E, Abbeddou S, Ouédraogo CT, Somé JW, Yakes Jimenez E, Ouédraogo JB, Vosti SA, Rouamba N, Brown KH.

**BACKGROUND:**

Of two community-based trials among young children in neighboring health districts of Burkina Faso, one found that small-quantity lipid-based nutrient supplements (LNS) increased child growth compared with a non-intervention control group, but zinc supplementation did not in the second study.

**OBJECTIVES:**

We explored whether the disparate growth outcomes were associated with differences in intervention components, household demographic variables, and/or children's morbidity.

**METHODS:**

Children in the LNS study received 20g LNS daily containing different amounts of zinc (LNS). Children in the zinc supplementation study received different zinc supplementation regimens (Z-Suppl). Children in both studies were visited weekly for morbidity surveillance. Free malaria and diarrhea treatment was provided by the field worker in the LNS study, and by a village-based community-health worker in the zinc study. Anthropometric assessments were repeated every 13-16 weeks. For the present analyses, study intervals of the two studies were matched by child age and month of enrollment. The changes in length-for-age z-score (LAZ) per interval were compared between LNS and Z-Suppl groups using mixed model ANOVA or ANCOVA. Covariates were added to the model in blocks, and adjusted differences between group means were estimated.

**RESULTS:**

Mean ages at enrollment of LNS (n = 1716) and Z-Suppl (n = 1720) were 9.4±0.4 and 10.1±2.7 months, respectively. The age-adjusted change in mean LAZ per interval declined less with LNS (-0.07±0.44) versus Z-Suppl (-0.21±0.43; p<0.0001). There was a significant group by interval interaction with the greatest difference found in 9-12 month old children (p<0.0001). Adjusting for demographic characteristics and morbidity did not reduce the observed differences by type of intervention, even though the morbidity burden was greater in the LNS group.

**CONCLUSIONS:**

Greater average physical growth in children who received LNS could not be explained by known cross-trial differences in baseline characteristics or morbidity burden, implying that the observed difference in growth response was partly due to LNS.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181770>

## Environmental enteric dysfunction

[Nutr.](#) 2018 Feb 1;148(2):267-274. doi: 10.1093/jn/nxx013.

### **Additional Common Bean in the Diet of Malawian Children Does Not Affect Linear Growth, but Reduces Intestinal Permeability.**

[Agapova SE](#), [Stephenson KB](#), [Divala O](#), [Kaimila Y](#), [Maleta KM](#), [Thakwalakwa C](#), [Ordiz MI](#), [Trehan I](#), [Manary MJ](#)

#### **BACKGROUND:**

Chronic malnutrition, as manifested by linear growth faltering, is pervasive among rural African children. Improvements in complementary feeding may decrease the burden of environmental enteric dysfunction (EED) and thus improve growth in children during the critical first 1000 d of development.

#### **OBJECTIVE:**

We tested the hypothesis that systematically including common bean or cowpea into complementary feeding would reduce EED and growth faltering among children in rural Malawi.

#### **METHODS:**

This was a double-blind clinical trial in which children 12-23 mo of age were randomly assigned to receive **complementary feeding with 1 of 3 foods: roasted cowpea or common bean flour, or an isoenergetic amount of corn-soy blend as a control food for 48 wk.** Children aged 12-23 mo received 155 kcal/d and thereafter until 35 mo received 200 kcal/d. **The primary outcomes were change in length-for-age z score (LAZ) and improvements in a biomarker of EED, the percentage of lactulose (%L) excreted as part of the lactulose:mannitol dual-sugar absorption test.** Anthropometric measurements and urinary %L excretion were compared between the 2 intervention groups and the control group separately with the use of linear mixed model analyses for repeated measures.

#### **RESULTS:**

A total of 331 children completed the clinical trial. Compliance with the study interventions was excellent, with >90% of the intervention flour consumed as intended. **No significant effects on LAZ, change in LAZ, or weight-for-length z score were observed due to either intervention legume, compared to the control.** %L was reduced with common bean consumption (effect estimate was -0.07 percentage points of lactulose,  $P = 0.0007$ ). The lactulose:mannitol test was not affected by the legume intervention.

#### **CONCLUSION:**

The addition of common bean to complementary feeding of rural Malawian children during the second year of life led to an improvement in a biomarker of gut health, although this did not directly translate into improved linear growth.

<https://academic.oup.com/jn/article/148/2/267/4913027>

[Am J Clin Nutr.](#) 2017 Dec;106(6):1500-1507. doi: 10.3945/ajcn.117.160986. Epub 2017 Nov 1.

### **Complementary feeding with cowpea reduces growth faltering in rural Malawian infants: a blind, randomized controlled clinical trial.**

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[Stephenson KB](#), [Agapova SE](#), [Divala O](#), [Kaimila Y](#), [Maleta KM](#), [Thakwalakwa C](#), [Ordiz MI](#), [Trehan I](#), [Manary MJ](#)

**Background:** Growth faltering is common in rural African children and is attributed to inadequate dietary intake and environmental enteric dysfunction (EED). **Objective:** We tested the hypothesis that complementary feeding with cowpea or common bean flour would reduce growth faltering and EED in 6-mo-old rural Malawians compared with the control group receiving a corn-soy blend.

**Design:** A prospective, double-blind, randomized controlled clinical trial was conducted in which children received daily feeding for 6 mo (200 kcal/d when 6-9 mo old and 300 kcal/d when 10-12 mo old). The primary outcomes were change in length-for-age z score (LAZ) and improvements in EED, as measured by percentage of lactulose excretion (%L). %L <0.2% was considered normal. Anthropometric measurements and %L through urine were compared between each legume group and the control group with Student's *t* test.

**Results:** Of the 355 infants enrolled, 291 infants completed the trial, and 288 were breastfed throughout the duration of the study. Cowpea and common bean added 4.6-5.2 g protein/d and 4-5 g indigestible carbohydrate/d to the diet. LAZ and weight-for-height z score were reduced in all 3 groups from 6 to 12 mo of age. The changes in LAZ [mean (95% CI)] for the cowpea, common bean, and control groups from 6 to 9 mo were -0.14 (-0.24, -0.04), -0.27 (-0.38, -0.16), and -0.27 (-0.35, -0.19), respectively. **LAZ was reduced less in infants receiving cowpea than in those receiving control food from 6 to 9 mo (*P* = 0.048).** The absolute value of %L did not differ between the dietary groups at 9 mo of age (mean  $\pm$  SD: 0.30  $\pm$  0.43, 0.23  $\pm$  0.21, and 0.26  $\pm$  0.31 for cowpea, common bean, and control, respectively), nor did the change in %L from 6 to 9 mo.

**Conclusion:** Addition of cowpea to complementary feeding in Malawian infants resulted in less linear growth faltering.

### Comment

*The two studies above seem very similar, but slightly different findings on length-for-age Z-score.*

<https://academic.oup.com/ajcn/article/106/6/1500/4823162>

[J Pediatr Gastroenterol Nutr](#). 2017 Jul;65(1):40-46. doi: 10.1097/MPG.0000000000001557.

### **Biomarkers of Environmental Enteric Dysfunction Among Children in Rural Bangladesh.**

[Campbell RK](#), [Schulze KJ](#), [Shaikh S](#), [Mehra S](#), [Ali H](#), [Wu L](#), [Raqib R](#), [Baker S](#), [Labrique A](#), [West KP Jr](#), [Christian P](#).

#### **OBJECTIVES:**

Environmental enteric dysfunction (EED) may inhibit growth and development in low- and middle-income countries, but available assessment methodologies limit its study. In rural Bangladesh, we measured EED using the widely used lactulose mannitol ratio (L:M) test and a panel of intestinal and systemic health biomarkers to evaluate convergence among biomarkers and describe risk factors for EED.

#### **METHODS:**

In 539 18-month-old children finishing participation in a randomized food supplementation trial, serum, stool, and urine collected after lactulose and mannitol dosing were analyzed for



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biomarkers of intestinal absorption, inflammation, permeability and repair, and systemic inflammation. EED scores for each participant were developed using principal component analysis and partial least squares regression. Associations between scores and L:M and with child sociodemographic and health characteristics were evaluated using regression analysis.

### RESULTS:

EED prevalence (L:M>0.07) was 39.0%; 60% had elevated acute phase proteins (C-reactive protein >5 mg/L or  $\alpha$ -1 acid glycoprotein >100 mg/dL). Correlations between intestinal biomarkers were low, with the highest between myeloperoxidase and  $\alpha$ -1 antitrypsin ( $r=0.33$ ,  $P<0.01$ ), and biomarker values did not differ by supplementation history. A 1-factor partial least squares model with L:M as the dependent variable explained only 8.6% of L:M variability. In adjusted models, L:M was associated with child sex and socioeconomic status index, whereas systemic inflammation was predicted mainly by recent illness, not EED.

### CONCLUSIONS:

Impaired intestinal health is widespread in this setting of prevalent stunting, but a panel of serum and stool biomarkers demonstrated poor agreement with L:M. **Etiologies of intestinal and systemic inflammation are likely numerous and complex in resource-poor settings, underscoring the need for a better case definition with corresponding diagnostic methods to further the study of EED.**

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5492885/>

*Trials*. 2017 Nov 6;18(1):523. doi: 10.1186/s13063-017-2278-8.

### **Lactoferrin and lysozyme to reduce environmental enteric dysfunction and stunting in Malawian children: study protocol for a randomized controlled trial.**

[Cheng WD](#), [Wold KJ](#), [Benzoni NS](#), [Thakwalakwa C](#), [Maleta KM](#), [Manary MJ](#), [Trehan I](#)

### BACKGROUND:

Chronic childhood malnutrition, as manifested by stunted linear growth, remains a persistent barrier to optimal child growth and societal development. Environmental enteric dysfunction (EED) is a significant underlying factor in the causal pathway to stunting, delayed cognitive development, and ultimately morbidity and mortality. Effective therapies against EED and stunting are lacking and further clinical trials are warranted to effectively identify and operationalize interventions.

### METHODS/DESIGN:

A prospective randomized placebo-controlled parallel-group randomized controlled trial will be conducted to determine if a daily supplement of lactoferrin and lysozyme, two important proteins found in breast milk, can decrease the burden of EED and stunting in rural Malawian children aged 12-23 months old. The intervention and control groups will have a sample size of 86 subjects each. All field and laboratory researchers will be blinded to the assigned intervention group, as will the subjects and their caregivers. The percentage of ingested lactulose excreted in the urine ( $\Delta\%$ ) after 4 h will be used as the biomarker for EED and linear growth as the measure of chronic malnutrition (stunting). The primary outcomes of interest will be change in  $\Delta\%$  from baseline to 8 weeks and to 16 weeks. Intention-to-treat analyses will be used.

### DISCUSSION:

A rigorous clinical trial design will be used to assess the biologically plausible use of lactoferrin and lysozyme as dietary supplements for children at high risk for EED. If proven effective, these

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safe proteins may serve to markedly reduce the burden of childhood malnutrition and improve survival.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674751/>

*J Pediatr.* 2017 Aug;187:225-233.e1. doi: 10.1016/j.jpeds.2017.04.005. Epub 2017 May 9.

### **Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.**

[Locks LM](#), [Mwiru RS](#), [Mtisi E](#), [Manji KP](#), [McDonald CM](#), [Liu E](#), [Kupka R](#), [Kisenge R](#), [Aboud S](#), [Gosselin K](#), [Gillman M](#), [Gewirtz AT](#), [Fawzi WW](#), [Duggan CP](#).

#### **OBJECTIVE:**

To assess whether growth and biomarkers of environmental enteric dysfunction in infancy are related to health outcomes in midchildhood in Tanzania.

#### **STUDY DESIGN:**

Children who participated in 2 randomized trials of micronutrient supplements in infancy were followed up in mid-childhood (4.6-9.8 years of age). Anthropometry was measured at age 6 and 52 weeks in both trials, and blood samples were available from children at 6 weeks and 6 months from 1 trial. Linear regression was used for height-for-age z-score, body mass index-for-age z-score, and weight for age z-score, and blood pressure analyses; log-binomial models were used to estimate risk of overweight, obesity, and stunting in midchildhood.

#### **RESULTS:**

One hundred thirteen children were followed-up. Length-for-age z-score at 6 weeks and delta length-for-age z-score from 6 to 52 weeks were associated independently and positively with height-for-age z-score and inversely associated with stunting in midchildhood. Delta weight-for-length and weight-for-age z-score were also positively associated with midchildhood height-for-age z-score. The 6-week and delta weight-for-length z-scores were associated independently and positively with midchildhood body mass index-for-age z-score and overweight, as was the 6-week and delta weight-for-age z-score. Delta length-for-age z-score was also associated with an increased risk of overweight in midchildhood. Body mass index-for-age z-score in midchildhood was associated positively with systolic blood pressure. Serum anti-flagellin IgA concentration at 6 weeks was also associated with increased blood pressure in midchildhood.

#### **CONCLUSIONS:**

Anthropometry at 6 weeks and growth in infancy independently predict size in midchildhood, while anti-flagellin IgA, a biomarker of environmental enteric dysfunction, in early infancy is associated with increased blood pressure in mid-childhood. Interventions in early life should focus on optimizing linear growth while minimizing excess weight gain and environmental enteric dysfunction.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0022347617304882?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0022347617304882%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## Macronutrient nutrition and complementary feeding

(See also Vitamin A)

[Pediatrics](#). 2017 Jul;140(1). pii: e20163459. doi: 10.1542/peds.2016-3459. Epub 2017 Jun 7.

**Eggs in Early Complementary Feeding and Child Growth: A Randomized Controlled Trial.**

[Iannotti LL](#), [Lutter CK](#), [Stewart CP](#), [Gallegos Riofrío CA](#), [Malo C](#), [Reinhart G](#), [Palacios A](#), [Karp C](#), [Chapnick M](#), [Cox K](#), [Waters WF](#)

**BACKGROUND:**

Eggs are a good source of nutrients for growth and development. We hypothesized that introducing eggs early during complementary feeding would improve child nutrition.

**METHODS:**

A randomized controlled trial was conducted in Cotopaxi Province, Ecuador, from March to December 2015. Children ages 6 to 9 months were randomly assigned to treatment (1 egg per day for 6 months [ $n = 83$ ]) and control (no intervention [ $n = 80$ ]) groups. Both arms received social marketing messages to encourage participation in the Lulun Project (*lulun* meaning "egg" in Kichwa). All households were visited once per week to monitor morbidity symptoms, distribute eggs, and monitor egg intakes (for egg group only). Baseline and end point outcome measures included anthropometry, dietary intake frequencies, and morbidity symptoms.

**RESULTS:**

Mothers or other caregivers reported no allergic reactions to the eggs. **Generalized linear regression modeling showed the egg intervention increased length-for-age z score by 0.63 (95% confidence interval [CI], 0.38-0.88) and weight-for-age z score by 0.61 (95% CI, 0.45-0.77).** Log-binomial models with robust Poisson indicated a reduced prevalence of stunting by 47% (prevalence ratio [PR], 0.53; 95% CI, 0.37-0.77) and underweight by 74% (PR, 0.26; 95% CI, 0.10-0.70). **Children in the treatment group had higher dietary intakes of eggs (PR, 1.57; 95% CI, 1.28-1.92) and reduced intake of sugar-sweetened foods (PR, 0.71; 95% CI, 0.51-0.97) compared with control.**

**CONCLUSIONS:**

The findings supported our hypothesis that early introduction of eggs significantly improved growth in young children. Generally accessible to vulnerable groups, eggs have the potential to contribute to global targets to reduce stunting.

<http://pediatrics.aappublications.org/content/early/2017/06/05/peds.2016-3459>

[Am J Clin Nutr](#). 2017 Dec;106(6):1482-1489. doi: 10.3945/ajcn.117.160515. Epub 2017 Nov 1.

**Eggs early in complementary feeding increase choline pathway biomarkers and DHA: a randomized controlled trial in Ecuador.**

[Iannotti LL](#), [Lutter CK](#), [Waters WF](#), [Gallegos Riofrío CA](#), [Malo C](#), [Reinhart G](#), [Palacios A](#), [Karp C](#), [Chapnick M](#), [Cox K](#), [Aguirre S](#), [Narvaez L](#), [López F](#), [Sidhu R](#), [Kell P](#), [Jiang X](#), [Fujiwara H](#), [Ory DS](#), [Young R](#), [Stewart CP](#).

**Background:** Choline status has been associated with stunting among young children. Findings from this study showed that an egg intervention improved linear growth by a length-for-age z score of 0.63. **Objective:** We aimed to test the efficacy of eggs introduced early in complementary feeding on plasma concentrations of biomarkers in choline pathways, vitamins B-12 and A, and essential fatty acids.

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**Design:** A randomized controlled trial, the Lulun ("egg" in Kichwa) Project, was conducted in a rural indigenous population of Ecuador. Infants aged 6-9 mo were randomly assigned to treatment (1 egg/d for 6 mo;  $n = 80$ ) and control (no intervention;  $n = 83$ ) groups.

Socioeconomic data, anthropometric measures, and blood samples were collected at baseline and endline. Household visits were made weekly for morbidity surveillance. We tested vitamin B-12 plasma concentrations by using chemiluminescent competitive immunoassay and plasma concentrations of choline, betaine, dimethylglycine, retinol, essential fatty acids, methionine, dimethylamine (DMA), trimethylamine, and trimethylamine-*N*-oxide (TMAO) with the use of liquid chromatography-tandem mass spectrometry.

**Results:** Socioeconomic factors and biomarker concentrations were comparable at baseline. Of infants, 11.4% were vitamin B-12 deficient and 31.7% marginally deficient at baseline. In adjusted generalized linear regression modeling, the egg intervention increased plasma concentrations compared with control by the following effect sizes: choline, 0.35 (95% CI: 0.12, 0.57); betaine, 0.29 (95% CI: 0.01, 0.58); methionine, 0.31 (95% CI: 0.03, 0.60); docosahexaenoic acid, 0.43 (95% CI: 0.13, 0.73); DMA, 0.37 (95% CI: 0.37, 0.69); and TMAO, 0.33 (95% CI: 0.08, 0.58). No significant group differences were found for vitamin B-12, retinol, linoleic acid (LA),  $\alpha$ -linolenic acid (ALA), or ratios of betaine to choline and LA to ALA.

**Conclusion:** The findings supported our hypothesis that early introduction of eggs significantly improved choline and other markers in its methyl group metabolism pathway. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT02446873](https://clinicaltrials.gov/ct2/show/study/NCT02446873).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5698841/>

[PLoS One](https://doi.org/10.1371/journal.pone.0185030). 2017 Sep 20;12(9):e0185030. doi: 10.1371/journal.pone.0185030. eCollection 2017.

### [An integrated nutrition and health program package on IYCN improves breastfeeding but not complementary feeding and nutritional status in rural northern India: A quasi-experimental randomized longitudinal study.](#)

[Singh V](#), [Ahmed S](#), [Dreyfuss ML](#), [Kiran U](#), [Chaudhery DN](#), [Srivastava VK](#), [Ahuja RC](#), [Baqui AH](#), [Darmstadt GL](#), [Santosham M](#), [West KP Jr](#)

#### **BACKGROUND:**

Undernutrition below two years of age remains a major public health problem in India. We conducted an evaluation of an integrated nutrition and health program that aimed to improve nutritional status of young children by improving breast and complementary feeding practices over that offered by the Government of India's standard nutrition and health care program.

#### **METHODS:**

In Uttar Pradesh state, through multi-stage cluster random sampling, 81 villages in an intervention district and 84 villages in a comparison district were selected. A cohort of 957 third trimester pregnant women identified during house-to-house surveys was enrolled and, following childbirth, mother-child dyads were followed every three months from birth to 18 months of age. The primary outcomes were improvements in weight-for-age and length-for-age z scores, with improved breastfeeding and complementary feeding practices as intermediate outcomes.

#### **FINDINGS:**

Optimal breastfeeding practices were higher among women in intervention than comparison areas, including initiating breastfeeding within one hour of delivery (17.4% vs. 2.7%,  $p < 0.001$ ), feeding colostrum (34.7% vs. 8.4%,  $p < 0.001$ ), avoiding pre-lacteals (19.6% vs. 2.1%,  $p < 0.001$ )

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and exclusively breastfeeding up to 6 months (24.1% vs. 15.3%,  $p = 0.001$ ). However, differences were few and mixed between study arms with respect to complementary feeding practices. The mean weight-for-age z-score was higher at 9 months (-2.1 vs. -2.4,  $p = 0.0026$ ) and the prevalence of underweight status was lower at 12 months (58.5% vs. 69.3%,  $p = 0.047$ ) among intervention children. The prevalence of stunting was similar between study arms at all ages. Coefficients to show the differences between the intervention and comparison districts (0.13 cm/mo) suggested significant faster linear growth among intervention district infants at earlier ages (0-5 months).

### INTERPRETATION:

Mothers participating in the intervention district were more likely to follow optimal breast, although not complementary feeding practices. The program modestly improved linear growth in earlier age and weight gain in late infancy. Comprehensive nutrition and health interventions are complex; the implementation strategies need careful examination to improve feeding practices and thus impact growth.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185030>

[Public Health Nutr.](#) 2017 Oct;20(15):2819-2826. doi: 10.1017/S136898001700163X. Epub 2017 Aug 14.

### [Evaluation of the efficacy, safety and acceptability of a fish protein isolate in the nutrition of children under 36 months of age.](#)

[Ochoa TJ](#), [Baiocchi N](#), [Valdiviezo G](#), [Bullon V](#), [Campos M](#), [Llanos-Cuentas A](#).

### OBJECTIVE:

To determine the effect of a fish protein isolate (FPi), administered over 6 months, on the growth of children aged 6-36 months, measured by Z-scores of height-for-age (HAZ) and weight-for-height (WHZ), compared with the standard meal without FPi; and to determine the safety and acceptability of FPi daily consumption.

### DESIGN:

Cluster-randomized community-based controlled trial. For 6 months, the centres received either FPi replacing 50 % of total proteins in the diet or standard protein. HAZ and WHZ were used to determine the effect on growth. Acceptability was determined by daily consumption, measured by weighing the servings before and after consumption.

### SETTING:

Day care centres and community nutritional centres in northern Lima, Peru.

### SUBJECTS:

Children (n 441) aged 6-36 months.

### RESULTS:

Four centres were randomized to the intervention with FPi, five centres were randomized to the standard control diet. More than 36 900 meals were prepared and administered in a supervised manner. Both groups received the same amounts of energy and proteins daily (proteins about 12-15 % of total energy). Growth of children who received the FPi diet was similar to that of children with the standard diet. Consumption was similar in the FPi and control groups (70 v. 80 % of amount offered, respectively). The protein was safe and well tolerated. No adverse events were reported. However, the cost of the intervention with FPi was 20-40 % lower v. the standard diet with animal protein derived from beef, chicken, eggs or liver.

### CONCLUSIONS:

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The FPI was well accepted and there was no significant difference in growth between both groups. FPI is a potential source of animal protein at lower cost.

[https://www.cambridge.org/core/services/aop-cambridge-core/content/view/10A6EE2B64DE43551318403B28F80361/S136898001700163Xa.pdf/evaluation\\_of\\_the\\_efficacy\\_safety\\_and\\_acceptability\\_of\\_a\\_fish\\_protein\\_isolate\\_in\\_the\\_nutrition\\_of\\_children\\_under\\_36\\_months\\_of\\_age.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/10A6EE2B64DE43551318403B28F80361/S136898001700163Xa.pdf/evaluation_of_the_efficacy_safety_and_acceptability_of_a_fish_protein_isolate_in_the_nutrition_of_children_under_36_months_of_age.pdf)

*J Int Med Res.* 2018 Jun;46(6):2186-2201. doi: 10.1177/0300060518757355. Epub 2018 Apr 3.

### **Effect of oral nutritional supplementation on growth and recurrent upper respiratory tract infections in picky eating children at nutritional risk: a randomized, controlled trial.**

[Ghosh AK](#), [Kishore B](#), [Shaikh I](#), [Satyavrat V](#), [Kumar A](#), [Shah T](#), [Pote P](#), [Shinde S](#), [Berde Y](#), [Low YL](#), [Tan VMH](#), [Huynh DTT](#).

**Objectives** To evaluate the effect of oral nutritional supplementation (ONS) plus dietary counselling (DC) (intervention) versus DC alone (control) on growth and upper respiratory tract infection (URTI) in nutritionally at-risk, picky eating children in India. **Methods** We performed a 90-day, prospective, randomized, controlled trial. A total of 255 children aged 24-72 months with a weight-for-age z-score  $\geq -2$  and  $< -1$ , picky eating behaviour, and acute URTI were randomized to the control (n = 128) or intervention group (n = 127). The outcomes included the change in weight-for-age z-score from days 1 to 90 and the URTI incidence. **Results** The mean age was  $44.0 \pm 14.3$  months. The intervention group showed a significantly greater increase in mean weight-for-age and body mass index-for-age z-scores compared with the control group from day 10 onwards. Higher energy intake in the intervention group was observed at all follow-up visits, except for day 10. The incidence of URTI in the control group was 2.01 times higher than that in the intervention group, controlling for confounding factors. **Conclusions** ONS plus DC is effective for improving weight and reducing the incidence of URTI in nutritionally at-risk, picky eating children with an acute URTI episode.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023057/>

*J Int Med Res.* 2018 Jul;46(7):2615-2632. doi: 10.1177/0300060518766982. Epub 2018 Apr 25.

### **Continuation of oral nutritional supplementation supports continued growth in nutritionally at-risk children with picky eating behaviour: A post-intervention, observational follow-up study.**

[Ghosh AK](#), [Kishore B](#), [Shaikh I](#), [Satyavrat V](#), [Kumar A](#), [Shah T](#), [Pote P](#), [Shinde S](#), [Berde Y](#), [Low YL](#), [Tan VMH](#), [Huynh DTT](#).

**Objectives** To evaluate the 120-day post-intervention growth trajectory of picky-eating children aged 2 to 6 years who previously completed a 90-day, randomized, controlled trial of oral nutritional supplementation (ONS) plus dietary counselling (DC) (SDC, n = 98) compared with DC alone (n = 105). **Methods** A total of 203 children were included. Children were free to consume ONS during follow-up. Information on ONS consumption was collected. Weight-for-age percentile (WAP) and height-for-age

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percentile (HAP) were measured at Day 90 (beginning) and Day 210 (end point). Results Despite continued weight gain, there was a significant decline in WAP in both groups during the post-intervention period. However, children who took ONS voluntarily had a smaller loss in WAP compared with those who did not. Children in the SDC group showed no difference in a decline in HAP between those who took ONS during follow-up and those who did not. However, children in the DC group showed a marginally larger decline in HAP in those who did not take ONS during the follow-up compared with those who did. Conclusions Continued parental self-administration of ONS to their children slows down the loss of growth percentiles, supporting continued weight gain in picky-eating children at nutritional risk.

<http://journals.sagepub.com/doi/full/10.1177/0300060518766982>

## Breastfeeding

*Global Health*. 2017 Dec 19;13(1):90. doi: 10.1186/s12992-017-0314-9.

### [Effectiveness of home-based nutritional counselling and support on exclusive breastfeeding in urban poor settings in Nairobi: a cluster randomized controlled trial.](#)

[Kimani-Murage EW](#), [Griffiths PL](#), [Wekesah FM](#), [Wanjohi M](#), [Muhia N](#), [Muriuki P](#), [Egondi T](#), [Kyobutungi C](#), [Ezeh AC](#), [McGarvey ST](#), [Musoke RN](#), [Norris SA](#), [Madise NJ](#)

#### **BACKGROUND:**

Exclusive breastfeeding (EBF) improves infant health and survival. We tested the effectiveness of a home-based intervention using Community Health Workers (CHWs) on EBF for six months in urban poor settings in Kenya.

#### **METHODS:**

We conducted a cluster-randomized controlled trial in Korogocho and Viwandani slums in Nairobi. **We recruited pregnant women and followed them until the infant's first birthday.** Fourteen community clusters were randomized to intervention or control arm. **The intervention arm received home-based nutritional counselling during scheduled visits by CHWs trained to provide specific maternal infant and young child nutrition (MIYCN) messages and standard care. The control arm was visited by CHWs who were not trained in MIYCN and they provided standard care (which included aspects of ante-natal and post-natal care, family planning, water, sanitation and hygiene, delivery with skilled attendance, immunization and community nutrition).** CHWs in both groups distributed similar information materials on MIYCN. Differences in EBF by intervention status were tested using chi square and logistic regression, employing intention-to-treat analysis.

#### **RESULTS:**

A total of 1110 mother-child pairs were involved, about half in each arm. At baseline, demographic and socioeconomic factors were similar between the two arms. The rates of EBF for 6 months increased from 2% pre-intervention to 55.2% (95% CI 50.4-59.9) in the intervention group and 54.6% (95% CI 50.0-59.1) in the control group. The adjusted odds of EBF (after adjusting for baseline characteristics) were slightly higher in the intervention arm compared to the control arm but not significantly different: for 0-2 months (OR 1.27, 95% CI 0.55 to 2.96;  $p = 0.550$ ); 0-4 months (OR 1.15; 95% CI 0.54 to 2.42;  $p = 0.696$ ), and 0-6 months (OR 1.11, 95% CI 0.61 to 2.02;  $p = 0.718$ ).

#### **CONCLUSIONS:**

EBF for six months significantly increased in both arms indicating potential effectiveness of using CHWs to provide home-based counselling to mothers. The lack of any difference in EBF

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rates in the two groups suggests potential contamination of the control arm by information reserved for the intervention arm. Nevertheless, this study indicates a great potential for use of CHWs when they are incentivized and monitored as an effective model of promotion of EBF, particularly in urban poor settings. Given the equivalence of the results in both arms, the study suggests that the basic nutritional training given to CHWs in the basic primary health care training, and/or provision of information materials may be adequate in improving EBF rates in communities. However, further investigations on this may be needed. One contribution of these findings to implementation science is the difficulty in finding an appropriate counterfactual for community-based educational interventions.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5735795/>

[PLoS One](#). 2018 Jul 16;13(7):e0200519. doi: 10.1371/journal.pone.0200519. eCollection 2018.

### [Impact of maternal nutritional supplementation in conjunction with a breastfeeding support program during the last trimester to 12 weeks postpartum on breastfeeding practices and child development at 30 months old.](#)

[Zhang Z](#), [Tran NT](#), [Nguyen TS](#), [Nguyen LT](#), [Berde Y](#), [Tey SL](#), [Low YL](#), [Huynh DTT](#).

#### **BACKGROUND:**

Maternal nutrition during pregnancy and breastfeeding is important for the healthy growth and development of the fetus and infant.

#### **PURPOSE:**

This study aimed to evaluate the long-term effects of a maternal milk supplementation (MMS) in conjunction with a breastfeeding support program on breastfeeding practices including duration of any breastfeeding and exclusive breastfeeding and child neurodevelopment outcomes at 30 months old.

#### **METHODS:**

We followed up the offspring of 204 Vietnamese women who completed a randomized controlled trial where the intervention group received MMS with a breastfeeding support program from the last trimester to 12 weeks postpartum while the control group received standard care. At 30 months postpartum, information on child feeding practices was collected and child neurodevelopment was assessed by the Bayley Scales of Infant and Toddler Development (Bayley-III).

#### **RESULTS:**

There was no significant difference in the duration of any breastfeeding (ABF) from birth between the groups. However, the intervention group had longer exclusive breastfeeding (EBF) duration ( $p = 0.0172$ ), higher EBF rate at 6 months ( $p = 0.0093$ ) and lower risk of discontinuing EBF ( $p = 0.0071$ ) than the control. Children in the intervention group had significantly higher Bayley-III composite scores in the domains of cognitive ( $p = 0.0498$ ) and motor ( $p = 0.0422$ ) functions, as well as a tendency toward better social-emotional behavior ( $p = 0.0513$ ) than children in the control group. The association between maternal intervention and child development was attenuated after further adjustment for birth weight but not EBF duration, suggesting that improvements in child development may be partially attributed to the benefits of prenatal nutrition supplementation on birth outcomes.

#### **CONCLUSIONS:**



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MMS with breastfeeding support during late pregnancy and early postpartum significantly improved EBF practices. The intervention was also associated with improvements in neurodevelopment in children at 30 months old.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0200519>

[PLoS One](https://doi.org/10.1371/journal.pone.0191001). 2018 Feb 23;13(2):e0191001. doi: 10.1371/journal.pone.0191001. eCollection 2018.

### **Exclusive breastfeeding promotion and neuropsychological outcomes in 5-8 year old children from Uganda and Burkina Faso: Results from the PROMISE EBF cluster randomized trial.**

[Tumwine JK](#), [Nankabirwa V](#), [Diallo HA](#), [Engebretsen IMS](#), [Ndeezi G](#), [Bangirana P](#), [Sanou AS](#), [Kashala-Abotnes E](#), [Boivin M](#), [Giordani B](#), [Elgen IB](#), [Holding P](#), [Kakooza-Mwesige A](#), [Skylstad V](#), [Nalugya J](#), [Tylleskar T](#), [Meda N](#).

#### **BACKGROUND:**

The beneficial effects from exclusive breastfeeding (EBF) have been widely acknowledged. We assessed the effect of exclusive breastfeeding promotion by peer counsellors in Uganda and Burkina Faso, on cognitive abilities, social emotional development, school performance and linear growth among 5-8 years old children.

#### **METHODS:**

Children in the PROMISE EBF trial (2006-2008) were re-enrolled in the follow-up PROMISE Saving Brains (SB) study (2013-2015). Caretaker interviews captured sociodemographic characteristics and social emotional development using the parent version of the Strengths and Difficulties Questionnaire (SDQ). Overall cognition and working memory were assessed using the Kaufman Assessment Battery for Children, second edition (KABC2), cognitive flexibility was measured with the Child Category Test (CCT), and attention with the Test of Variables of Attention (T.O.V.A), while school performance was measured by a standardized test on arithmetic and reading. Country-pooled, age adjusted z-scores from each of the above outcomes were entered into a linear regression model controlling for confounders.

#### **RESULTS:**

The number of children re-enrolled in the intervention and control arms were: 274/396 (69.2%) and 256/369 (69.4%) in Uganda and 265/392 (67.6%) and 288/402 (71.6%) in Burkina Faso. Assessment of cognitive ability showed small and no significant differences, of which general cognition (z-scores, 95% CI) showed the largest mean difference: -0.17 (-0.40; 0.05). Social emotional symptoms were similar across arms. There were no differences in school performance or linear growth for age detected.

#### **CONCLUSION:**

Peer promotion for exclusive breastfeeding in Burkina Faso and Uganda was not associated with differences at 5-8 years of age in a range of measures of child development: cognitive abilities, emotion-behaviour-social symptoms or linear growth. **This study from sub Saharan Africa did not reconfirm findings elsewhere that have shown an association between exclusive breastfeeding and cognitive performance.** This might be due to a number of methodological limitations inherent in the current study. For example since the majority of the children were breastfed, the benefits of the intervention could have been diluted. Other factors such as the mental and HIV status of the mothers (which were not assessed in the current study) could have affected our results. Hence regarding the effect of exclusive breastfeeding on measures of child neurocognitive development in sub Saharan Africa, the jury is still out.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0191001>

[BMC Complement Altern Med.](#) 2018 Feb 6;18(1):53. doi: 10.1186/s12906-018-2121-0.

**[Efficacy of Chinese herbal medicine Zengru Gao to promote breastfeeding: a multicenter randomized controlled trial.](#)**

[Wang S](#), [Zhang C](#), [Li C](#), [Li D](#), [He P](#), [Su Z](#), [Li Y](#), [Ding Y](#), [Lu A](#).

**BACKGROUND:**

Breastfeeding is recommended worldwide but not fully practiced. The first week after childbirth is regarded as a critical period for increasing breast milk production. The aim of the study was to investigate whether Chinese herbal medicine Zengru Gao would result in more women breastfeeding in the first week after childbirth.

**METHODS:**

A multicenter randomized controlled trial was conducted of 588 mothers considering breastfeeding in China. Among the mothers of the intervention group, the intervention included Chinese herbal medicine Zengru Gao; among those of the control group, it did not. Primary outcomes were the percentages of fully and partially breastfeeding mothers. Secondary outcome was baby's daily formula intake.

**RESULTS:**

At 3 d and 7 d after delivery, significant differences were found in favour of Zengru Gao group on the percentage of full/ partial breastfeeding ( $Z = - 3.0037$ ,  $p = 0.0027$ ). At day 7, the percentage of full/ partial breastfeeding of the active group increased to 71.48%/20.70% versus 58.67%/30.26% in the control group, the differences remained significant ( $Z = - 3.0037$ ,  $p = 0.0027$ ). No statistically significant differences were detected on primary measures at 1 d. While intake of formula differed between groups at 1 d and 3 d, this difference did not achieve statistical significance, but this difference was apparent by 7 d ( $55.45 \pm 115.39$  ml/day vs  $90.66 \pm 153.89$  ml/day).

**CONCLUSION:**

In conclusion, Chinese Herbal medicine Zengru Gao enhanced breastfeeding success during one week postpartum. The approach is acceptable to participants and merits further evaluation.

<https://bmccomplementalternmed.biomedcentral.com/articles/10.1186/s12906-018-2121-0>

## Community nutrition and agriculture

[J Health Econ.](#) 2017 Sep;55:219-231. doi: 10.1016/j.jhealeco.2017.07.005. Epub 2017 Aug 1.

**[Impact of caregiver incentives on child health: Evidence from an experiment with Anganwadi workers in India.](#)**

[Singh P](#), [Masters WA](#).

