

RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

6th Edition
July 2007-June 2008

www.ichrc.org

Please send suggestions about this booklet to:

A-Prof Trevor Duke

Centre for International Child Health

University Department of Paediatrics

Royal Children's Hospital

Parkville, 3052, Victoria, Australia

Telephone: (613) 9345 5968 / 9345 5522

Fax: (613) 9345 6667

Email: trevor.duke@rch.org.au

Randomised trials in child health in developing countries 2007-08

SEARCH STRATEGY

Pubmed Hayne's strategy, search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Asia-Pacific) and (Child*)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])).

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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/entrez/query.fcgi>

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 appropriately performed 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 there were 161 studies identified. These came from all regions of the world, mostly from developing country researchers. Several trials from 2007-08 may lead to significant changes in child health approaches or clinical recommendations. Some key findings include:

- Outpatient treatment of WHO defined severe pneumonia was shown to be safe and effective in children without complications and in areas that are not HIV endemic
- Giving zinc and ORS to children with diarrhoea improves prescribing of ORS, and reduces subsequent morbidity from acute respiratory infection
- In HIV-affected infants in Zambia, mortality was higher when there was abrupt weaning from breast milk at 4 months of age.
- Giving mothers nevirapine or nevirapine and zidovudine for 14 weeks has a strong protective effect against HIV transmission through breast milk.
- A package of home-based antenatal and neonatal care reduced neonatal mortality in Bangladesh
- In Kenya there has been sustained benefit on child survival of insecticide treated bed-nets; it was estimated that 7 deaths were averted for every 1000 bed-nets distributed.
- Topically applied sunflower oil improved survival rates among preterm hospitalized infants in Bangladesh.
- Rectally administered quinine is effective for the treatment of severe malaria, as has been shown with dihydroartemisinin and artesunate, useful where intravenous access is not possible or the child is vomiting
- IV phenytoin, IV valproate or buccal midazolam are effective and safe for the treatment of status epilepticus. Diazepam should not be given as an IV infusion.
- Artemisinin derivatives have important anti-schistosomal effects.

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We have again included the web-link for papers that are freely available in full-text on the Internet. This year there were 121 such studies, an increase on previous years indicating the increased numbers of open access on-line journals. More importantly, through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with major publishers, the full-text version of over 3750 journals are available to health institutions in 113 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 (2002-2007) are available at: www.ichrc.org

Trevor Duke
August 2008

Acute respiratory infection

(See also Measles)

[PLoS ONE](#). 2008 Apr 23;3(4):e1991.



Does 3-day course of oral amoxicillin benefit children of non-severe pneumonia with wheeze: a multicentric randomised controlled trial.

[Awasthi S](#), [Agarwal G](#), [Kabra SK](#), [Singhi S](#), [Kulkarni M](#), [More V](#), [Niswade A](#), [Pillai RM](#), [Luke R](#), [Srivastava NM](#), [Suresh S](#), [Verghese VP](#), [Raghupathy P](#), [Lodha R](#), [Walter SD](#).

King George's Medical University, Lucknow, India. sawasthi@sancharnet.in

BACKGROUND: WHO-defined pneumonias, treated with antibiotics, are responsible for a significant proportion of childhood morbidity and mortality in the developing countries. Since substantial proportion pneumonias have a viral etiology, where children are more likely to present with wheeze, there is a concern that currently antibiotics are being over-prescribed for it. Hence the current trial was conducted with the objective to show the therapeutic equivalence of two treatments (placebo and amoxicillin) for children presenting with non-severe pneumonia with wheeze, who have persistent fast breathing after nebulisation with salbutamol, and have normal chest radiograph. **METHODOLOGY:** This multi-centric, randomised placebo controlled double blind clinical trial intended to investigate equivalent efficacy of placebo and amoxicillin and was conducted in ambulatory care settings in eight government hospitals in India.

Participants were children aged 2-59 months of age, who received either oral amoxicillin (31-54 mg/Kg/day, in three divided doses for three days) or placebo, and standard bronchodilator therapy. Primary outcome was clinical failure on or before day- 4.

PRINCIPAL FINDINGS: We randomized 836 cases in placebo and 835 in amoxicillin group. **Clinical failures occurred in 201 (24.0%) on placebo and 166 (19.9%) on amoxicillin (risk difference 4.2% in favour of antibiotic, 95% CI: 0.2 to 8.1).** Adherence for both placebo and amoxicillin was >96% and 98.9% subjects were followed up on day- 4. Clinical failure was associated with (i) placebo treatment (adjusted OR = 1.28, 95% CI: 1.01 to 1.62), (ii) excess respiratory rate of >10 breaths per minute (adjusted OR = 1.51, 95% CI: 1.19, 1.92), (iii) vomiting at enrolment (adjusted OR = 1.49, 95% CI: 1.13, 1.96), (iv) history of use of bronchodilators (adjusted OR = 1.71, 95% CI: 1.30, 2.24) and (v) non-adherence (adjusted OR = 8.06, 95% CI: 4.36, 14.92). **CONCLUSIONS:** Treating children with non-severe pneumonia and wheeze with a placebo is not equivalent to treatment with oral amoxicillin. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00407394.

[BMJ](#). 2008 Jan 12;336(7635):80-4. Epub 2008 Jan 8.



Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study).

[Asghar R](#), [Banajeh S](#), [Egas J](#), [Hibberd P](#), [Iqbal I](#), [Katep-Bwalya M](#), [Kundi Z](#), [Law P](#), [MacLeod W](#), [Maulen-Radovan I](#), [Mino G](#), [Saha S](#), [Sempertegui F](#), [Simon J](#), [Santosham M](#), [Singhi S](#), [Thea DM](#), [Qazi S](#); [Severe Pneumonia Evaluation Antimicrobial Research Study Group](#).

Rawalpindi General Hospital, Rawalpindi, Pakistan.

OBJECTIVE: To evaluate whether five days' treatment with injectable ampicillin plus gentamicin compared with chloramphenicol reduces treatment failure in children aged 2-59 months with community acquired very severe pneumonia in low resource settings. **DESIGN:** Open label randomised controlled trial. **SETTING:** Inpatient wards within tertiary care hospitals in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia. **PARTICIPANTS:** Children aged 2-59 months with WHO defined very severe pneumonia. **INTERVENTION:** Chloramphenicol versus a combination of ampicillin plus gentamicin. **MAIN OUTCOME MEASURES:** Primary outcome measure was treatment failure at five days. Secondary outcomes were treatment failure defined similarly among all participants evaluated at 48 hours and at 10 and 21 days. **RESULTS:** **More children failed treatment with chloramphenicol at day 5 (16% v 11%; relative risk 1.43, 95% confidence interval 1.03 to 1.97) and also by days 10 and 21.** Overall, 112 bacterial isolates were obtained from blood and lung aspirates in 110 children (11.5%), with the most common organisms being *Staphylococcus aureus* (n=47) and *Streptococcus pneumoniae* (n=22). In subgroup analysis, bacteraemia with any organism increased the risk of treatment failure at 21 days in the chloramphenicol group (2.09, 1.41 to 3.10) but not in the ampicillin plus gentamicin group (1.12, 0.59 to 2.13). Similarly, isolation of *S pneumoniae* increased the risk of treatment failure at day 21 (4.06, 2.73 to 6.03) and death (5.80, 2.62 to 12.85) in the chloramphenicol group but not in the ampicillin plus gentamicin group. No difference was found in treatment failure for children with *S aureus* bacteraemia in the two groups, but the power to detect a difference in this subgroup analysis was low. Independent predictors of treatment failure by multivariate analysis were hypoxaemia (oxygen saturation <90%), receiving chloramphenicol, being female, and poor immunisation status. **CONCLUSION:** **Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings.** **TRIAL REGISTRATION:** Current Controlled Trials ISRCTN39543942.

[Lancet](#). 2008 Jan 5;371(9606):49-56.



Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial.

[Hazir T](#), [Fox LM](#), [Nisar YB](#), [Fox MP](#), [Ashraf YP](#), [MacLeod WB](#), [Ramzan A](#), [Maqbool S](#), [Masood T](#), [Hussain W](#), [Murtaza A](#), [Khawar N](#), [Tariq P](#), [Asghar R](#), [Simon JL](#), [Thea DM](#),

[Qazi SA; New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia Study Group.](#)

Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.

BACKGROUND: WHO case management guidelines for severe pneumonia involve referral to hospital for treatment with parenteral antibiotics. If equally as effective as parenteral treatment, home-based oral antibiotic treatment could reduce referral, admission, and treatment costs. Our aim was to determine whether home treatment with high-dose oral amoxicillin and inpatient treatment with parenteral ampicillin were equivalent for the treatment of severe pneumonia in children. **METHODS:** This randomised, open-label equivalency trial was done at seven study sites in Pakistan. **2037 children aged 3-59 months with severe pneumonia were randomly allocated to either initial hospitalisation and parenteral ampicillin (100 mg/kg per day in four doses) for 48 h, followed by 3 days of oral amoxicillin (80-90 mg/kg per day; n=1012) or to home-based treatment for 5 days with oral amoxicillin (80-90 mg/kg per day in two doses; n=1025).** Follow-up assessments were done at 1, 3, 6, and 14 days after enrollment. The primary outcome was treatment failure (clinical deterioration) by day 6. Analyses were done per protocol and by intention to treat. This trial is registered, ISRCTN95821329. **FINDINGS:** In the per-protocol population, 36 individuals were excluded from the hospitalised group and 37 from the ambulatory group, mainly because of protocol violations or loss to follow-up. There were 87 (8.6%) treatment failures in the hospitalised group and 77 (7.5%) in the ambulatory group (risk difference 1.1%; 95% CI -1.3 to 3.5) by day 6. Five (0.2%) children died within 14 days of enrollment, one in the ambulatory group and four in the hospitalised group. In each case, treatment failure was declared before death and the antibiotic had been changed. None of the deaths were considered to be associated with treatment allocation; there were no serious adverse events reported in the trial. **INTERPRETATION: Home treatment with high-dose oral amoxicillin is equivalent to currently recommended hospitalisation and parenteral ampicillin for treatment of severe pneumonia without underlying complications,** suggesting that WHO recommendations for treatment of severe pneumonia need to be revised.

Comment

A high proportion of children in this study had wheeze, suggesting respiratory viral infection was a common cause of illness. Also the probability of death was much lower (0.2%) than other studies of severe pneumonia (5-16%). Both these factors indicate the need for caution in extrapolating to high mortality regions, or regions with high HIV prevalence without further data.

[Trop Med Int Health.](#) 2007 Nov;12(11):1377-85.



Epidemiology and clinical features of pneumonia according to radiographic findings in Gambian children.

[Enwere G](#), [Cheung YB](#), [Zaman SM](#), [Akano A](#), [Oluwalana C](#), [Brown O](#), [Vaughan A](#), [Adegbola R](#), [Greenwood B](#), [Cutts F](#).

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Medical Research Council Laboratories, Fajara, The Gambia. enwereg@who.int

OBJECTIVE: To assess the effect of vaccines against pneumonia in Gambian children. **METHODS:** Data from a randomized, controlled trial of a 9-valent pneumococcal conjugate vaccine (PCV) were used. Radiographic findings, interpreted using WHO definitions, were classified as primary end point pneumonia, 'other infiltrates/abnormalities' pneumonia and pneumonia with no abnormality. We calculated the incidence of the different types of radiological pneumonia, and compared clinical and laboratory features between these groups. **RESULTS:** Among children who did not receive PCV, the incidence of pneumonia with no radiographic abnormality was about twice that of 'other infiltrates' pneumonia and three times that of primary endpoint pneumonia. Most respiratory symptoms, reduced feeding and vomiting occurred most frequently in children with primary endpoint pneumonia. These children were more likely to be malnourished, to have bronchial breath sounds or invasive bacterial diseases, and to die within 28 days of consultation than children in the other groups. Conversely, a history of convulsion, diarrhoea or fast breathing, malaria parasitaemia and isolation of salmonellae were commoner in children with pneumonia with no radiographic abnormality. Lower chest wall indrawing and rhonchi on auscultation were seen most frequently in children with 'other infiltrates/abnormalities' pneumonia. **CONCLUSION:** Primary endpoint pneumonia is strongly associated with bacterial aetiology and severe pneumonia. Since this category of pneumonia is significantly reduced after vaccination with Hib and pneumococcal vaccines, the risk-benefit of antimicrobial prescription for clinical pneumonia for children with increased respiratory rate may warrant re-examination once these vaccines are in widespread use.

[Am J Clin Nutr.](#) 2007 Aug;86(2):397-403.



Infectious etiology modifies the treatment effect of zinc in severe pneumonia.

[Coles CL](#), [Bose A](#), [Moses PD](#), [Mathew L](#), [Agarwal I](#), [Mammen T](#), [Santosham M](#).

Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA. ccoles@jhsph.edu

BACKGROUND: Zinc is undergoing evaluation as an inexpensive therapeutic adjuvant for severe pediatric pneumonia. **OBJECTIVE:** We explored the effect of etiology on the treatment effect of zinc in young children hospitalized for severe pneumonia. **DESIGN:** We analyzed data from a randomized, double-blind, placebo-controlled clinical trial conducted at the Christian Medical College Hospital, a teaching hospital in Tamilnadu, India. Children aged 2-23 mo (n = 299) were randomly assigned to receive a 10-mg tablet of zinc sulfate or placebo twice a day during hospitalization. The primary outcomes were length of hospitalization and time to resolution of severe pneumonia stratified by etiologic classification on the basis of serum C-reactive protein (CRP) concentrations at admission. **RESULTS:** CRP concentrations were available for 295 (98.7%) of the enrolled cases. Of these 295 cases, 223 (75.6%) were classified as suspected nonbacterial pneumonias (CRP concentrations \leq 40 mg/L). Etiology modified the treatment effect of zinc on the length of the hospital stay [hazard ratio (HR) for interaction term: 0.52; 95% CI: 0.31, 0.91; P = 0.022]. In the 72 suspected bacterial cases (CRP concentrations $>$ 40 mg/L), the median length of hospitalization was approximately 20 h longer

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in the zinc-supplemented group than in the placebo group (87.3 and 68.3 h, respectively; HR: 0.56; 95% CI: 0.34, 0.93; P = 0.025). The treatment effect was not modified in the suspected nonbacterial cases of pneumonia. **CONCLUSIONS:** Our results suggest that the treatment effect of zinc for severe pediatric pneumonia may be modified by bacterial infection. Further studies are required to develop appropriate recommendations for the use of zinc in the treatment of severe pneumonia. This trial was registered at clinicaltrials.gov as NCT00198666.

Comment

The validity of this study is based on the predictive value of C-reactive protein for bacterial pneumonia. Another study in 2008 showed children with bacterial pneumonia were significantly more likely to have serum CRP concentrations exceeding 35-60 mg/L than children with nonbacterial infections (odds ratio = 2.58, 95% confidence interval = 1.20-5.55). In children with pneumonia, serum CRP concentrations exceeding 40-60 mg/L weakly predict a bacterial etiology (Pediatr Infect Dis J. 2008 Feb;27:95-9). However CRP should not be relied upon to make decision about whether a child with pneumonia should receive antibiotics or not.

[Arch Dis Child](#). 2007 Nov;92(11):976-9. Epub 2007 Jun 26.



Impact of HIV-1 status on the radiological presentation and clinical outcome of children with WHO defined community-acquired severe pneumonia.

[Jeena PM](#), [Minkara AK](#), [Corr P](#), [Bassa F](#), [McNally LM](#), [Coovadia HM](#), [Fox M](#), [Hamer DH](#), [Thea D](#).

Department of Paediatrics and Child Health, University of KwaZulu-Natal, Congella, Durban, South Africa. jeena@ukzn.ac.za

AIMS: We compared the radiological features and outcome of WHO defined severe pneumonia among HIV infected and exposed uninfected children randomised to receive penicillin or oral amoxicillin in Durban, South Africa. **METHODS:** Of 425 children aged between 3 and 59 months with WHO defined severe pneumonia, 366 had anonymous HIV testing performed. Outcome was assessed by failure to improve at 48 h after enrolment or deterioration within 14 days. Chest radiographs were evaluated according to WHO defined radiological criteria for pneumonia and internationally standardised radiological criteria. Findings were stratified for HIV status. **RESULTS:** 82 (22.4%) children were HIV infected, 40 (10.9%) were HIV exposed and 244 (66.7%) were HIV uninfected. The day 14 outcome in children <12 months of age was significantly worse in HIV-1 infected than HIV uninfected children (OR 2.8 (95% CI 1.35 to 3.5), p = 0.002), while HIV-1 infected and uninfected children aged > or =12 months had equivalent outcomes. Parental penicillin and oral amoxicillin had equivalent response rates in all HIV groups. According to the WHO radiological classification, children who failed WHO standard antimicrobial treatment had significantly higher "other consolidates/infiltrates" than "endpoints for consolidation" in the HIV infected group (OR 5.45 (95% CI 1.58 to 21.38), p<0.002), while the reverse was true for HIV exposed uninfected children (OR 4.13 (95% CI 0.88 to 20.57), p<0.036). **CONCLUSIONS:** **The WHO standard treatment guideline for severe pneumonia is inadequate for HIV-1 infected infants. The increased prevalence of "other consolidates/infiltrates" among HIV-1 infected children who failed standard treatment supports the addition of co-trimoxazole to WHO standard treatment.**

Anaemia

(See also Nutrition)

[Cad Saude Publica](#). 2007 Jul;23(7):1547-52.

free full text
available at SciELO.org

Effectiveness of different iron supplementation strategies on hemoglobin and ferritin levels among schoolchildren in Teresina, Piauí State, Brazil

[Dos Santos MM](#), [Nogueira Ndo N](#), [Diniz Ada S](#).

