

RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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Randomised trials in child health in developing countries 2011-12

SEARCH STRATEGY

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Introduction

This booklet is compiled annually to summarize the evidence on child health derived from randomized 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. It is hoped that such information will be helpful in reviewing treatment policies, clinical practice and public health strategies.

The method of searching for studies to include 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 try to capture as many relevant studies as possible, although it is possible that some are missed. If you know of a relevant RCT 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 far from 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 appropriately they eliminate bias and confounding. However their results should not be accepted uncritically and 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 the wider applicability, feasibility and potential for sustainability.

This year 242 studies were identified. These came from all regions of the world, mostly from developing country researchers. Several trials from 2011-12 will lead to significant changes in child health approaches or clinical recommendations.

We have included the web-link for papers that are available in full-text on the Internet free of charge. More importantly, through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with major publishers, the full-text versions of over 8500 journal titles and 7000 e-books are now available to health institutions in 109 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 any colleagues. Previous editions (2002-2011) are available at: www.ichrc.org

Four trials reported significant reductions in mortality (marked with *** in the booklet), among these:

- In India the introduction of a program: Integrated Management of Maternal, Neonatal and Child Health reduced neonatal and infant mortality. In this program community health workers were trained to conduct postnatal home visits and women's group meetings, where physicians, nurses, and community health workers were trained to treat or refer sick newborns and children. Supply of drugs and supervision were strengthened.
- In rural Pakistan application of 4% chlorhexidine to the umbilical cord reduced neonatal mortality and omphalitis
- In Uganda a trial of zinc in the treatment of severe pneumonia showed a significant reduction in deaths in the zinc treated group. This is the first trial of zinc treatment in pneumonia with the power to show a mortality difference. The effect was especially strong in children with HIV. Two other trials this year – from India and Nepal - did not show a significant beneficial effect of zinc on resolution of pneumonia signs.

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- In Bangladesh, antenatal treatment of pregnant women from poor communities with multiple micronutrients, including iron and folic acid combined with early food supplementation decreased the risk of mortality in their children.

Other important results in 2011-12

- In South Africa, extended nevirapine during breast-feeding significantly reduced the risk of HIV infection: 1.1% (95% CI 0.3-1.8) of infants who received extended nevirapine developed HIV-1 between 6 weeks and 6 months compared with 2.4% (1.3-3.6) of infants who only received nevirapine for the first 6 weeks of life. However in a trial in Ethiopia, children who received nevirapine for 6 weeks and had prophylaxis failure - i.e. they developed HIV - had a higher risk of resistant strains of HIV.
- In the Americas, post-natal treatment with zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life, or zidovudine for 6 weeks plus nelfinavir and lamivudine for 2 weeks was more effective than zidovudine for 6 weeks at reducing parent-to-child transmission of HIV in mothers who did not receive ART during pregnancy.
- In 6 African countries initiation of HIV treatment in children who had no prior exposure to nevirapine, ART with zidovudine, lamivudine, and 'ritonavir-boosted lopinavir' resulted in lower virological failure than zidovudine, lamivudine and nevirapine. Nevirapine resistance was a common feature of treatment failure.
- In 7 African countries in a phase III trial the RTS,S/AS01 malaria vaccine provided protection against both clinical and severe malaria in African children, with vaccine efficacies of 50% for first episode of malaria, and 35% against severe malaria. Another study from 3 African countries in a phase II trial showed similar efficacy (53% and 59%) against the first episode of malaria and all malaria episodes, respectively, when children were followed up at 19 months. A third study of seroresponse in children in Mozambique showed protective anti-circumsporozoite antibodies at 42 months. The RTS,S/AS02 vaccine also induced high levels of anti-hepatitis B surface antigen antibodies.
- In a meta-analysis of 7 trials in malaria endemic countries in West Africa involving 12,000 children, intermittent preventative therapy of malaria (IPTc) during the malaria season prevented approximately three quarters of all clinical malaria episodes and a similar proportion of severe malaria episodes. These effects remain present even where insecticide treated net (ITN) usage is high.
- In Mali, a program for intermittent preventative treatment of malaria along with routine vaccines increased vaccine coverage. In Ghana health care delivery costs were less and coverage was the slightly higher when IPTi was delivered by village health workers, compared with when IPTi was delivered by clinic or outreach EPI nurses.
- In a large study in Uganda involving over 100,000 children with suspected malaria, use of rapid diagnostic tests (RDT), compared with presumptive diagnosis, significantly reduced the prescribing of artemether-lumefantrine. However 23% of children with negative RDT were still prescribed antimalarials. Compared with microscopy, RDTs reduced waiting time and were considered more convenient for patients and health workers. In Tanzania community health workers could use RDT: no fatal or severe malaria occurred among 682 RDT negative children who were not treated with antimalarials by CHWs. This suggests that it is safe to withhold malaria treatment to RDT negative patients and that lower level health workers can make decisions based on RDT.

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- As has been found in studies in previous years, in a multi-country study in Africa, dihydroartemisinin-piperaquine was as effective as artemisinin-based therapy for uncomplicated *P. falciparum*, and resulted in a lower malaria recurrence risk.
- In Lao, China, and Uganda trials of albendazole and mebendazole for the treatment of worm infestation showed that albendazole is more efficacious than mebendazole for hookworm. However single-dose albendazole had low efficacy against hookworm, and treatment daily for 3 days (in Lo and China), or 2 doses 8 hours apart (in Uganda) was better. Albendazole had lower efficacy than mebedazole against *Trichuris trichiura*, where 3 days of treatment (or 2 doses in the one day) was optimal for cure.
- In Kenya, the combination of albendazole and di-ethyl carbamazine (DEC) was more effective than either drug alone for filariasis. This is important for mass administration programs aiming to interrupt transmission of *W. bancrofti* in endemic areas.
- In Columbia, oral Meltifosone given for 28 days by directly-observed treatment was shown to be as effective as antimonial drugs given by intramuscular injection daily for 20 days in the treatment of cutaneous Leishmaniasis. Meltifosone is the first oral drug to be effective against visceral or cutaneous leishmaniasis, and is good news for efforts to eradicate the disease.
- In a trial involving over 66,000 people in Kolkata, India, the 2-dose killed whole-cell oral cholera vaccine provided 65% protection for at least 3 years. One case of cholera was averted for every 404 people vaccinated.
- In the Gambia, the 7-valent pneumococcal conjugate vaccine showed a marked herd immunity among children in neighbouring non-vaccinated villages, with no significant serotype replacement.
- In Malawi, South Africa, and Kenya, rotavirus vaccine given in the first 3 months of life remained effective against severe rotavirus diarrhoea in the second year of life. Three doses of RV vaccine in the first 3 months of life provided greater second year protection than two doses.
- In Papua New Guinea a single dose of oral azithromycin was as effective as a single injection of benzathine penicillin for the treatment of yaws. This may overcome the operational difficulties associated with administering an injection, raising the prospect of tackling yaws through the mass treatment of populations at risk.
- For Indian children with type I diabetes, drinking 500ml of camel milk daily improved glucose tolerance and reduced insulin requirements.
- In Angola, 12-hour infusions of cefotaxime resulted in a lower rate of the combined outcome of mortality and severe neurological sequelae in children with pneumococcal meningitis, than boluses of cefotaxime every 6 hours.
- In Bangladesh simple guidelines and training on child TB case detection together with basic logistics support were integrated into the existing National TB Control Programme and markedly improved case funding for children with TB.

There were some important negative trials:

- Despite strong evidence that children with vitamin D deficiency are at increased risk of pneumonia and bronchiolitis in some populations, two trials showed there was no beneficial effect of vitamin D as adjuvant therapy for severe pneumonia.
- Despite previous positive trials, a large trial in South Africa showed no evidence that isoniazid preventative therapy improved tuberculosis-disease-free survival among HIV-

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infected children or tuberculosis-infection-free survival among HIV-uninfected children who had received BCG vaccine.

It is important to understand the context in which benefit (or harm) occurs in a trial. This context may 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 reported incompletely), and is one reason why there is a need for more large-scale implementation trials – not necessarily randomised - that provide insight into local context.

In the last 10 years there have been 1342 trials summarised in the various editions of this booklet. The public health benefits that have come from the huge number of trials on malaria (about 22% of all RCTs in the last decade) can be seen in the uptake of new interventions and reductions in malaria in each affected country in the world. The funding of comprehensive programs of research to “roll-back” malaria and implement the results of trials is a good example of the optimum benefit of research. While malaria rates are falling, the same reductions are not being seen in pneumonia, malnutrition or neonatal illness – and taking similar comprehensive approaches to the research agenda and to research-driven public health interventions are needed. It is striking that despite over 60 randomised trials of zinc sulphate over the last decade, most children with diarrhoea or malnutrition in developing countries still do not have access to zinc, and many not even access to oral rehydration solution – proven by many decades of RCTs.

In 2011-12 the impact of economic transition, Western morbidities and high-technology research was more evident, with clinical trials this year from India and China on issues related to non-communicable diseases, including obesity, diabetes, congenital heart disease, allergy, and modifying risk factors in childhood for adult cardiovascular disease.

More support is needed for developing public health research capacity in developing countries. This would improve the quality, scale and relevance of future trials, and improve the process of local analysis and implementation. High quality local trials need to be valued higher. At present, mechanisms of research funding and publication have a bias towards international agency supported and organised trials. Flourishing local research efforts are essential for development.

Trevor Duke

July 2012

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Acute respiratory infection

(See also Zinc, Pneumococcal vaccine, Hygiene and environmental health)

Treatment of severe pneumonia

[Lancet](#). 2011 Nov 19;378(9805): 1796-803. Epub 2011 Nov 10.

[Community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomised trial.](#)

[Bari A](#), [Sadruddin S](#), [Khan A](#), [Khan Iu](#), [Khan A](#), [Lehri IA](#), [Macleod WB](#), [Fox MP](#), [Thea DM](#), [Qazi SA](#).

Save the Children US, Pakistan Country Office, Islamabad, Pakistan.

BACKGROUND: First dose oral co-trimoxazole and referral are recommended for WHO-defined severe pneumonia. Difficulties with referral compliance are reported in many low-resource settings, resulting in low access to appropriate treatment. The objective in this study was to assess whether community case management by lady health workers (LHWs) with oral amoxicillin in children with severe pneumonia was equivalent to current standard of care.

METHODS: In Haripur district, Pakistan, 28 clusters were randomly assigned with stratification in a 1:1 ratio to intervention and control clusters by use of a computer-generated randomisation sequence. Children were included in the study if they were aged 2-59 months with WHO-defined severe pneumonia and living in the study area. In the intervention clusters, community-based LHWs provided mothers with oral amoxicillin (80-90 mg/kg per day or 375 mg twice a day for infants aged 2-11 months and 625 mg twice a day for those aged 12-59 months) with specific guidance on its use. In control clusters, LHWs gave the first dose of oral co-trimoxazole (age 2-11 months, sulfamethoxazole 200 mg plus trimethoprim 40 mg; age 12 months to 5 years, sulfamethoxazole 300 mg plus trimethoprim 60 mg) and referred the children to a health facility for standard of care. Participants, carers, and assessors were not masked to treatment assignment. The primary outcome was treatment failure by day 6. Analysis was per protocol with adjustment for clustering within groups by use of generalised estimating equations. This study is registered, number ISRCTN10618300.

FINDINGS: We assigned 1995 children to treatment in 14 intervention clusters and 1477 in 14 control clusters, and we analysed 1857 and 1354 children, respectively. Cluster-adjusted treatment failure rates by day 6 were significantly reduced in the intervention clusters (165 [9%] vs 241 [18%], risk difference -8.9%, 95% CI -12.4 to -5.4). Further adjustment for baseline covariates made little difference (-7.3%, -10.1 to -4.5). Two deaths were reported in the control clusters and one in the intervention cluster. Most of the risk reduction was in the occurrence of fever and lower chest indrawing on day 3 (-6.7%, -10.0 to -3.3). Adverse events were diarrhoea (n=4) and skin rash (n=1) in the intervention clusters and diarrhoea (n=3) in the control clusters.

INTERPRETATION: Community case management could result in a standardised treatment for children with severe pneumonia, reduce delay in treatment initiation, and reduce the costs for families and health-care systems.

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[Lancet](#). 2012 Feb 25;379(9817): 729-37. Epub 2012 Jan 27.

[Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial.](#)

[Soofi S](#), [Ahmed S](#), [Fox MP](#), [MacLeod WB](#), [Thea DM](#), [Qazi SA](#), [Bhutta ZA](#).

Division of Women and Child Health, Aga Khan University, Karachi, Pakistan.

BACKGROUND: Pneumonia is a leading global cause of morbidity and mortality in children younger than 5 years. In Pakistan, the proportion of deaths due to pneumonia is higher in rural areas than it is in urban areas, with a substantial proportion of individuals dying at home because referral for care is problematic in such areas. We aimed to establish whether community case identification and management of severe pneumonia by oral antibiotics delivered through community health workers has the potential to reduce the number of infants dying at home.

METHODS: We did a cluster-randomised controlled trial in Matiari district of rural Sindh, Pakistan. Public-sector lady health workers (LHWs) undertook community case management of WHO-defined severe pneumonia. The children in intervention clusters with suspected pneumonia were screened by LHWs and those diagnosed with severe pneumonia were prescribed oral amoxicillin syrup (90 mg/kg per day in two doses) for 5 days at home. Children in control clusters were given one dose of oral co-trimoxazole and were referred to their nearest health facility for admission and intravenous antibiotics, as per government policy. In both groups, follow-up visits at home were done at days 2, 3, 6, and 14 by LHW. The primary outcome was treatment failure by day 6 after enrolment. We matched and randomly allocated 18 clusters (union councils, the smallest administrative unit of the district) to either intervention and control using a computer-generated randomisation scheme. Analyses were done per-protocol. This trial is registered with ClinicalTrials.gov, number NCT01192789.

FINDINGS: 2341 children in intervention clusters and 2069 children in control clusters participated in the study, enrolled between Feb 13, 2008, and March 15, 2010. We recorded 187 (8%) treatment failures by day 6 in the intervention group and 273 (13%) in the control group. After adjusting for clustering, the risk difference for treatment failure was -5.2% (95% CI -13.7% to 3.3%). We recorded three deaths, two by day 6 and one between days 7 and 14. We recorded no serious adverse events.

INTERPRETATION: Public sector LHWs in Pakistan were able to satisfactorily diagnose and treat severe pneumonia at home in rural Pakistan. This strategy might effectively reach children with pneumonia in settings where referral is difficult, and it could be a key component of community detection and management strategies for childhood pneumonia.



Comment

These two studies above were supported by the same research group in Pakistan, and demonstrate the effectiveness of trained community health workers in diagnosing and treating acute respiratory infection. The Lady Health Workers of Pakistan are local women with at least 8 years schooling, who undergo a 15 month training program, and are linked to formal health services closely, where they receive supplies of medications and other treatments. There is a

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program for ongoing training with monthly refresher sessions, and they are formally paid a salary of about \$45 per month. For these studies of pneumonia treatment, there was additional training in acute respiratory infection management, and the LHWs were given respiratory rate timers. The project itself replenished the antibiotics. Understanding the duration and nature of training, the support given to the community health workers, and the health systems support provided within the study are crucial to the wider implementation of this approach. Of nearly 29,981 children evaluated for inclusion in these 2 studies (of which 7663 fulfilled criteria), only 19 were excluded because they had very severe pneumonia, and 17 were excluded because of severe malnutrition. This, coupled with the very low death rate in the enrolled patients (4 deaths reported) suggests that the strategy is highly effective. If the LHWs had been under-recognising very severe pneumonia, then the number of deaths would be expected to be higher.

The safety of out-patient treatment of pneumonia depends on the context: having appropriately trained and supported community health workers, a reliable supply chain for antibiotics and other treatments, mechanisms to identify children with danger signs, hypoxaemia or other risk factors (such as severe malnutrition, HIV, neonates), and close links with a health facility for referral and replenishment of supplies.

Zinc and pneumonia

*** [BMC Med.](#) 2012 Feb 8;10:14.

Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial.

[Srinivasan MG](#), [Ndeezi G](#), [Mboijana CK](#), [Kiguli S](#), [Bimenya GS](#), [Nankabirwa V](#), [Tumwine JK](#).

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BACKGROUND: Pneumonia is a leading cause of children's deaths in developing countries and hinders achievement of the fourth Millennium Development Goal. This goal aims to reduce the under-five mortality rate, by two thirds, between 1990 and 2015. Few studies have examined the impact of zinc adjunct therapy on the outcome of childhood pneumonia. We determined the effect of zinc as adjunct therapy on time to normalization of respiratory rate, temperature and oxygen saturation. We also studied the effect of zinc adjunct therapy on case fatality of severe childhood pneumonia (as a secondary outcome) in Mulago Hospital, Uganda.

METHODS: In this double blind, randomized, placebo-controlled clinical trial, **352 children aged 6 to 59 months, with severe pneumonia were randomized to zinc (20 mg for children \geq 12 months, and 10 mg for those < 12 months) or a placebo once daily for seven days, in addition to standard antibiotics for severe pneumonia.** Children were assessed every six hours. Oxygen saturation was normal if it was above 92% (breathing room air) for more than 15 minutes. The respiratory rate was normal if it was consistently (more than 24 hours) below 50 breaths per minute in infants and 40 breaths per minute in children above 12 months of age. Temperature was normal if consistently below 37.5°C. The difference in case fatality was expressed by the risk ratio between the two groups.

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RESULTS: Time to normalization of the respiratory rate, temperature and oxygen saturation was not significantly different between the two arms. **Case fatality was 7/176 (4.0%) in the zinc group and 21/176 (11.9%) in the placebo group: Relative Risk 0.33 (95% CI 0.15 to 0.76). Relative Risk Reduction was 0.67 (95% CI 0.24 to 0.85), while the number needed to treat was 13. Among HIV infected children, case fatality was higher in the placebo (7/27) than in the zinc (0/28) group; RR 0.1 (95% CI 0.0, 1.0).** Among 127 HIV uninfected children receiving the placebo, case fatality was 7/127 (5.5%); versus 5/129 (3.9%) among HIV uninfected group receiving zinc: RR 0.7 (95% CI 0.2, 2.2). The excess risk of death attributable to the placebo arm (Absolute Risk Reduction or ARR) was 8/100 (95% CI: 2/100, 14/100) children. This excess risk was substantially greater among HIV positive children than in HIV negative children (ARR: 26 (95% CI: 9, 42) per 100 versus 2 (95% CI: -4, 7) per 100); P-value for homogeneity of risk differences = 0.006.

CONCLUSION: Zinc adjunct therapy for severe pneumonia had no significant effect on time to normalization of the respiratory rate, temperature and oxygen saturation. **However, zinc supplementation in these children significantly decreased case fatality. The difference in case fatality attributable to the protective effect of zinc therapy was greater among HIV infected than HIV uninfected children.** Given these results, zinc could be considered for use as adjunct therapy for severe pneumonia, especially among Highly Active Antiretroviral Therapynaïve HIV infected children in our environment.



[Pediatrics](#). 2012 Apr;129(4): 701-8. Epub 2012 Mar 5.

A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children.

[Basnet S](#), [Shrestha PS](#), [Sharma A](#), [Mathisen M](#), [Prasai R](#), [Bhandari N](#), [Adhikari RK](#), [Sommerfelt H](#), [Valentiner-Branth P](#), [Strand TA](#); [Zinc Severe Pneumonia Study Group](#).

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BACKGROUND AND OBJECTIVE: Diarrhea and pneumonia are the leading causes of illness and death in children <5 years of age. Zinc supplementation is effective for treatment of acute diarrhea and can prevent pneumonia. In this trial, we measured the efficacy of zinc when given to children hospitalized and treated with antibiotics for severe pneumonia.

METHODS: We enrolled 610 children aged 2 to 35 months who presented with severe pneumonia defined by the World Health Organization as cough and/or difficult breathing combined with lower chest indrawing. All children received standard antibiotic treatment and were randomized to receive zinc (10 mg in 2- to 11-month-olds and 20 mg in older children) or placebo daily for up to 14 days. The primary outcome was time to cessation of severe pneumonia.

RESULTS: Zinc recipients recovered marginally faster, but this difference was not statistically significant (hazard ratio = 1.10, 95% CI 0.94-1.30). Similarly, the risk of treatment failure was slightly but not significantly lower in those who received zinc (risk ratio = 0.88 95% CI 0.71-1.10).

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CONCLUSIONS: Adjunct treatment with zinc reduced the time to cessation of severe pneumonia and the risk of treatment failure only marginally, if at all, in hospitalized children.

[Indian J Pediatr.](#) 2011 Sep;78(9): 1085-90. Epub 2011 Jun 10.

[A randomized controlled trial of oral zinc in acute pneumonia in children aged between 2 months to 5 years.](#)

[Ganguly A](#), [Chakraborty S](#), [Datta K](#), [Hazra A](#), [Datta S](#), [Chakraborty J](#).

Department of Pharmacology, Institute of Post Graduate Medical Education & Research, Kolkata, India.

OBJECTIVE: To evaluate the effectiveness and safety of zinc supplementation as adjuvant in treatment of pneumonia.

METHODS: Ninety-eight children with acute bacterial pneumonia, aged between 2 months to 5 years, were studied in a randomized controlled single blind design. They received either zinc supplementation, as zinc acetate syrup, or placebo, as vitamin B-complex syrup, for 14 days, concomitantly with antimicrobial treatment (49 per group). Chest radiograph and blood tests were done for confirmation of diagnosis and severity of pneumonia was assessed by breathing rate, chest in-drawing and body temperature. Potentially immunosuppressed children or those with serious comorbidity were excluded. Follow-up was done daily while subjects were admitted (generally 7 days) and the final assessment made on the 14th day on out-patient basis.

RESULTS: Children enrolled in zinc and placebo groups were of comparable age [17 ± 10 and 10 ± 30 months (median \pm interquartile range) respectively] and sex distribution [34 (69.4%) vs 31 (63.3%) males respectively]. Duration of illness at diagnosis was also comparable. Patients supplemented with zinc showed no difference in clinical cure rate at 14 days when compared with placebo. Fast breathing was present after 1 wk of treatment in 49% subjects in zinc supplemented vs 43% on placebo ($p = 0.685$). There was also no difference in breathing rate at study end. Regarding fever, the mean temperature was $<99^{\circ}\text{F}$ in both groups at study end. Hemoglobin, total leukocyte count, standard liver function tests and creatinine showed no difference between groups either at baseline or at study end. There were no treatment emergent adverse events attributable to zinc.

CONCLUSIONS: Though well tolerated, the addition of zinc does not improve symptom duration or cure rate in acute bacterial pneumonia in under-five children.

Comment in

[Zinc in acute pneumonia in children: is it time to stop further trials?](#) [Indian J Pediatr. 2012]

Comment

In certain patient groups zinc may be effective in the treatment of severe pneumonia. In previous years this has been shown in large studies Bangladesh and in Nepal (Lancet 2004; 363(9422): 1683-1688, Pediatrics 2012; 129:doi:10.1542/peds.2010-3091). This year two small studies from India on the use of zinc in the treatment of severe pneumonia failed to show

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any beneficial effect (Ganguli, et al and Basnet, et al, above). These four studies from South Asia were in children with WHO-defined severe pneumonia (moderate pneumonia in PNG). The studies had very low mortality rates and high rates of viral infection as manifest by wheezing or virus isolation. A fifth controlled trial of zinc in the treatment of severe pneumonia, from Uganda (Srinivasan, et al, above), published this year in a population of children with high rates of HIV, malnutrition and bacterial pneumonia, showed a significant reduction in deaths in the zinc treated group. The dose given was 20mg per day until hospital discharge. This beneficial effect was especially strong in children with HIV. It is likely that in a zinc deficient population with high rates of malnutrition, bacterial pneumonia or HIV, zinc would have a significant benefit in the treatment of pneumonia.

Another study this year is zinc in the treatment of serious bacterial infection in infants in India. 10mg daily supplements of zinc or placebo were given to 655 infants who were being treated with antibiotics for suspected serious bacterial infection. Compared to the placebo group, children who were given zinc were 40% less likely to experience treatment failure, defined as needing to change antibiotics within a week or need for intensive care, or death.

Vitamin D and pneumonia

[Lancet](#). 2012 Apr 14;379(9824): 1419-27. Epub 2012 Apr 10.

[Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial.](#)

[Manaseki-Holland S](#), [Maroof Z](#), [Bruce J](#), [Mughal MZ](#), [Masher MI](#), [Bhutta ZA](#), [Walraven G](#), [Chandramohan D](#).

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BACKGROUND: Vitamin D has a role in regulating immune function, and its deficiency is a suggested risk factor for childhood pneumonia. Our aim was to assess whether oral supplementation of vitamin D(3) (cholecalciferol) will reduce the incidence and severity of pneumonia in a high-risk infant population.

METHODS: We did a randomised placebo-controlled trial to compare oral 100,000 IU (2.5 mg) vitamin D(3) with placebo given to children aged 1-11 months in Kabul, Afghanistan. Randomisation was by use of a computer-generated list. Vitamin D or placebo was given by fieldworkers once every 3 months for 18 months. Children presenting at the study hospital with signs of pneumonia had their diagnosis confirmed radiographically. Our primary outcome was the first or only episode of radiologically confirmed pneumonia. Our analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00548379.

FINDINGS: 1524 children were assigned to receive vitamin D(3) and 1522 placebo. There was no significant difference between the incidence of first or only pneumonia between the vitamin D (0.145 per child per year, 95% CI 0.129-0.164) and the placebo group (0.137, 0.121-0.155);

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the incidence rate ratio was 1.06 (95% CI 0.89-1.27). From 652 children during five separate periods of testing serum calcifediol, only one child in each of two testing periods had results greater than 375 nmol/L in the intervention group--a toxic level.

INTERPRETATIONS: Quarterly bolus doses of oral vitamin D(3) supplementation to infants are not an effective intervention to reduce the incidence of pneumonia in infants in this setting.



[Indian Pediatr.](#) 2011 Aug 15. pii: S097475591100214-1. [Epub ahead of print]

[Vitamin D Supplementation for Severe Pneumonia A Randomized Controlled Trial.](#)

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OBJECTIVE: To determine the role of oral vitamin D supplementation for resolution of severe pneumonia in under-five children.

DESIGN: Randomized double blind placebo-controlled trial.

SETTING: Inpatients from a tertiary care hospital.

PARTICIPANTS: Two hundred children [mean (SD) age: 13.9 (11.7) months; boys: 120] between 2 months to 5 years with severe pneumonia. Pneumonia was diagnosed in the presence of fever, cough, tachypnea (as per WHO cutoffs) and crepitations. Children with pneumonia and chest indrawing or at least one of the danger sign (inability to feed, lethargy, cyanosis) were diagnosed as having severe pneumonia. The two groups were comparable for baseline characteristics including age, anthropometry, socio-demographic profile and clinical and laboratory parameters.

INTERVENTION: Oral vitamin D (1000 IU for <1 year and 2000 IU for >1 year) (n=100) or placebo (lactose) (n=100) once a day for 5 days, from enrolment. Both the groups received antibiotics as per the Indian Academy of Pediatrics guidelines, and supportive care (oxygen, intravenous fluids and monitoring).

OUTCOME VARIABLES: Primary: time to resolution of severe pneumonia. SECONDARY: duration of hospitalization and time to resolution of tachypnea, chest retractions and inability to feed.

RESULTS: Median duration (SE, 95% CI) of resolution of severe pneumonia was similar in the two groups [vitamin D: 72 (3.7, 64.7-79.3) hours; placebo: 64 (4.5, 55.2-72.8) hours]. Duration of hospitalization and time to resolution of tachypnea, chest retractions, and inability to feed were also comparable between the two groups.

CONCLUSION: Short-term supplementation with oral vitamin D (1000-2000 IU per day for 5 days) has no beneficial effect on resolution of severe pneumonia in under-five children. Further

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studies needs to be conducted with higher dose of Vitamin D or longer duration of supplementation to corroborate these findings.

Comment

Despite strong evidence that children with vitamin D deficiency are at increased risk of pneumonia and bronchiolitis in some populations (Pediatric Pulmonology 2009; 44:1207–1215; Archives of Disease in Childhood, 1975;50; 63; www.pediatrics.org/cgi/doi/10.1542/peds.2010-3054) controlled trials such as these two from this year (above) have not shown a beneficial effect of vitamin D as adjuvant therapy for severe pneumonia.

Other preventative measures

[Influenza Other Respi Viruses](#). 2011 Jul;5(4): 256-67. doi: 10.1111/j.1750-2659.2011.00205.x. Epub 2011 Feb 17.

[Findings from a household randomized controlled trial of hand washing and face masks to reduce influenza transmission in Bangkok, Thailand.](#)

[Simmerman JM](#), [Suntarattiwong P](#), [Levy J](#), [Jarman RG](#), [Kaewchana S](#), [Gibbons RV](#), [Cowling BJ](#), [Sanasuttipun W](#), [Maloney SA](#), [Uyeki TM](#), [Kamimoto L](#), [Chotipitayasunondh T](#).

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BACKGROUND: Evidence is needed on the effectiveness of non-pharmaceutical interventions (NPIs) to reduce influenza transmission.

METHODOLOGY: We studied NPIs in households with a febrile, influenza-positive child. Households were randomized to control, hand washing (HW), or hand washing plus paper surgical face masks (HW + FM) arms. Study nurses conducted home visits within 24 hours of enrollment and on days 3, 7, and 21. Respiratory swabs and serum were collected from all household members and tested for influenza by RT-PCR or serology.

PRINCIPAL FINDINGS: Between April 2008 and August 2009, 991 (16.5%) of 5995 pediatric influenza-like illness patients tested influenza positive. Four hundred and forty-two index children with 1147 household members were enrolled, and 221 (50.0%) were aged <6 years. Three hundred and ninety-seven (89.8%) households reported that the index patient slept in the parents' bedroom. The secondary attack rate was 21.5%, and 56/345 (16.3%; 95% CI 12.4-20.2%) secondary cases were asymptomatic. Hand-washing subjects reported 4.7 washing episodes/day, compared to 4.9 times/day in the HW + FM arm and 3.9 times/day in controls ($P = 0.001$). The odds ratios (ORs) for secondary influenza infection were not significantly different in the HW arm (OR = 1.20; 95% CI 0.76-1.88; $P=0.442$), or the HW + FM arm (OR = 1.16; 95% CI .0.74-1.82; $P = 0.525$).

CONCLUSIONS: **Influenza transmission was not reduced by interventions to promote hand washing and face mask use. This may be attributable to transmission that occurred before the intervention, poor facemask compliance, little difference in hand-washing**

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frequency between study groups, and shared sleeping arrangements. A prospective study design and a careful analysis of sociocultural factors could improve future NPI studies.

[Nicotine Tob Res.](#) 2011 Sep;13(9): 840-7. Epub 2011 Apr 18.

[Reduction of secondhand smoke exposure among healthy infants in Iran: randomized controlled trial.](#)

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INTRODUCTION: The objective of this study was to assess whether counseling both mothers and fathers reduces their infants' exposure to secondhand smoke (SHS).

METHODS: Participants were 130 nonsmoking children aged less than 1 year, exposed to their fathers' or mothers' smoking, and recruited from a health center in southern Tehran. Eligible families were randomly assigned to intervention or control group. Infant urine samples were collected, and parents were interviewed at baseline and at a 3-month follow-up in each of the 2 groups. Mothers of the intervention group were provided 3 counseling sessions, one of which was face to face and 2 of which were by telephone. Fathers were provided 3 counseling sessions by telephone. Parents were also given an educational pamphlet and a sticker depicting a smoke-free home. The control group received usual care. Changes in infant urinary cotinine levels, parental cigarette consumption in the presence of the child, and home- and car-smoking bans were assessed.

RESULTS: The intervention was effective in reducing infant urinary cotinine levels (1-tailed $p = .029$). There was a greater decrease in the total daily cigarette consumption in the presence of the child in the intervention group compared with the control group, and the differences between the 2 groups were statistically significant (1-tailed $p = .03$). While the differences between home-smoking bans in the 2 groups were statistically significant (1-tailed $p = .049$), the differences between car-smoking bans did not reach significance. Conclusion: Counseling similar to that employed in other countries can reduce infant exposure to SHS, suggesting generalizability.



Adolescent health

(See also Asthma, Diabetes)

[JAMA.](#) 2011 Aug 3;306(5): 503-12.

[Community-implemented trauma therapy for former child soldiers in Northern Uganda: a randomized controlled trial.](#)

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CONTEXT: The psychological rehabilitation of former child soldiers and their successful reintegration into postconflict society present challenges. Despite high rates of impairment, there have been no randomized controlled trials examining the feasibility and efficacy of mental health interventions for former child soldiers.

OBJECTIVE: To assess the efficacy of a community-based intervention targeting symptoms of posttraumatic stress disorder (PTSD) in formerly abducted individuals.

DESIGN, SETTING, AND PARTICIPANTS: Randomized controlled trial recruiting 85 former child soldiers with PTSD from a population-based survey of 1113 Northern Ugandans aged 12 to 25 years, conducted between November 2007 and October 2009 in camps for internally displaced persons. Participants were randomized to 1 of 3 groups: narrative exposure therapy (n = 29), an academic catch-up program with elements of supportive counseling (n = 28), or a waiting list (n = 28). Symptoms of PTSD and trauma-related feelings of guilt were measured using the Clinician-Administered PTSD Scale. The respective sections of the Mini International Neuropsychiatric Interview were used to assess depression and suicide risk, and a locally adapted scale was used to measure perceived stigmatization. Symptoms of PTSD, depression, and related impairment were assessed before treatment and at 3 months, 6 months, and 12 months postintervention.

INTERVENTION: Treatments were carried out in 8 sessions by trained local lay therapists, directly in the communities.

MAIN OUTCOME MEASURES: Change in PTSD severity, assessed over a 1-year period after treatment. Secondary outcome measures were depression symptoms, severity of suicidal ideation, feelings of guilt, and perceived stigmatization.

RESULTS: PTSD symptom severity (range, 0-148) was significantly more improved in the narrative exposure therapy group than in the academic catch-up (mean change difference, -14.06 [95% confidence interval, -27.19 to -0.92]) and waiting-list (mean change difference, -13.04 [95% confidence interval, -26.79 to 0.72]) groups. Contrast analyses of the time × treatment interaction of the mixed-effects model on PTSD symptom change over time revealed a superiority of narrative exposure therapy compared with academic catch-up ($F(1,234.1) = 5.21$, $P = .02$) and wait-listing ($F(1,228.3) = 5.28$, $P = .02$). Narrative exposure therapy produced a larger within-treatment effect size (Cohen $d = 1.80$) than academic catch-up ($d = 0.83$) and wait-listing ($d = 0.81$).

CONCLUSION: Among former Ugandan child soldiers, short-term trauma-focused treatment compared either with an academic catch-up program including supportive counseling or with wait-listing resulted in greater reduction of PTSD symptoms.



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[J Neurosurg Pediatr.](#) 2012 May;9(5):562-8.

[Impact of an injury prevention program on teenagers' knowledge and attitudes: results of the Pense Bem-Caxias do Sul Project.](#)

[Falavigna A](#), [Teles AR](#), [Velho MC](#), [Medeiros GS](#), [Canabarro CT](#), [de Braga GL](#), [Barazzetti DO](#), [Vedana VM](#), [Kleber FD](#).

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OBJECT: Trauma is the leading cause of mortality and morbidity in children, young people, and working-age adults. Because of the high incidence of intentional and unintentional injuries in young people, it is necessary to implement injury-prevention programs and measure the efficacy of these initiatives. The authors evaluated the effectiveness of an injury-prevention program in high school students in a city in southern Brazil.

METHODS: In a randomized controlled study, 1049 high school students were divided into a control group and intervention group. The study was conducted in the following 3 stages: a questionnaire was applied 1 week before the educational intervention (P0), shortly after the intervention (P1), and 5 months later (P3). In the control group, a questionnaire based on the Pense Bem Project was applied at the 3 time stages, without any intervention between the stages.

RESULTS: The postintervention analysis evidenced a slight change in knowledge about unintentional spinal cord and brain injuries. Regarding attitudes, the only significant improvement after the intervention lecture was in the use of helmets, which remained high 5 months later. A substantial number of students only partially agreed with using safety behaviors. The only significant postintervention change was the major agreement to check swimming pool depth before entering the water (P0 89% and P1 97.8%, $p < 0.001$; P2 92.8%, $p = 0.005$).

CONCLUSIONS: An educational intervention based on a single lecture improved students' knowledge of traumatic brain and spinal cord injuries, but this type of intervention did not modify most attitudes toward injury prevention.



[J Clin Nurs.](#) 2011 Nov;20(21-22): 3081-91. doi: 10.1111/j.1365-2702.2011.03831.x. Epub 2011 Aug 26.

[A randomised trial on pubertal development and health in China.](#)

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BACKGROUND: Puberty signifies noticeable physical, psychosocial and sexual development. It is crucial to help adolescents reach an understanding about puberty and related health issues. Considering the sexually conservative culture in some areas, to explore appropriate ways to address sexuality and health-related concerns during puberty is of interest to all stakeholders.

AIMS: This study aimed to examine the effectiveness of the ecological approach to improve adolescents' understanding about puberty and related health risks.

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DESIGN: Modified Solomon four group design.

METHODS: Two Grade7 classes were randomly selected to form experiment and control group, respectively. A two-hour seminar and a brochure about health and development during puberty were provided, and some students, parents and instructors in the experimental group commented on the intervention. Pre- and post-tests were conducted to measure students' pubertal development status and their knowledge, attitudes and behaviours related to puberty.

RESULTS: Students (n = 228) were aged 13.0 years (SD 0.45). The majority was categorised at the stage of mid-puberty or later, and approximately 11.2% of 116 girls and 22.3% of 112 boys were classified as overweight or obese according to body mass index. No significant changes were identified within or between groups about knowledge, attitudes and behaviours related to puberty and health before and after the intervention. The intervention was considered helpful, and an enriched delivery was required.

CONCLUSIONS: Although the overall feedback was positive, this ecological approach to adolescent health and development targeting at Grade 7 students failed to generate significant effects on students' knowledge, attitudes and behaviours surrounding puberty and health.

RELEVANCE TO CLINICAL PRACTICE: This study reveals that sexuality, particularly romantic relationships during puberty, may be perceived negatively in the local society. There is a need for school nurses to help all relevant people to understand and respond to sexuality-related concerns in a cultural appropriate way.

Allergy

[Am J Otolaryngol](#). 2011 Sep-Oct;32(5): 402-7. Epub 2010 Oct 13.

Herbal treatment of allergic rhinitis: the use of *Nigella sativa*.

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BACKGROUND AND AIMS: Allergic rhinitis is the most common chronic and allergic disease, especially in children. This study aimed to investigate the anti-inflammatory effects of *Nigella sativa* and its effects on inflammatory factors in patients with allergic rhinitis symptoms and the process their clinical study charges.

SETTING: The present study is a clinical trial that conducted as prospective and double blind with descriptive analytic.

MATERIALS AND METHODS: The sample included 66 patients (case and placebo) with allergic rhinitis exposed to *N. sativa* oil. Individual characteristics, including age and sex, and characteristics of the disease, including nasal congestion, runny nose, itchy nose, and sneezing attacks, were evaluated. From the start of the study, that is, day 0, up to the end of the study, that is, day 30, an observer completed the symptoms severity questionnaire. STATISTICAL ANALYSIS: Data were presented as means \pm SEM. Comparisons between groups were

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performed by using paired Student t test. Differences were considered significant if P values are less than .05 and .01.

RESULTS: In the present study, 66 patients with allergic rhinitis, including 22 males (33.3%) and 44 females (66.7%) with a mean age of 47.19 years, were included. Immunoglobulin E total of more than 100 was reported in 38 patients before treatment. Immunoglobulin E in nasal wash from 7 patients was observed and was not measurable in 59 cases. Only 6.1% of the study population had nasal mucosal eosinophil.

CONCLUSION: The results show that *N. sativa* could reduce the presence of the nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor during the first 2 weeks (day 15). The present findings are consistent with evidence that the antiallergic effects of *N. sativa* components could be attributed to allergic rhinitis. Moreover, *N. sativa* should be considered for treating allergic rhinitis when the effects of other antiallergic drugs need to be avoided.

Comment

Nigella sativa is a flowering plant common in South and South West Asia. Its seeds are referred to as Black Cumin, and its oil has been used for a variety of medicinal purposes for centuries in Asia, the Middle East, and Africa. Read the fascinating description at:

http://en.wikipedia.org/wiki/Nigella_sativa.

[Curr Med Res Opin.](#) 2012 Jan;28(1): 121-30. Epub 2011 Nov 30.

[Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo in the treatment of perennial allergic rhinitis.](#)

[Sastre J, Mullol J, Valero A, Valiente R; Bilastine Study Group.](#)

[Arnolt RG, Bailleau R, Crisci C, de Falco A, Gandur A, Gómez M, Jares E, Ivancevich JC, Lisanti M, Medina I, Rojido G, Vucovich P, Yáñez A, Neffen H, Ramón G, Adamek-Guzik T, Janiak R, Kuna P, Mazur S, Panaszek B, Rys D, Skucha W, Bumbacea R, Samuilla S, Berghea C, Iacomi A, Ivan P, Popescu CR, Dragusin R, Zainea V, Negrila M, Davis G, Myers L, Groenewald M, Hofmayr LM, Jacobsz LA, Jacovides A, Gabriel GH, Moolman JZ, van der Walt WA, Janari EL, Jearey PL, Clarke D, Datzel GJ, Lakha DR, MacLeod AH, Makan HA, Desai UG, Mans WE, Nel AM, Pillay S, Potter PC, Emanuel SA, Hawarden ZF, Smit JD, Nel PR, Snyman JR, Cuyler R, Mareledwane NG, Meeding JP, Ratau NP, Vawda ZF, Viljoen A, de Molina M, Pinto E, Basomba A, Villamanzo IG, Giner A, Almero R, Baltasar M, Vidal C, Vázquez V, Justicia JL, Barasona MJ, Blanco C, Figueroa J.](#)

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OBJECTIVE: Bilastine is a non-sedating second-generation H(1) antihistamine with proven efficacy and safety in the treatment of patients with seasonal allergic rhinitis and urticaria. The objective of this study was to demonstrate the efficacy and safety of bilastine in patients with perennial allergic rhinitis (PAR).

METHODS: In a multicenter, randomized, placebo-controlled, double-blind, parallel-group study, patients with symptomatic PAR (n = 650) from Argentina, Europe, and South Africa received bilastine 20 mg, cetirizine 10 mg, or placebo once daily for 4 weeks. The primary

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efficacy outcome was the mean area under the curve (AUC) of reflective total 6-symptom scores (rT6SS) from baseline visit to day 28 (D28). Secondary outcome measures included mean AUC of instantaneous total 6-symptom scores (iT6SS), and mean AUCs of reflective and instantaneous total 4-nasal symptom scores (T4NSS) and total 2-ocular symptom scores (T2OSS) from baseline to D28. An open-label extension phase evaluated the safety of bilastine 20 mg administered to patients ($n = 513$) for one year.

RESULTS: In the overall population no significant differences in efficacy outcomes were found between active treatments and placebo. On account of the high placebo response in South Africa, a post-hoc analysis was conducted. This analysis demonstrated that statistically significant differences existed between active treatments and placebo in the mean AUC of rT6SS ($p < 0.05$) and T4NSS ($p < 0.02$), respectively, from baseline to D28 visit for the intent-to-treat population in patients from Europe and Argentina, whereas the difference was not statistically significant in South Africa. Whether this is related to differences in the demographic or clinical characteristics of South African patients (they had PAR for longer and reported more severe symptoms) and/or the disease management process compared with their European and Argentinean counterparts warrants further investigation.

CONCLUSIONS: A post-hoc analysis indicated that bilastine and cetirizine were similarly effective and more effective than placebo during a 4-week treatment period in patients with PAR. In addition, bilastine was shown to be safe and well-tolerated over a 1-year treatment period.

[Int J Immunopathol Pharmacol. 2012 Jan-Mar;25\(1\): 231-7.](#)

[A comparative study of loratadine syrup and cyproheptadine HCL solution for treating perennial allergic rhinitis in Taiwanese children aged 2-12 years.](#)

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We assessed the efficacy of loratadine syrup compared with cyproheptadine HCl solution for treating children aged from 2 to 12 years with perennial allergic rhinitis (PAR) in Taiwan. Sixty children with mite-induced PAR were enrolled and randomly placed into two treatment groups: loratadine syrup or cyproheptadine HCl solution. Treatment efficacy and symptom changes from baseline to post-treatment were evaluated by total symptom scores and visual analogue scales (VAS) during a 2-week period. There were no differences in age, gender, height, or weight between the two groups. After 2 weeks of treatment, there was a significantly greater reduction in symptom scores in the loratadine group than in the cyproheptadine group ($p < 0.001$). Clinical and subjective VAS showed significant differences in percentage changes from baseline between the loratadine and cyproheptadine groups at all time points (all $p < 0.001$, in favor of loratadine). Clinical VAS change at week 1: 95.1 vs 11.3; subjective VAS change at week 1: 88.6 vs 13.6; clinical VAS change at week 2: 125.5 vs 18.3; subjective VAS change at week 2: 101.4 vs 7.1. Thus, loratadine was superior to cyproheptadine for alleviating both nasal and non-nasal symptoms of perennial allergic rhinitis in Taiwanese children aged 2-12 years.

Anaemia and iron deficiency

[Econ Hum Biol.](#) 2012 Apr 30. [Epub ahead of print]

[Iron status, malaria parasite loads and food policies: Evidence from sub-Saharan Africa.](#)

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This brief article investigates the consequences of improving children's iron status for malaria parasite loads by analyzing data from Cote d'Ivoire, Zambia, and Tanzania; the treatment of iron deficiencies has been argued to flare up malaria in under-nourished populations. The data from a randomized controlled trial in Cote d'Ivoire showed statistically insignificant effects of the consumption of iron-fortified biscuits on children's malaria parasite loads. Second, nutrient intakes data from Zambia showed insignificant correlations and associations between children's iron and folate intakes and malaria parasite loads. Third, malaria parasite loads did not change significantly for Tanzanian children receiving anthelmintic treatment; malaria loads were lower for older children and for those using bed nets. Overall, the evidence from sub-Saharan African countries suggests that small improvements in iron status achieved via suitable food policies are unlikely to have detrimental effects for children's malaria parasite loads.

Comment

There is evidence from a large RCT in previous years that routine iron supplementation in some malaria-endemic communities increases the risk of malaria and rates of hospitalisation. However, as the summary of trials in Africa suggests, there is no evidence that food fortification with iron, use of iron-containing sprinkles, or giving iron supplementation to children with proven iron deficiency increases malaria severity or parasite load in a way that is clinically significant. The reasons for the discrepancy may be in the dose actually ingested (being greater for iron supplementation than for fortification), the different populations studied, or the size of trials (trials may be powered to identify beneficial effects, but not large enough to identify adverse effects).

[Am J Clin Nutr.](#) 2011 Nov;94(5): 1202-10. Epub 2011 Sep 21.

[Micronized ferric pyrophosphate supplied through extruded rice kernels improves body iron stores in children: a double-blind, randomized, placebo-controlled midday meal feeding trial in Indian schoolchildren.](#)

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BACKGROUND: Micronized ferric pyrophosphate (MFPP) in extruded rice kernels mixed in a rice-based meal could be an effective strategy for improving iron status of children in India.

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OBJECTIVE: The objective was to determine the impact of MFPP supplied through extruded rice kernels in a rice-based meal on iron status of children participating in the midday meal (MDM) scheme in India.

DESIGN: The sensory characteristics of cooked rice containing MFPP in extruded rice kernels, in vitro availability, and loss of iron during cooking from a typical MDM consisting of 125 g rice (dry weight) containing 19 mg Fe [fortified rice (FR); normal rice mixed with Ultra Rice (extruded kernels containing MFPP of ~3.14- μ m mean particle size)] in comparison with unfortified rice (UFR) were tested. A double-blind, 8-mo, placebo-controlled trial was conducted in 5-11-y-old schoolchildren (n = 140) who were randomly assigned to receive either an FR-MDM or a UFR-MDM. Average consumption amounts of the MDM, height, weight, hemoglobin, ferritin, and C-reactive protein were measured at baseline and at 8 mo.

RESULTS: The sensory qualities of cooked FR and UFR were similar. The in vitro iron availability from FR-MDM (1.3%) was significantly ($P < 0.05$) lower than that from UFR-MDM (3.3%). Providing FR-MDM to the schoolchildren for 8 mo improved ferritin significantly ($P < 0.001$), by $8.2 \pm 2.10 \mu\text{g/L}$. However, the increase in hemoglobin was similar between groups (FR: $0.99 \pm 0.10 \text{ g/dL}$; UFR: $1.15 \pm 0.10 \text{ g/dL}$), which suggests that other factors beyond additional iron intake had a large influence on hemoglobin concentration. The prevalence of iron deficiency decreased significantly ($P < 0.05$) in the FR group (33-14%) and increased marginally in the UFR group (31-37%). The prevalence of anemia and iron deficiency anemia was similar between groups at baseline and at 8 mo.

CONCLUSION: Regular intake of 19 mg Fe/d in MFPP supplied through extruded rice kernels improves iron stores and reduces iron deficiency among schoolchildren in India.



[Indian J Public Health](#). 2011 Oct-Dec;55(4): 332-5.

[A study on the role of parental involvement in control of nutritional anemia among children of free primary schools in a rural area of West Bengal.](#)

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An intervention study was conducted among students of three randomly selected free primary schools in rural West Bengal to assess the effect of health-nutrition education for behavior modification of parents on nutritional anemia of children. Clinically anemic students were school-wise randomized into 'groups of two' and intervened with anthelmintic, iron-folic acid (IFA) pediatric tablet and health-nutrition education by reoriented teachers. Parents of study group were involved in behavior change processes. Baseline overall prevalence of anemia was 64.4%. After IFA therapy, prevalence of anemia was not found to differ between two groups ($\chi^2 = 2.68$, $P > 0.05$, $RR = 0.48$, 95% C.I $0.2 < RR < 1.19$) while reducing 52.2% of relative risk. Reassessment after six months showed significantly lower prevalence in study group ($\chi^2 =$

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18.14, $P < 0.05$, $RR = 0.20$, 95% C.I. $0.08 < RR < 0.49$). Parental involvement for life style and dietary modification may curb childhood anemia.



[Public Health Nutr.](#) 2011 Aug;14(8): 1450-7. Epub 2010 Oct 5.

The impact of training for day-care educators on childhood anaemia in nurseries: an institutional randomised clinical trial.

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OBJECTIVE: To test the impact of training for educators on the health of children enrolled in public and philanthropic day-care nurseries.

DESIGN: A randomised, institutional, non-blind clinical trial was conducted. An educational intervention was performed in four day-care centres and the control group consisted of four other day-care centres. Interviews with the mothers, collection of blood from the children by digital puncture and anthropometry were performed. The chosen indicator for the improvement of health was anaemia (Hb < 11 g/dl). An unconditional logistic regression model was set for the risk factors for anaemia, considering associations with $P \leq 0.05$ as statistically significant.

SETTING: Eight day-care centres in the city of Sao Paulo, Brazil. **SUBJECTS:** Two hundred and fifty-two children from day-care nurseries.

RESULTS: The children from the day-care centres that were not subject to intervention presented a 2.11 times greater risk (95% CI 1.04, 4.30; $P = 0.40$) of having anaemia at the end of the study independent of the control variables (sex, age, time in the day-care centre, anaemia at the beginning of the study, maternal age, use of oral iron supplements, number of siblings, per capita family income, use of antibiotics and the necessity of avoidable hospitalisations) used in the construction of the final logistical model.

CONCLUSIONS: The assessed educational intervention promoted significant changes in the health status of the children, reinforcing the importance of training for professionals who care for young children in day-care centres in developing countries in order to promote child health.

Anaesthesia and intensive care

(See also Treatment of severe malaria)

[Indian J Anaesth.](#) 2012 Mar;56(2): 145-150.

[Intravenous infusion of ketamine-propofol can be an alternative to intravenous infusion of fentanyl-propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures.](#)

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BACKGROUND: Paediatric patients often present with different painful conditions that require immediate surgical interventions. Despite a plethora of articles on the ketamine-propofol combination, comprehensive evidence regarding the suitable sedoanalgesia regime is lacking due to heterogeneity in study designs.

METHODS: This prospective, randomized, double-blind, active-controlled trial was conducted in 100 children, of age 3-14 years, American Society of Anesthesiologist physical status IE-IIe, posted for emergency short surgical procedures. Patients were randomly allocated to receive either 2 mL of normal saline (pre-induction) plus calculated volume of drug from the 11 mL of ketamine-propofol solution for induction (group PK, n=50) or fentanyl 1.5 µg/kg diluted to 2 mL with normal saline (pre-induction) plus calculated volume of drug from the 11 mL of propofol solution for induction (group PF, n=50). In both the groups, the initial bolus propofol 1 mg/kg i.v. (assuming the syringes contained only propofol, for simplicity) was followed by adjusted infusion to achieve a Ramsay Sedation Scale score of six. Mean arterial pressure (MAP) was the primary outcome measurement.

RESULTS: Data from 48 patients in group PK and 44 patients in group PF were available for analysis. Hypotension was found in seven patients (14.6%) in group PK compared with 17 (38.6%) patients in group PF (P=0.009). Intraoperative MAP was significantly lower in group PF than group PK when compared with baseline.

CONCLUSION: The combination of low-dose ketamine and propofol is more effective and a safer sedoanalgesia regimen than the propofol-fentanyl combination in paediatric emergency short surgical procedures in terms of haemodynamic stability and lesser incidence of apnoea.

[Singapore Med J. 2011 Jul;52\(7\): 512-6.](#)

[Low- versus high-dose combination of midazolam-ketamine for oral premedication in children for ophthalmologic surgeries.](#)

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Erratum in

Singapore Med J. 2011 Sep;52(9): 704.

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INTRODUCTION: Midazolam and ketamine are useful for oral premedication in children to allay anxiety. We compared the effects of midazolam with a combination of high- and low-dose ketaminemidazolam as an oral premedication.

METHODS: This is a randomised, controlled prospective study conducted in 87 children who were scheduled for ophthalmologic surgeries. Group M received oral midazolam 0.5 mg/kg, Group MKL received oral midazolam 0.25 mg/kg and ketamine 3 mg/kg, and Group MKH received midazolam 0.5 mg/kg and ketamine 6 mg/kg. Standard general anaesthesia technique was used. Sedation levels and ease of parental separation were noted.

RESULTS: A linear increasing trend in sedation was seen in the preoperative sedation scores of all the three groups. At 30 minutes, 23 children in Group MKH had good sedation scores as opposed to 20 in Group MKL and 12 in Group M. The best parental separation time was much shorter in the combination groups. There were no statistically significant differences in the parental separation scores, mean response to induction and mask acceptance. The time to reach Aldrete score of 10 was shorter in Group MKL (22 +/- 5 min) and Group M (36 +/- 1 min) compared to Group MKH (52 +/- 2 min). Group MKH had a higher incidence of excessive salivation compared with the other groups.

CONCLUSION: A combination of low-dose midazolam and ketamine is as effective as high-dose midazolam and ketamine for achieving optimum anxiolysis and a faster recovery, with a lower incidence of excessive salivation in children undergoing ophthalmic surgery.



[J Clin Pediatr Dent.](#) 2011 Summer;35(4): 415-20.

[A comparative evaluation of intranasal midazolam, ketamine and their combination for sedation of young uncooperative pediatric dental patients: a triple blind randomized crossover trial.](#)

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OBJECTIVE: The purpose of this study was to evaluate and compare the efficacy and safety of intranasal (IN) administration of midazolam (M), ketamine (K) and their combination (MK) to produce moderate sedation in young, uncooperative pediatric dental patients.

STUDY DESIGN: In this three stage crossover trial forty five uncooperative ASA type-1 children, who required dental treatment, were randomly assigned to receive one of the three drugs/combination by IN route during three subsequent visits. The efficacy and safety of the agents were assessed by overall success rate and by monitoring of vital signs, respectively.

RESULTS: The onset of sedation was rapid with K as compared to M and MK. The difference was statistically significant ($P < 0.01$) between K and M. The overall success rate was 89% with

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K, MK was 84% and 69% with M. The difference between the overall success rates of K and M was statistically significant ($P < 0.01$). Vital signs were within physiological limits and there were no significant adverse effects with any medication.

CONCLUSIONS: M, K and MK are safe and effective by IN route to produce moderate sedation for providing dental care to pediatric dental patients who have been otherwise indicated for treatment under general anesthesia.

[J Anaesthesiol Clin Pharmacol.](#) 2012 Apr;28(2): 185-9.

[Efficacy of clonidine as an adjuvant to ropivacaine for caudal analgesia in children undergoing subumbilical surgery.](#)

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CONTEXT: The use of clonidine as an adjuvant to ropivacaine in different concentrations through the caudal space has been shown to improve the analgesic efficacy of local anesthetics.

AIMS: The purpose of our study was to compare the efficacy of ropivacaine 0.1% with clonidine 1 mcg/kg to that of plain 0.1% and 0.2% ropivacaine for caudal analgesia in children.

SETTINGS AND DESIGN: Prospective, double blind, randomized controlled trial.

MATERIALS AND METHODS: Sixty children in the age group of 1-6 years undergoing subumbilical surgeries were included in the study. Group A received 1 ml/kg of 0.1% ropivacaine, group B received 1 ml/kg of 0.1% ropivacaine with clonidine 1 mcg/kg, and group C received 1 ml/kg of 0.2% ropivacaine.

RESULTS: The mean duration of analgesia was 243.7 ± 99.29 min in group A, 590.25 ± 83.93 min in group B, and 388.25 ± 82.35 min in group C. The duration of analgesia was significantly prolonged in group B compared to groups A and C with the P value of 0.001. At 8 h, all the 20 children in group A had received the first rescue analgesic compared to 18 children in group C and 3 children in group B. The duration of motor blockade after extubation was 30.6 ± 7.8 min and was noted only in group C. Only 1 child in group B received two rescue medications compared to 15 (75%) children in group A and 8 (40%) children in group C. None of the groups were treated for bradycardia or hypotension and no significant sedation was noted.

CONCLUSIONS: Clonidine 1 mcg/kg with ropivacaine 0.1% prolongs the duration and quality of analgesia compared to plain ropivacaine 0.1% and 0.2% without any significant sedation.

[Pediatr Crit Care Med.](#) 2012 Mar;13(2): 131-5.

Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children.

Randomised trials in child health in developing countries 2011-12

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OBJECTIVE: To compare daily interruption vs. continuous sedative infusions in mechanically ventilated children with respect to lengths of mechanical ventilation and intensive care unit stay.

DESIGN: Prospective randomized controlled trial.

SETTING: Pediatric intensive care unit of a tertiary care teaching and referral hospital.

PATIENTS: One hundred two patients mechanically ventilated for >48 hrs.

INTERVENTIONS: Patients were randomized to receive either continuous (group 1) or interrupted (group 2) sedative infusion (midazolam bolus of 0.1 mg/kg, followed by infusion, to achieve a Ramsay score of 3-4). Each patient in group 2 had daily interruption of infusion at 8:00 AM till he/she became fully awake (response to verbal commands) or so agitated/uncomfortable that he/she needed restarting of infusion (whichever was earlier) at a dose 50% less than the previous dose. Primary outcome variables were the lengths of mechanical ventilation and intensive care unit stay, while the number and percentage of days awake on sedative infusions, frequency of adverse events, and total dose of sedatives required were the secondary outcome variables.

MEASUREMENTS AND MAIN RESULTS: Of the 102 patients included in the study, 56 were randomized into the continuous sedation protocol and 46 into the interrupted sedation protocol. Both were statistically similar with respect to demography, primary diagnosis, severity of illness score (Pediatric Risk of Mortality I and III), indication for mechanical ventilation, and initial ventilatory variables except that the patients under the interrupted arm had lower peak inspiratory pressure and positive end-expiratory pressure requirements at the start of ventilation ($p = .002$ and $p = .028$, respectively). The mean (SD) length of mechanical ventilation in the interrupted sedation protocol was significantly less than that in the continuous sedation protocol (7.0 ± 4.8 days vs. 10.3 ± 8.4 days; $p = .021$). Similarly, the difference in the median duration of pediatric intensive care unit stay was significantly less in the interrupted sedation as compared to the continuous sedation protocol (10.7 days vs. 14.0 days; $p = .048$). The mean total dose of midazolam and the total calculated cost of midazolam in the former were significantly less compared to those of the latter (7.1 ± 4.7 mL vs. 10.9 ± 6.9 mL, $p = .002$; 4827 \pm 5445 rupees vs. 13,865 \pm 25,338 rupees, $p = .020$). The frequencies of adverse events in both the groups were however similar.

CONCLUSION: The length of mechanical ventilation, duration of intensive care unit stay, total dose of midazolam, and average calculated cost of the therapy were significantly reduced in the interrupted as compared to the continuous group of sedation.

Comment

Interruption of sedation might benefit patients in intensive care by encouraging earlier weaning from mechanical ventilation, reducing muscle atrophy from increased movement, encouraging patient-triggered modes of ventilation rather than full ventilation with heavy continuous sedation, reducing nosocomial pneumonia, and reducing pressure areas. The downside might be increasing the risk of unplanned extubation.

[Paediatr Anaesth](#). 2011 Nov;21(11): 1142-7. doi: 10.1111/j.1460-9592.2011.03632.x. Epub 2011 Jun 21.

[Fiber-optic assessment of LMA position in children: a randomized crossover comparison of two techniques.](#)

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BACKGROUND: This crossover study compared fiber-optic assessment of laryngeal mask airway (LMA) position in children using two LMA insertion techniques, i.e., standard and rotational.

METHODS: Seventy-eight ASA I children, aged 2.5 months to 10 years, undergoing elective cataract surgery were included in this study. LMA was inserted in random order using either standard or rotational technique, removed, and thereafter crossed over to alternate technique. Positioning of LMA was assessed using fiber-optic bronchoscope with each technique. Change in the incidence of fiber-optic assessment grades 1 and 2 between two insertion techniques was measured as the primary outcome. Secondary outcome measures studied were first-attempt success rate, overall success rate, time for successful insertion, visual analogue scale for placement, complications, and maneuvers used to relieve airway obstruction.

RESULTS: Incidence of fiber-optic grades 1 and 2 was 61.5% with standard technique and increased to 92.3% with rotational technique ($P < 0.001$, McNemar's test) (RR 3.0, 95% CI 2.2-4.2). Median (IQR) fiber-optic grading was significantly better with rotational technique [2 (1-2)] as compared to standard technique [2 (2-3)], ($P < 0.001$, Wilcoxon signed rank test). First-attempt success rate was significantly higher (96.2%) with rotational technique compared with standard technique (80.7%) ($P = 0.04$, McNemar's test). Overall success rate (i.e., successful insertion with two attempts) was 100% with rotational technique compared with 89.7% with standard technique ($P = 0.003$, Fischer's exact test). Time for successful insertion and incidence of complications were significantly lesser with rotational technique.

CONCLUSION: Rotational technique of LMA insertion in children is associated with better seating of LMA (as observed on fiber-optic assessment) compared with the standard technique. Also, it is associated with higher success rate and lower incidence of complications.

[Paediatr Anaesth](#). 2011 Oct;21(10): 1036-40. doi: 10.1111/j.1460-9592.2011.03674.x. Epub 2011 Aug 12.

[Insertion of laryngeal mask airway does not increase the intraocular pressure in children with glaucoma.](#)

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OBJECTIVES: It is hypothesized that in children with glaucoma, the insertion of laryngeal mask airway (LMA) will cause lesser rise in intraocular pressure (IOP) than tracheal tube (TT).

AIM: To compare the IOP response to LMA and TT insertion in children with glaucoma.

METHODS/MATERIALS: A prospective, randomized, single-blind study was conducted in 30 glaucomatous ASA-1 children, aged 1-10 years scheduled to undergo trabeculectomy. Anesthesia was induced with halothane and maintained for 5 min with 1 MAC of halothane after administering atracurium 0.5 mg·kg(-1) following which LMA or TT was introduced. IOP was measured in both the eyes before and after insertion of airway device for 5 min.

RESULTS: The IOP increased significantly from 27.3 ± 5.2 to 31.2 ± 5.4 mmHg ($P < 0.001$) after tracheal intubation but returned to baseline within 5 min. The IOP did not change from the baseline after insertion of LMA. The IOP was significantly higher in group TT compared to group LMA at 2 min ($P = 0.004$) and 5 min ($P = 0.01$) after the device insertion. The heart rate (HR) increased significantly after tracheal intubation and returned to baseline 4 min after intubation. The HR increase was significantly more in TT group compared to LMA group at all times of observation. Both systolic blood pressure (SBP; $P = 0.01$) and diastolic blood pressure (DBP; $P = 0.02$) showed an increase at 1 min in children in group TT.

CONCLUSION: Insertion of LMA in glaucomatous children is not associated with an increased IOP response or cardiovascular changes.