This paper tests the effectiveness of performance pay and bonuses among government child care workers in India. In a controlled study of 160 ICDS centers serving over 4000 children, we randomly assign workers to either fixed bonuses or payments based on the nutritional status of children in their care, and also collect data from a control group receiving only standard salaries. In all three study arms mothers receive nutrition information. We find that performance pay reduces underweight prevalence by about 5 percentage points over 3 months, and height improves by about one centimeter. Impacts on weight continue when incentives are renewed and return to parallel trends thereafter. Fixed bonuses are less expensive but lead to smaller and less precisely estimated effects than performance pay, especially for children near malnutrition

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thresholds. Both treatments improve worker effort and communication with mothers, who in turn feed a more calorific diet to children at home.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5597043/>

*J Nutr.* 2017 Jul;147(7):1418-1425. doi: 10.3945/jn.116.244517. Epub 2017 May 31.

### **Unconditional Seasonal Cash Transfer Increases Intake of High-Nutritional-Value Foods in Young Burkinabe Children: Results of 24-Hour Dietary Recall Surveys within the Moderate Acute Malnutrition Out (MAM'Out) Randomized Controlled Trial.**

[Tonguet-Papucci A](#), [Houngbe F](#), [Huybregts L](#), [Ait-Aissa M](#), [Altare C](#), [Kolsteren P](#), [Huneau JF](#).

**Background:** Cash transfer programs have the potential to improve dietary intake by improving accessibility to food. However, quantitative data on the impact of cash transfer programs on children's energy and nutrient intakes are lacking.

**Objective:** The aim of this study was to evaluate the effect of seasonal unconditional cash transfers on children's energy, micro- and macronutrient, and food group intakes during the lean season in Burkina Faso.

**Methods:** Within the framework of the MAM'Out (Moderate Acute Malnutrition Out) cluster-randomized controlled trial, two 24-h dietary recall surveys were conducted in July and August 2014. Daily energy and macro- and micronutrient intakes, breastfeeding practices, and food group consumption were analyzed for 322 children aged 14-27 mo from an intervention group (benefiting from unconditional cash transfer during the lean season in 2013 and 2014) and a control group by using mixed linear, logistic, and Poisson regression models or a  $\gamma$ -generalized linear model with log-link. A dietary diversity score was calculated on the basis of 7 food groups.

**Results:** Unconditional cash transfers during the lean season improved the diets of rural children through a higher consumption of eggs ( $11.3 \pm 1.55$  compared with  $3.25 \pm 0.79$  g;  $P < 0.001$ ), fat ( $20.6 \pm 0.80$  compared with  $16.5 \pm 0.89$  g;  $P < 0.01$ ), and vitamin B-12 ( $0.40 \pm 0.02$  compared with  $0.34 \pm 0.02$  mg;  $P < 0.001$ ) compared with controls and higher proportions of children consuming dairy products (OR: 4.14; 95% CI: 1.48, 11.6;  $P < 0.05$ ), flesh foods (OR: 2.09; 95% CI: 1.18, 3.70;  $P < 0.05$ ), and iron-rich or iron-fortified foods (OR: 2.23; 95% CI: 1.20, 4.13;  $P < 0.05$ ). No difference was found in energy intake between the 2 groups. The minimum dietary diversity of two-thirds of the children who benefited from cash transfers was adequate compared with only one-third in the control group ( $P < 0.001$ ).

**Conclusions:** Unconditional seasonal cash transfer increases intakes of high-nutritional-value foods in Burkinabe children aged 14-27 mo. As such, their use can be recommended in actions addressing children's dietary intake during the lean season. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as [NCT01866124](#).

<https://academic.oup.com/jn/article/147/7/1418/4743659>

*J Nutr.* 2017 Jul;147(7):1410-1417. doi: 10.3945/jn.117.247858. Epub 2017 May 24.

### **Unconditional Cash Transfers Do Not Prevent Children's Undernutrition in the Moderate Acute Malnutrition Out (MAM'Out) Cluster-Randomized Controlled Trial in Rural Burkina Faso.**

[Houngbe F](#), [Tonguet-Papucci A](#), [Altare C](#), [Ait-Aissa M](#), [Huneau JF](#), [Huybregts L](#), [Kolsteren P](#)

## Randomised trials in child health in developing countries 2017-18

**Background:** Limited evidence is available on the impact that unconditional cash transfer (UCT) programs can have on child nutrition, particularly in West Africa, where child undernutrition is still a public health challenge.

**Objective:** This study examined the impact of a multiannual, seasonal UCT program to reduce the occurrence of wasting (weight-for-height, midupper arm circumference), stunting (height-for-age), and morbidity among children <36 mo old in Tapoa Province, in the eastern region of Burkina Faso.

**Methods:** The study was designed as a 2-arm cluster-randomized controlled trial, with 32 villages randomly assigned to either the intervention or the control group. The study population comprised households that were classified as poor or very poor according to household economy approach criteria and that had  $\geq 1$  child <1 y of age at inclusion. The intervention consisted of seasonal UCTs, provided monthly from July to November, over 2 y (2013 and 2014). A monthly allowance of 10,000 West African Financial Community of Africa francs (~US\$17) was given by mobile phone to mothers in participating households. Anthropometric measurements and morbidity were recorded on a quarterly basis.

**Results:** We found no evidence that multiannual, seasonal UCTs reduced the cumulative incidence of wasting in young children [incidence rate ratio: 0.92 (95% CI: 0.64, 1.32);  $P = 0.66$ ]. We observed no significant difference ( $P > 0.05$ ) in children's anthropometric measurements and stunting between the 2 groups at the end point. However, children in the intervention group had a lower risk [21% (95% CI: 18.6%, 21.3%);  $P < 0.001$ ] of self-reported respiratory tract infections than did children in the control group.

**Conclusions:** We found that seasonal UCTs in the framework of safety nets did not result in a significant decrease in the incidence of acute malnutrition among children in Tapoa Province. Cash transfers combined with complementary interventions targeted to child nutrition and health should be investigated further. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as [NCT01866124](https://clinicaltrials.gov/ct2/show/study/NCT01866124).

<https://academic.oup.com/jn/article/147/7/1410/4743674>

[Int J Equity Health](#). 2017 Oct 18;16(1):183. doi: 10.1186/s12939-017-0681-0.

**[Women's education level amplifies the effects of a livelihoods-based intervention on household wealth, child diet, and child growth in rural Nepal.](#)**

[Miller LC](#), [Joshi N](#), [Lohani M](#), [Rogers B](#), [Mahato S](#), [Ghosh S](#), [Webb P](#).

### BACKGROUND:

Many organizations seek to alleviate poverty in the developing world, often focusing their interventions on women. The role, status, and education of women are fundamentally important facets of development. Thus, understanding the interaction of women's educational level and the response to interventions is important. Therefore, we examined the impact of educational level of household adults on responses to a livestock-based community intervention.

### METHODS:

Six pair-matched communities in 3 districts of Nepal (Chitwan/Nawalparasi/Nuwakot), were randomly assigned to receive community development activities via women's self-help groups at baseline or 1 year later. At 6 intervals over 48 months, a 125-item questionnaire addressing family demographics and child health/nutrition was completed in each household, plus child growth monitoring. Results were analyzed in relation to the highest education attained by any woman in the household, the child's mother, men, or any other adult in the household.

### RESULTS:

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Outcomes (wealth, water/toilet availability, child diet diversity and growth) all significantly related to adult education. However, notable differences were found comparing the impact of men's and women's education. Percent change in wealth score was significant only in households where women had primary or secondary education (respectively,  $p = .0009$  and  $p < .0001$ ). Increased soap use related only to women's education ( $p < .0001$ ). When adjusted for group assignment, baseline income, wealth, and animal scores, higher women's education was significantly associated with increased household wealth ( $p < .0001$ ), better child height-for-age z scores (HAZ,  $p = .005$ ), and improved child diet diversity ( $p = .01$ ). Higher mother's education predicted better child HAZ (primary,  $p = .01$ , secondary,  $p = .03$ ) and diet diversity (primary,  $p = .05$ , secondary,  $p < .0001$ ). Higher men's education was significantly associated with household wealth ( $p = .02$ ) and child diet diversity ( $p = .04$ ), but not HAZ; higher education of any household member was associated only with household wealth ( $p < .0001$ ). Moreover, households where the mother's education was better than the best-educated man also were significantly more likely to have children with better HAZ and dietary diversity ( $p = .03$ ,  $p < .0001$ ). Thus, the educational level of women and mothers had the broadest impact on child outcome variables.

### CONCLUSIONS:

Household characteristics vary among participants in most community development projects. Of these, adult education likely mediates response to the inputs provided by the intervention. Particularly in interventions directed towards women, better education may enhance the ability of households to put interventions into practice, thus improving wealth, hygiene, and child diet and growth indices.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648516/>

[J Pediatr Gastroenterol Nutr.](#) 2017 Dec;65(6):667-672. doi: 10.1097/MPG.0000000000001662.

### Adaptation of New Colombian Food-based Complementary Feeding Recommendations Using Linear Programming.

[Tharrey M](#), [Olaya GA](#), [Fewtrell M](#), [Ferguson E](#).

### OBJECTIVE:

The aim of the study was to use linear programming (LP) analyses to adapt NewComplementary Feeding Guidelines (NCFg) designed for infants aged 6 to 12 months living in poor socioeconomic circumstances in Bogota to ensure dietary adequacy for young children aged 12 to 23 months.

### DESIGN:

A secondary data analysis was performed using dietary and anthropometric data collected from 12-month-old infants ( $n=72$ ) participating in a randomized controlled trial. LP analyses were performed to identify nutrients whose requirements were difficult to achieve using local foods as consumed; and to test and compare the NCFg and alternative food-based recommendations (FBRs) on the basis of dietary adequacy, for 11 micronutrients, at the population level.

### RESULTS:

Thiamine recommended nutrient intakes for these young children could not be achieved given local foods as consumed. NCFg focusing only on meat, fruits, vegetables, and breast milk ensured dietary adequacy at the population level for only 4 micronutrients, increasing to 8 of 11 modelled micronutrients when the FBRs promoted legumes, dairy, vitamin A-rich vegetables, and chicken giblets. None of the FBRs tested ensured population-level dietary adequacy for thiamine, niacin, and iron unless a fortified infant food was recommended.

### CONCLUSIONS:

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The present study demonstrated the value of using LP to adapt NCFg for a different age group than the one for which they were designed. Our analyses suggest that to ensure dietary adequacy for 12- to 23-month olds these adaptations should include legumes, dairy products, vitamin A-rich vegetables, organ meat, and a fortified food.

[https://journals.lww.com/jpgn/fulltext/2017/12000/Adaptation\\_of\\_New\\_Colombian\\_Food\\_base\\_d.16.aspx](https://journals.lww.com/jpgn/fulltext/2017/12000/Adaptation_of_New_Colombian_Food_base_d.16.aspx)

*Public Health Nutr.* 2017 Aug;20(11):2034-2041. doi: 10.1017/S1368980017000751. Epub 2017 May 23.

### **Effect of childhood nutrition counselling on intelligence in adolescence: a 15-year follow-up of a cluster-randomised trial.**

[Munhoz TN](#), [Santos IS](#), [Karam SM](#), [Martines J](#), [Pelto G](#), [Barcelos R](#), [Gonçalves H](#), [Valle NC](#), [Anselmi L](#), [Matijasevich A](#).

#### **OBJECTIVE:**

The present study aimed to assess the effects of an early childhood nutrition counselling intervention on intelligence (as measured by the intelligence quotient (IQ)) at age 15-16 years.

#### **DESIGN:**

A single-blind, cluster-randomised trial.

#### **SETTING:**

In 1998, in Southern Brazil, mothers of children aged 18 months or younger were enrolled in a nutrition counselling intervention (n 424). Counselling included encouragement and promotion of exclusive breast-feeding until 6 months of age and continued breast-feeding supplemented by protein-, lipid- and carbohydrate-rich foods after age 6 months up to age 2 years. The control group received routine feeding advice. In 2013, the fourth round of follow-up of these individuals, at the age of 15-16 years, was undertaken. IQ was assessed using the short form of the Wechsler Adult Intelligence Scale (WAIS-III). Mental disorders (evaluated using the Development and Well-Being Assessment (DAWBA)) and self-reported school failure, smoking and alcohol use were also investigated. Adjusted analyses were conducted using a multilevel model in accordance with the sampling process.

#### **SUBJECTS:**

Adolescents, mean (sd) age of 15.4 (0.5) years (n 339).

#### **RESULTS:**

Mean (sd) total IQ score was lower in the intervention group than the control group (93.4 (11.4) and 95.8 (11.2), respectively) but the association did not persist after adjustment. The prevalence of any mental disorders was similar between intervention and control groups (23.1 and 23.5 %, respectively). There were no differences between groups regarding school failure, smoking and alcohol use.

#### **CONCLUSIONS:**

Nutrition counselling intervention in early childhood had no effect on intelligence measured during adolescence.

[https://www.cambridge.org/core/services/aop-cambridge-core/content/view/911AFBBD3067D5857F97C23709CFB869/S1368980017000751a.pdf/effect\\_of\\_childhood\\_nutrition\\_counselling\\_on\\_intelligence\\_in\\_adolescence\\_a\\_15year\\_followup\\_of\\_a\\_clusterrandomised\\_trial.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/911AFBBD3067D5857F97C23709CFB869/S1368980017000751a.pdf/effect_of_childhood_nutrition_counselling_on_intelligence_in_adolescence_a_15year_followup_of_a_clusterrandomised_trial.pdf)

## Obesity

[BMJ Open](#). 2017 Dec 1;7(11):e018415. doi: 10.1136/bmjopen-2017-018415.

**Cluster-randomised controlled trial to assess the effectiveness and cost-effectiveness of an obesity prevention programme for Chinese primary school-aged children: the CHIRPY DRAGON study protocol.**

[Li B](#), [Liu WJ](#), [Adab P](#), [Pallan M](#), [Hemming K](#), [Frew E](#), [Lin R](#), [Martin J](#), [Liu W](#), [Cheng KK](#).

### **INTRODUCTION:**

Childhood obesity in China has increased more rapidly and over a shorter time period than in other countries. However, there is a paucity of rigorously developed and evaluated prevention interventions. We aim to evaluate the clinical and cost-effectiveness as well as the implementation process of a complex multicomponent intervention developed using the UK Medical Research Council (MRC) framework. This study provides one of the first examples of rigorous development and evaluation of a childhood obesity prevention programme in a non-western population using the MRC methods.

### **METHODS AND ANALYSIS:**

A cluster-randomised controlled trial in 40 primary schools in Guangzhou, China, including children aged 6-7 years at baseline. Schools will be randomly allocated to either the usual practice (n=20) or intervention arm (n=20). The 12-month intervention consists of four components targeting diet and physical activity behaviours in and outside school, with family involvement. The primary objective is to compare the difference in mean body mass index (BMI) z-score between the intervention and control arms at the end of the intervention (starting March/April 2017). A sample size of 1640 pupils recruited from 40 schools is sufficient to detect a difference of 0.17 units in the mean BMI z-score with a power of 80% (ICC=0.01, ICC, intraclass correlation coefficient) and a significance level of 5%. Treatment effects will be tested using a mixed linear model in STATA adjusting for the child baseline BMI z-score and clustering by school. All analyses will be by intention to treat. Secondary analyses will additionally adjust for prespecified school-level and child-level covariates. The incremental cost-effectiveness ratio for the intervention versus usual practice will be 'cost per quality-adjusted life year (QALY)'. Cost per change in BMI z-score will also be assessed. A range of methods will be used to evaluate intervention implementation, mechanisms of impact and contextual factors.

### **ETHICS AND DISSEMINATION:**

Ethical approval was obtained from the Life and Health Sciences Ethical Review Committee at the University of Birmingham and the Ethical Committee of Guangzhou Centre for Disease Control and Prevention. The primary, secondary, process evaluation and economic evaluation results of the trial will be disseminated through relevant international peer-reviewed journals and conferences.

<https://bmjopen.bmj.com/content/7/11/e018415>

[Pediatrics](#). 2017 Dec;140(6). pii: e20171221. doi: 10.1542/peds.2017-1221. Epub 2017 Nov 10.

**Effectiveness of a Kindergarten-Based Intervention for Preventing Childhood Obesity.**

[Hu Y](#), [He JR](#), [Liu FH](#), [Li WD](#), [Lu JH](#), [Xing YF](#), [Lin SF](#), [Liu X](#), [Bartington S](#), [Feng Q](#), [Xia HM](#), [Lam KBH](#), [Cheng KK](#), [Qiu X](#)

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### **BACKGROUND AND OBJECTIVES:**

Interventions to prevent childhood obesity targeting school age children have mostly reported limited effectiveness, suggesting such prevention programs may need to start at an earlier age, but evidence has been scarce. We reported a pilot study aiming to demonstrate the feasibility of a multifaceted intervention for preschool children and to provide a preliminary assessment of the effectiveness.

### **METHODS:**

This nonrandomized controlled trial recruited children aged 3 to 6 years from 6 kindergartens in Guangzhou, China. Based on the preference of the School and Parents Committees, 4 kindergartens (648 children) received a 3-component intervention (training of kindergarten staff, initiating healthy curriculum for children, and close collaboration between families and kindergartens) over 12 months, while the other 2 kindergartens (336 children), serving as controls, received routine health care provision. Outcome measures were the changes in BMI  $z$  score between baseline and the end of 12 months, and the prevalence of postintervention children who were overweight or obese.

### **RESULTS:**

By 12 months, children within the intervention group had a smaller BMI  $z$  score increase (0.24) compared to the control (0.41), with a difference of -0.31 (95% CI -0.47 to -0.15). The prevalence of overweight or obesity was also lower among the intervention group at the end of the study (OR: 0.43, 95% CI 0.19 to 0.96), adjusted for baseline status.

### **CONCLUSIONS:**

Our results indicated a multicomponent health behavior intervention might be effective in reducing the prevalence of obesity, but the longer term effects will need confirmation from randomized controlled trials.

<http://pediatrics.aappublications.org/content/140/6/e20171221.long>

[J Pediatr.](#) 2017 Oct;189:143-148.e1. doi: 10.1016/j.jpeds.2017.06.037. Epub 2017 Jul 11.

### **Validity and Reliability of the Brazilian Version of the Weight Control Behaviors Scale.**

[Dunker KLL](#), [Claudino AM](#).

### **OBJECTIVE:**

To develop and validate the weight-control behaviors (WCBs) scale and to evaluate its psychometric properties.

### **STUDY DESIGN:**

We made use of data from a cluster-randomized trial assessing the effectiveness of the Brazilian New Moves Program. The Brazilian New Moves Program was a multicomponent intervention aimed at preventing weight-related problems among adolescent girls in public schools in São Paulo, Brazil.

### **RESULTS:**

Healthy and unhealthy WCBs were strongly associated. A 2-factor solution was the best model to explain the correlation across items, including following constructs: (1) healthy WCB: exercising, eating more fruits and vegetables, drinking less regular soda or sweetened drinks, eating fewer sweets, and paying attention to portion sizes; and (2) unhealthy WCB: skipping meals and the presence of any other, combined unhealthy weight-control behaviors, including fasting, eating little, going on a diet, vomiting, taking diet pills, using diuretics (water pills), using laxatives, using food substitutes (powder/special drinks), and smoking more cigarettes. The WCB scale was determined to be reliable (internally consistent) and valid, with high scores



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positively associated with body dissatisfaction and high body mass index values. Individual reliability values were high for factors representing healthy and unhealthy WCBs.

### CONCLUSIONS:

Our findings support the use of the WCB scale as a screening tool for overall weight control behaviors among female adolescents. This assessment tool should be considered in future observational and experimental prospective studies.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0022347617308879?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0022347617308879%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## Oncology

(see also HIV – management of HIV related conditions)

[JAMA Oncol.](#) 2017 Sep 1;3(9):1222-1227. doi: 10.1001/jamaoncol.2017.0324.

### Metronomic Chemotherapy vs Best Supportive Care in Progressive Pediatric Solid Malignant Tumors: A Randomized Clinical Trial.

[Pramanik R](#), [Agarwala S](#), [Gupta YK](#), [Thulkar S](#), [Vishnubhatla S](#), [Batra A](#), [Dhawan D](#), [Bakhshi S](#).

#### IMPORTANCE:

Although oral metronomic chemotherapy is often used in progressive pediatric solid malignant tumors, a literature review reveals that only small single-arm retrospective or phase 1 and 2 studies have been performed. Skepticism abounds because of the lack of level 1 evidence.

#### OBJECTIVES:

To compare the effect of metronomic chemotherapy on progression-free survival (PFS) with that of placebo in pediatric patients with primary extracranial, nonhematopoietic solid malignant tumors that progress after at least 2 lines of chemotherapy.

#### DESIGN, SETTING, AND PARTICIPANTS:

A double-blinded, placebo-controlled randomized clinical trial was conducted from October 1, 2013, through December 31, 2015, at the cancer center at All India Institute of Medical Sciences in children aged 5 to 18 years with primary extracranial, nonhematopoietic solid malignant tumors that progressed after at least 2 lines of chemotherapy and had no further curative options.

#### INTERVENTIONS:

One arm received a 4-drug oral metronomic regimen of daily celecoxib and thalidomide with alternating periods of etoposide and cyclophosphamide, whereas the other arm received placebo. Disease status was assessed at baseline, 9 weeks, 18 weeks, and 27 weeks or at clinical progression.

#### MAIN OUTCOMES AND MEASURES:

The primary end point was PFS as defined by the proportion of patients without disease progression at 6 months, and PFS duration and overall survival (OS) were secondary end points.

#### RESULTS:

A total of 108 of the 123 patients screened were enrolled, with 52 randomized to the placebo group (median age, 15 years; 40 male [76.9%]) and 56 to the metronomic chemotherapy group (median age, 13 years; 42 male [75.0%]). At a median follow-up of 2.9 months, 100% of the patients had disease progression by 6 months in the placebo group vs 96.4% in the metronomic chemotherapy group ( $P = .24$ ). Median PFS and OS in the 2 groups was similar (hazard ratio [HR], 0.69; 95% CI, 0.47-1.03 [ $P = .07$ ] for PFS; and HR, 0.74; 95% CI, 0.50-1.09 [ $P = .13$ ] for OS). In post hoc subgroup analysis, cohorts receiving more than 3 cycles (HR for PFS, 0.46;

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95% CI, 0.23-0.93; P = .03) and those without a bone sarcoma (ie, neither primitive neuroectodermal tumor nor osteosarcoma) (HR for PFS, 0.39; 95% CI, 0.18-0.81; P = .01) appeared to benefit from metronomic chemotherapy.

### CONCLUSIONS AND RELEVANCE:

Metronomic chemotherapy does not improve 6-month PFS, compared with placebo, among pediatric patients with extracranial progressive solid malignant tumors. However, patients without bone sarcoma and those able to tolerate therapy for more than 3 cycles (9 weeks) benefit.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5824286/>

## Ophthalmology

*PLoS One*. 2017 Nov 21;12(11):e0187808. doi: 10.1371/journal.pone.0187808. eCollection 2017.

### Cluster-randomized controlled trial of the effects of free glasses on purchase of children's glasses in China: The PRICE (Potentiating Rural Investment in Children's Eyecare) study.

[Wang X](#), [Congdon N](#), [Ma Y](#), [Hu M](#), [Zhou Y](#), [Liao W](#), [Jin L](#), [Xiao B](#), [Wu X](#), [Ni M](#), [Yi H](#), [Huang Y](#), [Varga B](#), [Zhang H](#), [Cun Y](#), [Li X](#), [Yang L](#), [Liang C](#), [Huang W](#), [Rozelle S](#), [Ma X](#)

### BACKGROUND:

Offering free glasses can be important to increase children's wear. We sought to assess whether "Upgrade glasses" could avoid reduced glasses sales when offering free glasses to children in China.

### METHODS:

In this cluster-randomized, controlled trial, children with uncorrected visual acuity (VA)  $\leq 6/12$  in either eye correctable to  $>6/12$  in both eyes at 138 randomly-selected primary schools in 9 counties in Guangdong and Yunnan provinces, China, were randomized by school to one of four groups: glasses prescription only (Control); Free Glasses; Free Glasses + offer of \$15 Upgrade Glasses; Free Glasses + offer of \$30 Upgrade Glasses. Spectacle purchase (main outcome) was assessed 6 months after randomization.

### RESULTS:

Among 10,234 children screened, 882 (8.62%, mean age 10.6 years, 45.5% boys) were eligible and randomized: 257 (29.1%) at 37 schools to Control; 253 (28.7%) at 32 schools to Free Glasses; 187 (21.2%) at 31 schools to Free Glasses + \$15 Upgrade; and 185 (21.0%) at 27 schools to Free Glasses + \$30 Upgrade. Baseline ownership among these children needing glasses was 11.8% (104/882), and 867 (98.3%) children completed follow-up. Glasses purchase was significantly less likely when free glasses were given: Control: 59/250 = 23.6%; Free glasses: 32/252 = 12.7%,  $P = 0.010$ . Offering Upgrade Glasses eliminated this difference: Free + \$15 Upgrade: 39/183 = 21.3%, multiple regression relative risk (RR) 0.90 (0.56-1.43),  $P = 0.65$ ; Free + \$30 Upgrade: 38/182 = 20.9%, RR 0.91 (0.59, 1.42),  $P = 0.69$ .

### CONCLUSIONS:

Upgrade glasses can prevent reductions in glasses purchase when free spectacles are provided, providing important program income.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5697864/>

[Acta Ophthalmol.](#) 2017 Sep;95(6):567-575. doi: 10.1111/aos.13149. Epub 2016 Jun 20.

**[Self-refraction, ready-made glasses and quality of life among rural myopic Chinese children: a non-inferiority randomized trial.](#)**

[Zhou Z](#), [Chen T](#), [Jin L](#), [Zheng D](#), [Chen S](#), [He M](#), [Silver J](#), [Ellwein L](#), [Moore B](#), [Congdon NG](#)

**PURPOSE:**

To study, for the first time, the effect of wearing ready-made glasses and glasses with power determined by self-refraction on children's quality of life.

**METHODS:**

This is a randomized, double-masked non-inferiority trial. Children in grades 7 and 8 (age 12-15 years) in nine Chinese secondary schools, with presenting visual acuity (VA)  $\leq 6/12$  improved with refraction to  $\geq 6/7.5$  bilaterally, refractive error  $\leq -1.0$  D and  $< 2.0$  D of anisometropia and astigmatism bilaterally, were randomized to receive ready-made spectacles (RM) or identical-appearing spectacles with power determined by: subjective cycloplegic retinoscopy by a university optometrist (U), a rural refractionist (R) or non-cycloplegic self-refraction (SR). Main study outcome was global score on the National Eye Institute Refractive Error Quality of Life-42 (NEI-RQL-42) after 2 months of wearing study glasses, comparing other groups with the U group, adjusting for baseline score.

**RESULTS:**

Only one child (0.18%) was excluded for anisometropia or astigmatism. A total of 426 eligible subjects (mean age 14.2 years, 84.5% without glasses at baseline) were allocated to U [103 (24.2%)], RM [113 (26.5%)], R [108 (25.4%)] and SR [102 (23.9%)] groups, respectively. Baseline and endline score data were available for 398 (93.4%) of subjects. In multiple regression models adjusting for baseline score, older age ( $p = 0.003$ ) and baseline spectacle wear ( $p = 0.016$ ), but not study group assignment, were significantly associated with lower final score.

**CONCLUSION:**

Quality of life wearing ready-mades or glasses based on self-refraction did not differ from that with cycloplegic refraction by an experienced optometrist in this non-inferiority trial.

[Am J Ophthalmol.](#) 2018 Jun 12;193:33-44. doi: 10.1016/j.ajo.2018.06.005. [Epub ahead of print]

**[Five-Year Postoperative Outcomes of Bilateral Aphakia and Pseudophakia in Children up to 2 Years of Age: A Randomized Clinical Trial.](#)**

[Vasavada AR](#), [Vasavada V](#), [Shah SK](#), [Praveen MR](#), [Vasavada VA](#), [Trivedi RH](#), [Rawat F](#), [Koul A](#).

**PURPOSE:**

Comparative evaluation of complications and visual outcomes following bilateral congenital cataract surgery in children up to 2 years of age with and without primary intraocular lens (IOL) implantation at 5 years follow-up.

**DESIGN:**

Randomized controlled clinical trial.

**METHODS:**

Sixty children (120 eyes) up to 2 years of age undergoing bilateral congenital cataract surgery were randomized to Group 1, primary aphakia ( $n = 30$ ), or Group 2, primary IOL implantation

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(pseudophakia) (n = 30). A single surgeon performed surgeries with identical surgical technique. All patients were followed up regularly until 5 years postoperatively. At each follow-up, glaucoma, visual axis obscuration (VAO) requiring surgery, and inflammation (cell deposits, posterior synechiae) were assessed. Visual acuity was assessed until 5 years follow-up. The first operated eye was selected for statistical analysis.

### RESULTS:

Median age of the patients at time of surgery was 5.11 months (aphakia group) and 6.01 months (pseudophakia group) (P = .56). Five years postoperatively, incidence of glaucoma was 16% and 13.8% in Groups 1 and 2 (P = .82). Incidence of posterior synechiae was significantly higher in the pseudophakia group (27.6%) compared to the aphakia group (8%) (P = .004). VAO requiring surgery was seen in 8% and 10.3% of eyes in Groups 1 and 2 (P = .76). Mean logMAR visual acuity at 5 years follow-up was  $0.59 \pm 0.33$  and  $0.5 \pm 0.23$  in Groups 1 and 2, respectively (P = .79). However, more eyes in the pseudophakic group started giving documentable vision earlier in their postoperative follow-ups.

### CONCLUSIONS:

Incidence of postoperative complications was comparable between the groups, except for a higher incidence of posterior synechiae in pseudophakic eyes. Visual rehabilitation was faster in the pseudophakic group.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0002939418302691?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002939418302691%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## Trachoma

## Oral health / dentistry

[Int J Clin Pediatr Dent.](#) 2017 Jul-Sep;10(3):234-239. doi: 10.5005/jp-journals-10005-1442. Epub 2017 Feb 27.

### [Comparison of Antimicrobial Efficacy of Green Tea, Garlic with Lime, and Sodium Fluoride Mouth Rinses against \*Streptococcus mutans\*, \*Lactobacilli\* species, and \*Candida albicans\* in Children: A Randomized Double-blind Controlled Clinical Trial.](#)

[Thomas A](#), [Thakur S](#), [Habib R](#).

### INTRODUCTION:

With greater awareness worldwide, the use of herbs and herbal products has increased to a large extent.

### OBJECTIVE:

To evaluate and compare the antimicrobial efficacy of green tea, garlic with lime, and 0.05% sodium fluoride (NaF) mouth rinses against *Streptococcus mutans*, *Lactobacilli* species, and *Candida albicans*.

### MATERIALS AND METHODS:

A total of 45 children aged 4 to 6 years with severe early childhood caries (S-ECC; based on decayed extracted filled [def] score) were selected. Children were divided randomly into three equal groups and were asked to rinse with the prescribed mouth rinse once daily for 2 weeks after breakfast under supervision. A base-line and postrinsing nonstimulated whole salivary

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sample (2 mL) was collected and tested for the number of colony-forming units (CFUs). The data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0 software with one-way analysis of variance (ANOVA) and Tukey's *post hoc* test.

### RESULTS:

A statistically significant fall in colony count was found with the three mouth rinses in *S. mutans* ( $p < 0.001$ ,  $p < 0.001$ ) and *Lactobacilli* spp. ( $p < 0.001$ ,  $p < 0.001$ ), but not against *C. albicans* ( $p = 0.264$ ,  $p = 0.264$ ). On comparison, no statistically significant difference was found against *S. mutans* ( $p = 1$ ,  $p = 0.554$ ,  $p = 0.572$ ), *lactobacilli* spp. ( $p = 0.884$ ,  $p = 0.999$ ,  $p = 0.819$ ), and *C. albicans* ( $p = 0.999$ ,  $p = 0.958$ ,  $p = 0.983$ ).

### CONCLUSION:

The findings of this study indicate that green tea and garlic with lime mouth rinse can be an economical alternative to NaF mouth rinse both for prevention and therapeutics.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5661035/>

[J Contemp Dent Pract.](#) 2017 Dec 1;18(12):1190-1193.

### Caries Preventive Effect of Sodium Fluoride Varnish on Deciduous Dentition: A Clinical Trial.

[Patil SK](#), [Fatangare M](#), [Jadhav RG](#), [Shinde GR](#), [Pawar SS](#), [Kathariya MD](#).

### AIM:

The aim of the study is to evaluate the efficacy of intensive application of sodium fluoride varnish in reducing caries incidence among children aged 6 to 7 years.

### MATERIALS AND METHODS:

The study was a randomized controlled trial conducted among 6- to 7-year-old children of Sangamner, Maharashtra, India. Nearly 200 randomly selected children were randomized into two groups: Control group and intervention (varnish) group. Dental examination to record the caries experiences was conducted at baseline and at 1-year follow-up. The fluoride varnish was applied for three times in a week for a period of 1 year. Mean decayed, missed, and filled teeth (DMFT) were compared between and within groups using t-test.

### RESULTS:

Out of 200 participants, there were 3 dropouts for control group and 4 for intervention group. Nearly 55% study participants were males and remaining were females. There was a statistically significant difference between the baseline and follow-up caries levels in varnish group for deciduous dentition. Mean caries reduction in this study was 26%.

### CONCLUSION:

After 1 year of study, we found significant caries reversal in deciduous dentition among the 6- to 7-year-olds after intensive fluoride application. Such a regimen can be advocated to encourage the practitioners and the caregivers alike for early caries prevention.

### CLINICAL SIGNIFICANCE:

Intensive fluoride application (three times a week) once a year was found to be effective in reducing the incidence of detectable carious lesions and can be advocated to the dental professionals to be incorporated in their routine preventive clinical practice.

<https://pdfs.semanticscholar.org/660c/345c4e85654d4f30c68f3e4bd0731f24ee18.pdf>

[Int J Clin Pediatr Dent.](#) 2018 Mar-Apr;11(2):66-70. doi: 10.5005/jp-journals-10005-1487. Epub 2018 Apr 1.

**Comparison of the Effectiveness of Probiotic, Chlorhexidine-based Mouthwashes, and Oil Pulling Therapy on Plaque Accumulation and Gingival Inflammation in 10- to 12-year-old Schoolchildren: A Randomized Controlled Trial.**

Kandaswamy SK, Sharath A, Priya PG.

**INTRODUCTION:**

The use of a mouthwash augments mechanical removal of plaque by brushing and flossing and helps maintain oral health through its antiplaque and antibacterial chemical properties.

**AIM:**

To evaluate the effectiveness of a probiotic mouthwash, sesame oil pulling therapy, and chlorhexidine-based mouth-wash on plaque accumulation and gingival inflammation in schoolchildren aged 10 to 12 years.

**MATERIALS AND METHODS:**

The randomized controlled trial included 45 healthy schoolchildren aged 10 to 12 years and studying in Government High School, Tiruchengode, Tamil Nadu, India. The participants were randomly divided into three groups, I, II, and III, with 15 children in each group as follows: group I: probiotic mouthwash; group II: chlorhexidine mouthwash; and group III: sesame oil. Baseline scores of plaque index (PI) and modified gingival index (GI) were recorded followed by a full mouth oral prophylaxis. The designated mouth rinses were distributed to the respective groups and they were instructed to rinse once daily. Their parents supervised the children during the use of mouthwash. On the 15th and 30th day, the children were subjected to the same clinical measurements. Children's acceptance of their plaque control method was assessed using a modified facial image scale.

**RESULTS:**

Intragroup comparisons for both the GI and PI scores were statistically significant ( $p \leq 0.001$ ) in all the three groups. Difference in the GI scores between the 15th and 30th day was statistically significant for chlorhexidine group alone ( $p = 0.024$ ). Intergroup comparisons between the three groups were not statistically significant.

**CONCLUSION:**

Probiotic mouthwash, chlorhexidine mouthwash, and sesame oil were equally effective in reducing plaque and in improving the gingival status of children. The difference between the gingival scores on the 15th and 30th day was statistically significant in the chlorhexidine group.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6034046/>

J Indian Soc Periodontol. 2018 Jan-Feb;22(1):34-39. doi: 10.4103/jisp.jisp\_356\_17.

**Effectiveness of three mouthwashes - Manuka honey, Raw honey, and Chlorhexidine on plaque and gingival scores of 12-15-year-old school children: A randomized controlled field trial.**

Singhal R, Siddibhavi M, Sankeshwari R, Patil P, Jalihal S, Ankola A.

**OBJECTIVES:**

The aim of this study is to compare the effectiveness of three types of mouthwashes manuka honey (MH), raw honey (RH), and chlorhexidine (CHX) on plaque and gingival scores of 12-15-year-old government school children.

**STUDY DESIGN:**

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This study was a double-blind, randomized controlled field trial conducted in Belagavi city, India.

### **MATERIALS AND METHODS:**

One hundred and thirty-five government school children aged 12-15 years were randomly selected and allocated into three groups, RH, MH, and CHX mouthwash groups. Ten milliliters each of honey-based mouthwash formulation and CHX mouthwashes (0.2%) were administered according to the group allocation twice daily for 21 days. All the children were examined at baseline, 22<sup>nd</sup> day (after discontinuation of mouthwash) and 28<sup>th</sup> day (1 week after discontinuation of mouthwash) for Gingival (Loe and silness 1963) and Plaque Index (Silness and Loe, 1964).

### **RESULTS:**

Descriptive statistics was applied for distribution of study participants according to age and gender. One-way ANOVA followed by Tukey's *post hoc* test and repeated measures ANOVA test followed by Bonferroni's *post hoc* were applied for inter- and intragroup comparison, respectively. Statistically significant reductions ( $P < 0.001$ ) in plaque and gingival scores were observed in all the three types of mouthwash groups at the end of the 22<sup>nd</sup> day and 28<sup>th</sup> day. MH and RH mouthwash demonstrated equal effectiveness, whereas CHX mouthwash showed the maximum reduction in clinical parameters.