Departamento de Nutrição, Universidade Federal do Piauí, Teresina, Brasil.
marizesantos@ufpi.br

This study evaluated the effectiveness of supplementation with ferrous sulfate and iron bis-glycinate chelate on hemoglobin and serum ferritin levels among schoolchildren (7-11 years) of both sexes. A randomized community-based trial including 138 anemic children (hemoglobin < 11.5 g/dL) was conducted in Teresina, Piauí State, Brazil. Children were assigned to two treatment groups on an individual basis. **One group (n = 71) received 40 mg iron as ferrous sulfate once weekly and the other group (n = 67) received 3.8 mg of iron bis-glycinate chelate-enriched cookies, 3x/week, for 8 weeks. The interventions showed a significant increase (p < 0.01) in hemoglobin levels (1.1g/dL) for children who received ferrous sulfate and 0.9 g/dl in those who received iron bis-glycinate chelate, although not significant in the inter-group comparison (p > 0.05).** No effect was observed on body iron for either intervention (p > 0.05). Children with depleted iron stores (< 15 ng/mL) at the beginning of interventions showed increased serum ferritin concentrations after 8 weeks (p < 0.01), although no difference between treatments (p > 0.05) was observed. The results confirm the effectiveness of the iron supplementation interventions and corroborate the use of iron salts or ferrous bisglycinate chelate on a weekly basis to overcome iron deficiency and anemia.

Anaesthesia and intensive care

[Anaesth Intensive Care](#). 2008 Mar;36(2):174-9.

Comparison of caudal epidural bupivacaine with bupivacaine plus tramadol and bupivacaine plus ketamine for postoperative analgesia in children.

[Choudhuri AH](#), [Dharmani P](#), [Kumarl N](#), [Prakash A](#).

Department of Anaesthesiology, Aruna Asaf Ali Government Hospital, Delhi, India.

This study compared the effect of single-dose caudal epidural bupivacaine, bupivacaine plus ketamine and bupivacaine plus tramadol for postoperative pain management in children having

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surgery for inguinal hernia. Following ethics committee approval and informed parental consent, 75 children ASA PS I and II, between three and nine years of age and scheduled for elective unilateral inguinal hernia repair with general anaesthesia were recruited. The patients were randomly divided into three groups to receive 0.5 ml/kg caudal bupivacaine 0.25% (group B), bupivacaine 0.25% plus tramadol 1 mg/kg (group BT) or bupivacaine 0.25% plus ketamine 0.5 mg/kg (group BK). The injections were performed under general anaesthesia. Mean arterial pressure, heart rate, pulse oximetry, respiratory rate and sedation and pain scores were recorded at defined intervals following recovery from anaesthesia. The groups were similar in age, weight and duration of operation ($P > 0.05$). No patient experienced hypotension, bradycardia or respiratory depression. Duration of analgesia was (mean \pm SD) 6.5 \pm 4.1 h in group B, 9.2 \pm 3.9 h in group BK, and 8.5 \pm 3.1 h in group BT ($P < 0.05$). More patients in group B required supplementary analgesics in the first 24 h ($P < 0.05$). Sedation scores were comparable in all groups. Incidence of emesis and pruritus was similar in all the groups. Caudally administered 0.5 ml/kg bupivacaine 0.25% plus ketamine or bupivacaine 0.25% plus tramadol 1 mg/kg provided significantly longer duration of analgesia without an increase in the adverse effects when compared to bupivacaine alone.

[Paediatr Anaesth.](#) 2008 Apr;18(4):308-12.



Laryngeal mask airway insertion in children: comparison between rotational, lateral and standard technique.

[Ghai B](#), [Makkar JK](#), [Bhardwaj N](#), [Wig J](#).

Department of Anaesthesia and Intensive Care, Post Graduate Institute of Medical Education and Research, Chandigarh, India. ghaibabita@hotmail.com

BACKGROUND: The purpose of the study was to compare the success and ease of insertion of three techniques of laryngeal mask airway (LMA) insertion; the standard Brain technique, a lateral technique with cuff partially inflated and a rotational technique with cuff partially inflated. **METHODS:** One hundred and sixty-eight ASA I and II children aged 6 months to 6 years undergoing short elective surgical procedures lasting 40-60 min were included in the study. A standard anesthesia protocol was followed for all patients. Patients were randomly allocated into one of the three groups i.e. standard (S), rotational (R) and lateral (L). The primary outcome measure of the study was success rate at the first attempt using three techniques of LMA insertion. Secondary outcomes measures studied were overall success rate, time before successful LMA insertion, complications and maneuvers used to relieve airway obstruction. **RESULTS:** Successful insertion at the first attempt was significantly higher in group R (96%) compared with group L (84%) and group S (80%) ($P = 0.03$). Overall success rate (i.e. successful insertion with two attempts) was 100% for group R, 93% for group L and 87% for group S ($P = 0.03$). Time for successful insertion was significantly lower in group R compared with group L and S ($P < 0.001$). The incidence of complications was lower in group R. **CONCLUSIONS:** A rotational technique with partially inflated cuff is associated with the highest success rate of insertion and lowest incidence of complications and could be the technique of first choice for LMA insertion in pediatric patients.

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[J Clin Pediatr Dent.](#) 2007 Fall;32(1):1-4.

Sedation in uncooperative children undergoing dental procedures: a comparative evaluation of midazolam, propofol and ketamine.

[Rai K](#), [Hegde AM](#), [Goel K](#).

Department of Pedodontics and Preventive Children Dentistry, A.B. Shetty Memorial Institute of Dental Sciences, Mangalore, Karnataka, India.

Dentists usually face a common problem dealing with pediatric patients due to their high levels of anxiety and fear, associated with dental procedures. Such children are usually managed by various pharmacological methods. The efficacy and safety of conscious sedation, using intravenous short acting group of drugs (midazolam, propofol and ketamine) in uncooperative children, requiring oral rehabilitation was thus evaluated in this study. A total of 30 uncooperative children, aged 3-6 years, belonging to ASA I, II category formed the study group. The efficacy of the three group of drugs was evaluated on the basis of the onset of sedation, duration of action, side effects encountered, and the overall cooperative behavior of the child throughout the course of the procedure, after obtaining parental consent. Results showed that propofol was highly effective in terms of onset of sedation, although increased body movements and crying, pain on injection and intermittent cough was observed as the main side effects of the drug. Midazolam showed the longest duration of action, but was not very effective in terms of treatment completion due to increased movements and crying. Maximum cooperation during the procedure was obtained with ketamine and no adverse effects were encountered. We preferred ketamine from the results of our study and recommended future evaluation of ketamine in combination with other sedatives.

[J Paediatr Child Health.](#) 2008 Apr;44(4):201-4. Epub 2007 Oct 10.



Efficacy and safety of a mixture of ketamine, midazolam and atropine for procedural sedation in paediatric oncology: a randomised study of oral versus intramuscular route.

[Bhatnagar S](#), [Mishra S](#), [Gupta M](#), [Srikanti M](#), [Mondol A](#), [Diwedi A](#).

Department of Anaesthesia, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India.

AIM: To evaluate the efficacy and safety of a mixture of ketamine, midazolam and atropine given orally by comparing the same mixture given through the intramuscular route in children with malignancy undergoing minor invasive procedures. METHODS: Sixty children, aged between 1 and 10 years, scheduled to undergo minor procedures were randomised into two groups to receive a mixture of ketamine (6 mg/kg), midazolam (0.05 mg/kg) and atropine (0.02 mg/kg) intramuscularly (Group 1) or ketamine (10 mg/kg), midazolam (0.2 mg/kg) and atropine (0.05 mg/kg) orally (Group 2). Sedation score, observer-rated visual analogue scale for pain were noted by an observer blinded to the route of drug administration. RESULTS: Optimum

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sedation was present in all children in both groups after drug administration, with Group 1 being more deeply sedated than Group 2 at the start of the procedure. Supplementation with intravenous ketamine was required in four children in Group 1 and eight children in Group 2 ($P = 0.33$). The mean (\pm SD) observer-rated visual analogue scale for pain during the procedure was 8.33 (\pm 15.99) and 9.33 (\pm 16.39) in Group 1 and Group 2, respectively ($P = 0.892$). One patient in Group 1 had vomiting after the procedure. There were no differences in proportion of patients with hallucinations and nystagmus in both groups. CONCLUSIONS: A mixture of ketamine, midazolam and atropine given orally provides sedation and analgesia similar to that produced by the same drugs given intramuscularly. It offers advantage over the intramuscular route as it is painless and can be given for minor paediatric oncology procedures with appropriate monitoring.

[Anaesthesia](#). 2007 Nov;62(11):1110-3.



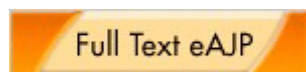
A prospective randomised double blind study to evaluate the effect of peribulbar block or topical application of local anaesthesia combined with general anaesthesia on intra-operative and postoperative complications during paediatric strabismus surgery.

[Gupta N](#), [Kumar R](#), [Kumar S](#), [Sehgal R](#), [Sharma KR](#).

Department of Anaesthesiology and Intensive Care, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi-110002, India. drnishkarsh@rediffmail.com

We studied 45 ASA I/II children aged between 2 and 13 years scheduled for elective strabismus surgery, randomly allocated to receive either a peribulbar block or topical lidocaine 2% combined with general anaesthesia, or general anaesthesia alone. The incidence and severity of the oculocardiac reflex, the requirement for atropine, the occurrence of arrhythmias and incidence of postoperative nausea and vomiting following surgery at 1, 2 and 4 h were studied. We found the incidence and severity of oculocardiac reflex intra-operatively was significantly reduced in children who received a peribulbar block. The incidence of postoperative nausea and vomiting was significantly reduced in patients receiving either peribulbar block or topical local anaesthesia combined with general anaesthesia, compared to general anaesthesia alone ($p = 0.008$).

[Aust J Physiother](#). 2007;53(3):163-9.



A recruitment manoeuvre performed after endotracheal suction does not increase dynamic compliance in ventilated paediatric patients: a randomised controlled trial.

[Morrow B](#), [Futter M](#), [Argent A](#).

Randomised trials in child health in developing countries 2007-08

University of Cape Town, South Africa. brenda.morrow@uct.ac.za

QUESTION: Does a recruitment manoeuvre after suctioning have any immediate or short-term effect on ventilation and gas exchange in mechanically-ventilated paediatric patients? **DESIGN:** Randomised controlled trial with concealed allocation, assessor blinding, and intention-to-treat analysis. **PARTICIPANTS:** Forty-eight paediatric patients with heterogeneous lung pathology. Fourteen patients were subsequently excluded from analysis due to large leaks around the endotracheal tube. **INTERVENTION:** The experimental group received a single standardised suctioning procedure followed five minutes later by a standardised recruitment manoeuvre. The control group received only the single suctioning procedure. **OUTCOME MEASURES:** Measurements of ventilation (dynamic lung compliance, expiratory airway resistance, mechanical and spontaneous expired tidal volume, respiratory rate) and gas exchange (transcutaneous oxygen saturation) were recorded, on three occasions before and on two occasions after the recruitment manoeuvre, using a respiratory profile monitor. **RESULTS:** There was no difference between the experimental and the control group in dynamic compliance, expired airway resistance, or oxygen saturation either immediately after the recruitment manoeuvre, or after 25 minutes. The experimental group decreased mechanical expired tidal volume by 0.3 ml/kg (95% CI 0.1 to 0.6), increased spontaneous expired tidal volume by 0.3 ml/kg (95% CI 0.0 to 0.6), and increased total respiratory rate by 3 bpm (95% CI 1 to 4) immediately after the recruitment manoeuvre compared with the control group, but these differences disappeared after 25 minutes. **CONCLUSION:** There is insufficient evidence to support performing recruitment manoeuvres after suctioning infants and children

[Int J Pediatr Otorhinolaryngol.](#) 2007 Nov;71(11):1687-92. Epub 2007 Aug 27.

Is topical local anaesthesia necessary when performing paediatric flexible nasendoscopy? A double-blind randomized controlled trial.

[Jonas NE](#), [Visser MF](#), [Oomen A](#), [Albertyn R](#), [van Dijk M](#), [Prescott CA](#).

Division of Otolaryngology, University of Cape Town, South Africa. nicojonas@gmail.com

OBJECTIVE: To evaluate the effectiveness of lignocain 2% and oxymetazoline 0.025% compared to oxymetazoline 0.025% alone when administered prior to fiberoptic nasendoscopy in paediatric patients. **STUDY DESIGN:** Prospective, randomized controlled, double-blind study. A group of 56 children, undergoing nasendoscopy to determine adenoidal size, were randomized into two groups and received either lignocain 2% and oxymetazoline 0.025% or oxymetazoline 0.025% alone prior to fiberoptic nasendoscopy. **SETTING:** A tertiary care Paediatric Hospital. **METHOD:** The endoscopist recorded the ease of performance of the procedure, cooperation of patient and quality of the view achieved using a visual analogue scale (VAS). The pain and anxiety levels of the child were recorded before, during and immediately after the procedure, using a VAS. The duration of performing the procedure was recorded from insertion of the endoscope into the nostril until removal. **RESULTS:** All 56 children were able to undergo the endoscopy and the full anxiety and pain assessment was done. Three children were excluded because they have undergone nasendoscopies before. Of the 53 patients included, 27 children received solution A (oxymetazoline 0.025%) and 26 children received solution B (oxymetazoline 0.025% and lignocain 2%). There was no statistical difference between the two groups regarding the duration of the endoscopy, quality of view, ease of performance and

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cooperation of the patients. The median pain and anxiety scores were not significantly different between the two groups. **CONCLUSIONS:** This study concludes that the use of a decongestant (oxymetazoline) for paediatric nasendoscopy is just as effective as the use of oxymetazoline with lignocain. Pain and anxiety is not increased in the absence of lignocain.

Asthma

[Fam Process.](#) 2008 Mar;47(1):115-30.

Incorporating family therapy into asthma group intervention: a randomized waitlist-controlled trial.

[Ng SM](#), [Li AM](#), [Lou VW](#), [Tso IF](#), [Wan PY](#), [Chan DF](#).

Centre on Behavioral Health, University of Hong Kong, G/F Pauline Chan Bldg., 10 Sassoon Rd., Pokfulam, Hong Kong, China. ngsiuman@hku.hk

Asthma psychoeducational programs have been found to be effective in terms of symptom-related outcome. They are mostly illness-focused, and pay minimal attention to systemic/familial factors. This study evaluated a novel asthma psychoeducation program that adopted a parallel group design and incorporated family therapy. A randomized waitlist-controlled crossover clinical trial design was adopted. Children with stable asthma and their parents were recruited from a pediatric chest clinic. Outcome measures included, for the patients: exhaled nitric oxide (eNO), spirometry, and adjustment to asthma; and for the parents: perceived efficacy in asthma management, Hospital Anxiety and Depression Scale anxiety subscale, Body Mind Spirit Well-being Inventory emotion subscale, and Short Form 12 health-related quality of life scale. Forty-six patients participated in the study. Attrition rates were 13.0% and 26.0% for the active and control groups, respectively. Repeated-measures ANOVA revealed a significant decrease in airway inflammation, as indicated by eNO levels, and an increase in patient's adjustment to asthma and parents' perceived efficacy in asthma management. Serial trend analysis revealed that most psychosocial measures continued to progress steadily after intervention. Significant improvements in both symptom-related measures and mental health and relationship measures were observed. The findings supported the value of incorporating family therapy into asthma psychoeducation programs.

[Indian Pediatr.](#) 2008 Mar;45(3):225-8.



Salmeterol vs. formoterol: a comparison of rapid bronchodilator effect in a randomized controlled trial.

[Singhania N](#), [Dhamija R](#), [Lodha R](#), [Kabra SK](#).

Pediatric Pulmonology Division, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

We conducted this double blind randomized controlled trial to compare the rapid bronchodilator

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effect of salmeterol and formoterol in 60 children with stable asthma. Participants were randomized to receive either salmeterol (50 microg) (n=31) or formoterol (24 microg) (n=29) by metered dose inhaler and spacer. Spirometry was performed at baseline, at 30 minutes, and at 60 minutes. Bronchodilatation was assessed by changes in FEV(1) at 30 and 60 minutes. Baseline parameters were comparable in the two groups. There was no significant difference in the FEV(1) at 30 and 60 minutes between two groups. We conclude that salmeterol and formoterol both cause bronchodilator response at end of 60 minutes and are not different with regards to their rapid bronchodilator response.

[Indian J Pediatr.](#) 2007 Jul;74(7):631-5.

Randomized trial of spacers in asthma.

[Dahiya B](#), [Mathew JL](#), [Singh M](#).

Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.
meenusingh4@rediffmail.com.