[Pediatr Crit Care Med.](#) 2012 Jul 11. [Epub ahead of print]

[Oral mucosal decontamination with chlorhexidine for the prevention of ventilator-associated pneumonia in children-A randomized, controlled trial.](#)
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OBJECTIVE: To study the efficacy of oral mucosal decontamination with chlorhexidine gel for the prevention of ventilator-associated pneumonia in children between 3 months and 15 yrs.

DESIGN: Double blind randomized placebo controlled trial.

SETTING: Pediatric intensive care unit of a tertiary care hospital in North India.

PATIENTS: Eligible participants were patients aged 3 months to 15 yrs who required orotracheal or nasotracheal intubation and mechanical ventilation. Two hundred eighty-three children admitted to the pediatric intensive care unit between November 2007 and April 2009 were screened. Eighty-six patients fulfilled the study requirements.

INTERVENTION: Either 1% chlorhexidine or placebo gel was applied on the buccal mucosa at 8-hr intervals for the entire duration of ventilation, subject to a maximum of 21 days. Patients were followed up for the development of ventilator-associated pneumonia, diagnosed using the Centers for Disease Control and Prevention criteria.

MAIN OUTCOME MEASURES: Incidence of ventilator-associated pneumonia, duration of hospital stay, duration of intensive care unit stay, mortality, and characteristics of organisms isolated.

RESULTS: Forty-one children received 1% chlorhexidine, whereas 45 received placebo application. Patients of both groups were comparable with respect to baseline characteristics.

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Incidence of ventilator-associated pneumonia was 39.6/1,000 ventilator days with 1% chlorhexidine and 38.1/1,000 ventilator days with placebo (relative risk 1.03, confidence interval 0.44-2.42, $p = .46$). The duration of intensive care unit stay and hospital stay was a mean of 8.4 ± 5.8 vs. 9.6 ± 11.4 days ($p = .58$) and 16.1 ± 10.2 days vs. 15.1 ± 14.3 days ($p = .19$) with chlorhexidine and placebo, respectively. The mortality rates were similar in the two groups ($p = .81$). All but two isolates causing ventilator-associated pneumonia were gram-negative, with *Acinetobacter* species being the most common (14 of 26). No side effects of the applied gel were seen in either group.

CONCLUSION: Oral mucosal application on 1% chlorhexidine gel did not prevent the development of ventilator-associated pneumonia in children 3 months to 15 yrs age.

Antibiotics

[Clin Infect Dis.](#) 2011 Jul 1;53(1): 33-41.

[Reduction in antibiotic use following a cluster randomized controlled multifaceted intervention: the Israeli judicious antibiotic prescription study.](#)

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BACKGROUND: Antibiotic overuse is of great public health concern. This study assessed whether intervention among physicians and their treated population could achieve a sustained reduction in antibiotic use, specifically in classes known to promote antibiotic resistance among children in a community setting.

METHODS: We performed a cluster randomized controlled multifaceted trial among 52 primary care pediatricians and the 88,000 children registered in their practices. The intervention was led by local leaders and engaged the participating physicians. It included physician focus group meetings, workshops, seminars, and practice campaigns. These activities focused on self-developed guidelines, improving parent and physician knowledge, diagnostic skills, and parent-physician communication skills that promoted awareness of antibiotic resistance. The main outcome measure was the change in annual antibiotic prescription rates (APRs) of children treated by the intervention group physicians as compared with rates among those treated by control group physicians. The study comprised a 2-year pre-intervention period, a 3-year intervention period, and a 1-year follow-up period. Mixed-effect models were used to assess risk ratios to account for the clustered study design.

RESULTS: A decrease in the total APR among children treated by the intervention physicians compared with those treated by the control physicians was observed in the first intervention year (APR decrease among control physicians, 40%; APR decrease among intervention physicians, 22%; relative risk [RR], .76; 95% confidence interval [CI], .75-.78). This reduction crossed over all antibiotic classes but was most prominent for macrolides (macrolide prescription rate among control physicians, 58%; macrolide prescription rate among intervention physicians, 27%; RR, .58; 95% CI, .55-.62). The effect was sustained during the 4 following years.

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CONCLUSIONS: A multifaceted intervention that engages the physicians in an educational process is effective in reducing APRs and can be sustained.



Asthma and chronic lung disease

[Pediatrics](#). 2012 Jan;129(1): e106-12. Epub 2011 Dec 12.

[Peer-led education for adolescents with asthma in Jordan: a cluster-randomized controlled trial.](#)

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OBJECTIVES: To determine the impact of a peer-led education program, developed in Australia, on health-related outcomes in high school students with asthma in Jordan.

METHODS: In this cluster-randomized controlled trial, 4 high schools in Irbid, Jordan, were randomly assigned to receive the Adolescent Asthma Action program or standard practice. Bilingual health workers trained 24 peer leaders from Year 11 to deliver asthma education to younger peers from Year 10 (n = 92), who in turn presented brief asthma skits to students in Years 8 and 9 (n = 148) and to other members of the school community in the intervention schools. Students with asthma (N = 261) in Years 8, 9, and 10 completed baseline surveys in December 2006 and 3 months after the intervention.

RESULTS: Students from the intervention group reported clinically significant improvements in health-related quality of life (mean difference: 1.35 [95% confidence interval: 1.04-1.76]), self-efficacy to resist smoking (mean difference: 4.63 [95% confidence interval: 2.93-6.35]), and knowledge of asthma self-management (mean difference: 1.62 [95% confidence interval: 1.15-2.19]) compared with the control group.

CONCLUSIONS: This trial demonstrated that the Adolescent Asthma Action program can be readily adapted to suit different cultures and contexts. Adolescents in Jordan were successful in teaching their peers about asthma self-management and motivating them to avoid smoking. The findings revealed that peer education can be a useful strategy for health promotion programs in Jordanian schools when students are given the opportunity and training.



[Respir Med](#). 2012 May;106(5): 642-50. Epub 2012 Feb 18.

[Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial.](#)

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BACKGROUND: This randomized, double-blind, multicenter study was designed to evaluate the efficacy of inhaled once-daily fluticasone furoate (FF) administered in the evening in patients with persistent asthma not controlled by short-acting beta(2) agonists, and to determine the dose(s) suitable for further development.

METHODS: Of 1459 patients screened, 598 received one of six treatments: placebo, FF (25 µg, 50 µg, 100 µg or 200 µg) once daily each evening, or fluticasone propionate (FP) 100 µg twice daily for 8 weeks. The primary endpoint was change from baseline in pre-dose evening forced expiratory volume in 1 s (FEV(1)).

RESULTS: A dose-response effect was observed for once-daily FF 25-200 µg including (p < 0.001) and excluding placebo (p = 0.03). FF 50-200 µg once daily significantly increased FEV(1) from baseline (p < 0.05 vs placebo), by >200 mL for FF 100 µg and 200 µg. Significant improvements were also achieved for peak expiratory flow, and percentage symptom-free and rescue-free 24 h periods. The magnitude of effect was at least as good as twice-daily FP. Overall, once-daily FF was well tolerated with no systemic corticosteroid effects.

CONCLUSION: FF 50-200 µg/day once daily in the evening demonstrated dose-related efficacy in asthma with 100-200 µg appearing to be the optimal doses for further evaluation. ClinicalTrials.gov: NCT00603382.

[BMC Pediatr.](#) 2012 Mar 7;12: 21.

[Bronchodilatory effect of inhaled budesonide/formoterol and budesonide/salbutamol in acute asthma: a double-blind, randomized controlled trial.](#)

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BACKGROUND: There are no published studies that have compared bronchodilatory effect of inhaled budesonide/formoterol combination with budesonide/salbutamol delivered by metered dose inhaler with a spacer in acute exacerbation of asthma in children. We, therefore, compared the bronchodilatory effects of inhaled budesonide/formoterol (dose: 200 µg and 12 µg respectively) combination with budesonide (200 µg)/salbutamol (200 µg) administered by metered dose inhaler and spacer in children of 5-15 years with mild acute exacerbation of asthma [Modified Pulmonary Index Score (MPIS) between 6-8] in this double-blind, randomized controlled trial. The primary outcome was FEV1 (% predicted) in the two groups at 1, 5, 15, 30, 60 min after administration of the study drug.

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RESULTS: We did not observe any significant differences in the % predicted FEV1 and MPIS between formoterol and salbutamol at various time points from 1 min to 60 min post drug administration. There was significant improvement in FEV1 (% predicted) from baseline in both the groups as early as 1 min after drug administration.

CONCLUSIONS: Salbutamol or formoterol delivered along with inhaled corticosteroid by metered dose inhaler with spacer in children between 5-15 years of age with mild acute exacerbation of asthma had similar bronchodilatory effects.



[J Trop Pediatr](#). 2012 Feb 28. [Epub ahead of print]
[Comparison of Effects of 3 and 7% Hypertonic Saline Nebulization on Lung Function in Children with Cystic Fibrosis: A Double-Blind Randomized, Controlled Trial.](#)

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BACKGROUND: Beneficial effects of hypertonic saline on lung function in cystic fibrosis patients are well documented. However, the effects of various concentrations of hypertonic saline are not well studied. We, therefore, compared the effects of 3 and 7% hypertonic saline administered by nebulization on lung function in children with cystic fibrosis. Method: In a double-blind randomized controlled trial, 31 children with cystic fibrosis were randomized to receive either 3% saline or 7% saline nebulization twice daily for 28 days. Spirometry was performed and functional status was measured on Day 14 and 28. Results: Of 31 children enrolled in the study, 30 completed the 28 days follow up (15 in each group). **Percentage change in Forced Expiratory Volume during first second (FEV(1)) from baseline to Day 14 and on Day 28 was significantly higher in the group receiving 3% saline as compared with those receiving 7% saline inhalation. There was some decrease in FEV(1) (percentage predicted) immediately after 7% saline inhalation unlike 3% saline.** The functional status remained comparable between the two groups.

Conclusion: The results suggest that **3% hypertonic saline nebulization was better than 7% saline inhalation**. There is a need for studies with larger sample size and longer duration to confirm our results.

Cardiovascular disease

[Am J Clin Nutr](#). 2011 Dec;94(6 Suppl): S1853-S1860. Epub 2011 Jun 15.
[Nutritional supplementation during pregnancy and offspring cardiovascular disease risk in The Gambia.](#)

Randomised trials in child health in developing countries 2011-12

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BACKGROUND: Maternal nutritional intake during pregnancy may have important consequences for long-term health in offspring.

OBJECTIVE: The objective was to follow up the offspring in 2 randomized trials of nutrient supplementation during pregnancy to investigate the effect on cardiovascular disease (CVD) risk in offspring.

DESIGN: We recruited offspring born during 2 trials in The Gambia, West Africa. One trial provided protein-energy-dense food supplements (1015 kcal and 22 g protein/d) to pregnant (intervention, from 20 wk gestation until delivery) or lactating (control, for 20 wk from birth) women and was randomized at the village level. The second was a double-blind, individually randomized, placebo-controlled trial of calcium supplementation (1.5 g/d), which was also provided from 20 wk gestation until delivery.

RESULTS: Sixty-two percent (n = 1267) of children (aged 11-17 y) born during the protein-energy trial were recruited and included in the analysis, and 64% (n = 350) of children (aged 5-10 y) born during the calcium trial were recruited and included in the analysis. Fasted plasma glucose was marginally lower in children born to mothers receiving protein-energy supplements during pregnancy than in those children of the lactating group (adjusted mean difference: -0.05 mmol/L; 95% CI: -0.10, -0.001 mmol/L). **There were no other differences in CVD risk factors, including blood pressure, body composition, and cholesterol, between children born to intervention and control women from the protein-energy trial.** Maternal calcium supplementation during pregnancy was unrelated to offspring blood pressure.

CONCLUSION: These data suggest that providing supplements to pregnant women in the second half of pregnancy may have little effect on the CVD risk of their offspring, at least in this setting and at the ages studied here. This trial was registered at www.controlled-trials.com as ISRCTN96502494.



[Am J Hypertens](#). 2011 Aug;24(8): 876-80. doi: 10.1038/ajh.2011.67. Epub 2011 Apr 21.
[Adiposity and blood pressure in South Asian children and adolescents in Karachi.](#)

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BACKGROUND: The association of adiposity during childhood with future risk of elevated blood pressure (BP) in South Asian children is not known. We aimed to investigate the relationship between waist circumference (WC) and body mass index (BMI) with BP over a 2-year period, independent of the baseline BP.

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METHODS: We analyzed data on children aged 5-14 years who participated in the Control of Blood Pressure and Risk Attenuation (COBRA) trial in Karachi, Pakistan. Separate multivariable models were built for WC and BMI using generalized estimation equations to determine the association between the baseline and changes in adiposity with the primary outcome of increase in systolic BP (SBP) over 2 years of follow-up.

RESULTS: We assessed 1,675 children: 51% were boys. At 2 years, 1,278 (76.5%) were available for follow-up. **On multivariate analysis, WC at baseline (β (95% confidence interval (CI)) = (0.20 (0.13, 0.29), for each 1 cm increase) and change in WC from baseline to follow-up (0.24 (0.16, 0.34), for each 1 cm increase) were associated with increase in SBP.** Similarly BMI at baseline (0.54 (0.33, 0.75) and change in BMI 1.32 (1.06, 1.59), for each 1 kg/m² increase) were associated with change in SBP. Categorical expression of adiposity yielded consistent results.

CONCLUSIONS: **Baseline adiposity and increase in adiposity, both, are associated with increase in BP**, independent of the baseline level of BP in South Asian children. Both WC and BMI can be used to identify children at high risk of increase in BP.



[Nutr Metab Cardiovasc Dis.](#) 2012 Jul 10. [Epub ahead of print]
[Is carbohydrate intake in the first years of life related to future risk of NCDs?](#)
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Studies on children's carbohydrate intake, especially fibre intake, and its associations with later health are rare. The current recommendations for fibre intake in children are based on average assumptions and data extrapolated from intakes in adults. Generally, increase in whole-grain consumption and decrease in sucrose intake are considered healthy. Due to fibre's high bulk volume however, excessive dietary fibre has been feared to decrease energy density have effects on growth, at least in developing countries and in children consuming very restricted diets. Furthermore, it has been speculated that if fats are reduced from the diet, it may become high in sucrose. In STRIP study, which is a long-term, randomized controlled trial designed to decrease the exposure of children to known risk factors of atherosclerosis, carbohydrate intakes have been investigated in detail in children aged 13 months to 9 years. The intervention was successful in decreasing saturated fat intake and cholesterol concentrations throughout childhood and adolescence. The study results also show that a higher than average fibre intake does not displace energy or disturb growth in children and that children with high fibre intake have better dietary quality than those with low fibre intake. Dietary fibre intake associated with lower serum total cholesterol concentrations whereas increases in total carbohydrate, sucrose and fructose intakes associated with increases in serum triglyceride concentrations. In conclusion, from the point of view of CHD risk factor prevention, efforts aiming at increasing the fibre intake while restricting that of refined sugar seem justified in the child population in developed countries.

Development and mental health

(See also maternal mental health)

[BMC Neurol.](#) 2011 Aug 4;11: 96.

[Cognition, behaviour and academic skills after cognitive rehabilitation in Ugandan children surviving severe malaria: a randomised trial.](#)

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BACKGROUND: Infection with severe malaria in African children is associated with not only a high mortality but also a high risk of cognitive deficits. There is evidence that interventions done a few years after the illness are effective but nothing is known about those done immediately after the illness. We designed a study in which children who had suffered from severe malaria three months earlier were enrolled into a cognitive intervention program and assessed for the immediate benefit in cognitive, academic and behavioral outcomes.

METHODS: This parallel group randomised study was carried out in Kampala City, Uganda between February 2008 and October 2010. **Sixty-one Ugandan children aged 5 to 12 years with severe malaria were assessed for cognition (using the Kaufman Assessment Battery for Children, second edition and the Test of Variables of Attention), academic skills (Wide Range Achievement Test, third edition) and psychopathologic behaviour (Child Behaviour Checklist) three months after an episode of severe malaria. Twenty-eight were randomised to sixteen sessions of computerised cognitive rehabilitation training lasting eight weeks and 33 to a non-treatment group.** Post-intervention assessments were done a month after conclusion of the intervention. Analysis of covariance was used to detect any differences between the two groups after post-intervention assessment, adjusting for age, sex, weight for age z score, quality of the home environment, time between admission and post-intervention testing and pre-intervention score. The primary outcome was improvement in attention scores for the intervention group. This trial is registered with Current Controlled Trials, number ISRCTN53183087.

RESULTS: **Significant intervention effects were observed in the intervention group for learning mean score (SE), [93.89 (4.00) vs 106.38 (4.32), P = 0.04] but for working memory the intervention group performed poorly [27.42 (0.66) vs 25.34 (0.73), P = 0.04].** No effect was observed in the other cognitive outcomes or in any of the academic or behavioural measures.

CONCLUSIONS: In this pilot study, our computerised cognitive training program three months after severe malaria had an immediate effect on cognitive outcomes but did not affect academic skills or behaviour. Larger trials with follow-up after a few years are needed to investigate whether the observed benefits are sustained.



[Eur J Clin Nutr.](#) 2012 Feb;66(2): 237-43. doi: 10.1038/ejcn.2011.165. Epub 2011 Sep 28.
[The mental development and behavior of low-birth-weight Bangladeshi infants from an urban low-income community.](#)

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BACKGROUND/OBJECTIVES: Adverse developmental consequences of low-birth-weight (LBW) infants have been frequently reported from developed countries where most of them are preterm. Few reports are available from developing countries, where the problem is huge and newborns are mostly term babies. **We aimed to compare mental and psychomotor development and behavior of LBW Bangladeshi infants with those of normal-birth-weight (NBW) infants.**

SUBJECT/METHODS: Secondary data analyses from a randomized controlled trial of fish oil supplementation during pregnancy on infants' development at 10 month. There was no effect of supplementation on infants' development. All LBW (n=66) and NBW (n=183) infants were assessed for their mental development index (MDI), psychomotor development index (PDI), behavior and quality of psychosocial stimulation received at home. Socioeconomic information and anthropometric measurements were available, and bivariate and multivariate analyses were performed to examine group differences.

RESULTS: LBW infants scored significantly lower than NBW infants on MDI, PDI, activity and emotional tone. They came from comparatively poorer families and had lower gestational age than the NBW infants. **After controlling for possible confounders, the NBW infants had significantly higher MDI (B=2.7, s.e.=1.1, 95% confidence interval (CI): 0.6-4.8), PDI (B=3.5, s.e.=1.3, 95% CI: 1.0-6.0) and activity (B=0.5, s.e.=0.2, 95% CI: 0.1-0.9) scores. Furthermore, in a subgroup analyses, a consistent pattern of developmental delay was also noted in favor of term-LBW infants.**

CONCLUSIONS: In a poor-urban Bangladeshi community, LBW infants had significantly lower mental and psychomotor developments and were less active than NBW infants at 10 months of age.



[Asia Pac J Clin Nutr.](#) 2012;21(2): 241-6.
[Greater length-for-age increases the odds of attaining motor milestones in Vietnamese children aged 5-18 months.](#)

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Randomised trials in child health in developing countries 2011-12

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Early childhood malnutrition has been associated with delayed development. Limited data exist however about the timing of developmental delay early in life. We assessed motor milestone (MM) achievement using the World Health Organization's windows of achievement for gross motor milestones. We performed secondary analysis of baseline data of 158 Vietnamese children aged 5-18 months from a randomized community intervention trial. Median age of motor milestone achievement was compared to WHO reported medians. Multivariate logistic regression was used to identify socioeconomic, anthropometric and dietary factors associated with motor milestone achievement during the windows of achievement. Thirty four per cent of the children were stunted. **Median age of MM achievement of Vietnamese children lagged by 2.4-3.7 months, compared to the WHO median for all MMs. Greater length-for-age increased the odds for walking with assistance, standing alone and walking alone by more than 3 times. Greater weight-for-age increased the odds by 3.6 for hand-and-knees crawling. Likewise, frequency of daily complementary feeding raised the odds by 3.6 for standing with assistance.** In this first application of WHO windows of achievement in Viet Nam, pre-schoolers achieved motor milestones later than WHO reported median age. **High prevalence of stunting and association of length-for-age with motor milestone achievement underscore the importance of addressing chronic malnutrition to optimize children's growth and development.**

Comment

These above two trials underline the adverse effects of under-nutrition on development. Low birth weight infants had delayed development, and infants with early stunting had delayed motor milestones. Another non-randomised study this year (from Barbados) showed that 40 years later, people who were malnourished in infancy had an increased risk of adverse social and economic outcomes. The finding in Vietnam, that increased frequency of complimentary feeding in infants was related positively to better developmental progress, is encouraging and suggests the need for increased focus on the quality and quantity of complimentary feeding, as well as the period of exclusive breast feeding.

[Disabil Rehabil.](#) 2012;34(4): 337-46. Epub 2011 Sep 30.

[Efficacy of constraint-induced movement therapy and electrical stimulation on hand function of children with hemiplegic cerebral palsy: a controlled clinical trial.](#)

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PURPOSE: The purpose of this study is to compare the efficacy of constraint therapy, constraint therapy plus electrical stimulation, and occupational therapy in the treatment of hand dysfunction.

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METHODS: Sixty-eight children with hemiplegic cerebral palsy were randomly allocated to constraint therapy, constraint therapy plus electrical stimulation, and occupational therapy group. Three groups received 2 weeks of treatment. All participants were measured at baseline and 2 weeks, 3 and 6 months after treatment using measures of active ROM, grip strength, nine-peg hole test, upper extremity functional test, Peabody developmental motor scales (PDMS), globe rating scale, and social life ability scale.

RESULTS: Three groups improved significantly ($p < 0.05$). The mean improvements between baseline and the end of follow-up were respectively 12.4, 11.4 and 11.3 degrees for active ROM; 12.8, 10.5 and 8.8 mmHg for grip strength; -22.3, -30.7 and -14.0 s for nine-peg hole test; 15.3, 10.3 and 10.4 for upper extremity functional test scores; 2.2, 1.8 and 1.8 for grasping scores of PDMS; 5.8, 3.7 and 2.8 for visual-motor integration scores of PDMS; 2.0, 2.5 and 0.9 for globe rating scale scores; 7.7, 5.7 and 5.3 for social life ability scale scores in constraint therapy plus electrical stimulation, constraint therapy, and occupational therapy group. The constraint therapy plus electrical stimulation group showed greater rate of improvement in upper extremity functional test scores ($p < 0.05$) and visual-motor integration scores of PDMS ($p < 0.05$) than the other two groups after treatment for 6 months.

CONCLUSIONS: Constraint therapy plus electrical stimulation is likely to be best in improving hand performance in children with hemiplegic cerebral palsy.



Comment

“Constraint therapy” means restraint of the non-involved hand and intensive practice with the involved hand. Electrical stimulation was applied for 20 minutes 5 times a week for 2 weeks on extensor carpi radialis and extensor digitorum of the affected upper limb. Frequencies used were 50 Hz, 30 pulses per second with the amplitude to a maximum of 100 mA.

[Indian J Pediatr](#). 2012 May;79(5): 659-63. Epub 2011 Aug 10.

[Neurofacilitation of Developmental Reaction \(NFDR\) approach: a practice framework for integration / modification of early motor behavior \(Primitive Reflexes\) in Cerebral Palsy.](#)

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A Randomized Controlled trial was done on 30 (CP) children of age range 6 mon to 2 y with an objective to see the efficacy of Neurofacilitation of Developmental Reaction (NFDR) approach over Neurodevelopmental Therapy (NDT) for integration / modification of early motor behavior (Primitive Reflexes) in Cerebral Palsy (CP). The baseline evaluation was done for tone, postural reactions and GMFM. The subjects were randomly allocated to two groups. With group A, NFDR and group B, conventional approach (NDT) was used for 3 mon followed by re-

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evaluation. Between groups analysis was done and p value was found to be significant. It was concluded that NFDR approach is more effective than NDT for integration / modification of early motor behavior in children with CP.

Diabetes

[Eur J Clin Nutr.](#) 2011 Sep;65(9): 1048-52. doi: 10.1038/ejcn.2011.98. Epub 2011 Jun 1.
[Effect of camel milk on glyceamic control and insulin requirement in patients with type 1 diabetes: 2-years randomized controlled trial.](#)

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BACKGROUND/OBJECTIVES: Hypoglycemic effect of camel milk supplementation in experimental rat model and significant reduction in doses of insulin in type 1 diabetic patients have been observed in our previous studies. This long-term study was undertaken to assess the efficacy, safety and acceptability of camel milk as an adjunct to insulin therapy in type 1 diabetics.

SUBJECTS/METHODS: In this 2-year randomized clinical, parallel design study, 24 type 1 diabetics were enrolled and divided into two groups. Group I (n=12) received usual care, that is, diet, exercise and insulin and Group II (n=12) received 500 ml camel milk in addition to the usual care. Insulin requirement was titrated weekly by blood glucose estimation. Results were analyzed by using the regression technique.

RESULTS: In camel milk group, there was decrease in mean blood glucose ($118.58 \pm 19.93.16 \pm 17.06$ mg/dl), hemoglobin A1c levels (7.81 ± 1.39 - $5.44 \pm 0.81\%$) and insulin doses (32.50 ± 9.99 - 17.50 ± 12.09 U/day, $P < 0.05$). Out of 12 subjects receiving camel milk, insulin requirement in 3 subjects reduced to zero. There was nonsignificant change in plasma insulin and anti-insulin antibodies in both the groups.

CONCLUSION: It may be stated that camel milk is safe and efficacious in improving long-term glyceamic control, with a significant reduction in the doses of insulin in type 1 diabetic patients.



Comment

Camel milk apparently is unique among milks in that (a) one of its proteins has many characteristics similar to insulin, and (b) it does not form a coagulum in acidic environment, thus, making it available for absorption in intestine. Camel milk has revealed that it contains a high concentration of insulin (53 U/ml) in comparison with cow milk (16 U/ml). Although there is significantly higher insulin (60 U/l) in human milk, the insulin is not available for absorption in intestine probably because of coagulation in stomach. Camel milk is also high in

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antibacterial proteins, lysozyme, lactoferrin and immunoglobulins, which contain activity against Gram positive and Gram negative bacteria and rotavirus. (J Dairy Research 1992;59: 169-175; J Food Chemistry 2000 Feb;68(2): 227–232). In some communities where camel milk is consumed, diabetes is absent (Diabetes Research Clin Practice 2007;76: 290–296).

[Trials](#). 2011 Sep 26;12: 209.

[DIABRISK-SL prevention of cardio-metabolic disease with life style modification in young urban Sri Lankan's--study protocol for a randomized controlled trial.](#)

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BACKGROUND: Urban South-Asian's are predisposed to early onset of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). There is an urgent need for country specific primary prevention strategies to address the growing burden of cardio-metabolic disease in this population. The aim of this clinical trial is to evaluate whether intensive (3-monthly) lifestyle modification advice is superior to a less-intensive (12 monthly; control group) lifestyle modification advice on a primary composite cardio-metabolic end point in 'at risk' urban subjects aged between 5-40 years.

METHODS/DESIGN: This is an open randomised controlled parallel group clinical trial performed at a single centre in Colombo, Sri-Lanka. A cluster sampling strategy was used to select a large representative sample of subjects aged between 5-40 years at high risk of T2DM and CVD for the intervention study. We have screened 23,298 (males 47% females 53%) healthy subjects for four risk factors: obesity, elevated waist circumference, family history of diabetes and physical inactivity, using a questionnaire and anthropometry. Those with two or more risk-factors were recruited to the intervention trial. We aim to recruit 4600 subjects for the intervention trial. The primary composite cardio-metabolic end point is; new onset T2DM, impaired glucose tolerance, impaired fasting glycaemia, new onset hypertension and albuminuria, following 5 years of intervention. The effect of the intervention on pre-specified secondary endpoints will also be evaluated. The study will be conducted according to good clinical and ethical practice, data analysis and reporting guidelines.

DISCUSSION: DIABRISK-SL is a large population based trial to evaluate the prevalence of diabetes, pre-diabetes and cardio-metabolic risk factors among young urban Sri-Lankans and the effect of a primary prevention strategy on cardio-metabolic disease end points. This work will enable country specific and regional cardio-metabolic risk scores to be derived. Further if the proposed intervention is successful the results of this study can be translated and implemented as a low-cost primary prevention tool in Sri-Lanka and other low/middle income developing countries.

TRIAL REGISTRATION: The trial is registered with the World Health Organisation and Sri-Lanka clinical trial registry number SLCTR/2008/003.



Diarrhoea

(See also Vaccines and immunization - Rotavirus vaccine)

[Cochrane Database Syst Rev. 2011 Dec 7;\(12\): CD003754.](#)

[Oral rehydration salt solution for treating cholera: \$\leq 270\$ mOsm/L solutions vs \$\geq 310\$ mOsm/L solutions.](#)

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BACKGROUND: Oral rehydration solution (ORS) is used to treat the dehydration caused by diarrhoeal diseases, including cholera. ORS formulations with an osmolarity (a measure of solute concentration) of ≤ 270 mOsm/L (ORS ≤ 270) are safe and more effective than ORS formulations with an osmolarity of ≥ 310 mOsm/L (ORS ≥ 310) for treating non-cholera diarrhoea. As cholera causes rapid electrolyte loss, it is important to know if these benefits are similar for people suffering from cholera.

OBJECTIVES: To compare the safety and efficacy of ORS ≤ 270 with ORS ≥ 310 for treating dehydration due to cholera.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register (April 2011), CENTRAL (The Cochrane Library Issue 4, 2011), MEDLINE (1966 to April 2011), EMBASE (1974 to April 2011), and LILACS (1982 to April 2011). We also contacted organizations and searched reference lists.

SELECTION CRITERIA: Randomized controlled trials comparing ORS ≤ 270 with ORS ≥ 310 for treating adults and children with acute diarrhoea due to cholera.

DATA COLLECTION AND ANALYSIS: Two reviewers independently applied eligibility criteria, assessed trial quality, and extracted data. We pooled dichotomous data using risk ratio (RR), pooled continuous data using mean difference (MD) or the standardized mean difference (SMD), and presented the results with 95% confidence intervals (CI).

MAIN RESULTS: For glucose-based ORS, seven trials (718 participants) met the inclusion criteria. **Biochemical hyponatraemia (blood sodium levels < 130 mmol/L) was more common with ORS ≤ 270 (RR 1.67, CI 1.09 to 2.57; 465 participants, four trials), while a higher level of severe biochemical hyponatraemia (blood sodium levels < 125 mmol/L) in the same group was not significant (RR 1.58, CI 0.62 to 4.04; 465 participants, four trials).** No instances of symptomatic hyponatraemia or death were noted in the trials that intended to record them. We found no statistically significant difference in the need for unscheduled intravenous infusion. Analyses separating children and adults showed no obvious trends. Two

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trials also examined rice-based ORS. In the ORS ≤ 270 group, duration of diarrhoea was shorter (MD -11.42 hours, CI -13.80 to -9.04; 102 participants, two trials).

AUTHORS' CONCLUSIONS: In people with cholera, ORS ≤ 270 is associated with biochemical hyponatraemia when compared with ORS ≥ 310 , but there are no differences in terms of other outcomes. Although this risk does not appear to be associated with any serious consequences, the total patient experience in existing trials is small. **Under wider practice conditions, especially where patient monitoring is difficult, caution is warranted.**



[Indian Pediatr.](#) 2012 Apr 1. pii: S097475591100640-1. [Epub ahead of print]

[Comparison of Ringers Lactate vs Normal Saline in Children with Acute Diarrhea and Severe Dehydration: A Double Blind Randomized Controlled Trial.](#)

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OBJECTIVE: WHO recommends Ringers lactate (RL) and Normal Saline (NS) for rapid intravenous rehydration in childhood diarrhea and severe dehydration. We compared these two fluids for improvement in pH over baseline during rapid intravenous rehydration in children with acute diarrhea.

DESIGN:

Double-blind randomized controlled trial.

SETTING: Pediatric emergency facilities at a tertiary-care referral hospital.

INTERVENTION: *Children* with acute diarrhea and severe dehydration received either RL (RL-group) or NS (NS-group), 100 mL/kg over three or six hours. *Children* were reassessed after three or six hours. Rapid rehydration was repeated if severe dehydration persisted. Blood gas was done at baseline and repeated after signs of severe dehydration disappeared.

OUTCOME MEASURES: Primary outcome was change in pH from baseline. Secondary outcomes included changes in serum electrolytes, bicarbonate levels, and base deficit from baseline; mortality, duration of hospital stay, and fluids requirement.

RESULTS: Twenty two children, 11 each were randomized to the two study groups. At primary end point (disappearance of signs of severe dehydration), the improvement in pH from baseline was not significant in RL-group [from 7.17 (0.11) to 7.28 (0.09)] as compared to NS-group [7.09 (0.11) to 7.21 (0.09)], $P=0.17$ (after adjusting for baseline serum Na/ Cl). Among this

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limited sample size, children in RL group required less fluids [median 310 versus 530 mL/kg, P=0.01] and had shorter median hospital stay [38 versus 51 hours, P=0.03].

CONCLUSION: There was no difference in improvement in pH over baseline between RL and NS among children with acute diarrhea and severe dehydration.

[J Trop Pediatr.](#) 2012 Feb;58(1): 63-7. Epub 2011 Apr 27.

[Efficacy of dioctahedral smectite in acute watery diarrhea in Indian children: a randomized clinical trial.](#)

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OBJECTIVE: To determine the effects and safety of dioctahedral smectite (DS) on the duration of acute watery diarrhea in children.

METHODS: A Randomized, open labeled, clinical controlled trial in a tertiary care hospital outpatient department (OPD) and emergency department. Participants were one hundred and seventeen children without any chronic illness between 2 and 5 years presenting to OPD, having **acute watery diarrhea for <48 h with mild to moderate dehydration**, not on antibiotics and requiring oral rehydration therapy. Intervention done was DS with a dose of 1.5 g thrice daily.

RESULTS: **Freshly dissolved DS in a dose of 1.5 g thrice daily for 5 days significantly shortened the duration of acute watery diarrhea in children aged 2-5 years.** There were no adverse effects on the use of DS. DS was acceptable to the children, and its administration was not accompanied with any side effects.

CONCLUSION: DS reduces the duration of diarrhea in Indian children and prevents a prolonged course, and therefore, may consistently reduce the costs in treatment of acute watery diarrhea.

[Cochrane Database Syst Rev.](#) 2011 Jul 6;(7): CD007296.

[Early versus Delayed Refeeding for Children with Acute Diarrhoea.](#)

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BACKGROUND: Acute diarrhoea is one of the principal causes of morbidity and mortality among children in low-income countries. The cornerstone of treatment is oral rehydration therapy and dietary management. However, there is a lack of data and studies on both the timing and type of feeding that should be adopted during the course of the illness.

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OBJECTIVES: To compare the efficacy and safety of early and late reintroduction of feeding in children with acute diarrhoea.

SEARCH STRATEGY: In May 2011, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2011, Issue 1), MEDLINE, EMBASE, LILACS, and mRCT. We also contacted researchers and organizations, and searched reference lists.

SELECTION CRITERIA: Randomized controlled trials of early versus late refeeding among children less than 10 years old with acute diarrhoea. Early refeeding was defined as within 12 hours of start of rehydration and late refeeding was defined as more than 12 hours after start of rehydration.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed the search results and the risk of bias, and extracted data. We present risk ratios for dichotomous outcomes and mean differences for continuous outcomes. We combined the results of the trials using meta-analysis when heterogeneity was not substantial.

MAIN RESULTS: Twelve trials involving 1283 participants were included; 1226 participants were used in the analysis (724 in the early refeeding group and 502 in the late refeeding group). Nine trials described their allocation sequence, but only two used concealed allocation. One trial reported single-blinding but did not clearly identify the person who was blinded. **Early refeeding meant intake during or immediately after start of rehydration, while late refeeding meant intake only 20 hours to 48 hours after start of rehydration.** Significant heterogeneity was noted in the data for the duration of diarrhoea. **There was no significant difference between the two refeeding groups in the number of participants who needed unscheduled intravenous fluids (six trials with 813 participants), who experienced episodes of vomiting (five trials with 466 participants), and who developed persistent diarrhoea (four trials with 522 participants).** The mean length of hospital stay was also similar (two trials with 246 participants).

AUTHORS' CONCLUSIONS: **There was no evidence that early refeeding increases the risk of unscheduled intravenous fluid use, episodes of vomiting, and development of persistent diarrhoea.** No conclusion could be made regarding the duration of diarrhoea.



Dysentery and antibiotics

[BMC Pediatr.](#) 2011 Nov 25;11: 109.

[Effect of a multi-faceted quality improvement intervention on inappropriate antibiotic use in children with non-bloody diarrhoea admitted to district hospitals in Kenya.](#)

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BACKGROUND: There are few reports of interventions to reduce the common but irrational use of antibiotics for acute non-bloody diarrhoea amongst hospitalised children in low-income settings. We undertook a secondary analysis of data from an intervention comprising training of health workers, facilitation, supervision and face-to-face feedback, to assess whether it reduced inappropriate use of antibiotics in children with non-bloody diarrhoea and no co-morbidities requiring antibiotics, compared to a partial intervention comprising didactic training and written feedback only. This outcome was not a pre-specified end-point of the main trial.

METHODS: Repeated cross-sectional survey data from a cluster-randomised controlled trial of an intervention to improve management of common childhood illnesses in Kenya were used to describe the **prevalence of inappropriate antibiotic use in a 7-day period in children aged 2-59 months with acute non-bloody diarrhoea**. Logistic regression models with random effects for hospital were then used to identify patient and clinician level factors associated with inappropriate antibiotic use and to assess the effect of the intervention.

RESULTS: 9, 459 admission records of children were reviewed for this outcome. Of these, 4, 232 (44.7%) were diagnosed with diarrhoea, with 130 of these being bloody (dysentery) therefore requiring antibiotics. 1, 160 children had non-bloody diarrhoea and no co-morbidities requiring antibiotics-these were the focus of the analysis. 750 (64.7%) of them received antibiotics inappropriately, 313 of these being in the intervention hospitals vs. 437 in the controls. **The adjusted logistic regression model showed the baseline-adjusted odds of inappropriate antibiotic prescription to children admitted to the intervention hospitals was 0.30 times that in the control hospitals (95%CI 0.09-1.02).**

CONCLUSION: We found some evidence that the multi-faceted, sustained intervention described in this paper led to a reduction in the inappropriate use of antibiotics in treating children with non-bloody diarrhoea.



Comment

The intervention in this project was training health workers in the use of evidence-based guidelines, which includes information on rational antibiotic prescribing and the management of diarrhoea. These training materials are available at: <http://www.idoc-africa.org/etat-courses.html>. WHO's evidence-based guidelines in Hospital Care for Children, on which the Kenya training materials were based, is available at: http://www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html and www.ichrc.org

[LoS Negl Trop Dis](#). 2011 Aug;5(8): e1264. Epub 2011 Aug 2.

[A multi-center randomized trial to assess the efficacy of gatifloxacin versus ciprofloxacin for the treatment of shigellosis in Vietnamese children.](#)

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BACKGROUND: The bacterial genus *Shigella* is the leading cause of dysentery. There have been significant increases in the proportion of *Shigella* isolated that demonstrate resistance to nalidixic acid. While nalidixic acid is no longer considered as a therapeutic agent for shigellosis, the fluoroquinolone ciprofloxacin is the current recommendation of the World Health Organization. Resistance to nalidixic acid is a marker of reduced susceptibility to older generation fluoroquinolones, such as ciprofloxacin. We aimed to assess the efficacy of gatifloxacin versus ciprofloxacin in the treatment of uncomplicated shigellosis in children.

METHODOLOGY/PRINCIPAL FINDINGS: We conducted a randomized, open-label, controlled trial with two parallel arms at two hospitals in southern Vietnam. The study was designed as a superiority trial and children with dysentery meeting the inclusion criteria were invited to participate. **Participants received either gatifloxacin (10 mg/kg/day) in a single daily dose for 3 days or ciprofloxacin (30 mg/kg/day) in two divided doses for 3 days.** The primary outcome measure was treatment failure; secondary outcome measures were time to the cessation of individual symptoms. Four hundred and ninety four patients were randomized to receive either gatifloxacin (n=249) or ciprofloxacin (n=245), of which 107 had a positive *Shigella* stool culture. **We could not demonstrate superiority of gatifloxacin and observed similar clinical failure rate in both groups (gatifloxacin; 12.0% and ciprofloxacin; 11.0%, p=0.72). The median (inter-quartile range) time from illness onset to cessation of all symptoms was 95 (66-126) hours for gatifloxacin recipients and 93 (68-120) hours for the ciprofloxacin recipients (Hazard Ratio [95%CI]=0.98 [0.82-1.17], p=0.83).**

CONCLUSIONS: We conclude that in Vietnam, where nalidixic acid resistant *Shigellae* are highly prevalent, ciprofloxacin and gatifloxacin are similarly effective for the treatment of acute shigellosis.



Probiotics

[J Clin Gastroenterol](#). 2011 Nov;45 Suppl: S149-53.

[Probiotics for prevention and treatment of diarrhea.](#)

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Probiotics have been extensively studied over the past several years in the prevention and, to a larger extent, in the treatment of diarrheal diseases, especially in pediatric populations. Diarrhea is a symptom, and not a disease. This review will not address chronic disorders associated with diarrhea, or *Clostridium difficile*-induced diarrhea. Rather it will focus on published clinical trials performed on acute-onset, likely infectious diarrhea occurring in the settings of day-care centers, in the community, acquired in the hospital, antibiotic-associated diarrhea, and treatment

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of acute infectious diarrhea. For prevention of diarrhea acquired in day-care centers, **9 randomized and placebo-controlled trials have been published, conducted in different parts of the world. Probiotics tested were Lactobacillus GG, Bifidobacterium lactis (alone or in combination with Streptococcus thermophilus, and Lactobacillus reuteri, Lactobacillus rhamnosus (not GG), and Lactobacillus acidophilus, in various trials either alone or in comparison with each other.** The evidence of their efficacy in these settings is only modest for the prevention of diarrhea, although somewhat better for prevention of upper respiratory infections. In the community, new trials conducted in underprivileged areas of India, again with modest efficacy. Previous trials that examined the potential role of probiotics in preventing the spreading of diarrhea in hospitalized children had yielded conflicting results. More recently, a large trial in Poland showed, however, rather good evidence of efficacy for Lactobacillus GG. The prevention of antibiotic-associated diarrhea has been the subject of many investigations, both in children and in adults. Most commonly used probiotics were Lactobacillus GG, Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium ssp, Streptococcus ssp, and the yeast Saccharomyces boulardii. In general, most of these trials do show clear evidence of efficacy, with the 2 most effective strains being Lactobacillus GG and S. boulardii. Evidence is also emerging on the importance of the dose in reducing the incidence of this type of diarrhea, and the incidence of Clostridium difficile-associated postantibiotic diarrhea. **As for treatment, a large body of data is available, especially in children, on the effect of several strains of probiotics in treating sporadic infectious diarrhea. The vast majority of the published trials show a statistically significant benefit and moderate clinical benefit of a few, well-identified probiotic strains-mostly Lactobacillus GG and S. boulardii-in the treatment of acute watery diarrhea, and particularly those due to rotavirus. Such a beneficial effect results, on average, in a reduction of diarrhea duration of approximately 1 day.** The effect is strain-dependent and dose-dependent.

[J Pediatr Gastroenterol Nutr.](#) 2011 Nov;53(5): 497-501.

[Treatment of acute diarrhea with Saccharomyces boulardii in infants.](#)

[Corrêa NB](#), [Penna FJ](#), [Lima FM](#), [Nicoli JR](#), [Filho LA](#).

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OBJECTIVE: The aim of the study was to determine whether an oral treatment with a commercial pharmaceutical product containing Saccharomyces boulardii would reduce the duration of diarrhea in infants with acute diarrhea.

PATIENTS AND METHODS: In the present double-blind, placebo-controlled study, 186 infants, 6 to 48 months old and hospitalized within 72 hours after the onset of acute diarrhea in 2 hospitals in Goiânia, Goiás, Brazil, were randomly assigned to receive twice per day for 5 days 200 mg of a commercial pharmaceutical product containing 4×10^8 viable cells of S boulardii or a placebo. Stool samples were submitted to search for rotavirus. **Among the 176 infants who completed the trial, those treated with S boulardii (90) showed a reduction in diarrhea duration ($P < 0.05$) when compared with the placebo group (86).**

RESULTS: The present study shows a reduction in diarrhea duration when S boulardii was given to children within 72 hours after the onset of acute diarrhea.

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CONCLUSIONS: The present study suggests a complementary treatment of acute diarrhea in infants with daily oral doses of *S. boulardii*.

Water purification

(See also Hygiene and environmental health)

[Environ Sci Technol.](#) 2011 Nov 1;45(21): 9315-23. Epub 2011 Oct 5.

[Randomized intervention study of solar disinfection of drinking water in the prevention of dysentery in Kenyan children aged under 5 years.](#)

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We report the results of a randomized controlled intervention study (September 2007 to March 2009) investigating the effect of solar disinfection (SODIS) of drinking water on the incidence of dysentery, nondysentery diarrhea, and anthropometric measurements of height and weight among children of age 6 months to 5 years living in peri-urban and rural communities in Nakuru, Kenya. **We compared 555 children in 404 households using SODIS with 534 children in 361 households with no intervention. Dysentery was recorded using a pictorial diary. Incidence rate ratios (IRR) for both number of days and episodes of dysentery and nondysentery diarrhea were significantly ($P < 0.001$) reduced by use of solar disinfection: dysentery days IRR = 0.56 (95% CI 0.40 to 0.79); dysentery episodes IRR = 0.55 (95% CI 0.42 to 0.73); nondysentery days IRR = 0.70 (95% CI 0.59 to 0.84); nondysentery episodes IRR = 0.73 (95% CI 0.63 to 0.84).** Anthropometry measurements of weight and height showed median height-for-age was significantly increased in those on SODIS, corresponding to an average of 0.8 cm over a 1-year period over the group as a whole (95% CI 0.7 to 1.6 cm, $P = 0.031$). **Median weight-for-age was higher in those on SODIS, corresponding to a 0.23 kg difference in weight over the same period; however, the confidence interval spanned zero and the effect fell short of statistical significance (95% CI -0.02 to 0.47 kg, $P = 0.068$).** SODIS and control households did not differ in the microbial quality of their untreated household water over the follow-up period ($P = 0.119$), but *E. coli* concentrations in SODIS bottles were significantly lower than those in storage containers over all follow-up visits ($P < 0.001$). This is the first trial to show evidence of the effect of SODIS on childhood anthropometry, compared with children in the control group and should alleviate concerns expressed by some commentators that the lower rates of dysentery associated with SODIS are the product of biased reporting rather than reflective of genuinely decreased incidence.

[Environ Sci Technol.](#) 2011 Sep 15;45(18): 7862-7. Epub 2011 Aug 25.

[High compliance randomized controlled field trial of solar disinfection of drinking water and its impact on childhood diarrhea in rural Cambodia.](#)

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Recent solar disinfection (SODIS) studies in Bolivia and South Africa have reported compliance rates below 35% resulting in no overall statistically significant benefit associated with disease rates. In this study, we report the results of a 1 year randomized controlled trial investigating the effect of SODIS of drinking water on the incidence of dysentery and nondysentery diarrhea among children of age 6 months to 5 years living in rural communities in Cambodia. **We compared 426 children in 375 households using SODIS with 502 children in 407 households with no intervention. Study compliance was greater than 90% with only 5% of children having less than 10 months of follow-up and 2.3% having less than 6 months. Adjusted for water source type, children in the SODIS group had a reduced incidence of dysentery, with an incidence rate ratio (IRR) of 0.50 (95% CI 0.27-0.93, p = 0.029). SODIS also had a protective effect against nondysentery diarrhea, with an IRR of 0.37 (95% CI 0.29-0.48, p < 0.001).** This study suggests strongly that SODIS is an effective and culturally acceptable point-of-use water treatment method in the culture of rural Cambodia and may be of benefit among similar communities in neighboring South East Asian countries.

Comment

This year, solar disinfection was shown to reduce diarrhoea and dysentery in children in Kenya and Cambodia. In this method used in these studies, contaminated water is filled in a transparent plastic or glass bottle and exposed to the sun for 6 hours. During this time, the water is exposed to UV-radiation that kills certain bacteria are associated with diarrhoea. For more information on this simple method see: http://www.sodis.ch/index_EN

Emergency care

[Resuscitation](#). 2011 Aug;82(8): 1047-52. Epub 2011 Mar 23.

[Impact of essential surgical skills with an emphasis on emergency maternal, neonatal and child health training on the practice of doctors: a cluster randomised controlled trial in Pakistan.](#)

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INTRODUCTION: Majority of studies on evaluation of emergency management courses have focused on outcomes such as knowledge and skills demonstrated in non-clinical or traditional testing manner. Such surrogate outcomes may not necessarily reflect vital changes in practice. The aim of this study was to determine if and to what extent, specific training in the management of life threatening emergencies resulted in an increased in compliance with established care guidelines of doctors working in the emergency departments of public sector hospitals in Pakistan.

METHODS: A cluster randomised controlled trial was conducted in three districts hospitals in three cities (Khairpur, Vehari and Peshawar) of Pakistan. Thirty-six doctors, 18 in intervention (trained in ESS-EMNCH training) and 18 in control (untrained), were enrolled and 248 life

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threatening emergency events, 124 in each group, were observed for the correct use of the Airway, Breathing, Circulation (ABC) structured approach. The outcome measure was structured approach defined a priori. Data was analysed by using STATA software.

RESULTS: At individual level, **79 (63.7%) life threatening episodes were managed according to the structured approach in the intervention group and 46 (37.1%) were managed according to the structured approach in controls (OR 2.98, 95%CI 1.78-4.99, p-value=0.0001)**. At cluster level, the mean percentage (95% CI) of the structured approach used by doctors in the intervention group [62.9% (50.4-75.3%)], was significantly higher than those in the control group, [36.3% (26.3-46.4)] (p-value=0.001).

CONCLUSIONS: 5-day training of ESS-EMNCH significantly increased the compliance with established care guidelines of doctors during their management of life threatening emergency episodes in the public sector hospitals in Pakistan.

Intravenous fluids

[Indian J Pediatr.](#) 2011 Jul;78(7): 833-7. Epub 2011 Feb 3.

Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock.

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OBJECTIVE: To compare the efficacy of 3% saline and 0.9% saline infusion as initial resuscitative fluid therapy in children with septic shock.

METHODS: Sixty children between 2 to 12 years of age with septic shock were randomized to receive normal saline or 3% saline as initial resuscitative fluid. **Fluid resuscitation was done with 0.9% saline in boluses of 20 ml/kg, each bolus over a duration of 15 min with a maximum of 2 boluses.** Fluid resuscitation with 3% saline was given as a single bolus of 15 ml/kg over 30 min. After initial fluid bolus completion, if hemodynamic stability was not achieved then further fluid boluses of 0.9% saline were given in volumes of 5-10 ml/kg guided by CVP.

RESULTS: There were 30 patients in both the groups. Both the groups were identical with respect to age, gender, primary diagnosis, laboratory parameters, initial hemodynamic parameters and PRISM score at time of admission. **The amount of total fluid bolus required for resuscitation was approximately half in the group who received 3% saline as compared to the group who received 0.9% saline.** The use of vasopressor drugs, shock reversal time, ICU stay and mortality rate were similar in both the groups. No adverse effects related to fluid therapy were observed in any of the groups.

CONCLUSIONS: Both normal saline and hypertonic saline were equally effective as resuscitation fluid with respect to restoration of hemodynamic stability, average duration of ICU

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stay and mortality. Hypertonic saline appears to be a promising fluid for resuscitation of septic shock.

Epilepsy and acute seizures

[Epilepsia](#). 2011 Oct;52(10): 1918-27. doi: 10.1111/j.1528-1167.2011.03189.x. Epub 2011 Jul 21.

[Perilesional gliosis around solitary cerebral parenchymal cysticerci and long-term seizure outcome: a prospective study using serial magnetization transfer imaging.](#)

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PURPOSE: Epilepsy following solitary cerebral cysticercosis (SCC) is possibly caused by perilesional gliosis, best visualized on magnetization transfer imaging (MTI). This study aims to describe development of gliosis around SCC by prospective serial MTI and to correlate this gliosis with long-term seizure outcome.

METHODS: We randomized 123 patients with SCC and new-onset seizures to treatment with albendazole plus antiepileptics (treatment), or antiepileptics only (control), and performed magnetic resonance imaging (MRI) scans at 0, 3, 6, 12, and 24 months.

Prospective follow-up data regarding seizure outcome up to 5 years later were collected. MRI studies were analyzed for lesion characteristics and perilesional magnetization transfer (MT) hyperintensity.

KEY FINDINGS: Clinical and radiologic data of 77 patients were analyzed. Demographic and seizure characteristics were similar in treatment and control groups. Clinical data were available up to 64 months after enrollment. At 12 months, 89.5% patients were seizure-free. MTI is more sensitive than routine imaging for detection of perilesional gliosis. **Albendazole treatment did not affect imaging or clinical outcome, including development of gliosis.** Independent of duration of follow-up, gliosis was associated with more seizures, and with seizure recurrence at 12 months; duration of seizures and antiepileptic therapy was longer. Gliosis was not dependent on seizure type or stage of degeneration at enrollment or persistence/calcification of the lesion.

SIGNIFICANCE: Perilesional gliosis around SCC helps prognosticate seizure outcome. **Poorer outcome in patients with persistent lesions is likely to be related to mechanisms other than gliosis.** The lack of effect of albendazole on seizure outcome may be due to its inability to decrease formation of gliosis.

[Epilepsy Res](#). 2011 Sep;96(1-2): 96-100. Epub 2011 May 28.

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Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study.

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PURPOSE: The ketogenic (lipid to non-lipid) ratio may play an important role in the efficacy and tolerability of ketogenic diets (KD). This study was planned to compare the efficacy and tolerability of 2.5:1 versus 4:1 lipid: non-lipid ratio KD in young children with refractory epilepsy.

METHODS: Children aged 6 months to 5 years with refractory epilepsy were enrolled. They were randomized to receive either a 4:1 or 2.5:1 ketogenic ratio diet, which was introduced using a non-fasting protocol. Seizure frequency, biochemical profile (liver and kidney function tests, fasting lipid profile, and spot urinary calcium-creatinine ratio), and adverse effects were recorded at three months in both groups.

RESULTS: Thirty eight children were enrolled, 19 in each group. **At three months, 11 children (58%) in the 4:1 group and 12 (63%) in the 2.5:1 group had more than 50% reduction in seizures (p=0.78).** Five children (26%) in the 4:1 group and four (21%) in 2.5:1 group became seizure free. There was no significant difference in the biochemical parameters between the two groups.

CONCLUSION: 2.5:1 ratio KD is possibly as effective as 4:1 KD in controlling seizures and has fewer adverse effects.

Filariasis

[Acta Trop.](#) 2011 Sep;120 Suppl 1: S33-8. Epub 2010 Oct 8.

Evaluation of effectiveness of diethylcarbamazine/albendazole combination in reduction of *Wuchereria bancrofti* infection using multiple infection parameters.

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OBJECTIVES: To evaluate the effect of multiple rounds of annual single dose of DEC (6 mg/kg) or albendazole (400mg) given alone or in combination on *Wuchereria bancrofti* microfilaraemia, anti-filarial IgG1 and IgG4 and antigenaemia.

METHODS: A total of 170 participants were randomly assigned to albendazole (n = 62), DEC (n = 54), and DEC plus albendazole (DEC/ALB) combination (n = 54). Blood samples were collected at pre-treatment in 1998, at 1 week and 6 months after the first treatment and thereafter before subsequent treatments in 1999 and 2000. **Effects of treatment on W.**

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bancrofti infection were determined by changes in levels of microfilaraemia, antifilarial antibodies and circulating filarial antigen.

RESULTS: Comparison of geometric mean microfilariae intensities between DEC/ALB combination and DEC or albendazole single therapy groups after two rounds of annual treatment and 24 months follow-up showed that **combination therapy resulted in a greater reduction of microfilaraemia than single therapy with either albendazole ($p < 0.001$) or DEC alone ($p = 0.146$).** The overall levels of anti-filarial antibodies decreased significantly ($p = 0.028$ for IgG1 and $p < 0.043$ for IgG4) in all treatment groups at 24 months follow-up. Additionally, overall reduction in geometric mean circulating filarial antigen levels at 24 months was 44%, 60% and 85% for albendazole, DEC and DEC/ALB groups, respectively.

CONCLUSIONS: **These study findings suggest that albendazole improved efficacy of DEC and mass administration of a combination of the two drugs would therefore enhance the interruption of transmission of *W. bancrofti* in endemic areas. This information has important implications for the ongoing Global Program for Elimination of Lymphatic Filariasis.**

Health education

[Lancet](#). 2011 Aug 27;378(9793): 795-803. Epub 2011 Aug 3.

[The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial.](#)

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BACKGROUND: Health workers' malaria case-management practices often differ from national guidelines. **We assessed whether text-message reminders sent to health workers' mobile phones could improve and maintain their adherence to treatment guidelines for outpatient paediatric malaria in Kenya.**

METHODS: From March 6, 2009, to May 31, 2010, we did a cluster-randomised controlled trial at 107 rural health facilities in 11 districts in coastal and western Kenya. With a computer-generated sequence, **health facilities were randomly allocated to either the intervention group, in which all health workers received text messages on their personal mobile phones on malaria case-management for 6 months, or the control group, in which health workers did not receive any text messages.** Health workers were not masked to the intervention, although patients were unaware of whether they were in an intervention or control facility. The **primary outcome was correct management with artemether-lumefantrine**, defined as a dichotomous composite indicator of treatment, dispensing, and counselling tasks concordant with Kenyan national guidelines. The primary analysis was by intention to treat. The trial is registered with Current Controlled Trials, ISRCTN72328636.

FINDINGS: 119 health workers received the intervention. Case-management practices were assessed for 2269 children who needed treatment (1157 in the intervention group and 1112 in the control group). **Intention-to-treat analysis showed that correct artemether-lumefantrine**

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management improved by 23.7 percentage-points (95% CI 7.6-40.0; p=0.004) immediately after intervention and by 24.5 percentage-points (8.1-41.0; p=0.003) 6 months later.

INTERPRETATION: In resource-limited settings, **malaria control programmes should consider use of text messaging to improve health workers' case-management practices.**

[J Telemed Telecare](#). 2011;17(8): 432-6. Epub 2011 Oct 24.

[Mobile-phone text messaging \(SMS\) for providing oral health education to mothers of preschool children in Belgaum City.](#)

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We compared the effectiveness of two media (text messages and pamphlets) in imparting health education to mothers of preschool children. Mothers and their children were randomized into two groups. **There were 72 mothers and their children in the pamphlet group and 71 in the text message group.** The mothers were given health education by one of the two modes for four weeks. Knowledge, attitude and practices of the mothers were assessed by a questionnaire pre- and post-intervention. Visible plaque scores of their children were also recorded pre- and post-intervention. There were significant improvements in knowledge ($P < 0.001$), attitude ($P < 0.001$) and practices ($P < 0.001$) in both groups. There was also a significant reduction in visible plaque scores ($P < 0.001$) in both groups. Text messaging was more effective than pamphlets in improving knowledge, attitude and practices of mothers, but the comparative reduction in plaque score between groups was not significant. Text messaging appears to be an effective means of imparting oral health education.



Hepatitis and liver disease

[Gastroenterology](#). 2012 Mar;142(3): 505-512.e1. Epub 2011 Nov 23.

[Granulocyte colony-stimulating factor mobilizes CD34\(+\) cells and improves survival of patients with acute-on-chronic liver failure.](#)

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BACKGROUND & #38; AIMS: **Acute-on-chronic liver failure (ACLF) develops in patients with chronic liver disease and has high mortality.** Mobilization of bone marrow-derived stem cells with granulocyte colony-stimulating factor (G-CSF) could promote hepatic regeneration.

METHODS: **Consecutive patients with ACLF were randomly assigned to groups given 5 µg/kg G-CSF subcutaneously (12 doses; group A, n = 23) or placebo (group B, n = 24) plus standard medical therapy.** We assessed survival until day 60; Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD), and Sequential Organ Failure Assessment (SOFA) scores; and the development of other related complications.

RESULTS: After 1 week of treatment, group A had higher median leukocyte and neutrophil counts than group B ($P < .001$). **Sixteen patients in group A (69.6%) and 7 in group B (29%) survived; the actuarial probability of survival at day 60 was 66% versus 26%, respectively ($P = .001$).** Treatment with G-CSF also reduced CTP scores in group A by a median of 33.3% compared with an increase of 7.1% in group B ($P = .001$), along with MELD (median reduction of 15.3% compared with an increase of 11.7% in group B; $P = .008$) and SOFA scores (median reduction of 50% compared with an increase of 50% in group B; $P = .001$). **The percentages of patients who developed hepatorenal syndrome, hepatic encephalopathy, or sepsis were lower in group A than in group B (19% vs 71% [$P = .0002$], 19% vs 66% [$P = .001$], and 14% vs 41% [$P = .04$], respectively).** After 1 month of treatment, G-CSF increased the number of CD34(+) cells in the liver (by 45% compared with 27.5% in group B; $P = .01$).

CONCLUSIONS: **G-CSF therapy more than doubles the percentage of patients with ACLF who survive for 2 months; it also significantly reduces CTP, MELD, and SOFA scores and prevents the development of sepsis, hepatorenal syndrome, and hepatic encephalopathy.**

[J Hepatol.](#) 2012 Jun;56(6): 1293-8. Epub 2012 Feb 6.

[Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: A randomized study.](#)

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BACKGROUND & #38; AIMS: **Various vasoconstrictors are useful in the management of hepatorenal syndrome (HRS). Terlipressin is the drug of choice; however, it is expensive. In this study, we evaluated safety and efficacy of terlipressin and noradrenaline in the treatment of HRS.**

METHODS: Forty-six patients with HRS type 1 were managed with terlipressin (group A, N=23) or noradrenaline (Group B, N=23) with albumin in a randomized controlled trial at a tertiary center.

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RESULTS: HRS reversal could be achieved in 9 (39.1%) patients in group A and 10 (43.4%) patients in group B (p=0.764). Univariate analysis showed baseline Child Turcotte Pugh score (CTP), model of end stage liver disease (MELD), urine output on day 1(D1), albumin, and mean arterial pressure (MAP) were associated with response. However, on multivariate analysis only CTP score was associated with response. Fourteen patients in group A and 12 in group B died at day 15 (p>0.05). Noradrenaline was less expensive than terlipressin (p<0.05). No major adverse effects were seen.

CONCLUSIONS: The results of this randomized study suggest that noradrenaline is as safe and effective as terlipressin, but less expensive in the treatment of HRS and baseline CTP score is predictive of response.

[J Gastroenterol Hepatol.](#) 2012 May 18. doi: 10.1111/j.1440-1746.2012.07186.x. [Epub ahead of print]

[Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labeled randomized controlled trial of lactulose versus no lactulose.](#)

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Development of overt hepatic encephalopathy (HE) is Background and Aims: associated with poor prognosis in patients with cirrhosis. Lactulose is used for the treatment of HE. **There is no study on the prevention of overt HE using lactulose in patients who never had HE earlier.** Patients and Methods: Consecutive cirrhotic patients who never had an episode of overt HE were randomized to receive lactulose (Gp-L) or no lactulose (Gp-NL). All patients were assessed by psychometry [(number connection test (NCT-A and B), figure connection test if illiterate (FCT-A and B), digit symbol test (DST), serial dot test (SDT), line tracing test (LTT)] and critical flicker frequency test (CFF) at inclusion and after 3 months. These patients were Of 250 followed every month for 12 months for development of overt HE. Results: patients screened, 120(48%) meeting the inclusion criteria were randomized to Gp-L(n=60) and Gp-NL(n=60). Twenty (19%) of 105 patients followed for 12 mo developed an episode of overt HE. Six (11%) of 55 in the lactulose (Gp-L) group and 14(28%) of 50 in the Gp-NL (p=0.02) developed overt HE. Ten (20%) of 50 patients in Gp-NL and 5(9%) of 55 patients in Gp-L group died, p=0.16. Number of patients with minimal hepatic encephalopathy (MHE) were comparable in two groups at baseline (Gp-L vs Gp-NL, 32:36, p=0.29). Lactulose improved MHE in 66% of patients in Gp-L. Taking a cutoff <38Hz sensitivity and specificity of CFF in predicting HE were 52% and 77% at baseline and 52% and 82% at 3 month of treatment. On multivariate analysis Child's score and presence of MHE at baseline were significantly associated with development of overt HE.

CONCLUSIONS: Lactulose is effective for primary prevention of overt hepatic encephalopathy in patients with cirrhosis.