### **CONCLUSION:**

Honey-based mouthwash showed a promising antimicrobial effect on dental caries and plaque and gingival scores.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5855267/>

### **Comment**

*An interesting result, the antibacterial effect of honey is well known, but given the sugar in honey it is surprising caries were reduced!*

[Int J Clin Pediatr Dent.](#) 2018 Jan-Feb;11(1):13-17. doi: 10.5005/jp-journals-10005-1476. Epub 2017 Feb 1.

### **Evaluating the Efficacy of Xylitol Wipes on Cariogenic Bacteria in 19- to 35-month-old Children: A Double-blind Randomized Controlled Trial.**

[Kayalvizhi G](#), [Nivedha D](#), [Sajeev R](#), [Prathima GS](#), [Suganya M](#), [Ramesh V](#).

### **INTRODUCTION:**

Dental caries is an infectious disease with *Streptococcus mutans* as the main cariogenic bacteria. Children with early *S. mutans* colonization have a higher risk of developing dental caries than those with later colonization. Therefore, prevention or delay of *S. mutans* colonization may be advantageous for the prevention of early childhood caries (ECC).

### **AIM:**

To evaluate and compare the effectiveness of xylitol and placebo wipes on *S. mutans* count in 19- to 35-month-old children.

### **MATERIALS AND METHODS:**

Forty-four children were randomly selected from a daycare center and divided into two groups. Allocation concealment was done and both (placebo and xylitol) wipes were distributed to their parents. Instructions were given regarding their use, to be used twice daily for 2 weeks and the *S. mutans* levels in the saliva were enumerated before and after wipes usage. The collected data were tabulated and statistically analyzed using paired and unpaired t-tests.

### **RESULTS:**

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A clinically significant decrease in the *S. mutans* count was observed in the xylitol wipes group than the placebo wipes group. Intergroup comparison results were found to be statistically insignificant.

### CONCLUSION:

Xylitol wipes usage could serve as a useful adjunct in reducing the cariogenic bacteria, especially *S. mutans*, and thus can be considered as an adjunct oral hygiene tool for caries prevention in young children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5968156/>

[Contemp Clin Dent](#). 2018 Apr-Jun;9(2):170-173. doi: 10.4103/ccd.ccd\_749\_17.

### Effectiveness of Plaque Control with Novel Pediatric Oral Hygiene Need Station (Modified Oral Irrigation Device) as Compared with Manual Brushing and Flossing: Randomized Controlled Pilot Trial.

[Murthy PS](#), [Shaik N](#), [Deshmukh S](#), [Girish MS](#).

### BACKGROUND:

Establishing good hygiene habits are valuable for present and future oral health. Below 6 years, tooth brushing should be performed by parents, as increasing dexterity and cognition may permit supervised brushing until the child is capable of independent brushing.

### AIM AND OBJECTIVES:

The aim of the present study was to evaluate the effectiveness of modified oral irrigation device in children in terms of plaque control and to compare the effectiveness of plaque control with manual brushing with the modified oral irrigation device in children.

### MATERIALS AND METHODS:

A randomized clinical trial was performed on 12 subjects who were allocated to the two study groups. After obtaining the consent, the control group was instructed tooth brushing with regular pediatric commercially available toothbrush and the intervention group with modified oral irrigation device. Plaque scores in both groups were assessed pre- and post-brushing using modified navy plaque index.

### RESULTS:

The data were subjected to Descriptive statistics and Paired *t*-test using SPSS version 22. Intragroup comparison of mean difference of plaque score in control group and intervention group pre- and post-brushing was statistically significant. Intergroup comparison of manual brushing group with modified oral irrigation group shows  $P < 0.05$  was statistically significant.

### CONCLUSION:

Within the limitation of the present study, it has been found novel pediatric oral hygiene need Station is more effective than manual brushing since it combined the effect of brushing, flossing (water floss), and rinsing in children simultaneously and at the same time did not demand any special motor skill.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5968677/>

## Poisoning and toxins

(See envenomation)



## Quality of care

[Trials](#). 2017 Sep 7;18(1):416. doi: 10.1186/s13063-017-2152-8.

### [Effect of enhanced feedback to hospitals that are part of an emerging clinical information network on uptake of revised childhood pneumonia treatment policy: study protocol for a cluster randomized trial.](#)

[Ayieko P](#), [Irimu G](#), [English M](#)

#### **BACKGROUND:**

The national pneumonia treatment guidelines in Kenya changed in February 2016 but such guideline changes are often characterized by prolonged delays in affecting practice. We designed an enhanced feedback intervention, delivered within an ongoing clinical network that provides a general form of feedback, aimed at improving and sustaining uptake of the revised pneumonia treatment policy. The objective was to determine whether **an enhanced feedback intervention will improve correctness of classification and treatment of childhood pneumonia**, compared to an existing approach to feedback, after nationwide treatment policy change and within an existing hospital network.

#### **METHODS/DESIGN:**

A pragmatic, cluster randomized trial conducted within a clinical network of 12 Kenyan county referral hospitals providing inpatient pediatric care to children (aged 2-59 months) with acute medical conditions between March and November 2016. The intervention comprised **enhanced feedback (monthly written feedback incorporating goal setting, and action planning delivered by a senior clinical coordinator for selected pneumonia indicators) and this was compared to standard feedback (2-monthly written feedback on multiple quality of pediatric care indicators)** both delivered within a clinical network promoting clinical leadership linked to mentorship and peer-to-peer support, and improved use of health information on service delivery. **The 12 hospitals were randomized to receive either enhanced feedback (n = 6) or standard feedback (n = 6) delivered over a 9-month period following nationwide pneumonia treatment policy change. The primary outcome is the proportion of all admitted patients with pneumonia (fulfilling criteria for treatment with orally administered amoxicillin) who are correctly classified and treated in the first 24 h.** The secondary outcome will be measured over the course of the admission as any change in treatment for pneumonia after the first 24 h.

#### **DISCUSSION:**

This trial protocol employs a pragmatic trial design during a period of nationwide change in treatment guidelines to address two high-priority areas within implementation research: promoting adoption of health policies and optimizing effectiveness of feedback.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5588612/>

## Schistosomiasis

[Lancet Glob Health](#). 2017 Jul;5(7):e688-e698. doi: 10.1016/S2214-109X(17)30187-0.

### [Efficacy and safety of praziquantel in preschool-aged and school-aged children infected with \*Schistosoma mansoni\*: a randomised controlled, parallel-group, dose-ranging, phase 2 trial.](#)

[Coulibaly JT](#), [Panic G](#), [Silué KD](#), [Kovač J](#), [Hattendorf J](#), [Keiser J](#)

## Randomised trials in child health in developing countries 2017-18

### BACKGROUND:

Praziquantel has been the drug of choice for schistosomiasis control for more than 40 years, yet surprisingly, the optimal dose for children younger than 4 years is not known. We aimed to assess the efficacy and safety of escalating praziquantel dosages in preschool-aged children (PSAC).

### METHODS:

We did a randomised controlled, parallel-group, single-blind, dose-ranging, phase 2 trial in PSAC (2-5 years) and school-aged children (SAC; aged 6-15 years) as a comparator group in southern Côte d'Ivoire. **Children were randomly assigned (1:1:1:1) to 20 mg/kg, 40 mg/kg, or 60 mg/kg praziquantel or placebo.** Participants, investigators, and laboratory technicians were masked to group assignment, while the investigator providing treatment was aware of the treatment group. The primary objective was to estimate the nature of the dose-response relation in terms of cure rate using the Kato Katz technique. Dose-response curves were estimated using  $E_{max}$  models. Available case analysis was done including all participants with primary endpoint data. This trial is registered with International Standard Randomised Controlled Trial, number ISRCTN15280205.

### FINDINGS:

Between Nov 11, 2014, and Feb 18, 2015, 660 PSAC and 225 SAC were assessed for eligibility; of whom 161 (24%) PSAC and 180 (80%) SAC had a detectable *Schistosoma mansoni* infection. 161 PSAC were randomly allocated of whom 154 received treatment: 42 were assigned to 20 mg/kg praziquantel, of whom 40 received treatment; 38 were assigned to 40 mg/kg praziquantel, of whom 38 received treatment; 41 were assigned to 60 mg/kg praziquantel, of whom 39 received treatment; and 40 were assigned to placebo, of whom 37 received placebo. 180 SAC were randomly allocated of whom 177 received treatment: 49 were assigned to 20 mg/kg praziquantel, of whom 47 received treatment; 46 were assigned to 40 mg/kg praziquantel, of whom 46 received treatment; 42 were assigned to 60 mg/kg praziquantel, of whom 42 received treatment; and 43 were assigned to placebo, of whom 43 received treatment. Follow-up (available-case) data were available for 143 PSAC and 174 SAC. In PSAC, the 20 mg/kg dose resulted in cure in 23 children (62%; 95% CI 44.8-77.5), **40 mg/kg in 26 children (72%; 54.8-85.8)**, 60 mg/kg in 25 children (71%; 53.7-85.4), and placebo in 13 children (37%; 21.5-55.1). In SAC, the 20 mg/kg dose resulted in cure in 14 children (30%; 95% CI 17.7-45.8), 40 mg/kg in 31 children (69%; 53.4-81.8), **60 mg/kg in 34 children (83%; 67.9-92.8)**, and placebo in five children (12%; 4.0-25.6). For both age groups, the number of adverse events was similar among the three praziquantel treatment groups, with fewer adverse events observed in the placebo groups. The most common adverse events in PSAC were diarrhoea (11 [9%] of 124) and stomach ache (ten [8%]) and in SAC were diarrhoea (50 [28%] of 177), stomach ache (66 [37%]), and vomiting (26 [15%]) 3 h post treatment. No serious adverse events were reported.

### INTERPRETATION:

Praziquantel shows a flat dose-response and overall lower efficacy in PSAC compared with in SAC. In the absence of treatment alternatives, a single dose of praziquantel of 40 mg/kg, recommended by the WHO for *S. mansoni* infections in SAC can be endorsed for PSAC in preventive chemotherapy programmes.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5471607/>

[Biomed Res Int.](#) 2017;2017:7035025. doi: 10.1155/2017/7035025. Epub 2017 Sep 28.

**[The Efficacy of Single-Dose versus Double-Dose Praziquantel Treatments on \*Schistosoma mansoni\* Infections: Its Implication on Undernutrition and](#)**

**Anaemia among Primary Schoolchildren in Two On-Shore Communities, Northwestern Tanzania.**

Munisi DZ, Buza J, Mpolya EA, Angelo T, Kinung'hi SM

Administering more than one treatment may increase Praziquantel cure and egg reduction rates, thereby hastening achievement of schistosomiasis transmission control. A total of 431 *S. mansoni*-infected schoolchildren were randomized to receive either a single or repeated 40 mg/kg Praziquantel dose. Heights, weights, and haemoglobin levels were determined using a stadiometer, weighing scale, and HemoCue, respectively. **At 8 weeks, cure rate was higher on repeated dose (93.10%) compared to single dose (68.68%) ( $p < 0.001$ ).** The egg reduction rate was higher on repeated dose (97.54%) compared to single dose (87.27%) ( $p = 0.0062$ ). Geometric mean egg intensity was lower among those on repeated dose (1.30 epg) compared to single dose (3.18 epg) ( $p = 0.036$ ) but not at 5 ( $p > 0.05$ ) and 8 ( $p > 0.05$ ) months with no difference in reinfection rate. No difference in the prevalence of stunting was observed between the two treatment regimens ( $p > 0.05$ ) at 8 months, but there was an increase in the prevalence of wasting among those on repeated dose ( $p < 0.001$ ). There was an increase in the mean haemoglobin levels at 8 months with no difference between the two arms ( $p > 0.05$ ). To achieve reduction of transmission intensity and disease control in highly endemic areas, repeated treatments alone may not be sufficient. This trial was registered with PACTR201601001416338.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637830/>

[PLoS Negl Trop Dis.](#) 2017 Oct 23;11(10):e0006033. doi: 10.1371/journal.pntd.0006033. eCollection 2017 Oct.

**Cluster randomized trial comparing school-based mass drug administration schedules in areas of western Kenya with moderate initial prevalence of *Schistosoma mansoni* infections.**

Karanja DMS, Awino EK, Wiegand RE, Okoth E, Abudho BO, Mwinzi PNM, Montgomery SP, Secor WE.

**BACKGROUND:**

Mass drug administration (MDA) using praziquantel is the WHO-recommended approach for control of schistosomiasis. However, few studies have compared the impact of different schedules of MDA on the resultant infection levels. We wished to evaluate whether annual MDA was more effective than less frequent treatments for reducing community-level prevalence and intensity of *Schistosoma mansoni* infections.

**METHODS:**

We performed a cluster randomized trial (ISRCTN 14849830) of 3 different MDA frequencies over a 5 year period in 75 villages with moderate (10%-24%) initial prevalence of *S. mansoni* in school children in western Kenya. **Praziquantel was distributed by school teachers to students either annually, the first 2 years, or every other year over a 4 year period.** Prevalence and intensity of infection were measured by stool examination in 9-12 year old students using the Kato-Katz method at baseline, each treatment year, and for the final evaluation at year 5. *S. mansoni* prevalence and intensity were also measured in first year students at baseline and year 5.

**RESULTS:**

Twenty-five schools were randomly assigned to each arm. ***S. mansoni* prevalence and infection intensity in 9-12 year old students significantly decreased within each arm from**

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**baseline to year 5 but there were no differences between arms.** There were no differences in infection levels in first year students either within or between arms.

### **CONCLUSIONS:**

Strategies employing 2 or 4 rounds of MDA had a similar impact in schools with moderate initial prevalence, suggesting that schistosomiasis control can be sustained by school-based MDA, even if provided only every other year.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006033>

[J Infect Dis.](#) 2017 Dec 12;216(11):1425-1433. doi: 10.1093/infdis/jix496.

### **[A Persistent Hotspot of Schistosoma mansoni Infection in a Five-Year Randomized Trial of Praziquantel Preventative Chemotherapy Strategies.](#)**

[Wiegand RE](#), [Mwinzi PNM](#), [Montgomery SP](#), [Chan YL](#), [Andiego K](#), [Omedo M](#), [Muchiri G](#), [Ogutu MO](#), [Rawago F](#), [Odiere MR](#), [Karanja DMS](#), [Secor WE](#)

### **BACKGROUND:**

Persistent hotspots have been described after mass drug administration (MDA) for the control of schistosomiasis, but they have not been studied during the course of a multiyear MDA program.

### **METHODS:**

In data from a 5-year study of school-based and village-wide preventive chemotherapy strategies for *Schistosoma mansoni*, spatial scan statistics were used to find infection hotspots in 3 populations: 5- to 8-year-olds, 9- to 12-year-olds, and adults. Negative binomial regression was used to analyze changes from baseline, and receiver operating characteristic analyses were used to predict which villages would reach prevalence and intensity endpoints.

### **RESULTS:**

We identified a persistent hotspot, not associated with study arm, where *S. mansoni* infection prevalence and intensity did not decrease as much as in villages outside the hotspot. Significant differences from baseline were realized after 1 year of MDA: we did not identify factors that moderated this relationship. Villages meeting specified endpoints at year 5 were predicted from prior year data with moderately high sensitivity and specificity.

### **CONCLUSIONS:**

The MDA strategies were less effective at reducing prevalence and intensity in the hotspot compared with other villages. Villages that reached year 5 endpoints could be detected earlier, which may provide the opportunity to amend intervention strategies.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5913648/>

[PLoS Negl Trop Dis.](#) 2017 Nov 13;11(11):e0006054. doi: 10.1371/journal.pntd.0006054. eCollection 2017 Nov.

### **[Rapid clearance of Schistosoma mansoni circulating cathodic antigen after treatment shown by urine strip tests in a Ugandan fishing community - Relevance for monitoring treatment efficacy and re-infection.](#)**

## Randomised trials in child health in developing countries 2017-18

[Kildemoes AO](#), [Vennervald BJ](#), [Tukahebwa EM](#), [Kabateraine NB](#), [Magnussen P](#), [de Dood CJ](#), [Deelder AM](#), [Wilson S](#), [van Dam GJ](#).

Schistosomiasis control and elimination has priority in public health agendas in several sub-Saharan countries. However, achieving these goals remains a substantial challenge. In order to assess progress of interventions and treatment efficacy it is pertinent to have accurate, feasible and affordable diagnostic tools. Detection of *Schistosoma mansoni* infection by circulating cathodic antigen (CCA) in urine is an attractive option as this measure describes live worm infection noninvasively. In order to interpret treatment efficacy and re-infection levels, knowledge about clearance of this antigen is necessary. The current study aims to investigate, whether antigen clearance as a proxy for decreasing worm numbers is reflected in decreasing CCA levels in urine shortly after praziquantel treatment. **Here CCA levels are measured 24 hours post treatment in response to both a single and two treatments.** The study was designed as a series of cross-sectional urine and stool sample collections from 446 individuals nested in a two-arm randomised single blinded longitudinal clinical trial cohort matched by gender and age (ClinicalTrials.gov Identifier: [NCT00215267](#)) receiving one or two praziquantel treatments. CCA levels in urine were determined by carbon-conjugated monoclonal antibody lateral flow strip assay and eggs per gram faeces for *S. mansoni* and soil-transmitted helminths by Kato-Katz. Significant correlations between CCA levels and *S. mansoni* egg count at every measured time point were found and confirmed the added beneficial effect of a second treatment at two weeks after baseline. Furthermore, presence of hookworm was found not to be a confounder for CCA test specificity. Twenty-four hours post treatment measures of mean CCA scores showed significant reductions. In conclusion, removal of CCA in response to treatment is detectable as a decline in CCA in urine already after 24 hours. This has relevance for use and interpretation of laboratory based and point-of-care CCA tests in terms of treatment efficacy and re-infection proportions as this measure provides information on the presence of all actively feeding stages of *S. mansoni*, which conventional faecal microscopy methods do not accurately reflect.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006054>

[PLoS Negl Trop Dis](#). 2017 Dec 8;11(12):e0006061. doi: 10.1371/journal.pntd.0006061. eCollection 2017 Dec.

### **Assessing the benefits of five years of different approaches to treatment of urogenital schistosomiasis: A SCORE project in Northern Mozambique.**

[Phillips AE](#), [Gazzinelli-Guimaraes PH](#), [Aurelio HO](#), [Ferro J](#), [Nala R](#), [Clements M](#), [King CH](#), [Fenwick A](#), [Fleming FM](#), [Dhanani N](#)

#### **BACKGROUND:**

In Mozambique, schistosomiasis is highly endemic across the whole country. The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) coordinates a five-year study that has been implemented in various African countries, including Mozambique. **The overall goal of SCORE was to better understand how to best apply preventive chemotherapy with praziquantel (PZQ) for schistosomiasis control by evaluating the impact of alternative treatment approaches.**

#### **METHODS:**

This was a cluster-randomised trial that compared the impact of different treatment strategies in study areas with prevalence among school children of  $\geq 21\%$  *S. haematobium* infection by urine dipstick. **Each village was randomly allocated to one of six possible combinations of community-wide treatment (CWT), school-based treatment (SBT), and/or drug holidays**

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over a period of four years, followed by final data collection in the fifth year. The most intense intervention arm involved four years of CWT, while the least intensive arm involved two years of SBT followed by two consecutive years of PZQ holiday. Each study arm included 25 villages randomly assigned to one of the six treatment arms. **The primary outcome of interest was change in prevalence and intensity of *S. haematobium* among 100 children aged 9-to-12-years that were sampled each year in every village.** In addition to children aged 9-to-12 years, 100 children aged 5-8 years in their first-year of school and 50 adults (aged 20-55 years) were tested in the first and final fifth year of the study. **Prevalence and intensity of *S. haematobium* infection was evaluated by two filtrations, each of 10mL, from a single urine specimen.**

### PRINCIPAL FINDINGS:

In total, data was collected from 81,167 individuals across 149 villages in ten districts of Cabo Delgado province, Northern Mozambique. **Overall PZQ treatment resulted in a significant reduction in the prevalence of *S. haematobium* infection from Year 1 to Year 5, where the average prevalence went from 60.5% to 38.8%, across all age groups and treatment arms.** The proportion of those heavily infected also reduced from 17.6% to 11.9% over five years. There was a significantly higher likelihood of males being infected than females at baseline, but no significant difference between the sexes in their response to treatment. The only significant response based on a study arm was seen in both the 9-to-12-year-old and first-year cross sections, where two consecutive treatment holidays resulted in a significantly higher final prevalence of *S. haematobium* than no treatment holidays. When the arms were grouped together, four rounds of treatment (regardless of whether it was CWT or SBT), however, did result in a significantly greater reduction in *S. haematobium* prevalence than two rounds of treatment (i.e. with two intermittent or consecutive holiday years) over a five-year period.

### CONCLUSIONS:

Although PC was successful in reducing the burden of active infection, even among those heavily infected, annual CWT did not have a significantly greater impact on disease prevalence or intensity than less intense treatment arms. This may be due to extremely high starting prevalence and intensity in the study area, with frequent exposure to reinfection, or related to challenges in achieving high treatment coverage. More frequent treatment had a greater impact on prevalence and intensity of infection when arms were grouped by number of treatments, however, cost efficiency was greater in arms only receiving two treatments. Finally, a significant reduction in prevalence of *S. haematobium* was seen in adults even in the SBT arms implying the rate of transmission in the community had been decreased, even where only school children have been treated, which has significant logistical and cost-saving implications for a national control programme in justifying CWT.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006061>

[BMC Public Health](#). 2018 Jan 29;18(1):186. doi: 10.1186/s12889-018-5044-2.

### **Interrupting seasonal transmission of *Schistosoma haematobium* and control of soil-transmitted helminthiasis in northern and central Côte d'Ivoire: a SCORE study protocol.**

[Tian-Bi YT](#), [Ouattara M](#), [Knopp S](#), [Coulibaly JT](#), [Hürlimann E](#), [Webster B](#), [Allan F](#), [Rollinson D](#), [Meité A](#), [Diakité NR](#), [Konan CK](#), [N'Goran EK](#), [Utzing J](#)

### BACKGROUND:

To achieve a world free of schistosomiasis, the objective is to scale up control and elimination efforts in all endemic countries. Where interruption of transmission is considered feasible, countries are encouraged to implement a comprehensive intervention package,

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including preventive chemotherapy, information, education and communication (IEC), water, sanitation and hygiene (WASH), and snail control. In northern and central Côte d'Ivoire, transmission of *Schistosoma haematobium* is seasonal and elimination might be achieved. In a cluster-randomised trial, we will assess different treatment schemes to interrupt *S. haematobium* transmission and control soil-transmitted helminthiasis over a 3-year period. We will compare the impact of (i) arm A: annual mass drug administration (MDA) with praziquantel and albendazole before the peak schistosomiasis transmission season; (ii) arm B: annual MDA after the peak schistosomiasis transmission season; (iii) arm C: two yearly treatments before and after peak schistosomiasis transmission; and (iv) arm D: annual MDA before peak schistosomiasis transmission, coupled with chemical snail control using niclosamide.

### **METHODS/DESIGN:**

The prevalence and intensity of *S. haematobium* and soil-transmitted helminth infections will be assessed using urine filtration and Kato-Katz thick smears, respectively, in six administrative regions in northern and central parts of Côte d'Ivoire. Once a year, urine and stool samples will be collected and examined from 50 children aged 5-8 years, 100 children aged 9-12 years and 50 adults aged 20-55 years in each of 60 selected villages. Changes in *S. haematobium* and soil-transmitted helminth prevalence and intensity will be assessed between years and stratified by intervention arm. In the 15 villages randomly assigned to intervention arm D, intermediate host snails will be collected three times per year, before niclosamide is applied to the selected freshwater bodies. The snail abundance and infection rates over time will allow drawing inference on the force of transmission.

### **DISCUSSION:**

This cluster-randomised intervention trial will elucidate whether in an area with seasonal transmission, the four different treatment schemes can interrupt *S. haematobium* transmission and control soil-transmitted helminthiasis. Lessons learned will help to guide schistosomiasis control and elimination programmes elsewhere in Africa.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789673/>

[BMC Infect Dis.](#) 2017 Sep 29;17(1):652. doi: 10.1186/s12879-017-2738-5.

### **[Protocol and baseline data for a multi-year cohort study of the effects of different mass drug treatment approaches on functional morbidities from schistosomiasis in four African countries.](#)**

[Shen Y](#), [King CH](#), [Binder S](#), [Zhang F](#), [Whalen CC](#), [Evan Secor W](#), [Montgomery SP](#), [Mwinzi PNM](#), [Olsen A](#), [Magnussen P](#), [Kinung'hi S](#), [Phillips AE](#), [Nalá R](#), [Ferro J](#), [Aurelio HO](#), [Fleming F](#), [Garba A](#), [Hamidou A](#), [Fenwick A](#), [Campbell CH Jr](#), [Colley DG](#)

### **BACKGROUND:**

The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) focus is on randomized trials of different approaches to mass drug administration (MDA) in endemic countries in Africa. Because their studies provided an opportunity to evaluate the effects of mass treatment on *Schistosoma*-associated morbidity, nested cohort studies were developed within SCORE's intervention trials to monitor changes in a suite of schistosomiasis disease outcomes. This paper describes the process SCORE used to select markers for prospective monitoring and the baseline prevalence of these morbidities in four parallel cohort studies.

### **METHODS:**

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In July 2009, SCORE hosted a discussion of the potential impact of MDA on morbidities due to *Schistosoma* infection that might be measured in the context of multi-year control. Candidate markers were reviewed and selected for study implementation. Baseline data were then collected from cohorts of children in four country studies: two in high endemic *S. mansoni* sites (Kenya and Tanzania), and two in high endemic *S. haematobium* sites (Niger and Mozambique), these cohorts to be followed prospectively over 5 years.

### RESULTS:

At baseline, 62% of children in the *S. mansoni* sites had detectable eggs in their stool, and 10% had heavy infections ( $\geq 400$  eggs/g feces). Heavy *S. mansoni* infections were found to be associated with increased baseline risk of anemia, although children with moderate or heavy intensity infections had lower risk of physical wasting. Prevalence of egg-positive infection in the combined *S. haematobium* cohorts was 27%, with 5% of individuals having heavy infection ( $\geq 50$  eggs/10 mL urine). At baseline, light intensity *S. haematobium* infection was associated with anemia and with lower scores in the social domain of health-related quality-of-life (HRQoL) assessed by Pediatric Quality of Life Inventory.

### CONCLUSIONS:

Our consensus on practical markers of *Schistosoma*-associated morbidity indicated that height, weight, hemoglobin, exercise tolerance, HRQoL, and ultrasound abnormalities could be used as reference points for gauging treatment impact. Data collected over five years of program implementation will provide guidance for future evaluation of morbidity control in areas endemic for schistosomiasis.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622450/>

## School health and education

(See Adolescent health, Schistosomiasis)

[Lancet](#). 2017 Jul 22;390(10092):389-398. doi: 10.1016/S0140-6736(17)31225-4. Epub 2017 May 22.

### [Effects of the Informed Health Choices podcast on the ability of parents of primary school children in Uganda to assess claims about treatment effects: a randomised controlled trial.](#)

[Semakula D](#), [Nsangi A](#), [Oxman AD](#), [Oxman M](#), [Austvoll-Dahlgren A](#), [Rosenbaum S](#), [Morelli A](#), [Glenton C](#), [Lewin S](#), [Kaseje M](#), [Chalmers I](#), [Fretheim A](#), [Kristoffersen DT](#), [Sewankambo NK](#).

### BACKGROUND:

As part of the Informed Health Choices project, we developed a podcast called The Health Choices Programme to help improve the ability of people to assess claims about the benefits and harms of treatments. We aimed to evaluate the effects of the podcast on the ability of parents of primary school children in Uganda to assess claims about the effects of treatments.

### METHODS:

We did this randomised controlled trial in central Uganda. We recruited parents of children aged 10-12 years who were in their fifth year of school at 35 schools that were participating in a linked trial of the Informed Health Choices primary school resources. The parents were randomly allocated (1:1), via a web-based random number generator with block sizes of four



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and six, to listen to either the Informed Health Choices podcast (intervention group) or typical public service announcements about health issues (control group). Randomisation was stratified by parents' highest level of formal education attained (primary school, secondary school, or tertiary education) and the allocation of their children's school in the trial of the primary school resources (intervention vs control). **The primary outcome, measured after listening to the entire podcast, was the mean score and the proportion of parents with passing scores on a test with two multiple choice questions for each of nine key concepts essential to assessing claims about treatments (18 questions in total).** We did intention-to-treat analyses.

This trial is registered with the Pan African Clinical Trial Registry, number PACTR201606001676150.

### FINDINGS:

We recruited parents between July 21, 2016, and Oct 7, 2016. We randomly assigned 675 parents to the podcast group (n=334) or the public service announcement group (n=341); 561 (83%) participants completed follow-up. **The mean score for parents in the podcast group was 67·8% (SD 19·6) compared with 52·4% (17·6) in the control group (adjusted mean difference 15·5%, 95% CI 12·5-18·6; p<0·0001).** In the podcast group, 203 (71%) of 288 parents had a predetermined passing score ( $\geq 11$  of 18 correct answers) compared with 103 (38%) of 273 parents in the control group (adjusted difference 34%, 95% CI 26-41; p<0·0001). No adverse events were reported.

### INTERPRETATION:

Listening to the Informed Health Choices podcast led to a large improvement in the ability of parents to assess claims about the effects of treatments. Future studies should assess the long-term effects of use of the podcast, the effects on actual health choices and outcomes, and how transferable our findings are to other countries.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)31225-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31225-4/fulltext)

*Lancet*. 2017 Jul 22;390(10092):374-388. doi: 10.1016/S0140-6736(17)31226-6. Epub 2017 May 22.

### **Effects of the Informed Health Choices primary school intervention on the ability of children in Uganda to assess the reliability of claims about treatment effects: a cluster-randomised controlled trial.**

[Nsangi A](#), [Semakula D](#), [Oxman AD](#), [Austvoll-Dahlgren A](#), [Oxman M](#), [Rosenbaum S](#), [Morelli A](#), [Glenton C](#), [Lewin S](#), [Kaseje M](#), [Chalmers I](#), [Fretheim A](#), [Ding Y](#), [Sewankambo NK](#).

### BACKGROUND:

Claims about what improves or harms our health are ubiquitous. People need to be able to assess the reliability of these claims. We aimed to evaluate an intervention designed to teach primary school children to assess claims about the effects of treatments (ie, any action intended to maintain or improve health).

### METHODS:

In this cluster-randomised controlled trial, we included primary schools in the central region of Uganda that taught year-5 children (aged 10-12 years). We excluded international schools, special needs schools for children with auditory and visual impairments, schools that had participated in user-testing and piloting of the resources, infant and nursery schools, adult education schools, and schools that were difficult for us to access in terms of travel time. We randomly allocated a representative sample of eligible schools to either an intervention or control group. **Intervention schools received the Informed Health Choices primary school resources (textbooks, exercise books, and a teachers' guide).** Teachers attended a 2 day introductory workshop and gave nine 80 min lessons during one school term. The lessons

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addressed 12 concepts essential to assessing claims about treatment effects and making informed health choices. We did not intervene in the control schools. The primary outcome, measured at the end of the school term, was the mean score on a test with two multiple-choice questions for each of the 12 concepts and the proportion of children with passing scores on the same test. This trial is registered with the Pan African Clinical Trial Registry, number PACTR201606001679337.

### FINDINGS:

Between April 11, 2016, and June 8, 2016, 2960 schools were assessed for eligibility; 2029 were eligible, and a random sample of 170 were invited to recruitment meetings. After recruitment meetings, **120 eligible schools consented and were randomly assigned to either the intervention group (n=60, 76 teachers and 6383 children) or control group (n=60, 67 teachers and 4430 children).** The mean score in the multiple-choice test for the intervention schools was **62.4% (SD 18.8) compared with 43.1% (15.2) for the control schools (adjusted mean difference 20.0%, 95% CI 17.3-22.7; p<0.00001).** In the intervention schools, 3967 (69%) of 5753 children achieved a predetermined passing score ( $\geq 13$  of 24 correct answers) compared with 1186 (27%) of 4430 children in the control schools (adjusted difference 50%, 95% CI 44-55). The intervention was effective for children with different levels of reading skills, but was more effective for children with better reading skills.

### INTERPRETATION:

The use of the Informed Health Choices primary school learning resources, after an introductory workshop for the teachers, led to a large improvement in the ability of children to assess claims about the effects of treatments. The results show that **it is possible to teach primary school children to think critically in schools with large student to teacher ratios and few resources.** Future studies should address how to scale up use of the resources, long-term effects, including effects on actual health choices, transferability to other countries, and how to build on this programme with additional primary and secondary school learning resources.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)31226-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31226-6/fulltext)

[Prev Sci.](#) 2017 Oct;18(7):839-853. doi: 10.1007/s11121-017-0775-3.

### [Does the Good Schools Toolkit Reduce Physical, Sexual and Emotional Violence, and Injuries, in Girls and Boys equally? A Cluster-Randomised Controlled Trial.](#)

[Devries KM](#), [Knight L](#), [Allen E](#), [Parkes J](#), [Kyegombe N](#), [Naker D](#)

We aimed to investigate whether the Good School Toolkit reduced emotional violence, severe physical violence, sexual violence and injuries from school staff to students, as well as emotional, physical and sexual violence between peers, in Ugandan primary schools. We performed a two-arm cluster randomised controlled trial with parallel assignment. **Forty-two schools in one district were allocated to intervention (n = 21) or wait-list control (n = 21) arms in 2012.** We did cross-sectional baseline and endline surveys in 2012 and 2014, and the Good School Toolkit intervention was implemented for 18 months between surveys. Analyses were by intention to treat and are adjusted for clustering within schools and for baseline school-level proportions of outcomes. **The Toolkit was associated with an overall reduction in any form of violence from staff and/or peers in the past week towards both male (aOR = 0.34, 95%CI 0.22-0.53) and female students (aOR = 0.55, 95%CI 0.36-0.84). Injuries as a result of violence from school staff were also lower in male (aOR = 0.36, 95%CI 0.20-0.65) and female students (aOR = 0.51, 95%CI 0.29-0.90).** Although the Toolkit seems to be effective at reducing violence in both sexes, there is some suggestion that the Toolkit may have stronger

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effects in boys than girls. The Toolkit is a promising intervention to reduce a wide range of different forms of violence from school staff and between peers in schools, and should be urgently considered for scale-up. Further research is needed to investigate how the intervention could engage more successfully with girls.

<https://link.springer.com/article/10.1007%2Fs11121-017-0775-3>

*Prev Sci.* 2017 Oct;18(7):772-782. doi: 10.1007/s11121-017-0770-8.

### **The #Tamojuntó Drug Prevention Program in Brazilian Schools: a Randomized Controlled Trial.**

[Sanchez ZM](#), [Valente JY](#), [Sanudo A](#), [Pereira APD](#), [Cruz JI](#), [Schneider D](#), [Andreoni S](#)

A randomized controlled trial was conducted in 2014 with 7th and 8th grade students from 72 public schools in 6 Brazilian cities. This trial aimed to evaluate the effects of an adapted European school-based drug prevention program Unplugged, called #Tamojuntó in Brazil, which was implemented by the Ministry of Health as part of public policy. **The experimental group (n = 3340) attended 12 classes in the #Tamojuntó program, and the control group (n = 3318) did not receive a school prevention program.** Baseline data were collected prior to program implementation, and follow-up data were collected 9 months later, allowing a matching of 4213 adolescents in both waves. The substances examined were alcohol, tobacco, marijuana, inhalants, cocaine, and crack. Multilevel analyses were used to evaluate the changes in consumption of each drug between time points and between groups. The intervention and control groups had similar baseline characteristics. The mean age of the adolescents was  $12.5 \pm 0.7$  years, and 51.3% were female. The program seemed to increase alcohol use initiation (first alcohol use); students in the experimental group had a 30% increased risk of initiating alcohol use during the 9-month follow-up (aRR = 1.30, 95% confidence interval (95%CI) 1.13-1.49,  $p < 0.001$ ) compared to the control group. The opposite was found for the first inhalant use: the risk of using inhalants for the first time after baseline was lower in the experimental group (aRR = 0.78, 95%CI 0.63-0.96,  $p = 0.021$ ) than the control group. **The results of the #Tamojuntó program suggest that the content and lessons regarding alcohol may enhance curiosity about its use among adolescents.** We suggest a re-evaluation of the expansion of the #Tamojuntó program in schools while analyzing why the program's effects were inconsistent with those of previous European studies.

<https://link.springer.com/article/10.1007%2Fs11121-017-0770-8>

### **Behavior-Based Intervention That Prevents Sexual Assault: the Results of a Matched-Pairs, Cluster-Randomized Study in Nairobi, Kenya.**

[Baiocchi M](#), [Omondi B](#), [Langat N](#), [Boothroyd DB](#), [Sinclair J](#), [Pavia L](#), [Mulinge M](#), [Githua O](#), [Golden NH](#), [Sarnquist C](#)

#### **DESIGN:**

The study's design was a cluster-randomized, matched-pairs, parallel trial of a behavior-based sexual assault prevention intervention in the informal settlements.

#### **METHODS:**

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The participants were primary school girls aged 10-16. Classroom-based interventions for girls and boys were delivered by instructors from the same settlements, at the same time, over six 2-h sessions. The girls' program had components of empowerment, gender relations, and self-defense. The boys' program promotes healthy gender norms. The control arm of the study received a health and hygiene curriculum. The primary outcome was the rate of sexual assault in the prior 12 months at the cluster level (school level). Secondary outcomes included the generalized self-efficacy scale, the distribution of number of times victims were sexually assaulted in the prior period, skills used, disclosure rates, and distribution of perpetrators. Difference-in-differences estimates are reported with bootstrapped confidence intervals.