OBJECTIVE: To compare the efficacy of all types of spacers commonly available to children in India. **METHODS:** 150 children 5-14 yr of age with persistent asthma presenting with peak expiratory flow (PEF) < 70% of personal best were randomized to receive 200 mg salbutamol through one of five spacers: A) 750 ml spacer with valve, B) 165 ml spacer with valve, C) 250 ml spacer without valve, D) 1000 ml indigenously made spacer without valve and E) 500 ml indigenously made spacer without valve. PEF measurement was repeated 15 minutes later. Children > 8 yr old performed spirometry in addition to PEF. Absolute change and percentage improvement of PEF and FEV1 were compared among the groups. **RESULTS:** Subjects in all groups had comparable baseline demographic characteristics and PEF. All showed significant improvement in PEF and FEV1 over baseline values. The change in PEF and percentage improvement were comparable among all five groups (p=0.780 and p=0.955 respectively). Likewise change in FEV1 and percentage improvement were also comparable. The five groups showed no difference in efficacy, irrespective of severity of baseline airway obstruction. **CONCLUSION:** The five spacers were equally efficacious for the delivery of bronchodilator in children with moderate persistent asthma presenting with airway obstruction.

[J Investig Allergol Clin Immunol.](#) 2007;17(4):216-26.



Group education on asthma for children and caregivers: a randomized, controlled trial addressing effects on morbidity and quality of life.

[Cano-Garcinuño A](#), [Díaz-Vázquez C](#), [Carvajal-Urueña I](#), [Praena-Crespo M](#), [Gatti-Viñoly A](#), [García-Guerra I](#).

Centro de Salud de Villamuriel de Cerrato, Palencia, Spain. acanog@compalencia.org

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OBJECTIVE: To establish the efficacy in terms of morbidity and quality of life of a group education program on asthma aimed at children and caregivers. **METHODS:** An open, randomized, controlled trial was undertaken in 13 primary health care centers in Spain, Cuba, and Uruguay and involved 245 children with active asthma aged 9 to 13 years and their caregivers. The intervention consisted of 3 educational sessions lasting 45 to 60 minutes each and was performed with 3 intervention groups: children alone, caregivers alone, and both children and caregivers. The outcome measures were difference between intervention and control groups in the rate of asthma attacks and hospital admission, as well as the quality of life of children and caregivers in the 6 months following the intervention. **RESULTS:** The rate of asthma attacks per patient-year decreased when the intervention was given only to children (mean difference, -1.61; 95% confidence interval [CI], -2.87 to -0.34) or to both children and caregivers (-1.60; 95% CI, -2.88 to -0.31). Hospital admissions per patient-year decreased in the intervention groups children alone (-0.28; 95% CI, -0.51 to -0.05) and both children and caregivers (-0.25; 95% CI, -0.49 to -0.02). Education provided to caregivers alone was not associated with any changes in morbidity. No differences were observed in terms of quality of life between controls and any of the intervention groups. **CONCLUSIONS:** Group education on asthma reduces morbidity but does not improve quality of life. The benefits are apparent when education is aimed at children but no additional benefit is obtained if the intervention is also aimed at their caregivers. Finally, group education for adult caregivers alone is not effective.

[J Trop Pediatr.](#) 2007 Oct;53(5):325-30. Epub 2007 Jul 10.



Montelukast vs. inhaled low-dose budesonide as monotherapy in the treatment of mild persistent asthma: a randomized double blind controlled trial.

[Kumar V](#), [Ramesh P](#), [Lodha R](#), [Pandey RM](#), [Kabra SK](#).

Department of Pediatrics, AIIMS, Ansari Nagar, New Delhi 110029, India.

BACKGROUND: Guidelines recommend daily controller therapy for mild persistent asthma. Montelukast has demonstrated consistent benefit in controlling symptoms of asthma and may be an alternative, orally administered, nonsteroidal agent for treating mild asthma. **Aim:** To determine whether montelukast is as effective as budesonide in controlling mild persistent asthma as determined by FEV(1). **METHODS:** Between November 2003 to October 2005, participants aged 5-15 years with recently diagnosed mild persistent asthma (n = 62) were randomized to oral montelukast (5 mg daily) [N(1) = 30] or inhaled budesonide (400 microg per day in two doses) [N(2) = 32] in a single center, double-blind study. **RESULTS:** Baseline demographic and spirometric parameters were comparable. The median (95% confidence interval) percentage predicted FEV(1) was similar in the two groups after 12 weeks of treatment (budesonide: 76.70 (67.96-90.53%), montelukast: 75 (67.40-88.47)%; p = 0.44). There was similar improvement in spirometric parameters and clinical symptom scores in both the groups. There was no statistically significant difference between the groups in the need for rescue drugs as well as side effects reported by parents. **CONCLUSION:** Montelukast is as effective as inhaled budesonide in the treatment of mild persistent asthma in children aged 5-15 years. Montelukast may be used as an alternative to low dose inhaled corticosteroids for management of mild persistent asthma

[Respir Med.](#) 2007 Oct;101(10):2182-91. Epub 2007 Jul 5.

Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma.

[Vermeulen JH](#), [Gyurkovits K](#), [Rauer H](#), [Engelstätter R](#).

Dorp Street 20, Panorama 7500, Cape Town, South Africa. jvm@iafrica.com

BACKGROUND: The aim of the study was to investigate the efficacy and safety of ciclesonide compared with budesonide in adolescents with severe asthma. **METHODS:** In this randomized, double-blind, double-dummy, parallel-group study, patients aged 12-17 years with severe asthma were treated with budesonide 400 microg once daily (QD) in a 2-week run-in period. At randomization, eligible patients were assigned 2:1 to ciclesonide 320 microg QD (ex-actuator) or budesonide 800 microg QD (metered dose), respectively, in the evening. Forced expiratory volume in 1s (FEV(1)) was the primary variable. Patients recorded asthma symptom score and rescue medication use in diaries. Safety assessments included adverse events (AEs) and 24-h urine cortisol. **RESULTS:** Four hundred and three patients were randomized. Ciclesonide 320 microg QD and budesonide 800 microg QD significantly increased FEV(1) (least-squares mean: 505 and 536 mL, respectively; both $p < 0.0001$ versus baseline) in the intention-to-treat (ITT) population. Lower limits of the 95% confidence intervals (ITT: -138 mL; per-protocol: -122 mL) were above the non-inferiority limit (-150 mL). Median percentage of days without asthma symptoms and without rescue medication use was 84% with ciclesonide and 85% with budesonide. AEs were unremarkable, with no cases of confirmed candidiasis. Median creatinine-adjusted urine cortisol significantly decreased with budesonide treatment (15.9-13.7 nmol cortisol/mmol creatinine; $p = 0.0086$ versus baseline), but not with ciclesonide ($p = 0.1125$). **CONCLUSIONS:** Ciclesonide 320 microg QD showed similar efficacy to budesonide 800 microg QD in adolescents with severe asthma. Ciclesonide was well tolerated and, unlike budesonide, had no effect on urine cortisol levels. **CLINICAL TRIAL REGISTRATION NUMBER:** EudraCT No.: 2004-001233-41.

[Pulm Pharmacol Ther.](#) 2008;21(2):264-75. Epub 2007 May 21.

Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma.

[Bateman ED](#), [Linnhof AE](#), [Homik L](#), [Freudensprung U](#), [Smau L](#), [Engelstätter R](#).

Division of Pulmonology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, PO Box 34560, Groote Schuur 7937, Cape Town, South Africa.
Eric.Bateman@uct.ac.za

OBJECTIVE: To investigate the relative efficacy of ciclesonide and fluticasone propionate (FP) administered at comparable microgram doses in maintaining asthma control in patients with moderate-to-severe persistent asthma. **METHODS:** This randomized, open-label, parallel-group study enrolled patients aged 12-75 years with a 6-month history of bronchial asthma. To enter a 2-week run-in period, patients had to have received FP 500-1000 microg/day or equivalent at a stable dose for 4 weeks and have a forced expiratory volume in 1s (FEV 1) 80% of predicted. To enter the treatment period, patients had to have the following during run-in: FEV 1 80% of predicted; reversibility of Delta FEV 1 12% after 200-400 microg salbutamol; and 1 day without

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asthma symptoms during the last 7 days. Patients were randomized to twice-daily ciclesonide 320 microg (ex-actuator) or twice-daily FP 330 microg (ex-actuator) for 6 months. Efficacy was assessed by lung function, asthma exacerbations, asthma symptoms and rescue medication use. Patients completed the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]). Adverse events (AEs), including local oropharyngeal AEs, were recorded. RESULTS: 528 patients were randomized (ciclesonide, n=255; FP, n=273). In both groups, FEV₁ was maintained from baseline to study end (mean increase: ciclesonide 11 mL, FP 24 mL; intention-to-treat [ITT] analysis). The least squares mean \pm standard error of the mean for the treatment difference was -13 \pm 29 (95% confidence interval [CI]: -70, 44) in the ITT analysis and -27 \pm 34 (95% CI: -93, 40) in the per-protocol (PP) analysis, demonstrating non-inferiority of ciclesonide to FP. Morning, evening and site-measured PEF improved significantly with both treatments (ITT and PP analyses: p<0.05). Six patients receiving ciclesonide and seven receiving FP (ITT analysis) experienced an asthma exacerbation requiring treatment with oral corticosteroids. Both treatments significantly decreased asthma symptom score sum (ITT and PP analyses: p0.0001) and rescue medication use (ITT and PP analyses: p<0.05), with no significant difference between treatments. Both treatments significantly improved overall AQLQ(S) score (ITT and PP analyses: p<0.05). Significantly more patients experienced candidiasis and dysphonia with FP compared with ciclesonide (p=0.0023). CONCLUSION: Ciclesonide 320 microg and FP 330 microg administered twice daily over 6 months provided similar efficacy in patients with moderate or severe persistent asthma previously well-controlled by high doses of ICS at baseline. Ciclesonide was associated with fewer local AEs than FP.

Dengue

[Am J Trop Med Hyg.](#) 2007 Dec;77(6):1135-8.



Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection.

[Dimaano EM](#), [Saito M](#), [Honda S](#), [Miranda EA](#), [Alonzo MT](#), [Valerio MD](#), [Mapua CA](#), [Inoue S](#), [Kumaori A](#), [Matias R](#), [Natividad FF](#), [Oishi K](#).

Department of Blood Borne Diseases, San Lazaro Hospital, Manila, Research and Biotechnology Division, St. Luke's Medical Center, Quezon City, The Philippines .

Because most cases of secondary dengue virus infection are associated with an increased level of platelet-associated IgG, a high dose of intravenous immunoglobulin (IVIG) may have an effect on the development of severe thrombocytopenia in this disease. **A randomized, controlled study was conducted with two treatment groups consisting of a treatment (IVIG) group (n = 15) and a non-treatment (non-IVIG) group (n = 16) to determine whether a high dose of IVIG is effective in hastening the recovery from thrombocytopenia in patients with secondary dengue virus infection. No significant difference was found in the baseline demographic data between the two groups.** No adverse effect of IVIG was observed, but no effect in hastening the recovery of platelet counts was found in patients with secondary dengue infections. The lack of efficacy of IVIG suggests that platelet clearance by macrophages through Fc gamma receptors is not a primary mechanism in this disease.

Diarrhoea

(see also zinc)

[Pediatrics](#). 2008 May;121(5):e1279-85.



Effectiveness of zinc supplementation plus oral rehydration salts compared with oral rehydration salts alone as a treatment for acute diarrhea in a primary care setting: a cluster randomized trial.

[Bhandari N](#), [Mazumder S](#), [Taneja S](#), [Dube B](#), [Agarwal RC](#), [Mahalanabis D](#), [Fontaine O](#), [Black RE](#), [Bhan MK](#).

Society for Applied Studies, 384 Chirag Delhi, New Delhi 110017, India.
community.research@cih.uib.no

OBJECTIVE: The purpose of this work was to evaluate whether education about zinc supplements and provision of zinc supplements to caregivers is effective in the treatment of acute diarrhea and whether this strategy adversely affects the use of oral rehydration salts. **PATIENTS AND METHODS:** Six clusters of 30,000 people each in Haryana, India, were randomly assigned to intervention and control sites. **Government and private providers and village health workers were trained to prescribe zinc and oral rehydration salts for use in diarrheal episodes in 1-month-old to 5-year-old children in intervention communities; in the control sites, oral rehydration salts alone was promoted.** In 2 cross-sectional surveys commencing 3 months (survey 2) and 6 months (survey 3) after the start of the intervention, care-seeking behavior, drug therapy, and oral rehydration salts use during diarrhea, diarrheal and respiratory morbidity, and hospitalization rates were measured. **RESULTS:** **In the 2 surveys, zinc was used in 36.5% (n = 1571) and 59.8% (n = 1649) and oral rehydration salts in 34.8% (n = 1571) and 59.2% (n = 1649) of diarrheal episodes occurring in the 4 weeks preceding interviews in the intervention areas. In control areas, oral rehydration salts were used in 7.8% (n = 2209) and 9.8% (n = 2609) of episodes. In the intervention communities, care seeking for diarrhea reduced by 34% (survey 3), as did the prescription of drugs of unknown identity (survey 3) and antibiotics (survey 3) for diarrhea. The 24-hour prevalences of diarrhea and acute lower respiratory infections were lower in the intervention communities (survey 3). All-cause, diarrhea, and pneumonia hospitalizations in the preceding 3 months were reduced in the intervention compared with control areas (survey 3).** **CONCLUSIONS:** Diarrhea is more effectively treated when caregivers receive education on zinc supplementation and have ready access to supplies of oral rehydration salts and zinc, and this approach does not adversely affect the use of oral rehydration salts; in fact, it greatly increases use of the same.

Comment

This important effectiveness study showed a concerningly low rate of utilization of ORS when children have diarrhoea. This rate of ORS use can be improved by training health workers in how to prescribe zinc also. Therefore, far from making the management of diarrhoea more complex, the addition of zinc in this large Indian population improved access to quality curative

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care for diarrhoea, and reduced the prescription of ineffective treatments. Overall health was improved, and this study provided some evidence that giving zinc as part of case management for diarrhoea will reduce respiratory infections also. Countries that are struggling with whether to introduce zinc as routine supplementation for the entire population should first introduce zinc as standard treatment for diarrhoea. Evidence suggests this is likely to also have preventative impacts on other diseases.

[Am J Trop Med Hyg.](#) 2008 Feb;78(2):214-6.



Effect of *Saccharomyces boulardii* in the treatment of acute watery diarrhea in Myanmar children: a randomized controlled study.

[Htwe K](#), [Yee KS](#), [Tin M](#), [Vandenplas Y](#).

Department of Child Health, North Okkalapa General Hospital, University of Medicine, Yangon, Myanmar.

This study was conducted to evaluate the efficacy of *Saccharomyces boulardii* in acute diarrhea. One hundred hospitalized children in Myanmar (age range = 3 months to 10 years) were included. Fifty were treated with *S. boulardii* for five days in addition to oral rehydration solution (ORS) and 50 were given ORS alone (control group) in an alternating order. The mean duration of diarrhea was 3.08 days in the *S. boulardii* group and 4.68 days ($P < 0.05$) in the control group. Stools had a normal consistency on day 3 in 38 (76%) of 50 patients in the *S. boulardii* group compared with only 12 (24%) of 50 in the control group ($P = 0.019$). On day 2, 27 (54%) of 50 had less than three stools per day in the *S. boulardii* group compared with only 15 (30%) of 50 in the control group ($P = 0.019$). *Saccharomyces boulardii* shortens the duration of diarrhea and normalizes stool consistency and frequency. The shortening of the duration of diarrhea results in a social and economic benefits.

[Acta Paediatr.](#) 2007 Nov;96(11):1655-9.



B 221, a medical food containing antisecretory factor reduces child diarrhoea: a placebo controlled trial.

[Zaman S](#), [Mannan J](#), [Lange S](#), [Lönnroth I](#), [Hanson LA](#).

Health Services Academy, Islamabad, Pakistan. zaman.shakila@gmail.com

AIM: We investigated whether egg yolk in the form of B221 (Salovum), a medical food containing antisecretory factor (AF) might be used for treatment of acute and prolonged diarrhoea. METHODS: 240 children 6-24 months of age, half with acute diarrhoea (<7 days) and half with prolonged diarrhoea (> or = 7 days) were randomly given 2 g of B221 or placebo every 5 h for 3 days, added to an oral rehydration salt solution. RESULTS: B221 reduced the number of stools in the acute diarrhoea group compared with placebo (day 3, $p = 0.0054$). Stools

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normalizing in consistency (day 3, $p = 0.053$) and recovery within 3 days was commoner in the B221 group ($p < 0.001$). A successful outcome was recorded in 82.8% in the B221 group, compared to 54.4% in the placebo group. In the group with prolonged diarrhoea the stool consistency normalized earlier in the patients receiving B221 than in the patients receiving placebo ($p = 0.008$). A successful outcome was obtained in 90.9% and 63.2%, ($p = 0.0011$) in the B221 and placebo-treated groups respectively. CONCLUSION: B221, which is a medical food, can be used to significantly improve the condition of children with acute, as well as prolonged diarrhoea caused by a broad range of undefined pathogens.

[J Paediatr Child Health](#). 2007 Dec;43(12):837-42. Epub 2007 Sep 4.



Efficacy of Lactobacillus rhamnosus GG in acute watery diarrhoea of Indian children: a randomised controlled trial.

[Basu S](#), [Chatterjee M](#), [Ganguly S](#), [Chandra PK](#).