Comment

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The above three studies suggest that lactulose, G-CSF and vasoconstrictors such as noradrenaline, can help prevent adverse outcomes from severe hepatic failure. The Child-Turchotte-Pugh score, referred to in the above 2 trials is a simple clinical score which can help in prognosis of acute liver failure. It uses a combination of serum bilirubin level, serum albumin level, prothrombin time / INR, degree of ascites and encephalopathy grade. A CTP-score calculator is available at: http://www.globalrph.com/child_pugh.htm, which provides a guide to survival and functional prognosis

[Trop Gastroenterol](#). 2011 Oct-Dec;32(4):299-303.

[Effectiveness of beta blockers in primary prophylaxis of variceal bleeding in children with portal hypertension.](#)

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AIM: The primary aim of our study was to assess the effectiveness of beta blockers in non bleeding portal hypertensive children. The secondary objective was to evaluate whether the newer generation beta blockers were superior compared to conventional ones.

METHODS: Conventional propranolol and newer generation carvedilol were administered to 31 subjects each, after stratifying them into nearly equal subgroups according to etiology (sinusoidal or presinusoidal).

RESULTS: At the end of 2 years study period, 3 children (4.83%) had breakthrough bleeding. A decrease, increase and no alteration in grade of oesophageal varices was seen in 40, 9 and 13 cases respectively. Of the 9 children with associated gastroesophageal varices (GOV), the severity of lesions was reduced in 8 of them. Both the drugs had efficacious outcome in sinusoidal as well as presinusoidal cases, having a significant coefficient of correlation ($r > 0.5$) with time. Carvedilol was more effective than propranolol statistically ($p = 0.035$ and $p = 0.034$ respectively), only at 4 and 5 month follow-up period.

CONCLUSION: Beta blockers are effective in preventing variceal bleed in children with portal hypertension. Long-term efficacy of carvedilol and propranolol was similar.

HIV / AIDS

(See also Tuberculosis)

[PLoS One](#). 2011;6(12): e28759. Epub 2011 Dec 15.

[Randomized controlled trials of HIV/AIDS prevention and treatment in Africa: results from the Cochrane HIV/AIDS Specialized Register.](#)

[Zani B](#), [Pienaar ED](#), [Oliver J](#), [Siegfried N](#).

Randomised trials in child health in developing countries 2011-12

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INTRODUCTION: To effectively address HIV/AIDS in Africa, evidence on preventing new infections and providing effective treatment is needed. Ideally, decisions on which interventions are effective should be based on evidence from randomized controlled trials (RCTs). Our previous research described African RCTs of HIV/AIDS reported between 1987 and 2003. This study updates that analysis with RCTs published between 2004 and 2008.

OBJECTIVES: **To describe RCTs of HIV/AIDS conducted in Africa and reported between 2004 and 2008.**

METHODS: We searched the Cochrane HIV/AIDS Specialized Register in September 2009. Two researchers independently evaluated studies for inclusion and extracted data using standardized forms. Details included location of trials, interventions, methodological quality, location of principal investigators and funders.

RESULTS: Our search identified **834 RCTs, with 68 conducted in Africa**. Forty-three assessed prevention-interventions and 25 treatment-interventions. Fifteen of the 43 prevention RCTs focused on preventing mother-to-child HIV transmission. Thirteen of the 25 treatment trials focused on opportunistic infections. **Trials were conducted in 16 African countries with most in South Africa (20), Zambia (12) and Zimbabwe (9)**. The median sample size was 628 (range 33-9645). Methods used for the generation of the allocation sequence and allocation concealment were adequate in 38 and 32 trials, respectively, and 58 reports included a CONSORT recommended flow diagram. Twenty-nine principal investigators resided in the United States of America (USA) and 18 were from African countries. Trials were co-funded by different agencies with most of the funding obtained from USA governmental and non-governmental agencies. Nineteen pharmaceutical companies provided partial funding to 15 RCTs and African agencies co-funded 17 RCTs. Ethical approval was reported in 65 trials and informed consent in 61 trials.

CONCLUSION: Prevention trials dominate the trial landscape in Africa. Of note, few principal investigators and funders are from Africa. These findings mirror our previous work and continue to indicate a need for strengthening trial research capacity in Africa.



[BMC Pediatr.](#) 2011 Nov 21;11: 104.

[Utility of clinical parameters to identify HIV infection in infants below ten weeks of age in South Africa: a prospective cohort study.](#)

[Jaspan HB](#), [Myer L](#), [Madhi SA](#), [Violari A](#), [Gibb DM](#), [Stevens WS](#), [Dobbels E](#), [Cotton MF](#).

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BACKGROUND: As HIV-infected infants have high mortality, the World Health Organization now recommends initiating antiretroviral therapy as early as possible in the first year of life. However, in many settings, laboratory diagnosis of HIV in infants is not readily available. We aimed to develop a clinical algorithm for HIV presumptive diagnosis in infants < 10 weeks old using screening data from the Children with HIV Early Antiretroviral therapy (CHER) study in South Africa. HIV-infected and HIV-uninfected exposed infants < 10 weeks of age were identified through Vertical Transmission Prevention programs. Clinical and laboratory data were systematically recorded, groups were compared using Kruskal-Wallis, analysis of variance (ANOVA), and Fisher's exact tests. Receiver Operating Characteristic (ROC) curves were compiled using combinations of clinical findings.

RESULTS: 417 HIV-infected and 125 HIV-exposed, uninfected infants, median age 46 days (IQR 38-55), were included. The median CD4 percentage in HIV-infected infants was 34 (IQR 28-41)%. **HIV-infected infants had lower weight-for-age, more lymphadenopathy, oral thrush, and hepatomegaly than exposed uninfected infants (Adjusted Odds Ratio 0.51, 8.8, 5.6 and 23.5 respectively; p < 0.001 for all). Sensitivity of individual signs was low (< 20%) but specificity high (98-100%). If any one of oral thrush, hepatomegaly, splenomegaly, lymphadenopathy, diaper dermatitis, weight < 50(th) centile are present, sensitivity for HIV infection amongst HIV-exposed infants was 86%.** These algorithms performed similarly when used to predict severe immune suppression.

CONCLUSIONS: A combination of physical findings is helpful in identifying infants most likely to be HIV-infected. This may inform management algorithms and provide guidance for focused laboratory testing in some settings, and should be further validated in these settings and elsewhere.



Anti-retroviral treatment

(See also BCG vaccine)

[N Engl J Med.](#) 2012 Jun 21;366(25):2380-9.

[Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children.](#)
[Violari A,](#) [Lindsey JC,](#) [Hughes MD,](#) [Mujuru HA,](#) [Barlow-Mosha L,](#) [Kamthunzi P,](#) [Chi BH,](#)
[Cotton MF,](#) [Moultrie H,](#) [Khadse S,](#) [Schimana W,](#) [Bobat R,](#) [Purdue L,](#) [Eshleman SH,](#) [Abrams EJ,](#)
[Millar L,](#) [Petzold E,](#) [Mofenson LM,](#) [Jean-Philippe P,](#) [Palumbo P.](#)

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BACKGROUND: Nevirapine-based antiretroviral therapy is the predominant (and often the only) regimen available for children in resource-limited settings. Nevirapine resistance after exposure to the drug for prevention of maternal-to-child human immunodeficiency virus (HIV) transmission is common, a problem that has led to the recommendation of ritonavir-boosted lopinavir in such settings. Regardless of whether there has been prior exposure to nevirapine, the performance of nevirapine versus ritonavir-boosted lopinavir in young children has not been rigorously established.

METHODS: In a randomized trial conducted in six African countries and India, we compared the initiation of HIV treatment with zidovudine, lamivudine, and either nevirapine or ritonavir-boosted lopinavir in HIV-infected **children** 2 to 36 months of age who had no prior exposure to

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nevirapine. The primary end point was virologic failure or discontinuation of treatment by study week 24.

RESULTS: A total of 288 children were enrolled; the median percentage of CD4+ T cells was 15%, and the median plasma HIV type 1 (HIV-1) RNA level was 5.7 log(10) copies per milliliter. **The percentage of children who reached the primary end point was significantly higher in the nevirapine group than in the ritonavir-boosted lopinavir group (40.8% vs. 19.3%; P<0.001).** Among the nevirapine-treated children with virologic failure for whom data on resistance were available, more than half (19 of 32) had resistance at the time of virologic failure. In addition, the time to a protocol-defined toxicity end point was shorter in the nevirapine group (P=0.04), as was the time to death (P=0.06).

CONCLUSIONS: Outcomes were superior with ritonavir-boosted lopinavir among young children with no prior exposure to nevirapine. Factors that may have contributed to the suboptimal results with nevirapine include elevated viral load at baseline, selection for nevirapine resistance, background regimen of nucleoside reverse-transcriptase inhibitors, and the standard ramp-up dosing strategy. The results of this trial present policymakers with difficult choices.



[J Acquir Immune Defic Syndr.](#) 2011 Dec 1;58(4): 392-8.

[Pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda.](#)

[Fillekes Q, Natukunda E, Balungi J, Kendall L, Bwakura-Dangarembizi M, Keishanyu R, Ferrier A, Lutakome J, Gibb DM, Burger DM, Walker AS; ARROW Trial Team.](#)

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OBJECTIVES: To evaluate international pediatric efavirenz dosing recommendations using full pharmacokinetic (PK) information.

DESIGN: Open-label, multicenter, PK study.

METHODS: Forty-one HIV-infected Ugandan children (3-12 years) on efavirenz + lamivudine + abacavir were enrolled in a study of twice-daily to once-daily lamivudine + abacavir 36 weeks after antiretroviral therapy initiation in the ARROW trial. Once-daily efavirenz doses were 200, 250, 300, 350 mg for children weighing 10 to <15, 15 to <20, 20 to <25, 25 to <30 kg, respectively, using 200/50 mg capsules or halved 600 mg tablets in case of 300 and 350 mg doses. Intensive plasma PK sampling (t = 0, 1, 2, 4, 6, 8, 12 hours postobserved ingestion) was performed at steady state (PK1) and repeated 4 weeks later (PK2, including a further 24-hour sample).

RESULTS: Forty-one and 39 children had evaluable efavirenz profiles at PK1 and PK2, respectively. Seventeen (41%) were boys. Five, 16, 17, 3 were in the 10 to <15, 15 to <20, 20 to <25, 25 to <30 kg weight bands. The geometric mean (%CV) the area under the concentration-time curve 0-24 hours postdose was 50.8 (90.8%) and 55.5 (82.7%) h·mg·L(-1) at PK1 and PK2, respectively. Six children at PK1 and 7 at PK2 had subtherapeutic C(8h) and/or C(12h) (<1.0 mg/L), 7 of 41 (17%) at either visit. At PK2, 15 of 39 (38%) children had C(24h) <1.0 mg/L

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(median (interquartile range) [range] 1.1 (0.7-2.9) [0.3-18.4]). Ten children at PK1 and 11 at PK2 had C(8h) and/or C(12h) >4.0 mg/L; 12 of 41 (29%) at either visit.

CONCLUSIONS: African children aged 3-12 years, on efavirenz dosed according to 2006 WHO/manufacture's recommendations, had lower and highly variable efavirenz PK parameters compared with adult data from manufacture's leaflet. There were no differences across weight bands, suggesting no major effect of using half tablets. Higher pediatric efavirenz doses, as per WHO 2010 recommendations, should be used and investigated further but may risk increasing the proportion of children with potentially toxic levels.

Comment

The 2010 paediatric guidelines for anti-retroviral therapy in children are available at: <http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html>, and a PDF of the dosing recommendations for all ARTs is available at: http://www.who.int/hiv/pub/paediatric/paediatric_arv_dosing.pdf

Management of HIV-related conditions

[J Nutr.](#) 2012 Apr;142(4): 757-63. Epub 2012 Feb 29.

[The prevalence of stunting is high in HIV-1-exposed uninfected infants in Kenya.](#)

[McGrath CJ](#), [Nduati R](#), [Richardson BA](#), [Kristal AR](#), [Mbori-Ngacha D](#), [Farquhar C](#), [John-Stewart GC](#).

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As prevention of mother-to-child HIV-1 transmission (PMTCT) programs decrease the numbers of HIV-1-infected infants, it remains important to improve growth in HIV-1-exposed, uninfected (EU) infants. To determine the growth rate and predictors of growth faltering in breast-fed and formula-fed EU infants, **growth analyses [weight-for-age (WAZ), weight-for-length (WLZ), and length-for-age (LAZ) Z-scores] were conducted by using data from a randomized feeding trial in HIV-1-infected women in Kenya.** Growth faltering in EU infants was compared based on randomization to breastfeeding (BF) or formula feeding (FF) using Cox proportional hazards regression models. Linear mixed-effects models determined rate and cofactors of length growth. **Among 338 EU infants, 164 (49%) were breast-fed and 174 (51%) formula-fed.** In both arms, growth declined steadily during follow-up. By 2 y, 29% of children were underweight (WAZ < -2), 18% were wasted (WLZ < -2), and 58% were stunted (LAZ < -2), with no differences by feeding arm. Higher maternal education (y) and taller stature (cm) were associated with a decreased risk of underweight and stunting [underweight: adjusted HR (aHR) = 0.90 (95% CI: 0.83, 0.99), P = 0.03, and aHR = 0.92 (95% CI: 0.87, 0.97), P = 0.002; and stunting: aHR = 0.91 (95% CI: 0.85, 0.97), P = 0.003, and aHR = 0.96 (95% CI: 0.92, 0.99), P = 0.02, respectively]. Diarrhea was associated with an increased risk of wasting [aHR = 2.26 (95% CI: 1.11, 4.62), P = 0.03]. In multivariate analyses, FF was associated with slower declines in length velocity [0.24 LAZ/y (95% CI: 0.06, 0.43), P = 0.009]. **Despite being**

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uninfected, HIV-1-exposed infants showed frequent growth faltering, suggesting the need for vigilance in recognizing stunting within PMTCT programs. The slower rate of decline in length growth with FF may reflect benefits of micronutrients. **Because BF is the best option for HIV-1-infected mothers in resource-limited settings, nutritional interventions should be examined for their impact on growth in exposed uninfected breast-fed infants.**

[Pediatr Infect Dis J.](#) 2011 Oct;30(10): 904-6.

[Bacteremia in human immunodeficiency virus-infected children in Cape Town, South Africa.](#)

[le Roux DM](#), [Cotton MF](#), [le Roux SM](#), [Whitelaw A](#), [Lombard CJ](#), [Zar HJ](#).

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Bacteremia contributes to morbidity of HIV-infected children. In a randomized controlled trial evaluating trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, 47 bacteremias were detected. The incidence rate of bacteremia increased in the first 3 months after starting combination antiretroviral therapy (cART), but decreased by 74% once children were established on cART for more than 3 months. Children should be prioritized for early cART.

[Pediatr Infect Dis J.](#) 2011 Oct;30(10): 877-82.

[Increased microbial translocation in \$\leq 180\$ days old perinatally human immunodeficiency virus-positive infants as compared with human immunodeficiency virus-exposed uninfected infants of similar age.](#)

[Papasavvas E](#), [Azzoni L](#), [Foulkes A](#), [Violari A](#), [Cotton MF](#), [Pistilli M](#), [Reynolds G](#), [Yin X](#), [Glencross DK](#), [Stevens WS](#), [McIntyre JA](#), [Montaner LJ](#).

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BACKGROUND: The effect of early versus deferred antiretroviral treatment (ART) on plasma concentration of lipopolysaccharide (LPS) and host LPS-binding molecules in human immunodeficiency virus (HIV)-infected infants up to 1 year of age was investigated.

METHODS: We evaluated 54 perinatally HIV-infected and 22 HIV-exposed uninfected infants (controls) at the first and second semester of life. All HIV-infected infants had a baseline CD4 of $\geq 25\%$, participated in the Comprehensive International Program of Research on AIDS Children with HIV Early Antiretroviral Therapy trial in South Africa, and were randomized in the following groups: **group 1 (n = 20), ART deferred until CD4 < 25% or severe HIV disease; and group 2 (n = 34), ART initiation within 6 to 12 weeks of age.** LPS, endotoxin-core antibodies, soluble CD14 (sCD14), and LPS-binding protein (LBP) were measured in cryopreserved plasma. T-cell activation was measured in fresh whole blood.

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RESULTS: At the first semester, LPS concentration was higher in HIV-infected infants than in controls; sCD14, LBP, and T-cell activation were higher in group 1 than in group 2 and controls. Although LPS was not correlated with study variables, viral load was positively associated with sCD14, LBP, or endotoxin-core antibodies. At the second semester, LPS was not detectable and elevated host LPS-control molecules values were sustained in all groups and in conjunction with ART in all HIV-infected infants.

CONCLUSIONS: Although plasma concentration of LPS was higher in perinatally HIV-infected infants 0 to 6 months of age than in controls independent of ART initiation strategy, **concentration of LPS-control molecules was higher in infants with deferred ART, suggesting the presence of increased microbial translocation in HIV-infected infants with sustained early viral replication.**

[J Acquir Immune Defic Syndr.](#) 2012 Jun 1;60(2): 150-157.

[A Randomized Controlled Trial of Highly Active Antiretroviral Therapy Versus Highly Active Antiretroviral Therapy and Chemotherapy in Therapy-Naive Patients With HIV-Associated Kaposi Sarcoma in South Africa.](#)

[Mosam A](#), [Shaik F](#), [Uldrick TS](#), [Esterhuizen T](#), [Friedland GH](#), [Scadden DT](#), [Aboobaker J](#), [Coovadia HM](#).

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BACKGROUND: The optimal approach to HIV-associated Kaposi sarcoma (HIV-KS) in sub-Saharan Africa is unknown. With large-scale rollout of highly active antiretroviral therapy (HAART) in South Africa, we hypothesized that survival in HIV-KS would improve and administration of chemotherapy in addition to HAART would be feasible and improve KS-specific outcomes.

METHODS: We conducted a randomized, controlled, open-label trial with intention-to-treat analysis. Treatment-naive patients from King Edward VIII Hospital, Durban, South Africa, a public-sector tertiary referral center, with HIV-KS, but no symptomatic visceral disease or fungating lesions requiring urgent chemotherapy, were randomized to HAART alone or HAART and chemotherapy (CXT). HAART arm received stavudine, lamivudine, and nevirapine (Triomune; CXT arm received Triomune plus bleomycin, doxorubicin, and vincristine every 3 weeks. When bleomycin, doxorubicin, and vincristine were not available, oral etoposide (50-100 mg for 1-21 days of a 28-day cycle) was substituted. Primary outcome was overall KS response using AIDS Clinical Trial Group criteria 12 months after HAART

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initiation. Secondary comparisons included time to response, progression-free survival, overall survival, adverse events, HIV control, CD4 reconstitution, adherence, and quality of life.

RESULTS: Fifty-nine subjects were randomized to HAART and 53 to CXT; 12-month overall KS response was 39% in the HAART arm and 66% in the CXT arm (difference, 27%; 95% confidence interval, 9%-43%; $P = 0.005$). At 12 months, 77% were alive (no survival difference between arms; $P = 0.49$), 82% had HIV viral load <50 copies per milliliter without difference between the arms ($P = 0.47$); CD4 counts and quality-of-life measures improved in all patients.

CONCLUSIONS: HAART with chemotherapy produced higher overall KS response over 12 months, whereas HAART alone provided similar improvement in survival and select measures of morbidity. In Africa, with high prevalence of HIV and human herpes virus-8 and limited resources, HAART alone provides important benefit in patients with HIV-KS.

[Cochrane Database Syst Rev.](#) 2011 Oct 5;(10): CD004776.

[Treatment for anemia in people with AIDS.](#)

[Martí-Carvajal AJ, Solà I, Peña-Martí GE, Comunián-Carrasco G.](#)

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BACKGROUND: Anemia is common in persons with HIV infection and is associated with poor prognosis. There is a need to assess the effects of anemia treatments, and to determine whether these interventions are beneficial.

OBJECTIVES: To determine the efficacy and safety of treatments for anemia in people with HIV infection and AIDS.

SEARCH STRATEGY: The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 10, 2010), MEDLINE (1980-November 25, 2010), EMBASE (1980-November 25, 2010), LILACS (1982 to November 25, 2010), Africa Index Medicus (up to November 9, 2010), ISI Web of Knowledge (2005 to October 9, 2010), Scirus (October 9, 2010) reference lists of relevant articles. We asked the Cochrane HIV/AIDS and Pregnancy and Childbirth Groups to check their Specialised Registers. We also checked the reference lists of all trials identified by the above methods.

SELECTION CRITERIA: Randomized trials assessing the effects of treatments for anemia in people diagnosed with HIV infection. There were no age restrictions.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed relevant studies for inclusion. Data extraction and quality assessment of relevant studies was performed by two authors and checked by the other two authors.

MAIN RESULTS: Six trials with a high risk of bias, including 537 patients, met the inclusion criteria. These trials only covered recombinant Human erythropoietin alfa (rHuEPO). Two of

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them including adult and paediatric participants (84 participants and 4 events) comparing rHuEPO to placebo did not reduce the risk of mortality with a follow up to 12 weeks (pooled RR 0.56, 95% confidence interval (CI) 0.08 to 4.05, I(2) = 0%). **Any trials that compared rHuEPO to placebo did not show any benefit on hematological values response, number of patients transfused, or number of packed red cell transfused.** Two trial compared the effects of two rHuEPO dosing regimens on hemoglobin value and quality of life, but the effects are unclear. Three RCT reported high risk of attrition bias; therefore, were not included in a meta-analysis.

AUTHORS' CONCLUSIONS: This updated Cochrane review provides evidence that **rHuEPO compared with placebo does not reduce mortality, does not reduce transfusion requirements, did not increase hemoglobin levels, and did not improve quality of life in HIV-infected patients with anemia.** The results are based on six RCTs with high risk of bias. Therefore prescription of this intervention for treating anemia in patients with AIDS is not justified, unless new evidence from a large high quality trial alters this conclusion.



Prevention of parent to child transmission

[Lancet](#). 2012 Jan 21;379(9812): 221-8. Epub 2011 Dec 22.

[Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission \(HPTN 046\): a randomised, double-blind, placebo-controlled trial.](#)

[Coovadia HM, Brown ER, Fowler MG, Chipato T, Moodley D, Manji K, Musoke P, Stranix-Chibanda L, Chetty V, Fawzi W, Nakabiito C, Msweli L, Kisenge R, Guay L, Mwatha A, Lynn DJ, Eshleman SH, Richardson P, George K, Andrew P, Mofenson LM, Zwierski S, Maldonado Y; HPTN 046 protocol team.](#)

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BACKGROUND: Nevirapine given once-daily for the first 6, 14, or 28 weeks of life to infants exposed to HIV-1 via breastfeeding reduces transmission through this route compared with single-dose nevirapine at birth or neonatally. We aimed to assess incremental safety and efficacy of extension of such prophylaxis to 6 months.

METHODS: In our phase 3, randomised, double-blind, placebo-controlled HPTN 046 trial, we assessed the incremental benefit of extension of once-daily infant nevirapine from age 6 weeks to 6 months. We enrolled breastfeeding infants born to mothers with HIV-1 in four African countries within 7 days of birth. **Following receipt of nevirapine from birth to 6 weeks, infants without HIV infection were randomly allocated (by use of a computer-generated permuted block algorithm with random block sizes and stratified by site and maternal**

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antiretroviral treatment status) to receive extended nevirapine prophylaxis or placebo until 6 months or until breastfeeding cessation, whichever came first. The primary efficacy endpoint was HIV-1 infection in infants at 6 months and safety endpoints were adverse reactions in both groups. We used Kaplan-Meier analyses to compare differences in the primary outcome between groups. This study is registered with ClinicalTrials.gov, number NCT00074412.

FINDINGS: Between June 19, 2008, and March 12, 2010, we randomly allocated 1527 infants (762 nevirapine and 765 placebo); five of whom had HIV-1 infection at randomisation and were excluded from the primary analyses. **In Kaplan-Meier analysis, 1.1% (95% CI 0.3-1.8) of infants who received extended nevirapine developed HIV-1 between 6 weeks and 6 months compared with 2.4% (1.3-3.6) of controls (difference 1.3%, 95% CI 0.2-2.6), equating to a 54% reduction in transmission (p=0.049). However, mortality (1.2% for nevirapine vs 1.1% for placebo; p=0.81) and combined HIV infection and mortality rates (2.3% vs 3.2%; p=0.27) did not differ between groups at 6 months.** 125 (16%) of 758 infants given extended nevirapine and 116 (15%) of 761 controls had serious adverse events, but frequency of adverse events, serious adverse events, and deaths did not differ significantly between treatment groups.

INTERPRETATION: Nevirapine prophylaxis can safely be used to provide protection from mother-to-child transmission of HIV-1 via breastfeeding for infants up to 6 months of age.



[AIDS Res Hum Retroviruses](#). 2011 Aug;27(8): 823-9. Epub 2011 Feb 25.

Slower clearance of nevirapine resistant virus in infants failing extended nevirapine prophylaxis for prevention of mother-to-child HIV transmission.

Persaud D, Bedri A, Ziemniak C, Moorthy A, Gudetta B, Abashawl A, Mengistu Y, Omer SB, Isehak A, Kumbi S, Adamu R, Lulseged S, Ashworth R, Hassen E, Ruff A; Ethiopian Swen Study Team.

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Nevirapine resistance mutations arise commonly following single or extended-dose nevirapine (ED-NVP) prophylaxis to prevent mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV), but decay within 6-12 months of single-dose exposure. Use of ED-NVP prophylaxis in infants is expected to rise, but data on decay of nevirapine resistance mutations in infants in whom ED-NVP failed remain limited. We assessed, in Ethiopian infants participating in the Six-Week Extended Nevirapine (SWEN) Trial, the prevalence and persistence of nevirapine resistance mutations at 6 and 12 months following single-dose or up to 6 weeks of ED-NVP, and correlated their presence with the timing of infection and the type of resistance mutations. Standard population genotyping followed by high-throughput cloning were done on dried blood spot samples collected during the trial. **More infants who received ED-NVP had nevirapine resistance detected by standard population genotyping (high frequencies) at age 6 months compared with those who received single-dose nevirapine (SD-NVP) (58% of 24 vs. 26% of 19, respectively; p = 0.06). Moreover, 56% of ED-NVP-exposed infants with nevirapine resistance at age 6 months still had nevirapine resistance**

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mutations present at high frequencies at age 1 year. Infants infected before 6 weeks of age who received either SD- or ED-NVP were more likely to have Y181C or K103N; these mutations were also more likely to persist at high frequencies through 1 year of age. **HIV-infected infants in whom ED-NVP prophylaxis fails are likely to experience delayed clearance of nevirapine-resistant virus in the first year of life, which in turn places them at risk for early selection of multidrug-resistant HIV after initial therapy with nonnucleoside reverse transcriptase inhibitor-based regimens.**

[N Engl J Med.](#) 2012 Jun 21;366(25):2368-79.

[Three postpartum antiretroviral regimens to prevent intrapartum HIV infection.](#)

[Nielsen-Saines K](#), [Watts DH](#), [Veloso VG](#), [Bryson YJ](#), [Joao EC](#), [Pilotto JH](#), [Gray G](#), [Theron G](#), [Santos B](#), [Fonseca R](#), [Kreitchmann R](#), [Pinto J](#), [Mussi-Pinhata MM](#), [Ceriotto M](#), [Machado D](#), [Bethel J](#), [Morgado MG](#), [Dickover R](#), [Camarca M](#), [Mirochnick M](#), [Siberry G](#), [Grinsztejn B](#), [Moreira RI](#), [Bastos FI](#), [Xu J](#), [Moye J](#), [Mofenson LM](#); [NICHD HPTN 040/PACTG 1043 Protocol Team](#).

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BACKGROUND: The safety and efficacy of adding antiretroviral drugs to standard zidovudine prophylaxis in infants of mothers with human immunodeficiency virus (HIV) infection who did not receive antenatal antiretroviral therapy (ART) because of late identification are unclear. We evaluated three ART regimens in such infants.

METHODS: Within 48 hours after their birth, we randomly assigned formula-fed infants born to women with a peripartum diagnosis of HIV type 1 (HIV-1) infection to one of three regimens: **zidovudine for 6 weeks (zidovudine-alone group), zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life (two-drug group), or zidovudine for 6 weeks plus nelfinavir and lamivudine for 2 weeks (three-drug group).** The primary outcome was HIV-1 infection at 3 months in infants uninfected at birth.

RESULTS: A total of 1684 infants were enrolled in the Americas and South Africa (566 in the zidovudine-alone group, 562 in the two-drug group, and 556 in the three-drug group). The overall rate of in utero transmission of HIV-1 on the basis of Kaplan-Meier estimates was 5.7% (93 infants), with no significant differences among the groups. **Intrapartum transmission occurred in 24 infants in the zidovudine-alone group (4.8%; 95% confidence interval [CI], 3.2 to 7.1), as compared with 11 infants in the two-drug group (2.2%; 95% CI, 1.2 to 3.9; P=0.046) and 12 in the three-drug group (2.4%; 95% CI, 1.4 to 4.3; P=0.046).** The overall transmission rate was 8.5% (140 infants), with an increased rate in the zidovudine-alone group (P=0.03 for the comparisons with the two- and three-drug groups). On multivariate analysis, zidovudine monotherapy, a higher maternal viral load, and maternal use of illegal substances were significantly associated with transmission. The rate of neutropenia was significantly increased in the three-drug group (P<0.001 for both comparisons with the other groups).

CONCLUSIONS: In neonates whose mothers did not receive ART during pregnancy, prophylaxis with a two- or three-drug ART regimen is superior to zidovudine alone for the prevention of intrapartum HIV transmission; the two-drug regimen has less toxicity than the three-drug regimen.



[BMC Public Health](#). 2011 Dec 22;11: 946.

[Effect of nutritional supplementation of breastfeeding HIV positive mothers on maternal and child health: findings from a randomized controlled clinical trial.](#)

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BACKGROUND: It has been well established that breastfeeding is beneficial for child health, however there has been debate regarding the effect of lactation on maternal health in the presence of HIV infection and the need for nutritional supplementation in HIV positive lactating mothers.

AIMS: To assess the effect of nutritional supplementation to HIV infected lactating mothers on nutritional and health status of mothers and their infants.

METHODS: A randomized controlled clinical trial to study the impact of nutritional supplementation on breastfeeding mothers. Measurements included anthropometry; body composition indicators; CD4 count, haemoglobin and albumin; as well as incidence rates of opportunistic infections; depression and quality of life scores. Infant measurements included anthropometry, development and rates of infections.

RESULTS: The supplement made no significant impact on any maternal or infant outcomes. However in the small group of mothers with low BMI, the intake of supplement was significantly associated with preventing loss of lean body mass (1.32 kg vs. 3.17 kg; $p = 0.026$). There was no significant impact of supplementation on the infants.

CONCLUSIONS: A 50 g daily nutritional supplement to breastfeeding mothers had no or limited effect on mother and child health outcomes.



[Am J Clin Nutr](#). 2012 Mar;95(3): 759-65. Epub 2012 Jan 18.

[A lipid-based nutrient supplement mitigates weight loss among HIV-infected women in a factorial randomized trial to prevent mother-to-child transmission during exclusive breastfeeding.](#)

[Kayira D](#), [Bentley ME](#), [Wiener J](#), [Mkhomawanthu C](#), [King CC](#), [Chitsulo P](#), [Chigwenembe M](#), [Ellington S](#), [Hosseinipour MC](#), [Kourtis AP](#), [Chasela C](#), [Tembo M](#), [Tohill B](#), [Piwoz EG](#), [Jamieson DJ](#), [van der Horst C](#), [Adair L](#); [BAN Study Team](#).

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BACKGROUND: Breastfeeding increases metabolic demands on the mother, and excessive postnatal weight loss increases maternal mortality.

OBJECTIVE: We evaluated the efficacy of a lipid-based nutrient supplement (LNS) for prevention of excess weight loss in breastfeeding, HIV-infected women.

DESIGN: The BAN (Breastfeeding, Antiretrovirals, and Nutrition) Study was a randomized controlled trial in Lilongwe, Malawi. At delivery, HIV-infected mothers and their infants were randomly assigned according to a 2-arm (with and without LNS) by 3-arm (maternal triple-antiretroviral prophylaxis, infant-nevirapine prophylaxis, or neither) factorial design. The 28-wk LNS intervention provided daily energy (700 kcal), protein (20 g), and micronutrients (except for vitamin A) to meet lactation needs. Women were counseled to breastfeed exclusively for 24 wk and to wean by 28 wk. Weight change (0-28 wk) was tested in an intent-to-treat analysis by using 2-factor ANOVA and with longitudinal mixed-effects models.

RESULTS: At delivery, the LNS (n = 1184) and control (n = 1185) groups had similar mean weights and BMIs. **Women receiving the LNS had less 0-28-wk weight loss (-1.97 compared with -2.56 kg, P = 0.003). This difference remained significant after adjustment for maternal antiretroviral drug therapy and baseline BMI.** Women receiving antiretroviral drugs had more weight loss than did those not receiving antiretroviral drugs (-2.93 compared with -1.90 kg, P < 0.001). The benefit of the LNS for reducing weight loss was observed both in those receiving antiretroviral drugs (-2.56 compared with -3.32 kg, P = 0.019) and in those not receiving antiretroviral drugs (-1.63 compared with -2.16 kg, P = 0.034).

CONCLUSIONS: **The LNS reduced weight loss among HIV-infected, breastfeeding women, both in those taking maternal antiretroviral prophylaxis to prevent postnatal HIV transmission and in those not receiving antiretroviral prophylaxis. Provision of an LNS may benefit HIV-infected, breastfeeding women in resource-limited settings.** This trial was registered at clinicaltrials.gov as NCT00164762.



[J Infect Dis.](#) 2012 Feb 1;205(3): 366-75. Epub 2011 Dec 6.

[Valacyclovir suppressive therapy reduces plasma and breast milk HIV-1 RNA levels during pregnancy and postpartum: a randomized trial.](#)

[Drake AL](#), [Roxby AC](#), [Ongecha-Owuor F](#), [Kiarie J](#), [John-Stewart G](#), [Wald A](#), [Richardson BA](#), [Hitti J](#), [Overbaugh J](#), [Emery S](#), [Farquhar C](#).

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BACKGROUND: The effect of herpes simplex virus type 2 (HSV-2) suppression on human immunodeficiency virus type 1 (HIV-1) RNA in the context of prevention of mother-to-child transmission (PMTCT) interventions is unknown.

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METHODS: Between April 2008 and August 2010, we conducted a **randomized, double-blind trial of twice daily 500 mg valacyclovir or placebo beginning at 34 weeks gestation in 148 HIV-1/HSV-2 coinfecting pregnant Kenyan women ineligible for highly active antiretroviral therapy (CD4 > 250 cells/mm)**. Women received zidovudine and single dose nevirapine for PMTCT and were followed until 12 months postpartum.

RESULTS: Mean baseline plasma HIV-1 RNA was 3.88 log(10) copies/mL. Mean plasma HIV-1 was lower during pregnancy (-.56 log(10) copies/mL; 95% confidence interval [CI], -.77 to -.34) and after 6 weeks postpartum (-.51 log(10) copies/mL; 95% CI, -.73 to -.30) in the valacyclovir arm than the placebo arm. Valacyclovir reduced breast milk HIV-1 RNA detection at 6 and 14 weeks postpartum compared with placebo (30% lower, $P = .04$; 46% lower, $P = .01$, respectively), but not after 14 weeks. Cervical HIV-1 RNA detection was similar between arms ($P = .91$).

CONCLUSIONS: **Valacyclovir significantly decreased early breast milk and plasma HIV-1 RNA among women receiving PMTCT.**



[J Acquir Immune Defic Syndr.](#) 2011 Dec 1;58(4): 399-407.

[Safety and efficacy of HIV hyperimmune globulin for prevention of mother-to-child HIV transmission in HIV-1-infected pregnant women and their infants in Kampala, Uganda \(HIVIGLOB/NVP STUDY\).](#)

[Onyango-Makumbi C, Omer SB, Mubiru M, Moulton LH, Nakabiito C, Musoke P, Mmiro F, Zwierski S, Wigzell H, Falksveden L, Wahren B, Antelman G, Fowler MG, Guay L, Jackson JB.](#) Makerere University, Johns Hopkins University Research Collaboration/MU-JHU CARE LTD, Kampala, Uganda. carolonyango@mujhu.org

BACKGROUND: This phase III, randomized, **clinical trial compared single-dose nevirapine (sdNVP) plus HIV hyperimmune globulin (HIVIGLOB) with sdNVP alone for preventing maternal-to-child transmission of HIV.** Primary objectives were to determine rates of HIV infection among infants and to assess the safety of HIVIGLOB in combination with sdNVP in HIV-infected Ugandan pregnant women and their infants.

METHODS: **Mother-infant pairs were randomized to receive 200 mg of nevirapine to women in labor and 2 mg/kg NVP to newborns within 72 hours after birth (sdNVP arm) or to receive sdNVP plus a single intravenous 240-mL dose of HIVIGLOB given to women at 36- to 38-week gestation and a single intravenous 24-mL dose to newborns within 18 hours of birth (HIVIGLOB/sdNVP arm).** Risk of HIV infection was determined using Kaplan-Meier and risk ratio estimates at birth, 2, 6, 14 weeks, 6, and 12 months of age.

RESULTS: Intent-to-treat analysis included 198 HIVIGLOB/sdNVP and 294 sdNVP mother-infant pairs. **At 6 months of age, the primary endpoint, there was no statistically significant difference in HIV transmission in the HIVIGLOB/sdNVP arm vs. the sdNVP arm [18.7% vs. 15.0%; risk ratio = 1.240 (95% confidence interval: 0.833 to 1.846); $P = 0.290$].** Similarly,

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the proportion of serious adverse events in the HIVIGLOB/sdNVP and sdNVP arms, respectively, for mothers (18.9% vs. 19.3%; $P = 0.91$) and infants (62.6% vs. 59.5%; $P = 0.51$) was not significantly different.

CONCLUSIONS: Giving mother-infant pairs an infusion of peripartum HIV hyperimmune globulin in addition to sdNVP for preventing maternal-to-child transmission was as safe as sdNVP alone but was no more effective than sdNVP alone in preventing HIV transmission.

[J Acquir Immune Defic Syndr.](#) 2011 Aug 1;57(4): e85-91.

[Improved detection of incident HIV infection and uptake of PMTCT services in labor and delivery in a high HIV prevalence setting.](#)

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OBJECTIVE: To maximize prevention of mother-to-child transmission of HIV (PMTCT) effectiveness and increase identification of HIV status in maternity units in Swaziland.

DESIGN: With a quasi-experimental design, 3 maternity units were randomly assigned to the training intervention and 3 units were controls.

METHODS: Targeted on-site training was provided to nurse-midwives in intervention sites. HIV status was recorded with testing offered to women presenting with unknown and distant negative status. Cord blood was obtained and tested for HIV antibodies and presence of nevirapine as a marker of PMTCT intervention coverage. Contingency tables and χ^2 tests were used to test for associations between frequencies of events.

RESULTS: Of the 2444 enrolled women, 215 (9%) arrived in maternity with unknown status and 1398 (58%) had tested HIV negative in antenatal clinic. **Significantly more HIV-negative women (45%) and women with unknown status (96%) in intervention sites were tested** compared with similar women in control sites, 14% and 65%, respectively ($P < 0.0001$ for both). **Nevirapine coverage in HIV-positive cord blood was significantly higher in intervention sites (80%) than in control sites (69%, $P < 0.0001$).** Cumulative HIV incidence was 4% with an incidence rate of 16.8 per 100 person-years. **Antiretroviral prophylaxis coverage in seroconverters was significantly higher in intervention sites 54% (13 of 24) than the control group [26% (9 of 34), $P = 0.03$].**

CONCLUSIONS: In high HIV prevalence settings, such as Swaziland, the incidence of HIV during pregnancy is high. An on-site training intervention for maternity nurses significantly increases the identification of HIV infection and maximizes the provision of PMTCT interventions.

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[Trials](#). 2011 Nov 1;12: 236.

[An effectiveness study of an integrated, community-based package for maternal, newborn, child and HIV care in South Africa: study protocol for a randomized controlled trial.](#)

[Tomlinson M](#), [Doherty T](#), [Jackson D](#), [Lawn JE](#), [Ijumba P](#), [Colvin M](#), [Nkonki L](#), [Daviaud E](#), [Goga A](#), [Sanders D](#), [Lombard C](#), [Persson LÅ](#), [Ndaba T](#), [Snetro G](#), [Chopra M](#).

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BACKGROUND: Progress towards MDG4 in South Africa will depend largely on scaling up effective prevention against mother to child transmission (PMTCT) of HIV and also addressing neonatal mortality. This imperative drives increasing focus on the neonatal period and particularly on the development and testing of appropriate models of sustainable, community-based care in South Africa in order to reach the poor. A number of key implementation gaps affecting progress have been identified. Implementation gaps for HIV prevention in neonates; implementation gaps for neonatal care especially home postnatal care; and implementation gaps for maternal mental health support. We have developed and are evaluating and costing an integrated and scaleable home visit package delivered by community health workers targeting pregnant and postnatal women and their newborns to provide essential maternal/newborn care as well as interventions for Prevention of Mother to Child Transmission (PMTCT) of HIV.

METHODS: The trial is a cluster randomized controlled trial that is being implemented in Umlazi which is a peri-urban settlement with a total population of 1 million close to Durban in KwaZulu Natal, South Africa. The trial consists of 30 randomized clusters (15 in each arm). A baseline survey established the homogeneity of clusters and neither stratification nor matching was performed. Sample size was based on increasing HIV-free survival from 74% to 84%, and calculated to be 120 pregnant women per cluster. Primary outcomes are higher levels of HIV free survival and levels of exclusive and appropriate infant feeding at 12 weeks postnatally. The intervention is home based with community health workers delivering two antenatal visits, a postnatal visit within 48 hours of birth, and a further four visits during the first two months of the infants life. We are undertaking programmatic and cost effectiveness analysis to cost the intervention.

DISCUSSION: The question is not merely to develop an efficacious package but also to identify and test delivery strategies that enable scaling up, which requires effectiveness studies in a health systems context, adapting and testing Asian community-based studies in various African contexts.



[BMC Public Health](#). 2011 Oct 10;11: 778.

[Promoting male involvement to improve PMTCT uptake and reduce antenatal HIV infection: a cluster randomized controlled trial protocol.](#)

[Peltzer K](#), [Jones D](#), [Weiss SM](#), [Shikwane E](#).

Randomised trials in child health in developing countries 2011-12

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BACKGROUND: Despite the availability of a dual therapy treatment protocol and infant feeding guidelines designed to prevent mother to child transmission (PMTCT) of HIV, of the over 1 million babies born in South Africa each year, only 70% of those born to HIV positive mothers receive dual therapy. Similar to other resource-poor nations facing the integration of PMTCT into routine pregnancy and infant care, efforts in South Africa to scale up PMTCT and reduce transmission to < 5% have fallen far short of the United Nation's goal of 50% reductions in paediatric HIV by 80% coverage of mothers.

METHODS/DESIGN: This study proposes to evaluate the impact of combining two evidence-based interventions: a couple's risk reduction intervention with an evidence based medication adherence intervention to enhance male participation in combination with improving medication and PMTCT adherence in antenatal clinics to increase PMTCT overall reach and effectiveness. The study will use a group-randomized design, recruiting 240 couples from 12 clinics. Clinics will be randomly assigned to experimental and control conditions and effectiveness of the combined intervention to enhance PMTCT as well as reduce antenatal seroconversion by both individuals and clinics will be examined.

DISCUSSION: Shared intervention elements may decrease sexual risk and enhance PMTCT uptake, e.g., increased male participation, enhanced communication, HIV counselling and testing, adherence, serostatus disclosure, suggest that a combined sexual risk reduction and adherence intervention plus PMTCT can increase male participation, increase couples' communication and encourage adherence to the PMTCT process. The findings will impact public health and will enable the health ministry to formulate policy related to male involvement in PMTCT, which will result in PMTCT.



[J Int AIDS Soc.](#) 2011 Sep 13;14: 43.

[Male partner antenatal attendance and HIV testing in eastern Uganda: a randomized facility-based intervention trial.](#)

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BACKGROUND: The objective of the study was to evaluate the effect of a written invitation letter to the spouses of new antenatal clinic attendees on attendance by couples and on male partner acceptance of HIV testing at subsequent antenatal clinic visits.

METHODS: The trial was conducted with 1060 new attendees from October 2009 to February 2010 in an antenatal clinic at Mbale Regional Referral Hospital, Mbale District, eastern Uganda. The intervention comprised an invitation letter delivered to the spouses of new antenatal

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attendees, while the control group received an information letter, a leaflet, concerning antenatal care. The primary outcome measure was the proportion of pregnant women who attended antenatal care with their male partners during a follow-up period of four weeks. Eligible pregnant women were randomly assigned to the intervention or non-intervention groups using a randomization sequence, which was computer generated utilizing a random sequence generator (RANDOM ORG) that employed a simple randomization procedure. Respondents, health workers and research assistants were masked to group assignments.

RESULTS: The trial was completed with 530 women enrolled in each group. Participants were analyzed as originally assigned (intention to treat). **For the primary outcome, the percentage of trial participants who attended the antenatal clinic with their partners were 16.2% (86/530) and 14.2% (75/530) in the intervention and non-intervention groups, respectively (OR = 1.2; 95% CI: 0.8, 1.6).** For the secondary outcome, most of the 161 male partners attended the antenatal clinic; 82 of 86 (95%) in the intervention group and 68 of 75 (91%) in the non-intervention group were tested for HIV (OR = 2.1; 95% CI: 0.6 to 7.5).

CONCLUSIONS: The effect of the intervention and the control on couple antenatal attendance was similar. In addition, the trial demonstrated that a simple intervention, such as a letter to the spouse, could increase couple antenatal clinic attendance by 10%. Significantly, the majority of male partners who attended the antenatal clinic accepted HIV testing. Therefore, to further evaluate this simple and cost-effective intervention method, adequately powered studies are required to assess its effectiveness in increasing partner participation in antenatal clinics and the programme for prevention of mother to child transmission of HIV.



Helminth and other gastrointestinal infections

(See also Anaemia, Diarrhoea)

[PLoS One](#). 2011;6(9): e25003. Epub 2011 Sep 27.

[Efficacy of single-dose and triple-dose albendazole and mebendazole against soil-transmitted helminths and *Taenia* spp.: a randomized controlled trial.](#)

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BACKGROUND: The control of soil-transmitted helminth (STH) infections currently relies on the large-scale administration of single-dose oral albendazole or mebendazole. However, these treatment regimens have limited efficacy against hookworm and *Trichuris trichiura* in terms of cure rates (CR), whereas fecal egg reduction rates (ERR) are generally high for all common STH species. We compared the efficacy of single-dose versus triple-dose treatment against hookworm and other STHs in a community-based randomized controlled trial in the People's Republic of China.

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METHODOLOGY/PRINCIPAL FINDINGS: The hookworm CR and fecal ERR were assessed in 314 individuals aged ≥ 5 years who submitted two stool samples before and 3-4 weeks after administration of single-dose oral albendazole (400 mg) or mebendazole (500 mg) or **triple-dose albendazole (3 \times 400 mg over 3 consecutive days)** or mebendazole (3 \times 500 mg over 3 consecutive days). Efficacy against *T. trichiura*, *Ascaris lumbricoides*, and *Taenia* spp. was also assessed. **Albendazole cured significantly more hookworm infections than mebendazole in both treatment regimens (single dose: respective CRs 69% (95% confidence interval [CI]: 55-81%) and 29% (95% CI: 20-45%); triple dose: respective CRs 92% (95% CI: 81-98%) and 54% (95% CI: 46-71%)).** ERRs followed the same pattern (single dose: 97% versus 84%; triple dose: 99.7% versus 96%). **Triple-dose regimens outperformed single doses against *T. trichiura*; three doses of mebendazole - the most efficacious treatment tested - cured 71% (95% CI: 57-82%).** Both single and triple doses of either drug were highly efficacious against *A. lumbricoides* (CR: 93-97%; ERR: all $>99.9\%$). Triple dose regimens cured all *Taenia* spp. infections, whereas single dose applications cured only half of them.

CONCLUSIONS/SIGNIFICANCE: Single-dose oral albendazole is more efficacious against hookworm than mebendazole. **To achieve high CRs against both hookworm and *T. trichiura*, triple-dose regimens are warranted.**



[PLoS Negl Trop Dis](#). 2012 Jan;6(1): e1417. Epub 2012 Jan 3.

[Low efficacy of single-dose albendazole and mebendazole against hookworm and effect on concomitant helminth infection in Lao PDR.](#)

[Soukhathammavong PA](#), [Sayasone S](#), [Phongluxa K](#), [Xayaseng V](#), [Utzingler J](#), [Vounatsou P](#), [Hatz C](#), [Akkhavong K](#), [Keiser J](#), [Odermatt P](#).

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BACKGROUND: Albendazole and mebendazole are increasingly deployed for preventive chemotherapy targeting soil-transmitted helminth (STH) infections. We assessed the efficacy of **single oral doses of albendazole (400 mg) and mebendazole (500 mg) for the treatment of hookworm infection in school-aged children in Lao PDR.** Since *Opisthorchis viverrini* is co-endemic in our study setting, the effect of the two drugs could also be determined against this liver fluke.

METHODOLOGY: We conducted a randomized, open-label, two-arm trial. In total, 200 children infected with hookworm (determined by quadruplicate Kato-Katz thick smears derived from two stool samples) were randomly assigned to albendazole (n=100) and mebendazole (n=100). Cure rate (CR; percentage of children who became egg-negative after treatment), and egg reduction rate (ERR; reduction in the geometric mean fecal egg count at treatment follow-up compared to baseline) at 21-23 days posttreatment were used as primary outcome measures. Adverse events were monitored 3 hours post treatment.

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PRINCIPAL FINDINGS: Single-dose albendazole and mebendazole resulted in CRs of 36.0% and 17.6% (odds ratio: 0.4; 95% confidence interval: 0.2-0.8; P=0.01), and ERRs of 86.7% and 76.3%, respectively. In children co-infected with *O. viverrini*, albendazole and mebendazole showed low CRs (33.3% and 24.2%, respectively) and moderate ERRs (82.1% and 78.2%, respectively).

CONCLUSIONS/SIGNIFICANCE: Both albendazole and mebendazole showed disappointing CRs against hookworm, but albendazole cured infection and reduced intensity of infection with a higher efficacy than mebendazole. Single-dose administrations showed an effect against *O. viverrini*, and hence it will be interesting to monitor potential ancillary benefits of a preventive chemotherapy strategy that targets STHs in areas where opisthorchiasis is co-endemic.



[Trans R Soc Trop Med Hyg. 2011 Oct;105\(10\): 586-90. Epub 2011 Aug 31.](#)
[Efficacy of single and double doses of albendazole and mebendazole alone and in combination in the treatment of *Trichuris trichiura* in school-age children in Uganda.](#)

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A randomised clinical trial was conducted in Kabale District, southwestern Uganda, to compare the efficacies of single and double doses of a combination of 400mg albendazole (ALB) and 500mg mebendazole (MBZ) with those of single and double doses of each drug given alone in the treatment of *Trichuris trichiura*. Infected pupils (n=611) were randomised to six treatment groups. Three groups received either a single dose of ALB, MBZ or the combination (ALB+MBZ). The other three groups received either a double dose of ALB (ALB/ALB), MBZ (MBZ/MBZ) or the combination (ALB+MBZ/ALB+MBZ). All double doses were given 8h apart. Children were followed-up weekly for 1 month. Cure rates were significantly higher using double doses compared with single doses (irrespective of drug; $z=-4.02$, $P<0.0005$) as well as using the drug combination compared with single drugs (irrespective of doses; $z=-7.64$, $P<0.0005$). Cure rates measured at Day 7 were significantly higher than on Days 14 and 21 after treatment (Day 14, $z=9.90$, $P<0.0005$; Day 21, $z=7.36$, $P<0.0005$). Geometric mean (GM) intensities of positives were significantly lower on Day 7 compared with all other subsequent days ($P<0.00005$), and on Day 28 GM intensities reached pre-treatment levels ($P=0.096$). Whilst there was no difference in egg excretion between single and double doses of the same drug or drug combination ($F((df)(1))=0.28$, $P=0.60$), the combination treatment resulted in lower egg excretion than use of single drugs ($F((df)(2))=50.90$, $P<0.00005$). All the tested regimens of ALB and MBZ had low cure rates against *T. trichiura* in Uganda, but both combination treatments showed satisfactory egg reduction rates 3 weeks after treatment.

[Am J Trop Med Hyg.](#) 2011 Aug;85(2): 333-40.

[Decreased parasite load and improved cognitive outcomes caused by deworming and consumption of multi-micronutrient fortified biscuits in rural Vietnamese schoolchildren.](#)

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Micronutrient deficiencies are associated with impaired growth and cognitive function. A school-based fortification program might benefit schoolchildren but a high prevalence of parasite infestation might affect effectiveness. A randomized, double-blind, placebo-controlled 2 × 2 factorial trial was conducted to assess the efficacy of multi-micronutrient fortified biscuits with or without de-worming on growth, cognitive function, and parasite load in Vietnamese schoolchildren. **Schoolchildren (n = 510), 6-8 years of age were randomly allocated to receive albendazole or placebo at baseline and four months of multi-micronutrient fortified biscuits (FB) or non-fortified biscuits. Children receiving FB for four months scored higher on two cognitive tests: Raven's Colored Progressive Matrices and the Digit Span Forward test. Children receiving albendazole plus FB had the lowest parasite load after four months. In children receiving FB, mid-upper arm circumference was slightly improved (+0.082 cm) but there were no differences in other indexes of anthropometry.** Combining multi-micronutrient fortified biscuits with de-worming is an effective strategy.

[Cochrane Database Syst Rev.](#) 2012 Jul 11;7:CD000371.

[Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin and school performance.](#)

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BACKGROUND: The World Health Organization (WHO) recommends treating all school children at regular intervals with deworming drugs in areas where helminth infection is common. The WHO state this will improve nutritional status, haemoglobin, and cognition and thus will improve health, intellect, and school attendance. Consequently, it is claimed that school performance will improve, child mortality will decline, and economic productivity will increase. Given the important health and societal benefits attributed to this intervention, we sought to determine whether they are based on reliable evidence.

OBJECTIVES: To summarize the effects of giving deworming drugs to children to treat soil-transmitted intestinal worms (nematode geohelminths) on weight, haemoglobin, and cognition; and the evidence of impact on physical well being, school attendance, school performance, and mortality.

SEARCH METHODS: In February 2012, we searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, EMBASE, LILACS, mRCT, and reference lists, and registers of ongoing and completed trials.

SELECTION CRITERIA: We selected randomized controlled trials (RCTs) and quasi-RCTs comparing deworming drugs for geohelminth worms with placebo or no treatment in children aged 16 years or less, reporting on weight, haemoglobin, and formal test of intellectual development. In cluster-RCTs treating communities or schools, we also sought data on school attendance, school performance, and mortality. We included trials that included health education with deworming.

DATA COLLECTION AND ANALYSIS: At least two authors independently assessed the trials, evaluated risk of bias, and extracted data. Continuous data were analysed using the mean difference (MD) with 95% confidence intervals (CI). Where data were missing, we contacted trial authors. We used GRADE to assess evidence quality, and this is reflected in the wording we used: high quality ("deworming improves...."); moderate quality ("deworming probably improves..."); low quality ("deworming may improve...."); and very low quality ("we don't know if deworming improves....").

MAIN RESULTS: We identified 42 trials, including eight cluster trials, that met the inclusion criteria. Excluding one trial where data are awaited, the 41 trials include 65,168 participants. For programmes that treat only children detected as infected (by screening), a single dose of deworming drugs probably increased weight (0.58 kg, 95% CI 0.40 to 0.76, three trials, 139 participants; moderate quality evidence) and may have increased haemoglobin (0.37 g/dL, 95% CI 0.1 to 0.64, two trials, 108 participants; low quality evidence), but we do not know if there is an effect on cognitive functioning (two trials, very low quality evidence). For a single dose of deworming drugs given to all children in endemic areas, there were mixed effects on weight, with no effects evident in seven trials, but large effects in two. Overall our analysis indicated that we are uncertain whether there was an effect on weight (nine trials, 3058 participants; very low quality evidence). For haemoglobin, deworming made little or no difference (0.02 g/dL, 95% CI -0.05 to 0.09, four trials, 1992 participants; low quality evidence), and we don't know if it improves cognition (one trial, very low quality evidence). For multiple doses of deworming drugs with follow up for up to one year given to all children in endemic areas, we are uncertain if there is an effect on weight (0.06 kg, 95% CI -0.17 to 0.30; seven trials, 2460 participants; very low quality evidence); cognition (three trials, very low quality evidence); or school attendance (4% higher attendance; 95% CI -6 to 14; two trials, 75 clusters and 143 individually randomized participants, very low quality evidence). For haemoglobin, the intervention may have little or no effect (mean 0.01 g/dL lower; 95% CI 0.14 lower to 0.13 higher; four trials, 807 participants; low quality evidence). For multiple doses of deworming drugs with follow up beyond one year given to all children in endemic areas there were five trials with weight measures. One cluster-RCT of 3712 children in a low prevalence area showed a large effect

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(average gain of 0.98kg), whilst the other four trials did not show an effect, including a cluster-RCT of 27,995 children in a moderate prevalence area. Overall, we are uncertain if there is an effect for weight (five trials, 302 clusters and 1045 individually randomized participants; very low quality evidence). For other outcomes, we are uncertain whether deworming affects height (-0.26 cm; 95%CI -0.84 to 0.31, three trials, 1219 participants); haemoglobin (0.02 g/dL, 95%CI 0.3 to 0.27, two trials, 1365 participants); cognition (two trials), or school attendance (mean attendance 5% higher, 95% CI -0.5 to 10.5, one trial, 50 clusters). Stratified analysis to seek subgroup effects into low, medium and high helminth endemicity areas did not demonstrate any pattern of effect. We did not detect any significant effects for any primary outcomes in a sensitivity analysis only including trials with adequate allocation concealment. One million children were randomized in a deworming trial from India with mortality as the primary outcome. This was completed in 2005 but the authors have not published the results.

AUTHORS' CONCLUSIONS: Screening children for intestinal helminths and then treating infected children appears promising, but the evidence base is small. Routine deworming drugs given to school children has been more extensively investigated, and has not shown benefit on weight in most studies, except for substantial weight changes in three trials conducted 15 years ago or more. Two of these trials were carried out in the same high prevalence setting. For haemoglobin, community deworming seems to have little or no effect, and the evidence in relation to cognition, school attendance, and school performance is generally poor, with no obvious or consistent effect. Our interpretation of this data is that it is probably misleading to justify contemporary deworming programmes based on evidence of consistent benefit on nutrition, haemoglobin, school attendance or school performance as there is simply insufficient reliable information to know whether this is so.



Hygiene and environmental health

[Am J Trop Med Hyg.](#) 2011 Sep;85(3): 518-23.

[Latrine promotion for trachoma: assessment of mortality from a cluster-randomized trial in Ethiopia.](#)

[Gebre T,](#) [Ayele B,](#) [Zerihun M,](#) [House JI,](#) [Stoller NE,](#) [Zhou Z,](#) [Ray KJ,](#) [Gaynor BD,](#) [Porco TC,](#) [Emerson PM,](#) [Lietman TM,](#) [Keenan JD.](#)

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Trachoma control strategies, including latrine construction and antibiotic distribution, are directed at reducing ocular chlamydia, but may have additional benefits. In a cluster-randomized clinical trial, 24 subkebeles (administrative geographic units) in Ethiopia were offered a single mass azithromycin treatment, and half were randomized to receive an intensive latrine promotion. At a follow-up census 26 months after the baseline treatment, 320 persons had died. The mortality rate of children 1-5 years of age was 3.87 (95% confidence interval [CI] = 2.19-6.82) per 1,000 person-years in the latrine promotion arm, and 2.72 (95% CI = 1.37-5.42) per

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1,000 person-years in the control arm. In a multi-level mixed effects logistic regression model controlling for age, there was no difference in mortality in persons randomized into the latrine or control arms (odds ratio = 1.18, 95% CI = 0.89-1.58). Latrine promotion provided no additional effect on mortality in the context of an azithromycin distribution program (clinicaltrials.gov, #NCT00322972).



[J Infect Dis.](#) 2012 Mar;205 Suppl 1: S65-76.

Integration of routine vaccination and hygiene interventions: a comparison of 2 strategies in Kenya.

[Ryman TK](#), [Briere EC](#), [Cartwright E](#), [Schlanger K](#), [Wannemuehler KA](#), [Russo ET](#), [Kola S](#), [Sadumah I](#), [Nygren BL](#), [Ochieng C](#), [Quick R](#), [Watkins ML](#).

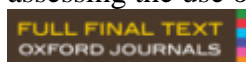
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BACKGROUND: Hygiene interventions reduce child mortality from diarrhea. Vaccination visits provide a platform for delivery of other health services but may overburden nurses. We compared 2 strategies to integrate hygiene interventions with vaccinations in Kenya's Homa Bay district, 1 using community workers to support nurses and 1 using nurses.

METHODS: Homa Bay was divided into 2 geographical areas, each with 9 clinics. Each area was randomly assigned to either the nurse or community-assisted strategy. **At infant vaccination visits hygiene kits were distributed by the nurse or community member.** Surveys pre- and post-intervention, measured hygiene indicators and vaccination coverage. Interviews and focus groups assessed acceptability.

RESULTS: Between April 2009 and March 2010, 39 158 hygiene kits were distributed. **Both nurse and community-assisted strategies were well-accepted. Hygiene indicators improved similarly in nurse and community sites.** However, residual chlorine in water changed in neither group. Vaccination coverage increased in urban areas. In rural areas coverage either remained unchanged or increased with 1 exception (13% third dose poliovirus vaccine decrease).

CONCLUSIONS: **Distribution of hygiene products and education during vaccination visits was found to be feasible using both delivery strategies.** Additional studies should consider assessing the use of community members to support integrated service delivery.



[Contemp Clin Trials.](#) 2011 Nov;32(6): 864-73. Epub 2011 Jul 6.

[A community randomised controlled trial evaluating a home-based environmental intervention package of improved stoves, solar water](#)

Randomised trials in child health in developing countries 2011-12

[disinfection and kitchen sinks in rural Peru: rationale, trial design and baseline findings.](#)

[Hartinger SM](#), [Lanata CF](#), [Hattendorf J](#), [Gil AI](#), [Verastegui H](#), [Ochoa T](#), [Mäusezahl D](#).

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INTRODUCTION: Pneumonia and diarrhoea are leading causes of death in children. There is a need to develop effective interventions.

OBJECTIVE: We present the design and baseline findings of a community-randomised controlled trial in rural Peru to evaluate the health impact of an Integrated Home-based Intervention Package in children aged 6 to 35 months.

METHODS: We randomised 51 communities. The intervention was developed through a community-participatory approach prior to the trial. They comprised the construction of improved stoves and kitchen sinks, the promotion of hand washing, and solar drinking water disinfection (SODIS). To reduce the potential impact of non-blinding bias, a psychomotor stimulation intervention was implemented in the control arm. The baseline survey included anthropometric and socio-economic characteristics. In a sub-sample we determined the level of faecal contamination of drinking water, hands and kitchen utensils and the prevalence of diarrhoeagenic *Escherichia coli* in stool specimen.

RESULTS: We enrolled 534 children. At baseline all households used open fires and 77% had access to piped water supplies. *E. coli* was found in drinking water in 68% and 64% of the intervention and control households. Diarrhoeagenic *E. coli* strains were isolated from 45/139 stool samples. The proportion of stunted children was 54%.

CONCLUSIONS: Randomization resulted in comparable study arms. Recently, several critical reviews raised major concerns on the reliability of open health intervention trials, because of uncertain sustainability and non-blinding bias. In this regard, the presented trial featuring objective outcome measures, a simultaneous intervention in the control communities and a 12-month follow up period will provide valuable evidence.

Integrated management of childhood illness

*** [BMJ](#). 2012 Mar 21;344: e1634. doi: 10.1136/bmj.e1634.

[Effect of implementation of Integrated Management of Neonatal and Childhood Illness \(IMNCI\) programme on neonatal and infant mortality: cluster randomised controlled trial.](#)

[Bhandari N](#), [Mazumder S](#), [Taneja S](#), [Sommerfelt H](#), [Strand TA](#); [IMNCI Evaluation Study Group](#).

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[Dube B](#), [Kaur J](#), [Aggarwal RC](#), [Pandey D](#), [Purohit V](#), [Mehrotra A](#), [Martines J](#), [Bahl R](#), [Mohan P](#), [Kirkwood BR](#), [Van Den Hombergh H](#), [Bhan MK](#).

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OBJECTIVE: To evaluate the Indian Integrated Management of Neonatal and Childhood Illness (IMNCI) programme, which integrates improved treatment of illness for children with home visits for newborn care, to inform its scale-up.

DESIGN: Cluster randomised trial.

SETTING: 18 clusters (population 1.1 million) in Haryana, India.

PARTICIPANTS: 29,667 births in intervention clusters and 30,813 in control clusters.