### RESULTS:

Fourteen schools with 3147 girls from the intervention group and 14 schools with 2539 girls from the control group were included in the analysis. We estimate a 3.7 % decrease,  $p = 0.03$  and 95 % CI = (0.4, 8.0), in risk of sexual assault in the intervention group due to the intervention (initially 7.3 % at baseline). We estimate an increase in mean generalized self-efficacy score of 0.19 (baseline average 3.1, on a 1-4 scale),  $p = 0.0004$  and 95 % CI = (0.08, 0.39).

### INTERPRETATION:

This innovative intervention that combined parallel training for young adolescent girls and boys in school settings showed significant reduction in the rate of sexual assault among girls in this population.

<https://link.springer.com/article/10.1007/s11121-016-0701-0>

## Sepsis and serious bacterial infection

*Crit Care Med.* 2018 Jun 27. doi: 10.1097/CCM.0000000000003279. [Epub ahead of print]

**[Evaluation of Effect of Probiotics on Cytokine Levels in Critically Ill Children With Severe Sepsis: A Double-Blind, Placebo-Controlled Trial.](#)**  
[Angurana SK](#), [Bansal A](#), [Singhi S](#), [Aggarwal R](#), [Jayashree M](#), [Salaria M](#), [Mangat NK](#).

### OBJECTIVES:

To evaluate the effect of probiotics on cytokines in children with severe sepsis.

### DESIGN:

Randomized, double-blind, placebo-controlled trial.

### SETTING:

ICU of a tertiary care teaching hospital in North India.

### PATIENTS:

Children 3 months to 12 years old with severe sepsis.

### INTERVENTIONS:

Enrolled children were randomized to probiotic ( $n = 50$ ) and placebo ( $n = 50$ ) groups. Probiotic group received VSL#3 (VSL Pharmaceuticals, Towson, MD) (Lactobacillus paracasei, L. plantarum, L. acidophilus, L. delbrueckii, Bifidobacterium longum, B. breve, B. infantis, Streptococcus salivarius; maltose; and silicon dioxide), and placebo group received maltose and silicon dioxide. Dose was 1 sachet twice daily for 7 days. Blood was collected on days 1 and 7 for estimation of interleukin-6, interleukin-12p70, interleukin-17, tumor necrosis factor- $\alpha$ , interleukin-10, and transforming growth factor - $\beta$ 1. "Primary outcome": Change in cytokine

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levels in probiotic and placebo groups from day 1 to 7. "Secondary outcomes": Sequential Organ Failure Assessment score, healthcare-associated infections, ICU stay, and mortality.

### MEASUREMENTS AND MAIN RESULTS:

On day 7, probiotic group had significantly lower levels of proinflammatory cytokines (interleukin-6 [80 vs 186 pg/mL,  $p = 0.001$ ]; interleukin-12p70 [44 vs 79 pg/mL,  $p = 0.001$ ]; interleukin-17 [217 vs 293 pg/mL,  $p = 0.01$ ]; and tumor necrosis factor- $\alpha$  [192 vs 348 pg/mL,  $p = 0.01$ ]) and higher levels of antiinflammatory cytokines (interleukin-10 [320 vs 240 pg/mL,  $p = 0.02$ ] and TGF- $\beta$ 1 [311 vs 221 ng/mL,  $p = 0.01$ ]) than placebo group. From day 1 to 7, probiotic group showed significant decrease in proinflammatory cytokines (interleukin-6 [196-80 pg/mL,  $p = 0.001$ ]; interleukin-12p70 [71-44 pg/mL,  $p = 0.01$ ]; interleukin-17 [258-217 pg/mL,  $p = 0.01$ ]; and tumor necrosis factor- $\alpha$  [347-192 pg/mL,  $p = 0.001$ ]) and increase in antiinflammatory cytokines (interleukin-10 [198-320 pg/mL,  $p = 0.001$ ] and TGF- $\beta$ 1 [216-311 ng/mL,  $p = 0.001$ ]) as compared to placebo group. Sequential Organ Failure Assessment score on day 7 was significantly less in probiotic group (1 vs 3). There was a nonsignificant trend toward lower incidence of HCAs (14% vs 20%) and duration of ICU stay (6.5 vs 9 d) in probiotic group. Mortality was similar in two groups.

### CONCLUSIONS:

**Probiotics supplementation for 7 days resulted in significant decrease in proinflammatory and increase in antiinflammatory cytokines in children with severe sepsis.**

<https://insights.ovid.com/pubmed?pmid=29957709>

[Eur J Pediatr.](#) 2018 Jun 23. doi: 10.1007/s00431-018-3195-x. [Epub ahead of print]

### **Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial.**

[Baske K](#), [Saini SS](#), [Dutta S](#), [Sundaram V](#)

We compared epinephrine and dopamine as a first-line vasoactive drug in 40 neonates (enrolled in two gestational age strata  $\leq 30^{6/7}$  and  $\geq 31^{0/7}$  weeks) with fluid-refractory septic shock. Epinephrine or dopamine was initiated at 0.2 or 10  $\mu\text{g}/\text{kg}/\text{min}$ , respectively. If shock persisted after 15 min, epinephrine or dopamine was increased to 0.3 or 15  $\mu\text{g}/\text{kg}/\text{min}$ , respectively (16-30 min), and thereafter to 0.4 or 20  $\mu\text{g}/\text{kg}/\text{min}$  (31-45 min). Proportion of neonates achieving 'reversal of shock' (defined as systolic and diastolic BP > fifth centile and capillary filling time < 3 s and left ventricular output  $\geq 150 \text{ mL}/\text{kg}/\text{min}$ ) by 45 min [5 (25%) vs 6 (30%), RR 0.83 (95% CI 0.30, 2.29)]; haemodynamic stability (shock reversal for  $\geq 120$  min without escalation of vasoactive drugs) anytime during therapy [10 (50%) vs 6 (30%), RR 1.67 (95% CI 0.75, 3.71)]; and all-cause mortality by 28 days [14 (70%) vs 16 (80%), RR 0.87 (95% CI 0.61, 1.26)] were comparable in the epinephrine and dopamine groups, respectively. On stratified analysis, we observed an interaction of gestational age strata with the group of allocation favouring epinephrine in neonates  $\leq 30^{6/7}$  weeks.

### CONCLUSION:

**Epinephrine (0.2-0.4  $\mu\text{g}/\text{kg}/\text{min}$ ) and dopamine (10-20  $\mu\text{g}/\text{kg}/\text{min}$ ) had comparable efficacy and safety in neonatal septic shock.**

<https://link.springer.com/article/10.1007%2Fs00431-018-3195-x>

[Pediatr Res.](#) 2018 Apr;83(4):784-790. doi: 10.1038/pr.2017.299. Epub 2017 Dec 20.

### **Predictors of death in infants with probable serious bacterial infection.**

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[Singh P](#), [Arora A](#), [Strand TA](#), [Sommerfelt H](#), [Lodha R](#), [Kabra SK](#), [Aneja S](#), [Natchu UCM](#), [Chandra J](#), [Rath B](#), [Sharma VK](#), [Kumari M](#), [Saini S](#), [Bhatnagar S](#), [Wadhwa N](#)

**Background.** Bacterial infections account for a significant proportion of neonatal and infant mortality globally. We aimed to identify predictors of death in infants with probable serious bacterial infection (PSBI) defined as signs/symptoms of possible serious bacterial infection along with baseline C-reactive protein (CRP)  $\geq 12$  mg/l.

**Methods.** We did a secondary analysis using the data collected from 700 infants with PSBI who participated in a randomized controlled trial in India in which zinc or placebo was given in addition to the standard antibiotics. Logistic regression was used to estimate the associations between relevant variables and death within 21 days.

**Results.** **Those infants who were fed cow's milk or formula before the illness episode had 3.7-fold (95% confidence interval (CI) 1.5-9.3) and 5.3-fold (95% CI 2.0-13.6) higher odds of death, respectively.** Lethargy (odds ratio (OR) 2.4, 95% CI 1.1-5.4) and CRP (OR 1.9, 95% CI 1.1-3.3) were also independent predictors of death. In the model including only clinical features, female gender (OR 2.25, 95% CI 1.0-5.0), abdominal distention (3.7, 95% CI 1.1-12.3), and bulging fontanelle (5.8, 95% CI 1.1-30.5) were also independent predictors for death.

**Conclusion.** Formula or cow milk feeding prior to the illness, lethargy at the time of presentation, and high serum CRP levels predicted death in infants with PSBI.

<https://www.nature.com/articles/pr2017299>

[Pediatr Crit Care Med.](#) 2017 Oct;18(10):e435-e445. doi: 10.1097/PCC.0000000000001269.

### **Fluid Bolus Over 15-20 Versus 5-10 Minutes Each in the First Hour of Resuscitation in Children With Septic Shock: A Randomized Controlled Trial.**

[Sankar J](#), [Ismail J](#), [Sankar MJ](#), [C P S](#), [Meena RS](#).

#### **OBJECTIVES:**

To compare the effect of administration of 40-60 mL/kg of fluids as fluid boluses in aliquots of 20 mL/kg each over 15-20 minutes with that over 5-10 minutes each on the composite outcome of need for mechanical ventilation and/or impaired oxygenation-increase in oxygenation index by 5 from baseline in the initial 6 and 24 hours in children with septic shock.

#### **DESIGN:**

Randomized controlled trial.

#### **SETTING:**

Pediatric emergency and ICU of a tertiary care institute.

#### **PATIENTS:**

Children (< 18 yr old) with septic shock.

#### **INTERVENTIONS:**

We randomly assigned participants to 15-20 minutes bolus (study group) or 5-10 minutes bolus groups (control group).

#### **MEASUREMENTS AND MAIN RESULTS:**

We assessed the composite outcomes in the initial 6 and 24 hours after fluid resuscitation in both groups. We performed logistic regression to evaluate factors associated with need for ventilation in the first hour. Data were analyzed using Stata 11.5. Of the 96 children, 45 were randomly assigned to "15-20 minutes group" and 51 to "5-10 minutes group." Key baseline characteristics were not different between the groups. **When compared with 5-10 minutes group, fewer children in 15-20 minutes group needed mechanical ventilation or had an increase in oxygenation index in the first 6 hours (36% vs 57%; relative risk, 0.62; 95%**

CI, 0.39-0.99) and 24 hours (43% vs 68%; relative risk, 0.63; 95% CI, 0.42-0.93) after fluid resuscitation. We did not find any difference in secondary outcomes such as death (1.2; 0.70-2.03), length of stay (mean difference: 0.52; -1.72 to 2.7), or resolution of shock (0.98; 0.63-1.53).

### CONCLUSION:

**Children receiving fluid boluses over 5-10 minutes each had a higher risk of intubation than those receiving boluses over 15-20 minutes each.** Notwithstanding the lack of difference in risk of mortality and the possibility that a lower threshold of intubation and mechanical ventilation was used in the presence of fluid overload, our results raise concerns on the current recommendation of administering boluses over 5-10 minutes each in children with septic shock.

[https://journals.lww.com/pccmjournal/fulltext/2017/10000/Fluid\\_Bolus\\_Over\\_15\\_20\\_Versus\\_5\\_10\\_Minutes\\_Each\\_in.27.aspx](https://journals.lww.com/pccmjournal/fulltext/2017/10000/Fluid_Bolus_Over_15_20_Versus_5_10_Minutes_Each_in.27.aspx)

PLoS Med. 2017 Oct 23;14(10):e1002411. doi: 10.1371/journal.pmed.1002411. eCollection 2017 Oct.

### [A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illnesses in Tanzanian children \(e-POCT\):](#)

#### [A randomized, controlled non-inferiority trial.](#)

[Keitel K](#), [Kagoro F](#), [Samaka J](#), [Masimba J](#), [Said Z](#), [Temba H](#), [Mlaganile T](#), [Sangu W](#), [Rambaud-Althaus C](#), [Gervais A](#), [Genton B](#), [D'Acremont V](#)

### BACKGROUND:

The management of childhood infections remains inadequate in resource-limited countries, resulting in high mortality and irrational use of antimicrobials. Current disease management tools, such as the Integrated Management of Childhood Illness (IMCI) algorithm, rely solely on clinical signs and have not made use of available point-of-care tests (POCTs) that can help to identify children with severe infections and children in need of antibiotic treatment. e-POCT is a novel electronic algorithm based on current evidence; it guides clinicians through the entire consultation and recommends treatment based on a few clinical signs and POCT results, some performed in all patients (malaria rapid diagnostic test, hemoglobin, oximeter) and others in selected subgroups only (C-reactive protein, procalcitonin, glucometer). The objective of this trial was to determine whether the clinical outcome of febrile children managed by the e-POCT tool was non-inferior to that of febrile children managed by a validated electronic algorithm derived from IMCI (ALMANACH), while reducing the proportion with antibiotic prescription.

### METHODS AND FINDINGS:

We performed a randomized (at patient level, blocks of 4), controlled non-inferiority study among children aged 2-59 months presenting with acute febrile illness to 9 outpatient clinics in Dar es Salaam, Tanzania. In parallel, routine care was documented in 2 health centers. The primary outcome was the proportion of clinical failures (development of severe symptoms, clinical pneumonia on/after day 3, or persistent symptoms at day 7) by day 7 of follow-up. Non-inferiority would be declared if the proportion of clinical failures with e-POCT was no worse than the proportion of clinical failures with ALMANACH, within statistical variability, by a margin of 3%. The secondary outcomes included the proportion with antibiotics prescribed on day 0, primary referrals, and severe adverse events by day 30 (secondary hospitalizations and deaths). We enrolled 3,192 patients between December 2014 and February 2016 into the randomized study; 3,169 patients (e-POCT: 1,586; control [ALMANACH]: 1,583) completed the intervention and day 7 follow-up. Using e-POCT, in the per-protocol population, the absolute proportion of clinical failures was 2.3% (37/1,586), as compared with 4.1%

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(65/1,583) in the ALMANACH arm (risk difference of clinical failure -1.7, 95% CI -3.0, -0.5), meeting the prespecified criterion for non-inferiority. In a non-prespecified superiority analysis, we observed a 43% reduction in the relative risk of clinical failure when using e-POCT compared to ALMANACH (risk ratio [RR] 0.57, 95% CI 0.38, 0.85,  $p = 0.005$ ). The proportion of severe adverse events was 0.6% in the e-POCT arm compared with 1.5% in the ALMANACH arm (RR 0.42, 95% CI 0.20, 0.87,  $p = 0.02$ ). The proportion of antibiotic prescriptions was substantially lower, 11.5% compared to 29.7% (RR 0.39, 95% CI 0.33, 0.45,  $p < 0.001$ ). Using e-POCT, the most common indication for antibiotic prescription was severe disease (57%, 103/182 prescriptions), while it was non-severe respiratory infections using the control algorithm (ALMANACH) (70%, 330/470 prescriptions). The proportion of clinical failures among the 544 children in the routine care cohort was 4.6% (25/544); 94.9% (516/544) of patients received antibiotics on day 0, and 1.1% (6/544) experienced severe adverse events. e-POCT achieved a 49% reduction in the relative risk of clinical failure compared to routine care (RR 0.51, 95% CI 0.31, 0.84,  $p = 0.007$ ) and lowered antibiotic prescriptions to 11.5% from 94.9% ( $p < 0.001$ ). Though this safety study was an important first step to evaluate e-POCT, its true utility should be evaluated through future implementation studies since adherence to the algorithm will be an important factor in making use of e-POCT's advantages in terms of clinical outcome and antibiotic prescription.

### CONCLUSIONS:

e-POCT, an innovative electronic algorithm using host biomarker POCTs, including C-reactive protein and procalcitonin, has the potential to improve the clinical outcome of children with febrile illnesses while reducing antibiotic use through improved identification of children with severe infections, and better targeting of children in need of antibiotic prescription.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5653205/>

[Trials](#). 2017 Oct 2;18(1):450. doi: 10.1186/s13063-017-2199-6.

### Co-trimoxazole versus azithromycin for the treatment of undifferentiated febrile illness in Nepal: study protocol for a randomized controlled trial.

[Pokharel S](#), [Basnyat B](#), [Arjyal A](#), [Mahat SP](#), [Kc RK](#), [Bhujju A](#), [Poudyal B](#), [Kestelyn E](#), [Shrestha R](#), [Phuong DNT](#), [Thapa R](#), [Karki M](#), [Dongol S](#), [Karkey A](#), [Wolbers M](#), [Baker S](#), [Thwaites G](#)

### BACKGROUND:

Undifferentiated febrile illness (UFI) includes typhoid and typhus fevers and generally designates fever without any localizing signs. UFI is a great therapeutic challenge in countries like Nepal because of the lack of available point-of-care, rapid diagnostic tests. Often patients are empirically treated as presumed enteric fever. Due to the development of high-level resistance to traditionally used fluoroquinolones against enteric fever, azithromycin is now commonly used to treat enteric fever/UFI. The re-emergence of susceptibility of *Salmonella typhi* to co-trimoxazole makes it a promising oral treatment for UFIs in general. We present a protocol of a randomized controlled trial of azithromycin versus co-trimoxazole for the treatment of UFI.

### METHODS/DESIGN:

This is a parallel-group, double-blind, 1:1, randomized controlled trial of co-trimoxazole versus azithromycin for the treatment of UFI in Nepal. Participants will be patients aged 2 to 65 years, presenting with fever without clear focus for at least 4 days, complying with other study criteria and willing to provide written informed consent. Patients will be randomized either to azithromycin 20 mg/kg/day (maximum 1000 mg/day) in a single daily dose and an identical placebo or co-trimoxazole 60 mg/kg/day (maximum 3000 mg/day) in two divided doses for



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7 days. Patients will be followed up with twice-daily telephone calls for 7 days or for at least 48 h after they become afebrile, whichever is later; by home visits on days 2 and 4 of treatment; and by hospital visits on days 7, 14, 28 and 63. The endpoints will be fever clearance time, treatment failure, time to treatment failure, and adverse events. The estimated sample size is 330. The primary analysis population will be all the randomized population and subanalysis will be repeated on patients with blood culture-confirmed enteric fever and culture-negative patients.

### DISCUSSION:

Both azithromycin and co-trimoxazole are available in Nepal and are extensively used in the treatment of UFI. Therefore, it is important to know the better orally administered antimicrobial to treat enteric fever and other UFIs especially against the background of fluoroquinolone-resistant enteric fever.

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2199-6>

## Skin and hair disease

*MC Dermatol.* 2017 Jul 24;17(1):10. doi: 10.1186/s12895-017-0062-9.

### [Prevalence of head lice infestation and pediculicidal effect of permethrin shampoo in primary school girls in a low-income area in southeast of Iran.](#)

[Soleimani-Ahmadi M](#), [Jaberhashemi SA](#), [Zare M](#), [Sanei-Dehkordi A](#)

### BACKGROUND:

Head lice infestation is a common public health problem that is most prevalent in primary school children throughout the world, especially in developing countries including different parts of Iran. This study aimed to determine the prevalence and risk factors associated with head lice infestation and pediculicidal effect of 1% permethrin shampoo in primary schools girls of Bashagard County, one of the low socioeconomic areas in southeast of Iran.

### METHODS:

In this interventional study six villages with similar demographical situations were selected and randomly assigned into intervention and control areas. In each area **150 girl students aged 7-12 years were selected randomly and screened for head lice infestation by visual scalp examination. In intervention area, treatment efficacy of 1% permethrin shampoo was evaluated via re-examination for infestation after one, two, and three weeks. Pre-tested structured questionnaire was used to collect data on socio-demographic and associated factors of head lice infestation.**

### RESULTS:

The prevalence of head lice infestation was 67.3%. There was significant association between head lice infestation and school grade, family size, parents' literacy, bathing facilities, frequency of hair washing, and use of shared articles ( $p < 0.05$ ). **The effectiveness of 1% permethrin shampoo for head lice treatment was 29.2, 68.9, and 90.3% after the first, second, and third weeks, respectively.**

### CONCLUSION:

The head lice infestation is a health problem in primary school girls of Bashagard County. Improvement of socioeconomic status and providing appropriate educational programs about head lice risk factors and prevention can be effective for reduction of infestation in this area.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5525205/>

[Parasitol Res.](#) 2017 Jul;116(7):1863-1870. doi: 10.1007/s00436-017-5461-7. Epub 2017 May 9.

**Randomized, investigator-blinded, controlled clinical study with lice shampoo (Licener®) versus dimethicone (Jacutin® Pedicul Fluid) for the treatment of infestations with head lice.**

[Semmler M](#), [Abdel-Ghaffar F](#), [Gestmann F](#), [Abdel-Aty M](#), [Rizk I](#), [Al-Quraishy S](#), [Lehmacher W](#), [Hoff NP](#)

The present clinical trial was conducted to obtain additional data for the safety and efficacy of a head lice shampoo that is free of silicone compared with an anti-head lice product containing dimethicone. Both products act by a physical mode of action. This randomized, investigator-blinded, controlled clinical study was conducted between July and November 2016 in households of two villages (Abou Rawash and Shandalat) in Egypt. Children older than 2 years with an active head lice infestation were treated with either a shampoo-based head lice treatment containing neem extract (Licener®) or dimethicone (Jacutin® Pedicul Fluid) on day 1 and additionally on day 9. Assessment for living lice by combing was conducted before and 1-2 h after treatment and on days 5 and 13. The main objective was to demonstrate a cure rate of the test product of at least 85% after a single application (day 5 and 9). Secondary objectives were to scrutinize patient safety and satisfaction as well as cure rates on day 13 after two treatments and the evaluation of ovicidal and licialicidic efficacies of the products. Sixty-one children in the test-group (Licener®) and 58 children in the reference group (Jacutin® Pedicul Fluid) were included in this study. The test product and the reference product were very well tolerated. **Both products exceeded the objective of cure rates of over 85% after single treatment (test group 60/60 = 100%; 95% CI = 94.04-100.00%; reference group 54/57 = 94.74%; 95% CI = 85.38-98.90%; p = 0.112; CI by Clopper-Pearson) and after two treatments (test group 58/58 = 100%; 95% CI = 93.84-100.00%; reference group 52/54 = 96.30%; 95% CI = 87.25-99.55%; p = 0.230) with higher cure rates and non-inferiority for the test product.** The combined success rate shows significant superiority of the test product against the reference product (test group 58/58 = 100%; 95% CI = 93.84-100.00%; reference group 49/54 = 90.7%; 95% CI = 79.70-96.92%; p = 0.024). The test product showed higher ovicidal efficacy than the reference product. Thus, the present study demonstrates that a single treatment with a head lice product like Licener® can be sufficient to eliminate a head lice infestation.

<https://www.ncbi.nlm.nih.gov/pubmed/28488042>

[Microbiol Immunol Infect.](#) 2017 Oct;50(5):684-692. doi: 10.1016/j.jmii.2015.10.003. Epub 2015 Nov 27.

**Evaluation of efficacy and safety of Lactobacillus rhamnosus in children aged 4-48 months with atopic dermatitis: An 8-week, double-blind, randomized, placebo-controlled study.**

[Wu YJ](#), [Wu WF](#), [Hung CW](#), [Ku MS](#), [Liao PF](#), [Sun HL](#), [Lu KH](#), [Sheu JN](#), [Lue KH](#).

**OBJECTIVE:**

The main objective of this study was to evaluate the efficacy and safety of Lactobacillus rhamnosus in children aged 4-48 months with atopic dermatitis.

**METHODS:**

The design of this study was a two-center, double-blind, randomized, and placebo-controlled study with two parallel groups to evaluate the efficacy and safety profile of L. rhamnosus in children aged 4-48 months with atopic dermatitis diagnosed using Hanifin and Rajka criteria and with a Scoring of Atopic Dermatitis (SCORAD)  $\geq 15$  at enrollment. The

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duration of this study was 8 weeks with a total of five visits. The enrolled patients were allocated into either a treatment group (one ComProbi capsule containing *L. rhamnosus* a day) or a control group (one capsule of placebo a day) at a ratio of 1:1. The primary endpoint was to compare the mean change from baseline in SCORAD after 8 weeks of treatment. The other secondary end points were to compare the following: the mean changes from baseline in SCORAD at postbaseline visits, the frequency and total amount of the use of corticosteroids during the 8-week treatment, the frequency of atopic dermatitis and the symptom-free duration, the mean changes from baseline in Infant Dermatitis Quality of Life Questionnaire at Week 4 and Week 8, and the mean changes from baseline in the Dermatitis Family Impact Questionnaire at Week 4 and Week 8.

### RESULTS:

The mean changes in SCORAD from baseline at Week 8 was  $-21.69 \pm 16.56$  in the *L. rhamnosus* group and  $-12.35 \pm 12.82$  in the placebo group for the intent-to-treat population ( $p = 0.014$ ). For the per-protocol population, the mean change of SCORAD from baseline was  $-23.20 \pm 15.24$  in the *L. rhamnosus* group and  $-12.35 \pm 12.82$  in the placebo group ( $p = 0.003$ ). Significant differences were demonstrated between groups at Week 8 in intensity in the intent-to-treat population and per-protocol population. Throughout the period, the amount of topical corticosteroids used showed no difference between groups. No significant difference was noted in the overall symptom-free durations compared with the placebo group. Infant Dermatitis Quality of Life Questionnaires and Dermatitis Family Impact Questionnaires scores improved significantly at Week 4 and Week 8 but did not reach statistical significance. Adverse events were documented in 14/33 patients in the *L. rhamnosus* group (42.42%, 35 events) and in 15/33 placebo patients (45.45%, 37 events).

### CONCLUSIONS:

The results of this study indicated that *L. rhamnosus* was effective in decreasing symptoms of atopic dermatitis after an 8-week treatment by comparing the mean change of SCORAD from baseline with a placebo ( $p < 0.05$ ). The reduction in SCORAD resulted from a consistent decrease in all components of SCORAD. Patients who took *L. rhamnosus* for 8 weeks expressed less SCORAD in the three components: area of affected skin, intensity of atopic dermatitis, and patient symptoms, with a significant decrease in the mean change of intensity from baseline compared with placebo.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S1684118215008981?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1684118215008981%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Benef Microbes](#). 2017 Oct 13;8(5):833-840. doi: 10.3920/BM2017.0011. Epub 2017 Oct 12.

### [\*\*Lactobacillus plantarum IS-10506 supplementation reduced SCORAD in children with atopic dermatitis.\*\*](#)

[Prakoewa CRS](#), [Herwanto N](#), [Prameswari R](#), [Astari L](#), [Sawitri S](#), [Hidayati AN](#), [Indramaya DM](#), [Kusumowidagdo ER](#), [Surono IS](#)

*Lactobacillus plantarum* IS-10506 is a novel probiotic isolated from dadih, an Indonesian traditional fermented buffalo milk. Its in vitro and in vivo probiotic properties have been assessed. Probiotic function has been shown in vivo by the suppression of allergic reactions in BALB/c mice through the action of T-regulatory cells cytokines by balancing Th1 and Th2 immune response. Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease characterised by the imbalance of Th1 and Th2. The aim of the study was to assess the probiotic function of *L. plantarum* IS-10506 in children with mild and moderate AD. A randomised

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double-blind placebo-controlled trial comparing microencapsulated *L. plantarum* IS-10506 ( $10^{10}$  cfu/day) and placebo (skim milk-Avicel) twice daily for 12 weeks was conducted in an outpatient clinic on children with mild and moderate AD. The trial included 22 AD children divided into intervention and control groups of  $n=12$  and  $n=10$  patients, respectively. Scoring Atopic Dermatitis Index (SCORAD) and serum immunoglobulin E (IgE), interleukin (IL)-4, interferon gamma (IFN- $\gamma$ ), forkhead box P3 (Foxp3+)/IL-10, and IL-17 levels were assessed. Demographic and baseline characteristics were not significantly different between the two groups. **SCORAD and levels of IL-4, IFN- $\gamma$ , and IL-17 were significantly lower in the probiotic group than those in the placebo group, while the IgE levels were not significantly changed.** The ratio of Foxp3+ to IL-10 was significantly higher in the probiotic group than that in placebo group. Supplementation with the probiotic *L. plantarum* IS-10506 offered a potential treatment for children with AD. Further long-term studies with a larger sample size are required to confirm the therapeutic efficacy of *L. plantarum* IS-10506 in AD.

<https://www.wageningenacademic.com/doi/pdf/10.3920/BM2017.0011>

[Indian J Dermatol Venereol Leprol.](#) 2017 Sep-Oct;83(5):561-568. doi: 10.4103/ijdv.IJDVL\_551\_16.

**[Effectiveness and safety of levocetirizine 10 mg versus a combination of levocetirizine 5 mg and montelukast 10 mg in chronic urticaria resistant to levocetirizine 5 mg: A double-blind, randomized, controlled trial.](#)**

[Sarkar TK](#), [Sil A](#), [Pal S](#), [Ghosh C](#), [Das NK](#)

### BACKGROUND:

Chronic urticaria is a vexing problem for patients and treating physicians alike. The EAACI/GA[2]LEN/EDF/WAO guidelines advocate an increased antihistamine dosage up to four times the standard, before adding leukotriene receptor antagonists. Patients are frequently intolerant of these higher dosages. We conducted this study to determine whether the addition of leukotriene receptor antagonists to the standard antihistamine dose was comparable to higher dosages of antihistamines alone, in terms of efficacy, safety and quality of life changes. We compared levocetirizine 10 mg (double dose of standard) versus a combination of levocetirizine 5 mg and montelukast 10 mg in cases of chronic urticaria not responding to single daily dose of 5 mg levocetirizine.

### METHODS:

A single-center, double-blind, randomized, active-controlled, parallel group phase IV trial (CTRI/2014/12/005261) was conducted on 120 patients of chronic urticaria of either sex not responding to 5 mg levocetirizine. Patients were randomized into receiving either levocetirizine 10 mg or levocetirizine 5 mg + montelukast 10 mg for 4 weeks. Primary outcome measures were Urticaria Activity Score (UAS) and Urticaria Total Severity Score (TSS). Routine hematological and biochemical tests and treatment-emergent adverse events were monitored for safety.

### RESULTS:

Fifty-two patients on levocetirizine 10 mg group and 51 patients on levocetirizine 5 mg + montelukast 10 mg group were analyzed. UAS and TSS reduced significantly in both treatment groups and reduction of score were comparable in between the groups ( $P = 0.628$ ,  $P = 0.824$ , respectively). Among adverse effects, sedation was noted significantly more ( $P = 0.013$ ) in levocetirizine 10 mg group. Quality of life was significantly improved in levocetirizine 5 mg + montelukast 10 mg group ( $P = 0.031$ ).

### LIMITATIONS:

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The limitation of the study was that the follow-up period was 4 weeks.

### CONCLUSION:

EAACI/GA[2]LEN/EDF/WAO guidelines need to be more flexible in allowing usage of montelukast before escalation of anti-histamine dosage.

<http://www.ijdv1.com/article.asp?issn=0378-6323;year=2017;volume=83;issue=5;spage=561;epage=568;auiast=Sarkar>

## Snake bite and envenomation

*PLoS Negl Trop Dis.* 2017 Nov 27;11(11):e0006068. doi: 10.1371/journal.pntd.0006068. eCollection 2017 Nov.

### Safety and efficacy of a freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: An open randomized controlled phase IIb clinical trial.

Mendonça-da-Silva I, Magela Tavares A, Sachett J, Sardinha JF, Zaparolli L, Gomes Santos MF, Lacerda M, Monteiro WM

### BACKGROUND:

In tropical areas, a major concern regarding snakebites treatment effectiveness relates to the failure in liquid antivenom (AV) distribution due to the lack of an adequate cold chain in remote areas. To minimize this problem, freeze-drying has been suggested to improve AV stability.

### METHODS AND FINDINGS:

This study compares the safety and efficacy of a freeze-dried trivalent antivenom (FDTAV) and the standard liquid AV provided by the Brazilian Ministry of Health (SLAV) to treat Bothrops, Lachesis and Crotalus snakebites. This was a prospective, randomized, open, phase IIb trial, carried out from June 2005 to May 2008 in the Brazilian Amazon. Primary efficacy endpoints were the suppression of clinical manifestations and return of hemostasis and renal function markers to normal ranges within the first 24 hours of follow-up. Primary safety endpoint was the presence of early adverse reactions (EAR) in the first 24 hours after treatment. FDTAV thermal stability was determined by estimating AV potency over one year at 56°C. Of the patients recruited, 65 and 51 were assigned to FDTAV and SLAV groups, respectively. Only mild EARs were reported, and they were not different between groups. There were no differences in fibrinogen ( $p = 0.911$ ) and clotting time ( $p = 0.982$ ) recovery between FDTAV and SLAV treated groups for Bothrops snakebites. For Lachesis and Crotalus snakebites, coagulation parameters and creatine phosphokinase presented normal values 24 hours after AV therapy for both antivenoms.

### CONCLUSIONS/SIGNIFICANCE:

Since promising results were observed for efficacy, safety and thermal stability, our results indicate that FDTAV is suitable for a larger phase III trial.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006068>

*PLoS Negl Trop Dis.* 2017 Jul 10;11(7):e0005745. doi: 10.1371/journal.pntd.0005745. eCollection 2017 Jul.

**Poor efficacy of preemptive amoxicillin clavulanate for preventing secondary infection from Bothrops snakebites in the Brazilian Amazon:**

**A randomized controlled clinical trial.**

Sachett JAG, da Silva IM, Alves EC, Oliveira SS, Sampaio VS, do Vale FF, Romero GAS, Dos Santos MC, Marques HO, Colombini M, da Silva AMM, Wen FH, Lacerda MVG, Monteiro WM, Ferreira LCL

**BACKGROUND:**

Secondary bacterial infections from snakebites contribute to the high complication rates that can lead to permanent function loss and disabilities. Although common in endemic areas, routine empirical prophylactic use of antibiotics aiming to prevent secondary infection lacks a clearly defined policy. The aim of this work was to estimate the efficacy of amoxicillin clavulanate for reducing the secondary infection incidence in patients bitten by Bothrops snakes, and, secondarily, identify risk factors for secondary infections from snakebites in the Western Brazilian Amazon.

**METHODS AND FINDINGS:**

This was an open-label, two-arm individually randomized superiority trial to prevent secondary infection from Bothrops snakebites. The antibiotic chosen for this clinical trial was oral amoxicillin clavulanate per seven days compared to no intervention. A total of 345 patients were assessed for eligibility in the study period. From this total, 187 accomplished the inclusion criteria and were randomized, 93 in the interventional group and 94 in the untreated control group. All randomized participants completed the 7 days follow-up period. Enzyme immunoassay confirmed Bothrops envenoming diagnosis in all participants. Primary outcome was defined as secondary infection (abscess and/or cellulitis) until day 7 after admission. Secondary infection incidence until 7 days after admission was 35.5% in the intervention group and 44.1% in the control group [RR = 0.80 (95%CI = 0.56 to 1.15; p = 0.235)]. Survival analysis demonstrated that the time from patient admission to the onset of secondary infection was not different between amoxicillin clavulanate treated and control group (Log-rank = 2.23; p = 0.789). Secondary infections incidence in 7 days of follow-up was independently associated to fibrinogen >400 mg/dL [AOR = 4.78 (95%CI = 2.17 to 10.55; p<0.001)], alanine transaminase >44 IU/L [AOR = 2.52 (95%CI = 1.06 to 5.98; p = 0.037)], C-reactive protein >6.5 mg/L [AOR = 2.98 (95%CI = 1.40 to 6.35; p = 0.005)], moderate pain [AOR = 24.30 (95%CI = 4.69 to 125.84; p<0.001)] and moderate snakebites [AOR = 2.43 (95%CI = 1.07 to 5.50; p = 0.034)].

**CONCLUSIONS/SIGNIFICANCE:**

Preemptive amoxicillin clavulanate was not effective for preventing secondary infections from Bothrops snakebites. Laboratorial markers, such as high fibrinogen, alanine transaminase and C-reactive protein levels, and severity clinical grading of snakebites, may help to accurately diagnose secondary infections.

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005745>

## **Surgical problems**

N Engl J Med. 2017 Dec 21;377(25):2456-2464. doi: 10.1056/NEJMoa1707568.

**Endoscopic Treatment versus Shunting for Infant Hydrocephalus in Uganda.**

Kulkarni AV, Schiff SJ, Mbabazi-Kabachelor E, Mugamba J, Ssenyonga P, Donnelly R, Levenbach J, Monga V, Peterson M, MacDonald M, Cherukuri V, Warf BC

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### BACKGROUND:

Postinfectious hydrocephalus in infants is a major health problem in sub-Saharan Africa. The conventional treatment is ventriculoperitoneal shunting, but surgeons are usually not immediately available to revise shunts when they fail. **Endoscopic third ventriculostomy with choroid plexus cauterization (ETV-CPC)** is an alternative treatment that is less subject to late failure but is also less likely than shunting to result in a reduction in ventricular size that might facilitate better brain growth and cognitive outcomes.

### METHODS:

We conducted a randomized trial to evaluate cognitive outcomes after **ETV-CPC versus ventriculoperitoneal shunting** in Ugandan infants with postinfectious hydrocephalus. The primary outcome was the Bayley Scales of Infant Development, Third Edition (BSID-3), cognitive scaled score 12 months after surgery (scores range from 1 to 19, with higher scores indicating better performance). The secondary outcomes were BSID-3 motor and language scores, treatment failure (defined as treatment-related death or the need for repeat surgery), and brain volume measured on computed tomography.