Department of Paediatrics, North Bengal Medical College and Hospital, Sushrutnagar, Darjeeling, India. drsriparnabasu@rediffmail.com

AIM: To evaluate the role of Lactobacillus rhamnosus GG (LGG) as probiotic in acute watery diarrhoea (AWD). SETTING: Hospital-based study. DESIGN: Randomised, controlled, blinded trial. PATIENTS AND METHOD: All patients of AWD ($n = 684$) admitted over 1-year period were invited to participate in the study as per predefined inclusion and exclusion criteria and were randomised to intervention and control groups. After adequate rehydration the intervention group ($n = 330$) received ORS with probiotic powder containing 60 million cells of LGG, while the control group ($n = 332$) received ORS alone twice daily for a minimum period of 7 days or till diarrhoea ceased. During the study period all patients received ORS and/or IV fluids for ongoing losses, and nutritional supplementation. None of them received any antibiotic or antidiarrhoeal medication. After exclusion of 16 patients, 646 (323 in each arm) patients completed the study. The daily frequency and total duration of diarrhoea and vomiting and the length of hospital stay were studied. Data were analysed by SPSS-10 software. Statistical significance was calculated by Student's t-test and chi2-test. RESULTS: **Rotavirus was isolated in 75.85%. There was no significant difference between treatment groups in the daily frequency or duration of diarrhoea or vomiting or in the length of hospital stay.** No complication was observed from the use of LGG. CONCLUSION: **LGG supplementation does not decrease the frequency and duration of diarrhoea and vomiting in children with AWD, and does not reduce hospital stay in these patients.**

[J Clin Gastroenterol](#). 2007 Sep;41(8):756-60.

Effect of Lactobacillus rhamnosus GG in persistent diarrhea in Indian children: a randomized controlled trial.

[Basu S](#), [Chatterjee M](#), [Ganguly S](#), [Chandra PK](#).

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Department of Pediatrics, North Bengal Medical College and Hospital, Sushrutnagar, Darjeeling, India. drsriparnabasu@rediffmail.com

AIM: To evaluate the role of *Lactobacillus rhamnosus* GG (LGG) as probiotic in persistent diarrhea (PD) in children of North Bengal, India. **SETTING:** Hospital-based study. **DESIGN:** Randomized, double-blind controlled trial. **PATIENTS AND METHODS:** All patients of PD admitted over a period of 2 years were included in the study as per predefined inclusion criteria. They were randomized to receive oral rehydration solution (ORS) alone, or ORS plus LGG powder containing 60 million cells, twice daily for a minimum period of 7 days or till diarrhea has stopped along with correction of dehydration with ORS and/or intravenous fluids as per WHO protocol and antibiotics in culture positive patients. The duration and frequency of purge and vomiting were studied. Data were analyzed by SPSS-10 software. Statistical significance was calculated by Student t test and chi2 test. **RESULTS:** The study comprised of 235 patients randomized into 2 groups, cases (117) and controls (118). Both the groups were similar with respect to age, number of breastfed infants, presentation with dehydration, degree of protein energy malnutrition, and distribution of infections. Stool culture was positive in 90 (38.3%) patients, *Escherichia coli* being the commonest organism followed by *Shigella* spp. and *Clostridium difficile*. **The mean duration of diarrhea was significantly lower in the cases than in controls (5.3 vs. 9.2 d). The average duration of hospital stay was also significantly lesser in cases. No complication was observed from the dose of LGG used.** **CONCLUSIONS:** LGG (dose of 60 million cells) could decrease the frequency and duration of diarrhea and vomiting and reduced hospital stay in patients of PD.

Comment

*The two trials this year on *Lactobacillus rhamnosus* GG as a treatment for diarrhoea are discordant. One trial showed a reduction in duration of diarrhoea and length of hospital stay and the other showed no difference.*

[J Infect Dis.](#) 2007 Aug 15;196(4):537-40. Epub 2007 Jun 29.

The University of
Chicago Press

Efficacy of the human rotavirus vaccine RIX4414 in malnourished children.

[Perez-Schael I](#), [Salinas B](#), [Tomat M](#), [Linhares AC](#), [Guerrero ML](#), [Ruiz-Palacios GM](#), [Bouckennooghe A](#), [Yarzabal JP](#).

Instituto de Biomedicina-Fuvesin, Universidad Central de Venezuela, Ministerio de Salud, Caracas, Venezuela. ireneperezschael@cantv.net

The effect of nutritional status on protective efficacy of a live attenuated human rotavirus vaccine (RIX4414) was studied. Vaccine protection was evaluated through a secondary analysis of data from an efficacy study conducted in Brazil, Mexico, and Venezuela. **Vaccine efficacy against rotavirus gastroenteritis (RVGE) was similar in well-nourished and malnourished infants: 74.1% (95% confidence interval [CI], 52.2%-86.2%) and 73% (95% CI, 11.2%-92.3%) for severe RVGE and 60.9% (95% CI, 37.4%-75.4%) and 61.2% (95% CI, 10.4%-**

83.1%) for RVGE of any severity, respectively. RIX4414 significantly decreased the rate of RVGE regardless of nutritional status, which suggests that this patient group can also benefit from rotavirus vaccination. CLINICAL TRIALS REGISTRY: e-Track 444563-006, NCT00385320 (<http://www.clinicaltrials.gov>).

Epilepsy

[Epilepsia](#). 2008 Mar;49(3):535-9.



Primary care treatment of epilepsy with phenobarbital in rural China: cost-outcome analysis from the WHO/ILAE/IBE global campaign against epilepsy demonstration project.

[Ding D](#), [Hong Z](#), [Chen GS](#), [Dai XY](#), [Wu JZ](#), [Wang WZ](#), [De Boer HM](#), [Sander JW](#), [Prilipko L](#), [Chisholm D](#).

Department of Biostatistics and Epidemiology, Institute of Neurology, Huashan Hospital, Fudan University, Shanghai, China. dding99@yahoo.com

Phenobarbital (PB) is recommended by the World Health Organization (WHO) as a broad-spectrum first-line drug for partial and generalized tonic-clonic seizures. A demonstration project of epilepsy management at primary health level was carried out in rural China under the auspices of the WHO/International League against Epilepsy (ILAE)/International Bureau for Epilepsy (IBE) Global Campaign Against Epilepsy. It offered an opportunity to obtain data related to resource utilization and costs for PB treatment in primary care settings, which together with clinical outcomes can be used to inform decisions about cost-effectiveness and resource allocation in the context of low-income populations.

Comment

A useful article for which there was no abstract, but the full text is available at: <http://www3.interscience.wiley.com/cgi-bin/fulltext/119390158/HTMLSTART>

[Pediatrics](#). 2008 Jan;121(1):e58-64.



Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial.

[Mpimbaza A](#), [Ndeezi G](#), [Staedke S](#), [Rosenthal PJ](#), [Byarugaba J](#).

Randomised trials in child health in developing countries 2007-08

Makerere University, Department of Pediatrics and Child Health, Faculty of Medicine, PO Box 7072, Kampala, Uganda. arthurwakg@yahoo.com

OBJECTIVE: Our goal was to compare the efficacy and safety of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children. **METHODS:** This was a single-blind, randomized clinical trial in which **330 patients were randomly assigned to receive buccal midazolam or rectal diazepam.** The trial was conducted in the pediatric emergency unit of the national referral hospital of Uganda. **Consecutive patients who were aged 3 months to 12 years and presented while convulsing or who experienced a seizure that lasted >5 minutes were randomly assigned to receive buccal midazolam plus rectal placebo or rectal diazepam plus buccal placebo.** The primary outcome of this study was **cessation of visible seizure activity within 10 minutes without recurrence in the subsequent hour.** **RESULTS:** Treatment failures occurred in **71 (43.0%) of 165 patients who received rectal diazepam compared with 50 (30.3%) of 165 patients who received buccal midazolam.** Malaria was the most common underlying diagnosis (67.3%), although the risk for failure of treatment for malaria-related seizures was similar: 35.8% for rectal diazepam compared with 31.8% for buccal midazolam. For children without malaria, buccal midazolam was superior (55.9% vs 26.5%). Respiratory depression occurred uncommonly in both of the treatment arms. **CONCLUSION: Buccal midazolam was as safe as and more effective than rectal diazepam for the treatment of seizures in Ugandan children, although benefits were limited to children without malaria.**

[J Child Neurol.](#) 2007 Oct;22(10):1191-7.



Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial.

[Mehta V](#), [Singhi P](#), [Singhi S](#).

Department of Pediatrics, Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

An open-label, randomized controlled study was conducted at a tertiary care teaching hospital to compare efficacy and safety of intravenous sodium valproate versus diazepam infusion for control of refractory status epilepticus. **Forty children with refractory status epilepticus were randomized to receive either intravenous sodium valproate or diazepam infusion.**

Refractory status epilepticus was controlled in 80% of the valproate and 85% of the diazepam patients. **The median time to control refractory status epilepticus was less in the valproate group (5 minutes) than the diazepam group (17 minutes; P < .001). None of the patients in the valproate group required ventilation or developed hypotension, whereas in the diazepam group 60% required ventilation and 50% developed hypotension after starting diazepam infusion.** No adverse effects on liver functions were seen with valproate. It is concluded that intravenous sodium valproate is an effective alternative to diazepam infusion in controlling refractory status epilepticus in children and is free of respiratory depression and hypotension.

[Seizure.](#) 2007 Sep;16(6):527-32. Epub 2007 Jul 9.

Randomized study of intravenous valproate and phenytoin in status epilepticus.

[Agarwal P](#), [Kumar N](#), [Chandra R](#), [Gupta G](#), [Antony AR](#), [Garg N](#).

Neurology Unit, KPS PG Institute of Medicine, GSVM Medical College, Kanpur 208002, India.
pgpuneet@gmail.com

INTRODUCTION: The evidence based data to guide management in patients of benzodiazepine refractory status epilepticus (SE) is still lacking. We conducted a randomized study to evaluate the comparative effect of intravenous (IV) phenytoin and intravenous valproate (IV VA) in patients of benzodiazepine refractory SE. **BACKGROUND AND METHODS:** Hundred, age and sex matched, patients of benzodiazepine refractory SE were randomly divided into Group A (50 patients), treated with IV VA and Group B (50 patients) treated with IV phenytoin. Twelve patients, in whom SE was not controlled with a single drug, were switched over to the other group. Treatment was considered successful when all motor or EEG seizure activity ceased within 20 min after the beginning of the drug infusion and no return of seizure activity during the next 12h. Secondary study end points were adverse events to treatment, in-hospital complications and the neurological outcome at discharge. **RESULTS: In this study, IV VA was successful in 88% and IV phenytoin in 84% ($p>0.05$) of patients of SE with a significantly better response in patients of SE $<2h$ ($p<0.05$).** The total number of adverse events did not differ significantly between the two groups ($p>0.05$). There were no differences among the treatments with respect to recurrence after 12-h study period or the outcome at 7 days. **CONCLUSION:** IV VA is as effective as IV phenytoin. It is easy to use, better tolerated and can be used as an alternative to IV phenytoin in patients of benzodiazepine refractory SE, especially in patients of cardio-respiratory disease. The better outcome in patients having shorter duration of SE ($<2h$) suggests need of immediate treatment.

Comment

The above two studies compared intravenous sodium valproate with intravenous diazepam and phenytoin for the management of status epilepticus. Valproate was found to be much more effective and safer than IV diazepam, and marginally better than IV phenytoin. The high rate of respiratory depression and hypotension with intravenous diazepam confirms giving diazepam as an IV infusion is very dangerous. This is similar to the findings of a previous trial in Kenya. Another study this year in Ugandan children with status epilepticus showed buccal midazolam was as effective as rectal diazepam. Putting these 3 trials together it can be concluded that IV phenytoin, IV valproate or buccal midazolam are effective and safe in the treatment of status epilepticus. If diazepam must be used it should not be given as an IV infusion.

Fever

[Indian Pediatr.](#) 2007 Dec;44(12):903-11.



Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo controlled trial.

[Gupta H](#), [Shah D](#), [Gupta P](#), [Sharma KK](#).

Department of Pediatrics, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi 110 095, India.

OBJECTIVE: To investigate whether paracetamol administration (i) increases the overall duration of fever; and (ii) is effective and safe, in symptomatic treatment of febrile children. **DESIGN:** Randomized double blind placebo controlled trial. **METHODS:** The trial was conducted at a tertiary care setting. 210 febrile children (6 months - 6 years) with uncomplicated respiratory tract infection received oral paracetamol (15 mg/kg) or placebo, if axillary temperature was 37.6C. Outcome measures included fever clearance time, rate of fall of temperature, percent reduction of temperature, proportion of afebrile children, symptomatic improvement (based on categorical improvement in activity, alertness mood, comfort, appetite and fluid intake) and clinical and biochemical adverse effects. **RESULTS:** Fever clearance time [median (SE, 95% CI)] was comparable between the two groups [paracetamol: 32 (2, 22-37) h; placebo: 36 (1, 33-39) h; P = 0.23]. **Paracetamol resulted in significantly higher rate of fall of temperature (paracetamol: 0.33 +/- 0.16 degrees C/h; placebo 0.07 +/- 0.13 degrees C/h; P <0.001), and percentage reduction of temperature (paracetamol: 85.4 +/- 22.4; placebo 45.5 +/- 34.1; mean difference 39.9; 95% CI 31.9-47.9; P<0.001) during first four hours after drug administration. Proportion of afebrile children after 4 hours (paracetamol: 46.6%; placebo: 12.1%; P <0.001) and symptomatic improvement at 6 hours were significantly higher (P<0.001) after administration of paracetamol as compared to placebo.** No serious clinical or biochemical adverse drug effects were observed. **CONCLUSIONS:** Paracetamol achieves effective antipyresis and provides early symptomatic improvement in children with febrile illness without prolongation of fever duration or excessive adverse effects.

[Malar J](#). 2008 May 26;7:91



Antipyretic effect of ibuprofen in Gabonese children with uncomplicated falciparum malaria: a randomized, double-blind, placebo-controlled trial.

[Matsiégui PB](#), [Missinou MA](#), [Necek M](#), [Mavoungou E](#), [Issifou S](#), [Lell B](#), [Kremsner PG](#).

Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon. matsiegbp@yahoo.fr

BACKGROUND: Antipyretic drugs are widely used in children with fever, though there is a controversy about the benefit of reducing fever in children with malaria. In order to assess the effect of ibuprofen on fever compared to placebo in children with uncomplicated Plasmodium falciparum malaria in Gabon, a randomized double blind placebo controlled trial, was designed. **METHODS:** Fifty children between two and seven years of age with uncomplicated malaria were included in the study. For the treatment of fever, all patients "received" mechanical treatment when the temperature rose above 37.5 degrees C. In addition to the mechanical treatment, continuous fanning and cooling blanket, patients were assigned randomly to receive ibuprofen (7 mg/kg body weight, every eight hours) or placebo. **RESULTS: The fever clearance time using a fever threshold of 37.5 degrees C was similar in children receiving ibuprofen compared to those receiving placebo. The difference was also not statistically significant using a fever threshold of 37.8 degrees C or 38.0 degrees C. However, the fever**

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time and the area under the fever curve were significantly smaller in the ibuprofen group compared to the placebo group. CONCLUSION: Ibuprofen is effective in reducing the time with fever. The effect on fever clearance is less obvious and depends on definition of the fever threshold. TRIAL REGISTRATION: The trial registration number is: NCT00167713

Filariasis

[Ann Trop Med Parasitol.](#) 2007 Jul;101(5):423-33.

Children and adolescents infected with *Wuchereria bancrofti* in Greater Recife, Brazil: a randomized, year-long clinical trial of single treatments with diethylcarbamazine or diethylcarbamazine-albendazole.

[Rizzo JA](#), [Belo C](#), [Lins R](#), [Dreyer G](#).

Centro de Pesquisas em Alergia e Imunologia Clínica, Ambulatório de Alergia, Hospital das Clínicas, Universidade Federal de Pernambuco, Avenida Moraes Rego s/n, Cidade Universitária, CEP 50740-900, Recife, PE, Brazil.

In filariasis-endemic areas beyond sub-Saharan Africa, the World Health Organization's recommended strategy for interrupting transmission of the causative parasites is annual, single-dose, mass treatment with a combination of diethylcarbamazine (DEC; given at 6 mg/kg) and albendazole (ALB; given at 400 mg) for 4-6 years (the minimum estimated life-span of the adult parasites). In an open, hospital-based, randomized and controlled trial, with a blinded evaluation of outcome, 82 children and adolescents from Recife, all with *Wuchereria bancrofti* microfilaraemias, were given either DEC alone (6 mg/kg) or the same dose of DEC combined with ALB (at 400 mg/patient). **Every 90 days for 1 year after the single treatment, each patient was checked for microfilaraemia by the filtration of up to 5 ml of venous blood collected at night. One year post-treatment, 16 (39%) of the 41 patients given DEC alone and 20 (49%) of the 41 given DEC-ALB were found microfilaraemic (relative risk=0.8, with a 95% confidence interval of 0.49-1.31) and the corresponding geometric mean levels of microfilaraemia were 2.0% and 1.8% of the levels recorded immediately pre-treatment, respectively (P>0.05).** In terms of the prevalences and intensities of microfilaraemia, therefore, the addition of ALB to the DEC appeared to offer no significant benefit.

Gastrointestinal parasitic infections

[Ann Trop Med Parasitol.](#) 2008 Jan;102(1):39-44.

The antischistosomal efficacies of artesunate-sulfamethoxypyrazine-pyrimethamine and artemether-lumefantrine administered as treatment for uncomplicated, *Plasmodium falciparum* malaria.

[Adam I](#), [Elhardello OA](#), [Elhadi MO](#), [Abdalla E](#), [Elmardi KA](#), [Jansen FH](#).