INTERVENTION: **Community health workers were trained to conduct postnatal home visits and women's group meetings; physicians, nurses, and community health workers were trained to treat or refer sick newborns and children; supply of drugs and supervision were strengthened.**

MAIN OUTCOME MEASURES: Neonatal and infant mortality; newborn care practices.

RESULTS: **The infant mortality rate (adjusted hazard ratio 0.85, 95% confidence interval 0.77 to 0.94) and the neonatal mortality rate beyond the first 24 hours (adjusted hazard ratio 0.86, 0.79 to 0.95) were significantly lower in the intervention clusters than in control clusters.** The adjusted hazard ratio for neonatal mortality rate was 0.91 (0.80 to 1.03). A significant interaction was found between the place of birth and the effect of the intervention for all mortality outcomes except post-neonatal mortality rate. The neonatal mortality rate was significantly lower in the intervention clusters in the subgroup born at home (adjusted hazard ratio 0.80, 0.68 to 0.93) but not in the subgroup born in a health facility (1.06, 0.91 to 1.23) (P value for interaction = 0.001). Optimal newborn care practices were significantly more common in the intervention clusters.

CONCLUSIONS: **Implementation of the IMNCI resulted in substantial improvement in infant survival and in neonatal survival in those born at home.** The IMNCI should be a part of India's strategy to achieve the millennium development goal on child survival.



Kidney disease

[Kidney Int.](#) 2012 Jul 4. doi: 10.1038/ki.2012.238. [Epub ahead of print]

[Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome.](#)

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[Gulati A](#), [Sinha A](#), [Gupta A](#), [Kanitkar M](#), [Sreenivas V](#), [Sharma J](#), [Mantan M](#), [Agarwal I](#), [Dinda AK](#), [Hari P](#), [Bagga A](#).

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There are limited data on the relative efficacy and safety of calcineurin inhibitors and alkylating agents for idiopathic steroid-resistant nephrotic syndrome in children. To clarify this, we compared tacrolimus and intravenous cyclophosphamide therapy in a multicenter, randomized, controlled trial of 131 consecutive pediatric patients with minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis, stratified for initial or late steroid resistance. Patients were randomized to receive tacrolimus for 12 months or 6-monthly infusions of intravenous cyclophosphamide with both arms receiving equal amounts of alternate-day prednisolone. The primary outcome of complete or partial remission at 6 months, based on spot urine protein to creatinine ratios, was significantly higher in children receiving tacrolimus compared to cyclophosphamide (hazard ratio 2.64). Complete remission was significantly higher with tacrolimus (52.4%) than with cyclophosphamide (14.8%). The secondary outcome of sustained remission or steroid-sensitive relapse of nephrotic syndrome at 12 months was significantly higher with tacrolimus than cyclophosphamide. Treatment withdrawal was higher with cyclophosphamide, chiefly due to systemic infections. Compared to cyclophosphamide, 3 patients required treatment with tacrolimus to achieve 1 additional remission. Thus, tacrolimus and prednisolone are effective, safe, and preferable to cyclophosphamide as the initial therapy for patients with steroid-resistant nephrotic syndrome. *Kidney International* advance online publication, 4 July 2012; doi:10.1038/ki.2012.238.

Lead poisoning

[J Pediatr](#). 2011 Nov;159(5): 845-850.e1. Epub 2011 Jun 14.

[The effect of calcium supplementation on blood lead levels in Nigerian children.](#)

[Keating EM](#), [Fischer PR](#), [Pettifor JM](#), [Pfitzner M](#), [Isichei CO](#), [Thacher TD](#).

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OBJECTIVE: To determine whether calcium supplementation alters the risk of lead toxicity.

STUDY DESIGN: **Children aged 12-18 months from 3 communities in Nigeria were assigned to receive daily calcium supplementation, as either calcium carbonate (400 mg) or ground dried fish (529 ± 109 mg), or placebo.** All children received 2500 IU of vitamin A. Levels of blood lead, calcium, and vitamin D metabolites were measured at baseline and after 12-18 months (n = 358).

RESULTS: The mean (± SD) baseline lead level was 11.1 ± 7.8 µg/dL (range, 1-43 µg/dL; median, 9 µg/dL); 44.7% of subjects had a lead level >10 µg/dL. After 12-18 months, the mean lead level was 8.1 ± 6.3 µg/dL (range, 1-48 µg/dL; median, 6 µg/dL), with 22.6% with a level >10 µg/dL. Lead levels at baseline varied among communities (P = .01) and were higher in children who used eye cosmetics or lived near a lead-acid battery melter (both P < .001). In a

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multiple regression model, the decrease in blood lead level was predicted by age, baseline lead level, and time of final lead value at 12-18 months ($R^2 = 31\%$), but not by calcium supplementation ($P = .98$).

CONCLUSIONS: Lead toxicity is common in Nigerian children, but calcium supplementation does not affect blood lead levels.

Leishmaniasis

Cutaneous leishmaniasis

[J Infect Dis.](#) 2012 Feb 15;205(4): 684-92. Epub 2012 Jan 11.

[Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children.](#)

[Rubiano LC](#), [Miranda MC](#), [Muvdi Arenas S](#), [Montero LM](#), [Rodríguez-Barraquer I](#), [Garcerant D](#), [Prager M](#), [Osorio L](#), [Rojas MX](#), [Pérez M](#), [Nicholls RS](#), [Gore Saravia N](#).

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BACKGROUND: Children have a lower response rate to antimonial drugs and higher elimination rate of antimony (Sb) than adults. Oral miltefosine has not been evaluated for pediatric cutaneous leishmaniasis.

METHODS: A randomized, noninferiority clinical trial with masked evaluation was conducted at 3 locations in Colombia where *Leishmania panamensis* and *Leishmania guyanensis* predominated. **One hundred sixteen children aged 2-12 years with parasitologically confirmed cutaneous leishmaniasis were randomized to directly observed treatment with meglumine antimoniate (20 mg Sb/kg/d for 20 days; intramuscular) (n = 58) or miltefosine (1.8-2.5 mg/kg/d for 28 days; by mouth) (n = 58). Primary outcome was treatment failure at or before week 26 after initiation of treatment.** Miltefosine was noninferior if the proportion of treatment failures was $\leq 15\%$ higher than achieved with meglumine antimoniate (1-sided test, $\alpha = .05$).

RESULTS: Ninety-five percent of children (111/116) completed follow-up evaluation. **By intention-to-treat analysis, failure rate was 17.2% (98% confidence interval [CI], 5.7%-28.7%) for miltefosine and 31% (98% CI, 16.9%-45.2%) for meglumine antimoniate.** The difference between treatment groups was 13.8%, (98% CI, -4.5% to 32%) ($P = .04$). Adverse events were mild for both treatments.

CONCLUSIONS: Miltefosine is noninferior to meglumine antimoniate for treatment of pediatric cutaneous leishmaniasis caused by *Leishmania* (*Viannia*) species. Advantages of oral administration and low toxicity favor use of miltefosine in children.

Comment

Miltefosine (Hexadecylphosphocholine) was a drug first developed to treat metastases of breast cancer, but has been shown in previous studies to be effective against visceral Leishmaniasis. The mechanism of action is to induce apoptosis or programmed cell death of the Leishmania parasites by interference with DNA. As the first effective oral drug against visceral Leishmaniasis, Miltefosine may be vital to efforts to eradicate the disease from many of the 47 countries affected. The alternative treatment antimonial drugs are not only less effective in the treatment of Leishmaniasis in children, but, for cutaneous disease, need to be given as a daily intramuscular injection for up to 20 days, which is difficult in remote settings where most affected children live.

Malaria

Malaria vaccines

[N Engl J Med. 2011 Nov 17;365\(20\): 1863-75. Epub 2011 Oct 18.](#)

[First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children.](#)

[Agnandji ST](#), [Lell B](#), [Soulanoudjingar SS](#), [Fernandes JF](#), [Abossolo BP](#), [Conzelmann C](#), [Methogo BG](#), [Doucka Y](#), [Flamen A](#), [Mordmüller B](#), [Issifou S](#), [Kremsner PG](#), [Sacarlal J](#), [Aide P](#), [Lanaspa M](#), [Aponte JJ](#), [Nhamuave A](#), [Quelhas D](#), [Bassat Q](#), [Mandjate S](#), [Macete E](#), [Alonso P](#), [Abdulla S](#), [Salim N](#), [Juma O](#), [Shomari M](#), [Shubis K](#), [Machera F](#), [Hamad AS](#), [Minja R](#), [Mtoro A](#), [Sykes A](#), [Ahmed S](#), [Urassa AM](#), [Ali AM](#), [Mwangoka G](#), [Tanner M](#), [Tinto H](#), [D'Alessandro U](#), [Sorgho H](#), [Valea I](#), [Tahita MC](#), [Kaboré W](#), [Ouédraogo S](#), [Sandrine Y](#), [Guiguemdé RT](#), [Ouédraogo JB](#), [Hamel MJ](#), [Kariuki S](#), [Odero C](#), [Oneko M](#), [Otieno K](#), [Awino N](#), [Omoto J](#), [Williamson J](#), [Muturi-Kioi V](#), [Laserson KF](#), [Slutsker L](#), [Otieno W](#), [Otieno L](#), [Nekoye O](#), [Gondi S](#), [Otieno A](#), [Ogotu B](#), [Wasuna R](#), [Owira V](#), [Jones D](#), [Onyango AA](#), [Njuguna P](#), [Chilengi R](#), [Akoo P](#), [Kerubo C](#), [Gitaka J](#), [Maingi C](#), [Lang T](#), [Olotu A](#), [Tsofa B](#), [Bejon P](#), [Peshu N](#), [Marsh K](#), [Owusu-Agyei S](#), [Asante KP](#), [Osei-Kwakye K](#), [Boahen O](#), [Ayamba S](#), [Kayan K](#), [Owusu-Ofori R](#), [Dosoo D](#), [Asante I](#), [Adjei G](#), [Adjei G](#), [Chandramohan D](#), [Greenwood B](#), [Lusingu J](#), [Gesase S](#), [Malabeja A](#), [Abdul O](#), [Kilavo H](#), [Mahende C](#), [Liheluka E](#), [Lemnge M](#), [Theander T](#), [Drakeley C](#), [Ansong D](#), [Agbenyega T](#), [Adjei S](#), [Boateng HO](#), [Rettig T](#), [Bawa J](#), [Sylverken J](#), [Sambian D](#), [Agyekum A](#), [Owusu L](#), [Martinson F](#), [Hoffman I](#), [Mvalo T](#), [Kamthunzi P](#), [Nkomo R](#), [Msika A](#), [Jumbe A](#), [Chome N](#), [Nyakuipa D](#), [Chintedza J](#), [Ballou WR](#), [Bruls M](#), [Cohen J](#), [Guerra Y](#), [Jongert E](#), [Lapierre D](#), [Leach A](#), [Lievens M](#), [Ofori-Anyinam O](#), [Vekemans J](#), [Carter T](#), [Leboulleux D](#), [Loucq C](#), [Radford A](#), [Savarese B](#), [Schellenberg D](#), [Sillman M](#), [Vansadia P](#); [RTS,S Clinical Trials Partnership](#).

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BACKGROUND: An ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 is being conducted in seven African countries.

METHODS: From March 2009 through January 2011, we enrolled 15,460 children in two age categories--6 to 12 weeks of age and 5 to 17 months of age--for vaccination with either

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RTS,S/AS01 or a non-malaria comparator vaccine. The primary end point of the analysis was **vaccine efficacy against clinical malaria during the 12 months after vaccination in the first 6000 children 5 to 17 months of age at enrollment who received all three doses of vaccine according to protocol**. After 250 children had an episode of severe malaria, we evaluated vaccine efficacy against severe malaria in both age categories.

RESULTS: In the 14 months after the first dose of vaccine, **the incidence of first episodes of clinical malaria in the first 6000 children in the older age category was 0.32 episodes per person-year in the RTS,S/AS01 group and 0.55 episodes per person-year in the control group, for an efficacy of 50.4% (95% confidence interval [CI], 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population**. Vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) in the intention-to-treat population and 47.3% (95% CI, 22.4 to 64.2) in the per-protocol population. Vaccine efficacy against severe malaria in the combined age categories was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population during an average follow-up of 11 months. Serious adverse events occurred with a similar frequency in the two study groups. Among children in the older age category, the rate of generalized convulsive seizures after RTS,S/AS01 vaccination was 1.04 per 1000 doses (95% CI, 0.62 to 1.64).

CONCLUSIONS: **The RTS,S/AS01 vaccine provided protection against both clinical and severe malaria in African children.** (Funded by GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative; RTS,S ClinicalTrials.gov number, NCT00866619).



[Malar J.](#) 2011 Aug 4;10: 222.

[Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children.](#)

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BACKGROUND: There has been much debate about the appropriate statistical methodology for the evaluation of malaria field studies and the challenges in interpreting data arising from these trials.

METHODS: The present paper describes, for a pivotal phase III efficacy of the RTS, S/AS01 malaria vaccine, the methods of the statistical analysis and the rationale for their selection. The methods used to estimate efficacy of the primary course of vaccination, and of a booster dose, in preventing clinical episodes of uncomplicated and severe malaria, and to determine the duration of protection, are described. The interpretation of various measures of efficacy in terms of the potential public health impact of the vaccine is discussed.

CONCLUSIONS: The methodology selected to analyse the clinical trial must be scientifically sound, acceptable to regulatory authorities and meaningful to those responsible for malaria control and public health policy.



[Malar J.](#) 2011 Aug 4;10: 224. doi: 10.1186/1475-2875-10-224.

[Design of a phase III multicenter trial to evaluate the efficacy of the RTS,S/AS01 malaria vaccine in children across diverse transmission settings in Africa.](#)

[Leach A](#), [Vekemans J](#), [Lievens M](#), [Ofori-Anyinam O](#), [Cahill C](#), [Owusu-Agyei S](#), [Abdulla S](#), [Macete E](#), [Njuguna P](#), [Savarese B](#), [Loucq C](#), [Ballou WR](#); [Clinical Trials Partnership Committee](#). GlaxoSmithKline Biologicals, Wavre, Belgium. amanda.leach@gskbio.com

BACKGROUND: GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative are working in partnership to develop a malaria vaccine to protect infants and children living in malaria endemic regions of sub-Saharan Africa, which can be delivered through the Expanded Programme on Immunization. The RTS,S/AS candidate vaccine has been evaluated in multiple phase I/II studies and shown to have a favourable safety profile and to be well-tolerated in both adults and children. This paper details the design of the phase III multicentre efficacy trial of the RTS,S/AS01 malaria vaccine candidate, which is pivotal for licensure and policy decision-making.

METHODS: The phase III trial is a randomized, controlled, multicentre, participant- and observer-blind study on-going in 11 centres associated with different malaria transmission settings in seven countries in sub-Saharan Africa. A minimum of 6,000 children in each of two age categories (6-12 weeks, 5-17 months) have been enrolled. Children were randomized 1:1:1 to one of three study groups: (1) primary vaccination with RTS,S/AS01 and booster dose of RTS,S/AS01; (2) primary vaccination with RTS,S/AS01 and a control vaccine at time of booster; (3) primary vaccination with control vaccine and a control vaccine at time of booster. Primary vaccination comprises three doses at monthly intervals; the booster dose is administered at 18 months post-primary course. Subjects will be followed to study month 32. The co-primary objectives are the evaluation of efficacy over one year post-dose 3 against clinical malaria when primary immunization is delivered at: (1) 6-12 weeks of age, with co-administration of DTPwHepB/Hib antigens and OPV; (2) 5-17 months of age. Secondary objectives include evaluation of vaccine efficacy against severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality and other serious illnesses including sepsis and pneumonia. Efficacy of the vaccine against clinical malaria under different transmission settings, the evolution of efficacy over time and the potential benefit of a booster will be evaluated. In addition, the effect of RTS,S/AS01 vaccination on growth, and the safety and immunogenicity in HIV-infected and malnourished children will be assessed. Safety of the primary course of immunization and the booster dose will be documented in both age categories.

CONCLUSIONS: This pivotal phase III study of the RTS,S/AS01 candidate malaria vaccine in African children was designed and implemented by the Clinical Trials Partnership Committee. The study will provide efficacy and safety data to fulfil regulatory requirements, together with data on a broad range of endpoints that will facilitate the evaluation of the public health impact of the vaccine and will aid policy and implementation decisions.



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[Lancet Infect Dis.](#) 2011 Oct;11(10): 741-9. Epub 2011 Jul 22.

[Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial.](#)

[Asante KP](#), [Abdulla S](#), [Agnandji S](#), [Lyimo J](#), [Vekemans J](#), [Soulanoudjingar S](#), [Owusu R](#), [Shomari M](#), [Leach A](#), [Jongert E](#), [Salim N](#), [Fernandes JF](#), [Dosoo D](#), [Chikawe M](#), [Issifou S](#), [Osei-Kwakye K](#), [Lievens M](#), [Paricek M](#), [Möller T](#), [Apanga S](#), [Mwangoka G](#), [Dubois MC](#), [Madi T](#), [Kwara E](#), [Minja R](#), [Hounkpatin AB](#), [Boahen O](#), [Kayan K](#), [Adjei G](#), [Chandramohan D](#), [Carter T](#), [Vansadia P](#), [Sillman M](#), [Savarese B](#), [Loucq C](#), [Lapierre D](#), [Greenwood B](#), [Cohen J](#), [Kremsner P](#), [Owusu-Agyei S](#), [Tanner M](#), [Lell B](#).

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BACKGROUND: The RTS,S/AS01(E) candidate malaria vaccine is being developed for immunisation of infants in Africa through the expanded programme on immunisation (EPI). 8 month follow-up data have been reported for safety and immunogenicity of RTS,S/AS01(E) when integrated into the EPI. We report extended follow-up to 19 months, including efficacy results.

METHODS: We did a randomised, open-label, **phase 2 trial of safety and efficacy of the RTS,S/AS01(E) candidate malaria vaccine given with EPI vaccines between April 30, 2007, and Oct 7, 2009, in Ghana, Tanzania, and Gabon. Eligible children were 6-10 weeks of age at first vaccination, without serious acute or chronic illness.** All children received the EPI diphtheria, tetanus, pertussis (inactivated whole-cell), and hepatitis-B vaccines, Haemophilus influenzae type b vaccine, and oral polio vaccine at study months 0, 1, and 2, and measles vaccine and yellow fever vaccines at study month 7. **Participants were randomly assigned (1:1:1) to receive three doses of RTS,S/AS01(E) at 6, 10, and 14 weeks (0, 1, 2 month schedule) or at 6 weeks, 10 weeks, and 9 months (0, 2, 7 month schedule) or placebo.** Randomisation was according to a predefined block list with a computer-generated randomisation code. Detection of serious adverse events and malaria was by passive case detection. Antibodies against Plasmodium falciparum circumsporozoite protein and HBsAg were monitored for 19 months. This study is registered with ClinicalTrials.gov, number NCT00436007.

FINDINGS: 511 children were enrolled. Serious adverse events occurred in 57 participants in the RTS,S/AS01(E) 0, 1, 2 month group (34%, 95% CI 27-41), 47 in the 0, 1, 7 month group (28%, 21-35), and 49 (29%, 22-36) in the control group; none were judged to be related to study vaccination. At month 19, anticircumsporozoite immune responses were significantly higher in the RTS,S/AS01(E) groups than in the control group. **Vaccine efficacy for the 0, 1, 2 month schedule (2 weeks after dose three to month 19, site-adjusted according-to-protocol analysis) was 53% (95% CI 26-70; p=0.0012) against first malaria episodes and 59% (36-74; p=0.0001) against all malaria episodes.** For the entire study period, (total vaccinated cohort) vaccine efficacy against all malaria episodes was higher with the 0, 1, 2 month schedule (57%, 95% CI 33-73; p=0.0002) than with the 0, 1, 7 month schedule (32% CI 16-45; p=0.0003). 1 year after dose three, vaccine efficacy against first malaria episodes was similar for both schedules (0, 1, 2 month group, 61.6% [95% CI 35.6-77.1], p<0.001; 0, 1, 7 month group, 63.8% [40.4-78.0], p<0.001, according-to-protocol cohort).

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INTERPRETATION: Vaccine efficacy was consistent with the target put forward by the WHO-sponsored malaria vaccine technology roadmap for a first-generation malaria vaccine. The 0, 1, 2 month vaccine schedule has been selected for phase 3 candidate vaccine assessment.

[PLoS One](#). 2011;6(7): e22525. Epub 2011 Jul 28.

[A randomized controlled phase Ib trial of the malaria vaccine candidate GMZ2 in African children.](#)

[Bélard S](#), [Issifou S](#), [Hounkpatin AB](#), [Schaumburg F](#), [Ngoa UA](#), [Esen M](#), [Fendel R](#), [de Salazar PM](#), [Mürbeth RE](#), [Milligan P](#), [Imbault N](#), [Imoukhuede EB](#), [Theisen M](#), [Jepsen S](#), [Noor RA](#), [Okech B](#), [Kremsner PG](#), [Mordmüller B](#).

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BACKGROUND: GMZ2 is a fusion protein of Plasmodium falciparum merozoite surface protein 3 (MSP3) and glutamate rich protein (GLURP) that mediates an immune response against the blood stage of the parasite. Two previous phase I clinical trials, one in naïve European adults and one in malaria-exposed Gabonese adults showed that GMZ2 was well tolerated and immunogenic. Here, we present data on safety and immunogenicity of GMZ2 in one to five year old Gabonese children, a target population for future malaria vaccine efficacy trials.

METHODOLOGY/PRINCIPAL FINDINGS: Thirty children one to five years of age were randomized to receive three doses of either 30 µg or 100 µg of GMZ2, or rabies vaccine. GMZ2, adjuvanted in aluminum hydroxide, was administered on Days 0, 28 and 56. All participants received a full course of their respective vaccination and were followed up for one year. Both 30 µg and 100 µg GMZ2 vaccine doses were well tolerated and induced antibodies and memory B-cells against GMZ2 as well as its antigenic constituents MSP3 and GLURP. After three doses of vaccine, the geometric mean concentration of antibodies to GMZ2 was 19-fold (95%CI: 11,34) higher in the 30 µg GMZ2 group than in the rabies vaccine controls, and 16-fold (7,36) higher in the 100 µg GMZ2 group than the rabies group. Geometric mean concentration of antibodies to MSP3 was 2.7-fold (1.6,4.6) higher in the 30 µg group than in the rabies group and 3.8-fold (1.5,9.6) higher in the 100 µg group. Memory B-cells against GMZ2 developed in both GMZ2 vaccinated groups.

CONCLUSIONS/SIGNIFICANCE: Both 30 µg as well as 100 µg intramuscular GMZ2 are immunogenic, well tolerated, and safe in young, malaria-exposed Gabonese children. This result confirms previous findings in naïve and malaria-exposed adults and supports further clinical development of GMZ2.



[Vaccine](#). 2011 Aug 11;29(35): 6059-67. Epub 2011 Apr 7.

Four year immunogenicity of the RTS,S/AS02(A) malaria vaccine in Mozambican children during a phase IIb trial.

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[Aide P](#), [Dobaño C](#), [Sacarlal J](#), [Aponte JJ](#), [Mandomando I](#), [Guinovart C](#), [Bassat Q](#), [Renom M](#), [Puyol L](#), [Macete E](#), [Herrerros E](#), [Leach A](#), [Dubois MC](#), [Demoitie MA](#), [Lievens M](#), [Vekemans J](#), [Loucq C](#), [Ballou WR](#), [Cohen J](#), [Alonso PL](#).

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Previous studies with the malaria vaccine RTS,S/AS02(A) in young children in a malaria endemic area of Mozambique have shown it to have a promising safety profile and to reduce the risk of Plasmodium falciparum infection and disease. In this study, we assessed the antibody responses to the P. falciparum and hepatitis B components of the RTS,S/AS02(A) vaccine over a 45 months surveillance period in a large phase IIb trial which included 2022 children aged 1-4 years at recruitment. The RTS,S/AS02(A) vaccine induced high anti-circumsporozoite antibody levels with at least 96% of children remaining seropositive during the entire follow-up period. IgG titers decayed over the first 6 months of follow-up to about 25% of the initial level, but still remained 30-fold higher until month 45 compared to controls. Children with higher levels of naturally acquired immunity at baseline, assessed by blood stage indirect fluorescent antibody test, had slightly higher anti-circumsporozoite levels, after adjusting for the effect of age. **The RTS,S/AS02(A) vaccine also induced high levels of anti-hepatitis B surface antigen antibodies (seroprotection >97%).** RTS,S/AS02(A) vaccine is immunogenic and induces long-lasting anti-circumsporozoite antibodies, persisting at least 42 months after immunization. These antibodies may play a role in protection against malaria.

Intermittent preventative treatment

(See also Hygiene and environmental health)

[BMC Public Health](#). 2011 Jul 18;11: 573. doi: 10.1186/1471-2458-11-573.

[Increase in EPI vaccines coverage after implementation of intermittent preventive treatment of malaria in infant with Sulfadoxine -pyrimethamine in the district of Kolokani, Mali: results from a cluster randomized control trial.](#)

[Dicko A](#), [Toure SO](#), [Traore M](#), [Sagara I](#), [Toure OB](#), [Sissoko MS](#), [Diallo AT](#), [Rogier C](#), [Salomon R](#), [de Sousa A](#), [Doumbo OK](#).

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BACKGROUND: Even though the efficacy of Intermittent Preventive Treatment in infants (IPTi) with Sulfadoxine-Pyrimethamine (SP) against clinical disease and the absence of its interaction with routine vaccines of the Expanded Immunization Programme (EPI) have been established, there are still some concerns regarding the addition of IPTi, which may increase the work burden and disrupt the routine EPI services especially in Africa where the target immunization coverage remains to be met. However IPTi may also increase the adherence of the community to EPI services and improve EPI coverage, once the beneficence of strategy is perceived.

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METHODS: To assess the impact of IPTi implementation on the coverage of EPI vaccines, 22 health areas of the district of Kolokani were randomized at a 1:1 ratio to either receive IPTi-SP or to serve as a control. The EPI vaccines coverage was assessed using cross-sectional surveys at baseline in November 2006 and after one year of IPTi pilot-implementation in December 2007.

RESULTS: At baseline, the proportion of children of 9-23 months who were completely vaccinated (defined as children who received BGG, 3 doses of DTP/Polio, measles and yellow fever vaccines) was 36.7% (95% CI 25.3% -48.0%). **After one year of implementation of IPTi-SP using routine health services, the proportion of children completely vaccinated rose to 53.8% in the non intervention zone and 69.5% in the IPTi intervention zone (P <0.001).** The proportion of children in the target age groups who received IPTi with each of the 3 vaccinations DTP2, DTP3 and Measles, were 89.2% (95% CI 85.9%-92.0%), 91.0% (95% CI 87.6% -93.7%) and 77.4% (95% CI 70.7%-83.2%) respectively. The corresponding figures in non intervention zone were 2.3% (95% CI 0.9% -4.7%), 2.6% (95% CI 1.0% -5.6%) and 1.7% (95% CI 0.4% - 4.9%).

CONCLUSION: This study shows that high coverage of the IPTi can be obtained when the strategy is implemented using routine health services and implementation results in a significant increase in coverage of EPI vaccines in the district of Kolokani, Mali.



[PLoS One](#). 2011;6(8): e23391. Epub 2011 Aug 12.

[Morbidity from malaria in children in the year after they had received intermittent preventive treatment of malaria: a randomised trial.](#)

[Konaté AT](#), [Yaro JB](#), [Ouédraogo AZ](#), [Diarra A](#), [Gansané A](#), [Soulama I](#), [Kangoyé DT](#), [Kaboré Y](#), [Ouédraogo E](#), [Ouédraogo A](#), [Tiono AB](#), [Ouédraogo IN](#), [Chandramohan D](#), [Cousens S](#), [Milligan PJ](#), [Sirima SB](#), [Greenwood BM](#), [Diallo DA](#).

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BACKGROUND: Interventions that reduce exposure to malaria infection may lead to delayed malaria morbidity and mortality. We investigated whether intermittent preventive treatment of malaria in children (IPTc) was associated with an increase in the incidence of malaria after cessation of the intervention.

METHODS: An individually randomised, trial of IPTc, comparing three courses of sulphadoxine pyrimethamine (SP) plus amodiaquine (AQ) with placebos was implemented in children aged 3-59 months during the 2008 malaria transmission season in Burkina Faso. All children in the trial were given a long lasting insecticide treated net; 1509 children received SP+AQ and 1505 received placebos. Passive surveillance for malaria was maintained until the end of the subsequent malaria transmission season in 2009, and active surveillance for malaria infection, anaemia and malnutrition was conducted.

RESULTS: On thousand, four hundred and sixteen children (93.8%) and 1399 children (93.0%) initially enrolled in the intervention and control arms of the trial respectively were followed during the 2009 malaria transmission season. **During the period July 2009 to November 2009,**

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incidence rates of clinical malaria were 3.84 (95%CI; 3.67-4.02) and 3.45 (95%CI; 3.29-3.62) episodes per child during the follow up period in children who had previously received IPT or placebos, indicating a small increase in risk for children in the former intervention arm (IRR = 1.12; 95%CI 1.04-1.20) (P = 0.003). Children who had received SP+AQ had a lower prevalence of malaria infection (adjusted PR: 0.88 95%CI: 0.79-0.98) (P = 0.04) but they had a higher parasite density (P = 0.001) if they were infected. There was no evidence that the risks of moderately severe anaemia (Hb<8 g/dL), wasting, stunting, or of being underweight in children differed between treatment arms.



[PLoS One](#). 2011;6(8): e23390. Epub 2011 Aug 12.

[Malaria morbidity in children in the year after they had received intermittent preventive treatment of malaria in Mali: a randomized control trial.](#)

[Dicko A](#), [Barry A](#), [Dicko M](#), [Diallo AI](#), [Tembine I](#), [Dicko Y](#), [Dara N](#), [Sidibe Y](#), [Santara G](#), [Conaré T](#), [Chandramohan D](#), [Cousens S](#), [Milligan PJ](#), [Diallo DA](#), [Doumbo OK](#), [Greenwood B](#).

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BACKGROUND: Intermittent preventive treatment of malaria in children (IPTc) is a promising strategy for malaria control. A study conducted in Mali in 2008 showed that administration of three courses of IPTc with sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ) at monthly intervals reduced clinical malaria, severe malaria and malaria infection by >80% in children under 5 years of age. Here we report the results of a follow-on study undertaken to establish whether children who had received IPTc would be at increased risk of malaria during the subsequent malaria transmission season.

METHODS: Morbidity from malaria and the prevalence of malaria parasitaemia and anaemia were measured in children who had previously received IPTc with SP and AQ using similar surveillance methods to those employed during the previous intervention period.

RESULTS:

1396 of 1508 children (93%) who had previously received IPTc and 1406 of 1508 children (93%) who had previously received placebos were followed up during the high malaria transmission season of the year following the intervention. **Incidence rates of clinical malaria during the post-intervention transmission season (July-November 2009) were 1.87 (95% CI 1.76-1.99) and 1.73 (95% CI; 1.62-1.85) episodes per child year in the previous intervention and placebo groups respectively; incidence rate ratio (IRR) 1.09 (95% CI 0.99-1.21) (P = 0.08).** The prevalence of malaria infection was similar in the two groups, 7.4% versus 7.5%, **prevalence ratio (PR) of 0.99 (95% CI 0.73-1.33) (P = 0.95).** At the end of post-intervention malaria transmission season, the prevalence of anaemia, defined as a haemoglobin concentration <11g/dL, was similar in the two groups (56.2% versus 55.6%; PR = 1.01 [95% CI 0.91-1.12]) (P = 0.84).

CONCLUSION:

IPTc with SP+AQ was not associated with an increase in incidence of malaria episodes, prevalence of malaria infection or anaemia in the subsequent malaria transmission season.



[PLoS One](#). 2011;6(11): e24871. Epub 2011 Nov 3.

[Coverage, adherence and costs of intermittent preventive treatment of malaria in children employing different delivery strategies in Jasikan, Ghana.](#)

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BACKGROUND: Intermittent preventive treatment of malaria in children (IPTc) involves the administration of a course of anti-malarial drugs at specified time intervals to children at risk of malaria regardless of whether or not they are known to be infected. IPTc provides a high level of protection against uncomplicated and severe malaria, with monthly sulphadoxine-pyrimethamine plus amodiaquine (SP&AQ) and sulphadoxine-pyrimethamine plus piperazine being the most efficacious regimens. A key challenge is the identification of a cost-effective delivery strategy.

METHODS: A community randomized trial was undertaken in Jasikan district, Ghana to assess IPTc effectiveness and costs using SP&AQ delivered in three different ways. **Twelve villages were randomly selected to receive IPTc from village health workers (VHWs) or facility-based nurses working at health centres' outpatient departments (OPD) or EPI outreach clinics.** Children aged 3 to 59 months-old received one IPT course (three doses) in May, June, September and October. Effectiveness was measured in terms of children covered and adherent to a course and delivery costs were calculated in financial and economic terms using an ingredient approach from the provider perspective.

RESULTS: **The economic cost per child receiving at least the first dose of all 4 courses was US\$4.58 when IPTc was delivered by VHWs, US\$4.93 by OPD nurses and US\$ 5.65 by EPI nurses.** The unit economic cost of receiving all 3 doses of all 4 courses was US\$7.56 and US\$8.51 when IPTc was delivered by VHWs or facility-based nurses respectively. **The main cost driver for the VHW delivery was supervision, reflecting resources used for travelling to more remote communities rather than more intense supervision, and for OPD and EPI delivery, it was the opportunity cost of the time spent by nurses in dispensing IPTc.**

CONCLUSIONS: VHWs achieve higher IPTc coverage and adherence at lower costs than facility-based nurses in Jasikan district, Ghana.



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[Malar J.](#) 2011 Dec 13;10: 358.

[Impact of combining intermittent preventive treatment with home management of malaria in children less than 10 years in a rural area of Senegal: a cluster randomized trial.](#)

[Tine RC](#), [Faye B](#), [Ndour CT](#), [Ndiaye JL](#), [Ndiaye M](#), [Bassene C](#), [Magnussen P](#), [Bygbjerg IC](#), [Sylla K](#), [Ndour JD](#), [Gaye O](#).

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BACKGROUND: Current malaria control strategies recommend (i) early case detection using rapid diagnostic tests (RDT) and treatment with artemisinin combination therapy (ACT), (ii) pre-referral rectal artesunate, (iii) intermittent preventive treatment and (iv) impregnated bed nets. However, these individual malaria control interventions provide only partial protection in most epidemiological situations. Therefore, there is a need to investigate the potential benefits of integrating several malaria interventions to reduce malaria prevalence and morbidity.

METHODS: A randomized controlled trial was carried out to assess the impact of combining seasonal intermittent preventive treatment in children (IPTc) with home-based management of malaria (HMM) by community health workers (CHWs) in Senegal. Eight CHWs in eight villages covered by the Bonconto health post, (South Eastern part of Senegal) were trained to diagnose malaria using RDT, provide prompt treatment with artemether-lumefantrine for uncomplicated malaria cases and pre-referral rectal artesunate for complicated malaria occurring in children under 10 years. Four CHWs were randomized to also administer monthly IPTc as single dose of sulphadoxine-pyrimethamine (SP) plus three doses of amodiaquine (AQ) in the malaria transmission season, October and November 2010. Primary end point was incidence of single episode of malaria attacks over 8 weeks of follow up. Secondary end points included prevalence of malaria parasitaemia, and prevalence of anaemia at the end of the transmission season. Primary analysis was by intention to treat. The study protocol was approved by the Senegalese National Ethical Committee (approval 0027/MSP/DS/CNRS, 18/03/2010).

RESULTS: A total of 1,000 children were enrolled. The incidence of malaria episodes was 7.1/100 child months at risk [95% CI (3.7-13.7)] in communities with IPTc + HMM compared to 35.6/100 child months at risk [95% CI (26.7-47.4)] in communities with only HMM (aOR = 0.20; 95% CI 0.09-0.41; $p = 0.04$). At the end of the transmission season, malaria parasitaemia prevalence was lower in communities with IPTc + HMM (2.05% versus 4.6% $p = 0.03$). Adjusted for age groups, sex, *Plasmodium falciparum* carriage and prevalence of malnutrition, IPTc + HMM showed a significant protective effect against anaemia (aOR = 0.59; 95% CI 0.42-0.82; $p = 0.02$).

CONCLUSION: Combining IPTc and HMM can provide significant additional benefit in preventing clinical episodes of malaria as well as anaemia among children in Senegal.



[Malar J.](#) 2011 Sep 20;10: 273.

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[Cost analysis of school-based intermittent screening and treatment of malaria in Kenya.](#)

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BACKGROUND: The control of malaria in schools is receiving increasing attention, but there remains currently no consensus as to the optimal intervention strategy. This paper analyses the costs of intermittent screening and treatment (IST) of malaria in schools, implemented as part of a cluster-randomized controlled trial on the Kenyan coast.

METHODS: Financial and economic costs were estimated using an ingredients approach whereby all resources required in the delivery of IST are quantified and valued. Sensitivity analysis was conducted to investigate how programme variation affects costs and to identify potential cost savings in the future implementation of IST.

RESULTS: The estimated financial cost of IST per child screened is US\$ 6.61 (economic cost US\$ 6.24). Key contributors to cost were salary costs (36%) and malaria rapid diagnostic tests (RDT) (22%). Almost half (47%) of the intervention cost comprises redeployment of existing resources including health worker time and use of hospital vehicles. Sensitivity analysis identified changes to intervention delivery that can reduce programme costs by 40%, including use of alternative RDTs and removal of supervised treatment. Cost-effectiveness is also likely to be highly sensitive to the proportion of children found to be RDT-positive.

CONCLUSION: In the current context, school-based IST is a relatively expensive malaria intervention, but reducing the complexity of delivery can result in considerable savings in the cost of intervention. (Costs are reported in US\$ 2010).



[Lancet Infect Dis.](#) 2012 Mar;12(3): 191-200. Epub 2011 Dec 13.

[Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial.](#)

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BACKGROUND: Young children with severe malarial anaemia in Africa are at high risk of readmittance to hospital or death within 6 months of discharge. We aimed to assess whether 3 months of chemoprevention with artemether-lumefantrine reduced this risk.

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METHODS: We did a randomised, placebo-controlled, multicentre trial in four hospitals in Malawi testing the efficacy and safety of intermittent preventive therapy post-discharge (IPTpd) in children aged 4-59 months admitted for severe malarial anaemia. **All convalescent children who had completed a blood transfusion received artemether-lumefantrine at discharge and were randomly assigned by a computer-generated sequence to receive placebo or artemether-lumefantrine at 1 month and 2 months after discharge**, providing about 1 month and 3 months of protection, respectively. Patients and study staff were masked throughout the study. **The primary endpoint was a composite of all-cause mortality or hospital readmittance because of all-cause severe anaemia or severe malaria between 1 and 6 months after enrolment.** This trial is registered, number ISRCTN89727873.

RESULTS: Of 1414 children enrolled, 708 were assigned to receive placebo and 706 the intervention. **By 6 months, 192 children (14%) had died or were readmitted with severe malaria or severe anaemia. 1-6 months after randomisation, 109 primary events occurred in 85 children in the placebo group and 86 in 74 children in the intervention group (adjusted protective efficacy [PE] 31%, 95% CI 5-50; absolute rate reduction 11.7 per 100 children years, 95% CI 1.8-18.9; p=0.024).** The protective effect was greatest during the IPTpd period (1-3 months), when 58 primary events occurred in 49 children in the placebo group and 37 in 34 children in the intervention group (PE 41%, 10-62; p=0.01), but was not sustained after the third month (4-6 months, PE 17%, -27 to 45; p=0.395). When episodes in the first month were included--ie, before the first dose of IPTpd, when both groups benefited from the post-treatment prophylactic effect of artemether-lumefantrine provided at discharge--the overall cumulative PE by 6 months was 26% (-2 to 46; p=0.06).

INTERPRETATION: **In areas with intense malaria transmission, chemoprevention with IPTpd given to children with severe malarial anaemia might reduce rates of readmittance to hospital for severe anaemia or malaria.** Studies to confirm these findings and to investigate different delivery mechanisms and cost-effectiveness are needed.

FUNDING: The Netherlands African Partnership for Capacity Development and Clinical Interventions Against Poverty Related Diseases, the UBS-Optimus Foundation, and the Gates Malaria Partnership.

[Malar J.](#) 2011 Dec 30;10: 387.

[Cluster-randomized study of intermittent preventive treatment for malaria in infants \(IPTi\) in southern Tanzania: evaluation of impact on survival.](#)

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BACKGROUND: Intermittent Preventive Treatment for malaria control in infants (IPTi) consists of the administration of a treatment dose of an anti-malarial drug, usually sulphadoxine-pyrimethamine, at scheduled intervals, regardless of the presence of *Plasmodium falciparum* infection. A pooled analysis of individually randomized trials reported that IPTi reduced clinical

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episodes by 30%. **This study evaluated the effect of IPTi on child survival in the context of a five-district implementation project in southern Tanzania.** [Trial registration: clinical trials.gov NCT00152204].

METHODS: After baseline household and health facility surveys in 2004, **five districts comprising 24 divisions were randomly assigned either to receive IPTi (n = 12) or not (n = 12).** Implementation started in March 2005, led by routine health services with support from the research team. In 2007, a large household survey was undertaken to assess the impact of IPTi on survival in infants aged two-11 months through birth history interviews with all women aged 13-49 years. The analysis is based on an "intention-to-treat" ecological design, with survival outcomes analysed according to the cluster in which the mothers lived.

RESULTS: Survival in infants aged two-11 months was comparable in IPTi and comparison areas at baseline. In intervention areas in 2007, 48% of children aged 12-23 months had documented evidence of receiving three doses of IPTi, compared to 2% in comparison areas ($P < 0.0001$). **Over the three years of the study there was a marked improvement in survival in both groups. Between 2001-4 and 2005-7, mortality rates in two-11 month olds fell from 34.1 to 23.6 per 1,000 person-years in intervention areas and from 32.3 to 20.7 in comparison areas. In 2007, divisions implementing IPTi had a 14% (95% CI -12%, 49%) higher mortality rate in two-11 month olds in comparison with non-implementing divisions ($P = 0.31$).**

CONCLUSION: **The lack of evidence of an effect of IPTi on survival** could be a false negative result due to a lack of power or imbalance of unmeasured confounders. Alternatively, there could be no mortality impact of IPTi due to low coverage, late administration, drug resistance, decreased malaria transmission or improvements in vector control and case management. This study raises important questions for programme evaluation design.



[Cochrane Database Syst Rev.](#) 2012 Feb 15;2: CD003756.

[Intermittent preventive treatment for malaria in children living in areas with seasonal transmission.](#)

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BACKGROUND: In malaria endemic areas, pre-school children are at high risk of severe and repeated malaria illness. One possible public health strategy, known as Intermittent Preventive Treatment in children (IPTc), is to treat all children for malaria at regular intervals during the transmission season, regardless of whether they are infected or not.

OBJECTIVES: To evaluate the effects of IPTc to prevent malaria in preschool children living in endemic areas with seasonal malaria transmission.

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SEARCH METHODS: We searched the Cochrane Infectious Diseases Group Specialized Register (July 2011), CENTRAL (The Cochrane Library 2011, Issue 6), MEDLINE (1966 to July 2011), EMBASE (1974 to July 2011), LILACS (1982 to July 2011), mRCT (July 2011), and reference lists of identified trials. We also contacted researchers working in the field for unpublished and ongoing trials.

SELECTION CRITERIA: **Individually randomized and cluster-randomized controlled trials of full therapeutic dose of antimalarial or antimalarial drug combinations given at regular intervals compared with placebo or no preventive treatment in children aged six years or less living in an area with seasonal malaria transmission.**

DATA COLLECTION AND ANALYSIS: Two authors independently assessed eligibility, extracted data and assessed the risk of bias in the trials. Data were meta-analysed and measures of effects (ie rate ratio, risk ratio and mean difference) are presented with 95% confidence intervals (CIs). The quality of evidence was assessed using the GRADE methods.

MAIN RESULTS: **Seven trials (12,589 participants), including one cluster-randomized trial, met the inclusion criteria. All were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years. IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high quality evidence), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, high quality evidence). These effects remain present even where insecticide treated net (ITN) usage is high (two trials, 5964 participants, high quality evidence). IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, moderate quality evidence). The effect on anaemia varied between studies, but the risk of moderately severe anaemia is probably lower with IPTc (risk ratio 0.71, 95% CI 0.52 to 0.98; 8805 participants, five trials, moderate quality evidence). Serious drug-related adverse events, if they occur, are probably rare, with none reported in the six trials (9533 participants, six trials, moderate quality evidence). Amodiaquine plus sulphadoxine-pyrimethamine is the most studied drug combination for seasonal chemoprevention. Although effective, it causes increased vomiting in this age-group (risk ratio 2.78, 95% CI 2.31 to 3.35; two trials, 3544 participants, high quality evidence). When antimalarial IPTc was stopped, no rebound increase in malaria was observed in the three trials which continued follow-up for one season after IPTc.**

AUTHORS' CONCLUSIONS: **In areas with seasonal malaria transmission, giving antimalarial drugs to preschool children (age < 6 years) as IPTc during the malaria transmission season markedly reduces episodes of clinical malaria, including severe malaria. This benefit occurs even in areas where insecticide treated net usage is high.**



[PLoS Med.](#) 2012 Mar;9(3): e1001195. Epub 2012 Mar 27.

[Intermittent preventive treatment for malaria in Papua New Guinean infants exposed to Plasmodium falciparum and P. vivax: a randomized controlled trial.](#)

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[Senn N](#), [Rarau P](#), [Stanisic DI](#), [Robinson L](#), [Barnadas C](#), [Manong D](#), [Salib M](#), [Iga J](#), [Tarongka N](#), [Ley S](#), [Rosanas-Urgell A](#), [Aponte JJ](#), [Zimmerman PA](#), [Beeson JG](#), [Schofield L](#), [Siba P](#), [Rogerson SJ](#), [Reeder JC](#), [Mueller I](#).

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BACKGROUND: Intermittent preventive treatment in infants (IPTi) has been shown in randomized trials to reduce malaria-related morbidity in African infants living in areas of high *Plasmodium falciparum* (Pf) transmission. **It remains unclear whether IPTi is an appropriate prevention strategy in non-African settings or those co-endemic for *P. vivax* (Pv).**

METHODS AND FINDINGS: In this study, 1,121 Papua New Guinean infants were enrolled into a **three-arm placebo-controlled randomized trial and assigned to sulfadoxine-pyrimethamine (SP) (25 mg/kg and 1.25 mg/kg) plus amodiaquine (AQ) (10 mg/kg, 3 d, n = 374), SP plus artesunate (AS) (4 mg/kg, 3 d, n = 374), or placebo (n = 373), given at 3, 6, 9 and 12 mo.** Both participants and study teams were blinded to treatment allocation. The primary end point was protective efficacy (PE) against all episodes of clinical malaria from 3 to 15 mo of age. Analysis was by modified intention to treat. **The PE (compared to placebo) against clinical malaria episodes (caused by all species) was 29% (95% CI, 10-43, p ≤ 0.001) in children receiving SP-AQ and 12% (95% CI, -11 to 30, p = 0.12) in those receiving SP-AS.** Efficacy was higher against Pf than Pv. **In the SP-AQ group, Pf incidence was 35% (95% CI, 9-54, p = 0.012) and Pv incidence was 23% (95% CI, 0-41, p = 0.048) lower than in the placebo group. IPTi with SP-AS protected only against Pf episodes (PE = 31%, 95% CI, 4-51, p = 0.027), not against Pv episodes (PE = 6%, 95% CI, -24 to 26, p = 0.759).** Number of observed adverse events/serious adverse events did not differ between treatment arms (p > 0.55). None of the serious adverse events were thought to be treatment-related, and the vomiting rate was low in both treatment groups (1.4%-2.0%). No rebound in malaria morbidity was observed for 6 mo following the intervention.

CONCLUSIONS: IPTi using a long half-life drug combination is efficacious for the prevention of malaria and anemia in infants living in a region highly endemic for both Pf and Pv.



Comment

*This is an important study showing the differential effect of some drug combinations used for IPTi on *P. falciparum* and *P. vivax*. In PNG, protective efficacy was higher with sulfadoxine-pyrimethamine plus amodiaquine, than with SP plus artesunate, and this effect was greatest against vivax malaria.*

Other malaria preventative strategies

[PLoS One](#). 2011;6(7): e21862. Epub 2011 Jul 7.

[Malaria parasitaemia among infants and its association with breastfeeding peer counselling and vitamin A supplementation: a secondary analysis of a cluster randomized trial.](#)

[Nankabirwa V](#), [Tylleskar T](#), [Nankunda J](#), [Engebretsen IM](#), [Sommerfelt H](#), [Tumwine JK](#); PROMISE EBF Research Consortium.

[Tylleskär T](#), [Van de Perre P](#), [Ekström EC](#), [Meda N](#), [Tumwine JK](#), [Kankasa C](#), [Jackson D](#), [Tylleskär T](#), [Engebretsen IM](#), [Fadnes LT](#), [Fjeld E](#), [Fylkesnes K](#), [Klungsoyr J](#), [Nordrehaug-Åstrøm A](#), [Olsen ØE](#), [Robberstad B](#), [Sommerfelt H](#), [Van de Perre P](#), [Ekström EC](#), [Meda N](#), [Diallo H](#), [Ouedrago T](#), [Rouamba J](#), [Traoré B](#), [Traoré G](#), [Zabsonré E](#), [Tumwine JK](#), [Bwengye C](#), [Karamagi C](#), [Nankabirwa V](#), [Nankunda J](#), [Ndeezi G](#), [Wandera M](#), [Kankasa C](#), [Katepa-Bwalya M](#), [Siuluta C](#), [Siziya S](#), [Jackson D](#), [Chopra M](#), [Colvin M](#), [Doherty T](#), [Googa AE](#), [Matizirofa L](#), [Nkonki L](#), [Sanders D](#), [Zembe W](#).

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BACKGROUND: Malaria is the second highest contributor to the disease burden in Africa and there is a need to identify low cost prevention strategies. The objectives of this study were to estimate the prevalence of malaria parasitaemia among infants and to measure the association between peer counselling for exclusive breastfeeding (EBF), vitamin A supplementation, anthropometric status (weight and length) and malaria parasitaemia.

METHODS: A cluster randomized intervention trial was conducted between 2006 and 2008 where 12 of 24 clusters, each comprising one or two villages, in Eastern Uganda were allocated to receive peer counselling for EBF. Women in their third trimester of pregnancy (based on the last normal menstrual period) were recruited in all 24 clusters and followed up until their children's first birthday. Blood was drawn from 483 infants between 3 and 12 months of age, to test for malaria parasitaemia.

RESULTS: The prevalence of malaria parasitaemia was 11% in the intervention areas and 10% in the control areas. The intervention did not seem to decrease the prevalence of malaria (PR 1.7; 95% CI: 0.9, 3.3). After controlling for potential confounders, infants not supplemented with Vitamin A had a higher prevalence for malaria compared to those who had been supplemented (PR 6.1; 95% CI: 2.1, 17.6). Among children supplemented with vitamin A, every unit increase in length-for-age Z (LAZ) scores was associated with a reduced prevalence in malaria (PR 0.5; 95% CI: 0.4, 0.6). There was no association between LAZ scores and malaria among children that had not been supplemented.

CONCLUSION: Peer counselling for exclusive breastfeeding did not decrease the prevalence of malaria parasitaemia. **Children that had not received Vitamin A supplementation had a higher prevalence of malaria compared to children that had been supplemented.**



Comment

Although a randomised trial, this was not a randomised trial of Vitamin A, but of peer counselling for exclusive breastfeeding, so limited conclusions can be drawn from the vitamin A result. Low serum retinol concentrations are commonly found in children suffering from

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malaria, but it is not certain whether this represents pre-existing vitamin A deficiency, a contribution of malaria to vitamin A deficiency, or an acute effect of malaria on retinol metabolism or binding ([Malar J. 2009 Jun 17;8: 134](#), [Int J Vitam Nutr Res. 1998;68: 384-8](#)). Either way, vitamin A supplementation may reduce malaria risk, and better control of malaria may improve vitamin A status and reduce the risk or effect of other infectious diseases.

Insecticide-treated bed nets

(See also Zinc)

[Malar J. 2012 Jan 6;11: 8.](#)

[The effect of household heads training about the use of treated bed nets on the burden of malaria and anaemia in under-five children: a cluster randomized trial in Ethiopia.](#)

[Deribew A](#), [Birhanu Z](#), [Sena L](#), [Dejene T](#), [Reda AA](#), [Sudhakar M](#), [Alemseged F](#), [Tessema F](#), [Zeynudin A](#), [Biadgilign S](#), [Deribe K](#).

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BACKGROUND: Long-lasting insecticide-treated bed nets (LLITN) have demonstrated a significant effect in reducing malaria-related morbidity and mortality. However, barriers on the utilization of LLITN have hampered the desired outcomes. The aim of this study was to assess the effect of community empowerment on the burden of malaria and anaemia in under-five children in Ethiopia.

METHODS: A cluster randomized trial was done in 22 (11 intervention and 11 control) villages in south-west Ethiopia. **The intervention consisted of tailored training of household heads about the proper use of LLITN and community network system.** The burden of malaria and anaemia in under-five children was determined through mass blood investigation at baseline, six and 12 months of the project period. Cases of malaria and anaemia were treated based on the national protocol. The burden of malaria and anaemia between the intervention and control villages was compared using the complex logistic regression model by taking into account the clustering effect. Eight Focus group discussions were conducted to complement the quantitative findings.

RESULTS: A total of 2,105 household heads received the intervention and the prevalence of malaria and anaemia was assessed among 2410, 2037 and 2612 under-five children at baseline, six and 12 months of the project period respectively. **During the high transmission/epidemic season, children in the intervention arm were less likely to have malaria as compared to children in the control arm (OR = 0.42; 95%CI: 0.32, 0.57).** Symptomatic malaria also steadily declined in the intervention villages compared to the control villages in the follow up periods. **Children in the intervention arm were less likely to be anaemic compared to those in the control arm both at the high (OR = 0.84; 95%CI: 0.71, 0.99) and low (OR = 0.73; 95%CI: 0.60, 0.89) transmission seasons.**

CONCLUSION: **Training of household heads on the utilization of LLITN significantly reduces the burden of malaria in under-five children.** The Ministry of Health of Ethiopia in

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collaboration with other partners should design similar strategies in high-risk areas to control malaria in Ethiopia.



Other preventative interventions

[Acta Trop.](#) 2011 Aug;119(2-3): 107-13. Epub 2011 May 4.

[Evaluating indoor residual spray for reducing malaria infection prevalence in Eritrea: results from a community randomized control trial.](#)

[Keating J, Locatelli A, Gebremichael A, Ghebremeskel T, Mufunda J, Mihreteab S, Berhane D, Carneiro P.](#)

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This paper examines the relationship between indoor residual spray (IRS) and malaria parasite infection in Gash Barka Zone, Eritrea, an area with near universal coverage of insecticide treated bednets (ITN) and already low malaria parasite prevalence. A community randomized control trial was conducted in 2009. Malaria parasite infection prevalence was 0.5% [95% confidence interval (CI): 0.37-0.78%], with no significant difference detected between treatment and control areas. ITN possession remains high, with over 70% of households reporting ITN ownership [95% CI: 68.4-72.9]. ITN use among individuals within ITN-owning households was just under half [46.7% (95% CI: 45.4-48.0)]. Slight differences in ITN possession and use were detected between treatment and control areas. There was no significant difference in malaria parasite infection prevalence among individuals in households with ≥ 1 ITN compared to those in households without ITNs, nor among individuals reporting ITN use. Among individuals in ITN-owning households, sleeping under an ITN offered no statistically significant protection from malaria parasite infection. Community participation in environmental and larval habitat management activities was low: 17.9% (95% CI: 16.0-19.7). **It is likely that IRS, larval habitat management and ITN distribution alone may be insufficient to interrupt transmission without corresponding high ITN use, sustained IRS application in areas where infections are clustered, and promptly seeking laboratory diagnosis and treatment of all fevers.** Eritrea is ready for elimination, irrespective of inconclusive impact evaluation results.

[Malar J.](#) 2011 Aug 24;10: 247.

[A cluster-randomized trial of mass drug administration with a gametocytocidal drug combination to interrupt malaria transmission in a low endemic area in Tanzania.](#)

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[Shekalaghe SA](#), [Drakeley C](#), [van den Bosch S](#), [ter Braak R](#), [van den Bijllaardt W](#), [Mwanziva C](#), [Semvua S](#), [Masokoto A](#), [Mosha F](#), [Teelen K](#), [Hermsen R](#), [Okell L](#), [Gosling R](#), [Sauerwein R](#), [Bousema T](#).

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BACKGROUND: Effective mass drug administration (MDA) with anti-malarial drugs can clear the human infectious reservoir for malaria and thereby interrupt malaria transmission. The likelihood of success of MDA depends on the intensity and seasonality of malaria transmission, the efficacy of the intervention in rapidly clearing all malaria parasite stages and the degree to which symptomatic and asymptomatic parasite carriers participate in the intervention. **The impact of MDA with the gametocytocidal drug combination sulphadoxine-pyrimethamine (SP) plus artesunate (AS) plus primaquine (PQ, single dose 0.75 mg/kg) on malaria transmission was determined in an area of very low and seasonal malaria transmission in northern Tanzania.**

METHODS: In a cluster-randomized trial in four villages in Lower Moshi, Tanzania, eight clusters (1,110 individuals; cluster size 47- 209) were randomized to observed treatment with SP+AS+PQ and eight clusters (2,347 individuals, cluster size 55- 737) to treatment with placebo over three days. Intervention and control clusters were 1 km apart; households that were located between clusters were treated as buffer zones where all individuals received SP+AS+PQ but were not selected for the evaluation. Passive case detection was done for the entire cohort and active case detection in 149 children aged 1-10 year from the intervention arm and 143 from the control arm. Four cross-sectional surveys assessed parasite carriage by microscopy and molecular methods during a five-month follow-up period.

RESULTS: The coverage rate in the intervention arm was 93.0% (1,117/1,201). Parasite prevalence by molecular detection methods was 2.2-2.7% prior to the intervention and undetectable during follow-up in both the control and intervention clusters. None of the slides collected during cross-sectional surveys had microscopically detectable parasite densities. Three clinical malaria episodes occurred in the intervention (n = 1) and control clusters (n = 2).

CONCLUSIONS: This study illustrates the possibility to achieve high coverage with a three-day intervention but also the difficulty in defining suitable outcome measures to evaluate interventions in areas of very low malaria transmission intensity. The decline in transmission intensity prior to the intervention made it impossible to assess the impact of MDA in the chosen study setting.



Rapid diagnostic tests and malaria diagnosis

[Malar J](#). 2011 Dec 19;10: 373.

[Comparative feasibility of implementing rapid diagnostic test and microscopy for parasitological diagnosis of malaria in Uganda.](#)

[Batwala V](#), [Magnussen P](#), [Nuwaha F](#).

Randomised trials in child health in developing countries 2011-12

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BACKGROUND: In Uganda, parasite-based diagnosis is recommended for every patient suspected to have malaria before prescribing anti-malarials. However, the majority of patients are still treated presumptively especially in low-level health units. **The feasibility of implementing parasite-based diagnosis for uncomplicated malaria in rural health centres (HCs) was investigated with a view to recommending measures for scaling up the policy.**

METHODS: **Thirty HCs were randomized to implement parasite-based diagnosis based on rapid diagnostic tests [RDTs] (n = 10), blood microscopy (n = 10) and presumptive diagnosis (control arm) (n = 10).** Feasibility was assessed by comparing the proportion of patients who received parasite-based diagnosis; with a positive malaria parasite-based diagnosis who received artemether-lumefantrine (AL); with a negative malaria parasite-based diagnosis who received AL; and patient waiting time. Clinicaltrials.gov: NCT00565071.

RESULTS: 102, 087 outpatients were enrolled. Patients were more likely to be tested in the RDT 44, 565 (96.6%) than in microscopy arm 19, 545 (60.9%) [RR: 1.59]. RDTs reduced patient waiting time compared to microscopy and were more convenient to health workers and patients. Majority 23, 804 (99.7%) in presumptive arm were prescribed AL. All (100%) of patients who tested positive for malaria in RDT and microscopy arms were prescribed anti-malarials. **Parasitological-based diagnosis significantly reduced AL prescription in RDT arm [RR: 0.62] and microscopy arm [RR: 0.72] compared to presumptive treatment.** Among patients not tested in the two intervention arms, 12, 044 (96.1%) in microscopy and 965 (61.6%) in RDT arm were treated with AL [RR: 1.56]. **Overall 10, 558 (29.4%) with negative results [5, 110 (23.4%) in RDT and 5, 448 (39.0%) in microscopy arms] were prescribed AL.**

CONCLUSION: **It was more feasible to implement parasite-based diagnosis for malaria using RDT than with microscopy. A high proportion of patients with negative malaria results are still prescribed anti-malarials.** There is need to increase access to parasite-based diagnosis where microscopy is used. In order to fully harness the benefits of parasitological confirmation of malaria, it is necessary to reduce the prescription of anti-malarials in negative patients.



[Malar J.](#) 2011 Aug 4;10: 226. doi: 10.1186/1475-2875-10-226.

[Strict adherence to malaria rapid test results might lead to a neglect of other dangerous diseases: a cost benefit analysis from Burkina Faso.](#)

[Bisoffi Z](#), [Sirima SB](#), [Meheus F](#), [Lodesani C](#), [Gobbi F](#), [Angheben A](#), [Tinto H](#), [Neya B](#), [Van den Ende K](#), [Romeo A](#), [Van den Ende J](#).

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BACKGROUND: Malaria rapid diagnostic tests (RDTs) have generally been found reliable and cost-effective. **In Burkina Faso, the adherence of prescribers to the negative test result was found to be poor.** Moreover, the test accuracy for malaria-attributable fever (MAF) is not the

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same as for malaria infection. This paper aims at determining the costs and benefits of two competing strategies for the management of MAF: presumptive treatment for all or use of RDTs.

METHODS: A cost benefit analysis was carried out using a decision tree, based on data previously obtained, including a randomized controlled trial (RCT) recruiting 852 febrile patients during the dry season and 1,317 in the rainy season. Cost and benefit were calculated using both the real adherence found by the RCT and assuming an ideal adherence of 90% with the negative result. The main parameters were submitted to sensitivity analysis.

RESULTS AND DISCUSSION: At real adherence, the test-based strategy was dominated. Assuming ideal adherence, at the value of 525 € for a death averted, the total cost of managing 1,000 febrile children was 1,747 vs. 1,862 € in the dry season and 1,372 vs. 2,138 in the rainy season for the presumptive vs. the test-based strategy. For adults it was 2,728 vs. 1,983 and 2,604 vs. 2,225, respectively. At the subsidized policy adopted locally, assuming ideal adherence, the RDT would be the winning strategy for adults in both seasons and for children in the dry season. At sensitivity analysis, the factors most influencing the choice of the better strategy were the value assigned to a death averted and the proportion of potentially severe NMFI treated with antibiotics in patients with false positive RDT results. The test-based strategy appears advantageous for adults if a satisfactory adherence could be achieved. For children the presumptive strategy remains the best choice for a wide range of scenarios.

CONCLUSIONS: For RDTs to be preferred, a positive result should not influence the decision to treat a potentially severe NMFI with antibiotics. In the rainy season the presumptive strategy always remains the better choice for children.



Comment

This analysis does not take account of the long-term cost of over-prescribing of antimalarials for children without malaria or drug resistance. It does suggest, however, that the cost benefit of RDTs depends on the prevalence of malaria, with seasonal changes, and that the optimal cost-benefit depends on children with negative results not being given antimalarials. The safety of the RDT-based treatment in holoendemic areas depends on children with positive tests not being denied antibiotics if they have signs of sepsis.

[PLoS One](#). 2011;6(7): e19753. Epub 2011 Jul 5.

[Malaria rapid testing by community health workers is effective and safe for targeting malaria treatment: randomised cross-over trial in Tanzania.](#)

[Mubi M](#), [Janson A](#), [Warsame M](#), [Mårtensson A](#), [Källander K](#), [Petzold MG](#), [Ngasala B](#), [Maganga G](#), [Gustafsson LL](#), [Massele A](#), [Tomson G](#), [Premji Z](#), [Björkman A](#).

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BACKGROUND: Early diagnosis and prompt, effective treatment of uncomplicated malaria is critical to prevent severe disease, death and malaria transmission. We assessed the impact of rapid malaria diagnostic tests (RDTs) by community health workers (CHWs) on provision of artemisinin-based combination therapy (ACT) and health outcome in fever patients.