### RESULTS:

**A total of 100 infants were enrolled; 51 were randomly assigned to undergo ETV-CPC, and 49 were assigned to undergo ventriculoperitoneal shunting.** The median BSID-3 cognitive scores at 12 months did not differ significantly between the treatment groups (a score of 4 for ETV-CPC and 2 for ventriculoperitoneal shunting; Hodges-Lehmann estimated difference, 0; 95% confidence interval [CI], -2 to 0; P=0.35). There was no significant difference between the ETV-CPC group and the ventriculoperitoneal-shunt group in BSID-3 motor or language scores, rates of treatment failure (35% and 24%, respectively; hazard ratio, 0.7; 95% CI, 0.3 to 1.5; P=0.24), or brain volume (z score, -2.4 and -2.1, respectively; estimated difference, 0.3; 95% CI, -0.3 to 1.0; P=0.12).

### CONCLUSIONS:

This single-center study involving Ugandan infants with postinfectious hydrocephalus showed no significant difference between endoscopic ETV-CPC and ventriculoperitoneal shunting with regard to cognitive outcomes at 12 months.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5784827/>

[J Pediatr Surg.](#) 2018 Feb;53(2):247-249. doi: 10.1016/j.jpedsurg.2017.11.022. Epub 2017 Nov 14.

### **Laparoscopic versus open appendectomy in children: a randomized controlled trial from a developing country.**

[Ali R](#), [Anwar M](#), [Akhtar J](#)

### BACKGROUND:

Acute appendicitis is a common surgical emergency. This study was conducted to compare the outcome in terms of duration of surgery, length of hospital stay, and wound infection rate following laparoscopic versus open appendectomy in children with acute appendicitis.

### METHODS:

A prospective randomized controlled trial was conducted. Patients with the diagnosis of acute appendicitis were randomly assigned to Group A: Laparoscopic appendectomy (LA) and Group B: Open appendectomy (OA). Age and sex of patients, signs, and symptoms were noted. Duration of surgery, length of hospital stay (LOS), and postoperative wound infection were recorded.

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### RESULTS:

A total of 126 patients were operated, with 63 in each group. Mean age of the patients was  $9.7 \pm 2.1$  years in LA group and  $9.8 \pm 2.3$  years in OA group. In LA group, inflamed appendix was found in 68% patients, perforated in 17%, gangrenous in 9%, and suppurative in 5%. In OA group, inflamed appendix was found in 60% patients, perforated in 22%, gangrenous in 5%, and suppurative in 13%. The mean duration of operation was  $56 \pm 24$  min in LA group and  $39 \pm 8$  min in OA group ( $p < 0.0001$  in favor of OA group). The mean length of hospital stay was  $34 \pm 13$  h in LA group and  $40 \pm 11$  h in OA group ( $p = 0.01$  in favor of LA group). The results showed no significant association of wound infection between the two groups ( $p = 0.31$ ).

### CONCLUSION:

There was no difference in terms of LOS and rate of wound infection among the groups. However, the laparoscopic procedure was technically demanding.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0022346817307406?returnurl=https%3F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0022346817307406%3Fshowall%3Dtrue&referrer=https%3F%2Fwww.ncbi.nlm.nih.gov%2F>

[Burns](#). 2018 Feb;44(1):175-182. doi: 10.1016/j.burns.2017.07.004. Epub 2017 Aug 8.

### Assessing and addressing the problem of pain and distress during wound care procedures in paediatric patients with burns.

[van der Heijden MJE](#), [de Jong A](#), [Rode H](#), [Martinez R](#), [van Dijk M](#)

### OBJECTIVE:

While the prevalence of burns in children is highest in low and middle-income countries, most research on burn-related pain intensity and distress is carried out in high-income countries. In this study we assessed pain intensity and distress in paediatric patients with burns undergoing wound care procedures without distraction and parental presence in a South-African children's hospital and sought to identify predictors for the outcomes.

### METHODS:

This observational study, carried out as part of a randomized controlled trial, took place at a burns unit in Cape Town, South Africa and included patients between the ages of 0 and 13 years undergoing their first or second wound care procedure. We measured pain intensity and distress using the COMFORT Behavioural scale (COMFORT-B) across four distinct phases of wound care procedures: removal of bandage; washing the wound; administering wound care; putting on new dressings. COMFORT-B scores  $\geq 21$  indicate severe pain intensity and distress.

### RESULTS:

124 patients were included, median age 21.2 months (IQR 14.9-39.5 months), 90% suffered scalds, and median total body surface 8% (IQR 5-14%). Assessment scores for the majority of patients were indicative of severe pain intensity and distress during wound care procedures. Median COMFORT-B scores across the four phases were 24, 25, 25 and 22 respectively. Across the four phases respectively 76%; 89%; 81% and 62% of the patients were indicated with severe pain intensity and distress. Age was a predictor for pain intensity and distress as younger children were assigned higher scores than older children (Unstandardized B -.052; 95% CI -.071 to -.032  $p < 0.001$ ).

### CONCLUSIONS:

In this study children received wound care procedures without distraction or parental presence and were assessed to have high pain intensity and distress. There is a correlation between age and COMFORT-B scores: younger children show higher distress, indicating a great need for



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better pain and distress control during wound care procedures. It is difficult to identify whether pain or distress is the specific primary cause for the high COMFORT-B scores.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0305417917303856?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0305417917303856%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Burns](#). 2018 Feb;44(1):99-107. doi: 10.1016/j.burns.2017.10.002. Epub 2017 Oct 28.

### **Massage has no observable effect on distress in children with burns: A randomized, observer-blinded trial.**

[van Dijk M](#), [O'Flaherty LA](#), [Hoedemaker T](#), [van Rosmalen J](#), [Rode H](#)

#### **IMPORTANCE:**

In a previous observational study we found that massage therapy reduced anxiety and stress in pediatric burn patients. We aimed to test this effect in a randomized controlled trial.

#### **OBJECTIVE:**

To determine whether (1) aromatherapy massage can provide relaxation to hospitalized children with burns; (2) massage with aromatherapy oil is more effective than without; and (3) massage sessions are more effective when repeated.

#### **DESIGN, SETTING, AND PARTICIPANTS:**

Randomized controlled clinical trial with 3 arms conducted in a burns unit from April 2013 to December 2014 in Cape Town, South Africa.

#### **INTERVENTIONS:**

Massage with carrier oil, massage with aromatherapy oil, and standard nursing care only.

#### **MAIN OUTCOMES AND MEASURES:**

Scores on the Muscle Tension Inventory (MTI) and Behavioral Relaxation Scale (BRS) to assess level of relaxation. Scores on the COMFORT behaviour scale and Numeric Rating Scale Distress to assess level of distress. Secondary outcomes were heart rate and oxygen saturation levels. Linear mixed models were used to determine the effect of condition and session number (1 to a maximum of 5 sessions per child) correcting for baseline outcomes of COMFORT behaviour scores and heart rates after sessions. Secondary analyses included the addition of sex, age, and total body surface area (TBSA) burned as covariates.

#### **RESULTS:**

We included 284 children aged 5 weeks to 13 years with TBSA burned between 10 and 45%. Two-thirds (65.5%) were under the age of 3 years. Mixed model analyses revealed no significant difference in reduction of COMFORT behavior scores ( $p=0.18$ ), or heart rates ( $p=0.18$ ) between the three study arms. These outcomes were also not associated with the session number ( $p=0.92$  and  $p=0.13$ , respectively). Level of relaxation could not be reliably assessed with the MTI and BRS because 119 patients (41.9%) had bandages covering the larger part of the face, and in 40.1% of cases the child was not in the required position.

#### **CONCLUSION AND RELEVANCE:**

**Massage therapy with or without essential oil was not effective in reducing distress behavior or heart rate in hospitalized children with burns.** Evaluating the effectiveness of massage in terms of relaxation proved difficult in young children.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0305417917305466?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0305417917305466%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Burns](#). 2018 Jun;44(4):823-833. doi: 10.1016/j.burns.2017.12.013. Epub 2018 Feb 1.

**Can live music therapy reduce distress and pain in children with burns after wound care procedures? A randomized controlled trial.**

[van der Heijden MJE](#), [Jeekel J](#), [Rode H](#), [Cox S](#), [van Rosmalen J](#), [Hunink MGM](#), [van Dijk M](#)

**OBJECTIVE:**

Burn wound care procedures are very painful and lead to distress. Live music therapy has shown beneficial effects on distress and pain in specific pediatric patient populations. In this study we measured whether live music therapy has beneficial effects in terms of less distress and pain in children with burns after wound care procedures.

**METHODS:**

This randomized assessor-blinded controlled trial (RCT) took place at the burns unit of the Red Cross War Memorial Children's Hospital, Cape Town, South Africa. It included newly admitted inpatients between the ages of 0 and 13 years undergoing their first or second wound care procedures. Excluded were children with a hearing impairment or low level of consciousness. The intervention group received one live music therapy session directly after wound care in addition to standard care. The control group received standard care only. The primary outcome was distress measured with the Observational Scale of Behavioral Distress-revised (OSBD-r). The secondary outcome was pain measured with the COMFORT-behavioral scale (COMFORT-B). In addition, in children older than 5 years self-reported distress with the validated Wong-Baker scale (FACES) and pain with the Faces Pain Scale-Revised (FPS-R) were measured. Patients in both groups were videotaped for three minutes before wound care; during the music therapy or the control condition; and for two minutes thereafter. Two researchers, blinded to the study condition, independently scored the OSBD-r and the COMFORT-B from the video footage before and after music therapy.

**RESULTS:**

We included 135 patients, median age 22.6 months (IQR 15.4-40.7 months). Change scores did not significantly differ between the intervention and the control groups for either distress ( $p=0.53$ ;  $d=0.11$ ; 95% CI -0.23 to 0.45) or pain ( $p=0.99$ ;  $d=0.04$ ; 95% CI -0.30 to 0.38). Self-reported distress in a small group of children ( $n=18$ ) older than 5 years indicated a significant reduction in distress after live music therapy ( $p=0.05$ ).

**CONCLUSIONS:**

**Live music therapy was not found effective in reducing distress and pain in young children after burn wound care.** Older children might be more responsive to this intervention.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0305417917306927?returnurl=https%3F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0305417917306927%3Fshowall%3Dtrue&referrer=https%3F%2Fwww.ncbi.nlm.nih.gov%2F>

## **Training for health workers**

[Global Health](#). 2017 Dec 6;13(1):88. doi: 10.1186/s12992-017-0313-x.

**Incremental cost and cost-effectiveness of low-dose, high-frequency training in basic emergency obstetric and newborn care as compared to status quo: part of a cluster-randomized training intervention evaluation in Ghana.**

## Randomised trials in child health in developing countries 2017-18

[Willcox M](#), [Harrison H](#), [Asiedu A](#), [Nelson A](#), [Gomez P](#), [LeFevre A](#)

### BACKGROUND:

Low-dose, high-frequency (LDHF) training is a new approach best practices to improve clinical knowledge, build and retain competency, and transfer skills into practice after training. LDHF training in Ghana is an opportunity to build health workforce capacity in critical areas of maternal and newborn health and translate improved capacity into better health outcomes.

### METHODS:

This study examined the costs of an LDHF training approach for basic emergency obstetric and newborn care and calculates the incremental cost-effectiveness of the LDHF training program for health outcomes of newborn survival, compared to the status quo alternative of no training. The costs of LDHF were compared to costs of traditional workshop-based training per provider trained. Retrospective program cost analysis with activity-based costing was used to measure all resources of the LDHF training program over a 3-year analytic time horizon. Economic costs were estimated from financial records, informant interviews, and regional market prices. Health effects from the program's impact evaluation were used to model lives saved and disability-adjusted life years (DALYs) averted. Uncertainty analysis included one-way and probabilistic sensitivity analysis to explore incremental cost-effectiveness results when fluctuating key parameters.

### RESULTS:

For the 40 health facilities included in the evaluation, the total LDHF training cost was \$823,134. During the follow-up period after the first LDHF training-1 year at each participating facility-approximately 544 lives were saved. With deterministic calculation, these findings translate to \$1497.77 per life saved or \$53.07 per DALY averted. Probabilistic sensitivity analysis, with mean incremental cost-effectiveness ratio of \$54.79 per DALY averted (\$24.42-\$107.01), suggests the LDHF training program as compared to no training has 100% probability of being cost-effective above a willingness to pay threshold of \$1480, Ghana's gross national income per capita in 2015.

### CONCLUSION:

This study provides insight into the investment of LDHF training and value for money of this approach to training in-service providers on basic emergency obstetric and newborn care. The LDHF training approach should be considered for expansion in Ghana and integrated into existing in-service training programs and health system organizational structures for lower cost and more efficiency at scale.

<https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-017-0313-x>

[Acquir Immune Defic Syndr](#). 2017 Aug 15;75(5):e120-e127. doi: 10.1097/QAI.0000000000001378.

### [Improved HIV and TB Knowledge and Competence Among Mid-level Providers in a Cluster-Randomized Trial of One-on-One Mentorship for Task Shifting.](#)

[Naikoba S](#), [Senjovu KD](#), [Mugabe P](#), [McCarthy CF](#), [Riley PL](#), [Kadengye DT](#), [Dalal S](#).

### INTRODUCTION:

Health worker shortages pose a challenge to the scale up of HIV care and treatment in Uganda. Training mid-level providers (MLPs) in the provision of HIV and tuberculosis (TB) treatment can expand existing health workforce capacity and access to HIV services.

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### **METHODS:**

We conducted a cluster-randomized trial of on-site clinical mentorship for HIV and TB care at 10 health facilities in rural Uganda. Twenty MLPs at 5 randomly assigned to an intervention facilities received 8 hours a week of one-on-one mentorship, every 6 weeks over a 9-month period; and another 20 at 5 control facilities received no clinical mentorship. Enrolled MLPs' clinical knowledge and competence in management of HIV and TB was assessed using case scenarios and clinical observation at baseline and immediately after the 9-month intervention. The performance of the study health facilities on 8 TB and HIV care indicators was tracked over the 9-month period using facility patient records.

### **RESULTS:**

Thirty-nine out of 40 enrolled MLPs had case scenario and clinical observation scores for both the baseline and end of intervention assessments. Mentorship was associated with a mean score increase of 16.7% (95% confidence interval: 9.8 to 23.6,  $P < 0.001$ ) for the case scenario assessments and 25.9% (95% confidence interval: 14.4 to 37.5,  $P < 0.001$ ) for the clinical observations. On-site clinical mentorship was significantly associated with an overall improvement for 5 of the 8 health facility TB and HIV indicators tracked.

### **CONCLUSIONS:**

**One-on-one on-site mentorship improves individual knowledge and competence, has a downstream effect on facility performance, and is a simple approach to training MLPs for task shifting.**

<https://insights.ovid.com/pubmed?pmid=28406806>

## Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

[Engl J Med.](#) 2018 Jan 18;378(3):221-229. doi: 10.1056/NEJMoa1700209.

[Household-Contact Investigation for Detection of Tuberculosis in Vietnam.](#)  
[Fox GJ,](#) [Nhung NV,](#) [Sy DN,](#) [Hoa NLP,](#) [Anh LTN,](#) [Anh NT,](#) [Hoa NB,](#) [Dung NH,](#) [Buu TN,](#) [Loi NT,](#) [Nhung LT,](#) [Hung NV,](#) [Lieu PT,](#) [Cuong NK,](#) [Cuong PD,](#) [Bestrashniy J,](#) [Britton WJ,](#) [Marks GB](#)

### **BACKGROUND:**

Active case finding is a top priority for the global control of tuberculosis, but robust evidence for its effectiveness in high-prevalence settings is lacking. We sought to evaluate the effectiveness of household-contact investigation, as compared with standard, passive measures alone, in Vietnam.

### **METHODS:**

We performed a cluster-randomized, controlled trial at clinics in 70 districts (local government areas with an average population of approximately 500,000 in urban areas and 100,000 in rural areas) in eight provinces of Vietnam. **Health workers at each district clinic or hospital were assigned to perform either household-contact intervention plus standard passive case finding (intervention group) or passive case finding alone (control group).** In the intervention districts, household contacts of patients with positive results for tuberculosis on sputum smear microscopy (smear-positive tuberculosis) were invited for clinical assessment and chest radiography at baseline and at 6, 12, and 24 months. The primary outcome was the cumulative incidence of registered cases of tuberculosis among household contacts of patients with tuberculosis during a 2-year period.

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### RESULTS:

In 70 selected districts, we enrolled 25,707 household contacts of 10,964 patients who had smear-positive pulmonary tuberculosis. **In the 36 districts that were included in the intervention group, 180 of 10,069 contacts were registered as having tuberculosis (1788 cases per 100,000 population), as compared with 110 of 15,638 contacts (703 per 100,000) in the control group (relative risk of the primary outcome in the intervention group, 2.5; 95% confidence interval [CI], 2.0 to 3.2; P<0.001); the relative risk of smear-positive disease among household contacts in the intervention group was 6.4 (95% CI, 4.5 to 9.0; P<0.001).**

### CONCLUSIONS:

Household-contact investigation plus standard passive case finding was more effective than standard passive case finding alone for the detection of tuberculosis in a high-prevalence setting at 2 years.

<https://www.nejm.org/doi/full/10.1056/NEJMoa1700209>

[Int J Tuberc Lung Dis.](#) 2017 Jul 1;21(7):778-783. doi: 10.5588/ijtld.16.0709.

### **Impact of isoniazid preventive therapy on the evaluation of long-term effectiveness of infant MVA85A vaccination.**

[Bunyasi EW](#), [Luabeya AKK](#), [Tameris M](#), [Geldenhuys H](#), [Mulenga H](#), [Landry BS](#), [Scriba TJ](#), [Schmidt BM](#), [Hanekom WA](#), [Mahomed H](#), [McShane H](#), [Hatherill M](#)

### SETTING:

South Africa.

### OBJECTIVE:

To evaluate the long-term effectiveness of infant modified vaccinia Ankara virus-expressing antigen 85A (MVA85A) vaccination against tuberculosis (TB).

### DESIGN:

We analysed data from a double-blind randomised placebo-controlled Phase 2b MVA85A infant TB vaccine trial (2009-2012), with extended post-trial follow-up (2012-2014). Isoniazid preventive therapy (IPT) was provided by public health services according to national guidelines. The primary outcome was curative treatment for TB disease. Survival analysis and Poisson regression were used for study analysis.

### RESULTS:

Total follow-up was 10 351 person-years of observation (pyo). Median follow-up age was 4.8 years (interquartile range 4.4-5.2). There were 328 (12%) TB cases. TB disease incidence was 3.2/100 pyo (95%CI 2.8-3.5) overall, and respectively 3.3 (95%CI 2.9-3.9) and 3.0 (95%CI 2.6-3.5)/100 pyo in the MVA85A vaccine and placebo arms. A total of 304 children (11%) received IPT, with respectively 880 and 9471 pyo among IPT and non-IPT recipients. There were 23 (7.6%) TB cases among 304 IPT recipients vs. 305 (12.9%) among 2374 non-IPT recipients (P = 0.008). IPT effectiveness was 85% (95%CI 76-91).

### CONCLUSION:

Extended follow-up confirms no long-term effectiveness of infant MVA85A vaccination, but a six-fold reduction in TB risk can be attributed to IPT. National TB programmes in high TB burden countries should ensure optimal implementation of IPT for eligible children.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5502581/>

[Pediatr Infect Dis J.](#) 2018 Aug;37(8):773-780. doi: 10.1097/INF.0000000000001879.

**Isoniazid for the Prevention of Tuberculosis in HIV-Infected Children: A Systematic Review and Meta-Analysis.**

[Charan J](#), [Goyal JP](#), [Reljic T](#), [Emmanuel P](#), [Patel A](#), [Kumar A](#)

**BACKGROUND:**

Isoniazid is recommended for prevention of tuberculosis (TB) in HIV-infected adults, but its efficacy in children living with HIV (CLHIV) is not known. We performed a systematic review to assess the efficacy of isoniazid for the prevention of TB in CLHIV.

**METHODS:**

We searched PubMed, Cochrane Clinical Trial Registry and Google Scholar from inception to December 2016. Any randomized controlled trial assessing the role of isoniazid for the prevention of TB in CLHIV was eligible for inclusion. The primary endpoint was TB incidence; secondary end points were mortality, overall survival and severe adverse events. Dual independent extraction of all data was performed. Data were pooled under a random effects model and summarized either as risk ratio (RR) or hazard ratio along with 95% confidence intervals (CIs).

**RESULTS:**

Of 931 references, 3 randomized controlled trials enrolling 977 patients met the inclusion criteria. **Pooled results showed a statistically nonsignificant reduction in TB incidence (RR: 0.70; 95% CI: 0.47-1.04; P = 0.07) and mortality (RR: 0.94; 95% CI: 0.39-2.23; P = 0.88) with the use of isoniazid compared with placebo.** One study was stopped early because of excess deaths in the placebo arm. However, results from subgroup analysis restricted to only completed trials did not change the overall findings.

**CONCLUSIONS:**

Isoniazid did not reduce the incidence of TB in CLHIV. All included studies were performed in regions with high prevalence of TB making the overall generalizability limited.

[https://journals.lww.com/pidj/Fulltext/2018/08000/Isoniazid\\_for\\_the\\_Prevention\\_of\\_Tuberculosis\\_in.11.aspx](https://journals.lww.com/pidj/Fulltext/2018/08000/Isoniazid_for_the_Prevention_of_Tuberculosis_in.11.aspx)

[Cochrane Database Syst Rev.](#) 2017 Aug 29;8:CD006418. doi: 10.1002/14651858.CD006418.pub3.

**Isoniazid for preventing tuberculosis in HIV-infected children.**

[Zunza M](#), [Gray DM](#), [Young T](#), [Cotton M](#), [Zar HJ](#).

**BACKGROUND:**

Tuberculosis (TB) is an important cause of illness and death in HIV-positive children living in areas of high TB prevalence. We know that isoniazid prophylaxis prevents TB in HIV-negative children following TB exposure, but there is uncertainty related to its role in TB preventive treatment in HIV-positive children.

**OBJECTIVES:**

To summarise the effects of TB preventive treatment versus placebo in HIV-positive children with no known TB contact on active TB, death, and reported adverse events.

**SEARCH METHODS:**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed, Embase and two trial registers up to February 2017.

**SELECTION CRITERIA:**

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We included trials of HIV-positive children with and without known TB exposure, randomized to receive TB preventive treatment or placebo.

### DATA COLLECTION AND ANALYSIS:

Two review authors independently used the study selection criteria, assessed risk of bias, and extracted data. We assessed effects using risk, incidence rate and hazard ratios and assessed the certainty of evidence using GRADE.

### MAIN RESULTS:

We included three trials, involving 991 participants, below the age of 13 years, from South Africa and Botswana. Children were randomized to isoniazid prophylaxis or placebo, given daily or three times weekly. The median length of follow-up ranged from 5.7 to 34 months; some were on antiretroviral therapy (ART). In HIV-positive children not on ART, isoniazid prophylaxis may reduce the risk of active TB (hazard ratio (HR) 0.31, 95% confidence interval (CI) 0.11 to 0.87; 1 trial, 240 participants, low certainty evidence), and death (HR 0.46, 95% CI 0.22 to 0.95; 1 trial, 240 participants, low certainty evidence). One trial (182 participants) reported number of children with laboratory adverse events, which was similar between the isoniazid prophylaxis and placebo groups. No clinical adverse events were reported. In HIV-positive children on ART, we do not know if isoniazid prophylaxis reduces the **risk of active TB (risk ratio (RR) 0.76, 95% CI 0.50 to 1.14; 3 trials, 737 participants, very low certainty evidence) or death (RR 1.45, 95% CI 0.78 to 2.72; 3 trials, 737 participants, very low certainty evidence)**. Two trials (714 participants) reported number of clinical adverse events and three trials (795 participants) reported number of laboratory adverse events; for both categories, the number of adverse events were similar between the isoniazid prophylaxis and placebo groups.

### AUTHORS' CONCLUSIONS:

Isoniazid prophylaxis given to all children diagnosed with HIV may reduce the risk of active TB and death in HIV-positive children not on ART in studies from Africa. For children on ART, no clear benefit was detected. .

[https://journals.lww.com/pidj/Fulltext/2018/08000/Isoniazid\\_for\\_the\\_Prevention\\_of\\_Tuberculosis\\_in.11.aspx](https://journals.lww.com/pidj/Fulltext/2018/08000/Isoniazid_for_the_Prevention_of_Tuberculosis_in.11.aspx)

[Antimicrob Agents Chemother.](#) 2017 Jun 27;61(7). pii: e01834-16. doi: 10.1128/AAC.01834-16. Print 2017 Jul.

### [Effects on the QT Interval of a Gatifloxacin-Containing Regimen versus Standard Treatment of Pulmonary Tuberculosis.](#)

[Olliaro PL](#), [Merle C](#), [Mthiyane T](#), [Bah B](#), [Kassa F](#), [Amukoye E](#), [N Diaye A](#), [Perronne C](#), [Lienhardt C](#), [McIlleron H](#), [Fielding K](#)

The effects on ventricular repolarization-recorded on the electrocardiogram (ECG) as lengthening of the QT interval-of acute tuberculosis and those of standard and alternative antituberculosis regimens are underdocumented. A correction factor (QTc) is introduced to make the QT independent of the heart rate, translating into the slope of the regression line between QT and heart rate being close to zero. ECGs were performed predosing and 1 to 5 h postdosing (month 1, month 2, and end of treatment) around drugs' peak concentration time in tuberculosis patients treated with either the standard 6-month treatment (rifampin and isoniazid for 6 months and pyrazinamide and ethambutol for 2 months; "control") or a test regimen with gatifloxacin, rifampin, and isoniazid given for 4 months (pyrazinamide for the first 2 months) as part of the OFLOTUB study, a randomized controlled trial conducted in five African countries.

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Drug levels were measured at steady state (month 1) in a subset of patients. We compared treatment effects on the QTc and modeled the effect of individual drugs' maximum concentrations of drug in serum ( $C_{max}$ ) on the Fridericia-corrected QT interval. A total of 1,686 patients were eligible for the correction factor analysis of QT at baseline (mean age, 30.7 years; 27% female). Median heart rate decreased from 96/min at baseline to 71/min at end of treatment, and body temperature decreased from 37.2 to 36.5°C. Pretreatment, the nonlinear model estimated the best correction factor at 0.4081 in between Bazett's (0.5) and Fridericia's (0.33) corrections. On treatment, Fridericia (QTcF) was the best correction factor. A total of 1,602 patients contributed to the analysis of QTcF by treatment arm. The peak QTcF value during follow-up was >480 ms for 21 patients (7 and 14 in the test and control arms, respectively) and >500 ms for 9 patients (5 and 4, respectively), corresponding to a risk difference of -0.9% (95% confidence interval [CI], -2.0% to 2.3%;  $P = 0.12$ ) and 0.1% (95% CI, -0.6% to 0.9%;  $P = 0.75$ ), respectively, between the test and control arms. One hundred six (6.6%) patients had a peak measurement change from baseline of >60 ms (adjusted between-arm difference, 0.8%; 95% CI, -1.4% to 3.1%;  $P = 0.47$ ). No evidence was found of an association between  $C_{max}$  of the antituberculosis drugs 1 month into treatment and the length of QTcF. Neither a standard 6-month nor a 4-month gatifloxacin-based regimen appears to carry a sizable risk of QT prolongation in patients with newly diagnosed pulmonary tuberculosis. This is to date the largest data set studying the effects of antituberculosis regimens on the QT, both for the standard regimen and for a fluoroquinolone-containing regimen. (This study has been registered at ClinicalTrials.gov under identifier [NCT00216385](https://clinicaltrials.gov/ct2/show/study/NCT00216385)).

<http://aac.asm.org/content/61/7/e01834-16.full>

[AIDS](#). 2018 Jan 2;32(1):69-78. doi: 10.1097/QAD.0000000000001662.

### **Stool Xpert MTB/RIF and urine lipoarabinomannan for the diagnosis of tuberculosis in hospitalized HIV-infected children.**

[LaCourse SM](#), [Pavlinac PB](#), [Cranmer LM](#), [Njuguna IN](#), [Mugo C](#), [Gatimu J](#), [Stern J](#), [Walson JL](#), [Maleche-Obimbo E](#), [Oyugi J](#), [Wamalwa D](#), [John-Stewart G](#)

#### **BACKGROUND:**

Tuberculosis (TB) causes substantial morbidity and mortality in HIV-infected children. Sample collection and the paucibacillary nature of TB in children makes diagnosis challenging. Rapid diagnostic tools using easily obtained specimens are urgently needed.

#### **METHODS:**

Hospitalized, HIV-infected children aged 12 years or less enrolled in a randomized controlled trial ([NCT02063880](#)) comparing urgent to post-stabilization antiretroviral therapy initiation in Kenya underwent TB evaluation. At enrollment, sputum or gastric aspirates were collected for TB culture and Xpert, stool for Xpert, and urine for lipoarabinomannan (LAM). When possible, a second sputum/gastric aspirate for culture was obtained. Stool Xpert and urine LAM performance were compared to reference sputum/gastric aspirate culture.

#### **RESULTS:**

**Among 165 HIV-infected children**, median age was 24 months [interquartile range (IQR) 13-58], median CD4% was 14.3 (IQR 8.9-22.0%), and 114 (69.5%) had severe immunosuppression. **Thirteen (7.9%) children had confirmed TB (positive culture and/or Xpert). Sputum/gastric aspirate Xpert, stool Xpert, and urine LAM sensitivities were 60% [95% confidence interval (CI) 26-88%], 63% (95% CI 25-92%), and 43% (95% CI 10-82%), respectively. Specificity was 98% (95% CI 94-100%) for sputum/gastric aspirate Xpert, 99% (95% CI 95-100%) for stool Xpert, and 91% (95% CI 84-95%) for urine**



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LAM. Stool Xpert and urine LAM sensitivity increased among children with severe immunosuppression [80% (95% CI 28-100) and 60% (95% CI 15-95%)].

### CONCLUSION:

**Stool Xpert had similar performance compared with sputum/gastric aspirate Xpert to detect TB.** Urine LAM had lower sensitivity and specificity, but increased among children with severe immunosuppression. Stool Xpert and urine LAM can aid rapid detection of TB in HIV-infected children using easily accessible samples.

<https://insights.ovid.com/pubmed/?pmid=29028662>

[Trials](#). 2017 Nov 21;18(1):552. doi: 10.1186/s13063-017-2184-0.

### [The PREVENT study to evaluate the effectiveness and acceptability of a community-based intervention to prevent childhood tuberculosis in Lesotho: study protocol for a cluster randomized controlled trial.](#)

[Hirsch-Moverman Y](#), [Howard AA](#), [Frederix K](#), [Lebelo L](#), [Hesseling A](#), [Nachman S](#), [Mantell JE](#), [Lekhela T](#), [Maama LB](#), [El-Sadr WM](#)

### BACKGROUND:

Effective, evidence-based interventions to prevent childhood tuberculosis (TB) in high TB/HIV-burden, resource-limited settings are urgently needed. There is limited implementation of evidence-based contact management strategies, including isoniazid preventive therapy (IPT), for child contacts of TB cases in Lesotho.

### METHODS/DESIGN:

This mixed-methods implementation science study utilizes a two-arm cluster-randomized trial design with randomization at the health facility level. The study aims to evaluate the effectiveness and acceptability of a combination community-based intervention (CBI) versus standard of care (SOC) for the management of child TB contacts. The study includes three phases: (I) exploratory phase; (II) intervention implementation and testing phase; (III) post-intervention explanatory phase. Healthcare provider interviews to inform intervention refinement (phase I) were completed in December 2015. In phase II, 10 health facilities were randomized to deliver the CBI or SOC, with stratification by facility type (i.e., hospital vs. health center). CBI holistically addresses the complex provider-related, patient-related, and caregiver-related barriers to prevention of childhood TB through nurse training and mentorship; health education for caregivers and patients by village health workers; adherence support using text messaging and village health workers; and multidisciplinary team meetings, where programmatic data are reviewed and challenges and solutions are discussed. SOC sites follow country guidelines for child TB contact management. Routine TB program data will be abstracted for all adult TB cases newly registered during the study period and their child contacts from TB registers and cards. The anticipated sample size is 1080 child contacts. Primary outcomes are yield (number) of child contacts, including children < 5 years of age and HIV-positive children < 15 years of age; IPT initiation; and IPT completion. Secondary outcomes include HIV testing; yield of active prevalent TB among child contacts; and acceptability and utilization of CBI components. Intervention implementation began in February 2016 and is ongoing. Post-intervention interviews with healthcare providers and caregivers (phase III) commenced in February 2017.

### DISCUSSION:

The PREVENT study tests the effectiveness and acceptability of a novel combination CBI for child TB contact management in Lesotho. If effective, CBI will have important implications for addressing childhood TB in Lesotho and elsewhere.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5697438/>

## Urinary tract infection

### Urology

## Vaccines and immunization

(see also deworming)

### Vaccine coverage

[BMC Public Health](#). 2018 Apr 23;18(1):534. doi: 10.1186/s12889-018-5458-x.

### [Impact evaluation of a community engagement intervention in improving childhood immunization coverage: a cluster randomized controlled trial in Assam, India.](#)

[Pramanik S](#), [Ghosh A](#), [Nanda RB](#), [de Rouw M](#), [Forth P](#), [Albert S](#)

#### **BACKGROUND:**

To improve immunization coverage, most interventions that are part of the national immunization program in India address supply-side challenges. But, there is growing evidence that addressing demand-side factors can potentially contribute to improvement in childhood vaccination coverage in low- and middle-income countries. Participatory engagement of communities can address demand-side barriers while also mobilizing the community to advocate for better service delivery. The objective of this study is to evaluate the impact of a novel community engagement approach in improving immunization coverage. In our proposed intervention, we go a step beyond merely engaging the community and strive towards increasing 'ownership' by the communities.

#### **METHODS/DESIGN:**

We adopt a cluster randomized design with two groups to evaluate the intervention in Assam, a state in the northeast region of India. To recruit villages and participants at baseline, we used a two-stage stratified random sampling method. We stratified villages; our unit of randomization, based on census data and randomly selected villages from each of the four strata. At the second-stage, we selected random sub-sample of eligible households (having children in the age group of 6-23 months) from each selected village. The study uses a repeated cross sectional design where we track the same sampled villages but draw independent random samples of households at baseline and endline. Total number of villages required for the study is 180 with 15 eligible HHs from each village. Post-baseline survey, we adopt a stratified randomization strategy to achieve better balance in intervention and control groups, leveraging information from the extensive baseline survey.

#### **DISCUSSION:**

The proposed intervention can help identify barriers to vaccination at the local level and potentially lead to more sustainable solutions over the long term. Our sampling design, sample size calculation, and randomization strategy address internal validity of our evaluation design. We believe that it would allow us to causally relate any observed changes in immunization coverage to the intervention.

<https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-018-5458-x>

*Vaccine*. 2017 Nov 18. pii: S0264-410X(17)31582-7. doi: 10.1016/j.vaccine.2017.11.023.

**A cluster randomized trial to determine the effectiveness of a novel, digital pendant and voice reminder platform on increasing infant immunization adherence in rural Udaipur, India.**

Nagar R, Venkat P, Stone LD, Engel KA, Sadda P, Shahnawaz M.

**BACKGROUND:**

Five hundred thousand children under the age of 5 die from vaccine preventable diseases in India every year. More than just improving coverage, increasing timeliness of immunizations is critical to ensuring infant health in the first year of life. Novel, culturally appropriate community engagement strategies are worth exploring to close the immunization gap. In our study, a digital NFC (Near Field Communication) pendant worn on black thread and voice call reminder system was tested for the effectiveness in improving DTP3 adherence within 2 monthly camps from DTP1 administration.

**METHOD:**

A cluster randomized controlled trial was conducted in which 96 village health camps were randomized to 3 arms: NFC sticker, NFC pendant, and NFC pendant with voice call reminder in local dialect. Randomization was done across 5 blocks in the Udaipur District serviced by Seva Mandir from August 2015 to April 2016.

**RESULTS:**

In terms of our three primary outcomes related to DTP3 adherence, point estimates show conflicting results. Two outcomes presented adherence in the control. DTP3 completion within two camps after DTP1 showed higher adherence in the Control (Sticker) (74.2%) arm compared to the Pendant (67.2%) and Pendant and Voice arms (69.3%). Likewise, the estimate for DTP3 completion within 180 days of birth in the Control (Sticker) (69.4%) arm was higher than estimates in the Pendant (57.4%) and Pendant and Voice arms (58.7%). However, one outcome displayed higher adherence in the intervention. DTP3 completion within two months from the time of registration was higher in the Pendant (37.7%) and Pendant and Voice arms (38.7%) compared to the Control (Sticker) arm (27.4%). In all primary outcomes, differences in adherence were statistically insignificant both before and after controlling for confounding factors. In terms of secondary outcomes, our results suggest that providing a necklace generated significant community discussion ( $H = 8.8796$ ,  $df = 2$ ,  $p = .0118$ ), had strong satisfaction among users ( $\chi^2 = 26.039$ ,  $df = 4$ ,  $p < .0001$ ), and resulted in increased visibility within families (grandmothers:  $\chi^2 = 34.023$ ,  $df = 2$ ,  $p < .0001$ , fathers:  $\chi^2 = 34.588$ ,  $df = 2$ ,  $p < .0001$ ).

**CONCLUSION:**

Neither the NFC necklace nor the necklace with additional voice call reminders in the local dialect directly resulted in an increase in infant immunization timeliness through DTP3, the primary outcome. Still our process outcomes suggest that our culturally symbolic necklace has potential to be an assistive tool in immunization campaigns. Follow-on work will seek to examine whether positive behavior change towards vaccines can be fostered with earlier engagement of this platform beginning in the prenatal stage, under a continuum of care framework.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0264410X17315827?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0264410X17315827%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[MC Public Health](#). 2018 Jan 16;18(1):144. doi: 10.1186/s12889-018-5070-0.