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Faculty of Medicine, University of Khartoum, P.O. Box 102, Khartoum, Sudan.
ishagadam@hotmail.com

Although artemisinin and its derivatives are widely used for the treatment of malaria, they also have antischistosomal activity. In a small study in eastern Sudan, the effects of the treatment of uncomplicated, *Plasmodium falciparum* malaria with artesunate-sulfamethoxypyrazine-pyrimethamine (AS-SMP) and artemether-lumefantrine (AT-LU) on co-infections with *Schistosoma mansoni* were therefore investigated. Faecal samples from 14 of the 306 patients screened on presentation, at the start of a clinical trial of antimalarial treatment, were found to contain *Schistosoma mansoni* eggs. For the treatment of their malaria, the 14 egg-positive cases, who were aged 6-40 years (mean = 13.7 years), were each subsequently treated with three tablets of a fixed combination of AS-SMP, with a 12-h (six patients) or 24-h interval (five patients) between each tablet, or with six doses of AT-LU given over 3 days. When checked 28 and 29 days after the initiation of treatment, all 14 patients were found stool-negative for schistosome eggs. **These results indicate that AS-SMP and AT-LU are currently very effective treatments not only for uncomplicated, *P. falciparum* malaria but also for *S. mansoni* infections.**

Comment

The anti-schistosomal effects of artemisinin derivatives are now well established. The artemisinins and synthetic trioxolanes possess a broad spectrum of activity against trematodes. High worm-burden reductions were obtained with these drugs in experiments in rodents with infections of Schistosoma japonicum, S. mansoni, Clonorchis sinensis, Fasciola hepatica and Opisthorchis viverrini. Clinical trials carried out in Africa, utilizing artemether or artesunate singly or as artemisinin-based combination therapies, following recommended malaria treatment schedules, found an effect against schistosomiasis (Curr Opin Infect Dis. 2007 Dec;20(6):605-12.)

[Am J Trop Med Hyg.](#) 2007 Nov;77(5):866-74.



A cluster-randomized bovine intervention trial against *Schistosoma japonicum* in the People's Republic of China: design and baseline results.

[Gray DJ](#), [Williams GM](#), [Li Y](#), [Chen H](#), [Li RS](#), [Forsyth SJ](#), [Barnett AG](#), [Guo J](#), [Feng Z](#), [McManus DP](#).

Australian Centre for International and Tropical Health and Nutrition, The University of Queensland and The Queensland Institute of Medical Research, Brisbane, Queensland, Australia. d.gray1@uq.edu.au

We describe the design and report baseline results of a cluster-randomized intervention to determine the importance of bovines for *Schistosoma japonicum* transmission in southern China. The study involves four matched village pairs in Hunan and Jiangxi Provinces, with a village within each pair randomly selected as intervention (human and bovine praziquantel treatment) or control (human praziquantel treatment only). Total study population prevalences at baseline were 12.4% (n = 5,390) and 15.2% (n = 1,573) for humans and bovines, respectively;

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village prevalences were similar within pairs. Bovine contamination index calculations showed that bovines less than 24 months of age were responsible for 74% of daily bovine environmental contamination with *S. japonicum* eggs. The village characteristics and baseline results underpin a rigorous study, which has major implications for deployment of a transmission-blocking bovine vaccine against *S. japonicum*. The combination of such a vaccine with other control strategies could potentially eliminate *S. japonicum* from southern China.

HIV / AIDS

Case management and anti-retroviral therapy

(see also treatment of uncomplicated malaria: Gasasira AF, et al.)

[BMC Public Health](#). 2008 May 20;8:169.



18-month occurrence of severe events among early diagnosed HIV-infected children before antiretroviral therapy in Abidjan, Côte d'Ivoire: a cohort study.

[Harambat J](#), [Fassinou P](#), [Becquet R](#), [Touré P](#), [Rouet F](#), [Dabis F](#), [Msellati P](#), [Blanche S](#), [Timité-Konan M](#), [Salamon R](#), [Leroy V](#); [ANRS 1201/1202 Ditrame Plus Study Group](#).

INSERM, Unité 897, Bordeaux, France. jerome.harambat@libertysurf.fr

OBJECTIVE: To assess the 18-month field effectiveness on severe events of a pediatric package combining early HIV-diagnosis and targeted cotrimoxazole prophylaxis in HIV-infected children from age six-week before the antiretroviral era, in Abidjan, Côte d'Ivoire. **METHODS:** Data from two consecutive prevention of HIV mother-to-child transmission programs were compared: the ANRS 1201/1202 Ditrame-Plus cohort (2001-2005) and the pooled data of the ANRS 049a Ditrame randomized trial and its following open-labeled cohort (1995-2000), used as a reference group. HIV-infected pregnant women ≥ 32 -36 weeks of gestation were offered a short-course peri-partum antiretroviral prophylaxis (ZDV in Ditrame, and ZDV +/- 3TC+single-dose (sd) NVP in Ditrame-Plus). Neonatal prophylaxis was provided in Ditrame-Plus only: 7-day ZDV and sdNVP 48-72 h after birth. A 6-week pediatric HIV-RNA diagnosis was provided on-line in the Ditrame-Plus while it was only oriented on clinical symptoms in Ditrame. Six-week HIV-infected children received a daily cotrimoxazole prophylaxis in Ditrame-Plus while no prophylaxis was provided in Ditrame. The determinants of severe events (death or hospitalization > 1 day) were assessed in a Cox regression model. **RESULTS:** Between 1995 and 2003, 98 out of the 1121 live-births were diagnosed as HIV-infected in peri-partum: 45 from Ditrame-Plus and 53 from Ditrame. The 18-month Kaplan-Meier cumulative probability of presenting a severe event was 66% in Ditrame-Plus (95% confidence interval [95%CI]: 50%-81%) and 77% in Ditrame (95%CI: 65%-89%), Log Rank test: $p = 0.47$. After adjustment on maternal WHO clinical stage, maternal death, 6-week pediatric viral load, birth-weight, and breastfeeding exposure, the 18-month risk of severe event was lower in Ditrame-Plus than in Ditrame (adjusted Hazard Ratio (aHR): 0.55, 95%CI: 0.3-1.1), although the difference was not statistically significant; $p = 0.07$). Maternal death was the only variable determinant of the occurrence of severe events in children (aHR: 3.73; CI: 2.2-11.2; $p = 0.01$).

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CONCLUSION: Early cotrimoxazole from 6 weeks of age in HIV-infected infants seemed to reduce probability of severe events but the study lacked statistical power to prove this. Even with systematic cotrimoxazole prophylaxis, infant morbidity and mortality remained high pointing towards a need for early pediatric HIV-diagnosis and antiretroviral treatment in Africa.

[J Med Assoc Thai](#). 2007 Nov;90(11):2437-41.

Incidence and risk factors for non-nucleoside reverse transcriptase inhibitors (NNRTI)-related rash in Thai children with HIV infection.

[Vemula S](#), [Kerr S](#), [Pancharoen C](#), [Siripong A](#), [Kosalaraksa P](#), [Engchanil C](#), [Chuamchaitrakool A](#), [Intasan J](#), [Lumbiganond P](#), [Phanuphak P](#), [Ananworanich J](#).

Washington University, St. Louis, USA.

The present study evaluated the incidence and risk factors that correlated with the development of non-nucleoside reverse transcriptase inhibitor (NNRTI) related rash in 69 Thai children followed prospectively. The overall incidence of NNRTI-related rash was 16% (22% for NVP and 4% for EFV rash). The only significant predictive factor that correlated with the development of NNRTI-related rash in a multivariate logistic regression model was a CD4% decrease at week 12.

[J Trop Pediatr](#). 2008 Feb;54(1):19-24. Epub 2007 Sep 17.



Use of probiotics in HIV-infected children: a randomized double-blind controlled study.

[Trois L](#), [Cardoso EM](#), [Miura E](#).

Department of Nutrition, Unilasalle, Brazil. liviatrois@gmail.com

HIV/AIDS is an infection characterized by immune cell dysfunction and subsequent immunodeficiency, as well as intestinal disorder. Probiotics are live microbial feed supplements that beneficially affect the host animal by improving intestinal microbial balance and promoting health benefits. The goals of this study were to determine whether the use of probiotics could improve the immune response determined by CD4 cells mm⁻³ counts and reduce liquid stool episodes. A randomized double-blind controlled trial with 77 HIV-infected children (2-12 years), divided into two groups: one receiving probiotics (formula containing *Bifidobacterium bifidum* with *Streptococcus thermophilus* -2.5 x 10¹⁰ colony forming units) and the other, a standard formula (control group), for 2 months. The CD4 counts (cells mm⁻³) were collected at the beginning and end of the study. The quality and number of stools were assessed by a questionnaire (watery to normal stool consistency). **There was an increase in the mean CD4 count in the probiotics group (791 cells mm⁻³) and a small decrease in the control group (538 cells mm⁻³). The change from baseline in mean CD4 cell count was +118 cells mm⁻³ vs. -42 cells mm⁻³ for children receiving the probiotic formula and control formula,**

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respectively ($p = 0.049$). A similar reduction in liquid stool consistency in both the groups ($p < 0.06$), with a slight enhancement in the probiotics group, was observed, but without significant difference ($p < 0.522$). The incidence of loose-soft stools showed a small decrease in both groups ($p < 0.955$) and there was an increase in the incidence of normal stool consistency in both the groups ($p < 0.01$). Our study showed that probiotics have immunostimulatory properties and might be helpful in the treatment of HIV-infected children.

HIV education

[Am J Public Health](#). 2008 Feb;98(2):201-4. Epub 2008 Jan 2.



Young citizens as health agents: use of drama in promoting community efficacy for HIV/AIDS.

[Kamo N](#), [Carlson M](#), [Brennan RT](#), [Earls F](#).

Harvard Medical School, Cambridge, MA 02138, USA.

A community-based cluster randomized control trial in a medium-sized municipality in Tanzania was designed to increase local competence to control HIV/AIDS through actions initiated by children and adolescents aged 10 to 14 years. Representative groups from the 15 treatment communities reached mutual understanding about their objectives as health agents, prioritized their actions, and skillfully applied community drama ("skits") to impart knowledge about the social realities and the microbiology of HIV/AIDS. In independently conducted surveys of neighborhood residents, differences were found between adults who did and did not witness the skits in their beliefs about the efficacy of children as HIV/AIDS primary change agents.

[J Adolesc Health](#). 2008 Jan;42(1):102-4.

A novel economic intervention to reduce HIV risks among school-going AIDS orphans in rural Uganda.

[Ssewamala FM](#), [Alicea S](#), [Bannon WM Jr](#), [Ismayilova L](#).

Columbia University School of Social Work, New York, New York, USA.
fs2114@columbia.edu

This study tested an economic intervention to reduce HIV risks among AIDS-orphaned adolescents. Adolescents ($n = 96$) were randomly assigned to receive the intervention or usual care for orphans in Uganda. Data obtained at baseline and 12-month follow-up revealed significant differences between the treatment and control groups in HIV prevention attitudes and educational planning.

Prevention of parent to child transmission

[N Engl J Med](#). 2008 Jul 10;359(2):130-41. Epub 2008 Jun 4.



Effects of early, abrupt weaning on HIV-free survival of children in Zambia.

[Kuhn L](#), [Aldrovandi GM](#), [Sinkala M](#), [Kankasa C](#), [Semrau K](#), [Mwiya M](#), [Kasonde P](#), [Scott N](#), [Vwalika C](#), [Walter J](#), [Bulterys M](#), [Tsai WY](#), [Thea DM](#); [Zambia Exclusive Breastfeeding Study](#). Collaborators (14)

[Abrams E](#), [Colton T](#), [Fawzi W](#), [Kapiga S](#), [Chomba E](#), [Allen S](#), [Luo C](#), [Mofenson L](#), [Piwoz E](#), [Ryan K](#), [Simon J](#), [Stein Z](#), [Stringer J](#), [Vermund S](#).

Gertrude H. Sergievsky Center and the Department of Epidemiology, Mailman School of Public Health, Columbia University, New York 10032, USA. lk24@columbia.edu

BACKGROUND: In low-resource settings, many programs recommend that women who are infected with the human immunodeficiency virus (HIV) stop breast-feeding early. We conducted a randomized trial to evaluate whether abrupt weaning at 4 months as compared with the standard practice has a net benefit for HIV-free survival of children. **METHODS:** We enrolled 958 HIV-infected women and their infants in Lusaka, Zambia. All the women planned to breast-feed exclusively to 4 months; **481 were randomly assigned to a counseling program that encouraged abrupt weaning at 4 months, and 477 to a program that encouraged continued breast-feeding for as long as the women chose. The primary outcome was either HIV infection or death of the child by 24 months.** **RESULTS:** In the intervention group, 69.0% of the mothers stopped breast-feeding at 5 months or earlier; 68.8% of these women reported the completion of weaning in less than 2 days. In the control group, the median duration of breast-feeding was 16 months. In the overall cohort, there was no significant difference between the groups in the rate of HIV-free survival among the children; 68.4% and 64.0% survived to 24 months without HIV infection in the intervention and control groups, respectively ($P=0.13$). Among infants who were still being breast-fed and were not infected with HIV at 4 months, there was no significant difference between the groups in HIV-free survival at 24 months (83.9% and 80.7% in the intervention and control groups, respectively; $P=0.27$). **Children who were infected with HIV by 4 months had a higher mortality by 24 months if they had been assigned to the intervention group than if they had been assigned to the control group (73.6% vs. 54.8%, $P=0.007$).** **CONCLUSIONS:** Early, abrupt cessation of breast-feeding by HIV-infected women in a low-resource setting, such as Lusaka, Zambia, does not improve the rate of HIV-free survival among children born to HIV-infected mothers and is harmful to HIV-infected infants. (ClinicalTrials.gov number, NCT00310726.)
2008 Massachusetts Medical Society

Comment

This is an important trial, adding to the evidence from Botswana published in 2006 showing that although formula feeding is associated with lower risk of mother-to-child HIV transmission, it was associated with a higher mortality (JAMA. 2006 Aug 16;296(7):794-805) This year we learn that in HIV-affected infants in Zambia, mortality is higher if there is abrupt weaning at 4

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months of age. This shows that evidence on breast-feeding in HIV is highly context specific, as are the results of most RCTs!

[N Engl J Med.](#) 2008 Jul 10;359(2):119-29. Epub 2008 Jun 4.



Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission.

[Kumwenda NI](#), [Hoover DR](#), [Mofenson LM](#), [Thigpen MC](#), [Kafulafula G](#), [Li Q](#), [Mipando L](#), [Nkanaunena K](#), [Mebrahtu T](#), [Bulterys M](#), [Fowler MG](#), [Taha TE](#).

Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA.

BACKGROUND: Effective strategies are urgently needed to reduce mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) through breast-feeding in resource-limited settings. **METHODS:** Women with HIV-1 infection who were breast-feeding infants were enrolled in a randomized, phase 3 trial in Blantyre, Malawi. **At birth, the infants were randomly assigned to one of three regimens: single-dose nevirapine plus 1 week of zidovudine (control regimen) or the control regimen plus daily extended prophylaxis either with nevirapine (extended nevirapine) or with nevirapine plus zidovudine (extended dual prophylaxis) until the age of 14 weeks.** Using Kaplan-Meier analyses, we assessed the risk of HIV-1 infection among infants who were HIV-1-negative on DNA polymerase-chain-reaction assay at birth. **RESULTS:** Among 3016 infants in the study, the control group had consistently higher rates of HIV-1 infection from the age of 6 weeks through 18 months. **At 9 months, the estimated rate of HIV-1 infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-nevirapine group (P<0.001) and 6.4% in the extended-dual-prophylaxis group (P=0.002).** There were no significant differences between the two extended-prophylaxis groups. The frequency of breast-feeding did not differ significantly among the study groups. Infants receiving extended dual prophylaxis had a significant increase in the number of adverse events (primarily neutropenia) that were deemed to be possibly related to a study drug. **CONCLUSIONS:** Extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants. (ClinicalTrials.gov number, NCT00115648.) 2008 Massachusetts Medical Society

Comment

This important information, coupled with the results of the study above, suggests there are effective strategies to make prolonged breast feeding safer in HIV affected infants in settings where abrupt cessation of breast feeding may be dangerous. 90% of infants in this trial were breast fed to 6 months, one-quarter to one-third up to 9 months, and almost 20% to 15 months.

[J Acquir Immune Defic Syndr.](#) 2007 Dec 1;46(4):472-8.

Independent effects of nevirapine prophylaxis and HIV-1 RNA suppression in breast milk on early perinatal HIV-1 transmission.

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[Chung MH](#), [Kiarie JN](#), [Richardson BA](#), [Lehman DA](#), [Overbaugh J](#), [Njiri F](#), [John-Stewart GC](#).

Department of Medicine, University of Washington, Seattle, WA 98104, USA.
mhchung@u.washington.edu

BACKGROUND: The mechanism of action of single-dose nevirapine on reducing mother-to-child transmission of HIV-1 may involve reduction of maternal HIV-1 or prophylaxis of infants. **METHODS:** In a study that randomized pregnant mothers to HIVNET 012 nevirapine versus short-course antenatal zidovudine, we compared breast milk HIV-1 RNA viral shedding and administration of single-dose nevirapine between mothers who transmitted HIV-1 to their infants at 6 weeks postpartum and those who did not. **RESULTS:** In multivariate analyses, maximum breast milk HIV-1 RNA levels (hazard ratio [HR] = 2.50, 95% confidence interval [CI]: 1.25 to 4.99; P = 0.01) and nevirapine use (HR = 0.12, 95% CI: 0.02 to 0.97; P = 0.05) were each independently associated with perinatal transmission at 6 weeks postpartum. Mothers who transmitted HIV-1 to their infants had significantly higher HIV-1 RNA levels in their breast milk between the second day and sixth week postpartum. Among mothers with maximum breast milk virus levels less than a median of 3.5 log(10) copies/mL, the administration of nevirapine further decreased HIV-1 transmission risk from 22.2% to 0.0% (P = 0.04). **CONCLUSIONS:** **Peripartum administration of single-dose nevirapine to mother and infant decreases early perinatal HIV-1 transmission by means of breast milk HIV-1 RNA suppression and, independently, by providing the infant with exposure prophylaxis**

[J Infect Dis.](#) 2007 Dec 1;196(11):1629-36. Epub 2007 Oct 25.