METHODOLOGY/PRINCIPAL FINDINGS: Twenty-two CHWs from five villages in Kibaha District, a high-malaria transmission area in Coast Region, Tanzania, were trained to manage uncomplicated malaria using RDT aided diagnosis or clinical diagnosis (CD) only. **Each CHW was randomly assigned to use either RDT or CD the first week and thereafter alternating weekly.** Primary outcome was provision of ACT and main secondary outcomes were referral rates and health status by days 3 and 7. The CHWs enrolled 2930 fever patients during five months of whom 1988 (67.8%) presented within 24 hours of fever onset. **ACT was provided to 775 of 1457 (53.2%) patients during RDT weeks and to 1422 of 1473 (96.5%) patients during CD weeks (Odds Ratio (OR) 0.039, 95% CI 0.029-0.053).** The CHWs adhered to the RDT results in 1411 of 1457 (96.8%, 95% CI 95.8-97.6) patients. More patients were referred on inclusion day during RDT weeks (10.0%) compared to CD weeks (1.6%). Referral during days 1-7 and perceived non-recovery on days 3 and 7 were also more common after RDT aided diagnosis. However, **no fatal or severe malaria occurred among 682 patients in the RDT group who were not treated with ACT, supporting the safety of withholding ACT to RDT negative patients.**

CONCLUSIONS/SIGNIFICANCE: RDTs in the hands of CHWs may safely improve early and well-targeted ACT treatment in malaria patients at community level in Africa.



Treatment of uncomplicated malaria

[N Engl J Med.](#) 2012 Apr 5;366(14): 1298-309.

[Pyronaridine-artesunate versus mefloquine plus artesunate for malaria.](#)

[Rueangweerayut R](#), [Phyo AP](#), [Uthaisin C](#), [Poravuth Y](#), [Binh TQ](#), [Tinto H](#), [Pénali LK](#), [Valecha N](#), [Tien NT](#), [Abdulla S](#), [Borghini-Fuhrer I](#), [Duparc S](#), [Shin CS](#), [Fleckenstein L](#); [Pyronaridine–Artesunate Study Team](#).

[Rueangweerayut K](#), [Sila P](#), [Socheat D](#), [Huot M](#), [Hung le Q](#), [Guiguemdé RT](#), [Zeba A](#), [Offianan TA](#), [Rao BH](#), [Ghosh SK](#), [Thanh NV](#), [Juma V](#).

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BACKGROUND: Pyronaridine-artesunate is an artemisinin-based combination therapy under evaluation for the treatment of *Plasmodium falciparum* and *P. vivax* malaria.

METHODS: We conducted a phase 3, open-label, multicenter, noninferiority trial that included 1271 patients between 3 and 60 years of age from Asia (81.3%) or Africa (18.7%) with microscopically confirmed, uncomplicated *P. falciparum* malaria. **Patients underwent randomization for treatment with a fixed-dose combination of 180 mg of pyronaridine and**

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60 mg of artesunate or with 250 mg of mefloquine plus 100 mg of artesunate. Doses were calculated according to body weight and administered once daily for 3 days.

RESULTS: Pyronaridine-artesunate was noninferior to mefloquine plus artesunate for the primary outcome: adequate clinical and parasitologic response in the per-protocol population on day 28, corrected for reinfection with the use of polymerase-chain-reaction (PCR) genotyping. For this outcome, efficacy in the group receiving pyronaridine-artesunate was 99.2% (743 of 749 patients; 95% confidence interval [CI], 98.3 to 99.7) and that in the group receiving mefloquine plus artesunate was 97.8% (360 of 368 patients; 95% CI, 95.8 to 99.1), with a treatment difference of 1.4 percentage points (95% CI, 0.0 to 3.5; $P=0.05$). In the intention-to-treat population, efficacy on day 42 in the group receiving pyronaridine-artesunate was 83.1% (705 of 848 patients; 95% CI, 80.4 to 85.6) and that in the group receiving mefloquine plus artesunate was 83.9% (355 of 423 patients; 95% CI, 80.1 to 87.3). In Cambodia, where there were 211 study patients, the median parasite clearance time was prolonged for both treatments: 64 hours versus 16.0 to 38.9 hours in other countries ($P<0.001$, on the basis of Kaplan-Meier estimates). Kaplan-Meier estimates of the recrudescence rate in the intention-to-treat population in Cambodia until day 42 were higher with pyronaridine-artesunate than with mefloquine plus artesunate (10.2% [95% CI, 5.4 to 18.6] vs. 0%; $P=0.04$ as calculated with the log-rank test), but similar for the other countries combined (4.7% [95% CI, 3.3 to 6.7] and 2.8% [95% CI, 1.5 to 5.3], respectively; $P=0.24$). Elevated levels of aminotransferases were observed in those receiving pyronaridine-artesunate. Two patients receiving mefloquine plus artesunate had seizures.

CONCLUSIONS: Fixed-dose pyronaridine-artesunate was efficacious in the treatment of uncomplicated *P. falciparum* malaria. In Cambodia, extended parasite clearance times were suggestive of in vivo resistance to artemisinin. (Funded by Shin Poong Pharmaceutical Company and the Medicines for Malaria Venture; ClinicalTrials.gov number, NCT00403260.).



[PLoS Med.](#) 2011 Nov;8(11): e1001119. Epub 2011 Nov 8.

[A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial.](#)

[Four Artemisinin-Based Combinations \(4ABC\) Study Group.](#)

[Atwine D](#), [Balikagala B](#), [Bassat Q](#), [Chalwe V](#), [D'Alessandro U](#), [Dhorda M](#), [Donegan S](#), [Garner P](#), [González R](#), [Tinga Guiguemde R](#), [Hachizovu S](#), [Kajungu D](#), [Kamya M](#), [Karema C](#), [Kibuuka A](#), [Kremsner PG](#), [Lell B](#), [Machevo S](#), [Menéndez C](#), [Menten J](#), [Meremikwu M](#), [Mombo-Ngoma G](#), [Mudangha F](#), [Mulenga M](#), [Munyaneza T](#), [Nabasumba C](#), [Nambozi M](#), [Odey F](#), [Okello S](#), [Oringange C](#), [Oyo-Ita A](#), [Piola P](#), [Ravinetto R](#), [Tinto H](#), [Rouamba N](#), [Strecker F](#), [Talisuna AO](#), [Umulisa N](#), [Uwimana A](#), [Valéa I](#), [Van Geertruyden JP](#), [van Loen H](#), [Williamson P](#), [Yeka A](#).

BACKGROUND: Artemisinin-based combination therapies (ACTs) are the mainstay for the management of uncomplicated malaria cases. However, up-to-date data able to assist sub-Saharan African countries formulating appropriate antimalarial drug policies are scarce.

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METHODS AND FINDINGS: Between 9 July 2007 and 19 June 2009, a randomized, non-inferiority (10% difference threshold in efficacy at day 28) clinical trial was carried out at **12 sites in seven sub-Saharan African countries. Each site compared three of four ACTs, namely amodiaquine-artesunate (ASAQ), dihydroartemisinin-piperaquine (DHAPQ), artemether-lumefantrine (AL), or chlorproguanil-dapsone-artesunate (CD+A).** Overall, 4,116 children 6-59 mo old with uncomplicated *Plasmodium falciparum* malaria were treated (1,226 with AL, 1,002 with ASAQ, 413 with CD+A, and 1,475 with DHAPQ), actively followed up until day 28, and then passively followed up for the next 6 mo. At day 28, for the PCR-adjusted efficacy, non-inferiority was established for three pair-wise comparisons: DHAPQ (97.3%) versus AL (95.5%) (odds ratio [OR]: 0.59, 95% CI: 0.37-0.94); DHAPQ (97.6%) versus ASAQ (96.8%) (OR: 0.74, 95% CI: 0.41-1.34), and ASAQ (97.1%) versus AL (94.4%) (OR: 0.50, 95% CI: 0.28-0.92). For the PCR-unadjusted efficacy, AL was significantly less efficacious than DHAPQ (72.7% versus 89.5%) (OR: 0.27, 95% CI: 0.21-0.34) and ASAQ (66.2% versus 80.4%) (OR: 0.40, 95% CI: 0.30-0.53), while DHAPQ (92.2%) had higher efficacy than ASAQ (80.8%) but non-inferiority could not be excluded (OR: 0.35, 95% CI: 0.26-0.48). CD+A was significantly less efficacious than the other three treatments. Day 63 results were similar to those observed at day 28.

CONCLUSIONS: This large head-to-head comparison of most currently available ACTs in sub-Saharan Africa showed that AL, ASAQ, and DHAPQ had excellent efficacy, up to day 63 post-treatment. **The risk of recurrent infections was significantly lower for DHAPQ, followed by ASAQ and then AL, supporting the recent recommendation of considering DHAPQ as a valid option for the treatment of uncomplicated *P. falciparum* malaria.**



Comment

*That dihydroartemisinin-piperaquine is as effective as artemisinin-based combination therapy against *P falciparum* and results in a lower recurrence risk has been shown in studies published in previous years (PLoS One. 2009 Nov 17;4(11): e7871. Clin Infect Dis. 2009 Dec 1;49(11): 1629-37).*

[PLoS One](#). 2011;6(11): e26005. Epub 2011 Nov 10.

[Declining responsiveness of Plasmodium falciparum infections to artemisinin-based combination treatments on the Kenyan coast.](#)

[Borrmann S](#), [Sasi P](#), [Mwai L](#), [Bashraheil M](#), [Abdallah A](#), [Muriithi S](#), [Frühauf H](#), [Schaub B](#), [Pfeil J](#), [Peshu J](#), [Hanpithakpong W](#), [Rippert A](#), [Juma E](#), [Tsofa B](#), [Mosobo M](#), [Lowe B](#), [Osier F](#), [Fegan G](#), [Lindegårdh N](#), [Nzila A](#), [Peshu N](#), [Mackinnon M](#), [Marsh K](#).

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BACKGROUND: The emergence of artemisinin-resistant *P. falciparum* malaria in South-East Asia highlights the need for continued global surveillance of the efficacy of artemisinin-based combination therapies.

METHODS: On the Kenyan coast we studied the treatment responses in 474 children 6-59 months old with uncomplicated *P. falciparum* malaria in a randomized controlled trial of dihydroartemisinin-piperaquine vs. artemether-lumefantrine from 2005 to 2008. (ISRCTN88705995).

RESULTS: The proportion of patients with residual parasitemia on day 1 rose from 55% in 2005-2006 to 87% in 2007-2008 (odds ratio, 5.4, 95% CI, 2.7-11.1; $P < 0.001$) and from 81% to 95% (OR, 4.1, 95% CI, 1.7-9.9; $P = 0.002$) in the DHA-PPQ and AM-LM groups, respectively. In parallel, Kaplan-Meier estimated risks of apparent recrudescence infection by day 84 increased from 7% to 14% ($P = 0.1$) and from 6% to 15% ($P = 0.05$) with DHA-PPQ and AM-LM, respectively. Coinciding with decreasing transmission in the study area, clinical tolerance to parasitemia (defined as absence of fever) declined between 2005-2006 and 2007-2008 (OR body temperature $>37.5^{\circ}\text{C}$, 2.8, 1.9-4.1; $P < 0.001$). Neither in vitro sensitivity of parasites to DHA nor levels of antibodies against parasite extract accounted for parasite clearance rates or changes thereof.

CONCLUSIONS: The significant, albeit small, decline through time of parasitological response rates to treatment with ACTs may be due to the emergence of parasites with reduced drug sensitivity, to the coincident reduction in population-level clinical immunity, or both. Maintaining the efficacy of artemisinin-based therapy in Africa would benefit from a better understanding of the mechanisms underlying reduced parasite clearance rates.



[Malar J.](#) 2011 Sep 21;10: 275.

[Effects of amodiaquine and artesunate on sulphadoxine-pyrimethamine pharmacokinetic parameters in children under five in Mali.](#)

[Tekete MM](#), [Toure S](#), [Fredericks A](#), [Beavogui AH](#), [Sangare CP](#), [Evans A](#), [Smith P](#), [Maiga H](#), [Traore ZI](#), [Doumbo OK](#), [Barnes KI](#), [Djimde AA](#).

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BACKGROUND: Sulphadoxine-pyrimethamine, in combination with artesunate or amodiaquine, is recommended for the treatment of uncomplicated malaria and is being evaluated for intermittent preventive treatment. Yet, limited data is available on pharmacokinetic interactions between these drugs.

METHODS: In a randomized controlled trial, children aged 6-59 months with uncomplicated falciparum malaria, received either one dose of sulphadoxine-pyrimethamine alone (SP), one dose of SP plus three daily doses of amodiaquine (SP+AQ) or one dose of SP plus 3 daily doses of artesunate (SP+AS). Exactly 100 μl of capillary blood was collected onto filter paper before

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drug administration at day 0 and at days 1, 3, 7, 14, 21 and 28 after drug administration for analysis of sulphadoxine and pyrimethamine pharmacokinetic parameters.

RESULTS: Forty, 38 and 31 patients in the SP, SP+AQ and SP+AS arms, respectively were included in this study. The concentrations on day 7 (that are associated with therapeutic efficacy) were similar between the SP, SP+AQ and SP+AS treatment arms for sulphadoxine (median [IQR] 35.25 [27.38-41.70], 34.95 [28.60-40.85] and 33.40 [24.63-44.05] µg/mL) and for pyrimethamine (56.75 [46.40-92.95], 58.75 [43.60-98.60] and 59.60 [42.45-86.63] ng/mL). There were statistically significant differences between the pyrimethamine volumes of distribution (4.65 [3.93-6.40], 4.00 [3.03-5.43] and 5.60 [4.40-7.20] L/kg; $p = 0.001$) and thus elimination half-life (3.26 [2.74 -3.82], 2.78 [2.24-3.65] and 4.02 [3.05-4.85] days; $p < 0.001$). This study confirmed the lower SP concentrations previously reported for young children when compared with adult malaria patients.

CONCLUSION: Despite slight differences in pyrimethamine volumes of distribution and elimination half-life, these data show similar exposure to SP over the critical initial seven days of treatment and support the current use of SP in combination with either AQ or AS for uncomplicated falciparum malaria treatment in young Malian children.



[Malar J.](#) 2011 Jul 8;10: 185.

[Comparative study of the efficacy and tolerability of dihydroartemisinin-piperaquine-trimethoprim versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroon, Ivory Coast and Senegal.](#)

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BACKGROUND: The ACT recommended by WHO is very effective and well-tolerated. However, these combinations need to be administered for three days, which may limit adherence to treatment. The combination of dihydroartemisinin-piperaquine phosphate-trimethoprim (Artecom®, Odypharm Ltd), which involves treatment over two days, appears to be a good alternative, particularly in malaria-endemic areas. This study intends to compare the efficacy and tolerability of the combination dihydroartemisinin-piperaquine phosphate-trimethoprim (DPT) versus artemether-lumefantrine (AL) in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroon, Ivory Coast and Senegal.

METHODS: This was a randomized, controlled, open-label clinical trial with a 28-day follow-up period comparing DPT to AL as the reference drug. The study involved patients of at least two years of age, suffering from acute, uncomplicated Plasmodium falciparum malaria with fever. The WHO 2003 protocol was used.

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RESULTS: A total of 418 patients were included in the study and divided into two treatment groups: 212 in the DPT group and 206 in the AL group. The data analysis involved the 403 subjects who correctly followed the protocol (per protocol analysis), i.e. 206 (51.1%) in the DPT group and 197 (48.9%) in the AL group. **The recovery rate at D14 was 100% in both treatment groups.** The recovery rate at D28 was 99% in the DPT and AL groups before and after PCR results with one-sided 97.5% Confidence Interval of the rates difference > -1.90%. **More than 96% of patients who received DPT were apyrexial 48 hours after treatment compared to 83.5% in the AL group (p < 0.001).** More than 95% of the people in the DPT group had a parasite clearance time of 48 hours or less compared to approximately 90% in the AL group (p = 0.023). Both drugs were well tolerated. No serious adverse events were reported during the follow-up period. All of the adverse events observed were minor and did not result in the treatment being stopped in either treatment group. The main minor adverse events reported were vomiting, abdominal pain and pruritus.

CONCLUSION: **The overall efficacy and tolerability of DPT are similar to those of AL. The ease of taking DPT and its short treatment course (two days) may help to improve adherence to treatment.** Taken together, these findings make this medicinal product a treatment of choice for the effective management of malaria in Africa.



[Malar J.](#) 2011 Dec 16;10: 369.

[Similar efficacy and safety of artemether-lumefantrine \(Coartem®\) in African infants and children with uncomplicated falciparum malaria across different body weight ranges.](#)

[Bassat Q, González R, Machevo S, Nahum A, Lyimo J, Maiga H, Mårtensson A, Bashraheil M, Ouma P, Ubben D, Walter V, Nwaiwu O, Kipkeu C, Lefèvre G, Ogutu B, Menéndez C.](#)

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BACKGROUND: Artemisinin-based combination therapy, including artemether-lumefantrine (AL), is currently recommended for the treatment of uncomplicated Plasmodium falciparum malaria. The objectives of the current analysis were to compare the efficacy and safety of AL across different body weight ranges in African children, and to examine the age and body weight relationship in this population.

METHODS: Efficacy, safety and pharmacokinetic data from a randomized, investigator-blinded, multicentre trial of AL for treatment of acute uncomplicated P. falciparum malaria in infants and children in Africa were analysed according to body weight group.

RESULTS: The trial included 899 patients (intent-to-treat population 886). The modified intent-to-treat (ITT) population (n = 812) comprised 143 children 5 to < 10 kg, 334 children 10 to < 15 kg, 277 children 15 to < 25 kg, and 58 children 25 to < 35 kg. **The 28-day PCR cure rate, the primary endpoint, was comparable across all four body weight groups (97.2%, 98.9%, 97.8% and 98.3%, respectively).** There were no clinically relevant differences in

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safety or tolerability between body weight groups. In the three AL body weight dosing groups (5 to < 15 kg, 15 to < 25 kg and 25 to < 35 kg), 80% of patients were aged 10-50 months, 46-100 months and 90-147 months, respectively.

CONCLUSION: Efficacy of AL in uncomplicated falciparum malaria is similar across body weight dosing groups as currently recommended in the label with no clinically relevant differences in safety or tolerability. AL dosing based on body weight remains advisable.



[Am J Trop Med Hyg.](#) 2011 Sep;85(3): 573-8.

[Efficacy and effectiveness of mefloquine and artesunate combination therapy for uncomplicated Plasmodium falciparum malaria in the Peruvian Amazon.](#)

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We evaluated the efficacy and effectiveness of mefloquine (MQ) plus artesunate (AS) to treat patients with uncomplicated malaria in the Peruvian Amazon Basin in April 2005-March 2006. Patients \geq 1 year of age with fever (axillary temperature \geq 37.5°C) or history of fever and Plasmodium falciparum mono-infection were included. Patients received antimalarial treatment with MQ (12.5 mg/kg/day for two days) and AS (4.0 mg/kg/day for three days) either by directly observed therapy or without directly observed therapy. After a 28-day follow-up, treatment efficacy and effectiveness were assessed on the basis of clinical and parasitologic outcomes. **Ninety-six patients were enrolled in each study group; nine patients were lost to follow-up. All patients, except for one in the observed group, demonstrated adequate clinical and parasitologic response; none had detectable parasitemia on day 3.** The efficacy of MQ + AS efficacy was 98.9% (95% confidence interval = 94.1-100.0%) and the effectiveness was 100.0% (95% confidence interval = 95.9-100.0%). Our study shows that MQ + AS is highly efficacious in the Peruvian Amazon.



[Am J Trop Med Hyg.](#) 2012 Jan;86(1): 75-83.

[Randomized, prospective, three-arm study to confirm the auditory safety and efficacy of artemether-lumefantrine in Colombian patients with uncomplicated Plasmodium falciparum malaria.](#)

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The safety of artemether-lumefantrine in patients with acute, uncomplicated *Plasmodium falciparum* malaria was investigated prospectively using the auditory brainstem response (ABR) and pure-tone thresholds. Secondary outcomes included polymerase chain reaction-corrected cure rates. Patients were randomly assigned in a 3:1:1 ratio to either artemether-lumefantrine (N = 159), atovaquone-proguanil (N = 53), or artesunate-mefloquine (N = 53). The null hypothesis (primary outcome), claiming that the percentage of patients with a baseline to Day-7 ABR Wave III latency increase of > 0.30 msec is $\geq 15\%$ after administration of artemether-lumefantrine, was rejected; 2.6% of patients (95% confidence interval: 0.7-6.6) exceeded 0.30 msec, i.e., significantly below 15% ($P < 0.0001$). **A model-based analysis found no apparent relationship between drug exposure and ABR change.** In all three groups, average improvements (2-4 dB) in pure-tone thresholds were observed, and polymerase chain reaction-corrected cure rates were > 95% to Day 42. The results support the continued safe and efficacious use of artemether-lumefantrine in uncomplicated *falciparum* malaria.



[PLoS One](#). 2012;7(1): e28957. Epub 2012 Jan 31.

[Defining *Plasmodium falciparum* treatment in South West Asia: a randomized trial comparing artesunate or primaquine combined with chloroquine or SP.](#)

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INTRODUCTION: Antimalarial resistance has led to a global policy of artemisinin-based combination therapy. Despite growing resistance chloroquine (CQ) remained until recently the official first-line treatment for *falciparum* malaria in Pakistan, with sulfadoxine-pyrimethamine (SP) second-line. Co-treatment with the gametocytocidal primaquine (PQ) is recommended for transmission control in South Asia. The relative effect of artesunate (AS) or primaquine, as partner drugs, on clinical outcomes and gametocyte carriage in this setting were unknown.

METHODS: A single-blinded, randomized trial among Afghan refugees in Pakistan compared six treatment arms: CQ; CQ+(single-dose)PQ; CQ+(3 d)AS; SP; SP+(single-dose)PQ, and SP+(3 d)AS. The objectives were to compare treatment failure rates and effect on gametocyte carriage, of CQ or SP monotherapy against the respective combinations (PQ or AS). Outcomes included trophozoite and gametocyte clearance (read by light microscopy), and clinical and parasitological failure.

FINDINGS: **A total of 308 (87%) patients completed the trial. Failure rates by day 28 were: CQ 55/68 (81%); CQ+AS 19/67 (28%), SP 4/41 (9.8%), SP+AS 1/41 (2.4%).** The addition of PQ to CQ or SP did not affect failure rates (CQ+PQ 49/67 (73%) failed; SP+PQ 5/33 (16%) failed). AS was superior to PQ at clearing gametocytes; gametocytes were seen on d7 in 85% of CQ, 40% of CQ+PQ, 21% of CQ+AS, 91% of SP, 76% of SP+PQ and 23% of SP+AS

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treated patients. PQ was more effective at clearing older gametocyte infections whereas AS was more effective at preventing emergence of mature gametocytes, except in cases that recrudesced.

CONCLUSIONS: CQ is no longer appropriate by itself or in combination. These findings influenced the replacement of CQ with SP+AS for first-line treatment of uncomplicated falciparum malaria in the WHO Eastern Mediterranean Region. The threat of SP resistance remains as SP monotherapy is still common. Three day AS was superior to single-dose PQ for reducing gametocyte carriage.



[Malar J.](#) 2011 Aug 12;10: 237.

[Repeated treatment of recurrent uncomplicated Plasmodium falciparum malaria in Senegal with fixed-dose artesunate plus amodiaquine versus fixed-dose artemether plus lumefantrine: a randomized, open-label trial.](#)

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BACKGROUND: The use of artemisinin-based combination therapy (ACT) is currently recommended for treating uncomplicated malaria. The objective was to assess the efficacy and safety of repeated administrations of two fixed-dose presentations of ACT--artesunate plus amodiaquine (ASAQ) and artemether-lumefantrine (AL)--in subsequent episodes of Plasmodium falciparum malaria.

METHODS: A randomized comparative study was conducted in a rural community of central Senegal from August 2007 to January 2009. **Children and adults with uncomplicated P. falciparum malaria were randomized to receive open-label ASAQ once daily or AL twice daily for three days.** Drug doses were given according to body weight. Treatments for first episodes were supervised. For subsequent episodes, only the first intake of study drug was supervised. ECGs and audiograms were performed in patients ≥ 12 years of age. Primary outcome was adequate clinical and parasitological response rate (ACPR) after polymerase chain reaction (PCR) correction on day 28 for the first episode.

RESULTS: A total of 366 patients were enrolled in the two groups (ASAQ 184, AL 182) and followed up during two malaria transmission seasons. In the intent-to-treat population, PCR-corrected ACPRs at day 28 for the first episode were 98.4% and 96.2%, respectively, in the ASAQ and AL groups. For the per-protocol population (ASAQ 183, AL 182), PCR-corrected ACPRs at day 28 for the first episode were 98.9% and 96.7%, respectively. A 100% ACPR rate was obtained at day 28 in the 60 and four patients, respectively, who experienced second and third episodes. Treatment-related adverse events were reported in 11.7% of the patients, without significant differences between the two groups. A better improvement of haemoglobin at day 28 was noted in the ASAQ versus the AL group (12.2

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versus 11.8 g/dL; $p = 0.03$). No sign of ototoxicity was demonstrated. A prolongation of the QTc interval was observed in both groups during treatment with no clinical consequence.

CONCLUSIONS: Study results confirmed the satisfactory efficacy and safety profile of ASAQ and AL. Moreover, in patients who were treated at least twice, repeated administration of ASAQ or AL did not identify any major safety issues.



[Am J Trop Med Hyg. 2012 Mar;86\(3\): 403-8.](#)

[No evidence for spread of Plasmodium falciparum artemisinin resistance to Savannakhet Province, Southern Laos.](#)

[Mayxay M, Khanthavong M, Chanthongthip O, Imwong M, Lee SJ, Stepniewska K, Soonthornsata B, Pongvongsa T, Phompida S, Hongvanthong B, Ringwald P, White NJ, Newton PN.](#)

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We conducted an open-label, randomized clinical trial to assess parasite clearance times (PCT) and **the efficacy of 4 mg/kg (group 1, n = 22) and 2 mg/kg (group 2, n = 22) of oral artesunate for three days followed by artemether-lumefantrine in patients with uncomplicated Plasmodium falciparum malaria** at Xepon Interdistrict Hospital, Savannakhet Province in southern Laos. Slides were read in duplicate. **The overall mean (95% confidence interval; range) PCT in hours was 23.2 (21.2-25.3; 12-46) and 22.4 (20.3-24.5; 12-46) for the first and second microscopists, respectively (P = 0.57).** Ten (23%) patients remained parasitemic on day 1 after treatment (4 [18%] in group 1 and 6 [27%] in group 2; $P = 0.47$). No patient had patent asexual parasitemia on the second and third days of treatment. **The 42-day polymerase chain reaction-corrected cure rates were 100% in both treatment groups.** Serious adverse events did not develop during or after treatment in any patients. In conclusion, **no evidence of P. falciparum in vivo resistance to artesunate was found in southern Laos.**



[Am J Trop Med Hyg. 2011 Oct;85\(4\): 619-25.](#)

[Hematologic parameters in pediatric uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa.](#)

[Olliaro P, Djimdé A, Dorsey G, Karema C, Mårtensson A, Ndiaye JL, Sirima SB, Vaillant M, Zwang J.](#)

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Hematologic changes in acute and convalescent uncomplicated Plasmodium falciparum malaria have not been well studied, particularly in young children in Africa. **Hematologic data were obtained for 3,044 children less than five years of age in seven randomized controlled trials at 14 sites.** Using paired analysis between day 28 and baseline in patients without parasitologic failure as a proxy for malaria-induced effects, we found a statistically significant but clinically **modest increase in leukocyte counts (5%) resulting from a larger increase in neutrophils (43%) than the decrease in lymphocytes counts (-16%); levels of hemoglobin and platelets decreased (-13% and -49%, respectively).** Multivariate random effects analysis showed trends during follow-up (increased levels of hemoglobin, platelets and lymphocytes, and decreased levels of leukocytes and neutrophils) and identified explanatory variables. The risk of neutropenia increased with follow-up time independent of treatment outcome, and was lower with age, higher baseline parasitemia, and artemisinin combination treatment. These analyses provide information on hematologic variations caused by malaria.



[Malar J.](#) 2011 Aug 17;10: 241.

[Frequency of glucose-6-phosphate dehydrogenase deficiency in malaria patients from six African countries enrolled in two randomized anti-malarial clinical trials.](#)

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BACKGROUND: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is common in populations living in malaria endemic areas. G6PD genotype and phenotype were determined for malaria patients enrolled in the chlorproguanil-dapsone-artesunate (CDA) phase III clinical trial programme.

METHODS: **Study participants, aged > 1 year, with microscopically confirmed uncomplicated Plasmodium falciparum malaria, and haemoglobin \geq 70 g/L or haematocrit \geq 25%, were recruited into two clinical trials conducted in six African countries (Burkina Faso, Ghana, Kenya, Nigeria, Tanzania, Mali).** G6PD genotype of the three most common African forms, G6PD*B, G6PD*A (A376G), and G6PD*A- (G202A, A542T, G680T and T968C), were determined and used for frequency estimation. G6PD phenotype was assessed qualitatively using the NADPH fluorescence test. Exploratory analyses investigated the effect of G6PD status on baseline haemoglobin concentration, temperature, asexual parasitaemia and anti-malarial efficacy after treatment with CDA 2/2.5/4 mg/kg or chlorproguanil-dapsone 2/2.5 mg/kg (both given once daily for three days) or six-dose artemether-lumefantrine.

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RESULTS: Of 2264 malaria patients enrolled, 2045 had G6PD genotype available and comprised the primary analysis population (1018 males, 1027 females). **G6PD deficiency prevalence was 9.0% (184/2045; 7.2% [N = 147] male hemizygous plus 1.8% [N = 37] female homozygous), 13.3% (273/2045) of patients were heterozygous females, 77.7% (1588/2045) were G6PD normal.** All deficient G6PD*A- genotypes were A376G/G202A. G6PD phenotype was available for 64.5% (1319/2045) of patients: 10.2% (134/1319) were G6PD deficient, 9.6% (127/1319) intermediate, and 80.2% (1058/1319) normal. Phenotype test specificity in detecting hemizygous males was 70.7% (70/99) and 48.0% (12/25) for homozygous females. Logistic regression found no significant effect of G6PD genotype on adjusted mean baseline haemoglobin ($p = 0.154$), adjusted mean baseline temperature ($p = 0.9617$), or adjusted log mean baseline parasitaemia ($p = 0.365$). There was no effect of G6PD genotype ($p = 0.490$) or phenotype ($p = 0.391$) on the rate of malaria recrudescence, or reinfection ($p = 0.134$ and $p = 0.354$, respectively).

CONCLUSIONS: G6PD deficiency is common in African patients with malaria and until a reliable and simple G6PD test is available, the use of 8-aminoquinolines will remain problematic. G6PD status did not impact baseline haemoglobin, parasitaemia or temperature or the outcomes of anti-malarial therapy.



[Trop Med Int Health](#). 2012 May 30. doi: 10.1111/j.1365-3156.2012.03018.x. [Epub ahead of print]

[Is home management of fevers a cost-effective way of reducing under-five mortality in Africa? The case of a rural Ghanaian District.](#)

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Objective To assess the cost-effectiveness of two strategies of home management of under-five fevers in Ghana – treatment using antimalarials only (artesunate–amodiaquine – AAQ) and combined treatment using antimalarials and antibiotics (artesunate–amodiaquine plus amoxicillin – AAQ + AMX).

Methods We assessed the costs and cost-effectiveness of AAQ and AAQ + AMX compared with a control receiving standard care. Data were collected as part of a cluster randomized controlled trial with a step-wedged design. **Approximately, 12 000 children aged 2–59 months in Dangme West District in southern Ghana were covered.** Community health workers delivered the interventions. Costs were analysed from societal perspective, using anaemia cases averted, under-five deaths averted and disability-adjusted life years (DALYs) averted as effectiveness measures.

Results Total economic costs for the interventions were US\$ 204 394.72 (AAQ) and US\$ 260 931.49 (AAQ + AMX). Recurrent costs constituted 89% and 90% of the total direct costs of AAQ and AAQ + AMX, respectively. Deaths averted were 79.1 (AAQ) and 79.9 (AAQ + AMX), with DALYs averted being 2264.79 (AAQ) and 2284.57 (AAQ + AMX). The

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results show that cost per anaemia case averted were US\$ 150.18 (AAQ) and US\$ 227.49 (AAQ + AMX) and **cost per death averted was US\$ 2585.58 for AAQ and US\$ 3272.20 for AAQ + AMX.** Cost per DALY averted were US\$ 90.25 (AAQ) and US\$ 114.21 (AAQ + AMX).

Conclusion Both AAQ and AAQ + AMX approaches were cost-effective, each averting one DALY at less than the standard US\$ 150 threshold recommended by the World Health Organization. However, AAQ was more cost-effective. Home management of under-five fevers in rural settings is cost-effective in reducing under-five mortality.

[Malar J.](#) 2011 Aug 10;10: 231.

[Randomized trials of artemisinin-piperaquine, dihydroartemisinin-piperaquine phosphate and artemether-lumefantrine for the treatment of multi-drug resistant falciparum malaria in Cambodia-Thailand border area.](#)

[Song J, Socheat D, Tan B, Seila S, Xu Y, Ou F, Sokunthea S, Sophorn L, Zhou C, Deng C, Wang Q, Li G.](#)

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BACKGROUND: Drug resistance of falciparum malaria is a global problem.

Sulphadoxine/pyrimethamine-resistant and mefloquine-resistant strains of falciparum malaria have spread in Southeast Asia at lightning speed in 1980s-1990s, and the Cambodia-Thailand border is one of the malaria epidemic areas with the most severe forms of multi-drug resistant falciparum malaria.

METHODS: Artemisinin-piperaquine (AP), dihydroartemisinin-piperaquine phosphate (DHP) and artemether-lumefantrine (AL) were used to treat 110, 55 and 55 uncomplicated malaria patients, respectively. The total dosage for adults is 1,750 mg (four tablets, twice over 24 hours) of AP, 2,880 mg (eight tablets, four times over two days) of DHP, and 3,360 mg (24 tablets, six times over three days) of AL. The 28-day cure rate, parasite clearance time, fever clearance time, and drug tolerance of patients to the three drugs were compared. All of the above methods were consistent with the current national guidelines.

RESULTS: The mean parasite clearance time was similar in all three groups (66.7 ± 21.9 hrs, 65.6 ± 27.3 hrs, 65.3 ± 22.5 hrs in AP, DHP and AL groups, respectively), and there was no remarkable difference between them; the fever clearance time was also similar (31.6 ± 17.7 hrs, 34.6 ± 21.8 hrs and 36.9 ± 15.4 hrs, respectively). **After following up for 28-days, the cure rate was 95.1%(97/102), 98.2%(54/55) and 82.4%(42/51); and the recrudescence cases was 4.9%(5/102), 1.8%(1/55) and 17.6%(9/51), respectively.** Therefore, the statistical data showed that 28-day cure rate in AP and DHP groups was superior to AL group obviously. The patients had good tolerance to all the three drugs, and some side effects (anoxia, nausea, vomiting, headache and dizziness) could be found in every group and they were self-limited; patients in control groups also had good tolerance to DHP and AL, there was no remarkable difference in the three groups.

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CONCLUSIONS: AP, DHP and AL all remained efficacious treatments for the treatment of falciparum malaria in Cambodia-Thailand border area. However, in this particular setting, the AP regimen turned out to be favourable in terms of efficacy and effectiveness, simplicity of administration, cost and compliance.



Treatment of severe or complicated malaria

(See also Emergency care, Development)

[PLoS One](#). 2011;6(11): e27273. Epub 2011 Nov 16.

[Timing of enteral feeding in cerebral malaria in resource-poor settings: a randomized trial.](#)

[Maude RJ](#), [Hoque G](#), [Hasan MU](#), [Sayeed A](#), [Akter S](#), [Samad R](#), [Alam B](#), [Yunus EB](#), [Rahman R](#), [Rahman W](#), [Chowdhury R](#), [Seal T](#), [Charunwatthana P](#), [Chang CC](#), [White NJ](#), [Faiz MA](#), [Day NP](#), [Dondorp AM](#), [Hossain A](#).

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BACKGROUND: Early start of enteral feeding is an established treatment strategy in intubated patients in intensive care since it reduces invasive bacterial infections and length of hospital stay. There is equipoise whether early enteral feeding is also beneficial in non-intubated patients with cerebral malaria in resource poor settings. We hypothesized that the risk of aspiration pneumonia might outweigh the potential benefits of earlier recovery and prevention of hypoglycaemia.

METHOD AND FINDINGS: **A randomized trial of early (day of admission) versus late (after 60 hours in adults or 36 hours in children) start of enteral feeding was undertaken in patients with cerebral malaria** in Chittagong, Bangladesh from May 2008 to August 2009. The primary outcome measures were incidence of aspiration pneumonia, hypoglycaemia and coma recovery time. **The trial was terminated after inclusion of 56 patients because of a high incidence of aspiration pneumonia in the early feeding group (9/27 (33%)), compared to the late feeding group (0/29 (0%)), $p = 0.001$.** One patient in the late feeding group, and none in the early group, had hypoglycaemia during admission. There was no significant difference in overall mortality (9/27 (33%) vs 6/29 (21%), $p = 0.370$), but mortality was 5/9 (56%) in patients with aspiration pneumonia.

CONCLUSIONS: In conclusion, early start of enteral feeding is detrimental in non-intubated patients with cerebral malaria in many resource-poor settings. Evidence gathered in resource rich settings is not necessarily transferable to resource-poor settings.



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[Trials](#). 2011 Jul 13;12: 176.

[Inhaled nitric oxide for the adjunctive therapy of severe malaria: protocol for a randomized controlled trial.](#)

[Hawkes M](#), [Opoka RO](#), [Namasopo S](#), [Miller C](#), [Thorpe KE](#), [Lavery JV](#), [Conroy AL](#), [Liles WC](#), [John CC](#), [Kain KC](#).

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BACKGROUND: Severe malaria remains a major cause of global morbidity and mortality. Despite the use of potent anti-parasitic agents, the mortality rate in severe malaria remains high. Adjunctive therapies that target the underlying pathophysiology of severe malaria may further reduce morbidity and mortality. Endothelial activation plays a central role in the pathogenesis of severe malaria, of which angiopoietin-2 (Ang-2) has recently been shown to function as a key regulator. Nitric oxide (NO) is a major inhibitor of Ang-2 release from endothelium and has been shown to decrease endothelial inflammation and reduce the adhesion of parasitized erythrocytes. Low-flow inhaled nitric oxide (iNO) gas is a US FDA-approved treatment for hypoxic respiratory failure in neonates.

METHODS/DESIGN: This prospective, parallel arm, randomized, placebo-controlled, blinded clinical trial compares adjunctive continuous inhaled nitric oxide at 80 ppm to placebo (both arms receiving standard anti-malarial therapy), among Ugandan children aged 1-10 years of age with severe malaria. The primary endpoint is the longitudinal change in Ang-2, an objective and quantitative biomarker of malaria severity, which will be analysed using a mixed-effects linear model. Secondary endpoints include mortality, recovery time, parasite clearance and neurocognitive sequelae.

DISCUSSION: Noteworthy aspects of this trial design include its efficient sample size supported by a computer simulation study to evaluate statistical power, meticulous attention to complex ethical issues in a cross-cultural setting, and innovative strategies for safety monitoring and blinding to treatment allocation in a resource-constrained setting in sub-Saharan Africa.



Treatment of vivax malaria

Malnutrition

(Papers 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](#). 2012 Jan;95(1): 212-9. Epub 2011 Dec 14.

[A novel fortified blended flour, corn-soy blend "plus-plus," is not inferior to lipid-based ready-to-use supplementary foods for the treatment of moderate acute malnutrition in Malawian children.](#)

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BACKGROUND: Children with moderate acute malnutrition (MAM) are often treated with fortified blended flours, most commonly a **corn-soy blend (CSB)**. However, recovery rates remain <75%, lower than the rate achieved with peanut paste-based ready-to-use supplementary foods (RUSFs). To bridge this gap, a novel CSB recipe fortified with oil and dry skim milk, "CSB++," has been developed.

OBJECTIVE: In this trial we compared CSB++ with 2 RUSF products for the treatment of MAM to test the hypothesis that the recovery rate achieved with CSB++ will not be >5% worse than that achieved with either RUSF.

DESIGN: We conducted a prospective, randomized, investigator-blinded, controlled noninferiority trial involving rural Malawian children aged 6-59 mo with MAM. **Children received 75 kcal CSB++ · kg(-1) · d(-1), locally produced soy RUSF, or an imported soy/whey RUSF for ≤12 wk.**

RESULTS: **The recovery rate for CSB++ (n = 763 of 888; 85.9%) was similar to that for soy RUSF (795 of 806, 87.7%; risk difference: -1.82%; 95% CI: -4.95%, 1.30%) and soy/whey RUSF (807 of 918, 87.9%; risk difference: -1.99%; 95% CI: -5.10%, 1.13%).** On average, children who received CSB++ required 2 d longer to recover, and the rate of weight gain was less than that with either RUSF, although height gain was the same among all 3 foods studied.

CONCLUSIONS: A novel, locally produced, fortified blended flour (CSB++) was not inferior to a locally produced soy RUSF and an imported soy/whey RUSF in facilitating recovery from MAM. The recovery rate observed for CSB++ was higher than that for any other fortified blended flour tested previously. This trial is registered at clinicaltrials.gov as NCT00998517.



[J Pediatr Gastroenterol Nutr.](#) 2011 Sep;53(3): 310-9.

[Effects of community-based follow-up care in managing severely underweight children.](#)

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OBJECTIVE: The aim of the present study was to assess the effects of community-based follow-up care, food supplementation, and/or psychosocial stimulation on the recovery of severely underweight children.

PATIENTS AND METHODS: A total of 507 severely underweight children (weight-for-age z score <-3) ages 6 to 24 months hospitalized at the International Center for Diarrheal Disease Research, Bangladesh, were randomly assigned to 1 of the following regimens for 3 months once they recovered from diarrhea: **fortnightly follow-up care at the International Center for Diarrheal Disease Research, Bangladesh Hospital, including growth monitoring, health education, and micronutrient supplementation** (group H-C, n = 102); **fortnightly follow-up at community clinics, using the same treatment regimen as group H-C** (group C-C, n = 99); **community-based follow-up as per group C-C plus cereal-based supplementary food (SF)** (group C-SF, n = 101); **follow-up as per group C-C plus psychosocial stimulation (PS)** (group C-PS, n = 102); **or follow-up as per group C-C plus both SF and PS** (group C-SF + PS, n = 103).

RESULTS: There were no significant differences in baseline characteristics by treatment group. Attendance at scheduled follow-up visits was greater in groups C-SF, C-SF + PS, and C-PS than in C-C and H-C; $P < 0.05$. **Rates of weight gain were greater in groups C-SF + PS, C-SF, and C-PS (0.88-1.01 kg) compared with groups C-C and H-C (0.63-0.76 kg), $P < 0.05$.** Three-factor analysis of covariance of the effects of treatment components indicated that weight gain and change in weight-for-age z score and weight-for-length z score were greater in groups that received SF ($P < 0.05$) and linear growth was greater among children managed in the community ($P = 0.002$).

CONCLUSIONS: **Positioning follow-up services in the community increases follow-up visits and promotes greater linear growth; providing SF, with or without PS, increases clinic attendance and enhances nutritional recovery.** Community-based service delivery, especially including SF, permits better rehabilitation of greater numbers of severely underweight children.

Maternal health

[Int J Gynaecol Obstet.](#) 2012 Feb;116(2): 138-42. Epub 2011 Nov 17.

[Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women.](#)

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OBJECTIVE: To compare sublingual misoprostol with intramuscular oxytocin for prevention of postpartum hemorrhage (PPH) in low-risk vaginal birth.

METHODS: In a prospective, randomized, double-blind trial, **530 women without risk of PPH were randomly allocated to receive either 400 µg of misoprostol sublingually or 10 units of oxytocin intramuscularly within 1 minute of delivery.** The outcome measures were

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incidence of PPH, postpartum blood loss, drop in hemoglobin level in 24 hours, need for additional uterotonic drug, incidence of adverse effects, and need for blood transfusion. Student t , χ^2 , Mann-Whitney U , and Fisher exact tests were used for comparison.

RESULTS: Incidence of postpartum hemorrhage (≥ 500 mL) and postpartum blood loss in the misoprostol group were similar to those in the oxytocin group (6% versus 5.7%, $P=0.85$; 153 mL versus 146 mL, $P=0.36$). Shivering and pyrexia were encountered more often in the misoprostol than in the oxytocin group (shivering: 19% versus 0.8%, $P<0.001$, relative risk [RR] 0.86, 95% confidence interval [CI] 0.82-0.90; pyrexia: 2.3% versus 0%, $P=0.03$, RR 0.97, 95% CI 0.95-0.99).

CONCLUSION: The efficacy of 400 μg of misoprostol administered sublingually was equivalent to that of 10 units of oxytocin given intramuscularly for prevention of PPH in low-risk vaginal delivery.

[Prev Sci.](#) 2011 Dec;12(4): 372-88.

[Philani Plus \(+\): a Mentor Mother community health worker home visiting program to improve maternal and infants' outcomes.](#)

[Rotheram-Borus MJ](#), [le Roux IM](#), [Tomlinson M](#), [Mbewu N](#), [Comulada WS](#), [le Roux K](#), [Stewart J](#), [O'Connor MJ](#), [Hartley M](#), [Desmond K](#), [Greco E](#), [Worthman CM](#), [Idemundia F](#), [Swendeman D](#).

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Pregnant mothers in South African townships face multiple health risks for themselves and their babies. Existing clinic-based services face barriers to access, utilization, and human resource capacities. Home visiting by community health workers (CHW) can mitigate such barriers. The Philani Plus (+) Intervention Program builds upon the original Philani CHW home-visiting intervention program for maternal and child nutrition by integrating content and activities to address HIV, alcohol, and mental health. Pregnant Mothers at Risk (MAR) for HIV, alcohol, and/or nutrition problems in 24 neighborhoods in townships in Cape Town, South Africa ($n = 1,239$) were randomly assigned by neighborhood to an intervention (Philani Plus (+), $N = 12$ neighborhoods; $n = 645$ MAR) or a standard-care control condition of neighborhood clinic-based services ($N = 12$ neighborhoods; $n = 594$ MAR). Positive peer deviant "Mentor Mother" CHWs are recruited from the township neighborhoods and trained to deliver four antenatal and four postnatal home visits that address HIV, alcohol, nutrition, depression, health care regimens for the family, caretaking and bonding, and securing government-provided child grants. The MAR and their babies are being monitored during pregnancy, 1 week post-birth, and 6 and 18 months later. Among the 1,239 MAR recruited: 26% were HIV-positive; 27% used alcohol during pregnancy; 17% previously had low-birthweight babies; 23% had at least one chronic condition (10% hypertension, 5% asthma, 2% diabetes); 93% had recent sexual partners with 10% known to be HIV+; and 17% had clinically significant prenatal depression and 42% had borderline depression. This paper presents the intervention protocol and baseline sample characteristics for the "Philani Plus (+)" CHW home-visiting intervention trial.

Maternal nutrition and micronutrient supplementation

(See also HIV - Prevention of parent to child transmission, Cardiovascular disease)

[J Nutr.](#) 2012 Mar;142(3): 548-54. Epub 2012 Feb 1.

[Prenatal micronutrient supplements cumulatively increase fetal growth.](#)

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Prenatal multiple micronutrients (UNIMMAP) improve fetal growth only moderately compared to iron and folic acid alone (IFA). Whether this is due to insufficient amounts of UNIMMAP or to IFA being in reality an active control is unknown. We assessed the association between cumulative micronutrient intake (CMI) and fetal growth by secondary analysis of a randomized controlled trial in Burkina Faso where tablet intake was directly observed. We applied 2-part residual regression models adjusted for main confounders. Among the 1056 single pregnancies included, the mean CMI (\pm SD) was 124 ± 54 tablets. The odds of delivering a small-for-gestational-age baby was reduced by 21% [(95%CI: 5, 35); $P = 0.013$] for each additional tertile of CMI. The association between CMI and birth weight was positively modified by gestational age at enrollment (P -interaction = 0.001). Each unit of CMI was associated with a 1.6-g [(95%CI: 0.3, 3.1); $P = 0.019$] higher birth weight at a mean-centered gestational age at enrollment, with a higher gradient observed later in pregnancy. Maternal BMI at enrollment was also a positive modifying factor (P -interaction = 0.02), with no association of CMI with birth weight for low BMI. There was no evidence of an effect modification by group allocation; i.e., we observed the same change in birth weight per unit of CMI with either IFA or UNIMMAP. Yet UNIMMAP increased birth weight by 69 g [(95%CI: 58, 81); $P < 0.001$] relative to IFA. We found similar results for thoracic and cephalic circumferences. In conclusion, for both IFA and UNIMMAP, the effect on fetal growth is cumulative. The supplementation should therefore begin as early as possible in pregnancy, even if the growth increment per CMI is higher in late than in early pregnancy. Women with a low BMI should also receive extra energy.

[J Nutr.](#) 2011 Oct;141(10): 1912-7. Epub 2011 Aug 24.

[Low maternal vitamin B-12 status is associated with offspring insulin resistance regardless of antenatal micronutrient supplementation in rural Nepal.](#)

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Questions have been raised about potentially negative effects of antenatal folic acid use in populations with a high prevalence of vitamin B-12 deficiency. Our objective was to examine the association between maternal folate and vitamin B-12 status in pregnancy on offspring

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insulin resistance and examine whether the effects of maternal micronutrient supplementation varied by baseline maternal folate and/or vitamin B-12 status. **Pregnant women were cluster randomized to receive daily supplements containing vitamin A alone or with folic acid, folic acid+iron, folic acid+iron+zinc, or a multiple micronutrient.** In a subsample (n = 1132), micronutrient status biomarkers were analyzed at baseline and late pregnancy. Children born to the women who participated in the trial were visited at 6-8 y of age. Fasting plasma glucose and insulin were used to estimate insulin resistance using the homeostasis model assessment (HOMA-IR). Children whose mothers were deficient in vitamin B-12 (<148 pmol/L, 27%) during early pregnancy had a 26.7% increase in HOMA-IR (P = 0.02), but there was no association with maternal folate status. Among children born to women who were vitamin B-12 deficient at baseline, the percent difference in HOMA-IR compared to the control group was 15.1% (95% CI: -35.9, 106.4), 4.9% (-41.6, 88.5), 3.3% (-38.4, 73.5), and 18.1% (-29.0, 96.7) in the folic acid, folic acid-iron, folic acid-iron-zinc, and multiple micronutrient supplementation groups, respectively, none of which were significant. Maternal vitamin B-12 deficiency is associated with an elevated risk of insulin resistance, but supplementation with folic acid or other micronutrients led to no significant change in insulin resistance in school-aged offspring.



*** [JAMA](#). 2012 May 16;307(19): 2050-9.

[Effects of prenatal micronutrient and early food supplementation on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat randomized trial.](#)

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CONTEXT: Nutritional insult in fetal life and small size at birth are common in low-income countries and are associated with serious health consequences.

OBJECTIVES: To test the hypothesis that prenatal multiple micronutrient supplementation (MMS) and an early invitation to food supplementation would increase maternal hemoglobin level and birth weight and decrease infant mortality, and to assess whether a combination of these interventions would further enhance these outcomes.

DESIGN, SETTING, AND PARTICIPANTS: A randomized trial with a factorial design in Matlab, Bangladesh, of 4436 pregnant women, recruited between November 11, 2001, and October 30, 2003, with follow-up until June 23, 2009.

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INTERVENTIONS: Participants were randomized into 6 groups; a double-masked supplementation with capsules of 30 mg of iron and 400 µg of folic acid, 60 mg of iron and 400 µg of folic acid, or MMS containing a daily allowance of 15 micronutrients, including 30 mg of iron and 400 µg of folic acid, was combined with food supplementation (608 kcal 6 days per week) randomized to either early invitation (9 weeks' gestation) or usual invitation (20 weeks' gestation).

MAIN OUTCOME MEASURES: Maternal hemoglobin level at 30 weeks' gestation, birth weight, and infant mortality. Under 5-year mortality was also assessed.

RESULTS: Adjusted maternal hemoglobin level at 30 weeks' gestation was 115.0 g/L (95% CI, 114.4-115.5 g/L), with no significant differences among micronutrient groups. Mean maternal hemoglobin level was lower in the early vs usual invitation groups (114.5 vs 115.4 g/L; difference, -0.9 g/L; 95% CI, -1.7 to -0.1; P = .04). There were 3625 live births out of 4436 pregnancies. Mean birth weight among 3267 singletons was 2694 g (95% CI, 2680-2708 g), with no significant differences among groups. **The early invitation with MMS group had an infant mortality rate of 16.8 per 1000 live births vs 44.1 per 1000 live births for usual invitation with 60 mg of iron and 400 µg of folic acid (hazard ratio [HR], 0.38; 95% CI, 0.18-0.78). Early invitation with MMS group had an under 5-year mortality rate of 18 per 1000 live births (54 per 1000 live births for usual invitation with 60 mg of iron and 400 µg of folic acid; HR, 0.34; 95% CI, 0.18-0.65).** Usual invitation with MMS group had the highest incidence of spontaneous abortions and the highest infant mortality rate.

CONCLUSION: Among pregnant women in poor communities in Bangladesh, treatment with multiple micronutrients, including iron and folic acid combined with early food supplementation, vs a standard program that included treatment with iron and folic acid and usual food supplementation, resulted in decreased childhood mortality.



[Nutr J.](#) 2011 Dec 8;10: 134.

[Effects of prenatal food and micronutrient supplementation on child growth from birth to 54 months of age: a randomized trial in Bangladesh.](#)

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BACKGROUND: There is a lack of information on the optimal timing of food supplementation to malnourished pregnant women and possible combined effects of food and multiple micronutrient supplementations (MMS) on their offspring's growth. We evaluated the effects of prenatal food and micronutrient interventions on postnatal child growth. The hypothesis was that prenatal MMS and early invitation to food supplementation would increase physical growth in

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the offspring during 0-54 months and a combination of these interventions would further improve these outcomes.

METHODS: In the large, randomized MINIMat trial (Maternal and Infant Nutrition Interventions in Matlab), Bangladesh, 4436 pregnant women were enrolled between November 2001 and October 2003 and their children were followed until March 2009. Participants were randomized into six groups comprising 30 mg Fe and 400 µg folic acid (Fe30F), 60 mg Fe and 400 µg folic acid (Fe60F) or MMS combined with either an early (immediately after identification of pregnancy) or a later usual (at the time of their choosing, i.e., usual care in this community) program invitation to food supplementation. The anthropometry of 3267 children was followed from birth to 54 months, and 2735 children were available for analysis at 54 months.

RESULTS: There were no differences in characteristics of mothers and households among the different intervention groups. The average birth weight was 2694 g and birth length was 47.7 cm, with no difference among intervention groups. **Early invitation to food supplementation (in comparison with usual invitation) reduced the proportion of stunting from early infancy up to 54 months for boys ($p = 0.01$), but not for girls ($p = 0.31$). MMS resulted in more stunting than standard Fe60F ($p = 0.02$).** There was no interaction between the food and micronutrient supplementation on the growth outcome.

CONCLUSIONS: **Early food supplementation in pregnancy reduced the occurrence of stunting during 0-54 months in boys, but not in girls, and prenatal MMS increased the proportion of stunting in boys.** These effects on postnatal growth suggest programming effects in early fetal life.



[Am J Clin Nutr.](#) 2012 Apr;95(4): 916-24. Epub 2012 Feb 29.

[Impact of prenatal multiple micronutrients on survival and growth during infancy: a randomized controlled trial.](#)

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BACKGROUND: Although prenatal multiple micronutrients can improve fetal growth, their benefit on postnatal health remains uncertain.

OBJECTIVE: **We assessed the effect of the UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women (UNIMMAP)**

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compared with the usual iron and folic acid supplement (IFA) on survival, growth, and morbidity during infancy.

DESIGN: In a double-blind, randomized trial, we followed **1294 singleton newborns whose mothers had prenatally received either the UNIMMAP or IFA**. We assessed monthly anthropometric measures and health variables up to age 12 mo. Children were assessed again at a mean age of 30 mo. Mixed-effects models accounted for repeated measurements.

RESULTS: **The UNIMMAP resulted in a 27% (HR: 0.73; 95% CI: 0.60, 0.87; P = 0.002) reduction in the rate of stunting in 15,261 infant-months with a higher length-for-age z score of 0.13 (95% CI: 0.02, 0.24; P = 0.02) over the whole observation period.** However, by age 30 mo, this difference was not observed. An effect of the UNIMMAP on weight-for-length (P-interaction = 0.004) and head circumference-for-age (P-interaction = 0.03) became apparent by the end of the first year of life. **By the age of 30 mo, children from the UNIMMAP group had a higher weight-for-height z score of 0.20 (95% CI: 0.06, 0.34; P = 0.004).** No difference in mortality or morbidity was identified in groups, except a 14% reduction in reported episodes of fever (95% CI: 1%, 28%; P = 0.04).

CONCLUSIONS: Improved linear fetal growth with continuation into early life and enhanced postnatal growth were 2 mechanisms that mediated the effect of the prenatal UNIMMAP on infant nutritional status. Additional follow-up to assess long-term effects is warranted.

Comment

A meta-analysis of previous trials of maternal micronutrient supplementation was published in June 2011 in Bulletin WHO: 2011. 89; 6: 402-411B

(<http://www.who.int/bulletin/volumes/89/6/10-083758/en/index.html>). This review concluded that maternal micronutrient supplementation can reduce the risk of low birth weight. However it found there was no overall effect on perinatal mortality in developing countries. Indeed some trials conducted in poor rural settings found detrimental effects on perinatal mortality, although these were not statistically significant in the overall meta-analysis. The reasons for any detrimental effects of multiple micronutrient supplementations on perinatal mortality are unknown, but several causes are speculated upon in the review. The MINIMat trial from Bangladesh did not only test micronutrient supplementation, but also macronutrient supplementation early in pregnancy. This found improved survival in infancy and childhood.

[Matern Child Health J.](#) 2012 Mar 7. [Epub ahead of print]

[Patterns of Body Composition Among HIV-Infected, Pregnant Malawians and the Effects of Famine Season.](#)

[Ramlal RT, Tembo M, Soko A, Chigwenembe M, Tohill BC, Kayira D, King CC, Chasela C, Jamieson D, van der Horst C, Bentley ME, Adair LS; the BAN Study Team.](#)

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We describe change in weight, midupper arm circumference (MUAC), arm muscle area (AMA) and arm fat area (AFA) in 1130 pregnant HIV-infected women with CD4 counts > 200 as part

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of the BAN Study (www.thebanstudy.org), a randomized, controlled clinical trial to evaluate antiretroviral and nutrition interventions to reduce mother-to-child transmission of HIV during breast feeding. In a longitudinal analysis, we found a linear increase in weight with a mean rate of weight gain of 0.27 kgs/week, from baseline (12 to 30 weeks gestation) until the last follow-up visit (32-38 weeks). Analysis of weight gain showed that 17.1% of the intervals between visits resulted in a weight loss. In unadjusted models, MUAC and AMA increased and AFA declined during late pregnancy. Based on multivariable regression analysis, exposure to the famine season resulted in larger losses in AMA [-0.08, 95% CI -0.14, -0.02; p = 0.01] while AFA losses occurred irrespective of season [-0.55, 95%: -0.95, -0.14, p = 0.01]. CD4 was associated with AFA [0.21, 95% CI 0.01, 0.41, p = .04]. Age was positively associated with MUAC and AMA. Wealth was positively associated with MUAC, AFA, and weight. While patterns of anthropometric measures among HIV-infected, pregnant women were found to be similar to those reported for uninfected women in sub-Saharan Africa, effects of the famine season among undernourished, Malawian women are of concern. Strategies to optimize nutrition during pregnancy for these women appear warranted.

Womens groups

[Trials](#). 2011 Jul 25;12: 182. doi: 10.1186/1745-6215-12-182.

[Community mobilisation with women's groups facilitated by Accredited Social Health Activists \(ASHAs\) to improve maternal and newborn health in underserved areas of Jharkhand and Orissa: study protocol for a cluster-randomised controlled trial.](#)

[Tripathy P, Nair N, Mahapatra R, Rath S, Gope RK, Rath S, Bajpai A, Singh V, Nath V, Ali S, Kundu AK, Choudhury D, Ghosh S, Sarbani S, Sinha R, Pagel C, Costello A, Houweling TA, Prost A.](#)

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BACKGROUND: Around a quarter of the world's neonatal and maternal deaths occur in India. Morbidity and mortality are highest in rural areas and among the poorest wealth quintiles. Few interventions to improve maternal and newborn health outcomes with government-mandated community health workers have been rigorously evaluated at scale in this setting. The study aims to assess the impact of a community mobilisation intervention with women's groups facilitated by ASHAs to improve maternal and newborn health outcomes among rural tribal communities of Jharkhand and Orissa.

METHODS/DESIGN: The study is a cluster-randomised controlled trial and will be implemented in five districts, three in Jharkhand and two in Orissa. The unit of randomisation is a rural cluster of approximately 5000 population. We identified villages within rural, tribal areas of five districts, approached them for participation in the study and enrolled them into 30 clusters, with approximately 10 ASHAs per cluster. Within each district, 6 clusters were randomly allocated to receive the community intervention or to the control group, resulting in 15 intervention and 15 control clusters. Randomisation was carried out in the presence of local stakeholders who selected the cluster numbers and allocated them to intervention or control

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using a pre-generated random number sequence. The intervention is a participatory learning and action cycle where ASHAs support community women's groups through a four-phase process in which they identify and prioritise local maternal and newborn health problems, implement strategies to address these and evaluate the result. The cycle is designed to fit with the ASHAs' mandate to mobilise communities for health and to complement their other tasks, including increasing institutional delivery rates and providing home visits to mothers and newborns. The trial's primary endpoint is neonatal mortality during 24 months of intervention. Additional endpoints include home care practices and health care-seeking in the antenatal, delivery and postnatal period. The impact of the intervention will be measured through a prospective surveillance system implemented by the project team, through which mothers will be interviewed around six weeks after delivery. Cost data and qualitative data are collected for cost-effectiveness and process evaluations.

STUDY REGISTRATION: ISRCTN: ISRCTN31567106.



[Trials](#). 2011 Sep 26;12: 208.

[The effect of participatory women's groups on birth outcomes in Bangladesh: does coverage matter? Study protocol for a randomized controlled trial.](#)

[Houweling TA](#), [Azad K](#), [Younes L](#), [Kuddus A](#), [Shaha S](#), [Haq B](#), [Nahar T](#), [Beard J](#), [Fottrell EF](#), [Prost A](#), [Costello A](#); [PCP study team](#).

[Collaborators \(18\)](#)

[Azad K](#), [Dhaki AS](#), [Haq B](#), [Hossen M](#), [Kuddus A](#), [Mandiz P](#), [Nahar T](#), [Pal C](#), [Shah SK](#), [Chowdhury RA](#), [Azam G](#), [Chakraborty BM](#), [Beard J](#), [Costello A](#), [Fottrell E](#), [Houweling TA](#), [Prost A](#), [Younes L](#).

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BACKGROUND: Progress on neonatal survival has been slow in most countries. While there is evidence on what works to reduce newborn mortality, there is limited knowledge on how to deliver interventions effectively when health systems are weak. Cluster randomized trials have shown strong reductions in neonatal mortality using community mobilisation with women's groups in rural Nepal and India. A similar trial in Bangladesh showed no impact. A main hypothesis is that this negative finding is due to the much lower coverage of women's groups in the intervention population in Bangladesh compared to India and Nepal. For evidence-based policy making it is important to examine if women's group coverage is a main determinant of their impact. The study aims to test the effect on newborn and maternal health outcomes of a participatory women's group intervention with a high population coverage of women's groups.

METHODS: A cluster randomised trial of a participatory women's group intervention will be conducted in 3 districts of rural Bangladesh. As we aim to study a women's group intervention with high population coverage, the same 9 intervention and 9 control unions will be used as in the 2005-2007 trial. These had been randomly allocated using the districts as strata. To increase coverage, 648 new groups were formed in addition to the 162 existing groups that were part of

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the previous trial. An open cohort of women who are permanent residents in the union in which their delivery or death was identified, is enrolled. Women and their newborns are included after birth, or, if a woman dies during pregnancy, after her death. Excluded are women who are temporary residents in the union in which their birth or death was identified. The primary outcome is neonatal mortality in the last 24 months of the study. A low cost surveillance system will be used to record all birth outcomes and deaths to women of reproductive age in the study population. Data on home care practices and health care use are collected through interviews.

TRIAL REGISTRATION: ISRCTN: ISRCTN01805825.



Meningitis

[Lancet Infect Dis.](#) 2011 Aug;11(8): 613-21. Epub 2011 May 5.

[Slow initial \$\beta\$ -lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial.](#)

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BACKGROUND: New antimicrobials or adjunctive treatments have not substantially reduced mortality from acute childhood bacterial meningitis. Paracetamol seems to have beneficial effects in bacteraemic adults and some experts recommend initial slow β -lactam infusion. We investigated whether these treatments had benefits in children with bacterial meningitis.