**Evaluation of two health education interventions to improve the varicella vaccination: a randomized controlled trial from a province in the east China.**

[Hu Y](#), [Li Q](#), [Chen Y](#)

**BACKGROUND:**

We evaluated the effect of two Elaboration Likelihood Model (ELM)-based health educational interventions on varicella vaccine (VarV) vaccination among pregnant women in a province in the east China.

**METHODS:**

A prospective randomized controlled trial was conducted among 200 pregnant women with  $\geq 12$  gestation weeks to test two interventions, including a messaging video and a messaging booklet. The participants were randomly assigned into the control group, the video group or the booklet group. The VarV coverage at 12 and 24 months old was compared among the children of the three groups and relative risks (RRs) were calculated, by using the coverage of the control group as reference. The timeliness of VarV was also assessed. Furthermore, differences in the effects on the knowledge and attitude of VarV vaccination between the two interventions was evaluated.

**RESULTS:**

The VarV coverage of their children by 24 months of age was 86.4%, 76.1% and 56.7% for the video group, the booklet group and the control group, respectively. The relative risks (RRs) for the coverage of VarV at 24 months of age were 4.8 (95% CI: 2.06-11.3) for the video group and 2.4 (95% CI: 1.2-5.1) for the booklet group. The means of delays were 57.3 days in the video group, 76.9 days in the booklet group, and 100.6 days in the control group. The proportion of women who intended to vaccinate their children with VarV was higher in the video group than the booklet group (93.9% vs. 82.1%,  $p < 0.05$ ).

**CONCLUSIONS:**

Our findings indicated that perinatal health education through booklet or video could improve the coverage and schedule adherence for children's VarV vaccination.

<https://bmcpublihealth.biomedcentral.com/articles/10.1186/s12889-018-5070-0>

## Vaccine-related adverse effects

[Complement Ther Med](#). 2018 Feb;36:59-62. doi: 10.1016/j.ctim.2017.11.020. Epub 2017 Dec 2.

**Efficacy of Arsenicum album 30cH in preventing febrile episodes following DPT-HepB-Polio vaccination - a randomized, double-blind, placebo-controlled clinical trial.**

[Ghosh S](#), [Ghosh T](#), [Mondal R](#), [Patra S](#), [Das S](#), [Ali SS](#), [Koley M](#), [Saha S](#)

**BACKGROUND:**

Among the post-immunization adverse events, especially of Diphtheria-Pertussis-Tetanus (DPT), fever is a common systemic reaction. There is anecdotal support for the use of the homeopathic medicine Arsenicum album in preventing post-vaccination fever. The investigators intended to evaluate its efficacy in preventing febrile episodes following vaccination.

**METHODS:**

In the community medicine out-patient of Mahesh Bhattacharyya Homoeopathic Medical College and Hospital, West Bengal, India, between August 2014 and January 2017, a double-blind, randomized, placebo-controlled trial was conducted on 120 children (verum: 60, placebo:

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60) who presented for the 2nd and 3rd dose of DPT-HepB-Polio vaccination and reported febrile episodes following the 1st dose. Intervention used was Arsenicum album 30cH 6 doses or placebo (indistinguishable from verum), thrice daily for two subsequent days. Parents were advised to report any event of febrile attacks within 48h of vaccination, either directly or over telephone.

### RESULTS:

The groups were comparable at baseline. Children reporting fever after the 2nd dose was 29.8% and 30.4% respectively for the homeopathy group and control group respectively [Relative Risk (RR)=1.008] with no significant difference (P=0.951) between groups. Again after the 3rd dose, children reporting fever were 31.5% and 28.3% respectively for the homeopathy group and control group respectively (RR=0.956) with no significant difference (P=0.719) between groups.

### CONCLUSION:

Empirically selected Arsenicum album 30cH could not produce differentiable effect from placebo in preventing febrile episodes following DPT-HepB-Polio vaccination.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0965229917303059?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0965229917303059%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## BCG vaccine

(See also Vaccine - Tuberculosis vaccine)

## Cholera vaccine

[Int J Infect Dis.](#) 2018 Jan;66:90-95. doi: 10.1016/j.ijid.2017.11.020. Epub 2017 Nov 22.

### [Use of oral cholera vaccine as a vaccine probe to define the geographical dimensions of person-to-person transmission of cholera.](#)

[Ali M, Kim DR, Kanungo S, Sur D, Manna B, Digilio L, Dutta S, Marks F, Bhattacharya SK, Clemens J](#)

### BACKGROUND:

Cholera is known to be transmitted from person to person, and inactivated oral cholera vaccines (OCVs) have been shown to confer herd protection via interruption of this transmission. However, the geographic dimensions of chains of person-to-person transmission of cholera are uncertain. The ability of OCVs to confer herd protection was used to define these dimensions in two cholera-endemic settings, one in rural Bangladesh and the other in urban India.

### METHODS:

Two large randomized, placebo-controlled trials of inactivated OCVs, one in rural Matlab, Bangladesh and the other in urban Kolkata, India, were reanalyzed. Vaccine herd protection was evaluated by relating the risk of cholera in placebo recipients to vaccine coverage of surrounding residents residing within concentric rings. In Matlab, concentric rings in 100-m increments up to 700m were evaluated; in Kolkata, 50-m increments up to 350m were evaluated.

### RESULTS:

One hundred and eight cholera cases among 24667 placebo recipients were detected during 1 year of post-vaccination follow-up at Matlab; 128 cholera cases among 34968 placebo recipients were detected during 3 years of follow-up in Kolkata. Consistent inverse relationships were observed between vaccine coverage of the ring and the risk of cholera in the central placebo recipient for rings with radii up to 500m in Matlab and up to 150m in Kolkata.

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### CONCLUSIONS:

These results suggest that the dimensions of chains of person-to-person transmission in endemic settings can be quite large and may differ substantially from setting to setting. Using OCVs as 'probes' to define these dimensions can inform geographical targeting strategies for the deployment of these vaccines in endemic settings.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S1201971217303028?returnurl=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1201971217303028%3Fshowall%3Dtrue&referrer=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2F>

### Dengue vaccine

[Am J Trop Med Hyg.](#) 2017 Dec;97(6):1898-1903. doi: 10.4269/ajtmh.16-0952. Epub 2017 Oct 12.

#### **Resource Use and Costs of Dengue: Analysis of Data from Phase III Efficacy Studies of a Tetravalent Dengue Vaccine.**

[El Fezzazi H](#), [Branchu M](#), [Carrasquilla G](#), [Pitisuttithum P](#), [Perroud AP](#), [Frago C](#), [Coudeville L](#).

A tetravalent dengue vaccine (CYD-TDV) has recently been approved in 12 countries in southeast Asia and Latin America for individuals aged 9-45 years or 9-60 years (age indication approvals vary by country) living in endemic areas. **Data on utilization of medical and nonmedical resources as well as time lost from school and work were collected during the active phase of two phase III efficacy studies performed in 10 countries in the Asia-Pacific region and Latin America** ([NCT01373281](#); [NCT01374516](#)). We compared dengue-related resource utilization and costs among vaccinated and nonvaccinated participants. Country-specific unit costs were derived from available literature. There were 901 virologically confirmed dengue episodes among participants aged  $\geq 9$  years ( $N = 25,826$ ): corresponding to 373 episodes in the CYD-TDV group ( $N = 17,230$ ) and 528 episodes in the control group ( $N = 8,596$ ). **Fewer episodes in the CYD-TDV group resulted in hospitalization than in the control group (7.0% versus 13.3%;  $P = 0.002$ ), but both had a similar average length of stay of 4 days. Overall, a two-thirds reduction in resource consumption and missed school/work days was observed in the CYD-TDV group relative to the control group.** The estimated direct and indirect cost (2014 I\$) associated with dengue episodes per participant in the CYD-TDV group was 73% lower than in the control group (I\$6.72 versus I\$25.08); representing a saving of I\$18.36 (95% confidence interval [CI]: 17.05-19.78) per participant with vaccination. This is the first study providing information on dengue costs among vaccinated individuals and direct confirmation that vaccination has the potential to reduce dengue illness costs.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805027/>

[Front Immunol.](#) 2017 Aug 4;8:863. doi: 10.3389/fimmu.2017.00863. eCollection 2017.

#### **Clinical Efficacy, Safety, and Immunogenicity of a Live Attenuated Tetravalent Dengue Vaccine (CYD-TDV) in Children: A Systematic Review with Meta-analysis.**

[Malisheni M](#), [Khaiboullina SF](#), [Rizvanov AA](#), [Takah N](#), [Murewanhema G](#), [Bates M](#)

## Randomised trials in child health in developing countries 2017-18

### BACKGROUND:

Dengue hemorrhagic fever is the leading cause of hospitalization and death in children living in Asia and Latin America. There is an urgent need for an effective and safe dengue vaccine to reduce morbidity and mortality in this high-risk population given the lack of dengue specific treatment at present. This review aims to determine the efficacy, safety, and immunogenicity of CYD-TDV vaccine in children.

### METHODS:

This is a systematic review including meta-analysis of randomized controlled clinical trial data from Embase, Medline, the Cochrane Library, Web of Science, and ClinicalTrials.gov. Studies that assessed CYD-TDV vaccine efficacy  $[(1 - RR) * 100]$ , safety (RR), and immunogenicity (weighted mean difference) in children were included in this study. Random effects model was employed to analyze patient-level data extracted from primary studies.

### RESULTS:

**The overall efficacy of CYD-TDV vaccine was 54% (40-64), while serotype-specific efficacy was 77% (66-85) for DENV4, 75% (65-82) for DENV3, 50% (36-61) for DENV1, and 34% (14-49) for DENV2. 15% (-174-74) vaccine efficacy was obtained for the unknown serotype.** Meta-analysis of included studies with longer follow-up time (25 months) revealed that CYD-TDV vaccine significantly increased the risk of injection site reactions (RR = 1.1: 1.04-1.17;  $p$ -value = 0.001). Immunogenicity (expressed as geometric mean titers) in descending order was 439.7 (331.7-547.7), 323 (247 - 398.7), 144.1 (117.9-170.2), and 105 (88.7-122.8) for DENV3, DENV2, DENV1, and DENV4, respectively.

### CONCLUSION:

**CYD-TDV vaccine is effective and immunogenic in children overall.** Reduced efficacy of CYD-TDV vaccine against DENV2 notoriously known for causing severe dengue infection and dengue outbreaks cause for serious concern. *Post hoc* meta-analysis of long-term follow-up data ( $\geq 25$  months) from children previously vaccinated with CYD-TDV vaccine is needed to make a conclusion regarding CYD-TDV vaccine safety in children. However, CYD-TDV vaccine should be considered for use in regions where DENV2 is not endemic as currently there is no specific treatment for dengue infection.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5543029/>

## Ebola vaccine

[PLoS Med.](#) 2017 Oct 6;14(10):e1002402. doi: 10.1371/journal.pmed.1002402. eCollection 2017 Oct.

### **Safety and immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccine in adults and children in Lambaréné, Gabon: A phase I randomised trial.**

[Agnandji ST](#), [Fernandes JF](#), [Bache EB](#), [Obiang Mba RM](#), [Brosnahan JS](#), [Kabwende L](#), [Pitzinger P](#), [Staarink P](#), [Massinga-Loembe M](#), [Krähling V](#), [Biedenkopf N](#), [Fehling SK](#), [Strecker T](#), [Clark DJ](#), [Staines HM](#), [Hooper JW](#), [Silvera P](#), [Moorthy V](#), [Kieny MP](#), [Adegnika AA](#), [Grobusch MP](#), [Becker S](#), [Ramharter M](#), [Mordmüller B](#), [Lell B](#); [VEBICON Consortium](#), [Krishna S](#), [Kremsner PG](#)

### BACKGROUND:

The rVSVΔG-ZEBOV-GP vaccine prevented Ebola virus disease when used at  $2 \times 10^7$  plaque-forming units (PFU) in a trial in Guinea. This study provides further safety and immunogenicity data.

### **METHODS AND FINDINGS:**

A randomised, open-label phase I trial in Lambaréné, Gabon, studied 5 single intramuscular vaccine doses of  $3 \times 10^3$ ,  $3 \times 10^4$ ,  $3 \times 10^5$ ,  $3 \times 10^6$ , or  $2 \times 10^7$  PFU in 115 adults and a dose of  $2 \times 10^7$  PFU in 20 adolescents and 20 children. The primary objective was safety and tolerability 28 days post-injection. Immunogenicity, viraemia, and shedding post-vaccination were evaluated as secondary objectives. In adults, mild-to-moderate adverse events were frequent, but there were no serious or severe adverse events related to vaccination. Before vaccination, Zaire Ebola virus (ZEBOV)-glycoprotein (GP)-specific and ZEBOV antibodies were detected in 11% and 27% of adults, respectively. In adults, 74%-100% of individuals who received a dose  $3 \times 10^4$ ,  $3 \times 10^5$ ,  $3 \times 10^6$ , or  $2 \times 10^7$  PFU had a  $\geq 4.0$ -fold increase in geometric mean titres (GMTs) of ZEBOV-GP-specific antibodies at day 28, reaching GMTs of 489 (95% CI: 264-908), 556 (95% CI: 280-1,101), 1,245 (95% CI: 899-1,724), and 1,503 (95% CI: 931-2,426), respectively. Twenty-two percent of adults had a  $\geq 4$ -fold increase of ZEBOV antibodies, with GMTs at day 28 of 1,015 (647-1,591), 1,887 (1,154-3,085), 1,445 (1,013-2,062), and 3,958 (2,249-6,967) for the same doses, respectively. These antibodies persisted up to day 180 for doses  $\geq 3 \times 10^5$  PFU. Adults with antibodies before vaccination had higher GMTs throughout. Neutralising antibodies were detected in more than 50% of participants at doses  $\geq 3 \times 10^5$  PFU. As in adults, no serious or severe adverse events related to vaccine occurred in adolescents or children. At day 2, vaccine RNA titres were higher for adolescents and children than adults. At day 7, 78% of adolescents and 35% of children had recombinant vesicular stomatitis virus RNA detectable in saliva. The vaccine induced high GMTs of ZEBOV-GP-specific antibodies at day 28 in adolescents, 1,428 (95% CI: 1,025-1,989), and children, 1,620 (95% CI: 806-3,259), and in both groups antibody titres increased up to day 180. The absence of a control group, lack of stratification for baseline antibody status, and imbalances in male/female ratio are the main limitations of this study.

### **CONCLUSIONS:**

Our data confirm the acceptable safety and immunogenicity profile of the  $2 \times 10^7$  PFU dose in adults and support consideration of lower doses for paediatric populations and those who request boosting.

<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002402>

Enterovirus 71 vaccine

Hepatitis A vaccine

Hepatitis B vaccine

[Indian Pediatr.](#) 2017 Dec 15;54(12):1017-1020. Epub 2017 Aug 24.

### **Double Dose Versus Standard Dose Hepatitis B Vaccine in HIV-infected Children: A Randomized Controlled Trial.**

[Siddiqui SA](#), [Maurya M](#), [Singh DK](#), [Srivastava A](#), [Rai R](#).

### **OBJECTIVE:**

To compare the efficacy of double dose (20  $\mu$ g) with standard dose (10  $\mu$ g) of hepatitis B vaccine in HIV-infected children.

### **METHODS:**



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Unvaccinated HIV-infected children were randomized to receive 3 doses of double dose (N=27) or standard dose (N=28) of recombinant Hepatitis B vaccine. Anti-HBs antibody titres were measured 3 mo after the last dose. An antibody titre  $\geq 10$  mIU/mL 12 weeks after the third dose was considered as seroprotection.

### RESULTS:

Seroprotection was achieved by 17 (60.7%) children in standard dose group against 20 (74%) in the double dose group [RR (95%CI) 0.8 (0.17-1.7); P=0.29]. CD4 count  $< 500$  cells/mm<sup>3</sup> was significantly associated with lower rates of seroprotection.

### CONCLUSION:

Double dose of hepatitis B vaccine does not seem to provide any advantage when compared to standard dose in HIV-infected children.

<https://www.indianpediatrics.net/dec2017/1017.pdf>

HIV vaccine

HPV vaccine

Influenza vaccine

[Lancet Infect Dis.](#) 2017 Sep;17(9):981-989. doi: 10.1016/S1473-3099(17)30252-9. Epub 2017 May 15.

### [Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial.](#)

[Steinhoff MC](#), [Katz J](#), [Englund JA](#), [Khatry SK](#), [Shrestha L](#), [Kuypers J](#), [Stewart L](#), [Mullany LC](#), [Chu HY](#), [LeClerq SC](#), [Kozuki N](#), [McNeal M](#), [Reedy AM](#), [Tielsch JM](#)

### BACKGROUND:

Influenza immunisation during pregnancy is recommended but not widely implemented in some low-income regions. We assessed the safety and efficacy in mothers and infants of year-round maternal influenza immunisation in Nepal, where influenza viruses circulate throughout the year.

### METHODS:

In this phase 4, randomised, placebo-controlled trial, we enrolled two consecutive sequential annual cohorts of pregnant women from the Sarlahi district in southern Nepal. **We randomised mothers 1:1 to receive seasonally recommended trivalent inactivated influenza vaccine or saline placebo in blocks of eight, stratified by gestational age at enrolment (17-25 weeks vs 26-34 weeks).** Women were eligible if they were married, 15-40 years of age, 17-34 weeks' gestation at enrolment, and had not previously received any influenza vaccine that season. We collected serum samples before and after immunisation, and cord blood from a subset of women and infants. Staff masked to allocation made home visits every week from enrolment to 6 months after delivery. Midnasal swabs for respiratory virus PCR testing were collected during maternal acute febrile respiratory infections, and from infants with any respiratory symptom. We assessed vaccine immunogenicity, safety, and three primary outcomes: the incidence of maternal influenza-like illness in pregnancy and 0-180 days postpartum, the incidence of low birthweight ( $< 2500$  g), and the incidence of laboratory-confirmed infant influenza disease from 0 to 180 days. This trial is registered with ClinicalTrials.gov, number [NCT01034254](#).

### FINDINGS:

From April 25, 2011, to Sept 9, 2013, we enrolled 3693 women in two cohorts of 2090 (1041 assigned to placebo and 1049 to vaccine) and 1603 (805 assigned to placebo and 798 to

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vaccine), with 3646 liveborn infants (cohort 1, 999 in placebo group and 1010 in vaccine group; cohort 2, 805 in placebo group and 798 in vaccine group). **Immunisation reduced maternal febrile influenza-like illness with an overall efficacy of 19% (95% CI 1 to 34) in the combined cohorts; 9% efficacy (-16 to 29) in the first cohort, and 36% efficacy (9 to 55) in the second cohort.** For laboratory-confirmed influenza infections in infants aged 0-6 months, immunisation had an overall efficacy for the combined cohorts of 30% (95% CI 5 to 48); in the first cohort, the efficacy was 16% (-19 to 41), and in the second cohort it was 60% (26 to 88). **Maternal immunisation reduced the rates of low birthweight by 15% (95% CI 3-25) in both cohorts combined.** The rate of small for gestational age infants was not modified by immunisation. The number of adverse events was similar regardless of immunisation status. Miscarriage occurred in three (0.2%) participants in the placebo group versus five (0.3%) in the vaccine group, stillbirth occurred in 31 (1.7%) versus 33 (1.8%), and congenital defects occurred in 18 (1.0%) versus 20 (1.1%). Five women died in the placebo group and three died in the vaccine group. The number of infant deaths at age 0-6 months was similar in each group (50 in the placebo group and 61 in the vaccine group). No serious adverse events were associated with receipt of immunisation.

### INTERPRETATION:

**Year-round maternal influenza immunisation significantly reduced maternal influenza-like illness, influenza in infants, and low birthweight over the entire course of the study, indicating the strategy could be useful in subtropical regions.**

<https://www.sciencedirect.com/science/article/pii/S1473309917302529?via%3Dihub>

*Vaccine*. 2017 Dec 4;35(48 Pt B):6743-6750. doi: 10.1016/j.vaccine.2017.09.095. Epub 2017 Oct 31.

### **Nutritional status of infants at six months of age following maternal influenza immunization: A randomized placebo-controlled trial in rural Nepal.**

[Katz J](#), [Englund JA](#), [Steinhoff MC](#), [Khatry SK](#), [Shrestha L](#), [Kuypers J](#), [Mullany LC](#), [Chu HY](#), [LeClerq SC](#), [Kozuki N](#), [Tielsch JM](#)

### BACKGROUND:

Maternal influenza vaccination has increased birth weight in two randomized trials in South Asia but the impact on infant growth is unknown.

### METHODS:

A randomized placebo-controlled trial of year round maternal influenza immunization was conducted in two annual cohorts in Sarlahi District, southern plains of Nepal, from April 2011 through April 2014. Infants born to women enrolled in the trial had weight, length, and head circumference measured at birth and 6 months of age. The study was powered for the 3 primary trial outcomes but not for stunting and wasting at 6 months of age.

### RESULTS:

3693 women received placebo or influenza vaccine between 17 and 34 weeks gestation, resulting in 3646 live births. About 72% of infants who survived had weight and length measurements between 150 and 210 days of age. Prevalence of stunting (<-2 Z scores length-for-age) was 14.8% in the placebo and 13.6% in the vaccine groups, respectively. Stunting < -3 Z scores was 3.2% versus 2.0% in placebo versus vaccine groups (RR: 0.64 (95% CI: 0.39, 1.04)). Wasting (< -2 Z scores weight for length) was 10.3% versus 11.0% for placebo versus vaccine groups. Severe wasting (< -3 Z scores weight for length) was 3.8% for placebo versus 2.6% for vaccine (RR: 0.69 (95% CI: 0.44, 1.07)). The impact of flu vaccine on wasting was greater in cohort 2 than in cohort 1, (RR: 0.66 (0.44, 0.99) for any wasting), and RR: 0.45 (0.19,

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1.09) for severe wasting. This corresponded to a larger impact on birth weight and a better vaccine match with circulating viruses in cohort 2.

### CONCLUSIONS:

Although maternal immunization reduced low birth weight by 15%, only wasting at 6 months in the 2nd cohort was statistically significantly difference. However, the study was underpowered to detect reductions of public health importance.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5714610/>

[Int J Gynaecol Obstet.](#) 2018 Jan;140(1):65-72. doi: 10.1002/ijgo.12341. Epub 2017 Nov 9.

### **Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal.**

[Kozuki N](#), [Katz J](#), [Englund JA](#), [Steinhoff MC](#), [Khatry SK](#), [Shrestha L](#), [Kuypers J](#), [Mullany LC](#), [Chu HY](#), [LeClerq SC](#), [Tielsch JM](#)

### OBJECTIVE:

To describe the effect of maternal vaccination on birth outcomes in rural Nepal, modified by timing of vaccination in pregnancy and influenza virus activity.

### METHODS:

A secondary analysis was conducted using data from two annual cohorts of a randomized controlled trial. A total of 3693 pregnant women from Sarlahi District were enrolled between April 25, 2011, and September 9, 2013. All participants were aged 15-40 years and received a trivalent inactivated influenza vaccine or placebo. The outcome measures included birth weight, pregnancy length, low birth weight (<2500 g), preterm birth, and small-for-gestational-age birth.

### RESULTS:

Data were available on birth weight for 2741 births and on pregnancy length for 3623 births.

**Maternal vaccination increased mean birthweight by 42 g (95% confidence interval [CI] 8-76).** The magnitude of this increase varied by season but was greatest among pregnancies with high influenza virus circulation during the third trimester. Birth weight increased by 111 g (95% CI -51 to 273) when 75%-100% of a pregnancy's third trimester had high influenza virus circulation versus 38 g (95% CI -6 to 81) when 0%-25% of a pregnancy's third trimester had high influenza virus circulation. However, these results were nonsignificant.

### CONCLUSION:

Seasonal maternal influenza vaccination in rural Nepal increased birth weight; the magnitude appeared larger during periods of high influenza virus circulation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765513/>

[Clin Infect Dis.](#) 2017 Nov 13;65(11):1914-1920. doi: 10.1093/cid/cix674.

### **Influenza Among Young Children in Bangladesh: Clinical Characteristics and Outcomes From a Randomized Clinical Trial.**

[Rotrosen E](#), [Zaman K](#), [Feser J](#), [Ortiz JR](#), [Goswami D](#), [Sharmeen AT](#), [Rahman M](#), [Lewis KDC](#), [Rahman MZ](#), [Barin B](#), [Brooks WA](#), [Neuzil KM](#)

## Randomised trials in child health in developing countries 2017-18

### BACKGROUND:

Influenza causes substantial morbidity in children worldwide, although influenza vaccine is seldom used in low-resource settings. More information on the clinical presentation of influenza and the efficacy of vaccine is needed to inform policy.

### METHODS:

In 2013 we conducted a randomized, placebo-controlled clinical trial of live attenuated influenza vaccine (LAIV) in children aged 24-59 months in Bangladesh (N = 1761). If participants met prespecified specimen collection criteria, we collected nasopharyngeal washes for testing by singleplex reverse-transcription polymerase chain reaction (RT-PCR) for laboratory-confirmed influenza virus infection (LCI). A panel of RT-PCR assays was used to detect noninfluenza respiratory viruses. Primary efficacy results have been reported. In this analysis of prespecified and post hoc objectives from the trial, we compared signs and symptoms between LCI and non-LCI cases and estimated the efficacy of LAIV against moderate-to-severe LCI and other prespecified non-LCI clinical outcomes including all-cause pneumonia and acute otitis media.

### RESULTS:

The most common signs and symptoms of LCI were fever, cough, and runny nose. The combination of subjective fever and cough had a 63% sensitivity for LCI. The combination of measured fever, cough, and runny nose was most specific (90%) but had low sensitivity (32%) for LCI. The efficacy of LAIV against vaccine-strain moderate-to-severe LCI was 56.7% (95% confidence interval, 9.5%-79.2%). No statistically significant vaccine efficacy was found against the non-laboratory-confirmed clinical outcomes.

### CONCLUSIONS:

It was not possible to distinguish LCI from noninfluenza viral infections on clinical evaluations alone in this population of Bangladeshi children. LAIV was efficacious against moderate-to-severe LCI.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850015/>

*Vaccine*. 2017 Dec 15;35(50):6967-6976. doi: 10.1016/j.vaccine.2017.10.074. Epub 2017 Oct 31.

### [Efficacy of trivalent influenza vaccine against laboratory-confirmed influenza among young children in a randomized trial in Bangladesh.](#)

[Rolfes MA](#), [Goswami D](#), [Sharmeen AT](#), [Yeasmin S](#), [Parvin N](#), [Nahar K](#), [Rahman M](#), [Barends M](#), [Ahmed D](#), [Rahman MZ](#), [Bresee J](#), [Luby S](#), [Moulton LH](#), [Santosham M](#), [Fry AM](#), [Brooks WA](#)

### BACKGROUND:

Few trials have evaluated influenza vaccine efficacy (VE) in young children, a group particularly vulnerable to influenza complications. We aimed to estimate VE against influenza in children aged <2 years in Bangladesh; a subtropical setting, where influenza circulation can be irregular.

### METHODS:

Children aged 6-23 months were enrolled 1:1 in a parallel, double-blind, randomized controlled trial of trivalent inactivated influenza vaccine (IIV3) versus inactivated polio vaccine (IPV); conducted August 2010-March 2014 in Dhaka, Bangladesh. Children received two pediatric doses of vaccine, one month apart, and were followed for one year for febrile and respiratory illness. Field assistants conducted weekly home-based, active surveillance and ill children were referred to the study clinic for clinical evaluation and nasopharyngeal wash specimen collection. Analysis included all children who received a first vaccine dose and compared yearly incidence

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of reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza between trial arms. The VE was estimated as  $1 - (\text{rate ratio of illness}) \times 100\%$ , using unadjusted Poisson regression. The trial was registered with ClinicalTrials.gov, number [NCT01319955](https://www.clinicaltrials.gov/ct2/show/study/NCT01319955).

### RESULTS:

Across four vaccination rounds, 4081 children were enrolled and randomized, contributing 2576 child-years of observation to the IIV3 arm and 2593 child-years to the IPV arm. Influenza incidence was 10 episodes/100 child-years in the IIV3 arm and 15 episodes/100 child-years in the IPV arm. **Overall, the VE was 31% (95% confidence interval 18, 42%) against any RT-PCR-confirmed influenza.** The VE varied by season, but was similar by influenza type/subtype and participant age and sex.

### CONCLUSIONS:

Vaccination of young children with IIV3 provided a significant reduction in laboratory-confirmed influenza; however, exploration of additional influenza vaccine strategies, such as adjuvanted vaccines or standard adult vaccine doses, is warranted to find more effective influenza vaccines for young children in low-income countries.

Published by Elsevier Ltd.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5723570/>

[Postgrad Med.](#) 2017 Nov;129(8):907-914. doi: 10.1080/00325481.2017.1369133. Epub 2017 Sep 5.

### [Safety and effectiveness assessment of 2011-2012 seasonal influenza vaccine produced in China: a randomized trial.](#)

[Jing-Xia G](#), [Yu-Liang Z](#), [Jin-Feng L](#), [Shu-Zhen L](#), [Guo-Yang L](#), [Qi L](#)

### OBJECTIVE:

This study evaluated the effectiveness and safety of the egg-based, trivalent, inactivated split influenza vaccine produced by the Institute of Medical Biology, Chinese Academy of Medical Sciences, Peking Union Medical College, China.

### METHODS:

From March 2012 through May 2012, we enrolled a total of 1390 healthy volunteers between the ages of 3 and 80 years in a randomized clinical trial at the Hebei Disease Control Center Vaccine Clinical Evaluation Center. For all subjects, body part adverse reactions and whole-body adverse reactions were observed 30 min, 6 h, and 1-7 days' post-inoculation. If no severe adverse effects were observed 7 days' post-vaccination, the local and systemic reactions of preliminary test participants were recorded until day 28. There was no placebo group in this study. Blood samples were taken for serological testing before vaccination and 28 days' post-vaccination.

### RESULTS:

Twenty-eight days after vaccination, the seroconversion rates of experimental and control groups were H1N1 75.3% and 75.7%, H3N2 75.8% and 71.8%, B 70.7% vs. 69.4%, ( $P > 0.05$ ). The antibody Geometric Mean Titer (GMT) of experimental and control groups were H1N1 (179.7, 182.4), H3N2 (584.0, 445.7), B (201.4, 191.6). The protection rate of experimental and control groups was not statistically significant (H1N1: 86% vs. 87%, H3N2: 99% vs. 98%, B: 98% vs. 98%). Also, 95% confidence intervals of the protection rate difference between the experimental and the control group were H1N1: -0.1% (-4.1, 3.8) %, H3N2: 0.3% (-1.0, 1.7) % and B: 0.2% (-1.5, 1.9) %; confidence intervals exceeded the limit of -5%. The rates of adverse reactions between experimental and control groups were 6.3% and 7.7% in local response

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reactions, and 19.5% and 18.0% in systemic reactions. Three hundred and twenty-seven adverse events (AEs) in 1200 (27.76%) subjects were reported within 28 d after vaccination. No serious adverse events occurred during the study.

### CONCLUSIONS:

The experimental vaccine three-antibody protection rate was non-inferior to the control vaccine. Our results demonstrated that the experimental vaccine achieved the primary immunogenic end point of the intended clinical protocol, as well as a secondary immunogenic end-point, with an acceptable level of safety. IRB approval for this study was issued under #2012Y0005 and registered as Clinical Trial No. [NCT01551810](#).

[Expert Rev Vaccines](#). 2017 Nov;16(11):1155-1169. doi: 10.1080/14760584.2017.1374181. Epub 2017 Sep 18.

### [Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccines in participants \$\geq\$ 3 years of age: a double-blind, randomized, parallel-controlled phase III clinical trial in China.](#)

[Wang SY](#), [Liu SZ](#), [Chu K](#), [Zhao Y](#), [Zhu FC](#), [Hu YM](#), [Meng FY](#), [Li JX](#), [Luo L](#), [Yang JY](#), [Liu P](#), [Yu J](#)

### BACKGROUND:

Viruses from two antigenically distinct influenza B strains have co-circulated since the mid-1980s, yet inactivated trivalent influenza vaccines (TIVs) with either the Victoria or Yamagata lineage could only provide limited protection from influenza B strain. Quadrivalent influenza vaccine (QIV) including both influenza B lineages can improve protection against circulating influenza B viruses.

### METHODS:

Participants  $\geq$  3 years of age were recruited, stratified by age, and then randomly allocated at a ratio of 2:1:1 to receive one-injection of the experimental QIV, TIV-Victoria (Vic) or TIV-Yamagata (Yam). The primary objective of this study was to demonstrate that the hemagglutination-inhibition (HI) antibodies induced by the QIV candidate are not inferior to the licensed TIVs.

### RESULTS:

First, 3661 participants received the inoculation. The QIV was found to be non-inferior to TIVs in terms of the geometric mean titers (GMTs) and seroconversion rates (SCRs) of the HI antibodies against shared strains 28 days after completion of inoculation, and was superior to the TIVs against the alternate B strain, which is absent from the TIVs. The occurrences of adverse events (AEs) post-vaccination were similar across the treatment groups.

### CONCLUSION:

The experimental QIV showed good immunogenicity and an acceptable safety profile.

## Japanese encephalitis virus vaccine

[Pediatr Infect Dis J](#). 2017 Sep;36(9):898-904. doi: 10.1097/INF.0000000000001615.

### [Immunogenicity of the Inactivated Japanese Encephalitis Virus Vaccine IXIARO in Children From a Japanese Encephalitis Virus-endemic Region.](#)

[Dubischar KL](#), [Kadlecek V](#), [Sablan JB](#), [Borja-Tabora CF](#), [Gatchalian S](#), [Eder-Lingelbach S](#), [Kiermayr S](#), [Spruth M](#), [Westritschnig K](#).

**BACKGROUND:**

Japanese encephalitis (JE) is a major public health concern in Asia and poses a small but potentially fatal threat to travelers from nonendemic countries, including children. No JE vaccine for pediatric use has been available in Europe and the United States.

**METHODS:**

Age-stratified cohorts of children between 2 months and 17 years received 2 doses of Vero cell-derived inactivated JE virus vaccine (IXIARO; Valneva Austria GmbH, Vienna, Austria) administered 28 days apart [ $<3$  years, 0.25 mL (half adult dose);  $\geq 3$  years, 0.5 mL (full adult dose)]. Immunogenicity endpoints were seroconversion rate, 4-fold increase in JE neutralizing antibody titer and geometric mean titer assessed 56 days and 7 months after the first vaccination in 496 subjects of the intent-to-treat population. The immune response to JE virus at both time points was also analyzed according to prevaccination JE virus and dengue virus serostatus.

**RESULTS:**

At day 56, seroconversion was attained in  $\geq 99.2\%$  of subjects with age-appropriate dosing, 4-fold increases in titer were reported for 77.4%-100% in various age groups, and geometric mean titers ranged from 176 to 687, with younger children having the strongest immune response. At month 7, seroconversion was maintained in 85.5%-100% of subjects. Pre-existing JE virus immunity did not impact on immune response at day 56; however, it led to a better persistence of protective antibody titers at month 7.

**CONCLUSIONS:**

IXIARO is highly immunogenic at both doses tested in the pediatric population, leading to protective antibody titers at day 56 in  $>99\%$  of subjects who received the age-appropriate dose. [https://journals.lww.com/pidj/fulltext/2017/09000/Immunogenicity\\_of\\_the\\_Inactivated\\_Japanese.21.aspx](https://journals.lww.com/pidj/fulltext/2017/09000/Immunogenicity_of_the_Inactivated_Japanese.21.aspx)

## Malaria vaccine

[Sci Rep.](#) 2017 Aug 3;7(1):7200. doi: 10.1038/s41598-017-07533-w.

**[RTS,S/AS01 Malaria Vaccine Efficacy is Not Modified by Seasonal Precipitation: Results from a Phase 3 Randomized Controlled Trial in Malawi.](#)**

[Han L](#), [Hudgens MG](#), [Emch ME](#), [Juliano JJ](#), [Keeler C](#), [Martinson F](#), [Kamthunzi P](#), [Tegha G](#), [Lievens M](#), [Hoffman IF](#)

The World Health Organization has selected Malawi as one of three sites to pilot the roll-out of RTS,S/AS01 in phase 4 trials. As policy discussions for the expanded use of RTS,S/AS01 continue, it will be critical to determine the performance of the vaccine according to seasonal patterns of malaria transmission in regions of Africa. Given waning vaccine efficacy over time, this secondary analysis demonstrates that administering the vaccine to children in the months prior to malaria season could maximize impact of the vaccine. We followed children (5-17 months) and infants (6-12 weeks) assigned to one of three groups: (1) vaccine with four doses; (2) vaccine with three doses; (3) control. The primary endpoint was defined as episodes of clinical malaria. During the 4-years of follow-up, 658 of 1544 (42.6%) children and infants had at least one episode of clinical malaria. With each 1-inch increase in rainfall per month there was an associated increase in the rate of malaria by 12.6% (95% CI 9.6%, 15.6%,  $P < 0.0001$ ) among children and 15.9% (95% CI 12.8%, 18.9%,  $P < 0.0001$ ) among infants. There was no evidence of effect modification of vaccine efficacy by precipitation (89% power).

<https://www.nature.com/articles/s41598-017-07533-w>

*Hum Vaccin Immunother.* 2018 Jun 3;14(6):1489-1500. doi: 10.1080/21645515.2018.1442996. Epub 2018 Apr 13.