Risk factors for in utero or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand.

[Jourdain G](#), [Mary JY](#), [Coeur SL](#), [Ngo-Giang-Huong N](#), [Yuthavisuthi P](#), [Limtrakul A](#), [Traisathit P](#), [McIntosh K](#), [Lallemant M](#); [Perinatal HIV Prevention Trial Group, Thailand](#).

Institut de Recherche pour le Developpement, UMI 174 "Epidemiologie Clinique, Sante Maternelle et Infantile et Sida", Paris, France. gjourdain@hsph.harvard.edu

BACKGROUND: The identification of risk factors for in utero and intrapartum transmission of human immunodeficiency virus type 1 (HIV-1) is crucial to the design and understanding of preventive interventions. **METHODS:** The randomized Perinatal HIV Prevention Trial-1 enrolled 1437 pregnant women and their non-breast-fed infants, to compare the efficacy of various durations of zidovudine prophylaxis. Using univariate and multivariate logistic regression analyses, we studied the role that factors known or occurring at various times during gestation or delivery play in in utero and intrapartum transmission. **RESULTS:** Variables independently associated with in utero transmission were HIV-1 load >35,000 copies/mL (adjusted odds ratio [AOR], 4.2) and delayed initiation of maternal zidovudine prophylaxis until >31.4 weeks gestation (AOR, 3.0). Variables associated with intrapartum transmission were HIV-1 load >10,000 copies/mL (AOR, 3.8 for 10,000-35,000 copies/mL and 7.1 for >35,000 copies/mL), induction of labor (AOR, 2.6), and premature labor with tocolysis (AOR, 15.1). **CONCLUSIONS:** With the exception of very high HIV-1 load, risk factors for in utero

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transmission were different from those for intrapartum transmission. Optimal prophylactic interventions must address each of the major risk factors, with appropriate timing.

[AIDS Patient Care STDS](#). 2007 Sep;21(9):638-43.

Mary Ann Liebert,

Maternal HIV-1 DNA load and mother-to-child transmission.

[Arvold ND](#), [Ngo-Giang-Huong N](#), [McIntosh K](#), [Suraseranivong V](#), [Warachit B](#), [Piyaworawong S](#), [Changchit T](#), [Lallemant M](#), [Jourdain G](#); [Perinatal HIV Prevention Trial \(PHPT-1\), Thailand](#).

Harvard Medical School, Boston, Massachusetts 02115, USA. narvold@partners.org

While many factors contribute to mother-to-child transmission (MTCT) of HIV-1, maternal plasma HIV-1 RNA viral load (RNA-VL) has been consistently found as the main risk factor, including when antiretroviral prophylaxis was used to prevent MTCT. However the predictive value of RNA-VL is poor. A recent study of HIV-1-positive pregnant women who did not receive antiretroviral prophylaxis reported an association between HIV-1 DNA viral load (DNA-VL) and MTCT that was stronger than the association between RNA-VL and MTCT. We sought to determine if HIV-1 DNA-VL was independently associated with MTCT of HIV in a population of women who received zidovudine prophylaxis during pregnancy and whose infants received zidovudine after birth. Patients were 33 non-breastfeeding transmitting (TR) and 33 nontransmitting mothers (NTR) from Perinatal HIV Prevention Trial (PHPT-1), a multicenter clinical trial conducted in Thailand comparing zidovudine prophylaxis durations to prevent MTCT. TR and NTR mothers were matched according to baseline RNA-VL. Maternal peripheral blood mononuclear cell (PBMC)-associated HIV-1 DNA was extracted from whole blood, and DNA-VL was established by quantitative real-time polymerase chain reaction. We found that TR had a significantly higher cell-associated HIV-1 DNA viral load than did NTR. Median TR DNA-VL was 2.54 log(10) copies per microgram PBMC DNA, while it was 2.28 log(10) copies per microgram PBMC DNA in NTR (Wilcoxon $p = 0.02$). **In summary, HIV-1 DNA viral load was associated with MTCT in a population of women who received antiretroviral prophylaxis during pregnancy, independently from RNA viral load.**

[J Infect Dis](#). 2007 Jul 1;196(1):15-22. Epub 2007 May 16.

The University of
Chicago Press

Effects of nevirapine, compared with lamivudine, on lipids and lipoproteins in HIV-1-uninfected newborns: the stopping infection from mother-to-child via breast-feeding in Africa lipid substudy.

[Sankatsing RR](#), [Wit FW](#), [Pakker N](#), [Vyankandondera J](#), [Mmiro F](#), [Okong P](#), [Kastelein JJ](#), [Lange JM](#), [Stroes ES](#), [Reiss P](#).

Department of Vascular Medicine, University of Amsterdam, Amsterdam, The Netherlands.
r.r.sankatsing@amc.uva.nl

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BACKGROUND: The objective of the present study was to assess whether the high-density lipoprotein cholesterol (HDL-c)-increasing effect of nevirapine (NVP), as observed in human immunodeficiency virus type 1 (HIV-1)-infected subjects, at least in part may relate to intrinsic properties of NVP. **METHODS:** At 2, 6, and 12 weeks after birth, complete lipid profiles as well as plasma apolipoproteins levels were assessed in 80 HIV-uninfected newborns, half of whom received NVP and half lamivudine (3TC), respectively. Newborns were randomly selected from a randomized trial in which NVP or 3TC had been administered to HIV-uninfected infants born to HIV-infected mothers to try and prevent HIV-1 transmission from occurring during breast-feeding. **RESULTS:** After 6 weeks of therapy, the expected physiological decline in HDL-c levels in the newborns was attenuated in infants treated with NVP, compared with levels in those treated with 3TC. Apolipoprotein A-I (apoA-I) levels were higher at all time points in the NVP arm than they were in the 3TC arm ($P=.02$), reaching peak levels at 6 weeks. The difference in HDL-c was no longer significant at 12 weeks. **CONCLUSIONS:** apoA-I levels and HDL-c were elevated in HIV-1-uninfected newborns receiving NVP, compared with those receiving 3TC. These data support that NVP may indeed have intrinsic apoA-I and HDL-c elevating properties in humans.

Injury prevention

[Inj Prev](#). 2008 Jun;14(3):164-9.



Paraprofessional home visitation program to prevent childhood unintentional injuries in low-income communities: a cluster randomized controlled trial.

[Swart L](#), [van Niekerk A](#), [Seedat M](#), [Jordaan E](#).

UNISA Institute for Social and Health Sciences, Lenasia, South Africa. swartl@unisa.ac.za

OBJECTIVE: To investigate the effectiveness of a paraprofessional home visitation program (HVP) to improve home safety and prevent injuries among children living in low-income settings. **METHODS:** The HVP was implemented in two low-income communities in South Africa. In each community, approximately 200 households were randomly selected for the trial. Eligible households were those with children aged $< \text{or} = 10$ years. **Intervention households received four visits, one every two weeks, by trained paraprofessionals that focused on a specific injury topic and consisted of: information dissemination about specific injury prevention practices; home inspection accompanied by information about home hazards; and the supply of safety devices.** The key outcomes to measure the presence of home hazards were scores for burns (safety practices, paraffin, and electrical), poisoning, and falls. **RESULTS:** **Significant reductions were found for injury risks related to burn safety practices.** For injury risks related to electrical burns, paraffin burns, and poisoning, a decline was also noted although this was not statistically significant. No decline was noted for fall-related risks. **CONCLUSIONS:** Subject to further replication and evaluation, **home visits by paraprofessionals providing safety education, home inspection, and safety devices be considered for integration into a comprehensive child injury prevention strategy in low-income communities.**

Leishmaniasis

[Am J Trop Med Hyg.](#) 2008 Feb;78(2):210-1.



Efficacy of miltefosine for Bolivian cutaneous leishmaniasis.

[Soto J](#), [Rea J](#), [Balderrama M](#), [Toledo J](#), [Soto P](#), [Valda L](#), [Berman JD](#).

Fundación FADER, Bogota, Colombia.

Oral miltefosine (2.5 mg/kg/d for 28 days) was compared with intramuscular antimony (20 mg/kg/d for 20 days) in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis* in Palos Blancos, Bolivia. The cure rates with 6 months of follow-up were statistically similar: 36 of 41 evaluable miltefosine patients (88%) versus 15 of 16 (94%) evaluable antimony patients. However, antimony cured more rapidly, because, by 1 month after therapy, 31 of 44 miltefosine patients (70%) compared with 16 of 16 antimony patients (100%) had achieved cure. The two conclusions from this work are that oral miltefosine can be used for cutaneous disease in this part of Bolivia and that miltefosine was more effective for *L. braziliensis* in this region than for *L. braziliensis* in Guatemala. Chemotherapy needs to be evaluated in each endemic region, even if the "same" species of *Leishmania* causes disease in these locales.

[Trans R Soc Trop Med Hyg.](#) 2008 Jan;102(1):58-63. Epub 2007 Oct 25.

Immunochemotherapy of persistent post-kala-azar dermal leishmaniasis: a novel approach to treatment.

[Musa AM](#), [Khalil EA](#), [Mahgoub FA](#), [Elgawi SH](#), [Modabber F](#), [Elkadaru AE](#), [Aboud MH](#), [Noazin S](#), [Ghalib HW](#), [El-Hassan AM](#); [Leishmaniasis Research Group/Sudan](#).

Institute of Endemic Diseases, University of Khartoum, Khartoum, Sudan.

Post-kala-azar dermal leishmaniasis (PKDL) is a recognized dermatosis that follows successful treatment of visceral leishmaniasis in the Sudan. This randomized and double-blind study aimed to assess safety, immunogenicity and curative potentials of a novel immunochemotherapy regimen in patients with persistent PKDL. Following informed consent, 30 patients were randomized to receive alum-precipitated autoclaved *Leishmania major* (Alum/ALM) vaccine+Bacille Calmette-Guérin (BCG) and sodium stibogluconate (SSG) or vaccine diluent and SSG. The SSG+Alum/ALM+BCG proved safe with minimal local adverse events. In the SSG+vaccine group, 87% of the patients were cured by day 60 compared with 53% in the SSG alone group (SSG+vaccine efficacy=71%, 95% CI for risk ratio 0.7-1.16). On day 90 of follow-up there were two relapses in the SSG alone arm and none in the SSG+vaccine arm. Pre-treatment cytokines showed high IFN-gamma or high IFN-gamma/IL-10 levels and leishmanin skin test (LST) non-reactivity, while healing/clinical improvement were associated with LST reactivity and low IFN-gamma levels in both study groups (P=0.004). In conclusion, SSG+Alum/ALM+BCG is safe and immunogenic with significant healing potentials in

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persistent PKDL lesions. Immunochemotherapy probably augmented IFN-gamma production, which induced healing. Leishmanin skin reactivity is a good surrogate marker of cure in persistent PKDL lesions.

Leprosy

[Nihon Hansenbyo Gakkai Zasshi](#). 2008 Feb;77(1):3-10.

Serological response to chemoprophylaxis in extended contacts in leprosy--a randomized controlled trial.

[Oo KN](#), [Yin NN](#), [Han TT](#), [Wai KT](#), [Myint K](#), [Gyi MM](#).

Bacteriology Research Division, Department of Medical Research (Lower Myanmar), Yangon. knopk@yangon.net.mm

Chemoprophylaxis was carried out on high risk group of extended contacts of new leprosy cases in Nyaungdon Township, Ayeyarwaddy Division, Myanmar and serological response was followed up for two years. In September 2003, blood samples were collected from 829 contacts after getting informed consent and sera were tested for immunoglobulin M antibodies using NTP-BSA ELISA test. These 300 seropositives were randomized to treated and non-treated groups. In each group 102 each were enrolled in adults and 48 each in children. A single dose of ROM (rifampicin, ofloxacin and minocycline) and RMP (rifampicin) by body weight was administered to treated group of above 15 years and those below 15 years respectively. The vitamins were administered to non-treated group. The blood samples of all contacts were collected again in September 2004 and September 2005 and ELISA was carried out on paired samples on one plate. The mean optical density (OD) titers before vs after chemoprophylaxis were 0.24 vs 0.10 and 0.20 vs 0.09 in treated and non-treated group respectively in adults and 0.25 vs 0.11 and 0.22 vs 0.11 respectively in children after one year. These were 0.24 vs 0.17 and 0.20 vs 0.19 respectively in adults and 0.25 vs 0.19 and 0.22 vs 0.20 respectively in children after two years. The difference of mean antibody titers before and after chemoprophylaxis in treated group was significantly reduced compared to non-treated group in adults but was not significant in children. The findings show that there is a significant role of chemoprophylaxis on serological response in the form of decreasing antibody titer among the adult group of extended contacts.

Malaria

(see also Vitamin A)

Malaria vaccine

[PLoS ONE](#). 2008 Feb 13;3(2):e1563.



Phase 1 study of a combination AMA1 blood stage malaria vaccine in Malian children.

[Dicko A](#), [Sagara I](#), [Ellis RD](#), [Miura K](#), [Guindo O](#), [Kamate B](#), [Sogoba M](#), [Niambelé MB](#), [Sissoko M](#), [Baby M](#), [Dolo A](#), [Mullen GE](#), [Fay MP](#), [Pierce M](#), [Diallo DA](#), [Saul A](#), [Miller LH](#), [Doumbo OK](#).

Malaria Research and Training Center, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy and Dentistry, University of Bamako, Bamako, Mali.

BACKGROUND: Apical Membrane Antigen-1 (AMA1) is one of the leading blood stage malaria vaccine candidates. AMA1-C1/Alhydrogel consists of an equal mixture of recombinant AMA1 from FVO and 3D7 clones of *P. falciparum*, adsorbed onto Alhydrogel. A Phase 1 study in semi-immune adults in Mali showed that the vaccine was safe and immunogenic, with higher antibody responses in those who received the 80 microg dose. The aim of this study was to assess the safety and immunogenicity of this vaccine in young children in a malaria endemic area. **DESIGN:** This was a Phase 1 dose escalating study in 36 healthy children aged 2-3 years started in March 2006 in Donéguébougou, Mali. Eighteen children in the first cohort were randomized 2 ratio 1 to receive either 20 microg AMA1-C1/Alhydrogel or Haemophilus influenzae type b Hiberix vaccine. Two weeks later 18 children in the second cohort were randomized 2 ratio 1 to receive either 80 microg AMA1-C1/Alhydrogel or Haemophilus influenzae type b Hiberix vaccine. Vaccinations were administered on Days 0 and 28 and participants were examined on Days 1, 2, 3, 7, and 14 after vaccination and then about every two months. Results to Day 154 are reported in this manuscript. **RESULTS:** Of 36 volunteers enrolled, 33 received both vaccinations. There were 9 adverse events related to the vaccination in subjects who received AMA1-C1 vaccine and 7 in those who received Hiberix. All were mild to moderate. No vaccine-related serious or grade 3 adverse events were observed. There was no increase in adverse events with increasing dose of vaccine or number of immunizations. In subjects who received the test vaccine, antibodies to AMA1 increased on Day 14 and peaked at Day 42, with changes from baseline significantly different from subjects who received control vaccine. **CONCLUSION:** AMA-C1 vaccine is well tolerated and immunogenic in children in this endemic area although the antibody response was short lived. **TRIAL REGISTRATION:** Clinicaltrials.gov NCT00341250.

[Vaccine](#). 2008 Jan 10;26(2):174-84. Epub 2007 Nov 26.



Safety of the RTS,S/AS02A malaria vaccine in Mozambican children during a Phase IIb trial.

[Sacarlal J](#), [Aponte JJ](#), [Aide P](#), [Mandomando I](#), [Bassat Q](#), [Guinovart C](#), [Leach A](#), [Milman J](#), [Macete E](#), [Espasa M](#), [Ofori-Anyinam O](#), [Thonnard J](#), [Corachan S](#), [Dubois MC](#), [Lievens M](#), [Dubovsky F](#), [Ballou WR](#), [Cohen J](#), [Alonso PL](#).

Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique.
Jahit.sacarlal@manhica.net <Jahit.sacarlal@manhica.net>

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RTS,S/AS02A is a pre-erythrocytic vaccine candidate based on the Plasmodium falciparum circumsporozoite surface antigen and is currently the most advanced malaria vaccine candidate in development. A proof of concept phase IIb trial of the RTS,S/AS02A in Mozambican children aged 1-4 years determined a vaccine efficacy against risk of clinical malaria of 35.3% (95% CI 21.6-46.6; $p < 0.0001$) and against severe malaria of 48.6% (95% CI 12.3-71.0; $p = 0.02$). We evaluated the safety of the RTS,S/AS02A vaccine. **2022 children that received at least one vaccine dose of RTS,S/AS02A or control vaccines were included in the intention to treat safety analysis. Vaccine safety was evaluated using active and passive follow-up.**

Participants were observed for at least 1h after each dose. Trained field workers visited children at home daily for the next 3 days to record solicited and unsolicited local and general symptoms. Investigators followed-up participants with severe adverse events until month 21. Overall, we recorded 1712 unsolicited adverse events after vaccination, 53% in the intervention and 47% in the control group. Most unsolicited adverse events reported with RTS,S/AS02A were self-limited, and participants recovered without sequelae. Local reactogenicity increased with the number of doses. The proportion of children experiencing serious adverse events was lower in the RTS,S/AS02A recipients compared to the control group (Engerix-B trade mark or Prevnar trade mark and Hiberix trade mark). Overall, these results indicate that the RTS,S/AS02A vaccine has a good safety profile and well tolerated when given in three doses to semi-immune children living in malaria-endemic areas.

[Lancet](#). 2007 Nov 3;370(9598):1543-51. Epub 2007 Oct 18.



Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial.

[Aponte JJ](#), [Aide P](#), [Renom M](#), [Mandomando I](#), [Bassat Q](#), [Sacarlal J](#), [Manaca MN](#), [Lafuente S](#), [Barbosa A](#), [Leach A](#), [Lievens M](#), [Vekemans J](#), [Sigauque B](#), [Dubois MC](#), [Demoitié MA](#), [Sillman M](#), [Savarese B](#), [McNeil JG](#), [Macete E](#), [Ballou WR](#), [Cohen J](#), [Alonso PL](#).

Barcelona Centre for International Health Research (CRESIB), Hospital Clínic/Institut d'Investigacions Biomèdiques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain.

BACKGROUND: Malaria remains a leading global health problem that requires the improved use of existing interventions and the accelerated development of new control methods. We aimed to assess the safety, immunogenicity, and initial efficacy of the malaria vaccine RTS,S/AS02D in infants in Africa. **METHODS:** We did a phase I/IIb double-blind randomised trial of 214 infants in Mozambique. Infants were randomly assigned to receive three doses either of RTS,S/AS02D or the hepatitis B vaccine Engerix-B at ages 10 weeks, 14 weeks, and 18 weeks of age, as well as routine immunisation vaccines given at 8, 12, and 16 weeks of age. The primary endpoint was safety of the RTS,S/AS02D during the first 6 months of the study, and analysis was by intention to treat. Secondary endpoints included immunogenicity and analysis of new Plasmodium falciparum infections during a 3-month follow up after the third dose. Time to new infections in the per-protocol cohort were compared between groups using Cox

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regression models. This study is registered with ClinicalTrials.gov, number NCT00197028.

FINDINGS: There were 17 children (15.9%; 95% CI 9.5-24.2) with serious adverse events in each group. In the follow-up which ended on March 6, 2007, there were 31 serious adverse events in the RTS,S/AS02D group and 30 serious adverse events in the Engerix-B group, none of which were reported as related to vaccination. There were four deaths during this same follow-up period; all of them after the active detection of infection period had finished at study month 6 (two in RTS,S/AS02D group and two in the Engerix-B group). RTS,S/AS02D induced high titres of anti-circumsporozoite antibodies. 68 first or only *P. falciparum* infections were documented: 22 in the RTS,S/AS02D group and 46 in the control group. **The adjusted vaccine efficacy was 65.9% (95% CI 42.6-79.8%, $p < 0.0001$).** **INTERPRETATION: The RTS,S/AS02D malaria vaccine was safe, well tolerated, and immunogenic in young infants. These findings set the stage for expanded phase III efficacy studies to confirm vaccine efficacy against clinical malaria disease.**

Intermittent preventative treatment

[J Infect Dis.](#) 2008 Jun 15;197(12):1737-42.

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Molecular markers of resistance to sulfadoxine-pyrimethamine during intermittent preventive treatment for malaria in Mozambican infants.

[Mayor A](#), [Serra-Casas E](#), [Sanz S](#), [Aponte JJ](#), [Macete E](#), [Mandomando I](#), [Puyol L](#), [Berzosa P](#), [Dobaño C](#), [Aide P](#), [Sacarlal J](#), [Benito A](#), [Alonso P](#), [Menéndez C](#).

Centre de Recerca en Salut Internacional de Barcelona, Hospital Clínic/Institut d'Investigacions Biomèdiques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain.
agmayor@clinic.ub.es

BACKGROUND: Intermittent preventive treatment in infants (IPTi) with sulfadoxine-pyrimethamine (SP) is a potential malaria control strategy. There is concern about the impact that increasing in vivo resistance to SP has on the efficacy of IPTi, as well as about the potential contribution of IPTi to increases in resistance. **METHODS: We compared the frequency of clinical episodes of malaria caused by *P. falciparum* parasites with mutations in *dhfr* and *dhps* among sick children who received SP or placebo in the context of a randomized, double-blind, placebo-controlled IPTi trial in Mozambique.** **RESULTS:** Half of the children who received placebo harbored quintuple-pure mutant parasites. Nevertheless, the protective efficacy of IPTi within the 35 days after the third dose was 70.8% (95% confidence interval [CI], 40.7%-85.6%). Between month 2 after the third IPTi dose and the end of the follow-up period, children receiving SP harbored more *dhps* codon 437 mixed infections (odds ratio [OR], 10.56 [95% CI, 1.30-86.14]) and fewer *dhps* double-pure mutant parasites (OR, 0.43 [95% CI, 0.22-0.84]) than did placebo recipients. **CONCLUSIONS: IPTi appears to be associated with some changes in the prevalence of genotypes involved in SP resistance.** In the face of a high prevalence of quintuple-mutant parasites, SP exhibited a high level of efficacy in the prevention of new episodes of malaria in infants.

[Malar J.](#) 2008 Mar 25;7:50.



Process and effects of a community intervention on malaria in rural Burkina Faso: randomized controlled trial.

[Kouyaté B](#), [Somé F](#), [Jahn A](#), [Coulibaly B](#), [Eriksen J](#), [Sauerborn R](#), [Gustafsson L](#), [Tomson G](#), [Becher H](#), [Mueller O](#).

Centre de Recherche en Santé de Nouna, Nouna, Burkina Faso, Africa. bkouyate@hotmail.com

BACKGROUND: In the rural areas of sub-Saharan Africa, the majority of young children affected by malaria have no access to formal health services. **Home treatment through mothers of febrile children supported by mother groups and local health workers has the potential to reduce malaria morbidity and mortality.** **METHODS:** A cluster-randomized controlled effectiveness trial was implemented from 2002-2004 in a malaria endemic area of rural Burkina Faso. **Six and seven villages were randomly assigned to the intervention and control arms respectively.** Febrile children from intervention villages were treated with chloroquine (CQ) by their mothers, supported by local women group leaders. CQ was regularly supplied through a revolving fund from local health centres. The trial was evaluated through two cross-sectional surveys at baseline and after two years of intervention. **The primary endpoint of the study was the proportion of moderate to severe anaemia in children aged 6-59 months.** For assessment of the development of drug efficacy over time, an in vivo CQ efficacy study was nested into the trial. The study is registered under <http://www.controlled-trials.com> (ISRCTN 34104704). **RESULTS:** The intervention was shown to be feasible under program conditions and a total of 1,076 children and 999 children were evaluated at baseline and follow-up time points respectively. Self-reported CQ treatment of fever episodes at home as well as referrals to health centres increased over the study period. At follow-up, CQ was detected in the blood of high proportions of intervention and control children. **Compared to baseline findings, the prevalence of anaemia (29% vs 16%, $p < 0.0001$) and malaria parameters such as prevalence of *P. falciparum* parasitaemia, fever and palpable spleens was lower at follow-up but there were no differences between the intervention and control group. CQ efficacy decreased over the study period but this was not associated with the intervention.** **DISCUSSION:** The decreasing prevalence of malaria morbidity including anaemia over the study period can be explained by an overall increase of malaria prevention and treatment activities in the study area. The lack of effectiveness of the intervention was likely caused by contamination, pre-existing differences in the coverage of malaria treatment in both study groups and an unexpectedly rapid increase of resistance against CQ, the first-line treatment drug at the time of the study.

Comment

This effectiveness study shows that the importance of context in understanding the lessons from RCTs. In settings where malaria control programs are working, the impact of IPTi or home based treatment will be less, and local drug resistance may markedly reduce effectiveness.

[Malar J.](#) 2007 Dec 9;6:163.



Malaria incidence and efficacy of intermittent preventive treatment in infants (IPTi).

[Kobbe R](#), [Adjei S](#), [Kreuzberg C](#), [Kreuels B](#), [Thompson B](#), [Thompson PA](#), [Marks F](#), [Busch W](#), [Tosun M](#), [Schreiber N](#), [Opoku E](#), [Adjei O](#), [Meyer CG](#), [May J](#).

Infectious Disease Epidemiology Group, Bernhard Nocht Institute for Tropical Medicine, Bernhard-Nocht-Strasse 74, D-20359 Hamburg, Germany. kobbe@bni-hamburg.de

BACKGROUND: Intermittent preventive antimalarial treatment in infants (IPTi) is currently evaluated as a malaria control strategy. Among the factors influencing the extent of protection that is provided by IPTi are the transmission intensity, seasonality, drug resistance patterns, and the schedule of IPTi administrations. The aim of this study was to determine how far the protective efficacy of IPTi depends on spatio-temporal variations of the prevailing incidence of malaria. **METHODS:** **One thousand seventy infants were enrolled in a registered controlled trial on the efficacy of IPTi with sulphadoxine-pyrimethamine (SP) in the Ashanti Region, Ghana, West Africa** (ClinicalTrial.gov: NCT00206739). Stratification for the village of residence and the month of birth of study participants demonstrated that the malaria incidence was dependent on spatial (range of incidence rates in different villages 0.6-2.0 episodes/year) and temporal (range of incidence rates in children of different birth months 0.8-1.2 episodes/year) factors. The range of spatio-temporal variation allowed ecological analyses of the correlation between malaria incidence rates, anti-Plasmodium falciparum lysate IgG antibody levels and protective efficacies provided by IPTi. **RESULTS:** **Protective efficacy of the first SP administration was positively correlated with malaria incidences in children living in a distinct village or born in a distinct month (R2 0.48, p < 0.04 and R2 0.63, p < 0.003, respectively).** Corresponding trends were seen after the second and third study drug administration. Accordingly, IgG levels against parasite lysate increased with malaria incidence. This correlation was stronger in children who received IPTi, indicating an effect modification of the intervention. **CONCLUSION:** The spatial and temporal variations of malaria incidences in a geographically and meteorologically homogeneous study area exemplify the need for close monitoring of local incidence rates in all types of intervention studies. The increase of the protective efficacy of IPTi with malaria incidences may be relevant for IPTi implementation strategies and, possibly, for other malaria control measures.

[J Infect Dis](#). 2007 Dec 1;196(11):1595-602. Epub 2007 Oct 25.



Intermittent preventive treatment against malaria in infants in Gabon--a randomized, double-blind, placebo-controlled trial.

[Grobusch MP](#), [Lell B](#), [Schwarz NG](#), [Gabor J](#), [Dornemann J](#), [Potschke M](#), [Oyakhrome S](#), [Kiessling GC](#), [Necsek M](#), [Langin MU](#), [Klouwenberg PK](#), [Klopfer A](#), [Naumann B](#), [Altun H](#), [Agnandji ST](#), [Goesch J](#), [Decker M](#), [Salazar CL](#), [Supan C](#), [Kombila DU](#), [Borchert L](#), [Koster KB](#), [Pongratz P](#), [Adegnika AA](#), [Glasenapp I](#), [Issifou S](#), [Kremsner PG](#).

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Medical Research Unit, Albert Schweitzer Hospital, Lambarene, Gabon.
martin.grobusch@wits.ac.za

BACKGROUND: Intermittent preventive treatment aims to maximize the protective effects of malaria chemoprophylaxis while minimizing the deleterious effects. **METHODS:** In Gabon, 1189 infants received either sulfadoxine-pyrimethamine (SP; 250 and 12.5 mg, respectively) or placebo at 3, 9, and 15 months of age. Children were actively followed-up until 18 months of age. **RESULTS:** In the intention-to-treat population at 18 months of follow-up, 84 children (17%) in the SP group had ≥ 1 episode of anemia, versus 108 (21%) in the placebo group (protective efficacy, 22% [95% confidence interval {CI}, -1% to 40%]; $P=0.06$). In the intervention group, there were 66 episodes during 485 person-years at risk, compared with 79 episodes during 497 years in the placebo group (protective efficacy, 17% [95% CI, -24% to 45%]; $P=0.36$). The effects were similar at 12 months of follow-up. The study drug was safe and well tolerated. **CONCLUSIONS:** The intervention was efficacious, producing a reduction in risk for anemia but a smaller effect against malaria. It is a valuable additional tool to control malaria in a highly vulnerable age group. Remaining important questions are currently being addressed in further studies. **TRIAL REGISTRATION:** ClinicalTrials.gov identifier: NCT00167843.

[Trop Med Int Health](#). 2007 Oct;12(10):1157-63.



Immune responses after single-dose sulphadoxine-pyrimethamine indicate underestimation of protective efficacy of intermittent preventive treatment in infants.

[Schreiber N](#), [Kobbe R](#), [Adjei S](#), [Adjei O](#), [Klinkert MQ](#), [May J](#).

Infectious Disease Epidemiology Group, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany.

OBJECTIVE: To assess how intermittent preventive treatment in infants (IPTi) with sulphadoxine-pyrimethamine (SP) affects Immunoglobulin (IgG) immune responses against *Plasmodium falciparum* in infants from rural Ghana. **METHODS:** Randomized, placebo-controlled and double-blinded clinical trial with participants randomized in blocks of 10 to receive either 250 mg sulphadoxine/2.5 mg pyrimethamine or placebo at the age of 3 (IPTi-1), 9 (IPTi-2) and 15 (IPTi-3) months and followed-up for 21 months. (i) Anti-*P. falciparum* IgG levels were measured in 180 children at the age of 9 months. (ii) Longitudinal study of the relationship between IgG levels and *P. falciparum* infections and/or clinical malaria in 17 naive children until they reached the age of 2 years. **RESULTS:** IgG antibody levels against crude *P. falciparum* lysate were dependent on the frequency of preceding infections and significantly lower in children treated with SP. **CONCLUSION:** Placebo-treated children had an indifferentially higher incidence of *P. falciparum* infections than clinically observed, which implicates an underestimation of the protective efficacy of IPTi. IgG profiles in 17 children followed up until the age of 2 years provided no evidence for impaired immune responses after a single dose of SP within the framework of IPTi.

[Am J Trop Med Hyg.](#) 2007 Sep;77(3):411-7.



Impact of intermittent preventive anti-malarial treatment on the growth and nutritional status of preschool children in rural Senegal (west Africa).

[Ntab B](#), [Cissé B](#), [Boulanger D](#), [Sokhna C](#), [Targett G](#), [Lines J](#), [Alexander N](#), [Trape JF](#), [Simondon F](#), [Greenwood BM](#), [Simondon KB](#).

Epidemiology and Prevention Research Unit, Institut de Recherche pour le Développement, Montpellier, France and Dakar, Senegal.

Negative consequences of malaria might account for seasonality in nutritional status in children in the Sahel. We report the impact of a randomized, double-blind, placebo-controlled trial of seasonal intermittent preventive anti-malarial treatment on growth and nutritional status in 1,063 Senegalese preschool children. A combination of artesunate and sulfadoxine-pyrimethamine was given monthly from September to November. **In the intervention arm, mean weight gain was significantly greater (122.9 +/- 340 versus 42.9 +/- 344 [SD] g/mo, P < 0.0001) and losses in triceps and subscapular skinfold measurements were less (-0.39 +/- 1.01 versus -0.66 +/- 1.01 mm/mo, and -0.15 +/- 0.64 versus -0.36 +/- 0.62 mm/mo, respectively, P < 0.0001 for both).** There was no difference in height increments. **The prevalence of wasting increased significantly in the control arm (4.6% before versus 9.5% after, P < 0.0001), but remained constant in intervention children: 5.6% versus 7.0% (P = 0.62).** The prevention of malaria would improve child nutritional status in areas with seasonal transmission.

[PLoS Med.](#) 2007 Jul 31;4(7):e242.



Age interactions in the development of naturally acquired immunity to Plasmodium falciparum and its clinical presentation.

[Aponte JJ](#), [Menendez C](#), [Schellenberg D](#), [Kahigwa E](#), [Mshinda H](#), [Vountasou P](#), [Tanner M](#), [Alonso PL](#).