METHODS: We did a prospective, double-blind, single-centre study with a two-by-two factorial design in Luanda, Angola. **723 participants aged 2 months to 13 years were randomly assigned two 12 h intravenous infusions, without loading doses, of 125 mg/kg bodyweight cefotaxime (total dose 250 mg/kg) given over 24 h, or 250 mg/kg bodyweight cefotaxime given as four boluses, one every 6 h over 24 h.** Patients also received oral paracetamol at an initial dose of 30 mg/kg then 20 mg/kg every 6 h for 48 h or placebo. Two primary endpoints, death or severe neurological sequelae and deafness, were analysed by intention to treat. The study was registered as ISRCTN62824827.

FINDINGS: 183 patients were assigned cefotaxime infusion plus paracetamol and 180 patients to each of the other three treatment groups. Causative agents were identified in 63% of cases and were mostly Haemophilus influenzae type b, Streptococcus pneumoniae, or Neisseria meningitidis. Death or severe neurological sequelae were seen in 340 (47%) of 723 children and deafness in 45 (12%) of 374 tested, both distributed similarly across treatment groups. **In a predefined subgroup analysis of death or any sequelae, by causative agent, a benefit was seen in favour of infusion over bolus in children with pneumococcal meningitis (infusion plus placebo, odds ratio 0.18, 95% CI 0.03-0.90, p=0.04).** A similar effect was seen for children receiving cefotaxime infusion plus paracetamol, but the difference was not significant (OR 0.22, 95% CI 0.04-1.09, p=0.06). A post-hoc analysis suggested that cefotaxime infusion plus paracetamol lowered mortality at least during the first 3 days, irrespective of cause.

INTERPRETATION: Although no tested regimen improved the final outcomes of these very ill children, studies of longer courses of β -lactam infusion plus paracetamol seem warranted.



Neonatal care

*** [Lancet](#). 2012 Mar 17;379(9820): 1029-36. Epub 2012 Feb 8.

[Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomised trial.](#)

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BACKGROUND: Umbilical cord infection (omphalitis) is a risk factor for neonatal sepsis and mortality in low-resource settings where home deliveries are common. We aimed to assess the effect of umbilical-cord cleansing with 4% chlorhexidine (CHX) solution, with or without handwashing with antiseptic soap, on the incidence of omphalitis and neonatal mortality.

METHODS: We did a two-by-two factorial, cluster-randomised trial in Dadu, a rural area of Sindh province, Pakistan. Clusters were defined as the population covered by a functional traditional birth attendant (TBA), and were randomly allocated to one of four groups (groups A to D) with a computer-generated random number sequence. Implementation and data collection teams were masked to allocation. Liveborn infants delivered by participating TBAs who received birth kits were eligible for enrolment in the study. **One intervention comprised birth kits containing 4% CHX solution for application to the cord at birth by TBAs and once daily by family members for up to 14 days along with soap and educational messages promoting handwashing. One intervention was CHX solution only and another was handwashing only.** Standard dry cord care was promoted in the control group. The primary outcomes were incidence of neonatal omphalitis and neonatal mortality. The trial is registered with ClinicalTrials.gov, number NCT00682006.

FINDINGS:

187 clusters were randomly allocated to one of the four study groups. **Of 9741 newborn babies delivered by participating TBAs, factorial analysis indicated a reduction in risk of omphalitis with CHX application (risk ratio [RR]=0.58, 95% CI 0.41-0.82; p=0.002) but no evidence of an effect of handwashing (RR=0.83, 0.61-1.13; p=0.24).** We recorded strong evidence of a **reduction in neonatal mortality in neonates who received CHX cleansing (RR=0.62, 95 % CI 0.45-0.85; p=0.003)** but no evidence of an effect of handwashing promotion on neonatal mortality (RR=1.08, 0.79-1.48; p=0.62). We recorded no serious adverse events.

INTERPRETATION: **Application of 4% CHX to the umbilical cord was effective in reducing the risk of omphalitis and neonatal mortality in rural Pakistan. Provision of CHX in birth kits might be a useful strategy for the prevention of neonatal mortality in high-mortality settings.**



Comment

This is an important trial, clarifying what optimal umbilical cord care is in a rural setting. WHO has not yet adopted this as part of immediate newborn care, as there has been concern about detracting from other interventions. Other aspects of newborn care include immediate and thorough drying, which stimulates breathing and prevents hypothermia. Sustained skin-to-skin contact prevents hypothermia, reduces infection, and facilitates successful intake of colostrum and sustained breastfeeding. Delaying cord clamping until cord pulsations stop - typically around one to three minutes from birth - reduces the risk of anaemia and in preterm infants and other complications. Ensuring that the cord is cut with a sterile blade and clamped with a sterile clamp is also essential. These interventions, plus exclusive breastfeeding and avoidance of harmful practices (such as separation of babies from their mothers in the first hours of life for bathing or unnecessary observation) can prevent a large proportion of neonatal sepsis deaths.

[Acta Med Iran. 2012;50\(1\): 21-5.](#)

[The effect of clofibrate on hyperbilirubinemia of term neonates.](#)

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Clofibrate is a glucuronosyl transferase inducer that has been proposed to increase the elimination of bilirubin in neonates with hyperbilirubinemia. This study was conducted to determine the therapeutic effect of clofibrate in term neonates with non-hemolytic jaundice. This study was conducted on 52 newborns with pathologic unconjugated jaundice in Qazvin children hospital. Newborns divided randomly in two groups. **Case group treated with clofibrate and intensive phototherapy, while control group treated only with intensive phototherapy.** Serum bilirubin level was measured before and 6, 12, 24 and 48 hours after treatment. Results were compared and analyzed. The mean serum level of bilirubin before treatment in the case and control groups were 20.78 ± 2.38 and 20.52 ± 2.44 mg/dl, respectively ($P=0.69$). The mean serum level of bilirubin in 6, 12, 24 and 48 hours after treatment in the case group were 18.20 ± 2.20 , 14.70 ± 2.06 , 10.72 ± 2.40 and 8.90 ± 0.83 mg/dl, respectively. These values in control group were 18.26 ± 2.42 , 15.36 ± 2.59 , 12.29 ± 2.28 and 10.23 ± 1.50 mg/dl, respectively. **There was significant difference between two groups regarding mean serum level of bilirubin 24 hours ($P=0.019$) and 48 hours after treatment ($P=0.005$). In conclusion, clofibrate was effective in reducing neonatal jaundice and its effect appeared 24 hours after treatment.**

Nutrition

(See epilepsy)

Nutrition, micronutrients and breast feeding

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(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Micronutrients and food fortification

(See also School health, Zinc)

[Br J Nutr.](#) 2012 Feb;107(4): 556-66. Epub 2011 Jul 5.

[Rich micronutrient fortification of locally produced infant food does not improve mental and motor development of Zambian infants: a randomised controlled trial.](#)

[Manno D](#), [Kowa PK](#), [Bwalya HK](#), [Siame J](#), [Grantham-McGregor S](#), [Baisley K](#), [De Stavola BL](#), [Jaffar S](#), [Filteau S](#).

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It is uncertain whether multiple micronutrients benefit the mental and psychomotor development of young children in developing countries. **We conducted a randomised double-blind controlled trial to evaluate the effect of a richly micronutrient-fortified v. a basal fortified porridge on mental and psychomotor development in Zambian infants. Infants (n 743) were randomised at age 6 months to receive either the richly fortified or the basal fortified infant food and were followed up until 18 months of age.** All the infants were evaluated monthly for achievement of a series of developmental milestones. The Bayley scales of infant development II were administered to a subsample of 502 infants at 6, 12 and 18 months. Rich micronutrient fortification had no significant benefit on the following: (a) number of developmental milestones achieved (rate ratio at 12 months = 1.00; 95 % CI 0.96, 1.05; P = 0.81, adjusted for sex, socio-economic status and maternal education, with similar results at 15 and 18 months); (b) ages of walking unsupported (hazard ratio (HR) 1.04; 95 % CI 0.88, 1.24; P = 0.63, adjusted for the above covariates) and of speaking three or four clear words (HR 1.01; 95 % CI 0.84, 1.20; P = 0.94, adjusted for the above covariates); (c) mental development index (MDI) and psychomotor development index (PDI) of the Bayley scales (scores difference adjusted for baseline scores, age at the assessment, sex, socio-economic status, maternal education, language, age and HIV status: MDI 0.3 (95 % CI - 0.5, 1.1), P = 0.43; PDI - 0.1 (95 % CI - 0.9, 0.7), P = 0.78). **In conclusion, the results do not support the hypothesis that rich micronutrient fortification improves Zambian infants' mental and motor development.**



[Nutr J.](#) 2011 Nov 24;10: 129.

[Effect of daily versus weekly home fortification with multiple micronutrient powder on haemoglobin concentration of young children in a rural area, Lao People's Democratic Republic: a randomised trial.](#)

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BACKGROUND: Multiple micronutrient deficiencies, in particular iron deficiency anaemia (IDA) is a severe public health problem in Lao People's Democratic Republic (Lao PDR). Because of the practical difficulties encountered in improving the nutritional adequacy of traditional complementary foods and the limitations associated with the use of liquid iron supplementation for the treatment and prevention of IDA in infants and young children, recently, home-fortification with multivitamins and minerals sprinkles was recommended. This study aims to compare the effect of twice weekly versus daily supplementation with multivitamins and minerals powder (MMP) on anaemia prevalence, haemoglobin concentration, and growth in infants and young children in a rural community in Lao PDR.

METHODS: A randomized trial was conducted in six rural communities. Children aged 6 to 52 months ($n = 336$) were randomly assigned to a control group ($n = 110$) or to one of two intervention groups receiving either two sachets per week ($n = 115$) or a daily sachet ($n = 111$) of MMP for 24 weeks; 331 children completed the study. A finger prick of blood was taken at baseline, at week 12, and again at week 24 to determine haemoglobin concentration. Anthropometric measurements were taken every 4 weeks. The McNemar test was used to assess within group differences at three time points in the study subjects with anaemia and one-way ANOVA was used to assess changes in mean haemoglobin concentration in the treatment groups.

RESULTS: **MMP supplementation resulted in significant improvements in haemoglobin concentration and in the reduction of anaemia prevalence in the two treatment groups compared with the control group ($p < 0.001$).** The severely to moderately anaemic children ($Hb < 100$ g/L) on daily supplementation recovered faster than those on twice weekly supplementation. MMP was well accepted and compliance was high in both treatment groups. Overall, the improvement in the weight for age Z-score was very small and not statistically significant across the three study groups.

CONCLUSIONS: MMP supplementation had positive effects in reduction of anaemia prevalence and in improving haemoglobin concentration. For severely to moderately anaemic children, daily MMP supplementation was more effective in improving haemoglobin concentration and reducing anaemia prevalence. A longer intervention period is probably needed to have a positive effect on growth.



Comment

*The micronutrient supplementation was: vitamin A (400 μ g), vitamin D3 (5 μ g), vitamin E (5 mg), vitamin B1, B2, B6 each (0.5 mg), folic acid (150 μ g), niacin (6 mg), vitamin B12 (0.9 μ g), vitamin C (30 mg), **iron (10 mg)**, zinc (4.1 mg), selenium (17 μ g), copper (0.56 mg), and iodine (90 μ g). Even in the daily supplemented group, 32% remained anaemic at the end of the study period.*

[Br J Nutr.](#) 2012 Mar;107(6): 893-902. Epub 2011 Sep 8.

[The effects of micronutrient-fortified complementary/replacement food on intestinal permeability and systemic markers of inflammation among maternally HIV-exposed and unexposed Zambian infants.](#)

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The present randomised trial investigated the **effects of feeding Zambian infants from 6 to 18 months old either a richly or basal micronutrient-fortified complementary/replacement food on gut integrity and systemic inflammation**. Blood samples were obtained from all infants (n 743) at 6 and 18 months for the assessment of serum C-reactive protein (CRP) and α 1-acid glycoprotein (AGP). A subsample of 502 infants, selected from the main cohort to include a larger proportion of infants with HIV-positive mothers, was assigned to lactulose/mannitol gut permeability tests. Lactulose:mannitol (L:M) ratio analyses were adjusted for baseline urinary L:M ratio, socio-economic status, mother's education, season of birth and baseline stunting, and stratified by maternal antenatal HIV status, child's sex, concurrent breast-feeding status and anaemia at baseline. There was no significant difference in geometric mean L:M ratio between the richly fortified and basal-fortified porridge arms at 12 months (0.47 (95 % CI 0.41, 0.55) v. 0.41 (95 % CI 0.34, 0.49); $P = 0.16$ adjusted). At 18 months, the richly fortified porridge group had a significantly higher geometric mean L:M ratio than the basal-fortified group (0.23 (95 % CI 0.19, 0.28) v. 0.15 (95 % CI 0.12, 0.19); $P = 0.02$ adjusted). This effect was evident for all stratifications, significantly among boys ($P = 0.04$), among the infants of HIV-negative mothers ($P = 0.01$), among the infants of HIV-negative mothers not concurrently breast-fed ($P = 0.01$) and among those who were not anaemic at baseline ($P = 0.03$). CRP, but not AGP, was positively associated with L:M ratio, but there were no significant effects of the diet on either CRP or AGP. In conclusion, a richly fortified complementary/replacement food did not benefit and may have worsened intestinal permeability.



[J Health Popul Nutr](#). 2011 Dec;29(6): 593-604.

[Inconsistent effects of iron-folic acid and/or zinc supplementation on the cognitive development of infants.](#)

[Siegel EH](#), [Kordas K](#), [Stoltzfus RJ](#), [Katz J](#), [Khatry SK](#), [LeClerq SC](#), [Tielsch JM](#).

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Despite concerns over the neurocognitive effects of micronutrient deficiencies in infancy, few studies have examined the effects of micronutrient supplementation on specific cognitive indicators. This study investigated, in 2002, the effects of iron-folic acid and/or zinc supplementation on the results of Fagan Test of Infant Intelligence (FTII) and the A-not-B Task of executive functioning among 367 Nepali infants living in Sarlahi district. **Infants were enrolled in a cluster-randomized, placebo-controlled clinical trial of daily supplementation with 5 mg of zinc, 6.25 mg of iron with 25 microg of folic acid, or zinc-iron-folic acid, or placebo.** These were tested on both the tasks using five indicators of information processing: preference for novelty (FTII), fixation duration (FTII), accelerated performance ($>$ or $=$ 85% correct; A-not-B), deteriorated performance ($<$ 75% correct and $>$ 1 error on repeat-following-correct trails; A-not-B), and the A-not-B error (A-not-B). At 39 and 52 weeks, 247 and 333 infants respectively attempted the cognitive tests; 213 made an attempt to solve both the tests.

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The likelihood of females completing the A-not-B Task was lower compared to males when cluster randomization was controlled [odds ratio = 0.67; 95% confidence interval 0.46-0.97; $p < 0.05$]. All of the five cognitive outcomes were modelled in linear and logistic regression. The results were not consistent across either the testing sessions or the information-processing indicators. Neither the combined nor the individual micronutrient supplements improved the performance on the FTII or the A-not-B Task ($p > 0.05$). These findings suggest that broader interventions (both in terms of scope and duration) are needed for infants who face many biological and social stressors.



[Asia Pac J Clin Nutr.](#) 2012;21(1): 3-11.

[Effects of vitamin A, vitamin A plus zinc, and multiple micronutrients on anemia in preschool children in Chongqing, China.](#)

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This study is to clarify the impact of vitamin A or vitamin A combined with other micronutrients supplementation on anemia and growth in preschoolers. In the present study, a total of **290 preschoolers, aged 36-72 months old were randomly assigned to 3 treatment groups: vitamin A (A group), vitamin A plus zinc (AZ group), and vitamin A combined with additional multiple-micronutrient (AMM group)**. After 6-month supplementation, the height and height-for-age z-score gains of the AZ group were significantly higher than the other groups; the weight gain of the AMM group was greater than the other groups. Compared with baseline values, the concentrations of hemoglobin, and zinc at the end significantly increased in all 3 groups. The incremental concentrations of hemoglobin in the AMM group were significant higher than in the other two groups. Furthermore, the incremental concentrations of serum retinol in the AMM group, and the increase in serum zinc concentrations in the AZ group were significantly higher, respectively, than in the other groups. These 3 kinds of supplements in the present study are effective in enhancing height gains and are effective in reducing the prevalence of anemia. **Supplementation of zinc plus vitamin A is a better way for improving children's height and height-for-age z-score. Vitamin A combined with multiple-micronutrient is more effective in improving the hemoglobin concentrations in preschool children.**

[J Nutr.](#) 2012 May;142(5): 846-52. Epub 2012 Mar 21.

[Multiple micronutrient-fortified rice affects physical performance and plasma vitamin B-12 and homocysteine concentrations of Indian school children.](#)

[Thankachan P, Rah JH, Thomas T, Selvam S, Amalrajan V, Srinivasan K, Steiger G, Kurpad AV.](#)

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Fortifying rice with multiple micronutrients could be a promising strategy for combat micronutrient deficiencies in developing countries. We determined the efficacy of extruded rice grains fortified with multiple micronutrients on the prevalence of anemia, micronutrient status, and physical and cognitive performance in 6- to 12-y-old, low-income school children in Bangalore, India. In a randomized, double-blind, controlled trial, 258 children were assigned to 1 of 3 intervention groups to receive rice-based lunch meals fortified with multiple micronutrients with either low-iron (6.25 mg) or high-iron (12.5 mg) concentrations or identical meals with unfortified rice. The meals were provided 6 d/wk for 6 mo. Anthropometric, biochemical, physical performance, and cognitive assessments were taken at baseline and endpoint. At baseline, study groups were comparable, with 61% of the children being anemic. However, only <10% were deficient in iron, vitamin A, and zinc. After 6 mo, plasma vitamin B-12 and homocysteine concentrations (both $P < 0.001$) as well as physical performance ($P < 0.05$) significantly improved in the intervention arms. No between-group differences were observed in hemoglobin concentration, anemia, and deficiencies of other micronutrients or cognitive function after 6 mo, but paired analyses revealed a small reduction in anemia prevalence in children in the low-iron group. The fortified rice was efficacious in improving vitamin B-12 status and physical performance in Indian school children.

[J Nutr.](#) 2011 Nov;141(11): 2017-23. Epub 2011 Sep 14.

[Micronutrient supplementation improves physical performance measures in Asian Indian school-age children.](#)

[Vaz M](#), [Pauline M](#), [Unni US](#), [Parikh P](#), [Thomas T](#), [Bharathi AV](#), [Avadhany S](#), [Muthayya S](#), [Mehra R](#), [Kurpad AV](#).

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Micronutrients are important in physical work capacity and therefore performance. The impact of a multi-micronutrient-fortified nutritional beverage on physical performance measures among clinically healthy school-age children was assessed in a double-blind (for test and placebo groups), placebo-controlled, randomized trial in children aged between 7 and 10.5 y ($n = 300$). The participants with height- and weight-for-age Z-scores between 0 and ≥ -3 were randomized to 1 of 3 study arms: fortified choco-malt beverage powder (F), matched energy equivalent unfortified placebo (U), and untreated control (C). Participants in the F and C groups were given 40 g fortified (19 key vitamins and minerals) and unfortified choco-malt beverage, respectively, daily for 120 d. Primary efficacy outcomes included endurance and aerobic capacity using a 20-m shuttle test and step test. Other physical performance measures included speed (40-m sprint), visual reaction time, maximal hand grip, and forearm static endurance. Micronutrient status included thiamin, riboflavin, folate, niacin, iron, pyridoxal phosphate, and vitamins B-12 and C. All measurements were made at baseline and the end of the intervention. There was a within-subject increase in aerobic capacity and whole body endurance ($P < 0.05$) accompanied by a significant improvement in the status of iron thiamin, riboflavin, pyridoxal phosphate, folate, and vitamins C and B-12 in the F group compared to the within-subject changes in the other 2 groups ($P < 0.05$). The study suggests that multiple micronutrient supplementation in similar

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populations may be beneficial in improving micronutrient status and enhancing aerobic capacity and endurance in children.



[Am J Clin Nutr.](#) 2012 May;95(5): 1223-30. Epub 2012 Apr 4.

[Selling Sprinkles micronutrient powder reduces anemia, iron deficiency, and vitamin A deficiency in young children in Western Kenya: a cluster-randomized controlled trial.](#)

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BACKGROUND: Although the efficacy of micronutrient powders [MNPs; eg, Sprinkles MNP (Sprinkles Global Health Initiative)] in the reduction of anemia has been established, the effectiveness of these powders in real-world programs has seldom been assessed.

OBJECTIVE: **In this study, we evaluated the effect of community-based marketing and distribution of Sprinkles MNP on childhood rates of anemia and iron and vitamin A deficiency.**

DESIGN: In a cluster-randomized trial in children aged 6-35 mo in Western Kenya, 60 villages were randomly assigned to either intervention or control groups. Community vendors marketed and sold sachets of Sprinkles MNP in intervention villages. Biweekly household visits monitored the use of Sprinkles MNP. Hemoglobin, ferritin, retinol binding protein, malaria, and anthropometric measures were assessed at baseline (n = 1063) and 12 mo of follow-up (n = 862). Data were analyzed by using an intention-to-treat analysis and generalized linear mixed models.

RESULTS: **On average, 33% of households in intervention villages purchased Sprinkles MNP; the average weekly intake per child was 0.9 sachets (~11.3 mg Fe and ~328 µg vitamin A). Compared with control subjects, intervention children had greater improvements in hemoglobin concentrations (increase of 0.9 compared with 0.6 g/dL, respectively; P = 0.02), iron deficiency (decrease of 19.3% compared with 5.3%, respectively; P = 0.001), and vitamin A deficiency (decrease of 7.5% compared with an increase of 2.5%, respectively; P = 0.01).** Results adjusted for age, sex, socioeconomic status, and maternal education showed a significant association between the hemoglobin, iron, and vitamin A concentrations of children and the number of Sprinkles MNP sachets the children consumed. The prevalence of malaria, wasting, and stunting did not change significantly in either group.

CONCLUSION: **Even with relatively low and infrequent use, Sprinkles MNP sales through community vendors were associated with decreased rates of anemia and iron and vitamin A deficiency in children in a resource-poor setting.** This trial was registered at clinicaltrials.gov as NCT01088958.

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Comment

This is an important trial. There have been many efficacy trials of micronutrients, evaluating the effects of micronutrients when given to subjects enrolled in the trial. This trial showed a feasible real-world mechanism for scaling up micronutrients. The results suggest a significant public benefit of a market approach to micronutrients, although the encouraging effects of home visits to monitor micronutrient usage may have influenced uptake.

[Eur J Clin Nutr.](#) 2011 Dec;65(12): 1287-94. doi: 10.1038/ejcn.2011.124. Epub 2011 Jul 13.
[Randomised comparison of the effects of Sprinkles and Foodlets with the currently recommended supplement \(Drops\) on micronutrient status and growth in Iranian children.](#)

[Samadpour K](#), [Long KZ](#), [Hayatbakhsh R](#), [Marks GC](#).

School of Population Health, The University of Queensland, Brisbane, Queensland, Australia.

BACKGROUND/OBJECTIVES: Multiple micronutrient supplementation with Sprinkles powder and crushable Foodlets tablets may be effective means of controlling micronutrient deficiencies in infants. Their efficacy has not been tested in countries like Iran where wheat as the staple food may affect nutrient bioavailability. This study aimed to compare the efficacy of Sprinkles, Foodlets and the current supplement (Drops) for improving micronutrient status and growth among Iranian infants.

SUBJECTS/METHODS: Infants of 6-18 months of age, living in an urban district of Iran were randomised to receive daily Sprinkles (n=120), Foodlets (n=121) or Drops (n=121) for 4 months. Haemoglobin (Hb), serum ferritin, serum retinol, serum zinc, 25(OH) D concentration and anthropometry were assessed at baseline and at 4 months.

RESULTS: Iron status improved with all treatments. Drops showed significantly greater changes in Hb and serum ferritin, though changes in anaemia prevalence were not different across groups. Infants having Foodlets and Sprinkles had significantly greater reductions in proportion of children with zinc deficiency compared with Drops. No significant differences in treatment effects were observed for mean serum 25(OH) D and retinol, or for growth of infants across groups.

CONCLUSION: The study was the first efficacy trial with Sprinkles and Foodlets in the Middle East where wheat or rice is the principal complementary foods. Differences across treatment groups were largely consistent with supplement micronutrient composition for iron and zinc, with no benefit in this population for serum retinol, 25(OH) D, growth or anthropometric status. The trial identified trade-offs in combining multiple micronutrients in a single delivery mechanism.

[Nutrition.](#) 2011 Jul-Aug;27(7-8): 761-5. Epub 2010 Oct 8.

Calcium bioavailability from a fortified cereal-legume snack (laddoo).

Randomised trials in child health in developing countries 2011-12

Ekbote VH, Khadilkar AV, Chiplonkar SA, Kant S, Khadilkar VV, Mughal MZ. Growth and Endocrine Department, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India.

OBJECTIVE: Calcium intakes in underprivileged Indian children are often low. Improving calcium intake fortification of indigenous foods may be a viable strategy. The aim of this study was to evaluate calcium absorption, as judged by an acute increase in serum ionized calcium concentration, after ingestion of a calcium-fortified cereal-legume snack (laddoo).

METHODS: Three groups of eight children (8-12 y old) with low habitual dietary calcium intake were recruited for the study. After an overnight fast, a calcium-fortified (500 mg of calcium carbonate) cereal-legume snack (laddoo) was given to group A, a similar but non-fortified snack was given to group B, and group C received calcium carbonate (500 mg) alone. Serum concentrations of ionized calcium and intact parathyroid hormone were measured at 0, 1, 2, 3, 4, and 5 h.

RESULTS: In group A, a peak of 6% above baseline was observed at 1 h in serum ionized calcium, whereas group C showed a peak of 5.5% at 4 h and group B showed a small increase of 1.8% at 1 h. The change in area under curve of groups A and C were of similar order (4.6 and 5.5, respectively), whereas that of group B was significantly lower (0.82). Serum parathyroid hormone was lowest at 2 h in groups A and B and at 3 h in group C.

CONCLUSION: The fortified cereal-legume laddoo may act as a novel vehicle for increasing calcium intake in children.

Breastfeeding and Complementary feeding

[Pan Afr Med J.](#) 2011;10: 8. Epub 2011 Sep 23.

[Using community volunteers to promote exclusive breastfeeding in Sokoto State, Nigeria.](#)

[Qureshi AM](#), [Oche OM](#), [Sadiq UA](#), [Kabiru S](#).

University Research Co LLC, Bethesda, MD, USA.

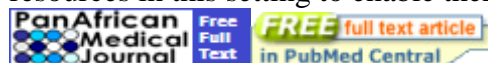
BACKGROUND: Exclusive Breastfeeding (EBF) refers to the practice of feeding breast milk only, (including expressed breast milk) to infants; and excluding water, other liquids, breast milk substitutes, and solid foods. Inadequately breastfed infants are likely to be undernourished and have childhood infections. EBF knowledge and infant feeding practices have not been studied sufficiently in Sokoto State, Nigeria. **We describe the results of a randomized community trial to promote Exclusive Breastfeeding (EBF) in two local government areas** Kware and Bodinga selected as intervention and control groups respectively.

METHODS: During advocacy meetings with community leaders, a Committee was formed. Members of the Committee were consulted for informed consent and **selection of ten female volunteers who would educate mothers about breastfeeding during home visits**. Participants comprised mothers of infants who were breastfeeding at the time of the study. **A total of 179 mothers were recruited through systematic random sampling from each community**. Volunteers conducted in-person interviews using a structured questionnaire and counseled mothers in the intervention group only.

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RESULTS: At baseline, intervention and control groups differed significantly regarding maternal occupation ($P=0.07$), and age of the index child ($P=0.07$). 42% of infants in the intervention group were up to 6 months old and about 30% of them were exclusively breastfed. Intention to EBF was significantly associated with maternal age ($P=0.01$), education ($P=0.00$) and women who were exclusively breastfeeding ($P=0.00$). **After counseling, all infants up to 6 months of age were exclusively breastfed.** The proportion of mothers with intention to EBF increased significantly with maternal age ($P=0.00$), occupation ($P=0.00$) and women who were exclusively breastfeeding ($P=0.01$). Post-intervention surveys showed that source of information and late initiation of breastfeeding was not significantly associated with intention to EBF. Mothers who reported practicing EBF for 6 months, were older ($P=0.00$) multi-parous ($P=0.05$) and more educated ($P=0.00$) compared to those who did not practice EBF. Among them, significantly increased proportion of women agreed that EBF should be continued during the night ($P=0.03$), infant should be fed on demand ($P=0.05$), sick child could be given medication ($P=0.02$), EBF offered protection against childhood diarrhea ($P=0.01$), and helped mothers with birth spacing ($P=0.00$).

CONCLUSION: This study shows that there is a need for reaching women with reliable information about infant nutrition in Sokoto State. **The results show decreased EBF practice among working mothers, young women, mothers with poor education and fewer than five children.** Counseling is a useful strategy for promoting the duration of EBF for six months and for developing support systems for nursing mothers. Working mothers may need additional resources in this setting to enable them to practice EBF.



[Matern Child Nutr.](#) 2011 Oct;7(4): 368-77. doi: 10.1111/j.1740-8709.2011.00297.x. Epub 2011 Apr 21.

[Acceptability of three novel lipid-based nutrient supplements among Malawian infants and their caregivers.](#)

[Phuka J](#), [Ashorn U](#), [Ashorn P](#), [Zeilani M](#), [Cheung YB](#), [Dewey KG](#), [Manary M](#), [Maleta K](#). Community Health Department, College of Medicine, University of Malawi, P/Bag 360 Blantyre, Malawi. johnphuka@yahoo.co.uk

We tested the acceptability of three new lipid-based nutrient supplements (LNSs) in two independent phases among 18 8-12-month-old healthy rural Malawians and their caregivers. In phase 1, acceptability was assessed by offering three new LNSs in random order, and an LNS already determined to be acceptable, Nutributter(®), each added to 30 g of warm maize porridge over three consecutive days. In phase 2, infants from each village were provided one of the new supplements for a 2-week home-use trial. Outcome measures included the amount consumed, time completion of the dose and the maternal rating of likeability on a 5-point scale. The supplements were rated acceptable if consumption was over 50% of the offered dose in phase 1. The mean (95% confidence interval) proportion of the LNS test meals consumed under direct observation was 88% (82-94%) for LNS-10gM, 90% (84-95%) for LNS-20gM, 87% (79-95%) for LNS-20gNoM, and 86% (83-90%) for Nutributter. The median (25th

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and 75th centile) time (minutes) for completing the offered test meal was 4 (2, 7) for LNS-10gM, 5 (3, 6) for LNS-20gM, 4 (3, 8) for LNS-20gNoM and 4 (2, 6) for Nutributter. During both phases, almost all caregivers rated all study foods very likeable for themselves and their children, with mean scores slightly lower among the caregivers than among the infants. In the home-use phase, the test foods were almost exclusively used by the study participants with minimal sharing with siblings and other household members. Some infants were reported to prefer the new investigational products over traditional complementary food. Considering that the novel LNS was largely acceptable. Efficacy trials are now needed to assess their impact on child growth and development.



[Soc Sci Med.](#) 2011 Aug;73(3): 447-55. Epub 2011 Jun 17.

[Does maternal autonomy influence feeding practices and infant growth in rural India?](#)

[Shroff MR](#), [Griffiths PL](#), [Suchindran C](#), [Nagalla B](#), [Vazir S](#), [Bentley ME](#).

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The high prevalence of child under-nutrition remains a profound challenge in the developing world. Maternal autonomy was examined as a determinant of breast feeding and infant growth in children 3-5 months of age. Cross-sectional baseline data on 600 mother-infant pairs were collected in 60 villages in rural Andhra Pradesh, India. The mothers were enrolled in a longitudinal randomized behavioral intervention trial. In addition to anthropometric and demographic measures, an autonomy questionnaire was administered to measure different dimensions of autonomy (e.g. decision-making, freedom of movement, financial autonomy, and acceptance of domestic violence). We conducted confirmatory factor analysis on maternal autonomy items and regression analyses on infant breast feeding and growth after adjusting for socioeconomic and demographic variables, and accounting for infant birth weight, infant morbidity, and maternal nutritional status. **Results indicated that mothers with higher financial autonomy were more likely to breastfeed 3-5 month old infants. Mothers with higher participation in decision-making in households had infants that were less underweight and less wasted. These results suggest that improving maternal financial and decision-making autonomy could have a positive impact on infant feeding and growth outcomes.**

Obesity

[Malays J Nutr.](#) 2011 Aug;17(2): 229-36.

[The Malaysian Childhood Obesity Treatment Trial \(MASCOT\).](#)

[Sharifah WW](#), [Nur HH](#), [Ruzita AT](#), [Roslee R](#), [Reilly JJ](#).

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INTRODUCTION: The present study describes a randomised controlled trial (RCT) based on a novel, generalisable intervention for childhood obesity, comparing the intervention with a no-treatment control group.

METHOD: The Malaysian Childhood Obesity Treatment Trial (MASCOT) was a single-blind RCT of a dietetic treatment for childhood obesity in children of primary school age (7 to 11 years old) in Kuala Lumpur, Malaysia. The MASCOT comprising eight sessions, of an 8-hour family-centred group treatment programme is described, based on behavioural change techniques. The study sample was characterised by BMI z-score, health related quality of life reported by participants and their parents (PedsQL questionnaire), objectively measured habitual physical activity and sedentary behaviour (Actigraph accelerometry)

RESULTS: The MASCOT sample of 107 children was characterised by a low quality of life, mean total score on PedsQL 67.7 (4.5) as reported by the children, and 66.0 (16.4) as reported by their parents. The children spent, on average, 89% of their waking day on sedentary activity, and 1% of the day in moderate-vigorous intensity physical activity, equivalent to only around 8 minutes/day.

CONCLUSION: Obese children in the MASCOT study had an impaired quality of life, high levels of sedentary behaviour and very low levels of physical activity.

Oncology

(see also HIV – management of HIV related conditions)

[J Pediatr Hematol Oncol. 2011 Dec;33\(8\): e333-41.](#)

[Oral voriconazole versus intravenous low dose amphotericin B for primary antifungal prophylaxis in pediatric acute leukemia induction: a prospective, randomized, clinical study.](#)

[Mandhaniya S, Swaroop C, Thulkar S, Vishnubhatla S, Kabra SK, Xess I, Bakhshi S.](#)

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PURPOSE: Invasive fungal infections (IFI) are a major cause of infection-related mortality during induction chemotherapy of acute leukemia (AL) patients. Data on antifungal prophylaxis (AFP) in children are limited by retrospective design, small sample size, and variability of chemotherapy phases having different risk of IFI. There are no data comparing voriconazole versus amphotericin B (AmB) as AFP in either adult/pediatric AL. The objectives of this study were to compare efficacy and toxicity of AmB and voriconazole as AFP in pediatric AL patients.

PATIENTS AND METHODS: As a pilot study, total 100 children (≤ 15 y) with de novo acute myeloid leukemia and acute lymphoblastic leukemia were randomized to either oral voriconazole or low dose intravenous AmB as AFP during induction chemotherapy.

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RESULTS: Failure of prophylaxis occurred in 14/50 patients in voriconazole arm (1 proven mucormycosis, 1 possible IFI, 11 empirical antifungal therapy, and 1 withdrawal owing to hepatotoxicity) and 17/50 patients in AmB arm (3 possible IFI, 13 empirical antifungal therapy, and 1 withdrawal owing to difficult venous access) (**P=0.66**). Of the 29 patients who had failure of prophylaxis unrelated to drug toxicity, computed tomography of the chest showed infiltrates in 10 patients with 3/12 in voriconazole arm and 7/16 in AmB arm (**P=0.43**). Drug-related serious adverse events were 6% versus 30% in voriconazole and AmB arms, respectively (**P<0.01**). Further, total number of toxicities per patient in AmB arm were significantly higher as compared with voriconazole arm (**P<0.0001**).

CONCLUSION: This is the first randomized study comparing voriconazole with AmB in pediatric AL patients as AFP during induction chemotherapy; our results showed that oral voriconazole seems to be comparable with AmB with less toxicity and more convenience. (ClinicalTrials.gov identifier: NCT00624143).

Ophthalmology

[Ophthalmology](#). 2011 Dec;118(12): 2343-50. Epub 2011 Sep 1.

[Randomized, controlled trial of an educational intervention to promote spectacle use in rural China: the see well to learn well study.](#)

[Congdon N](#), [Li L](#), [Zhang M](#), [Yang A](#), [Gao Y](#), [Griffiths S](#), [Wu J](#), [Sharma A](#), [Lam DS](#).

Zhongshan Ophthalmic Center, State Key Laboratory and Division of Preventive Ophthalmology, Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: To test an educational intervention promoting the purchase of spectacles among Chinese children.

DESIGN: Randomized, controlled trial.

PARTICIPANTS: Children in years 1 and 2 of all 20 junior and senior high schools (ages 12-17 years) in 3 rural townships in Guangdong, China.

METHODS: Children underwent visual acuity (VA) testing, and parents of participants with presenting VA worse than 6/12 in either eye improving by more than 2 lines with cycloplegic refraction were recommended to purchase glasses. **Children at 10 randomly selected schools received a lecture, video, and classroom demonstration promoting spectacle purchase.**

MAIN OUTCOME MEASURES: Self-reported purchase of spectacles (primary outcome) and observed wear or possession of newly purchased glasses (secondary outcome) at follow-up examinations (mean, 219 ± 87 days after the baseline visit).

RESULTS: Among 15 404 eligible children, examinations were completed for 6379 (74.6%) at intervention schools and 5044 (73.6%) at control schools. Spectacles were recommended for 2236 (35.1%) children at intervention schools and for 2212 (43.9%) at control schools. Of these, **417 (25.7%) intervention schools children and 537 (34.0%, P = 0.45) control schools**

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children reported buying glasses. Predictors of purchase in regression models included female gender ($P = 0.02$), worse uncorrected VA ($P < 0.001$), and higher absolute value of refractive error ($P = 0.001$). Neither the rate of self-reported purchase of glasses or observed wear or possession of newly purchased glasses differed between control schools and intervention schools in mixed-effect logistic regression models. Among children not purchasing glasses, 21.7% had better-eye VA of worse than 6/18.

CONCLUSIONS:

An intervention based on extensive pilot testing and focus groups in the area failed to promote spectacle purchase or wear. The high burden of remaining uncorrected poor vision underscores the need to develop better interventions.

[Br J Ophthalmol](#). 2012 Mar;96(3): 323-8. Epub 2011 Oct 14.

[Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, Central Africa: a prospective, randomised, double-masked, controlled clinical trial.](#)

[De Smedt S](#), [Nkurikiye J](#), [Fonteyne Y](#), [Tuft S](#), [De Bacquer D](#), [Gilbert C](#), [Kestelyn P](#).

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AIM: To compare the short-term efficiency and safety of topical ciclosporin A (CsA) 2% with dexamethasone 0.1% in the treatment of predominantly limbal vernal keratoconjunctivitis (VKC) in Rwanda, Central Africa.

METHODS: Consecutive patients with VKC were randomised in a prospective, double-masked, clinical trial to receive either topical CsA 2% dissolved in olive oil vehicle or dexamethasone 0.1% drops for 4 weeks. Both groups then received sodium chromoglycate 2% drops for maintenance therapy for a further 4 weeks. The primary outcome was the reduction in composite score for VKC-related symptoms and signs at 4 weeks. Secondary outcomes included side effects, best-corrected visual acuity, comfort rating of the trial drops during 4 weeks' test medication and relapse rate thereafter.

RESULTS: The 366 participants recruited had the limbal (91.5%) or mixed form of VKC. **At the end of the 4-week treatment period, the composite score had decreased significantly ($p < 0.001$) from baseline without any significant difference between CsA and dexamethasone ($p = 0.20$).** There were no severe adverse reactions, but CsA drops caused more stinging than the oil placebo and dexamethasone ($p < 0.001$). In both treatment groups, the visual acuity had improved at 4 weeks compared with baseline ($p < 0.001$) with no significant difference between the treatment arms. The relapse rate following cessation of the trial treatments was similar ($p = 0.84$) in both groups.

CONCLUSION: **There is no significant difference between the efficiency of topical CsA 2% and dexamethasone 0.1% for the management of acute VKC in Central Africa, but tolerance needs to be improved.**



[Am J Ophthalmol](#). 2012 Apr 27. [Epub ahead of print]

[Anti-inflammatory Effect of Low-Molecular-Weight Heparin in Pediatric Cataract Surgery: A Randomized Clinical Trial.](#)

[Vasavada VA](#), [Praveen MR](#), [Shah SK](#), [Trivedi RH](#), [Vasavada AR](#).

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PURPOSE: To determine if intraocular infusion of low-molecular-weight heparin (enoxaparin) reduces postoperative inflammation in pediatric eyes undergoing cataract surgery with IOL implantation.

DESIGN: Prospective masked randomized controlled trial.

METHODS: Setting: Private, institutional practice. Study population: **Twenty children (40 eyes) undergoing bilateral cataract surgery with IOL implantation were randomized to receive enoxaparin in the intraocular infusion fluid (BSS) (Group I) or not to receive enoxaparin (Group II). The first eye was randomly assigned to 1 of the 2 groups and the second eye received alternate treatment.** Observation procedure: Patients were followed up in the first week and 1 and 3 months after surgery. Main outcome measures: Anterior chamber flare and cells (Hogan's criteria), cell deposits on IOL, posterior synechiae.

RESULTS: One week postoperatively, no eyes had >grade 2 flare/cells. Proportion of eyes with grade 2 cells was higher in eyes that did not receive enoxaparin (Group II: 80% vs Group I: 40%, $P = .009$). In the first week >10 small cell deposits were noted in the eyes that received enoxaparin (Group I: 20%, Group II: none, $P = .005$). Large cell deposits first appeared at 1 month in 40% of eyes in Group I and 55% of eyes in Group II ($P = .34$) and increased at 3 months (60% in both groups, $P > .999$). Posterior synechiae were seen in 10% of eyes in Group I at 1 month, which persisted at 3 months; no eyes in Group II showed posterior synechiae ($P = .14$).

CONCLUSION: **The results of our study suggest that there does not seem to be a benefit of using enoxaparin in the infusion fluid with respect to early postoperative inflammation.**

Trachoma

(See also Hygiene)

[Lancet](#). 2012 Jan 14;379(9811): 143-51. Epub 2011 Dec 20.

[Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomised trial.](#)

[Gebre T, Ayele B, Zerihun M, Genet A, Stoller NE, Zhou Z, House JI, Yu SN, Ray KJ, Emerson PM, Keenan JD, Porco TC, Lietman TM, Gaynor BD.](#)

The Carter Center, Addis Ababa, Ethiopia.

BACKGROUND: In trachoma control programmes, azithromycin is distributed to treat the strains of chlamydia that cause ocular disease. We aimed to compare the effect of annual versus twice-yearly distribution of azithromycin on infection with these strains.

METHODS: We did a cluster-randomised trial in 24 subdistricts in northern Ethiopia, which we randomly assigned to receive annual or twice-yearly treatment for all residents of all ages. Random assignment was done with the RANDOM and SORT functions of Microsoft Excel. All individuals were offered their assigned treatment of a single, directly observed, oral dose of azithromycin. A 6 week course of topical 1% tetracycline ointment, applied twice daily to both eyes but not directly observed, was offered as an alternative to azithromycin in patients younger than 12 months, and in patients with self-reported pregnancy, with allergy, or who refused azithromycin. **Our primary, prespecified outcome was the prevalence of ocular chlamydial infection in a random sample of children aged 0-9 years at baseline and every 6 months for a total of 42 months within sentinel villages.** Our analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00322972.

FINDINGS: Antibiotic coverage of children aged 1-9 years was greater than 80% (range 80.9 to 93.0) at all study visits. **In the groups treated annually, the prevalence of infection in children aged 0-9 years was reduced from a mean 41.9% (95% CI 31.5 to 52.2) at baseline to 1.9% (0.3 to 3.5) at 42 months. In the groups treated twice yearly, the prevalence of infection was reduced from a mean 38.3% (29.0 to 47.6) at baseline to 3.2 % (0.0 to 6.5) at 42 months.** The prevalence of ocular chlamydial infection in children aged 0-9 years in groups treated annually was not different from that of the groups treated twice yearly at 18, 30, and 42 months (pooled regression $p > 0.99$, 95 % CI -0.06 to 0.06). **The mean elimination time in the twice-yearly treatment group was 7.5 months earlier (2.3 to 17.3) than that of the annual group ($p = 0.10$, Cox proportional hazards model).**

INTERPRETATION: After 42 months of treatment, the prevalence of ocular infection with chlamydia was similar in the groups treated annually and twice yearly. However, elimination of infection might have been more rapid in the groups of villages that received treatment twice yearly.



[Am J Trop Med Hyg.](#) 2011 Aug;85(2): 291-4.

[Adverse events after mass azithromycin treatments for trachoma in Ethiopia.](#)

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[Ayele B](#), [Gebre T](#), [House JI](#), [Zhou Z](#), [McCulloch CE](#), [Porco TC](#), [Gaynor BD](#), [Emerson PM](#), [Lietman TM](#), [Keenan JD](#).

The Carter Center, Addis Ababa, Ethiopia.

During a cluster-randomized clinical trial for trachoma in Ethiopia, two rounds of adverse event surveillance were performed in a random sample of communities after community-wide mass azithromycin treatment. The prevalence of any reported adverse event ranged from 4.9% to 7.0% in children 1-9 years of age and from 17.0% to 18.7% in persons ≥ 10 years of age. Adverse events appeared to cluster by household and perhaps by village. Mass azithromycin distributions were well tolerated in this setting.



[Ophthalmic Epidemiol](#). 2012 Feb;19(1): 38-42.

[Two-day dosing versus one-day dosing of azithromycin in children with severe trachoma in Tanzania.](#)

[Campbell JP](#), [Mkocha H](#), [Munoz B](#), [West SK](#).

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PURPOSE: To determine whether 2-day dosing of azithromycin may improve the efficacy of azithromycin dosing in children with severe trachoma.

METHODS: **Fifty children with severe trachoma (defined as either trachoma intense or follicular trachoma with ten or more follicles) were enrolled from five villages in Kongwa, Tanzania.** Enrollment occurred within 1 month and within the same district as the historical control population of 99 children with severe trachoma, all of whom received 1-day dosing. Baseline data on age, sex, and trachoma status were obtained, and swabs for determination of *Chlamydia trachomatis* were taken. **All 50 children received 20 mg/kg azithromycin daily for 2 days, which was directly observed.** Children were followed up at 6 weeks for trachoma and infection. The laboratory was masked to treatment assignment.

RESULTS: Baseline characteristics were similar between the treatment group and the control group. **A total of 1/46 (2.2%) of children in the treatment group were polymerase chain reaction (PCR)-positive at 6 weeks, a 96.3% reduction from baseline, compared to 13/96 (13.5%) in the historical control group, an 89.4% reduction.** This difference was statistically significant. However when modeled using logistic regression and accounting for age, gender, weight, and baseline percent PCR positivity, the difference was not significant. Prevalence of clinical trachoma did not differ between the groups at 6 weeks.

CONCLUSION: For children with severe trachoma, a randomized controlled trial of 2-day versus 1-day treatment may be warranted.



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Comment

This is not a randomised trial, but used historical controls.

Oral health / dentistry

(See Health education)

[Eur Arch Paediatr Dent.](#) 2011 Aug;12(4): 211-5.

[A comparative evaluation of probiotics on salivary mutans streptococci counts in Indian children.](#)

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AIM: Probiotics and their effect on oral health have been a focus of numerous trials in recent times. No documented trials have been reported from developing countries such as India with its focus on probiotic use, especially in the paediatric population. **The aim of this study is to evaluate the effect of probiotics on salivary mutans streptococci (MS) counts of children using the two commercially and widely available preparations and to explore their anti-carries potential.**

STUDY DESIGN: A placebo controlled study was undertaken with 3 parallel arms comprising a total of 150 healthy children (7-14 years). The subjects were randomly divided into the groups (each comprising 50 children): **group A - placebo powder, Group B - a freeze dried powdered combination of Lactobacillus rhamnosus and Bifidobacterium species, Group C - a freeze dried powdered preparation of Bacillus coagulans.** The subjects were instructed to mix the preparation in 20 ml of water and to follow a swish and swallow method for 14 days. **Mutans streptococci colony counts per ml of saliva were performed on Mitis-Salivarius Bacitracin agar collected on the first day and 14 days post-intervention.**

RESULTS: **A statistically significant reduction ($p < 0.001$) in salivary mutans streptococci counts was recorded in both groups B and C after 14 days of probiotic ingestion.**

CONCLUSION: A cost-effective probiotic such as Bacillus coagulans might be a subject for further research for prevention of caries in children.

[Contemp Clin Trials.](#) 2011 Nov;32(6): 802-8. Epub 2011 Jul 6.

[Comparative evaluation of efficacy of 0.2% Chlorhexidine, Listerine and Tulsi extract mouth rinses on salivary Streptococcus mutans count of high school children--RCT.](#)

[Agarwal P](#), [Nagesh L](#).

Randomised trials in child health in developing countries 2011-12

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OBJECTIVE: To assess and compare the effect of 0.2% Chlorhexidine mouth rinse, Listerine mouth rinse and 4% Tulsi extract mouth rinse on salivary *Streptococcus mutans* level.

METHODS: The present study is an experimental study of cross over type, employing Latin square design. 45 school children aged 14-15 years were divided into three groups/blocks. **The baseline unstimulated saliva samples were obtained from each group and assessed for *Streptococcus mutans* counts. The study was divided in to three phases, each phase lasted for 8 days separated by a washout period of 15 days in between them. Groups A, B and C were treated with 0.2% Chlorhexidine, Listerine and 4% Tulsi extract mouth rinses respectively in the phase I.** The study subjects were instructed to use the assigned mouth rinse twice daily for 1 min for 7 days. On day 8th the subjects were instructed to use the mouth rinse only once in the morning. The follow up unstimulated saliva samples were collected 1h after the use of the assigned mouth rinse and assessed for salivary *Streptococcus mutans* counts. After phase I, mouth rinses were crossed over as dictated by the Latin square design in phase II and III.

RESULTS: All the three mouth rinses have individually shown a statistically significant reduction in the salivary *Streptococcus mutans* counts. When the three mouth rinses were compared the difference did not reach statistical significance.

CONCLUSION: Tulsi has stood the test and is as effective as Chlorhexidine and Listerine in reducing the salivary *S. mutans* levels.

Comment

Tulsi (Ocimum sanctum) is a herb used widely for medicinal purposes in India. It has been shown to have antimicrobial activity against Streptococcus mutans

[Acta Odontol Scand.](#) 2011 Nov;69(6): 389-94. Epub 2011 Apr 5.

[Salivary mutans streptococci and lactobacilli modulations in young children on consumption of probiotic ice-cream containing Bifidobacterium lactis Bb12 and Lactobacillus acidophilus La5.](#)

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OBJECTIVES: To compare the levels of mutans streptococci and lactobacilli in saliva of school children, before and after consumption of probiotic and control ice-cream.

MATERIALS AND METHODS: A double-blind, cross-over, placebo-controlled trial was carried out in forty, 12-14 year-old children, with no clinically detectable caries. **The selected children were randomized equally into two groups I and II. Following an initial run-in period of 1 week, children in group I and II were given ice-creams 'A' and 'B',**

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respectively, for 10 days. Being a cross-over study, the ice-creams were interchanged in the two groups after a 2-week wash-out period. Saliva samples at baseline and follow-up were assessed using Dentocult SM and Dentocult LB kits.

RESULTS: On statistical evaluation, it was seen that probiotic ice-cream brought about a statistically significant reduction (p-value = 0.003) in salivary mutans streptococci levels with no significant effect on lactobacilli levels.

CONCLUSION: In conclusion, probiotic ice-cream containing Bifidobacterium lactis Bb-12 ATCC27536 and Lactobacillus acidophilus La-5 can reduce the levels of certain caries-associated micro-organisms in saliva.

[Eur Arch Paediatr Dent.](#) 2011 Oct;12(5): 245-9.

[Comparative evaluation of chlorhexidine mouthrinse versus cacao bean husk extract mouthrinse as antimicrobial agents in children.](#)

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AIM: To compare the antimicrobial efficiency of chlorhexidine and cacao bean husk extract mouthrinses in children.

STUDY DESIGN: A randomised comparative study which employed purpose sampling.

METHODS: Study was conducted on 50 children of both sexes aged 6-10 years old. A group of 25 children were given 10 ml of 0.2% chlorhexidine mouthrinse and another 25 children were given 10 ml of 0.1% cacao bean extract mouthrinse to rinse twice daily for about 30 seconds. The salivary samples were collected from each child in Dentocult SM vials on day one (pre-rinse) and after 7 days, 1 month and 2 months. The readings were tabulated and subjected to statistical analysis.

STATISTICS: Mann-Whitney test and the p-value were used for statistical analysis.

RESULTS: There was significant reduction in streptococcus mutans counts in saliva at all follow-up intervals for both mouthrinse groups. However, there was no significant difference in reduction of streptococcus mutans counts in saliva, between chlorhexidine mouthrinse group and cacao bean husk extract mouthrinse group.

CONCLUSION: Cacao bean husk extract mouthrinse can be used in children as an alternative to chlorhexidine mouthrinse as it has similar antimicrobial properties and evades the side-effects of the latter.

[Int Dent J.](#) 2012 Feb;62(1): 47-51. doi: 10.1111/j.1875-595X.2011.00088.x.

[Paradigm shift in the effective treatment of caries in schoolchildren at risk.](#)

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BACKGROUND: Silver diamine fluoride (SDF) is an effective agent for the arrest of caries in children, is easy to apply and can be used outside the clinical environment. Interim restorative treatment (IRT) using glass ionomer cement has also been claimed to be a simple and effective method to arrest caries in deciduous teeth.

OBJECTIVE: **To examine whether, for underprivileged schoolchildren with cavities, treatment with 30% SDF gives better results than IRT for caries arrest.** This randomised Method: controlled study compares the effect of IRT (FUJI IX) with 30% SDF in 91 children aged 5-6 years.

RESULTS: **After 1 year, treatment with SDF was more effective [relative risk (RR) = 66.9%] than IRT (RR = 38.6%) for the arrest of caries; this was statistically significant (P<0.05).**

CONCLUSION: The SDF technique showed better results than IRT for the arrest of cavities in deciduous teeth, indicating that its use for underprivileged communities may justify a paradigm shift in paediatric dentistry.

[J Clin Pediatr Dent](#). 2011 Summer;35(4): 365-9.

[Endoflas, zinc oxide eugenol and metapex as root canal filling materials in primary molars--a comparative clinical study.](#)

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BACKGROUND: Several materials have been used to fill root canals of primary teeth. Traditionally, zinc oxide eugenol was used for the purpose, until the introduction of calcium hydroxide and iodoform based materials. Another root canal filling material that contains zinc oxide eugenol, calcium hydroxide and iodoform is commercially available as Endoflas. The aim of the study was to evaluate and compare the efficacy of Endoflas, zinc oxide eugenol and Metapex as root canal filling materials.

METHOD: A total of forty-five primary molars from children aged 5-9 years were selected for a one stage pulpectomy procedure. Teeth were randomly divided into three groups of fifteen teeth each based on the type of root canal filling material used. All the molars were evaluated

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clinically and radiographically at regular intervals of 3, 6, 12 and 18 months. The observations were tabulated and statistically analyzed.

RESULTS: Endoflas and zinc oxide eugenol showed 93.3% success, whereas a higher percentage of success was observed with Metapex (100%). Overfilling and voids were more commonly seen in teeth filled with Metapex.

CONCLUSION: There was no significant difference between the three root canal filling materials.

[J Indian Soc Pedod Prev Dent.](#) 2011 Jul-Sep;29(3): 235-8.

[Plaque removal efficacy of powered and manual toothbrushes under supervised and unsupervised conditions: a comparative clinical study.](#)

[Kallar S, Pandit IK, Srivastava N, Gugnani N.](#)

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The present study was undertaken to determine and compare the efficacy of manual and powered toothbrushes under supervised and unsupervised conditions in 200 school-going children between 6 and 13 years of age. Two hundred school-going children aged between 6 and 13 years were selected. Children were randomly divided into two groups of 100 in each. **Group 1 children were given manual brushes, while group 2 children were given powered brushes.** The groups were further divided into two subgroups, with supervised brushing in subgroup A and unsupervised brushing in subgroup B. At 3, 6, 9 and 12 weeks, plaque was recorded according to Turseky-Gilmore-Glickman modification of Quingley Hein index and oral hygiene performance index. Data were statistically analyzed. Both brushes significantly reduced the plaque accumulation, though to different degrees. **Powered brushes showed significant plaque reduction as compared to the manual brushes. Supervised group of both brushes showed a greater plaque reduction.**



School health

(See also Nutrition, Ophthalmology, Adolescent health, Anaemia and iron deficiency)

[J Nutr.](#) 2011 Aug;141(8): 1565-72. Epub 2011 Jun 15.

[A multi-micronutrient beverage enhances the vitamin A and zinc status of Nigerian primary schoolchildren.](#)

[Aaron GJ, Kariger P, Aliyu R, Flach M, Iya D, Obadiah M, Baker SK.](#)

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Schoolchildren in Nigeria are rarely targeted by micronutrient interventions. We completed a 6-mo, **double-blind, placebo-controlled trial to determine the effects of a multi-micronutrient beverage on biochemical and anthropometric indicators of nutritional status among schoolchildren participating in a pilot school feeding program in Nasarawa State, Nigeria.** Children received 1 of 2 interventions 5 d/wk during school hours: **1) 250 mL/d of a multi-micronutrient beverage that included vitamin A, iron, and zinc (micronutrient); or 2) an isoenergetic control beverage (control).** At baseline, 566 children 5-13 y old were randomized to groups (micronutrient: n = 288; control: n = 278). Height, weight, hemoglobin, and serum concentrations of C-reactive protein, ferritin, retinol, and zinc were measured at baseline and at the end of the study. **A total of 270 children in the micronutrient group and 264 children in the control group completed the study. Self-reports of vomiting increased in both groups at 6 mo; however, the prevalence tended to be greater in the micronutrient group (21%) compared to the control group (14%) (P = 0.06).** Biochemical changes were greater in the micronutrient group compared to control for serum retinol ($0.10 \pm 0.02 \mu\text{mol/L}$ vs. $0.02 \pm 0.02 \mu\text{mol/L}$; P = 0.016) and zinc ($1.0 \pm 0.2 \mu\text{mol/L}$ vs. $0.6 \pm 0.2 \mu\text{mol/L}$; P = 0.031). The intervention did not significantly affect hemoglobin or serum ferritin concentrations. The cost effectiveness of the intervention needs to be further evaluated, as does the efficacy of the beverage on anemia and indicators of iron status.



[Am J Clin Nutr.](#) 2011 Aug;94(2): 578-84. Epub 2011 Jun 22.

[Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia.](#)

[Rich-Edwards JW](#), [Ganmaa D](#), [Kleinman K](#), [Sumberzul N](#), [Holick MF](#), [Lkhagvasuren T](#), [Dulguun B](#), [Burke A](#), [Frazier AL](#).

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BACKGROUND: The optimal public health strategy for maintaining 25-hydroxyvitamin D [25(OH)D] concentrations in schoolchildren in Mongolia is unknown.

OBJECTIVE: The objective was to compare the effectiveness of different supplement and fortified milk regimens to increase 25(OH)D concentrations in Mongolian schoolchildren.

DESIGN: **Twenty-one classrooms of 579 children aged 9-11 y were randomized to interventions with an equivalent content of vitamin D(3): 1) a one-time seasonal supplement of 13,700 IU, 2) 300 IU/d from supplements, 3) 300 IU/d from fortified ultra-high-temperature pasteurized milk from the United States, 4) 300 IU/d from fortified pasteurized Mongolian milk, or 5) unfortified pasteurized Mongolian milk (control).**

RESULTS: In January, the mean (\pm SD) serum 25(OH)D concentration was $8 \pm 4 \text{ ng/mL}$ ($20 \pm 10 \text{ nmol/L}$), and 98% of the children had a concentration $<20 \text{ ng/mL}$ (50 nmol/L). **In March,**

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concentrations were 8 ± 4 ng/mL after unfortified milk, 20 ± 6 ng/mL after fortified Mongolian milk, 29 ± 10 ng/mL after fortified US milk, 21 ± 6 ng/mL after daily supplements, and 12 ± 4 ng/mL after seasonal supplements (each greater than unfortified milk, $P < 0.01$). Seasonal supplementation was less effective than was daily supplementation ($P < 0.0001$). Despite consuming daily supplements or fortified milk, 41% of the children still had concentrations <20 ng/mL (50 nmol/L). Children with lower baseline 25(OH)D concentrations experienced slightly larger 25(OH)D responses to intervention than did children with higher concentrations ($P = 0.002$).

CONCLUSIONS: In this population with extremely low vitamin D concentrations, delivery of 300 IU vitamin D/d via supplements or in fortified milk improved 25(OH)D concentrations but failed to raise concentrations uniformly to >20 ng/mL (50 nmol/L). The daily low-dose intervention was superior to the seasonal larger-dose intervention. Higher doses may be needed to prevent deficiency in schoolchildren in Mongolia and at other northern latitudes. This trial is registered at clinicaltrials.gov as NCT00886379.

Skin disease

[Indian J Dermatol Venereol Leprol.](#) 2011 Sep-Oct;77(5): 581-6.

[Topical permethrin and oral ivermectin in the management of scabies: a prospective, randomized, double blind, controlled study.](#)

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BACKGROUND: Scabies is a highly contagious and intensely pruritic parasitic infestation. It is a re-emerging infection in the new millennium especially with HIV pandemic and a significant health problem in developing countries. Various treatment modalities have been used since time immemorial but the search for an ideal scabicide is ongoing.

AIMS: In this study, we compared the therapeutic efficacy of single application of topical 5% permethrin with oral ivermectin (200 μ g/kg/dose) in a single-dose and a two-dose regimen in patients with scabies.

METHODS: 120 clinically diagnosed cases of scabies (>5 years of age and/or >15 kg) were randomized into three treatment groups A, B, C of 40 patients each; receiving either topical 5% permethrin (group A) or oral ivermectin (200 μ g/kg/dose) in a single dose (group B) or double dose regimen (group C) repeated at 2 weeks interval. Patients were followed up at 1, 2, and 4 weeks interval. At each visit, cure rate ($>50\%$ improvement in lesion count and pruritus and negative microscopy) was assessed and compared.

RESULTS: Cure rate in three treatment groups at the end of 4 weeks was 94.7% (A), 90% (B), 89.7% (C), and thus all three treatment modalities were equally efficacious. However,

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at 1 week follow up, group A patients reported better improvement in both lesion count and pruritus.

CONCLUSIONS: Both permethrin and ivermectin in both single and two dose regimen are equally efficacious and well tolerated in scabies. However, permethrin has a rapid onset of action.



[Mycopathologia](#). 2011 Nov;172(5): 365-72. Epub 2011 Jun 24.

[A random comparative study of terbinafine versus griseofulvin in patients with tinea capitis in Western China.](#)

[Deng S](#), [Hu H](#), [Abliz P](#), [Wan Z](#), [Wang A](#), [Cheng W](#), [Li R](#).

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OBJECTIVE: To compare the efficacy and safety of terbinafine with griseofulvin in the treatment of tinea capitis in Western China.

METHODS: Children (2-14 years of age) with clinically diagnosed and potassium hydroxide microscopy-confirmed tinea capitis were randomized into three groups: group GRI4 received 4 weeks of griseofulvin; group TBF2 received 2 weeks of terbinafine; and Group TBF4 received 4 weeks of terbinafine. Clinical and mycological evaluations were done in 0, 2, 4, and 8 weeks and 1 year after therapy started. The isolated pathogenic fungi were evaluated for in vitro susceptibility by detecting the minimal inhibitory concentration (MIC) against terbinafine, griseofulvin, itraconazole, and ketoconazole.

RESULTS: The clinical effectiveness rate of GRI4, TBF2, and TBF4 were 100% (95% CI-confidence interval: 82-100%), 96.3% (95% CI: 81-100%), and 100%(95% CI: 85-100%), respectively, at week 8 and 100% after 1 year for the 3 groups; clinical cure rates were 84.2%(95% CI: 77-99%), 85.2%(95% CI: 71-98%), and 78.3%(95% CI: 61-95%), respectively, at week 8 and 100% after 1 year for all agents; mycological cure rates were 100%(95% CI: 74-100%), 95.0%(95% CI: 74-100%), and 94.1%(95% CI: 50-93%) at week 8 and 100% after 1 year for the 3 groups. In vitro, all patient-derived cultures were sensitive to the four antifungal agents.

CONCLUSION: Data from the clinical trial and in vitro antifungal activity indicated that terbinafine is efficacious and well tolerated in the treatment for Trichophyton infections (*T. violaceum*; *Arthroderma vanbreuseghemii*; and *T. tonsurans*) of the scalp, i.e., a 2- to 4-week course of terbinafine is as effective as a 4-week course of griseofulvin; in fact, a 2-week course of terbinafine is sufficient. **Terbinafine is an effective alternative to griseofulvin against tinea capitis of Trichophyton infections.**

[Indian J Dermatol Venereol Leprol.](#) 2012 Jan;78(1): 68-73.