**Immune response to the hepatitis B antigen in the RTS,S/AS01 malaria vaccine, and co-administration with pneumococcal conjugate and rotavirus vaccines in African children: A randomized controlled trial.**

[Valéa I](#), [Adjei S](#), [Usuf E](#), [Traore O](#), [Ansong D](#), [Tinto H](#), [Owusu Boateng H](#), [Leach A](#), [Mwinnessobaonfou Some A](#), [Buabeng P](#), [Vekemans J](#), [Nana LA](#), [Kotey A](#), [Vandoolaeghe P](#), [Ouedraogo F](#), [Sambian D](#), [Lievens M](#), [Tahita MC](#), [Rettig T](#), [Jongert E](#), [Lompo P](#), [Idriss A](#), [Borys D](#), [Ouedraogo S](#), [Prempeh F](#), [Habib MA](#), [Schuerman L](#), [Sorgho H](#), [Agbenyega T](#)

The RTS,S/AS01 malaria vaccine (Mosquirix) reduces the incidence of *Plasmodium falciparum* malaria and is intended for routine administration to infants in Sub-Saharan Africa. We evaluated the immunogenicity and safety of 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; Synflorix) and human rotavirus vaccine (HRV; Rotarix) when co-administered with RTS,S/AS01 in African infants. **705 healthy infants aged 8-12 weeks were randomized to receive three doses of either RTS,S/AS01 or licensed hepatitis B (HBV; Engerix B) vaccine (control) co-administered with diphtheria-tetanus-acellular pertussis-Haemophilus influenzae type-b-conjugate vaccine (DTaP/Hib) and trivalent oral poliovirus vaccine at 8-12-16 weeks of age**, because DTaP/Hib was not indicated before 8 weeks of age. The vaccination schedule can still be considered broadly applicable because it was within the age range recommended for EPI vaccination. PHiD-CV or HRV were either administered together with the study vaccines, or after a 2-week interval. Booster doses of PHiD-CV and DTaP/Hib were administered at age 18 months. Non-inferiority of anti-HBV surface antigen antibody seroprotection rates following co-administration with RTS,S/AS01 was demonstrated compared to the control group (primary objective). Pre-specified non-inferiority criteria were reached for PHiD-CV (for 9/10 vaccine serotypes), HRV, and aP antigens co-administered with RTS,S/AS01 as compared to HBV co-administration (secondary objectives). RTS,S/AS01 induced a response to circumsporozoite protein in all groups. Pain and low grade fever were reported more frequently in the PHiD-CV group co-administered with RTS,S/AS01 than PHiD-CV co-administered with HBV. No serious adverse events were considered to be vaccine-related. RTS,S/AS01 co-administered with pediatric vaccines had an acceptable safety profile. Immune responses to RTS,S/AS01 and to co-administered PHiD-CV, pertussis antigens and HRV were satisfactory.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6037440/>

## Measles vaccine

*Vaccine.* 2018 Apr 5;36(15):1965-1971. doi: 10.1016/j.vaccine.2018.02.104. Epub 2018 Mar 6.

**No effect of an additional early dose of measles vaccine on hospitalization or mortality in children: A randomized controlled trial.**

[Schoeps A](#), [Nebié E](#), [Fisker AB](#), [Sié A](#), [Zakane A](#), [Müller O](#), [Aaby P](#), [Becher H](#)

## BACKGROUND:



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Non-specific effects (NSEs) of vaccines have increasingly gained attention in recent years. Recent studies suggest that live vaccines, such as measles vaccine (MV), have beneficial effects on health, while inactivated vaccines, such as the diphtheria-tetanus-pertussis (DTP) vaccine, may have harmful effects. If this is the case, it should improve child health to move MV closer to the last vaccination with DTP. The objective of this study was to investigate the NSEs of an additional early dose of MV on hospitalization or mortality.

### **METHODS:**

Children were randomized to receive either the standard MV at 9 months (control) or an additional early dose of MV 4 weeks after the third dose of DTP-containing Pentavalent vaccine and the standard MV at 9 months (intervention). In this analysis of a secondary outcome in the trial, we investigated the effect of the intervention on a composite endpoint of over-night hospitalization with or without recovery, or death without previous hospitalization, in children between 4.5 and 36 months of age in the Nouna HDSS in Burkina Faso. We used Cox proportional hazards regression with repeated events and time since study enrolment as underlying time-scale.

### **RESULTS:**

Among 2258 children in the intervention and 2238 children in the control group we observed a total of 464 episodes of hospitalization or mortality. There was no difference between intervention and control group (HR = 1.00, 95% Confidence Interval (CI) 0.83-1.20). Results from the per-protocol and intention-to-treat analysis were similar. Although no significant, results suggest a possible beneficial effect of early MV in children that had not been exposed to an OPV campaign after enrolment (HR = 0.83, 95% CI 0.55-1.29).

### **CONCLUSIONS:**

We did not detect any effect of early MV on subsequent hospitalization or mortality. However, possible effects of early MV could have been obscured by NSEs of the frequent OPV campaigns.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0264410X18303141?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0264410X18303141%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

## Measles, mumps, rubella (MMR) vaccine

[Hum Vaccin Immunother.](#) 2017 Jul 3;13(7):1523-1530. doi: 10.1080/21645515.2017.1302629. Epub 2017 Mar 31.

### **[Immunogenicity and safety of a novel MMR vaccine \(live, freeze-dried\) containing the Edmonston-Zagreb measles strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial.](#)**

[Sood A](#), [Mitra M](#), [Joshi HA](#), [Nayak US](#), [Siddaiah P](#), [Babu TR](#), [Mahapatro S](#), [Sanmukhani J](#), [Gupta G](#), [Mittal R](#), [Glueck R](#)

This phase III clinical trial was conducted to evaluate the immunogenicity and safety of the single-dose and multi-dose formulations of a novel MMR vaccine (live, freeze-dried) developed by M/s Cadila Healthcare Limited, India (Cadila MMR vaccine), containing the Hoshino mumps strain, compared to that of an existing MMR vaccine (live, freeze-dried) developed by M/s Serum Institute of India Limited, India (Serum MMR vaccine). These

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two vaccines have similar measles and rubella strains, but different mumps strains (Hoshino in Cadila MMR vaccine, and L-Zagreb in Serum MMR vaccine). Three hundred and twenty-eight subjects of either sex, aged 15-18 months, were randomized in a 2:1 ratio to receive either the Cadila or Serum MMR vaccine. Immunogenicity assessments (IgG antibodies against measles, mumps, and rubella viruses) were done at baseline and 42 d after vaccination. Solicited (local and systemic) and unsolicited adverse events were recorded for up to 42 d following vaccination. The Cadila MMR vaccine was found to be non-inferior to the Serum MMR vaccine in terms of end-of-study proportion of subjects seropositive for anti-measles antibodies (100.0% in both groups), anti-mumps antibodies (94.5% vs. 94.0%), and anti-rubella antibodies (95.5% vs. 91.0%). Both vaccines were well tolerated by all study participants; the most common adverse event reported in both groups was fever, followed by rash. The results of this phase III clinical trial show that the novel Cadila MMR vaccine is non-inferior to the Serum MMR vaccine.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5512778/>

### Meningococcal vaccine

[Pediatr Infect Dis J.](#) 2018 Jul;37(7):704-714. doi: 10.1097/INF.0000000000002061.

#### **Immunogenicity and Reactogenicity of DTPa-HBV-IPV/Hib and PHiD-CV When Coadministered With MenACWY-TT in Infants: Results of an Open, Randomized Trial.**

[Merino Arribas JM](#), [Carmona Martínez A](#), [Horn M](#), [Perez Porcuna XM](#), [Otero Reigada MDC](#), [Marès Bermúdez J](#), [Centeno Malfaz F](#), [Miranda M](#), [Mendez M](#), [Garcia Cabezas MA](#), [Christoph W](#), [Bleckmann G](#), [Fischbach T](#), [Kolhe D](#), [Van der Wielen M](#), [Baine Y](#)

#### **BACKGROUND:**

This study evaluated the immunogenicity and reactogenicity of a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus virus-Haemophilus influenzae type b vaccine (DTPa-HBV-IPV/Hib) and a 10-valent pneumococcal conjugate vaccine (PHiD-CV) coadministered with a quadrivalent meningococcal conjugate vaccine (MenACWY-TT) in infants/toddlers.

#### **METHODS:**

In this open, controlled, phase III study ([NCT01144663](#)), 2095 healthy infants were randomized (1:1:1:1) into 4 groups to receive MenACWY-TT at 2, 3, 4 and 12 months of age or MenACWY-TT, MenC-CRM197, or MenC-TT at 2, 4 and 12 months of age. All participants received PHiD-CV and DTPa-HBV-IPV/Hib at 2, 3, 4 and 12 months of age. Immunogenicity of DTPa-HBV-IPV/Hib was evaluated in exclusive randomized subsets of 25% of participants from each group postprimary, prebooster and postbooster vaccination, whereas immunogenicity of PHiD-CV was evaluated at all time points. Reactogenicity was evaluated on the total vaccinated cohorts during 8 days after each vaccination.

#### **RESULTS:**

For each DTPa-HBV-IPV/Hib antigen,  $\geq 97.2\%$ ,  $\geq 76.5\%$  and  $\geq 97.9\%$  of participants had seropositive/seroprotective levels 1 month postprimary vaccination, before the booster dose and 1 month postbooster, respectively. For each vaccine pneumococcal serotype,  $\geq 74.0\%$  of infants had antibody concentrations  $\geq 0.35 \mu\text{g/mL}$  at 1 month postprimary vaccination, and robust increases in antibody geometric mean concentrations were observed from prebooster to postbooster. Redness was the most frequent solicited local symptom at the DTPa-HBV-IPV/Hib and PHiD-CV injection sites, reported after up to 47.7% and 57.0% of doses postprimary and postbooster vaccination, respectively.

**CONCLUSIONS:**

Primary and booster vaccinations of infants/toddlers with DTPa-HBV-IPV/Hib and PHiD-CV coadministered with MenACWY-TT were immunogenic with clinically acceptable reactogenicity profiles. These results support the coadministration of MenACWY-TT with routine childhood vaccines.

[https://journals.lww.com/pidj/fulltext/2018/07000/Immunogenicity\\_and\\_Reactogenicity\\_of.18.a.spx](https://journals.lww.com/pidj/fulltext/2018/07000/Immunogenicity_and_Reactogenicity_of.18.a.spx)

**Pneumococcal vaccine**

[Pneumonia \(Nathan\)](#). 2017 Dec 25;9:20. doi: 10.1186/s41479-017-0044-z. eCollection 2017.

**[Rationale and methods of a randomized controlled trial of immunogenicity, safety and impact on carriage of pneumococcal conjugate and polysaccharide vaccines in infants in Papua New Guinea.](#)**

[Lehmann D](#), [Kirarock W](#), [van den Biggelaar AHJ](#), [Passey M](#), [Jacoby P](#), [Saleu G](#), [Masiria G](#), [Nivio B](#), [Greenhill A](#), [Orami T](#), [Francis J](#), [Ford R](#), [Kirkham LA](#), [Solomon V](#), [Richmond PC](#), [Pomat WS](#); [10v13v PCV trial team](#).

**[Collaborators \(41\)](#)**

**BACKGROUND:**

Children in third-world settings including Papua New Guinea (PNG) experience early onset of carriage with a broad range of pneumococcal serotypes, resulting in a high incidence of severe pneumococcal disease and deaths in the first 2 years of life. Vaccination trials in high endemicity settings are needed to provide evidence and guidance on optimal strategies to protect children in these settings against pneumococcal infections.

**METHODS:**

This report describes the rationale, objectives, methods, study population, follow-up and specimen collection for a vaccination trial conducted in an endemic and logistically challenging setting in PNG. The trial aimed to determine whether currently available pneumococcal conjugate vaccines (PCV) are suitable for use under PNG's accelerated immunization schedule, and that a schedule including pneumococcal polysaccharide vaccine (PPV) in later infancy is safe and immunogenic in this high-risk population.

**RESULTS:**

This open randomized-controlled trial was conducted between November 2011 and March 2016, enrolling 262 children aged 1 month between November 2011 and April 2014. The participants were randomly allocated (1:1) to receive 10-valent PCV (10vPCV) or 13-valent PCV (13vPCV) in a 1-2-3-month schedule, with further randomization to receive PPV or no PPV at age 9 months, followed by a 1/5<sup>th</sup> PPV challenge at age 23 months. A total of 1229 blood samples were collected to measure humoral and cellular immune responses and 1238 nasopharyngeal swabs to assess upper respiratory tract colonization and carriage load. Serious adverse events were monitored throughout the study. Of the 262 children enrolled, 87% received 3 doses of PCV, 79% were randomized to receive PPV or no PPV at age 9 months, and 67% completed the study at 24 months of age with appropriate immunization and challenge.

**CONCLUSION:**

Laboratory testing of the many samples collected during this trial will determine the impact of the different vaccine schedules and formulations on nasopharyngeal carriage, antibody production and function, and immune memory. The final data will inform policy on

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pneumococcal vaccine schedules in countries with children at high risk of pneumococcal disease by providing direct comparison of an accelerated schedule of 10vPCV and 13vPCV and the potential advantages of PPV following PCV immunization.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5742486/>

*Clin Microbiol Infect.* 2018 Apr;24(4):389-395. doi: 10.1016/j.cmi.2017.07.018. Epub 2017 Jul 23.

### **Maternal pneumococcal nasopharyngeal carriage and risk factors for neonatal carriage after the introduction of pneumococcal conjugate vaccines in The Gambia.**

[Usuf E](#), [Bojang A](#), [Camara B](#), [Jagne I](#), [Oluwalana C](#), [Bottomley C](#), [D'Alessandro U](#), [Roca A](#).

#### **OBJECTIVES:**

Pneumococcal nasopharyngeal carriage occurs early in life. However, the role of vertical transmission is not well understood. The aims of this study were to describe carriage among mothers and their newborns, and to assess for risk factors for neonatal carriage.

#### **METHODS:**

In a nested retrospective cohort study, we analysed data from the control arm of a randomized controlled trial conducted in The Gambia 2 to 3 years after introduction of pneumococcal conjugate vaccine (PCV) 13. Nasopharyngeal swabs were collected from 374 women and their newborns on the day of delivery, then 3, 6, 14 and 28 days later. Pneumococci were isolated and serotyped using conventional microbiologic methods.

#### **RESULTS:**

**Carriage increased from 0.3% (1/373) at birth to 37.2% (139/374) at day 28 (p <0.001) among neonates and from 17.1% (64/374) to 24.3% (91/374) (p 0.015) among women.** In both groups, PCV13 vaccine-type (VT) serotypes accounted for approximately one-third of the pneumococcal isolates, with serotype 19A being the most common VT. Maternal carriage (adjusted odds ratio (OR) = 2.82; 95% confidence interval (CI), 1.77-4.80), living with other children in the household (adjusted OR = 4.06; 95% CI, 1.90-8.86) and dry season (OR = 1.98; 95% CI, 1.15-3.43) were risk factors for neonatal carriage. Over half (62.6%) of the neonatal carriage was attributable to living with other children in the same household.

#### **CONCLUSIONS:**

Three years after the introduction of PCV in The Gambia, newborns are still rapidly colonized with pneumococcus, including PCV13 VT. Current strategies for pneumococcal control in Africa do not protect this age group beyond the herd effect.

<https://www.sciencedirect.com/science/article/pii/S1198743X17304020?via%3Dihub>

*Vaccine.* 2017 Aug 16;35(35 Pt B):4652-4657. doi: 10.1016/j.vaccine.2017.05.088. Epub 2017 Jul 21.

### **Pneumococcal conjugate vaccine induced IgG and nasopharyngeal carriage of pneumococci: Hyporesponsiveness and immune correlates of protection for carriage.**

[Ojal J](#), [Hammitt LL](#), [Gaitho J](#), [Scott JAG](#), [Goldblatt D](#)

### BACKGROUND:

Prior studies have demonstrated **hyporesponsiveness to pneumococcal conjugate vaccines (PCVs) when administered in the presence of homologous carriage**. This may be substantially more important in Africa where carriage prevalence is high. Deriving a correlate of protection (CoP) for carriage is important in guiding the future use of extended PCVs as population control of pneumococcal disease by vaccination is now focused principally on its indirect effect. We therefore explored the complex relationship between existing carriage and vaccine responsiveness, and between serum IgG levels and risk of acquisition.

### METHODS:

We undertook secondary analyses of data from two previously published clinical trials of the safety and immunogenicity of PCV in Kenya. We compared responses to vaccination between serotype-specific carriers and non-carriers at vaccination. We assessed the risk of carriage acquisition in relation to PCV-induced serum IgG levels using either a step- or continuous-risk function.

### RESULTS:

**For newborns, the immune response among carriers was 51-82% lower than that among non-carriers, depending on serotype. Among toddlers, for serotypes 6B, 14 and 19F the post-vaccination response among carriers was lower by between 29 and 70%.** The estimated CoP against acquisition ranged from 0.26 to 1.93µg/mL across serotypes, however, these thresholds could not be distinguished statistically from a model with constant probability of carriage independent of assay value.

### CONCLUSION:

We have confirmed hyporesponsiveness in an equatorial African setting in both infants and toddlers. **Population responses to vaccination are likely to improve with time as carriage prevalence of vaccine serotypes is reduced.** We have not found clear correlates of protection against carriage acquisition among toddlers in this population. Assessing the potential of new vaccines through the use of CoP against carriage is still difficult as there are no clear-cut serotype specific correlates.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0264410X17307582?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0264410X17307582%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Vaccine](#). 2017 Aug 16;35(35 Pt B):4583-4586. doi: 10.1016/j.vaccine.2017.07.011. Epub 2017 Jul 13.

### [Pneumococcal vaccination for splenectomized patients with thalassemia major in Indonesia.](#)

[Sari TT](#), [Akib AAP](#), [Gatot D](#), [Roswita Harahap A](#), [Bardosono S](#), [Hadinegoro SRS](#)

### INTRODUCTION:

*Streptococcus pneumoniae* is a capsulated bacterium that can cause severe infection in patients with thalassemia major, particularly those who have undergone splenectomy. The absence of the spleen as well as zinc deficiency in splenectomized patients with thalassemia major increases the possibility of developing invasive pneumococcal infection. The aims of this study are to evaluate pneumococcal IgG levels following PCV and PPV immunizations and the effect of zinc supplementation on qualitative specific immune responses in splenectomized patients with thalassemia.

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### **METHODS:**

Splenectomized patients with thalassemia major were administered a PCV pneumococcal vaccine (Prevenar 13®) at the start of the trial, after which they were randomly assigned to 2 groups (zinc and placebo group). After 8 weeks, the patients received a PPV pneumococcal vaccine (Pneumovax®). Zinc syrup was provided to the zinc group at a dose of 1.5mg/kg/day (maximum of 50mg/day). Pneumococcal IgG examinations were conducted at the start of the trial and after 12 weeks.

### **RESULTS:**

In the group without PPV, the median initial pneumococcal IgG value was 315 (ranging from 65 to 1419) mU/mL for the zinc group and 338.5 (ranging from 82 to 1648) mU/mL for the placebo group. The median final pneumococcal IgG value was 1812.5 (ranging from 834 to 2444) mU/mL for the zinc group and 2857.5 (ranging from 834 to 2624) for the placebo group. The increase in the pneumococcal IgG value between the two groups was comparable ( $p=0.642$ ). In the group with previous PPV, the median initial pneumococcal IgG value was 1333 (ranging from 793 to 2031) mU/mL for the zinc group and 880 (ranging from 74 to 1686) mU/mL for the placebo group. The median final pneumococcal IgG value was 1487 (ranging from 635 to 1757) mU/mL for the zinc group and 1012 (ranging from 292 to 1732) mU/mL for the placebo group. The increase in the pneumococcal IgG value between the two groups was comparable ( $p=0.528$ ).

### **CONCLUSION:**

There is no difference in the increase in pneumococcal IgG level in splenectomized patients with thalassemia major prior to and after receiving PPV. There were no differences observed in the development of pneumococcal IgG following zinc supplementation.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S0264410X17309076?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0264410X17309076%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[BMC Infect Dis.](#) 2017 Aug 25;17(1):588. doi: 10.1186/s12879-017-2685-1.

### **Prevalence and risk factors for Staphylococcus aureus nasopharyngeal carriage during a PCV trial.**

[Bojang A](#), [Kendall L](#), [Usuf E](#), [Egere U](#), [Mulwa S](#), [Antonio M](#), [Greenwood B](#), [Hill PC](#), [Roca A](#)

### **BACKGROUND:**

We conducted an ancillary study among individuals who had participated in a cluster-randomized PCV-7 trial in rural Gambia (some clusters were wholly-vaccinated while in others only young children had been vaccinated), to determine the prevalence and risk factors for Staphylococcus aureus nasopharyngeal carriage.

### **METHODS:**

Two hundred thirty-two children aged 5-10 years were recruited and followed from 4 to 20 months after vaccination started. We collected 1264 nasopharyngeal swabs (NPS). *S. aureus* was isolated following conventional microbiological methods. Risk factors for carriage were assessed by logistic regression.

### **RESULTS:**

Prevalence of *S. aureus* carriage was 25.9%. In the univariable analysis, prevalence of *S. aureus* carriage was higher among children living in villages wholly-vaccinated with PCV-7 [OR = 1.57 95%CI (1.14 to 2.15)] and children with least 1 year of education [OR = 1.44 95%CI (1.07 to 1.92)]. *S. aureus* carriage was also higher during the rainy season [OR = 1.59

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95%CI (1.20 to 2.11)]. Carriage of *S. pneumoniae* did not have any effect on *S. aureus* carriage for any pneumococcal, vaccine-type (VT) or non-vaccine-type (NVT) carriage. Multivariate analysis showed that the higher prevalence of *S. aureus* observed among children living in villages wholly-vaccinated with PCV-7 occurred only during the rainy season OR 2.72 95%CI (1.61-4.60) and not in the dry season OR 1.28 95%CI (0.78-2.09).

### CONCLUSIONS:

Prevalence of nasopharyngeal carriage of *S. aureus* among Gambian children increased during the rainy season among those children living in PCV-7 wholly vaccinated communities.

However, carriage of *S. aureus* is not associated with carriage of *S. pneumoniae*.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5574132/>

## Polio vaccine

[Lancet Infect Dis.](#) 2017 Oct;17(10):1069-1079. doi: 10.1016/S1473-3099(17)30358-4. Epub 2017 Jul 7.

### Community transmission of type 2 poliovirus after cessation of trivalent oral polio vaccine in Bangladesh: an open-label cluster-randomised trial and modelling study.

[Taniuchi M](#), [Famulare M](#), [Zaman K](#), [Uddin MJ](#), [Upfill-Brown AM](#), [Ahmed T](#), [Saha P](#), [Haque R](#), [Bandyopadhyay AS](#), [Modlin JF](#), [Platts-Mills JA](#), [Haupt ER](#), [Yunus M](#), [Petri WA Jr](#)

### BACKGROUND:

**Trivalent oral polio vaccine (tOPV) was replaced worldwide from April, 2016, by bivalent types 1 and 3 oral polio vaccine (bOPV) and one dose of inactivated polio vaccine (IPV) where available.** The risk of transmission of type 2 poliovirus or Sabin 2 virus on re-introduction or resurgence of type 2 poliovirus after this switch is not understood completely. **We aimed to assess the risk of Sabin 2 transmission after a polio vaccination campaign with a monovalent type 2 oral polio vaccine (mOPV2).**

### METHODS:

We did an open-label cluster-randomised trial in villages in the Matlab region of Bangladesh. We randomly allocated villages (clusters) to either: **tOPV at age 6 weeks, 10 weeks, and 14 weeks; or bOPV at age 6 weeks, 10 weeks, and 14 weeks and either one dose of IPV at age 14 weeks or two doses of IPV at age 14 weeks and 18 weeks.** After completion of enrolment, we implemented an mOPV2 vaccination campaign that targeted 40% of children younger than 5 years, regardless of enrolment status. **The primary outcome was Sabin 2 incidence in the 10 weeks after the campaign in per-protocol infants who did not receive mOPV2, as assessed by faecal shedding of Sabin 2 by reverse transcriptase quantitative PCR (RT-qPCR).** The effect of previous immunity on incidence was also investigated with a dynamical model of poliovirus transmission to observe prevalence and incidence of Sabin 2 virus.

### FINDINGS:

Between April 30, 2015, and Jan 14, 2016, individuals from 67 villages were enrolled to the study. 22 villages (300 infants) were randomly assigned tOPV, 23 villages (310 infants) were allocated bOPV and one dose of IPV, and 22 villages (329 infants) were assigned bOPV and two doses of IPV. **Faecal shedding of Sabin 2 in infants who did not receive the mOPV2 challenge did not differ between children immunised with bOPV and one or two doses of IPV and those who received tOPV (15 of 252 [6%] vs six of 122 [4%]; odds ratio [OR] 1.29, 95% CI 0.45-3.72; p=0.310).** However, faecal shedding of Sabin 2 in household contacts was increased significantly with bOPV and one or two doses of IPV compared with tOPV (17 of

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751 [2%] vs three of 353 [1%]; OR 3.60, 95% CI 0.82-15.9;  $p=0.045$ ). Dynamical modelling of within-household incidence showed that immunity in household contacts limited transmission.

### INTERPRETATION:

In this study, simulating 1 year of tOPV cessation, Sabin 2 transmission was higher in household contacts of mOPV2 recipients in villages receiving bOPV and either one or two doses of IPV, but transmission was not increased in the community as a whole as shown by the non-significant difference in incidence among infants. Dynamical modelling indicates that transmission risk will be higher with more time since cessation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610141/>

[Clin Infect Dis.](#) 2017 Aug 1;65(3):414-419. doi: 10.1093/cid/cix354.

### Nonspecific Effects of Oral Polio Vaccine on Diarrheal Burden and Etiology Among Bangladeshi Infants.

[Upfill-Brown A](#), [Taniuchi M](#), [Platts-Mills JA](#), [Kirkpatrick B](#), [Burgess SL](#), [Oberste MS](#), [Weldon W](#), [Haupt E](#), [Haque R](#), [Zaman K](#), [Petri WA Jr](#)

### BACKGROUND:

As the global polio eradication initiative prepares to cease use of oral polio vaccine (OPV) in 2020, there is increasing interest in understanding if oral vaccination provides non-specific immunity to other infections so that the consequences of this transition can be effectively planned for and mitigated.

### METHODS:

Data were collected from infants in an urban slum in Bangladesh (Mirpur, Dhaka) as part of the performance of rotavirus and oral polio vaccines in developing countries (PROVIDE) study. Following vaccination with trivalent oral polio vaccine (tOPV) at 6, 10, and 14 weeks, infants were randomly assigned to receive tOPV ( $n = 315$ ) or inactivated polio vaccine (IPV) ( $n = 299$ ) at 39 weeks. Episodes of diarrhea were documented through clinic visits and twice-weekly house visits through 52 weeks. In sum, 14 pathogens associated with diarrhea were analyzed with TaqMan Array Cards.

### RESULTS:

Although the proportion of children experiencing diarrhea was not different between the tOPV and IPV groups ( $P = .18$ ), the number of days with diarrhea ( $P = .0037$ ) and the number of separate diarrheal episodes ( $P = .054$ ) trended lower in the OPV arm. Etiological analysis revealed that male tOPV recipients were less likely to have diarrhea of bacterial etiology ( $P = .0099$ ) compared to male IPV recipients but equally likely to experience diarrhea due to viruses ( $P = .57$ ) or protozoa ( $P = .14$ ). Among the 6 bacterial enteric pathogens tested, only *Campylobacter jejuni/coli* detection was significantly reduced in the OPV arm ( $P = .0048$ ).

### CONCLUSIONS:

Our results suggest that OPV may cause nonspecific reductions in mortality, as has been studied elsewhere, by reducing etiology-specific diarrheal burden. This is likely driven by reductions in bacterial diarrhea. Further study of nonspecific OPV effects before global cessation is supported.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5848225/>



## Rotavirus vaccine

[N Engl J Med.](#) 2018 Feb 22;378(8):719-730. doi: 10.1056/NEJMoa1706804.

### **Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth.**

[Bines JE](#), [At Thobari J](#), [Satria CD](#), [Handley A](#), [Watts E](#), [Cowley D](#), [Nirwati H](#), [Ackland J](#), [Standish J](#), [Justice F](#), [Byars G](#), [Lee KJ](#), [Barnes GL](#), [Bachtiar NS](#), [Viska Icanervilia A](#), [Boniface K](#), [Bogdanovic-Sakran N](#), [Pavlic D](#), [Bishop RF](#), [Kirkwood CD](#), [Buttery JP](#), [Soenarto Y](#)

#### **BACKGROUND:**

A strategy of administering a neonatal rotavirus vaccine at birth to target early prevention of rotavirus gastroenteritis may address some of the barriers to global implementation of a rotavirus vaccine.

#### **METHODS:**

We conducted a randomized, double-blind, placebo-controlled trial in Indonesia to evaluate the efficacy of an oral human neonatal rotavirus vaccine (RV3-BB) in preventing rotavirus gastroenteritis. Healthy newborns received three doses of RV3-BB, administered according to a neonatal schedule (0 to 5 days, 8 weeks, and 14 weeks of age) or an infant schedule (8 weeks, 14 weeks, and 18 weeks of age), or placebo. The primary analysis was conducted in the per-protocol population, which included only participants who received all four doses of vaccine or placebo within the visit windows, with secondary analyses performed in the intention-to-treat population, which included all participants who underwent randomization.

#### **RESULTS:**

Among the 1513 participants in the per-protocol population, severe rotavirus gastroenteritis occurred up to the age of 18 months in 5.6% of the participants in the placebo group (28 of 504 babies), in 1.4% in the neonatal-schedule vaccine group (7 of 498), and in 2.7% in the infant-schedule vaccine group (14 of 511). **This resulted in a vaccine efficacy of 75% (95% confidence interval [CI], 44 to 91) in the neonatal-schedule group (P<0.001), 51% (95% CI, 7 to 76) in the infant-schedule group (P=0.03), and 63% (95% CI, 34 to 80) in the neonatal-schedule and infant-schedule groups combined (combined vaccine group) (P<0.001).** Similar results were observed in the intention-to-treat analysis (1649 participants); the vaccine efficacy was 68% (95% CI, 35 to 86) in the neonatal-schedule group (P=0.001), 52% (95% CI, 11 to 76) in the infant-schedule group (P=0.02), and 60% (95% CI, 31 to 76) in the combined vaccine group (P<0.001). Vaccine response, as evidenced by serum immune response or shedding of RV3-BB in the stool, occurred in 78 of 83 participants (94%) in the neonatal-schedule group and in 83 of 84 participants (99%) in the infant-schedule group. The incidence of adverse events was similar across the groups. No episodes of intussusception occurred within the 21-day risk period after administration of any dose of vaccine or placebo, and one episode of intussusception occurred 114 days after the third dose of vaccine in the infant-schedule group.

#### **CONCLUSIONS:**

**RV3-BB was efficacious in preventing severe rotavirus gastroenteritis when administered according to a neonatal or an infant schedule in Indonesia.**

<https://www.nejm.org/doi/full/10.1056/NEJMoa1706804>

[Vaccine.](#) 2017 Oct 27;35(45):6228-6237. doi: 10.1016/j.vaccine.2017.09.014. Epub 2017 Sep 26.

**[A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants.](#)**

[Kulkarni PS](#), [Desai S](#), [Tewari T](#), [Kawade A](#), [Goyal N](#), [Garg BS](#), [Kumar D](#), [Kanungo S](#), [Kamat V](#), [Kang G](#), [Bavdekar A](#), [Babji S](#), [Juvekar S](#), [Manna B](#), [Dutta S](#), [Angurana R](#), [Dewan D](#), [Dharmadhikari A](#), [Zade JK](#), [Dhere RM](#), [Fix A](#), [Power M](#), [Uprety V](#), [Parulekar V](#), [Cho I](#), [Chandola TR](#), [Kedia VK](#), [Raut A](#), [Flores J](#); [SII BRV-PV author group](#).

Rotavirus is the most common cause of moderate-to-severe infant diarrhoea in developing countries, resulting in enormous morbidity, mortality, and economic burden. A bovine-human reassortant pentavalent rotavirus vaccine (BRV-PV) targeting the globally most common strains was developed in India and tested in a randomized, double-blind, placebo-controlled end-point driven Phase III efficacy clinical trial implemented at six sites across India. **Infants 6 to 8 weeks of age were randomized (1:1) to receive three oral doses of BRV-PV or placebo at 6, 10, and 14 weeks of age along with routine vaccines.** Home visit surveillance was conducted to detect severe rotavirus gastroenteritis (SRVGE) and safety outcomes until the children reached two years of age. **A total of 3749 infants received BRV-PV while 3751 received placebo.** At the time of the primary end-point (when the minimum number of cases needed for analysis were accrued) **the vaccine efficacy against SRVGE was 36% (95% CI 11.7, 53.6, p=0.0067) in the per protocol (PP) analysis, and 41.9% (95% CI 21.1, 57.3, p=0.0005) in the intent to treat (ITT) analysis.** Vaccine efficacy over the entire follow-up period (until children reached two years of age) was 39.5% (95% CI 26.7, 50, p<0.0001) in the PP analysis and 38.8% (95% CI, 26.4, 49, p<0.0001) in the ITT analysis. **Vaccine efficacy against the very severe rotavirus cases (VSRVGE, Vesikari score≥16) was 60.5% (95% CI 17.7, 81, p=0.0131) at the time of the primary analysis and 54.7% (95% CI 29.7, 70.8, p=0.0004) for the complete follow-period in the PP population.** The incidence of solicited, unsolicited, and serious adverse events were similar in both the vaccine and placebo groups. Likewise, the number of intussusceptions and deaths were similar between both groups. Thus, BRV-PV is an effective, well tolerated and safe vaccine in Indian infants.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651219/>

[Lancet Infect Dis](#). 2017 Aug;17(8):843-853. doi: 10.1016/S1473-3099(17)30242-6. Epub 2017 May 5.

**[Safety and immunogenicity of a parenteral P2-VP8-P\[8\] subunit rotavirus vaccine in toddlers and infants in South Africa: a randomised, double-blind, placebo-controlled trial.](#)**

[Groome MJ](#), [Koen A](#), [Fix A](#), [Page N](#), [Jose L](#), [Madhi SA](#), [McNeal M](#), [Dally L](#), [Cho I](#), [Power M](#), [Flores J](#), [Cryz S](#)

**BACKGROUND:**

Efficacy of live oral rotavirus vaccines is reduced in low-income compared with high-income settings. Parenteral non-replicating rotavirus vaccines might offer benefits over oral vaccines. We assessed the safety and immunogenicity of the P2-VP8-P[8] subunit rotavirus vaccine at different doses in South African toddlers and infants.

**METHODS:**

This double-blind, randomised, placebo-controlled, dose-escalation trial was done at a single research unit based at a hospital in South Africa in healthy HIV-uninfected toddlers (aged 2 to

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<3 years) and term infants (aged 6 to <8 weeks, without previous rotavirus vaccination). Block randomisation (computer-generated, electronic allocation) was used to assign eligible toddlers (in a 6:1 ratio) and infants (in a 3:1 ratio) in each dose cohort (10 µg, followed by 30 µg, then 60 µg if doses tolerated) to parenteral P2-VP8-P[8] subunit rotavirus or placebo injection. The two highest tolerated doses were then assessed in an expanded cohort (in a 1:1:1 ratio). Parents of participants and clinical, data, and laboratory staff were masked to treatment assignment. P2-VP8-P[8] vaccine versus placebo was assessed first in toddlers (single injection) and then in infants (three injections 4 weeks apart). The primary safety endpoints were local and systemic reactions within 7 days after each injection, adverse events within 28 days after each injection, and all serious adverse events, assessed in toddlers and infants who received at least one dose. In infants receiving all study injections, primary immunogenicity endpoints were anti-P2-VP8-P[8] IgA and IgG and neutralising antibody seroresponses and geometric mean titres 4 weeks after the third injection. This trial is registered at ClinicalTrials.gov, number [NCT02109484](https://clinicaltrials.gov/ct2/show/study/NCT02109484).

### FINDINGS:

Between March 17, 2014, and Sept 29, 2014, 42 toddlers (36 to vaccine and six to placebo) and 48 infants (36 to vaccine and 12 to placebo) were enrolled in the dose-escalation phase, in which the 30 µg and 60 µg doses were found to be the highest tolerated doses. A further 114 infants were enrolled in the expanded cohort between Nov 3, 2014, and March 20, 2015, and all 162 infants (12 assigned to 10 µg, 50 to 30 µg, 50 to 60 µg, and 50 to placebo) were included in the safety analysis. Serum IgA seroresponses were observed in 38 (81%, 95% CI 67-91) of 47 infants in the 30 µg group and 32 (68%, 53-81) of 47 in the 60 µg group, compared with nine (20%, 10-35) of 45 in the placebo group; adjusted IgG seroresponses were seen in 46 (98%, 89-100) of 47 infants in the 30 µg group and 47 (100%; 92-100) of 47 in the 60 µg group, compared with four (9%, 2.5-21) of 45 in the placebo group; and adjusted neutralising antibody seroresponses against the homologous Wa-strain were seen in 40 (85%, 72-94) of 47 infants in both the 30 µg and 60 µg groups, compared with three (7%, 1.4-18) of 45 participants in the placebo group. Solicited reactions following any injection occurred with similar frequency and severity in participants receiving vaccine and those receiving placebo. Unsolicited adverse events were mostly mild and occurred at a similar frequency between groups. Eight serious adverse events (one with placebo, two with 30 µg, and five with 60 µg) occurred in seven infants within 28 days of any study injection, none of which were deemed related to study treatment.

### INTERPRETATION:

The parenteral P2-VP8-P[8] vaccine was well tolerated and immunogenic in infants, providing a novel approach to vaccination against rotavirus disease. On the basis of these results, a phase 1/2 trial of a trivalent P2-VP8 (P[4], P[6], and P[8]) subunit vaccine is underway at three sites in South Africa.