[Segmental vitiligo: A randomized controlled trial to evaluate efficacy and safety of 0.1% tacrolimus ointment vs 0.05% fluticasone propionate cream.](#)

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BACKGROUND: Segmental vitiligo is a small subset of vitiligo which responds very well to surgical therapy, but the role of medical treatment is not very well defined.

AIM: To compare the efficacy and safety of 0.1% tacrolimus ointment versus 0.05% fluticasone propionate cream in patients of segmental vitiligo.

METHODS: A randomized control trial was conducted in a tertiary care hospital on 60 consecutive patients with segmental vitiligo. Patients with segmental vitiligo exclusively or along with focal vitiligo, untreated or had not taken any topical treatment in previous 1 month or systemic treatment in previous 2 months, from May 2005 to January 2007, were block randomized into two groups. Children <5 years, pregnant and lactating women, and patients with known hypersensitivity to either drug and with associated multiple lesions of vitiligo were excluded. **Group A (n = 29) patients were treated with tacrolimus 0.1% ointment twice daily and group B (n = 31) patients were treated with 0.05% of fluticasone cream once daily for 6 months.** Response and side effects were recorded clinically and by photographic comparison. Results: **Nineteen patients treated with tacrolimus and 21 patients treated with fluticasone completed the treatment with median repigmentation of 15% and 5%, respectively, at 6 months (P = 0.38).** Transient side effects limited to the application site were observed.

CONCLUSIONS: Both tacrolimus and fluticasone propionate produce variable, but overall unsatisfactory, repigmentation in segmental vitiligo.



[Pak J Biol Sci.](#) 2012 Jan 15;15(2): 103-7.

[Comparison of topical triamcinolone and oral atorvastatin in treatment of paederus dermatitis Northern Iran.](#)

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Dermatitis caused by stimulation of beetle paederus, is a common health problem in Northern and some southern parts of Iran. Since by now, traditional medicine and some corticosteroid agents have been used for treatment of dermatitis caused by beetle paederus. Because, there are

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few researches about classical treatment of the disease at academic level, this study planned to compare the effectiveness of triamcinolone ointment and atorvastatin tablet with placebo in treatment of paederus dermatitis in Northern Iran. A randomized double-blind clinical trial was carried out on 30 patients referred to the hospital and clinics at Sari and Neka countries in Northern Iran during 6 months. **Patients were randomly divided into two therapeutic equal groups. The first group was triamcinolone ointment twice a day and a placebo atorvastatin tablet daily. The second group was oral atorvastatin one tablet (20 mg) daily and a placebo triamcinolone ointment twice a day. In Seventh day of visits, therapeutic response of the patients in triamcinolone and atorvastatin group were 93.33 and 80%, respectively. No significant differences were found in therapeutic outcome between the two groups ($p > 0.05$).** The results showed both of triamcinolone ointment and oral atorvastatin had similar effect on paederus dermatitis. Because the paederus dermatitis is a self-limited disease use of topical therapy for treatment of the disease is recommend.

[J Drugs Dermatol.](#) 2011 Dec;10(12): 1444-50.

[Rupatadine and levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety.](#)

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BACKGROUND: Chronic Idiopathic Urticaria is difficult to treat due to its persistent debilitating symptoms. New generation anti-histaminics are first line treatment for this condition. The aim of this study is to compare efficacy and safety of rupatadine and levocetirizine in chronic idiopathic urticaria.

METHODS: A randomized, single blinded, single-centred, parallel group outdoor based clinical study was conducted in 70 patients of CIU to compare the two drugs. After initial clinical assessment and baseline investigations, rupatadine was prescribed to 35 patients and levocetirizine to another 35 patients for 4 weeks. At follow-up, the patients were re-evaluated and then compared using different statistical tools. Main outcome measures were DC eosinophil, Absolute Eosinophil Count (AEC), serum IgE, Total Symptom Score, Aerijs Quality of Life Questionnaire score, and Global efficacy score.

RESULTS: Rupatadine significantly improved patients' clinical condition including symptom score from baseline to day 28. In rupatadine group, there was 27.9 percent decrease ($P=0.027$) in DC eosinophil, 35.6 percent decrease ($P=0.036$) in AEC, 15.3 percent decrease ($P=0.024$) in serum IgE, 28.2 percent decrease ($P=0.02$) in Total Symptom Scoring, and 27.3 percent decrease ($P=0.006$) in Aerijs Quality of Life Questionnaire score. Global efficacy score of rupatadine was found to be significantly greater ($P=0.009$) than levocetirizine. The overall incidence of adverse drug reactions was also found to be less in rupatadine group.

CONCLUSION: Rupatadine is a better choice in CIU in comparison to levocetirizine due to better efficacy and safety profile.

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[Clin Exp Dermatol](#). 2011 Aug;36(6): 613-6. doi: 10.1111/j.1365-2230.2011.04061.x. Epub 2011 Apr 20.

[Comparison of clobetasol propionate cream plus coal tar vs. topical psoralen and solar ultraviolet A therapy in palmoplantar psoriasis.](#)

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AIM: Palmoplantar psoriasis (PPP) produces significant morbidity and requires prompt treatment. Topical agents form the mainstay of therapy. We compared the efficacy and side-effect profile of a steroid/coal-tar combination with topical psoralen and solar ultraviolet A (PUVA_{sol}) in PPP.

METHODS: In total, 52 patients with PPP were randomized to receive either a combination of clobetasol propionate cream and coal tar weeks. daily (group 1) or topical PUVA_{sol} on alternate days (group 2) for 16 weeks. Response was assessed as change in Psoriasis Activity and Severity Index (PASI) and Patient Global Assessment (PGA).

RESULTS: Of the 52 patients, 43 completed the treatment phase. There was a reduction in PASI for the palms and soles in both treatment groups throughout the treatment period until week 16. There was a greater reduction in PASI in palmar psoriasis with topical PUVA_{sol}, and a greater reduction in psoriasis of the soles with the steroid/coal-tar combination. In both groups, patients perceived 'good improvement'. Improvement or cure in palmar lesions was observed in 90% of cases in the topical steroid/coal-tar group and in 75% of cases in the topical PUVA_{sol} group; for the soles, these figures were 76% and 79%, respectively. No adverse effects were experienced with the steroid/coal-tar combination, whereas for the topical PUVA_{sol}, phototoxicity occurred in 22% of cases.

CONCLUSION:

Both treatments had comparable efficacy. In both groups, patients experienced 'good improvement' after 16 weeks of therapy.



Surgical problems

[Burns](#). 2012 May;38(3): 396-403. Epub 2011 Nov 17.

[Moist occlusive dressing \(Aquacel\(®\) Ag\) versus moist open dressing \(MEBO\(®\)\) in the management of partial-thickness facial burns: a comparative study in Ain Shams University.](#)

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INTRODUCTION: The face is the central point of the physical features; it transmits expressions and emotions, communicates feelings and allows for individual identity. Facial burns are very common and are devastating to the affected patient and results into numerous physical, emotional and psychosocial sequels. Partial thickness facial burns are very common especially among children. **This study compares the effect of standard moist open technique management and a moist closed technique for partial thickness burns of the face.**

PATIENTS AND METHODS: Patients with **partial-thickness facial burns** admitted in the burn unit, Ain Shams University, Cairo, Egypt in the period from April 2009 to December 2009 were included in this study. **They were divided into two groups to receive either open treatment with MEBO(®) (n=20) or coverage with Aquacel(®) Ag (n=20).** Demographics (age, gender, ethnicity, TBSA, burn areas), length of hospital stay (LOS), rate of infections, time to total healing, frequency of dressing changes, pain, cost benefit and patient discomfort were compared between the two groups. **The long-term outcome (incidence of hypertrophic scarring) was assessed for up to 6 months follow-up period.**

RESULTS: There were no significant differences in demographics between the two groups. In the group treated with the Aquacel(®) Ag, the mean time for re-epithelialization was 10.5 days, while it was 12.4 days in the MEBO(®) group ($p < 0.05$). Frequency of changes, pain and patient discomfort were less with Aquacel(®) Ag. Cost was of no significant difference between the two groups. **Scar quality improved in the Aquacel(®) Ag treatment group.** Three and 6 months follow-up was done and long-term outcomes were recorded in both groups.

CONCLUSION: Moist occlusive dressing (Aquacel(®) Ag) significantly improves the management and healing rate of partial thickness facial burns with better long-term outcome compared to moist open dressing (MEBO(®)).

[Burns](#). 2011 Sep;37(6): 925-9. Epub 2011 Jul 1.

[A prospective randomized controlled trial comparing negative pressure dressing and conventional dressing methods on split-thickness skin grafts in burned patients.](#)

[Petkar KS](#), [Dhanraj P](#), [Kingsly PM](#), [Sreekar H](#), [Lakshmanarao A](#), [Lamba S](#), [Shetty R](#), [Zachariah JR](#).

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INTRODUCTION: Split-thickness skin grafting (SSG) is a technique used extensively in the care of burn patients and is fraught with suboptimal graft take when there is a less-than-ideal graft bed and/or grafting conditions. **The technique of Negative Pressure Dressing (NPD), initially used for better wound healing has been tried on skin-grafts and has shown to increase the graft take rates.** However, comparative studies between the conventional dressing

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and vacuum assisted closure on skin grafts in burn patients are unavailable. The present study was undertaken to find out if NPD improves graft take as compared to conventional dressing in burns patients.

MATERIALS AND METHODS: Consecutive burn patients undergoing split-skin grafting were randomized to receive either a conventional dressing consisting of Vaseline gauze and cotton pads or to have a NPD of 80 mm Hg for four days over the freshly laid SSG. The results in terms of amount of graft take, duration of dressings for the grafted area and the cost of treatment of wound were compared between the two groups.

RESULTS: A total of 40 split-skin grafts were put on 30 patients. The grafted wounds included acute and chronic burns wounds and surgically created raw areas during burn reconstruction. **Twenty-one of them received NPD and 19 served as controls.** Patient profiles and average size of the grafts were comparable between the two groups. The vacuum closure assembly was well tolerated by all patients. Final graft take at nine days in the study group ranged from 90 to 100 per cent with an average of 96.7 per cent (SD: 3.55). The control group showed a graft take ranging between 70 and 100 percent with an average graft take of 87.5 percent (SD: 8.73). Mean duration of continued dressings on the grafted area was 8 days in cases (SD: 1.48) and 11 days in controls (SD: 2.2) after surgery. Each of these differences was found to be statistically significant ($p < 0.001$).

CONCLUSION: Negative pressure dressing improves graft take in burns patients and can particularly be considered when wound bed and grafting conditions seem less-than-ideal. The negative pressure can also be effectively assembled using locally available materials thus significantly reducing the cost of treatment.

[Saudi J Gastroenterol](#). 2011 Jul-Aug;17(4): 236-40.

[Laparoscopic versus open appendectomy: a comparison of primary outcome measures.](#)

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BACKGROUND/AIM: The aim of the study was to compare laparoscopic and open appendectomy (OA) in terms of primary outcome measures. Study design: A randomized controlled trial. Place and duration of the study: Khyber Teaching Hospital, Peshawar, Pakistan, February 2008 to December 2009.

PATIENTS AND METHODS: A total of 160 patients were divided into two groups, A and B. Group A patients were subjected to laparoscopic appendectomy (LA), whereas Group B patients were subjected to OA. Data regarding age, gender, and primary outcome measures, such as hospital stay, operative duration, and postoperative complication, were recorded and analyzed. Percentages were calculated for categorical data, whereas numerical data were represented as mean \pm SD. Chi-square test and t test were used to compare categorical and numerical variables, respectively. Probability ≤ 0.05 ($P \leq 0.05$) was considered significant.

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RESULTS: After randomization, **72 patients in group A and 75 patients in group B were analyzed.** The mean age of patients in groups A and B was 23.09 ± 8.51 and 23.12 ± 10.42 years, respectively, ($P = 0.981$). The mean hospital stay was 1.52 ± 0.76 days in group A and 1.70 ± 1.06 days in group B ($P = 0.294$). The mean operative duration in group A and B were 47.54 ± 12.82 min and 31.36 ± 11.43 min, respectively ($P < 0.001$). **Pain (overall level) was significantly less in group A compared with group B ($P = 0.004$).** The two groups were comparable in terms of other postoperative complications, such as hematoma ($P = 0.87$), paralytic ileus ($P = 0.086$), urinary retention ($P = 0.504$), and wound infection ($P = 0.134$).

CONCLUSION: LA is an equivalent procedure and not superior to OA in terms of primary outcome measures.

[J Oral Maxillofac Surg.](#) 2011 Jul;69(7): 1995-2000. Epub 2011 Jan 26.

Prospective randomized clinical trial comparing bite force in 2-mm locking plates versus 2-mm standard plates in treatment of mandibular fractures.

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PURPOSE: To compare the efficacy of the 2-mm locking miniplates to 2-mm standard miniplates in the osteosynthesis of mandibular fractures on the basis of clinical parameters and bite force recording.

PATIENTS AND METHODS: A prospective randomized clinical trial was conducted at the Faculty of Dental Science, CSMMU (formerly King Georges Medical College), Lucknow, India, from January 1, 2007, to January 31, 2008, to treat consecutive mandible fractures. The patients were randomly divided into 2 groups. The patients underwent osteosynthesis--group 1 with Synthes 2-mm locking titanium miniplates and group 2 with Synthes 2-mm nonlocking titanium miniplates. The cause of trauma, the number of days from injury to surgery, average age, gender, and site distribution were all reviewed. The assessment of the patients was done at 1, 3, and 6 weeks and 3 months using the clinical parameters and bite force recording.

RESULTS: **A total of 20 patients with 32 fractures met the inclusion criteria. In our study, a statistically significant difference was not found in the clinical parameters such as pain, swelling, infection, paresthesia, hardware failure, and mobility between the fracture segments.** A statistically significant difference was found between the change in bite force from the previous follow-up visit in groups 1 and 2. From 1 week to 3 months, the change in the incisor bite force was significantly greater for group 1 than for group 2. At 6 weeks and 3 months, the change in right molar bite force from the previous follow-up visit was significantly greater for group 1 than for group 2. At the 1-, 3-, 6-week and 3-month follow-up visits, the change in left molar bite force from the previous follow-up visit was significantly greater for group 1 than for group 2.

CONCLUSION: These findings show that the use of locking miniplates plate in mandibular fracture was efficacious enough to bear the masticatory loads during osteosynthesis of the

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fracture. The locking miniplates provide the advantage of a greater bite force, with clinical results almost similar to those seen with nonlocking miniplate osteosynthesis.

[BJU Int.](#) 2012 Jan;109(1): 104-8. doi: 10.1111/j.1464-410X.2011.10259.x. Epub 2011 May 31.
[Evaluation of the safety and efficiency of the dorsal slit and sleeve methods of male circumcision provided by physicians and clinical officers in Rakai, Uganda.](#)

[Buwembo DR](#), [Musoke R](#), [Kigozi G](#), [Ssempijja V](#), [Serwadda D](#), [Makumbi F](#), [Watya S](#), [Namuguzi D](#), [Nalugoda F](#), [Kiwanuka N](#), [Sewankambo NK](#), [Wabwire-Mangen F](#), [Kiggundu V](#), [Wawer MJ](#), [Gray RH](#).

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OBJECTIVE: To assess the safety and efficiency of the dorsal slit and sleeve male circumcision (MC) procedures performed by physicians and clinical officers (COs).

PATIENTS AND METHODS: We evaluated the time required for the MC procedure (efficiency) and moderate/severe adverse events (AEs) for MC (safety) by trained physicians and COs using the sleeve and dorsal slit MC methods in a service programme. Univariate and multiple regressions with robust variance estimation were used to assess factors associated with operative duration (linear) and AEs (logistic).

RESULTS: Six physicians and eight COs conducted 1934 and 3218 MCs, respectively; there were 2471 dorsal slit and 2681 sleeve MC procedures. The overall mean operative duration was 33 min for newly trained providers, which decreased to ≈ 20 min after ≈ 100 MCs. The adjusted mean operative duration for dorsal slit MC was significantly shorter than that for the sleeve MC method ($\Delta - 2.7$ min, $P < 0.001$). The operative duration was longer for COs than physicians for the sleeve procedure, but not the dorsal slit procedure; however this difference reduced with increasing numbers of MCs completed. The unadjusted AE rates were 0.6% for dorsal slit MC and 1.4% for the sleeve method ($P = 0.006$) and 1.5% for physicians and 0.68% for COs ($P = 0.003$); however, there were no significant differences after multivariate adjustment. Use of bipolar cautery significantly reduced operative duration ($\Delta - 4.0$ min, $P = 0.008$), but was associated with higher AE rates (adjusted odds ratio 2.13, 95% confidence interval 1.26-3.61, $P = 0.005$).

CONCLUSION: The dorsal slit MC method is faster than sleeve resection, and can be safely performed by non-physicians; however, use of bipolar cautery may be inadvisable in this setting.

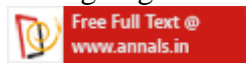
[Ann Card Anaesth.](#) 2012 Jan-Mar;15(1): 26-31.
[Utility of Sonoclot analysis and tranexamic acid in tetralogy of Fallot patients undergoing intracardiac repair.](#)

[Aggarwal V](#), [Kapoor PM](#), [Choudhury M](#), [Kiran U](#), [Chowdhury U](#).

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Sonoclot analysis is a point of care test to monitor the coagulation process, presenting a comprehensive evaluation of the clot formation and retraction as well as platelet function. This randomized double-blinded study was designed to investigate the utility of Sonoclot analysis in monitoring the coagulation profile as also the antifibrinolytic effects of tranexamic acid administered in patients with tetralogy of Fallot undergoing intracardiac repair. **Eighty of a total 94 patients were randomly divided into two groups of 40 each. In the study group, TA was administered thrice at a dosage of 10 mg/kg, i.e. before CPB, on CPB and after CPB, whereas in the control group, placebo was administered at the same time intervals.** Sonoclot analysis and D-dimer measurement were performed at baseline and following heparin neutralisation. An additional variable, DR₁₅ (diminishing rate of clot strength at 15 min postmaximal clot strength), was calculated from the Sonoclot graph and was compared with d-dimer levels as a measure of fibrinolysis. The three Sonoclot variables, i.e. activated clotting time, clot rate and platelet function, were deranged at baseline in all the patients. Post-CPB, the change in these variables was not significant. ACT, clot rate and platelet function showed no significant ($P > 0.05$) difference in both the groups at both the time intervals. DR₁₅ and d-dimer values were comparable at baseline in both the groups. However, a significant ($P < 0.05$) difference was seen in these variables in the control group as compared with the TA group following heparin neutralisation. To conclude, Sonoclot analysis is a useful, point of care method for the monitoring of coagulation and fibrinolysis in patients with tetralogy of Fallot undergoing intracardiac repair.



[Anaesth Intensive Care](#). 2012 Jan;40(1): 114-9.

[Comparison of haemodynamic responses following different concentrations of adrenaline with and without lignocaine for surgical field infiltration during cleft lip and cleft palate surgery in children.](#)

[Muthukumar M](#), [Arya VK](#), [Mathew PJ](#), [Sharma RK](#).

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Surgical field infiltration with adrenaline is common practice for quality surgical field during cleft lip and palate repair in children. Intravascular absorption of adrenaline infiltration often leads to adverse haemodynamic responses. In this prospective, **double-blinded, randomised study the haemodynamic effects, quality of surgical field and postoperative analgesia following surgical field infiltration with different concentrations of adrenaline with and without lignocaine were compared in 100 American Society of Anesthesiologists physical status I children aged six months to seven years undergoing cleft lip/palate surgery. A standard anaesthesia protocol was used and they were randomised into four groups based on solution for infiltration: adrenaline 1:400,000 (group A), adrenaline 1:200,000 (group B), lignocaine + adrenaline 1:400,000 (group C) and lignocaine + adrenaline 1:200,000 (group D).** Statistically significant tachycardia and hypertension occurred only in group B as compared to other groups ($P < 0.001$). The peak changes in heart rate and mean arterial pressure following infiltration occurred at 4.3 ± 2.4 , 3.8 ± 1.5 , 5.7 ± 3.2 and 5.9 ± 4.9 minutes in groups

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A, B, C and D respectively. Surgical field was comparable among all groups. **Postoperative pain scores and rescue analgesic requirements were lesser in the groups where lignocaine was added to the infiltrating solution ($P < 0.05$). We found that 1:400000 or 1:200000 adrenaline with lignocaine 0.5 to 0.7% is most suitable for infiltration in terms of stable haemodynamics, quality of surgical field and good postoperative analgesia in children.**

[J Orthop Surg Res.](#) 2012 Feb 15;7: 6.

[A prospective randomised, controlled clinical trial comparing medial and lateral entry pinning with lateral entry pinning for percutaneous fixation of displaced extension type supracondylar fractures of the humerus in children.](#)

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OBJECTIVE: To compare the efficacy of medial and lateral entry pinning with lateral entry pinning for percutaneous fixation of displaced (Gartland type II and type III) extension type supracondylar fractures of the humerus in children.

METHODS: The study was a single center, prospective, randomized controlled clinical trial. Between October 2007 and September 2010, 160 patients who satisfy the inclusion and exclusion criterias were enrolled in the study, with 80 patients in each group. All the percutaneous pinning was done according to a uniform standardized technique. **The patients were re-evaluated as outpatients at three weeks, six weeks and three months after the surgery.** At three months follow-up visit, following informations were recorded as outcome measures: (i) Carrying angle (deg) (ii) passive range of elbow motion (deg) (iii) Flynn's criteria for grading, based on the loss of carrying angle and loss of total range of elbow motion. (iv) Baumann angle (deg) (v) Change in Baumann angle (deg) between the Intraoperative radiographs after the surgery and radiographs at three months follow-up visit (vi) loss of reduction grading, based on the change in the Baumann angle.

RESULTS: There were no significant differences between the two groups with regard to base-line characteristics, withdrawals and complication rate. At three months follow-up visit, patients were evaluated by recording the various outcome measures. **There were no significant differences between the two groups with regard to the various outcome measures such as carrying angle, passive range of elbow motion, Flynn grading, Baumann angle, change in the Baumann angle and loss of reduction grading.**

CONCLUSIONS: If a uniform standardized operative technique is followed in each method, then the result of both the percutaneous fixation methods will be same in terms of safety and efficacy.



Tetanus

[Trans R Soc Trop Med Hyg.](#) 2012 Feb;106(2): 90-7. Epub 2011 Dec 22.

[Semi-recumbent body position fails to prevent healthcare-associated pneumonia in Vietnamese patients with severe tetanus.](#)

[Loan HT, Parry J, Nga NT, Yen LM, Binh NT, Thuy TT, Duong NM, Campbell JI, Thwaites L, Farrar JJ, Parry CM.](#)

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Healthcare-associated pneumonia (HCAP) is a common complication in patients with severe tetanus. Nursing tetanus patients in a semi-recumbent body position could reduce the incidence of HCAP. **In a randomised controlled trial we compared the occurrence of HCAP in patients with severe tetanus nursed in a semi-recumbent (30°) or supine position.** A total of 229 adults and children (aged ≥ 1 year) with severe tetanus admitted to hospital in Vietnam, were randomly assigned to a supine (n=112) or semi-recumbent (n=117) position. For patients maintaining their assigned positions and in hospital for >48h there was no significant difference between the two groups in the frequency of clinically suspected pneumonia [22/106 (20.8%) vs 26/104 (25.0%); p=0.464], pneumonia rate/1000 intensive care unit days (13.9 vs 14.6; p=0.48) and pneumonia rate/1000 ventilated days (39.2 vs 38.1; p=0.72). Mortality in the supine patients was 11/112 (9.8%) compared with 17/117 (14.5%) in the semi-recumbent patients (p=0.277). The overall complication rate [57/112 (50.9%) vs 76/117 (65.0%); p=0.03] and need for tracheostomy [51/112 (45.5%) vs 69/117 (58.9%); p=0.04] was greater in semi-recumbent patients. **Semi-recumbent body positioning did not prevent the occurrence of HCAP in severe tetanus patients.**



Tuberculosis

[N Engl J Med.](#) 2011 Jul 7;365(1): 21-31.

[Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children.](#)

[Madhi SA, Nachman S, Violari A, Kim S, Cotton MF, Bobat R, Jean-Philippe P, McSherry G, Mitchell C; P1041 Study Team.](#)

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BACKGROUND: The dual epidemic of human immunodeficiency virus (HIV) and tuberculosis is a major cause of sickness and death in sub-Saharan Africa. **We conducted a double-blind, randomized, placebo-controlled trial of preexposure isoniazid prophylaxis**

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against tuberculosis in HIV-infected children and uninfected children exposed to HIV during the perinatal period.

METHODS: We randomly assigned 548 HIV-infected and 804 HIV-uninfected infants (91 to 120 days of age) to isoniazid (10 to 20 mg per kilogram of body weight per day) or matching placebo for 96 weeks. All patients received bacille Calmette-Guérin (BCG) vaccination against tuberculosis within 30 days after birth. HIV-infected children had access to antiretroviral therapy. **The primary outcome measures were tuberculosis disease and death in HIV-infected children and latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children within 96 to 108 weeks after randomization.**

RESULTS: Antiretroviral therapy was initiated in 98.9% of HIV-infected children during the study. **Among HIV-infected children, protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group and 53 (19.3%) in the placebo group (P=0.93). Among HIV-uninfected children, there was no significant difference in the combined incidence of tuberculosis infection, tuberculosis disease, or death between the isoniazid group (39 children, 10%) and the placebo group (45 children, 11%; P=0.44).** The rate of tuberculosis was 121 cases per 1000 child-years (95% confidence interval [CI], 95 to 153) among HIV-infected children as compared with 41 per 1000 child-years (95% CI, 31 to 52) among HIV-uninfected children. There were no significant differences in clinical or severe laboratory toxic effects between treatment groups.

CONCLUSIONS: **Primary isoniazid prophylaxis did not improve tuberculosis-disease-free survival among HIV-infected children or tuberculosis-infection-free survival among HIV-uninfected children immunized with BCG vaccine.** Despite access to antiretroviral therapy, the burden of tuberculosis remained high among HIV-infected children. (Funded by the National Institutes of Health and Secure the Future; ClinicalTrials.gov number, NCT00080119.).

Comment

This is an important study. The results are different from those of a 2007 RCT (Zar HJ BMJ 2007;334: 136-143) that showed a 54% reduction in mortality and a 79% reduction in Tb infection in HIV-infected children given prophylaxis. The authors of the 2007 study speculated that close contact screening and INAH prophylaxis in this years study might have resulted in ultimately no effect of routine prophylaxis on risk of Tb. They point out that such close contact screening is difficult to achieve in remote areas, and that in some populations there is still a role for prophylaxis in selected patients. Whether a significant proportion of the children in the 2007 study, which showed a large effect from INAH prophylaxis were already infected with Tb was also speculated upon by the authors of this year's study (<http://www.nejm.org/doi/full/10.1056/NEJMc1109603>)



[Int J Tuberc Lung Dis.](#) 2012 Jan;16(1): 70-5.

[Intervention to increase detection of childhood tuberculosis in Bangladesh.](#)

[Talukder K](#), [Salim MA](#), [Jerin I](#), [Sharmin F](#), [Talukder MQ](#), [Marais BJ](#), [Nandi P](#), [Cooreman E](#), [Rahman MA](#).

Randomised trials in child health in developing countries 2011-12

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BACKGROUND: Despite a well-functioning adult tuberculosis (TB) control programme, children with TB remain grossly under-detected in Bangladesh. It is conservatively estimated that annually around 21,000 children with TB go undetected, due to an almost exclusive focus on sputum smear-positive TB and the absence of training or guidelines in paediatric TB.

OBJECTIVE: To double child TB detection by increasing general awareness and training of health care workers at microscopy centres supported by the Damien Foundation (DF) Bangladesh.

METHODS: A cluster-randomised trial was carried out with provision of child TB guidelines, training and logistics support to staff of 18 microscopy centres, while 18 non-adjacent microscopy centres continued their usual practice and served as controls. Paediatric data on TB suspect referral and case detection were collected at baseline and during the intervention at both control and intervention sites.

RESULTS: Child TB case detection increased in both intervention and control microscopy centres, but the increase was three times the baseline in the intervention centres (from 3.8% to 12%) in comparison to less than double the baseline in the control centres (from 4.3% to 7%, $P = 0.001$).

CONCLUSION: Simple guidelines and training on child TB case detection, together with basic logistics support, can be integrated into the existing National TB Control Programme and improve service delivery to children in TB-endemic areas.

[Int J Tuberc Lung Dis.](#) 2012 Feb;16(2): 185-91.

[Tuberculosis case finding for vaccine trials in young children in high-incidence settings: a randomised trial.](#)

[Moyo S, Verver S, Hawkrigde A, Geiter L, Hatherill M, Workman L, Ontong C, Msemburi W, Tameris M, Geldenhuys H, Mulenga H, Snowden MA, Hanekom WA, Hussey G, Mahomed H; South African Tuberculosis Vaccine Initiative Neonatal Study Team.](#)

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SETTING: A high tuberculosis (TB) burden rural area in South Africa.

OBJECTIVE: To compare TB case yield and disease profile among bacille Calmette-Guérin (BCG) vaccinated children using two case-finding strategies from birth until 2 years of age.

DESIGN: BCG-vaccinated infants were enrolled within 2 weeks of birth and randomised to 3-monthly home visits for questionnaire-based TB screening plus record surveillance of TB registers, hospital admission and X-ray lists at health facilities for TB suspects and

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cases (Group 1), or record surveillance (as above) only (Group 2). Both groups received a close-out visit after 2 years. Participants were evaluated for suspected TB disease using standardised investigations.

RESULTS: A total of 4786 infants were enrolled: 2392 were randomised to Group 1 and 2394 to Group 2. **The case-finding rate was significantly greater in Group 1 (2.2/100 py) than in Group 2 (0.8/100 py), with a case-finding rate ratio of 2.6 (95%CI 1.8-4.0, P < 0.001).** **Although the proportion of cases with bacteriological confirmation was lower in Group 1,** this difference did not reach statistical significance. There was also no significant difference in the proportions with TB symptoms and signs.

CONCLUSION: Home visits combined with record surveillance detected significantly more cases than record surveillance with a single study-end visit. The TB case profile did not differ significantly between the two groups.

[Int J Tuberc Lung Dis.](#) 2012 Feb;16(2): 192-5.

[High prevalence of drug resistance amongst HIV-exposed and -infected children in a tuberculosis prevention trial.](#)

[Hesseling AC, Kim S, Madhi S, Nachman S, Schaaf HS, Violari A, Victor TC, McSherry G, Mitchell C, Cotton MF; IMPAACT P1041 Team.](#)

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An emergence of drug-resistant tuberculosis (DR-TB) in settings affected by human immunodeficiency virus (HIV) and tuberculosis (TB) has been observed. We investigated the prevalence of DR-TB in P1041, a multicentered, randomised, double-blind trial which compared the administration of isoniazid (INH) to placebo, in HIV-exposed, non-infected and -infected African infants in the absence of any documented TB exposure. The prevalence of multidrug-resistant TB (MDR-TB) was 22.2% (95%CI 8.5-45.8) and INH monoresistance 5.6% (95%CI 0.1-27.6) among culture-confirmed cases, with all MDR-TB occurring in a single site. There was no association between INH treatment or placebo group, or between HIV infection status, and DR-TB prevalence. There was a high prevalence of DR-TB among HIV-exposed and -infected children. Surveillance of DR-TB among children in high-burden TB-HIV settings should be routine.



[J Nutrition](#) 2011 Oct 31;10: 120.

[A randomized trial of multivitamin supplementation in children with tuberculosis in Tanzania.](#)

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[Mehta S](#), [Mugusi FM](#), [Bosch RJ](#), [Aboud S](#), [Chatterjee A](#), [Finkelstein JL](#), [Fataki M](#), [Kisenge R](#), [Fawzi WW](#).

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BACKGROUND: Children with tuberculosis often have underlying nutritional deficiencies. Multivitamin supplementation has been proposed as a means to enhance the health of these children; however, the efficacy of such an intervention has not been examined adequately.

METHODS: 255 children, aged six weeks to five years, with tuberculosis were randomized to receive either a daily multivitamin supplement or a placebo in the first eight weeks of anti-tuberculous therapy in Tanzania. This was only 64% of the proposed sample size as the trial had to be terminated prematurely due to funding constraints. They were followed up for the duration of supplementation through clinic and home visits to assess anthropometric indices and laboratory parameters, including hemoglobin and albumin.

RESULTS: There was no significant effect of multivitamin supplementation on the primary endpoint of the trial: weight gain after eight weeks. However, significant differences in weight gain were observed among children aged six weeks to six months in subgroup analyses (n=22; 1.08 kg, compared to 0.46 kg in the placebo group; 95% CI=0.12, 1.10; p=0.01). Supplementation resulted in significant improvement in hemoglobin levels at the end of follow-up in children of all age groups; the median increase in children receiving multivitamins was 1.0 g/dL, compared to 0.4 g/dL in children receiving placebo (p<0.01). HIV-infected children between six months and three years of age had a significantly higher gain in height if they received multivitamins (n=48; 2 cm, compared to 1 cm in the placebo group; 95% CI=0.20, 1.70; p=0.01; p for interaction by age group=0.01).

CONCLUSIONS: Multivitamin supplementation for a short duration of eight weeks improved the hematological profile of children with tuberculosis, though it didn't have any effect on weight gain, the primary outcome of the trial. Larger studies with a longer period of supplementation are needed to confirm these findings and assess the effect of multivitamins on clinical outcomes including treatment success and growth failure. [CLINICALTRIALS.GOV](http://www.clinicaltrials.gov) IDENTIFIER: NCT00145184.



[Cochrane Database Syst Rev](#). 2011 Nov 9;(11): CD006086.

[Nutritional supplements for people being treated for active tuberculosis.](#)

[Sinclair D](#), [Abba K](#), [Grobler L](#), [Sudarsanam TD](#).

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BACKGROUND: Tuberculosis and malnutrition are linked in a complex relationship. The infection may cause undernutrition through increased metabolic demands and decreased intake, and nutritional deficiencies may worsen the disease, or delay recovery by depressing important immune functions. At present, there are no evidence-based nutritional guidance for adults and children being treated for tuberculosis.

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OBJECTIVES: To assess the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on tuberculosis treatment outcomes and recovery in people on antituberculous drug therapy for active tuberculosis.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE, LILACS, mRCT, and the Indian Journal of Tuberculosis to July 2011, and checked the reference lists of all included studies.

SELECTION CRITERIA: Randomized controlled trials comparing any oral nutritional supplement given for at least four weeks with no nutritional intervention, placebo, or dietary advice only for people being treated for active tuberculosis.

DATA COLLECTION AND ANALYSIS: Two authors independently selected trials, extracted data, and assessed the risk of bias. Results are presented as risk ratios (RR) for dichotomous variables, and mean differences (MD) for continuous variables, with 95% confidence intervals (CI). Where appropriate, data from trials with similar interventions and outcomes have been pooled. The quality of evidence was assessed using the GRADE methods.

MAIN RESULTS: Twenty-three trials, with 6842 participants, were included. **Macronutrient supplementation** Five trials assessed the provision of free food, or high energy supplements, although none were shown to provide a total daily kilocalorie intake above the current daily recommended intake for the non-infected population. The available trials were too small to reliably prove or exclude clinically important benefits on mortality, cure, or treatment completion. One small trial from India did find a statistically significant benefit on treatment completion, and clearance of the bacteria from the sputum, but these findings have not been confirmed in larger trials elsewhere (VERY LOW quality evidence). **The provision of free food or high-energy nutritional products probably does produce a modest increase in weight gain during treatment for active tuberculosis** (MODERATE quality evidence). Two small studies provide some evidence that physical function and quality of life may also be improved but the trials were too small to have much confidence in the result (LOW quality evidence). These effects were not seen in the one trial which included only human immunodeficiency virus (HIV)-positive patients. **Micronutrient supplementation** Five trials assessed multi-micronutrient supplementation in doses up to ten times the dietary reference intake, and 12 trials assessed single or dual micronutrient supplementation. There is insufficient evidence to judge whether multi-micronutrients have a beneficial effect on mortality in HIV- negative patients with tuberculosis (VERY LOW quality evidence), but **the available studies show that multi-micronutrients probably have little or no effect on mortality in HIV-positive patients with tuberculosis** (MODERATE quality evidence). **No studies have assessed the effects of multi-micronutrients on cure, or treatment completion.** Multi-micronutrient supplements may have little or no effect on the proportion of tuberculosis patients remaining sputum positive during the first eight weeks (LOW quality evidence), and probably have no effect on weight gain during treatment (MODERATE quality evidence). No studies have assessed quality of life. **Plasma levels of vitamin A appear to increase following initiation of tuberculosis treatment regardless of supplementation. In contrast, plasma levels of zinc, vitamin D and E, and selenium may be improved by supplementation during the early stages of tuberculosis treatment, but a consistent benefit on tuberculosis treatment outcomes or nutritional recovery has not been demonstrated.**

AUTHORS' CONCLUSIONS: There is insufficient research to know whether routinely providing free food or energy supplements results in better tuberculosis treatment outcomes, or

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improved quality of life. Further trials, particularly from food insecure settings, should have adequate sample sizes to identify, or exclude, clinically important benefits. Although blood levels of some vitamins may be low in patients starting treatment for active tuberculosis, there is currently no reliable evidence that routinely supplementing at or above recommended daily amounts has clinical benefits.



[J Child Neurol](#). 2011 Aug;26(8): 956-62. Epub 2011 May 31.

[The role of aspirin in childhood tuberculous meningitis.](#)

[Schoeman JF](#), [Janse van Rensburg A](#), [Laubscher JA](#), [Springer P](#).

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Arterial stroke is the main cause of poor outcome in childhood tuberculous meningitis. Aspirin has an antithrombotic action at low dose and anti-ischemic and anti-inflammatory properties, which are dose-related. The aim of the study was to explore the possible benefits of aspirin in children with tuberculous meningitis. **A total of 146 consecutive children with a diagnosis of probable tuberculous meningitis were studied. Patients were randomized into 3 groups: (1) placebo group, (2) low-dose aspirin group, and (3) high-dose aspirin group.** Twenty-nine additional patients who received aspirin before admission were excluded from the randomized study, but continued on low-dose aspirin. **Aspirin, irrespective of dose, did not show any significant benefit regarding morbidity (hemiparesis and developmental outcome) and mortality.** Aspirin was well tolerated, but 1 death was probably related to aspirin. The fact that the outcome of the high-dose aspirin group compared favorably with the other treatment groups despite younger age and more severe neurological involvement at baseline needs further investigation.



Vaccines and immunization

Immunization coverage

[Eval Program Plann](#). 2011 Aug;34(3): 303-15. Epub 2010 Nov 13.

Evaluability Assessment of an immunization improvement strategy in rural Burkina Faso: intervention theory versus reality, information need and evaluations.

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An innovative immunization improvement strategy was proposed by the CRSN (Centre de Recherche en Santé de Nouna) to improve the low coverage rate for children aged 0-11 months in the health district of Nouna in Burkina Faso. This article reports on the Evaluability Assessment (EA) study that aimed to orient decisions for its evaluation in close relationship with the information needs of the stakeholders. Various methods were used, including document reviews, individual interviews, focus group discussions, meetings, literature reviews and site visits. A description of the intervention theory and philosophy is provided with its logic models and its reality documented. Lessons on the procedure include the importance of the position of the evaluability assessor, the value of replicating some steps of the assessment and the relationships between EA and process evaluation. The evaluability study concludes that the intervention had some evaluable components. To satisfy the stakeholders' needs, the initially planned community randomized controlled trial can be maintained and complemented with a process evaluation. There is a need to provide sufficient information on the cost of the intervention. This will inform decision makers on the possibility of replicating the intervention in other contexts.

BCG vaccine

[J Infect Dis.](#) 2011 Jul 15;204(2): 245-52.

[Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period?](#)

[Aaby P](#), [Roth A](#), [Ravn H](#), [Napirna BM](#), [Rodrigues A](#), [Lisse IM](#), [Stensballe L](#), [Diness BR](#), [Lausch KR](#), [Lund N](#), [Biering-Sørensen S](#), [Whittle H](#), [Benn CS](#).

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BACKGROUND: Observational studies have suggested that BCG may have nonspecific beneficial effects on survival. Low-birth-weight (LBW) children are not given BCG at birth in Guinea-Bissau; we conducted a randomized trial of BCG at birth (early BCG) vs delayed BCG.

METHODS: In the period 2004-2008 we recruited **2320 LBW children in Bissau**. The children were visited at home at 2, 6, and 12 months of age. With a pretrial infant mortality of 250 per 1000, we hypothesized a 25% reduction in infant mortality for LBW children.

RESULTS: Infant mortality was only 101 per 1000 during the trial. **In the primary analysis, infant mortality was reduced insignificantly by 17% (mortality rate ratio [MRR] = .83 [.63-1.08]).** In secondary analyses, early BCG vaccine was safe with an MRR of .49 (.21-1.15) after 3 days and .55 (.34-.89) after 4 weeks. **The reduction in neonatal mortality was mainly due to fewer cases of neonatal sepsis, respiratory infection, and fever. The impact of early BCG on infant mortality was marked for children weighing <1.5 kg (MRR = .43 [.21-.85]) who had lower coverage for diphtheria-tetanus-pertussis vaccinations.**

CONCLUSIONS: Though early BCG did not reduce infant mortality significantly, it may have a beneficial effect in the neonatal period. This could be important for public health because BCG is often delayed in low-income countries.

Comment

*This is an important study. Prior to this there were many cohort studies suggesting a non-specific beneficial effect of BCG on survival, but this is the first randomised trial evaluating this issue. The results have generated a great deal of discussion. The beneficial effect on neonatal mortality was predominantly in the first few days after BCG vaccination, a finding that was seen in cohort studies. While some have raised questions on the study process and methodology, there is no reason to believe there was bias in recruiting. The authors point to the biological plausibility of an early beneficial effect of BCG, particularly the rapid induction of innate immune responses by BCG, including expression of perforin and granulysin by cord blood T cells, and purified protein derivative stimulation of cord blood natural killer cells releases these cytokines, effects that may protect neonates from infection. See: [Non-specific effects of BCG?](#) *J Infect Dis.* 2012; [No evidence of bias in trial showing BCG reduces neonatal mortality.](#) *J Infect Dis.* 2012; [The nonspecific effects of vaccines and the expanded program on immunization.](#) [*J Infect Dis.* 2011]*

[Vaccine.](#) 2011 Jul 12;29(31): 4875-7. Epub 2011 May 25.

[Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: second report of the BCG-REVAC cluster-randomised trial.](#)

[Barreto ML](#), [Pereira SM](#), [Pilger D](#), [Cruz AA](#), [Cunha SS](#), [Sant'Anna C](#), [Ichihara MY](#), [Genser B](#), [Rodrigues LC](#).

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BCG revaccination is still used in some tuberculosis endemic countries. Until now, the little evidence available suggested that BCG revaccination confers very limited additional protection, although there was no information on whether protection depends on the setting and age of revaccination, or if protection increases with time since vaccination. Here we report on an extended follow up of the BCG-REVAC trial, a cluster randomised trial conducted in the Brazilian cities Salvador and Manaus including over 200,000 children aged 7-14 years aimed to evaluate the efficacy of BCG revaccination in children who had received neonatal BCG vaccination. With the extended follow-up (9 years) and the additional cases accrued we now have enough power to report vaccine efficacy separately for the two cities (with different distances from Equator and presumably different prevalence of non-tuberculosis mycobacteria), and by age at vaccination and clinical form. **The overall vaccine efficacy was 12% (-2 to 24%) as compared to 9% (-16 to 29%) for the 5-year follow up. Vaccine efficacy was higher in Salvador (19%, 3 to 33%) than in Manaus (1%, -27 to 27%) with the highest vaccine efficacy in children from Salvador aged <11 years at revaccination (33%, 3 to 54%).** The findings are in line with the hypothesis that BCG vaccination offers higher efficacy in low NTMb prevalence, and show that revaccination with BCG can offer weak protection in selected subgroups.

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[Int J Tuberc Lung Dis.](#) 2011 Sep;15(9): 1194-200, i.

[Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis.](#)

[Rabie H](#), [Violari A](#), [Duong T](#), [Madhi SA](#), [Josipovic D](#), [Innes S](#), [Dobbels E](#), [Lazarus E](#), [Panchia R](#), [Babiker AG](#), [Gibb DM](#), [Cotton MF](#); [CHER team](#).

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SETTING: Two centres in Soweto and Cape Town, South Africa.

OBJECTIVE: To assess the effects of timing of initiation of antiretroviral treatment (ART) and other factors on the risk of bacille Calmette-Guérin (BCG) related regional adenitis due to immune reconstitution inflammatory syndrome (BCG-IRIS) in human immunodeficiency virus (HIV) infected infants.

DESIGN: **HIV-infected infants aged 6-12 weeks with CD4 count $\geq 25\%$ enrolled in the Children with HIV Early Antiretroviral Therapy (CHER) Trial received early (before 12 weeks) or deferred (after immunological or clinical progression) ART; infants with CD4 count $< 25\%$ all received early ART. All received BCG vaccination after birth. Reactogenicity to BCG was assessed prospectively during routine study follow-up.**

RESULTS: Of 369 infants, 32 (8.7%) developed BCG-IRIS within 6 months of starting ART, 28 (88%) within 2 months after ART initiation. Of the 32 cases, 30 (93.8%) had HIV-1 RNA $> 750\ 000$ copies/ml at initiation. Incidence of BCG-IRIS was 10.9 and 54.3 per 100 person-years (py) among infants with CD4 count $\geq 25\%$ at enrolment receiving early (at median age 7.4 weeks) vs. deferred (23.2 weeks) ART, respectively (HR 0.24, 95% CI 0.11-0.53, $P < 0.001$). Infants with CD4 count $< 25\%$ receiving early ART had intermediate incidence (41.7/100 py). Low CD4 counts and high HIV-1 RNA at initiation were the strongest independent risk factors for BCG-IRIS.

CONCLUSIONS: **Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis.**



Cholera vaccine

[PLoS Negl Trop Dis.](#) 2011 Oct;5(10): e1289. Epub 2011 Oct 18.

[Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomized, controlled trial.](#)

[Sur D](#), [Kanungo S](#), [Sah B](#), [Manna B](#), [Ali M](#), [Paisley AM](#), [Niyogi SK](#), [Park JK](#), [Sarkar B](#), [Puri MK](#), [Kim DR](#), [Deen JL](#), [Holmgren J](#), [Carbis R](#), [Rao R](#), [Nguyen TV](#), [Han SH](#), [Attridge S](#), [Donner A](#), [Ganguly NK](#), [Bhattacharya SK](#), [Nair GB](#), [Clemens JD](#), [Lopez AL](#).

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BACKGROUND: Killed oral cholera vaccines (OCVs) have been licensed for use in developing countries, but protection conferred by licensed OCVs beyond two years of follow-up has not been demonstrated in randomized, clinical trials.

METHODS/PRINCIPAL FINDINGS: We conducted a cluster-randomized, placebo-controlled trial of a two-dose regimen of a low-cost killed whole cell OCV in residents 1 year of age and older living in 3,933 clusters in Kolkata, India. The primary endpoint was culture-proven *Vibrio cholerae* O1 diarrhea episodes severe enough to require treatment in a health care facility. **Of the 66,900 fully dosed individuals (31,932 vaccinees and 34,968 placebo recipients), 38 vaccinees and 128 placebo-recipients developed cholera during three years of follow-up (protective efficacy 66%; one-sided 95%CI lower bound = 53%, $p < 0.001$).** Vaccine protection during the third year of follow-up was 65% (one-sided 95%CI lower bound = 44%, $p < 0.001$). Significant protection was evident in the second year of follow-up in children vaccinated at ages 1-4 years and in the third year in older age groups.

CONCLUSIONS/SIGNIFICANCE: **The killed whole-cell OCV conferred significant protection that was evident in the second year of follow-up in young children and was sustained for at least three years in older age groups.** Continued follow-up will be important to establish the vaccine's duration of protection.



Comment

In Kolkata India, the inexpensive 2-dose killed whole-cell oral cholera vaccine provided significant protection for at least 3 years. One case of cholera was averted for every 404 people vaccinated. This vaccine costs \$1.85 per dose, much cheaper than the more widely used beta-subunit vaccine. Based on this study, the vaccine cost of averting a case of cholera is \$1500. The costs of vaccine administration are additional.

[Vaccine](#). 2011 Oct 26;29(46): 8285-92. Epub 2011 Sep 9.

[Safety and immunogenicity study of a killed bivalent \(O1 and O139\) whole-cell oral cholera vaccine Shanchol, in Bangladeshi adults and children as young as 1 year of age.](#)

[Saha A, Chowdhury MI, Khanam F, Bhuiyan MS, Chowdhury F, Khan AI, Khan IA, Clemens J, Ali M, Cravioto A, Qadri F.](#)

International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh.

BACKGROUND: Safety and immunogenicity study of an oral, killed, bivalent whole-cell, cholera vaccine, Shanchol was carried out in Bangladeshi participants. This study was conducted prior to initiating a feasibility study in Bangladesh.

STUDY PARTICIPANTS: The double-blind, randomized placebo controlled study was carried out in adults (18-45 years), toddlers (2-5 years) and younger children (12-23 months). Two doses of the vaccine/placebo were given 14 days apart.

RESULTS: Shanchol did not elicit major adverse events in any age group. Vibriocidal antibody responses in adults were 60% against *Vibrio cholerae* O1 Inaba, 72% against *V. cholerae* O1

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Ogawa and 21% against *V. cholerae* O139. In toddlers, responses were 84%, 75% and 64% and in younger children it was 74%, 78% and 54% against Inaba, Ogawa and O139 serotypes. The responses in all ages were higher in vaccinees compared to pre-immune titers or to responses in placebo recipients ($P < 0.001$). Plasma IgA antibody response to O1 Inaba LPS was seen in 61%, 73% and 45% of adults, toddlers and younger children, respectively.

CONCLUSIONS: The safety and immunogenicity data for Shanchol is promising and warrants future use in large scale trial in cholera endemic areas, high risk Bangladeshi population and in other countries in the region.

[PLoS One](#). 2011;6(7): e22971. Epub 2011 Jul 29.

[The role of vaccine coverage within social networks in cholera vaccine efficacy.](#)

[Root ED](#), [Giebultowicz S](#), [Ali M](#), [Yunus M](#), [Emch M](#).

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BACKGROUND: Traditional vaccine trial methods have an underlying assumption that the effect of a vaccine is the same throughout the trial area. There are, however, many spatial and behavioral factors that alter the rates of contact among infectious and susceptible individuals and result in different efficacies across a population. We reanalyzed data from a field trial in Bangladesh to ascertain whether there is evidence of indirect protection from cholera vaccines when vaccination rates are high in an individual's social network.

METHODS: We analyzed the first year of surveillance data from a placebo-controlled trial of B subunit-killed whole-cell and killed whole-cell-only oral cholera vaccines in children and adult women in Bangladesh. We calculated whether there was an inverse trend for the relation between the level of vaccine coverage in an individual's social network and the incidence of cholera in individual vaccine recipients or placebo recipients after controlling for potential confounding variables.

RESULTS: Using bari-level social network ties, we found incidence rates of cholera among placebo recipients were inversely related to levels of vaccine coverage (5.28 cases per 1000 in the lowest quintile vs 3.27 cases per 1000 in the highest quintile; $p = 0.037$ for trend).

Receipt of vaccine by an individual and the level of vaccine coverage of the individual's social network were independently related to a reduced risk of cholera.

CONCLUSIONS: Findings indicate that progressively higher levels of vaccine coverage in bari-level social networks can lead to increasing levels of indirect protection of non-vaccinated individuals and could also lead to progressively higher levels of total protection of vaccine recipients.



Diphtheria – Tetanus – Pertussus - Haemophilus influenzae vaccine

[Vaccine](#). 2011 Nov 8;29(48): 8773-9. Epub 2011 Oct 1.

[A phase III randomized, controlled study to assess and compare the immunogenicity and tolerability of single and multi-dose vials of DTwP-Hib, a fully liquid quadravalent vaccine and their comparison with TETRAct-Hib vaccine in Indian infants aged 6-14 weeks.](#)

[Sharma H](#), [Yadav S](#), [Patil V](#), [Chacko B](#), [Kapre S](#), [Jadhav S](#), [Ravetkar S](#), [Bahl S](#), [Parekh S](#), [Chakravarty A](#), [Ashtagi G](#), [Prasath A](#).

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Both WHO and IAP encourage using combination vaccines, wherever feasible. The phase III trial reported here was conducted to assess and compare the immunogenicity, tolerability and safety of two quadravalent vaccines, Quadrovax(®) (new vaccine), and TETRAct-Hib(®) (available in the market) in a multicentre study, in India. In all, 361 infants aged 6-8 weeks were enrolled, out of which 339 completed the study. The vaccination was done at 6-10-14 weeks following EPI/WHO recommended immunization schedule. Blood samples were collected prior to the administration of first dose and one month after the third dose. Postvaccination, geometric mean titres for each component did not differ significantly between the single dose vial and multi dose vial subgroups and among the two study groups. Adverse events observed were within the range quoted in literature. Quadrovax(®) vaccine manufactured by SIIIL was found to be safe, immunogenic and non-inferior to the comparator vaccine. The quadravalent vaccine is best recommended in the second year of life when children receive their booster dose at 15-18 months. It can be given to infants during primary immunization series at 6, 10 and 14 weeks of age when Hepatitis B vaccine is given in a separate arm or to infants at 10 weeks who receive the Hepatitis B vaccine separately following the 0, 6 and 14 weeks or 0, 1 and 6 months schedule.

Comment

Both Quadrovax and TETRAct-Hib are quadrivalent: Diphtheria, Tetanus, whole-cell Pertussis, and Hib conjugate (purified capsular polysaccharide with tetanus toxoid as a carrier protein) and aluminium phosphate as adjuvant. Pentavac (below) also has Hepatitis B vaccine included in the 5-antigen combination.

[Vaccine](#). 2012 Jan 11;30(3): 510-6. Epub 2011 Nov 26.

[Assessment of safety and immunogenicity of two different lots of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b vaccine manufactured using small and large scale manufacturing process.](#)

[Sharma HJ](#), [Patil VD](#), [Lalwani SK](#), [Manglani MV](#), [Ravichandran L](#), [Kapre SV](#), [Jadhav SS](#), [Parekh SS](#), [Ashtagi G](#), [Malshe N](#), [Palkar S](#), [Wade M](#), [Arunprasath TK](#), [Kumar D](#), [Shewale SD](#).
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BACKGROUND: Hib vaccine can be easily incorporated in EPI vaccination schedule as the immunization schedule of Hib is similar to that of DTP vaccine. To meet the global demand of Hib vaccine, SIIIL scaled up the Hib conjugate manufacturing process. This study was conducted in Indian infants to assess and compare the immunogenicity and safety of DTwP-HB+Hib (Pentavac®) vaccine of SIIIL manufactured at large scale with the 'same vaccine' manufactured at a smaller scale.

METHODS: 720 infants aged 6-8 weeks were randomized (2:1 ratio) to receive 0.5 ml of Pentavac® vaccine from two different lots one produced at scaled up process and the other at a small scale process. Serum samples obtained before and at one month after the 3rd dose of vaccine from both the groups were tested for IgG antibody response by ELISA and compared to assess non-inferiority.

RESULTS: Neither immunological interference nor increased reactogenicity was observed in either of the vaccine groups. All infants developed protective antibody titres to diphtheria, tetanus and Hib disease. For hepatitis B antigen, one child from each group remained seronegative. The response to pertussis was 88% in large scale group vis-à-vis 87% in small scale group. Non-inferiority was concluded for all five components of the vaccine. No serious adverse event was reported in the study.

CONCLUSIONS: The scale up vaccine achieved comparable response in terms of the safety and immunogenicity to small scale vaccine and therefore can be easily incorporated in the routine childhood vaccination programme.

Hepatitis A vaccine

[Vaccine](#). 2011 Nov 8;29(48): 8855-62. Epub 2011 Oct 6.

[Immunogenicity and tolerability of a paediatric presentation of a virosomal hepatitis A vaccine in Chilean children aged 1-16 years.](#)

[Abarca K](#), [Ibáñez I](#), [de la Fuente P](#), [Cerdeña L](#), [Bergeret J](#), [Frösner G](#), [Ibarra H](#).

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We assessed the immunogenicity of the paediatric dose of Epaxal® (0.25 mL) and the degrees of seroprotection achieved with the standard dose (0.5 mL) of Epaxal® or a dose of Havrix® Junior, in children in an open, randomised, controlled, multi-centre, parallel-group study conducted at 2 Chilean study centres. 360 healthy children and adolescents 12 months to <17 years of age not previously vaccinated against hepatitis A were enrolled. Subjects were randomised 2:2:1 to be vaccinated with either Epaxal® 0.25 mL [n=146], Epaxal® 0.5 mL [n=142] or Havrix® Junior [n=72] intramuscularly on Day 1 and after 6 months (26 weeks±14 days). Primary end point was the proportion of subjects seroprotected (anti-HAV antibody concentration ≥10 mIU/mL) in the ATP population at Month 1. All vaccines elicited high seroprotection rates at Month 1: 95.7% with Epaxal® 0.25 mL, 99.3% with Epaxal® 0.5 mL and 94.0% with Havrix® Junior. After the booster vaccination, all subjects demonstrated 100% seroprotection with all vaccines. Antibody concentrations were similarly high in all age groups. The paediatric presentation achieved antibody concentrations similar to those achieved with the 0.5 mL dose across the entire age range, and there were no differences across the range

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of body weights from 9.0 kg to 82.7 kg. All study vaccines were well tolerated and there were no AEs leading to discontinuation. Thus, the paediatric 0.25 mL dose of Epaxal(®) fulfilled the primary objective of showing non-inferiority to the adult 0.5 mL dose and to Havrix(®) Junior, in terms of seroprotection rates achieved. The results show the paediatric dose of Epaxal(®) to be an attractive option when conducting childhood-vaccination programmes.

[Vaccine](#). 2011 Nov 8;29(48): 9098-103. Epub 2011 Aug 27.

[Comparing live attenuated and inactivated hepatitis A vaccines: an immunogenicity study after one single dose.](#)

[Zheng H](#), [Chen Y](#), [Wang F](#), [Gong X](#), [Wu Z](#), [Miao N](#), [Zhang X](#), [Li H](#), [Chen C](#), [Hou X](#), [Cui F](#), [Wang H](#).

Chinese Center for Disease Control and Prevention, Beijing, China.

INTRODUCTION: While three types of hepatitis A vaccines are available in China, little data are available to compare them in terms of early antibody response. We conducted a trial to compare antibody response at 7, 14 and 28 days.

METHODS: We randomized primary school children in Gansu and Jilin provinces into four groups to receive either (1) Chinese live attenuated hepatitis A vaccine (H2 strain), (2) domestic inactivated hepatitis A vaccine (Healive(®)), (3) imported inactivated hepatitis A vaccine (Havrix(®)) or (4) hepatitis B vaccine (Control group). We compared groups at 7, 14 and 28 days in terms of proportion of sero-conversions (≥ 10 mIU/ml), and Geometric Mean Concentration (GMC) of antibodies measured with a Microparticle Enzyme Immunoassay (MEIA). We compared rates of self-reported adverse events following immunization (AEFI) in the first three days.

RESULTS: 204 children received the H2 vaccine, 208 received Healive(®), 214 received Havrix(®), and 215 received hepatitis B vaccine (no differences across groups in terms of age, sex, weight and height). At seven days, sero-conversion proportions were 25%, 35%, 27% and 2% ($p < 0.0001$) with GMC of 6 mIU/ml, 8 mIU/ml, 6 mIU/ml and 3 mIU/ml, respectively for the four groups. At 28 days, sero-conversion proportions were 98%, 100%, 93% and 3% ($p < 0.0001$) with GMC of 47 mIU/ml, 71 mIU/ml, 67 mIU/ml and 3 mIU/ml, respectively. AEFI were benign and did not differ across groups ($p = 0.94$).

CONCLUSIONS: While our study was not able to identify differences between Havrix(®), Healive(®) and H2 vaccine in terms of sero-conversion proportion and GMC between seven and 28 days, further studies should evaluate non-inferiority or equivalence of the Chinese vaccines, particularly with respect to the GMC concentration for the H2 vaccine since it could affect long-term protection.

HPV vaccine

[Jpn J Clin Oncol](#). 2012 Jan;42(1): 36-41.

[Safety and immunogenicity profile of human papillomavirus-16/18 AS04 adjuvant cervical cancer vaccine: a randomized controlled trial in healthy adolescent girls of Bangladesh.](#)

[Khatun S, Akram Hussain SM, Chowdhury S, Ferdous J, Hossain F, Begum SR, Jahan M, Tabassum S, Khatun S, Karim AB.](#)

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AIM: Bangladesh has the highest level of incidence and mortality rates due to cervical cancer among women. The prevalence of cervical cancer in Bangladeshi women is 25-30/100,000. Human papillomavirus is an important cause of cervical cancer. The study was conducted to assess the immunogenicity and safety profile of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccines in healthy Bangladeshi girls aged 9-13 years. Procedure This was a randomized (3:1) controlled trial with two parallel groups, the vaccine and control groups, that included 67 participants in Bangladesh. Subjects were given GlaxoSmithKline human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine (and controls no vaccine) at the first day of vaccination (Day 0), at 1- and 6-month schedule and followed up until 7 months. Blood samples were taken for human papillomavirus antibody at enrollment and 1 month post-schedule at Month 7 from both subjects and controls. Safety data were gathered throughout the study period.

RESULTS: Fifty subjects received vaccine at Day 0, 1 month and 6 months. All subjects were initially sero-negative in the vaccine group, and developed sero-conversion for human papillomavirus-16 and -18 antibodies except for one at Month 7. Seventeen controls did not receive vaccine. Clients were followed up for serious medically important events and blood samples were taken for human papillomavirus antibody detection at Day 0 and Month 7. **Sero-conversion was found in 97.5% of subjects and no sero-conversion was found in the controls.** Bivalent human papillomavirus vaccine was generally well tolerated, with no vaccine-related serious adverse experiences.

CONCLUSIONS: **The human papillomavirus-16/18 AS04-adjuvanted vaccine was generally well tolerated and highly immunogenic when administered to young adolescent females and could be a promising tool for the prevention and control of cervical cancer in Bangladesh.**



Influenza vaccine

[J Korean Med Sci. 2011 Nov;26\(11\): 1421-7. Epub 2011 Oct 27.](#)

[Safety and immunogenicity of a new trivalent inactivated split-virus influenza vaccine in healthy Korean children: a randomized, double-blinded, active-controlled, phase III study.](#)

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[Kang JH](#), [Oh CE](#), [Lee J](#), [Lee SY](#), [Cha SH](#), [Kim DS](#), [Kim HH](#), [Lee JH](#), [Kim JT](#), [Ma SH](#), [Hong YJ](#), [Cheong HJ](#), [Lee HJ](#).

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We report results of a randomized, double-blinded, active-controlled, phase III study conducted to evaluate the immunogenicity and safety of a new trivalent inactivated split-virus influenza vaccine (GC501) manufactured by the Green Cross Corporation in Korea. A total of 283 healthy children aged 6 months to < 18 yr were randomized to receive either GC501 or control. **Of the GC501 recipients, seroconversion occurred in 48.5% for A/H1N1, 67.7% for A/H3N2 and 52% for influenza B.** The proportion of subjects who had post-vaccination hemagglutination-inhibition titers of 1:40 or greater was 90.7% for A/H1N1, 86.8% for A/H3N2 and 82.4% for influenza B in the GC501 recipients. No serious adverse events related to vaccination, or withdrawals because of adverse events were reported. The majority of solicited adverse events were mild in intensity. GC501 vaccine has good tolerability and favorable immunogenicity in children aged 6 months to < 18 yr. The addition of one more brand of influenza vaccine may allow for better global accessibility of vaccine for epidemics or future pandemics.



Measles vaccine

[J Infect Dis.](#) 2011 Jul;204 Suppl 1: S149-57.

[Persistence of vaccine-induced measles antibody beyond age 12 months: a comparison of response to one and two doses of Edmonston-Zagreb measles vaccine among HIV-infected and uninfected children in Malawi.](#)

[Fowlkes A](#), [Witte D](#), [Beeler J](#), [Audet S](#), [Garcia P](#), [Curns A](#), [Yang C](#), [Fudzulani R](#), [Broadhead R](#), [Bellini WJ](#), [Cutts F](#), [Helfand RF](#).

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BACKGROUND: Previously, we demonstrated that measles antibody prevalence was lower at age 12 months among children infected with human immunodeficiency virus (HIV) than uninfected children following measles vaccination (MV) at ages 6 and 9 months. Among HIV-uninfected children, measles antibody prevalence was lower among 1- than 2-dose MV recipients. Here, we report results through age 24 months.

METHODS: Children born to HIV-infected mothers received MV at 6 and 9 months, and children of HIV-uninfected mothers were randomized to MV at 6 and 9 months or MV at 9 months. We followed children through age 24 months. The child's HIV status was determined and measles immunoglobulin G (IgG) level was measured by enzyme immunoassay (EIA) and by plaque reduction neutralization (PRN) on a subset.

RESULTS: Among HIV-uninfected children, the difference in measles antibody prevalence at age 12 months between one- and two-dose recipients reported previously by EIA was shown to be smaller by PRN. **By age 24 months, 84% and 87% of HIV-uninfected children receiving**

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1 or 2 doses, respectively, were seroprotected. Only 41% of 22 HIV-infected children were measles seroprotected at age 20 months.

DISCUSSION: Measles seroprotection persisted through age 24 months among HIV-uninfected children who received 1 or 2 doses of MV. HIV-infected children demonstrated seroprotection through age 12 months, but this was not sustained.



Meningococcal vaccine

[Lancet](#). 2012 Feb 18;379(9816): 617-24. Epub 2012 Jan 18.

[Immunogenicity and tolerability of a multicomponent meningococcal serogroup B \(4CMenB\) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study.](#)

[Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Muñoz A, Toneatto D, Graña G, Wang H, Clemens R, Dull PM; V72P10 Meningococcal B Adolescent Vaccine Study group.](#)

[Arriagada C, Avendaño I, Bastías M, Bravo C, Bustamante C, Bustos G, Cerda X, Espinoza M, Fuentes C, Grez T, Henriques MT, Ibañez C, Izquierdo G, Krauss J, Manriquez M, Muñoz E, O'Ryan-Soriano MA, Osorio C, Rabello M, Reyes M, Salvatierra M, Schiaccaluga S, Silva D, Simian D, Ulloa P, Veliz A, Vera K, Vergara A, Villena R, Vorphal S.](#)

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BACKGROUND: Effective glycoconjugate vaccines against *Neisseria meningitidis* serogroups A, C, W-135, and Y have been developed, but serogroup B remains a major cause of severe invasive disease in infants and adolescents worldwide. We assessed immunogenicity and tolerability of a four-component vaccine (4CMenB) in adolescents.

METHODS: We did a randomised, observer-blind, placebo-controlled, study at 12 sites in Santiago and Valparaíso, Chile. Adolescents aged 11-17 years received one, two, or three doses of 4CMenB at 1 month, 2 month, or 6 month intervals. **Immunogenicity was assessed as serum bactericidal activity using human complement (hSBA) against three reference strains for individual vaccine antigens, and assessed by ELISA against the fourth strain.** Local and systemic reactions were recorded 7 days after each vaccination, and adverse events were monitored throughout the study. Participants were initially randomised to five groups (3:3:3:3:1) during the primary phase to receive either one dose, two doses 1 or 2 months apart, or three doses of 4CMenB, or three doses of placebo, with an additional three groups generated for the booster phase. All subjects received at least one dose of 4CMenB. Geometric mean titres, proportions of participants with serum bactericidal antibody titres of 4 or more, and Clopper-Pearson 95% CIs were calculated. The study is registered with ClinicalTrials.gov, number NCT00661713.

FINDINGS: Overall, **1631 adolescents (mean age 13·8 [SD 1·9] years) received at least one dose of 4CMenB.** After two or three doses, 99-100% of recipients had hSBA titres of 4 or more

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against test strains, compared with 92-97% after one dose ($p < 0.0145$) and 29-50% after placebo. At 6 months 91-100% of participants still had titres of 4 or more for each strain after two or three doses, but only 73-76% after one dose; seroresponse rates reached 99-100% for each strain after second or third doses at 6 months. Local and systemic reaction rates were similar after each 4CMenB injection and did not increase with subsequent doses, but remained higher than placebo. No vaccine-related serious adverse events were reported and no significant safety signals were identified.

INTERPRETATION: On the basis of immunogenicity responses this study provides evidence for an adolescent 4CMenB vaccine schedule of two doses, 1-6 months apart, to provide protection against meningococcal B infection. The extent of this protection against meningococcus B variants circulating worldwide will be determined by national surveys.



Pneumococcal vaccine

[BMC Public Health](#). 2011 Nov 23;11: 882.

[Primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine \(PHiD-CV\) in infants in Mali and Nigeria: a randomized controlled trial.](#)

[Dicko A](#), [Odusanya OO](#), [Diallo AI](#), [Santara G](#), [Barry A](#), [Dolo A](#), [Diallo A](#), [Kuyinu YA](#), [Kehinde OA](#), [François N](#), [Borys D](#), [Yarzabal JP](#), [Moreira M](#), [Schuerman L](#).

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BACKGROUND: Pneumonia is still the leading cause of death among children in Africa, and pneumococcal serotypes 1 and 5 are frequently isolated from African children with invasive pneumococcal disease below the age of 5 years. **The immunogenicity, safety and reactogenicity of 3-dose primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) were evaluated in infants in Mali and Nigeria.**

METHODS: In an open, randomized, controlled study, 357 infants received DTPw-HBV/Hib and OPV primary vaccination with (PHiD-CV group) or without (control group) PHiD-CV co-administration at 6, 10 and 14 weeks of age. Pneumococcal antibody responses and opsonophagocytic activity (OPA) were measured and adverse events (AEs) recorded.

RESULTS: **One month post-dose 3, $\geq 97.2\%$ of PHiD-CV-vaccinated infants had an antibody concentration $\geq 0.2 \mu\text{g/mL}$ for each vaccine pneumococcal serotype except for 6B (82.0%) and 23F (87.6%) versus $< 10\%$ in the control group except for serotypes 14 (35.7%) and 19F (22.5%).** For each vaccine serotype, $\geq 93.3\%$ of PHiD-CV recipients had an OPA titre ≥ 8 , except for serotypes 1 (87.6%) and 6B (85.4%), compared to $< 10\%$ in the control group, except for serotypes 7F (42.9%), 9V (24.1%) and 14 (24.5%). Anti-protein D geometric mean antibody concentrations were 3791.8 and 85.4 EL.U/mL in the PHiD-CV and control groups, respectively. Overall incidences of solicited and unsolicited AEs were similar between groups.

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CONCLUSIONS: In sub-Saharan African infants, PHiD-CV was immunogenic for all vaccine pneumococcal serotypes and protein D. Vaccine tolerability was generally comparable between the PHiD-CV and control groups.



[PLoS Med.](#) 2011 Oct;8(10): e1001107. Epub 2011 Oct 18.

[Effects of community-wide vaccination with PCV-7 on pneumococcal nasopharyngeal carriage in the Gambia: a cluster-randomized trial.](#)

[Roca A](#), [Hill PC](#), [Townend J](#), [Egere U](#), [Antonio M](#), [Bojang A](#), [Akisanya A](#), [Litchfield T](#), [Nsekpong DE](#), [Oluwalana C](#), [Howie SR](#), [Greenwood B](#), [Adegbola RA](#).

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BACKGROUND: Introduction of pneumococcal conjugate vaccines (PCVs) of limited valency is justified in Africa by the high burden of pneumococcal disease. Long-term beneficial effects of PCVs may be countered by serotype replacement. **We aimed to determine the impact of PCV-7 vaccination on pneumococcal carriage in rural Gambia.**

METHODS AND FINDINGS: A cluster-randomized (by village) trial of the impact of PCV-7 on pneumococcal nasopharyngeal carriage was conducted in 21 Gambian villages between December 2003 to June 2008 (5,441 inhabitants in 2006). Analysis was complemented with data obtained before vaccination. Because efficacy of PCV-9 in young Gambian children had been shown, it was considered unethical not to give PCV-7 to young children in all of the study villages. PCV-7 was given to children below 30 mo of age and to those born during the trial in all study villages. **Villages were randomized (older children and adults) to receive one dose of PCV-7 (11 vaccinated villages) or meningococcal serogroup C conjugate vaccine (10 control villages).** Cross-sectional surveys (CSSs) to collect nasopharyngeal swabs were conducted before vaccination (2,094 samples in the baseline CSS), and 4-6, 12, and 22 mo after vaccination (1,168, 1,210, and 446 samples in CSS-1, -2, and -3, respectively). **A time trend analysis showed a marked fall in the prevalence of vaccine-type pneumococcal carriage in all age groups following vaccination (from 23.7% and 26.8% in the baseline CSS to 7.1% and 8.5% in CSS-1, in vaccinated and control villages, respectively).** The prevalence of vaccine-type pneumococcal carriage was lower in vaccinated than in control villages among older children (5 y to <15 y of age) and adults (≥ 15 y of age) at CSS-2 (odds ratio [OR] = 0.15 [95% CI 0.04-0.57] and OR = 0.32 [95% CI 0.10-0.98], respectively) and at CSS-3 (OR = 0.37 [95% CI 0.15-0.90] for older children, and 0% versus 7.6% for adults in vaccinated and control villages, respectively). Differences in the prevalence of non-vaccine-type pneumococcal carriage between vaccinated and control villages were small.

CONCLUSIONS: **Vaccination of Gambian children reduced vaccine-type pneumococcal carriage across all age groups, indicating a "herd effect" in non-vaccinated older children and adults.** No significant serotype replacement was detected.



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[Vaccine](#). 2011 Jul 26;29(33): 5414-20. Epub 2011 Jun 7.

[Pneumococcal conjugate vaccination at birth in a high-risk setting: no evidence for neonatal T-cell tolerance.](#)

[van den Biggelaar AH](#), [Pomat W](#), [Bosco A](#), [Phuanukoonnon S](#), [Devitt CJ](#), [Nadal-Sims MA](#), [Siba PM](#), [Richmond PC](#), [Lehmann D](#), [Holt PG](#).

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Concerns about the risk of inducing immune deviation-associated "neonatal tolerance" as described in mice have restricted the widespread adoption of neonatal vaccination. The aim of this study was to demonstrate the immunological feasibility of neonatal pneumococcal conjugate vaccination (PCV) which could potentially protect high-risk infants in resource poor countries against severe pneumococcal disease and mortality in the early critical period of life. Papua New Guinean infants were randomized to be vaccinated with the 7-valent PCV (7vPCV) at birth, 1 and 2 months (neonatal group, n=104) or at 1, 2 and 3 months of age (infant group, n=105), or to not receive 7vPCV at all (control group, n=109). **Analysis of vaccine responses at 3 and 9 months of age demonstrated persistently higher type-1 (IFN- γ) and type-2 (IL-5 and IL-13) T-cell responses to the protein carrier CRM(197) and IgG antibody titres to 7vPCV serotypes in children vaccinated with 7vPCV according to either schedule as compared to unvaccinated children.** In a comprehensive immuno-phenotypic analysis at 9 months of age, no differences in the quantity or quality of vaccine-specific T cell memory responses were found between neonatal vaccinations versus children given their first PCV dose at one month. Hospitalization rates in the first month of life did not differ between children vaccinated with PCV at birth or not. These findings demonstrate that neonatal 7vPCV vaccination is safe and not associated with immunological tolerance. Neonatal immunisation schedules should therefore be considered in high-risk areas where this may result in improved vaccine coverage and the earliest possible protection against pneumococcal disease and death.



Polio vaccine

[Lancet Infect Dis](#). 2012 Feb;12(2): 128-35. Epub 2011 Nov 7.

[Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6-9 months in Moradabad, India: a community-based, randomised controlled trial.](#)

[Estívariz CF](#), [Jafari H](#), [Sutter RW](#), [John TJ](#), [Jain V](#), [Agarwal A](#), [Verma H](#), [Pallansch MA](#), [Singh AP](#), [Guirguis S](#), [Awale J](#), [Burton A](#), [Bahl S](#), [Chatterjee A](#), [Aylward RB](#).

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BACKGROUND: The continued presence of polio in northern India poses challenges to the interruption of wild poliovirus transmission and the management of poliovirus risks in the post-eradication era. **We aimed to assess the current immunity profile after routine doses of trivalent oral poliovirus vaccine (OPV) and numerous supplemental doses of type-1 monovalent OPV (mOPV1), and compared the effect of five vaccine formulations and dosages on residual immunity gaps.**

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METHODS: We did a community-based, randomised controlled trial of healthy infants aged 6-9 months at ten sites in Moradabad, India. **Serum neutralising antibody was measured before infants were randomly assigned to a study group and given standard-potency or higher-potency mOPV1, intradermal fractional-dose inactivated poliovirus vaccine (IPV, GlaxoSmithKline), or intramuscular full-dose IPV from two different manufacturers** (GlaxoSmithKline or Panacea). Follow-up sera were taken at days 7 and 28. Our primary endpoint was an increase of more than four times in antibody titres. We did analyses by per-protocol in children with a blood sample available before, and 28 days after, receiving study vaccine (or who completed study procedures). This trial is registered with Current Controlled Trials, number ISRCTN90744784.

FINDINGS: Of 1002 children enrolled, 869 (87%) completed study procedures (ie, blood sample available at day 0 and day 28). At baseline, 862 (99%), 625 (72%), and 418 (48%) had detectable antibodies to poliovirus types 1, 2, and 3, respectively. In children who were type-1 seropositive, an increase of more than four times in antibody titre was detected 28 days after they were given standard-potency mOPV1 (5/13 [38%]), higher-potency mOPV1 (6/21 [29%]), intradermal IPV (9/16 [56%]), GlaxoSmithKline intramuscular IPV (19/22 [86%]), and Panacea intramuscular IPV (11/13 [85%]). In those who were type-2 seronegative, 42 (100%) of 42 seroconverted after GlaxoSmithKline intramuscular IPV, and 24 (59%) of 41 after intradermal IPV ($p<0.0001$). 87 (90%) of 97 infants who were type-3 seronegative seroconverted after intramuscular IPV, and 21 (36%) of 49 after intradermal IPV ($p<0.0001$).

INTERPRETATION: Supplemental mOPV1 resulted in almost total seroprevalence against poliovirus type 1, which is consistent with recent absence of poliomyelitis cases; whereas seroprevalence against types 2 and 3 was expected for routine vaccination histories. The immunogenicity of IPV produced in India (Panacea) was similar to that of an internationally manufactured IPV (GSK). Intradermal IPV was less immunogenic.



[J Infect Dis.](#) 2012 Jan 15;205(2): 228-36. Epub 2011 Dec 8.

[Randomized trial of type 1 and type 3 oral monovalent poliovirus vaccines in newborns in Africa.](#)

[Waggie Z](#), [Geldenhuys H](#), [Sutter RW](#), [Jacks M](#), [Mulenga H](#), [Mahomed H](#), [De Kock M](#), [Hanekom W](#), [Pallansch MA](#), [Kahn AL](#), [Burton AH](#), [Sreevatsava M](#), [Hussey G](#).

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BACKGROUND: The Global Polio Eradication Initiative aims to eradicate wild poliovirus by the end of 2012. Therefore, more-immunogenic polio vaccines, including monovalent oral poliovirus vaccines (mOPVs), are needed for supplemental immunization activities. This trial assessed the immunogenicity of monovalent types 1 and 3, compared with that of trivalent oral poliovirus vaccine (tOPV), in South Africa.

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METHODS: We conducted a blinded, randomized, 4-arm controlled trial comparing the immunogenicity of a single dose of mOPV1 (from 2 manufacturers) and mOPV3 (from 1 manufacturer), given at birth, with the immunogenicity of tOPV.

RESULTS: Eight hundred newborns were enrolled; 762 (95%) were included in the analysis. At 30 days after vaccine administration, seroconversion to poliovirus type 1 was 73.4% and 76.4% in the 2 mOPV1 arms, compared with 39.1% in the tOPV arm ($P < .0000001$), and seroconversion to poliovirus type 3 was 58.0% in the mOPV3 arm, compared with 21.2% in the tOPV arm ($P < .0000001$). The vaccines were well tolerated, and no adverse events were attributed to trial interventions.

CONCLUSION: A dose of mOPV1 or mOPV3 at birth was superior to that of tOPV in inducing type-specific seroconversion in this sub-Saharan African population. Our results support continued use of mOPVs in supplemental immunization activities in countries where poliovirus types 1 or 3 circulate. Clinical Trials Registration. ISRCTN18107202.



Comment

The trivalent oral polio vaccine has been shown above, and in previous studies, to have reduced effectiveness against individual serotypes, especially strains 1 and 3. This is believed to be due to interference with vaccine serotypes. In some countries, mOPV or tOPV are less effective than shown above (single dose monovalent 35% and single dose trivalent as low as 12.5% against polio 1 in Pakistan and Afghanistan). Lancet 2012 [http://dx.doi.org/10.1016/S0140-6736\(12\)60648-5](http://dx.doi.org/10.1016/S0140-6736(12)60648-5). This low efficacy is explained partly by the high prevalence of diarrhoeal disease and enteric infections, including other enteroviruses, which may interfere with seroconversion.

Recently, a bivalent vaccine (serotype 1 & 3) OPV was licensed and found to be non-inferior to monovalent vaccines in a trial in India (Lancet 2010;376: 1682 - 88. This bivalent vaccine has been introduced in Pakistan and Afghanistan recently, where transmission of polio virus has not been interrupted. A major problem in these countries is low vaccine coverage.

Rotavirus vaccine

[Cochrane Database Syst Rev.](#) 2012 Feb 15;2: CD008521.

[Vaccines for preventing rotavirus diarrhoea: vaccines in use.](#)

[Soares-Weiser K](#), [Maclehose H](#), [Bergman H](#), [Ben-Aharon I](#), [Nagpal S](#), [Goldberg E](#), [Pitan F](#), [Cunliffe N](#).

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BACKGROUND: Rotavirus results in more diarrhoea-related deaths in children less than five years of age than any other single agent in low- and middle-income countries. It is also a common cause of diarrhoea-related hospital admissions in high-income countries. **The World Health Organization (WHO) recommends that all children should be vaccinated with a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) or a**

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pentavalent rotavirus vaccine (RV5; RotaTaq, Merck & Co., Inc.), with a stronger recommendation for countries where deaths due to diarrhoea comprise more than 10% of all deaths. Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products) is used in China only.

OBJECTIVES: To evaluate rotavirus vaccines approved for use (RV1, RV5, and LLR) for preventing rotavirus diarrhoea. Secondary objectives were to evaluate the efficacy of rotavirus vaccines on all-cause diarrhoea, hospital admission, death, and safety profiles.

SEARCH METHODS:

For this update, we searched MEDLINE (via PubMed) in October 2011, and in June 2011 we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in The Cochrane Library 2011, Issue 2), , EMBASE, LILACS, and BIOSIS. We also searched the ICTRP (28 June 2011) and checked reference lists of identified studies.

SELECTION CRITERIA: We selected randomized controlled trials in children comparing rotavirus vaccines approved for use with placebo, no intervention, or another vaccine.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial eligibility, extracted data, and assessed risk of bias. They combined dichotomous data using the risk ratio (RR) and 95% confidence intervals (CI) and used GRADE to evaluate evidence quality, which was reflected as follows: high quality ("vaccine prevents..."); moderate quality ("vaccine probably prevents..."); or low quality ("vaccine may prevent...").

MAIN RESULTS: Forty-three trials, including nine new trials for this update, met the inclusion criteria and enrolled 190,551 participants. Thirty-one trials assessed RV1, and 12 trials evaluated RV5. We did not find any trials assessing LLR. **In children aged less than one year, RV1, compared to placebo, probably prevents 70% of all cases of rotavirus diarrhoea (RR 0.30, 95% CI 0.18 to 0.50; seven trials, 12,130 participants; moderate-quality evidence), and 80% of severe rotavirus diarrhoea cases (RR 0.20, 95% CI 0.11 to 0.35; seven trials, 35,004 participants; moderate-quality evidence).** Similarly, RV5 prevents 73% of all rotavirus diarrhoea cases (RR 0.27, 95% CI 0.22 to 0.33; four trials, 7614 participants; high-quality evidence), and 77% of severe rotavirus diarrhoea cases (RR 0.23, 95% CI 0.08 to 0.71; three trials, 6953 participants; high-quality evidence). **Both vaccines prevent over 80% of rotavirus diarrhoea cases that require hospitalization.** For all-cause diarrhoea, based on two multi-centred trials from South Africa, Malawi, and Europe, RV1 may reduce severe cases by 42% (RR 0.58, 95% CI 0.40 to 0.84; two trials, 8291 participants; low-quality evidence). Also, based on one trial from Finland, RV5 may reduce severe cases by 72% (RR 0.28, 95% CI 0.16 to 0.48; one trial, 1029 participants; low-quality evidence). During the second year of life, compared to placebo, RV1 probably prevents 70% of all cases of rotavirus diarrhoea of any severity (RR 0.30, 95% CI 0.21 to 0.43; six trials, 8041 participants; moderate-quality evidence), and 84% of severe rotavirus diarrhoea cases (RR 0.16, 95% CI 0.12 to 0.21; eight trials, 32,854 participants; moderate-quality evidence). RV5 prevents 49% of all rotavirus diarrhoea cases of any severity (RR 0.51, 95% CI 0.36 to 0.72; four trials, 9784 participants; high-quality evidence), and 56% of severe rotavirus diarrhoea cases (RR 0.44, 95% CI 0.22 to 0.88; four trials, 9783 participants; high-quality evidence). For all-cause diarrhoea, RV1 probably reduces severe cases by 51% (RR 0.49, 95% CI 0.40 to 0.60; two trials, 6269 participants; moderate-quality evidence), and RV5 showed no difference with placebo (three trials, 8533 participants). Reported serious adverse events (including intussusception) after vaccination were measured in 95,178 children for RV1 and 77,480 for RV5, with no difference between the vaccines.

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AUTHORS' CONCLUSIONS: RV1 and RV5 vaccines are effective in preventing rotavirus diarrhoea. These data support the WHO's global vaccine recommendation. The potential for reduced vaccine efficacy in low-income countries needs to be investigated. No increased risk of intussusception was detected, but surveillance monitoring studies are probably advisable in countries introducing the vaccine nationally.



[Vaccine](#). 2012 Apr 27;30 Suppl 1:A106-13.

[Immunogenicity of the pentavalent rotavirus vaccine among infants in two developing countries in Asia, Bangladesh and Vietnam.](#)

[Shin S](#), [Anh DD](#), [Zaman K](#), [Yunus M](#), [Mai le TP](#), [Thiem VD](#), [Azim T](#), [Victor JC](#), [Dallas MJ](#), [Steele AD](#), [Neuzil KM](#), [Ciarlet M](#).

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BACKGROUND: We evaluated the immunogenicity of the pentavalent rotavirus vaccine (PRV) in two GAVI-eligible Asian countries, Bangladesh and Vietnam, nested in a larger randomized, double-blind, placebo-controlled efficacy trial conducted over a two-year period from 2007 through 2009.

METHODS: 2036 infants were randomly assigned, in a 1:1 ratio, to receive three oral doses of PRV or placebo approximately at 6, 10, and 14 weeks of age. Concomitant use of EPI vaccines, including oral poliovirus vaccine (OPV) and diphtheria-tetanus-whole cell pertussis (DTwP) vaccine, was encouraged in accordance to the local EPI schedule. A total of 303 infants were evaluated for immunogenicity and blood samples were collected before the first dose (pD1) and approximately 14 days following the third dose (PD3). The seroresponse rates (≥ 3 -fold rise from pD1 to PD3) and geometric mean titers (GMTs) were measured for anti-rotavirus immunoglobulin A (IgA) and serum neutralizing antibody (SNA) to human rotavirus serotypes G1, G2, G3, G4, and P1A[8], respectively.

RESULTS: Nearly 88% of the subjects showed a ≥ 3 -fold increase in serum anti-rotavirus IgA response in the analysis of the two countries combined. When analyzed separately, the IgA response was lower in Bangladeshi children (78.1% [95% CI: 66.0, 87.5]) than in Vietnamese children (97.0% [95% CI: 89.6, 99.6]), with a PD3 GMT of 29.1 (units/mL) and 158.5 (units/mL), respectively. In the combined population, the SNA responses to the individual serotypes tested ranged from 10 (G3) to 50 (G1) percentage points lower than the responses shown in the developed countries. However, the SNA response to G3 in Vietnamese subjects was 37.3% (95% CI: 25.8, 50.0), which was similar to the G3 response rate in developed countries.

CONCLUSIONS: Three oral doses of PRV were immunogenic in two GAVI-eligible Asian countries: Bangladesh and Vietnam. The GMTs of both the serum anti-rotavirus IgA and SNA responses were generally higher in Vietnamese than in Bangladeshi children. The SNA responses varied by individual serotypes and were lower than the results from developed countries. The clinical significance of these observations is not understood because an immune correlate of protection has not been established.

[Vaccine](#). 2012 Apr 27;30 Suppl 1:A36-43.

[Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial.](#)

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Rotavirus gastroenteritis is a major cause of morbidity and mortality among African infants and young children. **A phase III, placebo-controlled, multi-centre clinical trial of a live, oral G1P[8] human rotavirus vaccine (RIX4414) undertaken in Malawi and South Africa significantly reduced the incidence of severe rotavirus gastroenteritis in the first year of life. We now report on vaccine efficacy in the Malawi cohort of children who were followed into the second year of life.** A total of 1773 healthy infants were enrolled in Blantyre, Malawi into three groups. Two groups received three doses of RIX4414 or placebo at age 6, 10, and 14 weeks and the third group received placebo at 6 weeks and RIX4414 at age 10 and 14 weeks. Subjects were followed by weekly home visits for episodes of gastroenteritis until 1 year of age, and were then re-consented for further follow-up to 18-24 months of age. Severity of gastroenteritis episodes was graded according to the Vesikari scoring system. Seroconversion for anti-rotavirus IgA was determined on a subset of children by using ELISA on pre- and post-vaccine blood samples. Rotavirus VP7 (G) and VP4 (P) genotypes were determined by RT-PCR. A total of 70/1030 (6.8%, 95% CI 5.3-8.5) subjects in the pooled (2 dose plus 3 dose) RIX4414 group compared with 53/483 (11.0%, 8.3-14.1) subjects in the placebo group developed severe rotavirus gastroenteritis in the entire follow-up period (vaccine efficacy 38.1% (9.8-57.3)). **The point estimate of efficacy in the second year of life (17.6%; -59.2 to 56.0) was lower than in the first year of life (49.4%; 19.2-68.3).** There were non-significant trends towards a higher efficacy in the second year of life among children who received the three-dose schedule compared with the two-dose schedule, and a higher anti-rotavirus IgA seroresponse rate in the three-dose RIX4414 group. Rotavirus strains detected included genotype G12 (31%); G9 (23%); and G8 (18%); only 18% of strains belonged to the G1P[8] genotype. While the optimal dosing schedule of RIX4414 in African infants requires further investigation, vaccination with RIX4414 significantly reduced the incidence of severe gastroenteritis caused by diverse rotavirus strains in an impoverished African population with high rotavirus disease burden in the first two years of life.

[Vaccine](#). 2012 Apr 27;30 Suppl 1:A44-51.

[Efficacy and immunogenicity of two or three dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial.](#)

[Madhi SA](#), [Kirsten M](#), [Louw C](#), [Bos P](#), [Aspinall S](#), [Bouckenooghe A](#), [Neuzil KM](#), [Steele AD](#).

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BACKGROUND: Human rotavirus vaccine (HRV; i.e., Rotarix) reduced the incidence of severe rotavirus gastroenteritis (RVGE) by 77% (95% Confidence interval: 56-88%) during the first year of life in South Africa. Persistence of HRV-derived protection against RVGE during subsequent rotavirus seasons, although evident in industrialized settings, remains to be established in African settings. This study reports on the efficacy of HRV against severe RVGE over two consecutive rotavirus seasons in South African children.

METHODS: A prospective, double-blind, placebo controlled multi-centered trial in South Africa and Malawi randomly assigned **infants in a 1:1:1 ratio to receive either two (10 and 14 weeks; HRV_2D) or three (6, 10 and 14 weeks; HRV_3D) doses of HRV or placebo.** The primary analysis involved pooling of HRV_2D and HRV_3D arms. Episodes of gastroenteritis caused by wild-type rotavirus were identified through active follow-up surveillance and graded by the Vesikari scale.

RESULTS: 1339 infants (447 in the HRV_2D group, 447 in the HRV_3D group and 445 in the placebo group) were enrolled in Year 2 of the study, including 1035 (77.3%) who were followed up over two consecutive rotavirus seasons (i.e., Cohort 2 subjects). **Rotarix was associated with ongoing protection against severe RVGE, preventing 2.5 episodes per 100 vaccinated children over two consecutive rotavirus seasons; vaccine efficacy: 59% (95% Confidence interval: 1-83%). An exploratory analysis indicated better immunogenicity (among Cohort 1 subjects) and a higher point-efficacy estimate over two seasons in the HRV_3D compared to HRV_2D arms of the study in Cohort 2 subjects.**

CONCLUSION: Rotarix is associated with significant reductions in severe gastroenteritis episodes through 2 years of life among South African children. Further research is needed to determine the optimal dosing schedule of Rotarix in providing long-term protection against rotavirus illness in African children.

[Vaccine](#). 2012 Apr 27;30 Suppl 1:A52-60.

[Efficacy of pentavalent rotavirus vaccine in a high HIV prevalence population in Kenya.](#)

[Feikin DR](#), [Laserson KE](#), [Ojwando J](#), [Nyambane G](#), [Ssempijja V](#), [Audi A](#), [Nyakundi D](#), [Oyieko J](#), [Dallas MJ](#), [Ciarlet M](#), [Neuzil KM](#), [Breiman RF](#).

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BACKGROUND: Rotavirus gastroenteritis (RVGE) is a leading cause of death in African children. The efficacy of pentavalent rotavirus vaccine (PRV) against severe RVGE evaluated in Ghana, Kenya, and Mali in a randomized, double-blind, placebo-controlled trial, showed a combined regional efficacy of 39.3% (95% confidence interval [CI]: 19.1,54.7) in nearly 2 years of follow-up. This report concentrates on the Kenya findings.

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METHODS: Infants received 3 doses of PRV/placebo at approximately 6-, 10-, and 14-weeks of age. HIV testing was offered to all participants. Data on illness symptoms and signs were collected upon presentation to healthcare facilities, where stools were collected, and analyzed by rotavirus-specific enzyme-linked immunosorbent assay. The primary endpoint was severe RVGE (Vesikari score ≥ 11), occurring ≥ 14 days following the third dose. At monthly home visits, symptoms of illnesses during the past 2 weeks were solicited and limited physical exams were performed; dehydration was defined by WHO's Integrated Management of Childhood Illness.

FINDINGS: Vaccine efficacy (VE) against severe RVGE through nearly 2 years of follow-up among 1308 Kenyan children was 63.9% (95% CI: -5.9,89.8). Through the first year of life, VE against severe RVGE was 83.4% (95% CI: 25.5,98.2). From home visits, VE against all-cause gastroenteritis with severe dehydration was 34.4% (95% CI: 5.3,54.6) through the first year and 29.7% (95% CI: 2.5,49.3) through the entire follow-up period. The reduction in incidence of gastroenteritis with severe dehydration in the community during the first year of life (19.0 cases/100 person-years) was almost six times greater than the reduction in severe RVGE presenting to the clinic (3.3/100 person-years). Oral rehydration solution use was lower among PRV recipients (VE 23.1%, 95% CI: 8.8,35.1). An estimated 41% of gastroenteritis with severe dehydration in the first year reported at home was rotavirus-related.

CONCLUSIONS: PRV significantly reduced severe RVGE in Kenya. The impact of PRV might be greatest in rural Africa in protecting the many children who develop severe gastroenteritis and cannot access health facilities.

Comment

In three follow-up studies in Malawi, South Africa, and Kenya, rotavirus vaccine given in the first 3 months of life remained effective against severe rotavirus diarrhoea in the second year of life, although less effective than in the first year of life. Three doses of RV vaccine in the first 3 months provided greater 2nd year protection than two doses.

[Vaccine](#). 2012 Apr 27;30 Suppl 1:A71-8.

[Efficacy of the oral pentavalent rotavirus vaccine in Mali.](#)

[Sow SQ](#), [Tapia M](#), [Haidara FC](#), [Ciarlet M](#), [Diallo F](#), [Kodio M](#), [Doumbia M](#), [Dembélé RD](#), [Traoré O](#), [Onwuchekwa UU](#), [Lewis KD](#), [Victor JC](#), [Steele AD](#), [Neuzil KM](#), [Kotloff KL](#), [Levine MM](#).

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The oral, pentavalent rotavirus vaccine (PRV), RotaTeq was assessed for prevention of severe rotavirus gastroenteritis (RVGE) in young children in two multi-site, randomized, placebo-controlled field trials; one in Asia (Vietnam and Bangladesh) and the other in sub-Saharan Africa (Ghana, Kenya and Mali). The efficacy results for the Mali site of the multi-country trial are presented here. We randomly assigned infants in a 1:1 ratio to receive 3 doses of PRV/placebo at approximately 6, 10, and 14 weeks of age. Gastroenteritis episodes were captured passively at the local health centers and by home visits. The primary study outcome

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was severe RVGE, as defined by a score of ≥ 11 using the Vesikari Clinical Scoring System occurring ≥ 14 days after the third dose until the end of the study. Other efficacy analyses included efficacy against severe RVGE through the first year and during the second years of life, as well as efficacy after receiving at least one dose of vaccine. In total, 1960 infants were enrolled in the trial at the Mali site and sera were collected on a subset of infants (approximately 150) for immunogenicity testing. In the first year of follow-up, largely due to cultural practices to visit traditional healers as the first point of care, the point estimate of efficacy was unreliable: the per protocol vaccine efficacy against severe RVGE was 1% (95% confidence interval [CI]: -431.7, 81.6); the intention-to-treat vaccine efficacy was 42.9% (95% CI: -125.7, 87.7). **During the second year of follow-up, after the surveillance system was modified to adapt to local customs and health care seeking practices, the point estimate of per-protocol vaccine efficacy was 19.2% (95% CI: -23.1, 47.3%).** 82.5% of Malian infants (95% CI: 70.1, 91.3%) who received PRV mounted a seroresponse (≥ 3 -fold rise from baseline (prevaccination) to post-dose 3 vaccination) of anti-rotavirus immunoglobulin A antibody, with a post third-dose geometric mean titer (GMT) of 31.3 units/mL. By contrast, only 20.0% of placebo recipients (95% CI: 10.0, 33.7%) developed a seroresponse and the post-third dose GMT was 3.2 units/mL. None of the serious clinical adverse events observed were considered to be vaccine-related.

Typhoid vaccine

[PLoS One](#). 2011;6(9): e25398. Epub 2011 Sep 30.

[Safety, immunogenicity and dose ranging of a new Vi-CRM₁₉₇ conjugate vaccine against typhoid fever: randomized clinical testing in healthy adults.](#)

[van Damme P](#), [Kafeja F](#), [Anemona A](#), [Basile V](#), [Hilbert AK](#), [De Coster I](#), [Rondini S](#), [Micoli F](#), [Qasim Khan RM](#), [Marchetti E](#), [Di Cioccio V](#), [Saul A](#), [Martin LB](#), [Podda A](#).

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BACKGROUND: Typhoid fever causes more than 21 million cases of disease and 200,000 deaths yearly worldwide, with more than 90% of the disease burden being reported from Asia. Epidemiological data show high disease incidence in young children and suggest that immunization programs should target children below two years of age: this is not possible with available vaccines. The Novartis Vaccines Institute for Global Health developed a conjugate vaccine (Vi-CRM₁₉₇) for infant vaccination concomitantly with EPI vaccines, either starting at 6 weeks with DTP or at 9 months with measles vaccine. We report the results from a Phase 1 and a Phase 2 dose ranging trial with Vi-CRM₁₉₇ in European adults.

METHODOLOGY: Following randomized blinded comparison of single vaccination with either Vi-CRM₁₉₇ or licensed polysaccharide vaccines (both containing 25.0 μg of Vi antigen), a randomised observer blinded dose ranging trial was performed in the same center to compare three concentrations of Vi-CRM₁₉₇ (1.25 μg , 5.0 μg and 12.5 μg of Vi antigen) with the polysaccharide vaccine.

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PRINCIPAL FINDINGS: All vaccines were well tolerated. Compared to the polysaccharide vaccine, Vi-CRM₁₉₇ induced a higher incidence of mild to moderate short lasting local pain. All Vi-CRM₁₉₇ formulations induced higher Vi antibody levels compared to licensed control, with clear dose response relationship.

CONCLUSIONS: Vi-CRM₁₉₇ did not elicit safety concerns, was highly immunogenic and is therefore suitable for further clinical testing in endemic populations of South Asia.



Vitamin A

(See also Maternal health, nutrition and micronutrient supplementation, HIV prevention of mother to child transmission)

[BMJ](#). 2012 Jan 10;344: d7962. doi: 10.1136/bmj.d7962.

[Vitamin A supplementation in preschool children and risk of hearing loss as adolescents and young adults in rural Nepal: randomised trial cohort follow-up study.](#)

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OBJECTIVE: To determine whether vitamin A supplementation administered in the preschool years can lower the risk of hearing loss in adolescence and adulthood.

DESIGN: Follow-up study of adolescents and young adults who, as preschool aged children in 1989, were enrolled into a cluster randomised, double blinded, placebo controlled trial of vitamin A supplementation.

SETTING: South central, rural Nepal.

PARTICIPANTS: 2378 adolescents and young adults aged 14 to 23, representing 51% of those who finished the original trial and 71% of those living in the study area in 2006.

INTERVENTIONS: Every four months for 16 months preschool children were visited at home, given an oral 200,000 IU dose of vitamin A (half dose at age 1-11 months, quarter dose at <1 month) or placebo and the parents were queried about any childhood illnesses in the previous week, including purulent discharge from the ears.

MAIN OUTCOME MEASURES: Prevalence of mild or worse hearing loss (≥ 30 dB) in the most affected ear and tympanometric measures of middle ear function (peak height, ear canal volume, and gradient).

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RESULTS: During the original trial, the prevalence of middle ear infection during the preschool years did not differ between the supplement groups. By adolescence and early adulthood, a non-significant 17% reduction in hearing loss occurred among those who had periodically received vitamin A compared with placebo as preschool aged children (odds ratio 0.83, 95% confidence interval 0.62 to 1.12). **Among participants with any ear discharge in early childhood, vitamin A supplementation was associated with a reduced risk of hearing loss, by 42% (0.58, 0.37 to 0.92) compared with controls**, after adjusting the confidence interval for the design effect of the original trial. Abnormal tympanometric peak height of the middle ear system was less likely among participants supplemented with vitamin A in childhood.

CONCLUSION: In undernourished settings, periodic, high dose vitamin A supplementation may reduce the risk of hearing loss associated with purulent ear infections in early childhood.



[Pediatrics](#). 2012 Apr;129(4): e960-6. Epub 2012 Mar 12.

[Effect on infant illness of maternal supplementation with 400 000 IU vs 200 000 IU of vitamin A.](#)

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BACKGROUND AND OBJECTIVE: Postpartum vitamin A supplementation is a strategy used to combat vitamin A deficiency and seems to reduce maternal/infant morbidity and mortality. However, studies have shown that a dose of 200,000 IU (World Health Organization [WHO] protocol) does not seem to provide adequate retinol levels in maternal breast milk, infant serum, and infant tissue. The objective of this study was to compare the effect of postpartum maternal supplementation with 400,000 IU (International Vitamin A Consultative Group protocol) compared with 200,000 IU of vitamin A on infant morbidity.

METHODS: This was a randomized controlled, triple-blinded clinical trial conducted at 2 public maternity hospitals in Recife in northeastern Brazil. **There were 276 mother-child pairs that were allocated to 2 treatment groups: 400,000 IU or 200,000 IU of vitamin A. They were followed up for >6 months to evaluate infant morbidity.**

RESULTS: **Fever (rate ratio [RR]: 0.92 [95% confidence interval (CI): 0.75-1.14]), diarrhea (RR: 0.96 [95% CI: 0.72-1.28]), otitis (RR: 0.94 [95% CI: 0.48-1.85]), acute respiratory infection (RR: 1.03 [95% CI: 0.88-1.21]), the need for intravenous rehydration (RR: 2.08 [95% CI: 0.64-2.07]), and the use of antibiotic treatment (RR: 0.80 [95% CI: 0.43-1.47]) did not differ significantly between the 2 treatment groups.**

CONCLUSIONS: Our findings suggest that postpartum maternal supplementation with 400 000 IU of vitamin A does not provide any additional benefits in the reduction of illness in children aged <6 months; therefore, we do not support the proposal to increase the standard vitamin A dose in the existing WHO protocol.

[BMC Pediatr.](#) 2011 Sep 1;11: 77.

[The impact of different doses of vitamin A supplementation on male and female mortality. A randomised trial from Guinea-Bissau.](#)

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BACKGROUND: Vitamin A supplementation (VAS) given to children between 6 months and 5 years of age is known to reduce mortality in low-income countries. We have previously observed that girls benefit more from a lower dose of VAS than the one recommended by WHO, the effect being strongest if diphtheria-tetanus-pertussis vaccine (DTP) was the most recent vaccination. We aimed to test these observations.

METHODS: During national immunisations days in Guinea-Bissau, West Africa, combining oral polio vaccination and VAS, we randomised **8626 children between 6 months and 5 years of age to receive the dose of VAS recommended by WHO or half this dose.** Mortality rate ratios (MRRs) were assessed after 6 and 12 month.

RESULTS: The overall mortality rate among participants was lower than expected. **There was no significant difference in mortality at 6 months and 12 months of follow up between the low dose VAS group and the recommended dose VAS group.** The MRRs were 1.23 (0.60-2.54) after 6 months and 1.17 (0.73-1.87) after 12 months. This tendency was similar in boys and girls. The low dose was not associated with lower mortality in girls if the most recent vaccine was DTP (MRR = 0.60 (0.14-2.50) after 6 months).

CONCLUSION: Our sample size does not permit firm conclusions since mortality was lower than expected. **We could not confirm a beneficial effect of a lower dose of VAS on mortality in girls.**



[PLoS One.](#) 2011;6(8): e23265. Epub 2011 Aug 11.

[Vitamin A supplementation at birth might prime the response to subsequent vitamin A supplements in girls. Three year follow-up of a randomized trial.](#)

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OBJECTIVES: Within a randomised trial of neonatal vitamin A supplementation (VAS) in Guinea-Bissau, neonatal VAS did not affect overall infant mortality. We conducted a post-hoc analysis to test the hypothesis that neonatal VAS primes the response to subsequent vitamin A.

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METHODS: All trial children were offered VAS after follow-up ended at 1 year of age (FU-VAS). We compared mortality between 1 and 3 years of age according to initial randomization to neonatal VAS or placebo in Cox-regression models; we expected that children randomized to neonatal VAS compared with those randomized to placebo would have lower mortality after reception of FU-VAS.

RESULTS: Of 4345 infants enrolled in the original trial, 3646 lived in the study area at 1 year of age and 2958 received FU-VAS. Between 1 and 3 years of age, 112 children died. After FU-VAS, neonatal VAS was associated with lower mortality than placebo: Mortality Rate Ratio (MRR) =0.54 (95% CI: 0.31-0.94). The effect was more pronounced in girls (MRR=0.37 (0.16-0.89)) than boys (MRR=0.73 (0.35-1.51)). The beneficial effect of neonatal VAS may have been particularly strong for girls who received both VAS in a campaign and FU-VAS (MRR=0.15 (0.03-0.67)). Among children who had not received FU-VAS, mortality in the second and third year of life did not differ according to reception of neonatal VAS or placebo. Hence, in the second and third year of life the effect of neonatal VAS versus placebo was different in girls who had or had not received FU-VAS (p for homogeneity=0.01).

CONCLUSIONS: The present results suggest that neonatal VAS primes the response in girls such that they get a beneficial effect after a subsequent dose of VAS.



[Br J Nutr.](#) 2012 Mar;107(5): 615-20. Epub 2011 Jul 26.

[SNP may modify the effect of vitamin A supplementation at birth on cytokine production in a whole blood culture assay.](#)

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Within a neonatal vitamin A supplementation (VAS) trial, we investigated the effect of VAS on TNF- α , IL-10, IL-5 and IL-13 production after lipopolysaccharide, purified protein derivative (PPD) of Mycobacterium tuberculosis and phytohaemagglutinin stimulation using a whole blood culture protocol. We found that VAS recipients had lower unstimulated TNF- α concentrations than placebo recipients. In the present paper, we investigated whether the SNP TNF- α - 308, TNF- α - 238, IL-10 - 592, IL-10 - 1082 and toll-like receptor 4 (TLR4)+896 modified the effect of VAS on cytokine production. DNA and cytokine concentrations were available from 291 children. We found a significant interaction between TNF- α - 308 genotype and VAS for the unstimulated TNF- α production (Pinteraction = 0.04); among G homozygotes, TNF- α concentrations were significantly lower after VAS compared with placebo, whereas for A carriers, VAS did not appear to have any effect. For TNF- α - 238, there was a tendency towards an increase in PPD-stimulated TNF- α production after VAS for the G homozygotes, but the opposite tendency for A allele carriers (Pinteraction = 0.07). Stratification by sex revealed a significant VAS-genotype interaction for boys for TNF- α - 238. There was a borderline-significant three-way interaction (P = 0.05) between sex, VAS and TLR4+896 genotype. Although the present study had very limited representation of the genetic variation with potential for modification of the response to VAS, it adds to the efforts of untangling the diverse effects and impact of VAS.



[J Nutr.](#) 2012 Jun;142(6): 1088-94. Epub 2012 Apr 25.

[Pneumococcal Carriage at Age 2 Months Is Associated with Growth Deficits at Age 6 Months among Infants in South India.](#)

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Nasopharyngeal colonization is the first step in the pathway to *Streptococcus pneumoniae* (Spn) infection, a leading cause of childhood morbidity and mortality. We investigated the effect of Spn colonization at ages 2 and 4 mo on growth at age 6 mo among 389 infants living in rural South India by using data from an Spn carriage study nested within a randomized, double-blind, placebo-controlled community trial designed to evaluate the impact of newborn vitamin A supplementation on Spn carriage in the first 6 mo of life. Primary outcomes were weight, length, and anthropometric indices of nutritional status. Growth data at age 6 mo were available for 84% (389 of 464) of infants in the Spn carriage study. **Carriage at age 2 mo was associated with increased odds of stunting [OR: 3.07 (95% CI: 1.29, 7.36) P = 0.012] and lower weight [β : -266 g (95% CI: -527, -5) P = 0.045], length [β : -1.31 cm (95% CI: -2.32, -0.31) P = 0.010], and length-for-age Z scores [β : -0.59; (95% CI: -1.05, -0.13) P = 0.012] at age 6 mo.** Spn carriage at age 4 mo did not affect growth. Carriage of invasive serotypes at age 2 mo was associated with decreases in mean weight [β : -289 g; (95% CI: -491, -106) P = 0.002] and length [β : -0.38 cm (95% CI: -1.49, -0.01) P = 0.047] at age 6 mo. Newborn vitamin A supplementation did not modify the association between Spn carriage and growth. Results suggest that pneumococcal carriage at age 2 mo is an independent risk factor for poor growth in young infants. Future studies need to clarify the role of Spn carriage on growth retardation in low-income countries.

[Trials.](#) 2012 Feb 23; 13:22.

[Efficacy of early neonatal vitamin A supplementation in reducing mortality during infancy in Ghana, India and Tanzania: study protocol for a randomized controlled trial.](#)

[NEOVITA Study Author Group](#), [Bahl R](#), [Bhandari N](#), [Dube B](#), [Edmond K](#), [Fawzi W](#), [Fontaine O](#), [Kaur J](#), [Kirkwood BR](#), [Martines J](#), [Masanja H](#), [Mazumder S](#), [Msham S](#), [Newton S](#), [Oleary M](#), [Ruben J](#), [Shannon C](#), [Smith E](#), [Taneja S](#), [Yoshida S](#).

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BACKGROUND: Vitamin A supplementation of 6-59 month old children is currently recommended by the World Health Organization based on evidence that it reduces mortality. There has been considerable interest in determining the benefits of neonatal vitamin A supplementation, but the results of existing trials are conflicting. A technical consultation convened by WHO pointed to the need for larger scale studies in Asia and Africa to inform global policy on the use of neonatal vitamin A supplementation. Three trials were therefore initiated in Ghana, India and Tanzania to determine if vitamin A supplementation (50,000 IU) given to neonates once orally on the day of birth or within the next two days will reduce mortality in the period from supplementation to 6 months of age compared to placebo.

METHODS/DESIGN: The trials are individually randomized, double masked, and placebo controlled. The required sample size is 40,200 in India and 32,000 each in Ghana and Tanzania. The study participants are neonates who fulfil age eligibility, whose families are likely to stay in the study area for the next 6 months, who are able to feed orally, and whose parent(s) provide informed written consent to participate in the study. **Neonates randomized to the intervention group receive 50,000 IU vitamin A and the ones randomized to the control group receive placebo at the time of enrollment.** Mortality and morbidity information are collected through periodic home visits by a study worker during infancy. The primary outcome of the study is mortality from supplementation to 6 months of age. The secondary outcome of the study is mortality from supplementation to 12 months of age. The three studies will be analysed independent of each other. Subgroup analysis will be carried out to determine the effect by birth weight, sex, and timing of DTP vaccine, socioeconomic groups and maternal large-dose vitamin A supplementation.

DISCUSSION: **The three ongoing studies are the largest studies evaluating the efficacy of vitamin A supplementation to neonates.** Policy formulation will be based on the results of efficacy of the intervention from the ongoing randomized controlled trials combined with results of previous studies.



Yaws

[Lancet](#). 2012 Jan 28;379(9813): 342-7. Epub 2012 Jan 11.

[Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial.](#)

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BACKGROUND: Yaws--an endemic treponematosi and, as such, a neglected tropical disease--is re-emerging in children in rural, tropical areas. Oral azithromycin is effective for syphilis. **We assessed the efficacy of azithromycin compared with intramuscular long-acting penicillin to treat patients with yaws.**

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METHODS: We did an open-label, non-inferiority, randomised trial at Lihir Medical Centre, Papua New Guinea, between Sept 1, 2010, and Feb 1, 2011. **Children aged 6 months to 15 years with a serologically confirmed diagnosis of yaws were randomly allocated, by a computer-generated randomisation sequence, to receive either one 30 mg/kg oral dose of azithromycin or an intramuscular injection of 50,000 units per kg benzathine benzylpenicillin.** Investigators were masked to group assignment. The primary endpoint was treatment efficacy, with cure rate defined serologically as a decrease in rapid plasma reagin titre of at least two dilutions by 6 months after treatment, and, in participants with primary ulcers, also by epithelialisation of lesions within 2 weeks. Non-inferiority was shown if the upper limit of the two-sided 95% CI for the difference in rates was lower than 10%. The primary analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT01382004.

FINDINGS: We allocated 124 patients to the azithromycin group and 126 to the benzathine benzylpenicillin group. In the per-protocol analysis, after 6 months of follow-up, 106 (96%) of 110 patients in the azithromycin group were cured, compared with 105 (93%) of 113 in the benzathine benzylpenicillin group (treatment difference -3.4%; 95% CI -9.3 to 2.4), thus meeting prespecified criteria for non-inferiority. The number of drug-related adverse events (all mild or moderate) was similar in both treatment groups (ten [8%] in the azithromycin group vs eight [7%] in the benzathine benzylpenicillin group).

INTERPRETATION: A single oral dose of azithromycin is non-inferior to benzathine benzylpenicillin and avoids the need for injection equipment and medically trained personnel. A change to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programmes.



Comment

This is an important trial. However if adopting this strategy it will be important to monitor what affect the more widespread use of azithromycin in various settings, for trachoma and yaws, will have on bacterial resistance rates. The principle of always using an equally effective narrower-spectrum agent (benzathine penicillin) with lower potential for generating resistance is breached in this approach by the argument for a simpler delivery mechanism. The effect on resistance rates – not for trepanema, but for other common pathogens in the community such as pneumococcus and Staphylococcus, has not been adequately investigated.

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

[J Pediatr Gastroenterol Nutr.](#) 2011 Aug;53(2): 161-7.

[ORS containing zinc does not reduce duration or stool volume of acute diarrhea in hospitalized children.](#)

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Randomised trials in child health in developing countries 2011-12

BACKGROUND AND AIM: The World Health Organization recommends oral zinc (tablets or syrups) as adjunct therapy with oral rehydration solution (ORS) for acute childhood diarrhea. Mixing zinc with ORS can be an attractive approach for simultaneous provision of these 2 effective interventions. This double-masked randomized controlled trial evaluated the efficacy of ORS containing 40 mg/L elemental zinc per liter (zinc-ORS) in reducing stool weight and duration of diarrhea.

PATIENTS AND METHODS: **Five hundred northern Indian children ages 1 to 35 months with diarrhea <7 days' duration were randomized to zinc-ORS or ORS.** The primary outcomes were total stool output and time to recovery.

RESULTS:

The median total stool output was 2.12g/kg/hr (interquartile range [IQR] 0.9-3.76) in the zinc-ORS group compared with 1.78g/kg/h (IQR 0.83-3.45) in the ORS group. The time to recovery was also similar in the 2 groups (hazard ratio 1.06 [95% confidence interval 0.88-1.27]). **In subjects who received zinc-ORS, the median (IQR) zinc intakes were 27 (16-46) mg on day 1, 15 (6-27) mg on day 2, and negligible thereafter.**

CONCLUSIONS: **The World Health Organization-recommended daily dose of zinc for diarrhea was not achieved in most children beyond the first day of treatment.** This is the likely explanation for the lack of improvement in outcomes from zinc-ORS when compared with ORS alone. Our findings do not support a change from using zinc syrup or dispersible tablets for treatment of acute diarrhea in children.

Comment

This is an important study. In the past it has been assumed that zinc could simply be added to ORS. This study suggests that such an approach may result in inadequate zinc intake after the first day of diarrhoea treatment to be effective. For infants and children >12 months with diarrhoea, zinc 10mg and 20mg, respectively, is recommended for 5-10 days.

[Cochrane Database Syst Rev.](#) 2012 Jun 13;6: CD005436.

[Oral zinc for treating diarrhoea in children.](#)

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BACKGROUND: In developing countries, diarrhoea causes around two million child deaths annually. Zinc supplementation during acute diarrhoea is currently recommended by the World Health Organization and UNICEF.

OBJECTIVES: To evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea.

SEARCH METHODS: In February 2012, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2011, Issue 11), MEDLINE, EMBASE, LILACS, CINAHL, mRCT, and reference lists. We also contacted researchers.

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SELECTION CRITERIA: Randomized controlled trials comparing oral zinc supplementation with placebo in children aged one month to five years with acute or persistent diarrhoea, including dysentery.

DATA COLLECTION AND ANALYSIS: Both authors assessed trial eligibility and risk of bias, extracted and analysed data, and drafted the review. Diarrhoea duration and severity were the primary outcomes. We summarized dichotomous outcomes using risk ratios (RR) and continuous outcomes using mean differences (MD) with 95% confidence intervals (CI). Where appropriate, we combined data in meta-analyses (using the fixed- or random-effects model) and assessed heterogeneity. The quality of evidence has been assessed using the GRADE methods

MAIN RESULTS: Twenty-four trials, enrolling 9128 children, met our inclusion criteria. The majority of the data is from Asia, from countries at high risk of zinc deficiency, and may not be applicable elsewhere. Acute diarrhoea There is currently not enough evidence from well conducted randomized controlled trials to be able to say whether zinc supplementation during acute diarrhoea reduces death or hospitalization (very low quality evidence). In children aged greater than six months with acute diarrhoea, zinc supplementation may shorten the duration of diarrhoea by around 10 hours (MD -10.44 hours, 95% CI -21.13 to 0.25; 2091 children, five trials, low quality evidence), and probably reduces the number of children whose diarrhoea persists until day seven (RR 0.73, 95% CI 0.61 to 0.88; 3865 children, six trials, moderate quality evidence). In children with signs of moderate malnutrition the effect appears greater, reducing the duration of diarrhoea by around 27 hours (MD -26.98 hours, 95% CI -14.62 to -39.34; 336 children, three trials, high quality evidence). Conversely, In children aged less than six months, the available evidence suggests zinc supplementation may have no effect on mean diarrhoea duration (MD 5.23 hours, 95% CI -4.00 to 14.45; 1334 children, two trials, low quality evidence), and may even increase the proportion of children whose diarrhoea persists until day seven (RR 1.24, 95% CI 0.99 to 1.54; 1074 children, one trial, moderate quality evidence). No trials reported serious adverse events, but zinc supplementation during acute diarrhoea causes vomiting in both age groups (RR 1.59, 95% CI 1.27 to 1.99; 5189 children, 10 trials, high quality evidence). Persistent diarrhoea In children with persistent diarrhoea, zinc supplementation probably shortens the duration of diarrhoea by around 16 hours (MD -15.84 hours, 95% CI -25.43 to -6.24; 529 children, five trials, moderate quality evidence).

AUTHORS' CONCLUSIONS: In areas where the prevalence of zinc deficiency or the prevalence of moderate malnutrition is high, zinc may be of benefit in children aged six months or more. The current evidence does not support the use of zinc supplementation in children below six months of age.

Comment

The conclusion of this systematic review is luke-warm, based on the study quality rather than on the effect of zinc on diarrhoea duration that was consistently demonstrated in all but one of the 6 studies included which involved children over 6 months of age. Further trials are needed in infants less than 6 months of age.

[Zinc, vitamin A, and micronutrient supplementation in children with diarrhea: a randomized controlled clinical trial of combination therapy versus monotherapy.](#)

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OBJECTIVE: To compare the clinical efficacy of supplementation of zinc, zinc plus vitamin A, and zinc plus combination of micronutrients and vitamins (iron, copper, selenium, vitamin B(12), folate, and vitamin A) on acute diarrhea in children.

STUDY DESIGN: This was a double-blind, randomized, placebo-controlled trial. **Children aged 6 to 24 months with diarrhea and moderate dehydration were randomized to receive zinc plus placebo vitamin A (group 1), zinc plus other micronutrients plus vitamin A (group 2), zinc plus vitamin A (group 3), or placebo (group 4) as an adjunct to oral rehydration solution.** Duration, volume of diarrhea, and consumption of oral rehydration solution were compared as outcome variables within the supplemented groups and with the placebo group.

RESULTS: **The 167 study subjects included 41 in group 1, 39 in group 2, 44 in group 3, and 43 in group 4. All 3 supplemented groups demonstrated a significant reduction in outcome variables ($P < .0001$) compared with the placebo group.** Group 3 had the lowest reduction of outcome variables and group 2 had a speedy recovery, but differences among the supplemented groups were not statistically significant.

CONCLUSIONS: Supplementation with a combination of micronutrients and vitamins was not superior to zinc alone, confirming the clinical benefit of zinc in children with diarrhea.

[PLoS Med.](#) 2011 Nov;8(11): e1001125. Epub 2011 Nov 22.

[Effect of supplementation with zinc and other micronutrients on malaria in Tanzanian children: a randomised trial.](#)

[Veenemans J, Milligan P, Prentice AM, Schouten LR, Inja N, van der Heijden AC, de Boer LC, Jansen EJ, Koopmans AE, Enthoven WT, Kraaijenhagen RJ, Demir AY, Uges DR, Mbugi EV, Savelkoul HF, Verhoef H.](#)

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BACKGROUND: It is uncertain to what extent oral supplementation with zinc can reduce episodes of malaria in endemic areas. Protection may depend on other nutrients. We measured the effect of supplementation with zinc and other nutrients on malaria rates.

METHODS AND FINDINGS: In a 2×2 factorial trial, 612 rural Tanzanian children aged 6-60 months in an area with intense malaria transmission and with height-for-age z-score ≤ -1.5 SD were randomized to receive daily oral supplementation with either zinc alone (10 mg), multi-nutrients without zinc, multi-nutrients with zinc, or placebo. Intervention group was indicated by colour code, but neither participants, researchers, nor field staff knew who received what

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intervention. Those with Plasmodium infection at baseline were treated with artemether-lumefantrine. The primary outcome, an episode of malaria, was assessed among children reported sick at a primary care clinic, and pre-defined as current Plasmodium infection with an inflammatory response, shown by axillary temperature $\geq 37.5^{\circ}\text{C}$ or whole blood C-reactive protein concentration ≥ 8 mg/L. Nutritional indicators were assessed at baseline and at 251 days (median; 95% reference range: 191-296 days). In the primary intention-to-treat analysis, we adjusted for pre-specified baseline factors, using Cox regression models that accounted for multiple episodes per child. 592 children completed the study. The primary analysis included 1,572 malaria episodes during 526 child-years of observation (median follow-up: 331 days). Malaria incidence in groups receiving zinc, multi-nutrients without zinc, multi-nutrients with zinc and placebo was 2.89/child-year, 2.95/child-year, 3.26/child-year, and 2.87/child-year, respectively. There was no evidence that multi-nutrients influenced the effect of zinc (or vice versa). **Neither zinc nor multi-nutrients influenced malaria rates (marginal analysis; adjusted HR, 95% CI: 1.04, 0.93-1.18 and 1.10, 0.97-1.24 respectively).** The prevalence of zinc deficiency (plasma zinc concentration <9.9 $\mu\text{mol/L}$) was high at baseline (67% overall; 60% in those without inflammation) and strongly reduced by zinc supplementation.

CONCLUSIONS: We found no evidence from this trial that zinc supplementation protected against malaria.



[Indian J Pediatr.](#) 2011 Sep;78(9): 1085-90. Epub 2011 Jun 10.

[A randomized controlled trial of oral zinc in acute pneumonia in children aged between 2 months to 5 years.](#)

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OBJECTIVE: To evaluate the effectiveness and safety of zinc supplementation as adjuvant in treatment of pneumonia.

METHODS: Ninety-eight children with acute bacterial pneumonia, aged between 2 months to 5 years, were studied in a randomized controlled single blind design. They received either zinc supplementation, as zinc acetate syrup, or placebo, as vitamin B-complex syrup, for 14 days, concomitantly with antimicrobial treatment (49 per group). Chest radiograph and blood tests were done for confirmation of diagnosis and severity of pneumonia was assessed by breathing rate, chest in-drawing and body temperature. Potentially immunosuppressed children or those with serious comorbidity were excluded. Follow-up was done daily while subjects were admitted (generally 7 days) and the final assessment made on the 14th day on out-patient basis.

RESULTS: Children enrolled in zinc and placebo groups were of comparable age [17 ± 10 and 10 ± 30 months (median \pm interquartile range) respectively] and sex distribution [34 (69.4%) vs 31 (63.3%) males respectively]. Duration of illness at diagnosis was also comparable. Patients supplemented with zinc showed no difference in clinical cure rate at 14 days when compared with placebo. Fast breathing was present after 1 wk of treatment in 49% subjects in zinc supplemented vs 43% on placebo ($p=0.685$). There was also no difference in breathing rate at

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study end. Regarding fever, the mean temperature was $<99^{\circ}\text{F}$ in both groups at study end. Hemoglobin, total leukocyte count, standard liver function tests and creatinine showed no difference between groups either at baseline or at study end. There were no treatment emergent adverse events attributable to zinc.

CONCLUSIONS: Though well tolerated, the addition of zinc does not improve symptom duration or cure rate in acute bacterial pneumonia in under-five children.

[J Pediatr.](#) 2012 Jan;160(1): 129-35.e3. Epub 2011 Aug 25.

[Short-term zinc supplementation with dispersible tablets or zinc sulfate solution yields similar positive effects on plasma zinc concentration of young children in Burkina Faso: a randomized controlled trial.](#)

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OBJECTIVE: To assess zinc absorption from dispersible tablets by investigating the effects of short-term zinc supplementation, provided either as zinc (Zn) sulfate dispersible tablets or solution, on changes in plasma Zn concentration in young children.

STUDY DESIGN: We conducted a randomized, partially-masked, placebo-controlled trial in 451 children 6 to 23 months of age in Burkina Faso, randomly assigned to receive a dispersible tablet containing 5 mg Zn, a Zn solution containing 5 mg Zn/5 mL, or a placebo solution, daily for 3 weeks. The main outcome measure was change in plasma zinc concentration after supplementation compared with baseline.

RESULTS: The mean plus or minus SD change in plasma Zn concentration ($\mu\text{g}/\text{dL}$) was significantly greater in both Zn supplemented groups (tablets: $16.9\pm 13.1\mu\text{g}/\text{dL}$, liquid: $16.6\pm 14.2\mu\text{g}/\text{dL}$), compared with the placebo group ($0.2\pm 10.9\mu\text{g}/\text{dL}$; $P<.001$, ANOVA). In both Zn supplemented groups, but not in the placebo group, change in plasma Zn concentration was progressively less with increasing age in months ($-0.79\mu\text{g}/\text{dL}/\text{mo}$ and $-1.15\mu\text{g}/\text{dL}/\text{mo}$, respectively; $P<.001$); this effect did not differ in the Zn supplemented groups ($P=.18$).

CONCLUSIONS: Short-term supplementation results in a large increase in plasma Zn concentration, regardless of whether the additional Zn is provided as a dispersible tablet or solution.