<https://www.clinicalkey.com.au/#!/content/playContent/1-s2.0-S1473309917302426?returnurl=https%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1473309917302426%3Fshowall%3Dtrue&referrer=https%2F%2Fwww.ncbi.nlm.nih.gov%2F>

[Hum Vaccin Immunother.](#) 2017 Aug 3;13(8):1916-1920. doi: 10.1080/21645515.2017.1320007. Epub 2017 Apr 25.

### [Background rates of disease in Latin American children from a rotavirus vaccine study.](#)

[Baay M](#), [Bollaerts K](#), [Struchiner C](#), [Verstraeten T](#)

### BACKGROUND:

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Knowledge of background rates of adverse events is crucial to assess vaccine safety concerns. We used data from a rotavirus vaccine study (Ruiz-Palacios et al., NEJM, 2006) including 63,225 infants from 11 Latin American countries to investigate reporting rates of serious adverse events (SAEs) among these infants, and describe rates by country, gender, age, and season.

### **METHODS:**

For this randomized, double-blind, placebo-controlled, phase 3 trial, investigators from Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela recruited 6-to-13-week-old healthy infants. The infants received 2 oral doses of vaccine or placebo. The study population was followed 100 d for the assessment of adverse events. SAEs were captured by an active surveillance system.

### **RESULTS:**

Strong differences in event rates could be observed between countries (min. 48.1/10,000 person-years in Dominican Republic/Peru; max. 296.2/10,000 person-years in Brazil) and between genders: gastroenteritis, pneumonia, bronchiolitis and bronchitis occurred significantly more frequently in males. In addition, infections and infestations, and most disorders, including immune system and cardiac disorders, were more frequent at earlier ages. Finally, looking at seasonality we noted higher rates of SAEs in the second half of the year in all countries except Mexico.

### **DISCUSSION:**

Significant differences in reporting rates of SAEs between countries, gender and calendar months illustrate the importance of knowing the local epidemiology when interpreting SAEs. Data from clinical trials can be used to better understand background rates of diseases that may be perceived as potential adverse events following immunization.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5557225/>

## Salmonella typhi vaccine

## Tuberculosis vaccine

(also see Tuberculosis, Isoniazid preventative therapy)

[Engl J Med.](#) 2018 Jul 12;379(2):138-149. doi: 10.1056/NEJMoa1714021.

### **[Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination.](#)**

[Nemes E](#), [Geldenhuys H](#), [Rozot V](#), [Rutkowski KT](#), [Ratangee F](#), [Bilek N](#), [Mabwe S](#), [Makhethe L](#), [Erasmus M](#), [Toefy A](#), [Mulenga H](#), [Hanekom WA](#), [Self SG](#), [Bekker LG](#), [Ryall R](#), [Gurunathan S](#), [DiazGranados CA](#), [Andersen P](#), [Kromann I](#), [Evans T](#), [Ellis RD](#), [Landry B](#), [Hokey DA](#), [Hopkins R](#), [Ginsberg AM](#), [Scriba TJ](#), [Hatherill M](#); [C-040-404 Study Team](#).  
**[Collaborators \(103\)](#)**

### **BACKGROUND:**

Recent Mycobacterium tuberculosis infection confers a predisposition to the development of tuberculosis disease, the leading killer among global infectious diseases. H4:IC31, a candidate subunit vaccine, has shown protection against tuberculosis disease in preclinical models, and observational studies have indicated that primary bacille Calmette-Guérin (BCG) vaccination may offer partial protection against infection.

### **METHODS:**

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In this phase 2 trial, we randomly assigned 990 adolescents in a high-risk setting who had undergone neonatal BCG vaccination to receive the H4:IC31 vaccine, BCG revaccination, or placebo. All the participants had negative results on testing for *M. tuberculosis* infection on the QuantiFERON-TB Gold In-tube assay (QFT) and for the human immunodeficiency virus. The primary outcomes were safety and acquisition of *M. tuberculosis* infection, as defined by initial conversion on QFT that was performed every 6 months during a 2-year period. Secondary outcomes were immunogenicity and sustained QFT conversion to a positive test without reversion to negative status at 3 months and 6 months after conversion. Estimates of vaccine efficacy are based on hazard ratios from Cox regression models and compare each vaccine with placebo.

### RESULTS:

Both the BCG and H4:IC31 vaccines were immunogenic. QFT conversion occurred in 44 of 308 participants (14.3%) in the H4:IC31 group and in 41 of 312 participants (13.1%) in the BCG group, as compared with 49 of 310 participants (15.8%) in the placebo group; the rate of sustained conversion was 8.1% in the H4:IC31 group and 6.7% in the BCG group, as compared with 11.6% in the placebo group. Neither the H4:IC31 vaccine nor the BCG vaccine prevented initial QFT conversion, with efficacy point estimates of 9.4% ( $P=0.63$ ) and 20.1% ( $P=0.29$ ), respectively. However, the BCG vaccine reduced the rate of sustained QFT conversion, with an efficacy of 45.4% ( $P=0.03$ ); the efficacy of the H4:IC31 vaccine was 30.5% ( $P=0.16$ ). There were no clinically significant between-group differences in the rates of serious adverse events, although mild-to-moderate injection-site reactions were more common with BCG revaccination.

### CONCLUSIONS:

In this trial, the rate of sustained QFT conversion, which may reflect sustained *M. tuberculosis* infection, was reduced by vaccination in a high-transmission setting. This finding may inform clinical development of new vaccine candidates.

<https://www.nejm.org/doi/full/10.1056/NEJMoa1714021>

[Clin Infect Dis.](#) 2018 Feb 1;66(4):554-563. doi: 10.1093/cid/cix834.

### [Safety and Immunogenicity of Newborn MVA85A Vaccination and Selective, Delayed Bacille Calmette-Guérin for Infants of Human Immunodeficiency Virus-Infected Mothers: A Phase 2 Randomized, Controlled Trial.](#)

[Nemes E](#), [Hesseling AC](#), [Tameris M](#), [Mauff K](#), [Downing K](#), [Mulenga H](#), [Rose P](#), [van der Zalm M](#), [Mbaba S](#), [Van As D](#), [Hanekom WA](#), [Walzl G](#), [Scriba TJ](#), [McShane H](#), [Hatherill M](#); [MVA029 Study Team](#).

### [Collaborators \(53\)](#)

### BACKGROUND:

Vaccination of human immunodeficiency virus (HIV)-infected infants with bacille Calmette-Guérin (BCG) is contraindicated. HIV-exposed newborns need a new tuberculosis vaccination strategy that protects against tuberculosis early in life and avoids the potential risk of BCG disease until after HIV infection has been excluded.

### METHODS:

This double-blind, randomized, controlled trial compared newborn MVA85A prime vaccination ( $1 \times 10^8$  PFU) vs Candin® control, followed by selective, deferred BCG vaccination at age 8 weeks for HIV-uninfected infants and 12 months follow-up for safety and immunogenicity.

### RESULTS:

## Randomised trials in child health in developing countries 2017-18

A total of 248 HIV-exposed infants were enrolled. More frequent mild-moderate reactogenicity events were seen after newborn MVA85A vaccination. However, no significant difference was observed in the rate of severe or serious adverse events, HIV acquisition ( $n = 1$  per arm), or incident tuberculosis disease ( $n = 5$  MVA85A;  $n = 3$  control) compared to the control arm. MVA85A vaccination induced modest but significantly higher Ag85A-specific interferon gamma ( $\text{IFN}\gamma$ )+ CD4+ T cells compared to control at weeks 4 and 8 ( $P < .0001$ ). BCG did not further boost this response in MVA85A vaccinees. The BCG-induced Ag85A-specific  $\text{IFN}\gamma$ + CD4+ T-cell response at weeks 16 and 52 was of similar magnitude in the control arm compared to the MVA85A arm at all time points. Proliferative capacity, functional profiles, and memory phenotype of BCG-specific CD4 responses were similar across study arms.

### CONCLUSIONS:

MVA85A prime vaccination of HIV-exposed newborns was safe and induced an early modest antigen-specific immune response that did not interfere with, or enhance, immunogenicity of subsequent BCG vaccination. New protein-subunit and viral-vectored tuberculosis vaccine candidates should be tested in HIV-exposed newborns.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5849090/>

## Typhoid vaccine

[Cochrane Database Syst Rev.](#) 2018 May 31;5:CD001261. doi: 10.1002/14651858.CD001261.pub4.

### [Vaccines for preventing typhoid fever.](#)

[Milligan R](#), [Paul M](#), [Richardson M](#), [Neuberger A](#).

### BACKGROUND:

Typhoid fever and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and southeast Asia. Two typhoid vaccines are widely available, Ty21a (oral) and Vi polysaccharide (parenteral). Newer typhoid conjugate vaccines are at varying stages of development and use. The World Health Organization has recently recommended a Vi tetanus toxoid (Vi-TT) conjugate vaccine, Typbar-TCV, as the preferred vaccine for all ages.

### OBJECTIVES:

To assess the effects of vaccines for preventing typhoid fever.

### SEARCH METHODS:

In February 2018, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and mRCT. We also searched the reference lists of all included trials.

### SELECTION CRITERIA:

Randomized and quasi-randomized controlled trials (RCTs) comparing typhoid fever vaccines with other typhoid fever vaccines or with an inactive agent (placebo or vaccine for a different disease) in adults and children. Human challenge studies were not eligible.

### DATA COLLECTION AND ANALYSIS:

Two review authors independently applied inclusion criteria and extracted data, and assessed the certainty of the evidence using the GRADE approach. We computed vaccine efficacy per year of follow-up and cumulative three-year efficacy, stratifying for vaccine type and dose. The outcome addressed was typhoid fever, defined as isolation of *Salmonella enterica* serovar Typhi in blood. We calculated risk ratios (RRs) and efficacy ( $1 - \text{RR}$  as a percentage) with 95% confidence intervals (CIs).

### MAIN RESULTS:

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In total, 18 RCTs contributed to the quantitative analysis in this review: 13 evaluated efficacy (Ty21a: 5 trials; Vi polysaccharide: 6 trials; Vi-rEPA: 1 trial; Vi-TT: 1 trial), and 9 reported on adverse events. All trials but one took place in typhoid-endemic countries. There was no information on vaccination in adults aged over 55 years of age, pregnant women, or travellers. Only one trial included data on children under two years of age. Ty21a vaccine (oral vaccine, three doses). A three-dose schedule of Ty21a vaccine probably prevents around half of typhoid cases during the first three years after vaccination (cumulative efficacy 2.5 to 3 years: 50%, 95% CI 35% to 61%, 4 trials, 235,239 participants, moderate-certainty evidence). These data include patients aged 3 to 44 years. Compared with placebo, this vaccine probably does not cause more vomiting, diarrhoea, nausea or abdominal pain (2 trials, 2066 participants; moderate-certainty evidence), headache, or rash (1 trial, 1190 participants; moderate-certainty evidence); however, fever (2 trials, 2066 participants; moderate-certainty evidence) is probably more common following vaccination. Vi polysaccharide vaccine (injection, one dose) A single dose of Vi polysaccharide vaccine prevents around two-thirds of typhoid cases in the first year after vaccination (year 1: 69%, 95% CI 63% to 74%; 3 trials, 99,979 participants; high-certainty evidence). In year 2, trial results were more variable, with the vaccine probably preventing between 45% and 69% of typhoid cases (year 2: 59%, 95% CI 45% to 69%; 4 trials, 194,969 participants; moderate-certainty evidence). These data included participants aged 2 to 55 years of age. The three-year cumulative efficacy of the vaccine may be around 55% (95% CI 30% to 70%; 11,384 participants, 1 trial; low-certainty evidence). These data came from a single trial conducted in South Africa in the 1980s in participants aged 5 to 15 years. Compared with placebo, this vaccine probably did not increase the incidence of fever (3 trials, 132,261 participants; moderate-certainty evidence) or erythema (3 trials, 132,261 participants; low-certainty evidence); however, swelling (3 trials, 1767 participants; moderate-certainty evidence) and pain at the injection site (1 trial, 667 participants; moderate-certainty evidence) were more common in the vaccine group. Vi-rEPA vaccine (two doses) Administration of two doses of the Vi-rEPA vaccine probably prevents between 50% and 96% of typhoid cases during the first two years after vaccination (year 1: 94%, 95% CI 75% to 99%; year 2: 87%, 95% CI 56% to 96%, 1 trial, 12,008 participants; moderate-certainty evidence). These data came from a single trial with children two to five years of age conducted in Vietnam. Compared with placebo, both the first and the second dose of this vaccine increased the risk of fever (1 trial, 12,008 and 11,091 participants, low-certainty evidence) and the second dose increase the incidence of swelling at the injection site (one trial, 11,091 participants, moderate-certainty evidence). Vi-TT vaccine (two doses) We are uncertain of the efficacy of administration of two doses of Vi-TT (PedaTyph) in typhoid cases in children during the first year after vaccination (year 1: 94%, 95% CI -1% to 100%, 1 trial, 1625 participants; very low-certainty evidence). These data come from a single cluster-randomized trial in children aged six months to 12 years and conducted in India. For single dose Vi-TT (Typbar-TCV), we found no efficacy trials evaluating the vaccine with natural exposure. There were no reported serious adverse effects in RCTs of any of the vaccines studied.

### **AUTHORS' CONCLUSIONS:**

The licensed Ty21a and Vi polysaccharide vaccines are efficacious in adults and children older than two years in endemic countries. The Vi-rEPA vaccine is just as efficacious, although data is only available for children. The new Vi-TT vaccine (PedaTyph) requires further evaluation to determine if it provides protection against typhoid fever. At the time of writing, there were only efficacy data from a human challenge setting in adults on the Vi-TT vaccine (Tybar), which clearly justify the ongoing field trials to evaluate vaccine efficacy.

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001261.pub3/full>

## Varicella vaccine

[Hum Vaccin Immunother.](#) 2017 Sep 2;13(9):2032-2037. doi: 10.1080/21645515.2017.1318236. Epub 2017 May 16.

### [Safety and immunogenicity of Bio Pox™, a live varicella vaccine \(Oka strain\) in Indian children: A comparative multicentric, randomized phase II/III clinical trial.](#)

[Dubey AP](#), [Faridi MMA](#), [Mitra M](#), [Kaur IR](#), [Dabas A](#), [Choudhury J](#), [Mukherjee M](#), [Mishra D](#)

Varicella or chickenpox is a highly contagious disease with a high secondary attack rate. Almost 30% of Indian adolescents lack protective antibodies against varicella, emphasizing the need of routine varicella immunization. The Oka VZV is a well-established, safe and efficacious vaccine strain that is highly immunogenic and produces lifelong protective immunity. The present multicentric, open label, randomized, controlled Phase II/III study, compared the Bio Pox™ (indigenous investigational vaccine) with a licensed vaccine, Varivax™, for its safety and immunogenicity profile in 252 healthy subjects in the age group of 1-12 y (cohort I: 6-12 years, II: 1-6 years) in 3 tertiary medical institutions. Antibodies were measured by VZV Glycoprotein Enzyme Linked Immunoassay (IgG ELISA) kit. Seroconversion percentage in children having pre-vaccination anti VZV IgG titer <10 mIU/mL (< 5 gp ELISA units/mL) were 80% for Bio Pox™ and 77% for Varivax™ (p = 0.692). The seroconversion rate in the group receiving Bio Pox™ was non-inferior to the group that received Varivax™. There were mild local reactions for both the vaccines; none of the patient had fever or required hospitalization or medication. The Bio Pox™ was found to be safe and immunogenic in children against VZV infection.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612528/>

## Vitamin A

[Cochrane Database Syst Rev.](#) 2017 Sep 7;9:CD003648. doi: 10.1002/14651858.CD003648.pub4.

### [Vitamin A supplements for reducing mother-to-child HIV transmission.](#) [Wiysonge CS](#), [Ndze VN](#), [Kongnyuy EJ](#), [Shey MS](#).

#### **BACKGROUND:**

Strategies to reduce the risk of mother-to-child transmission of the human immunodeficiency virus (HIV) include lifelong antiretroviral therapy (ART) for HIV-positive women, exclusive breastfeeding from birth for six weeks plus nevirapine or replacement feeding plus nevirapine from birth for four to six weeks, elective Caesarean section delivery, and avoiding giving children chewed food. In some settings, these interventions may not be practical, feasible, or affordable. Simple, inexpensive, and effective interventions (that could potentially be implemented even in the absence of prenatal HIV testing programmes) would be valuable. Vitamin A, which plays a role in immune function, is one low-cost intervention that has been suggested in such settings.

#### **OBJECTIVES:**

To summarize the effects of giving vitamin A supplements to HIV-positive women during pregnancy and after delivery.

#### **SEARCH METHODS:**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and the World Health Organization International Clinical Trials Registry Platform



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(WHO ICTRP) up to 25 August 2017, and checked the reference lists of relevant articles for eligible studies.

### SELECTION CRITERIA:

We included randomized controlled trials conducted in any setting that compared vitamin A supplements to placebo or no intervention among HIV-positive women during pregnancy or after delivery, or both.

### DATA COLLECTION AND ANALYSIS:

At least two review authors independently assessed study eligibility and extracted data. We expressed study results as risk ratios (RR) or mean differences (MD) as appropriate, with their 95% confidence intervals (CI), and conducted random-effects meta-analyses. This is an update of a review last published in 2011.

### MAIN RESULTS:

Five trials met the inclusion criteria. These were conducted in Malawi, South Africa, Tanzania, and Zimbabwe between 1995 and 2005 and none of the participants received ART. **Women allocated to intervention arms received vitamin A supplements at a variety of doses (daily during pregnancy; a single dose immediately after delivery, or daily doses during pregnancy plus a single dose after delivery).** Women allocated to comparison arms received identical placebo (6601 women, 4 trials) or no intervention (697 women, 1 trial). Four trials (with 6995 women) had low risk of bias and one trial (with 303 women) had high risk of attrition bias. **The trials show that giving vitamin A supplements to HIV-positive women during pregnancy, the immediate postpartum period, or both, probably has little or no effect on mother-to-child transmission of HIV (RR 1.07, 95% CI 0.91 to 1.26; 4428 women, 5 trials, moderate certainty evidence) and may have little or no effect on child death by two years of age (RR 1.06, 95% CI 0.92 to 1.22; 3883 women, 3 trials, low certainty evidence).** However, giving vitamin A supplements during pregnancy may increase the mean birthweight (MD 34.12 g, 95% CI -12.79 to 81.02; 2181 women, 3 trials, low certainty evidence) and probably reduces the incidence of low birthweight (RR 0.78, 95% CI 0.63 to 0.97; 1819 women, 3 trials, moderate certainty evidence); but we do not know whether vitamin A supplements affect the risk of preterm delivery (1577 women, 2 trials), stillbirth (2335 women, 3 trials), or maternal death (1267 women, 2 trials).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5618453/>

*Am J Clin Nutr.* 2017 Jul;106(1):77-87. doi: 10.3945/ajcn.116.134478. Epub 2017 May 10.

### **Effect of maternal antenatal and newborn supplementation with vitamin A on cognitive development of school-aged children in rural Bangladesh: a follow-up of a placebo-controlled, randomized trial.**

[Ali H](#), [Hamadani J](#), [Mehra S](#), [Tofail F](#), [Hasan MI](#), [Shaikh S](#), [Shamim AA](#), [Wu LS](#), [West KP Jr](#), [Christian P](#)

**Background:** The impact of early vitamin A supplementation on neurodevelopmental function has not been adequately studied. In rural Bangladesh we examined cognitive and motor function and scholastic achievement in a cohort of children who were exposed to vitamin A in utero or at birth.

**Objective:** The aim of this study was to examine independent and combined effects of antenatal and newborn supplementation with vitamin A on the cognitive function of children at 8 y of age.

**Design:** A cohort of rural Bangladeshi children from 2 previous double-blind, placebo-controlled cluster-randomized trials were revisited at age 8 y between February 2013 and June

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2014. Data on sociodemographic, social, and physical conditions; schooling; child care behavior; anthropometric measures; and cognitive function were collected with the use of various psychometric assessment tools.

**Results:** Among 11,950 children from the parent trial who were last known to be alive, a subset of 1803 children balanced by treatment group in a selected contiguous study area were re-enrolled and 1613 (89%) provided consent for assessments. Of these, 1577 (87%) children had a complete cognitive evaluation. All groups were highly comparable on baseline variables collected in the previous trials and factors measured at re-enrollment. Overall, there was no impact of either maternal or newborn supplementation with vitamin A on intelligence, memory, and motor function. Compared with placebo, children who received both interventions had significantly better performance in reading, spelling, and math computation, with increased mean (95% CI) scores of 8.0 (2.2, 13.8), 6.8 (1.9, 11.7), and 4.8 (0.6, 9.0), respectively.

**Conclusions:** General intelligence or memory and motor functions were not affected by antenatal or newborn supplementation with vitamin A. Scholastic performance and aspects of executive function improved when both interventions were provided.

<https://academic.oup.com/ajcn/article/106/1/77/4634021>

[Yale J Biol Med.](#) 2018 Jun 28;91(2):83-94. eCollection 2018 Jun.

### **Improving Blood Retinol Concentrations with Complementary Foods Fortified with *Moringa oleifera* Leaf Powder - A Pilot Study.**

[Boateng L](#), [Ashley I](#), [Ohemeng A](#), [Asante M](#), [Steiner-Asiedu M](#)

Vitamin A deficiency (VAD) remains a major public health issue and is reported to be the cause of about 6 percent of child deaths under the age of 5 years in Africa. Inadequate dietary intake of vitamin A-rich foods is a major cause of VAD. *Moringa oleifera* leaf powder (MLP) is rich in nutrients particularly vitamin A and its use in infant feeding has been explored. This pilot study was designed to test the efficacy of MLP in improving blood retinol concentrations among infants in a rural district in Ghana. A subset of infants participating in a randomized controlled trial (ISRCTN14377902) were randomly assigned to receive one of the three study foods (*MCL-35g* and *MS-5g* both of which were fortified with MLP, and a third food, *CF-35g*, a cereal legume blend which served as the control food) in a feeding intervention that lasted for 6 weeks. Primary outcome of the pilot study was retinol levels measured in 5 ml of whole blood at baseline and endline using the iCheck™ Fluoro device. A total of 103 infant-mother pairs were recruited at baseline, of which 65 completed the study. All the infants in the study were vitamin A deficient at both baseline and endline when compared to the World Health Organization (WHO) threshold of 0.70µmol/l. There was however a marginal non-significant increase in blood vitamin A concentrations for all three groups at endline, with higher numerical increases seen in the two *Moringa* supplemented groups. VAD is a significant public health problem and MLP could be an affordable and sustainable means of combatting the issue. The efficacy of MLP in improving vitamin A status of infants however needs to be ascertained in well-designed trials involving larger numbers of infants and which will last for longer periods. Such studies will also be beneficial in helping to establish the long-term acceptability of complementary foods that incorporate MLP in the target population.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020727/>

[J Matern Fetal Neonatal Med.](#) 2018 Feb 22:1-8. doi: 10.1080/14767058.2018.1441282

**Role of vitamin A supplementation in prevention of bronchopulmonary dysplasia in extremely low birth weight neonates: a systematic review of randomized trials.**

Garg BD, Bansal A, Kabra NS

**BACKGROUND:**

Bronchopulmonary dysplasia (BPD) is one of the most common consequence of extreme prematurity (<28 weeks of gestation). BPD affects approximately 55% of extremely low birth weight (ELBW) neonates.

**AIMS:**

The aim of this systematic review is to evaluate the role of vitamin A supplementation in prevention of BPD in ELBW neonates.

**METHOD:**

The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, and ongoing clinical trials.

**RESULTS:**

This review included two RCTs that fulfilled inclusion criteria. There were statistically significant reduction in the incidence of BPD (oxygen requirement at 36 weeks of postmenstrual age (PMA)) (relative risk (RR) 0.88; 95% CI 0.77-0.99; p = .04; NNTB 14) and borderline significant reduction in combined outcomes of mortality/BPD (oxygen requirement at 36 weeks of PMA) (RR 0.90; 95% CI 0.82-1.00; p = .05). However, oxygen requirement at 28 days of life and combined outcome of mortality/BPD (oxygen requirement at 28 days of life) were not statistically significant.

**CONCLUSIONS:**

The role of vitamin A supplementation in the prevention of BPD is supported by the current evidences. However, due to limited number of studies, current evidences are not sufficient which can translate into routine clinical practice. We need large high-quality trials, with sufficient power to reliably assess clinically relevant differences in outcomes.

## Vitamin D

(See also Neonates – preterm and low birth weight)

Nutr J. 2017 Sep 18;16(1):59. doi: 10.1186/s12937-017-0285-y.

**Vitamin-D status and neurodevelopment and growth in young north Indian children: a secondary data analysis.**

Chowdhury R, Taneja S, Bhandari N, Kvestad I, Strand TA, Bhan MK.

**BACKGROUND:**

Vitamin-D deficiency has been linked with impaired development in animal studies; however, the evidence from human studies is scanty. Evidence as to whether vitamin-D deficiency during early childhood affects growth is also limited and conflicting. We examined the extent to which vitamin-D deficiency (<10 ng/ml) is associated with neurodevelopment and physical growth in young children.

**METHODS:**

We used data from a randomized controlled trial (RCT) of daily folic acid and/ or vitamin B12 supplementation for six months in children aged 6 to 30 months conducted in Delhi, India. We measured vitamin-D status and neurodevelopment by the Ages and Stages Questionnaire-3

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(ASQ-3) at 12 to 36 months of age. Multiple logistic and linear regressions were used to examine the association between vitamin-D deficiency at baseline and neurodevelopment and growth 6 months follow-up.

### RESULTS:

25-hydroxy-vitamin-D (25OHD) concentration was measured at baseline for 960 (96%) children. Of these, 331 (34.5%) children were vitamin-D deficient. The total and subscale (except for the Personal social scale) ASQ-3 scores, were not different between the vitamin-D deficient and non-deficient children. Vitamin-D deficiency was also not associated with physical growth at baseline and at follow -up.

### CONCLUSION:

Our data do not support the hypothesis that vitamin-D deficiency is associated with poor growth and neurodevelopment.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604419/>

[Public Health Nutr.](#) 2017 Jul;20(10):1865-1873. doi: 10.1017/S1368980015003092. Epub 2015 Nov 6.

### [Prenatal vitamin D supplementation and infant vitamin D status in Bangladesh.](#)

[Perumal N](#), [Al Mahmud A](#), [Baqui AH](#), [Roth DE](#)

### OBJECTIVE:

To determine the effect of prenatal maternal vitamin D supplementation on infant vitamin D status in a tropical region where vitamin D supplementation is not routine.

### DESIGN:

A prospective observational follow-up of a randomized trial.

### SETTING:

Maternal-child health facility in Dhaka, Bangladesh (23°N).

### SUBJECTS:

Infants born to pregnant women (n 160) randomized to receive 875 µg (35 000 IU) cholecalciferol (vitamin D<sub>3</sub>) per week (VD) or placebo (PL) during the third trimester were followed from birth until 6 months of age (n 115). Infant serum 25-hydroxyvitamin D concentration (25(OH)D) was measured at <1, 2, 4 and 6 months of age.

### RESULTS:

Mean infant 25(OH)D was higher in the VD v. PL group at <1 month of age (mean (sd): 80 (20) nmol/l v. 22 (18) nmol/l; P<0.001), but the difference was attenuated by 2 months (52 (19) nmol/l v. 40 (23) nmol/l; P=0.05). Groups were similar at 4 months (P=0.40) and 6 months (n 72; P=0.26). In the PL group, mean infant 25(OH)D increased to 78 (95 % CI 67, 88) nmol/l by 6 months of age (n 34). 25(OH)D was higher with infant formula-feeding and higher in summer v. winter.

### CONCLUSIONS:

Prenatal third-trimester vitamin D supplementation (875 µg (35 000 IU)/week) significantly ameliorated infant vitamin D status during the neonatal period when the risk of vitamin D deficiency is greatest. Further research is warranted to determine factors that contribute to the rise in 25(OH)D during the first 6 months of life among breast-fed infants in this setting.

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[https://www.cambridge.org/core/services/aop-cambridge-core/content/view/C3DF9171DACADE71A20033E604327A7B/S1368980015003092a.pdf/prenatal\\_vitamin\\_d\\_supplementation\\_and\\_infant\\_vitamin\\_d\\_status\\_in\\_bangladesh.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/C3DF9171DACADE71A20033E604327A7B/S1368980015003092a.pdf/prenatal_vitamin_d_supplementation_and_infant_vitamin_d_status_in_bangladesh.pdf)

[Trials](#). 2017 Sep 4;18(1):411. doi: 10.1186/s13063-017-2157-3.

### **Effect of maternal vitamin D<sub>3</sub> supplementation on maternal health, birth outcomes, and infant growth among HIV-infected Tanzanian pregnant women: study protocol for a randomized controlled trial.**

[Sudfeld CR](#), [Manji KP](#), [Duggan CP](#), [About S](#), [Muhihi A](#), [Sando DM](#), [Al-Beity FMA](#), [Wang M](#), [Fawzi WW](#)

#### **BACKGROUND:**

Vitamin D has significant immunomodulatory effects on both adaptive and innate immune responses. Observational studies indicate that adults infected with HIV with low vitamin D status may be at increased risk of mortality, pulmonary tuberculosis, and HIV disease progression. Growing observational evidence also suggests that low vitamin D status in pregnancy may increase the risk of adverse birth and infant health outcomes. As a result, antiretroviral therapy (ART) adjunct vitamin D<sub>3</sub> supplementation may improve the health of HIV-infected pregnant women and their children.

#### **METHODS/DESIGN:**

The Trial of Vitamins-5 (ToV5) is an individually randomized, double-blind, placebo-controlled trial of maternal vitamin D<sub>3</sub> (cholecalciferol) supplementation conducted among 2300 HIV-infected pregnant women receiving triple-drug ART under Option B+ in Dar es Salaam, Tanzania. HIV-infected pregnant women of 12-27 weeks gestation are randomized to either: 1) 3000 IU vitamin D<sub>3</sub> taken daily from randomization in pregnancy until trial discharge at 12 months postpartum; or 2) a matching placebo regimen. Maternal participants are followed-up at monthly clinic visits during pregnancy, at delivery, and then with their children at monthly postpartum clinic visits. The primary efficacy outcomes of the trial are: 1) maternal HIV disease progression or death; 2) risk of small-for-gestational age (SGA) births; and 3) risk of infant stunting at 1 year of age. The primary safety outcome of the trial is incident maternal hypercalcemia. Secondary outcomes include a range of clinical and biological maternal and child health outcomes.

#### **DISCUSSION:**

The ToV5 will provide causal evidence on the effect of vitamin D<sub>3</sub> supplementation on HIV progression and death, SGA births, and infant stunting at 1 year of age. The results of the trial are likely generalizable to HIV-infected pregnant women and their children in similar resource-limited settings utilizing the Option B+ approach.

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2157-3>

## Yaws

[Lancet Glob Health](#). 2018 Apr;6(4):e401-e410. doi: 10.1016/S2214-109X(18)30023-8. Epub 2018 Feb 16.

**Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: a randomised non-inferiority trial in Ghana and Papua New Guinea.**

Marks M, Mitjà O, Bottomley C, Kwakye C, Houinei W, Bauri M, Adwere P, Abdulai AA, Dua F, Boateng L, Wangi J, Ohene SA, Wangnapi R, Simpson SV, Miag H, Addo KK, Basing LA, Danavall D, Chi KH, Pillay A, Ballard R, Solomon AW, Chen CY, Bieb SV, Adu-Sarkodie Y, Mabey DCW, Asiedu K; study team.

**Collaborators (101)**

**BACKGROUND:**

A dose of 30 mg/kg of azithromycin is recommended for treatment of yaws, a disease targeted for global eradication. Treatment with 20 mg/kg of azithromycin is recommended for the elimination of trachoma as a public health problem. In some settings, these diseases are co-endemic. We aimed to determine the efficacy of 20 mg/kg of azithromycin compared with 30 mg/kg azithromycin for the treatment of active and latent yaws.

**METHODS:**

We did a non-inferiority, open-label, randomised controlled trial in children aged 6-15 years who were recruited from schools in Ghana and schools and the community in Papua New Guinea. Participants were enrolled based on the presence of a clinical lesion that was consistent with infectious primary or secondary yaws and a positive rapid diagnostic test for treponemal and non-treponemal antibodies. Participants were randomly assigned (1:1) to receive either **standard-dose (30 mg/kg) or low-dose (20 mg/kg) azithromycin** by a computer-generated random number sequence. Health-care workers assessing clinical outcomes in the field were not blinded to the patient's treatment, but investigators involved in statistical or laboratory analyses and the participants were blinded to treatment group. We followed up participants at 4 weeks and 6 months. The primary outcome was cure at 6 months, defined as lesion healing at 4 weeks in patients with active yaws and at least a four-fold decrease in rapid plasma reagin titre from baseline to 6 months in patients with active and latent yaws. Active yaws was defined as a skin lesion that was positive for *Treponema pallidum* ssp *pertenue* in PCR testing. We used a non-inferiority margin of 10%.

**FINDINGS:**

Between June 12, 2015, and July 2, 2016, 583 (65.1%) of 895 children screened were enrolled; **292 patients were assigned a low dose of azithromycin and 291 patients were assigned a standard dose of azithromycin.** 191 participants had active yaws and 392 had presumed latent yaws. Complete follow-up to 6 months was available for 157 (82.2%) of 191 patients with active yaws. In cases of active yaws, cure was achieved in 61 (80.3%) of 76 patients in the low-dose group and in 68 (84.0%) of 81 patients in the standard-dose group (difference 3.7%; 95% CI -8.4 to 15.7%; this result did not meet the non-inferiority criterion). There were no serious adverse events reported in response to treatment in either group. The most commonly reported adverse event at 4 weeks was gastrointestinal upset, with eight (2.7%) participants in each group reporting this symptom.

**INTERPRETATION:**

In this study, low-dose azithromycin did not meet the prespecified non-inferiority margin compared with standard-dose azithromycin in achieving clinical and serological cure in PCR-confirmed active yaws. Only a single participant (with presumed latent yaws) had definitive serological failure. This work suggests that 20 mg/kg of azithromycin is probably effective against yaws, but further data are needed.

[https://www.clinicalkey.com.au/service/content/pdf/watermarked/1-s2.0-S2214109X18300238.pdf?locale=en\\_AU](https://www.clinicalkey.com.au/service/content/pdf/watermarked/1-s2.0-S2214109X18300238.pdf?locale=en_AU)

## Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

[BMC Pharmacol Toxicol](#). 2017 Jul 10;18(1):56. doi: 10.1186/s40360-017-0162-5.

### [Zinc as an adjunct treatment for reducing case fatality due to clinical severe infection in young infants: study protocol for a randomized controlled trial.](#)

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#### **BACKGROUND:**

An estimated 2.7 of the 5.9 million deaths in children under 5 years of age occur in the neonatal period. Severe infections contribute to almost a quarter of these deaths. Mortality due to severe infections in developing country settings is substantial despite antibiotic therapy. Effective interventions that can be added to standard therapy for severe infections are required to reduce case fatality.

#### **METHODS/DESIGN:**

This is a double-blind randomized placebo-controlled parallel group superiority trial to investigate the effect of zinc administered orally as an adjunct to standard therapy to infants aged 3 days up to 2 months (59 days) hospitalized with clinical severe infection, that will be undertaken in seven hospitals in Delhi, India and Kathmandu, Nepal. In a 1:1 ratio, we will randomly assign young infants to receive 10 mg of elemental zinc or placebo orally in addition to the standard therapy for a total of 14 days. The primary outcomes hospital case fatality, which is death due to any cause and at any time after enrolment while hospitalized for the illness episode, and extended case fatality, which encompasses the period until 12 weeks after enrolment.

#### **DISCUSSION:**

A previous study showed a beneficial effect of zinc in reducing the risk of treatment failure, as well as a non-significant effect on case fatality. This study was not powered to detect an effect on case fatality, which this current study is. If the results are consistent with this earlier trial, we would have provided strong evidence for recommending zinc as an adjunct to standard therapy for clinical severe infection in young infants.

<https://bmcparmacoltoxicol.biomedcentral.com/articles/10.1186/s40360-017-0162-5>

[J Matern Fetal Neonatal Med](#). 2017 Aug;30(16):1953-1962. doi: 10.1080/14767058.2016.1234600. Epub 2016 Oct 17.

### [Role of oral zinc supplementation for reduction of neonatal hyperbilirubinemia: a systematic review of current evidence.](#)

[Sharma D](#), [Farahbakhsh N](#), [Sharma P](#), [Shastri S](#)

#### **BACKGROUND:**

Neonatal hyperbilirubinemia is frequently seen condition in the NICU. Oral zinc has been tried for the prevention of hyperbilirubinemia.

## **Randomised trials in child health in developing countries 2017-18**

### **AIMS:**

To evaluate the role of oral zinc supplementation for reduction of neonatal hyperbilirubinemia in term and preterm infants.

### **METHOD:**

The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Web of Science, Scopus, Index Copernicus, African Index Medicus (AIM), Thomson Reuters (ESCI), Chemical Abstracts Service (CAS) and other data base.

### **RESULTS:**

This review included six RCT that fulfilled inclusion criteria. One study evaluated the role of zinc in very low birth weight (VLBW) infants and remaining enrolled neonates  $\geq 35$  weeks of gestation. The dose of zinc varied from 5 to 20 mg/day and duration from 5-7 days. All the studies used zinc sulfate, only one study used zinc gluconate. The total neonates enrolled in these different RCT are 749.

### **CONCLUSION:**

**Role of zinc in the prevention of neonatal hyperbilirubinemia is not supported by the current evidence.** Only one study was able to show reduction in the mean TSB level and requirement of phototherapy with zinc, and the remaining studies did not report any positive effect. None of the studies showed any effect on the duration of phototherapy, incidence of phototherapy, age of starting of phototherapy and any serious adverse effect.