Barcelona Centre for International Health Research, Hospital Clinic/IDIBAPS, Universitat de Barcelona, Barcelona, Spain. jjairo@clinic.ub.es

BACKGROUND: Naturally acquired malaria immunity has many determinants and, in the absence of immunological markers of protection, studies assessing malaria incidence through clinical endpoints remain an approach to defining immunity acquisition. We investigated the role of age in disease incidence and the effects of chemoprophylaxis on clinical immunity development to Plasmodium falciparum during a randomised controlled trial. **METHODS AND FINDINGS:** **A total of 415 Tanzanian infants were randomly assigned to receive weekly malaria prophylaxis with Deltaprim (3.125 mg of pyrimethamine plus 25 mg of dapson)**

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or placebo between the ages of 2 and 12 mo. Children were followed up until 4 y of age. Uncomplicated febrile malaria, severe malaria, and anaemia morbidity were assessed through hospital-based passive surveillance. **Compared with the group of control participants, there was a marked reduction in the incidence of clinical malaria, severe malaria, and anaemia in the group of children who had received chemoprophylaxis during the first year of life. After discontinuing the intervention, there was a significant increase in the incidence of clinical malaria for 2 y.** The cumulative rates of clinical malaria, by age 4 y, were slightly higher in the group of children who had previously received chemoprophylaxis: 3.22 episodes versus 3.02 episodes in the group of control participants; rate difference 0.20 (95% confidence interval [CI]: -0.21 to 0.59). By age 4 y, the cumulative rates of severe malaria, however, were slightly lower in chemosuppressed children (0.47 versus 0.59) (rate difference -0.12 [95% CI: -0.27 to 0.03]). The number of episodes of anaemia was also slightly lower in chemosuppressed children by age 4 y: 0.93 episodes (95% CI: 0.79 to 0.97) versus 1.12 episodes in the group of control participants (95% CI: 0.97 to 1.28) (rate difference -0.19 [95% CI: -0.40 to 0.01]), respectively. **CONCLUSIONS: Reducing exposure to P. falciparum antigens through chemoprophylaxis early in life can delay immunity acquisition. Infants appear to acquire immunity faster than older children, but have a higher risk of developing severe forms of malaria and anaemia.** These findings provide insight on the interplay between immunity and exposure-reduction interventions.

[Antimicrob Agents Chemother.](#) 2007 Sep;51(9):3273-81. Epub 2007 Jul 16.



Intermittent preventive treatment in infants as a means of malaria control: a randomized, double-blind, placebo-controlled trial in northern Ghana.

[Mockenhaupt FP](#), [Reither K](#), [Zanger P](#), [Roepcke F](#), [Danquah I](#), [Saad E](#), [Ziniel P](#), [Dzisi SY](#), [Frempong M](#), [Agana-Nsiire P](#), [Amoo-Sakyi F](#), [Otchwemah R](#), [Cramer JP](#), [Anemana SD](#), [Dietz E](#), [Bienzle U](#).

Institute of Tropical Medicine and International Health, Charité--University Medicine Berlin, Berlin, Germany. frank.mockenhaupt@charite.de

Morbidity and mortality from malaria remain unacceptably high among young children in sub-Saharan Africa. Intermittent preventive treatment in infancy (IPTi) involves the administration of antimalarials alongside routine vaccinations and might be an option in malaria control. In an area of intense, perennial malaria transmission in northern Ghana, 1,200 children received IPTi with sulfadoxine-pyrimethamine or placebo at approximately 3, 9, and 15 months of age. Children were followed up until 24 months of age to assess morbidity and adverse events. During the intervention period (3 to 18 months of age), IPTi reduced the incidences of malaria and severe anemia by 22.5% (95% confidence interval, 12 to 32%) and 23.6% (95% confidence interval, 4 to 39%), respectively, and reduced hospitalizations and episodes of asymptomatic parasitemia by one-third. Protection was pronounced in the first year of life and not discernible in the second. The malaria-protective effect was largely confined to a period of 1 month after sulfadoxine-pyrimethamine treatments. Following the intervention, protection against asymptomatic parasitemia persisted. In contrast, a significant rebound of severe malaria, predominantly severe malarial anemia, occurred among children having received IPTi. Although

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the treatment was generally well tolerated, one case of moderately severe skin reaction followed sulfadoxine-pyrimethamine treatment. **IPTi reduces malaria and anemia in infants in northern Ghana.** Extension of IPTi into the second year of life by administering a dose at 15 months of age provided no substantial benefit beyond a 1-month prophylactic effect. Although this simple intervention offers one of the few available malaria-preventive measures for regions where malaria is endemic, the observed rebound of severe malaria advises caution and requires further investigation.

Comment

These IPTi studies show that infants receiving IPTi subsequently have an increased risk of severe malaria in the second year of life. However the net benefit of IPTi is still positive in areas of high malaria endemicity, as infants have a higher risk of severe forms of malaria and anaemia. In the study above by study by Aponte in Tanzania, while there may be a rebound in morbidity following the intervention, the cumulative rates of severe malaria and severe anaemia in the intervention group remained just below those of the control group until 4 years of age.

Rapid diagnostic tests

[Am J Trop Med Hyg.](#) 2007 Dec;77(6 Suppl):128-32.



The cost-effectiveness of parasitologic diagnosis for malaria-suspected patients in an era of combination therapy.

[Lubell Y](#), [Reyburn H](#), [Mbakilwa H](#), [Mwangi R](#), [Chonya K](#), [Whitty CJ](#), [Mills A](#).

Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom. yoel.lubell@lshtm.ac.uk

The introduction of artemisinin-based combination therapy in sub-Saharan Africa has prompted calls for increased use of parasitologic diagnosis for malaria. We evaluated the cost-effectiveness of rapid diagnostic tests (RDTs) in comparison to microscopy in guiding treatment of non-severe febrile illness at varying levels of malaria endemicity using data on test accuracy and costs collected as part of a Tanzanian trial. If prescribers complied with current guidelines, microscopy would give rise to lower average costs per patient correctly treated than RDTs in areas of both high and low transmission. **RDT introduction would result in an additional 2.3% and 9.4% of patients correctly treated, at an incremental cost of \$25 and \$7 in the low and high transmission settings, respectively.** Cost-effectiveness would be worse if prescribers do not comply with test results. **The cost of this additional benefit may be higher than many countries can afford without external assistance or lower RDT prices.**

Insecticide treated materials

[Trials.](#) 2008 Jun 6;9:33.



Study protocol for a three-armed randomized controlled trial to assess whether house screening can reduce exposure to malaria vectors and reduce malaria transmission in The Gambia.

[Kirby MJ](#), [Milligan PJ](#), [Conway DJ](#), [Lindsay SW](#).

Durham University, Science Laboratories, South Road, Durham, DH1 3LE, UK.
s.w.lindsay@durham.ac.uk.

ABSTRACT: BACKGROUND: Mosquito-proofing homes was one of the principal methods of environmental management in the early 1900s. House screening provides protection against malaria by reducing exposure to malaria parasites and has the added benefit of protecting everyone sleeping in the house, avoiding issues of inequity within the household. The aim of this study is to determine whether house screening protects people against malaria in Africa. It is hoped that this study will mark the beginning of a series of trials assessing a range of environmental interventions for malaria control in Africa. **DESIGN: A 3-armed randomised-controlled trial will be conducted in and around Farafenni town in The Gambia, West Africa, to assess whether screening windows, doors and closing eaves or installing netting ceilings in local houses can substantially reduce malaria transmission and anaemia compared to homes with no screening.** Eligible houses will be sorted and stratified by location and the number of children in each house, then randomly allocated to the interventions in blocks of 5 houses (2 with full screening, 2 with screened ceilings and 1 control house without screening). Risk of malaria transmission will be assessed in each house by routine collections of mosquitoes using light traps and an anaemia prevalence study in children at the end of the main transmission period. **DISCUSSION:** Practical issues concerning intervention implementation, as well as the potential benefits and risks of the study, are discussed. **TRIAL REGISTRATION:** ISRCTN51184253 - Screening-homes to prevent malaria.

[Lancet](#). 2007 Sep 22;370(9592):1035-9.



Effect of expanded insecticide-treated bednet coverage on child survival in rural Kenya: a longitudinal study.

[Fegan GW](#), [Noor AM](#), [Akhwale WS](#), [Cousens S](#), [Snow RW](#).

Malaria Public Health and Epidemiology Group, Centre for Geographic Medicine Research-Coast, Kenya Medical Research Institute/Wellcome Trust Research Programme, Nairobi, Kenya. gfegan@kilifi.kemri-wellcome.org

BACKGROUND: The potential of insecticide-treated bednets (ITNs) to contribute to child survival has been well documented in randomised controlled trials. ITN coverage has increased rapidly in Kenya from 7% in 2004 to 67% in 2006. We aimed to assess the extent to which this

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investment has led to improvements in child survival. **METHODS: A dynamic cohort of about 3500 children aged 1-59 months were enumerated three times at yearly intervals in 72 rural clusters located in four districts of Kenya.** The effect of ITN use on mortality was assessed with Poisson regression to take account of potential effect-modifying and confounding covariates. **FINDINGS: 100 children died over 2 years. Overall mortality rates were much the same in the first and second years of the study (14.5 per 1000 person-years in the first year and 15.4 per 1000 person-years in the second). After adjustment for age, time period, and a number of other possible confounding variables, ITN use was associated with a 44% reduction in mortality (mortality rate ratio 0.56, 95% CI 0.33-0.96; p=0.04). This level of protection corresponds to about seven deaths averted for every 1000 ITNs distributed.** **INTERPRETATION: A combined approach of social marketing followed by mass free distribution of ITNs translated into child survival effects that are comparable with those seen in previous randomised controlled trials**

Comment

This important effectiveness trial confirms the substantial and sustained benefit on child survival of insecticide treated net-nets. The effect size was very large in this study, with 7 deaths averted for every 1000 ITNs distributed.

Treatment of uncomplicated malaria

Comment

This year there are 21 studies of treatment for uncomplicated malaria treatment. Many of the results are locally relevant, but their generalizability depends on local rates of drug resistance. General findings include the results of studies that artesunate and amodiaquine and was associated with neutropenia in HIV-infected children in Uganda and amodiaquine and SP was associated with neutropenia in Malawi, where HIV-infection rates are high. Newer therapies this year include methylene blue (an old therapy re-visited in one study) and dihydroartemisinin-piperaquine (relatively new: 4 studies), both drugs showing promising results.

[Malar J.](#) 2008 Jun 11;7:106.



Safety and tolerability of combination antimalarial therapies for uncomplicated falciparum malaria in Ugandan children.

[Maiteki-Sebuguzi C](#), [Jagannathan P](#), [Yau VM](#), [Clark TD](#), [Njama-Meva D](#), [Nzarubara B](#), [Talisuna AO](#), [Kamya MR](#), [Rosenthal PJ](#), [Dorsey G](#), [Staedke SG](#).

Department of Medicine, Makerere University, Kampala, Uganda. cmaiteki@yahoo.com

BACKGROUND: Combination antimalarial therapy is recommended for the treatment of uncomplicated falciparum malaria in Africa; however, some concerns about the safety and tolerability of new regimens remain. This study compared the safety and tolerability of three combination antimalarial regimens in a cohort of Ugandan children. **METHODS:** A longitudinal, single-blind, randomized clinical trial of children was conducted between November 2004 and May 2007 in Kampala, Uganda. Upon diagnosis of the first episode of uncomplicated malaria, participants were randomized to treatment with amodiaquine + sulphadoxine-pyrimethamine (AQ+SP), artesunate + amodiaquine (AS+AQ), or artemether-

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lumefantrine (AL). Once randomized, participants received the same regimen for all subsequent episodes of uncomplicated malaria. Participants were actively monitored for adverse events for the first 14 days after each treatment, and then passively followed until their next study medication treatment, or withdrawal from study. Outcome measures included the risk of adverse events at 14 and 42 days after treatment. RESULTS: Of 601 enrolled children, 382 were diagnosed with at least one episode of uncomplicated malaria and were treated with study medications. The median age at treatment was 6.3 years (range 1.1 - 12.3 years). At 14 days of follow-up, AQ+SP treatment was associated with a higher risk of anorexia, weakness, and subjective fever than treatment with AL, and a higher risk of weakness, and subjective fever than treatment with AS+AQ. Treatment with AL was associated with a higher risk of elevated temperature. Repeated episodes of neutropaenia associated with AS+AQ were detected in one participant. Considering only children less than five years, those who received AQ+SP were at higher risk of developing moderate or severe anorexia and weakness than those treated with AL (anorexia: RR 3.82, 95% CI 1.59 - 9.17; weakness: RR 5.40, 95% CI 1.86 - 15.7), or AS+AQ (anorexia: RR 2.10, 95% CI 1.04 - 4.23; weakness: RR 2.26, 95% CI 1.01 - 5.05). Extending the analysis to 42 days of follow-up had little impact on the findings. CONCLUSION: This study confirms the safety and tolerability of AS+AQ and AL in Ugandan children, and suggests that AQ+SP is safe, but less well-tolerated, particularly in younger children. As newer antimalarial regimens are deployed, collecting data on their safety and tolerability will be essential. TRIAL REGISTRATION: Current Controlled Trials Identifier ISRCTN37517549.

[Clin Infect Dis.](#) 2008 Apr 1;46(7):985-91.



High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda.

[Gasasira AF](#), [Kamya MR](#), [Achan J](#), [Mebrahtu T](#), [Kalvango JN](#), [Ruel T](#), [Charlebois E](#), [Staedke SG](#), [Kekitiinwa A](#), [Rosenthal PJ](#), [Havilir D](#), [Dorsey G](#).

Department of Internal Medicine, Makerere University, Mulago Hospital, Kampala, Uganda.
agasasira@berkeley.edu

BACKGROUND: Artemisinin-based combination therapies are rapidly being adopted for the treatment of malaria in Africa; however, there are limited data on their safety and efficacy among human immunodeficiency virus (HIV)-infected populations. METHODS: We compared malaria treatment outcomes between cohorts of HIV-infected and HIV-uninfected children in Uganda who were observed for 18 and 29 months, respectively. Malaria was treated with artesunate plus amodiaquine, and outcomes were assessed using standardized guidelines. HIV-infected children received trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy in accordance with current guidelines. RESULTS: Twenty-six HIV-infected participants experiencing 35 episodes of malaria and 134 HIV-uninfected children experiencing 258 episodes of malaria were included in the study. Twelve HIV-infected children were receiving antiretroviral therapy, 11 of whom were receiving zidovudine. Malaria treatment was highly efficacious in both the HIV-infected and HIV-uninfected cohorts (28-day risk of recrudescence, 0% and 3.6%, respectively); however, there was a trend towards increased risk of recurrent malaria among the HIV-uninfected children (2.9% vs. 13.2%; $p = .08$). Importantly, the risk of

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neutropenia 14 days after initiation of treatment with artesunate plus amodiaquine was higher among HIV-infected children than among HIV-uninfected children (45% vs. 6%; $p < .001$). The severity of all episodes of neutropenia in HIV-uninfected children was mild to moderate, and 16% of episodes of neutropenia in the HIV-infected cohort were severe or life-threatening (neutrophil count, <750 cells/mm³). In the HIV-infected cohort, the risk of neutropenia was significantly higher among children who received antiretroviral therapy than among those who did not receive antiretroviral therapy (75% vs. 26%; $p < .001$). CONCLUSIONS: Artesunate plus amodiaquine was highly efficacious for malaria treatment in HIV-infected children but was associated with a high risk of neutropenia, especially in the context of concurrent antiretroviral use. Our findings highlight an urgent need for evaluation of alternative antimalarial therapies for HIV-infected individuals.

[Med Princ Pract.](#) 2008;17(3):197-201. Epub 2008 Apr 10.

Enhanced efficacy of amodiaquine and chlorpheniramine combination over amodiaquine alone in the treatment of acute uncomplicated Plasmodium falciparum malaria in children.

[Falade CO](#), [Michael SO](#), [Oduola AM](#).

Department of Pharmacology, College of Medicine, University of Ibadan, Ibadan, Nigeria.
fallady@skannet.com

OBJECTIVE: To evaluate the comparative efficacy of amodiaquine (AMQ) alone and the combination of AMQ and chlorpheniramine (CP) in the treatment of acute uncomplicated malaria in children. **SUBJECTS:** Of the 110 children enrolled in the study, 103 with acute uncomplicated malaria, aged 6 months to 12 years, were evaluated using the 14-day modification of the WHO field test. The patients were randomized to 2 groups. Group 1 received supervised treatment with AMQ alone (10 mg AMQ base/kg daily for 3 days), while group 2 received supervised treatment with AMQ (same dose as group 1) plus CP (AMQCP) for 7 days. **RESULTS:** Both treatment regimens were well tolerated and no patient was withdrawn as a result of recurrent vomiting or drug-related adverse events. There was no significant difference in mean fever and parasite clearance times. The cure rates at day 7 were 90.2 versus 100% ($\rho = 0.027$) for AMQ versus AMQCP, while the day 14 cure rates were 85.9 versus 98.1% for AMQ versus AMQCP, respectively ($\rho = 0.016$). **CONCLUSION:** The combination of AMQ plus CP proved significantly more effective than AMQ alone in the treatment of acute uncomplicated falciparum malaria, most probably due to the enhancement of the antimalarial effect of AMQ by CP. The combination of AMQCP could be a better alternative to AMQ alone as a companion drug in artemisinin-based combination therapies. (c) 2008 S. Karger AG, Basel

[PLoS ONE.](#) 2008 Mar 5;3(3):e1779.



Open-label comparative clinical study of chlorproguanil-dapsone fixed dose combination (Lapdap) alone or with three different doses of artesunate for

uncomplicated Plasmodium falciparum malaria.

[Wootton DG](#), [Opara H](#), [Biagini GA](#), [Kanjala MK](#), [Duparc S](#), [Kirby PL](#), [Woessner M](#), [Neate C](#), [Nyirenda M](#), [Blencowe H](#), [Dube-Mbeve Q](#), [Kanyok T](#), [Ward S](#), [Molyneux M](#), [Dunyo S](#), [Winstanley PA](#).

Department of Pharmacology & Therapeutics, University of Liverpool, Liverpool, United Kingdom.

The objective of this study was to determine the appropriate dose of artesunate for use in a fixed dose combination therapy with chlorproguanil-dapsone (CPG-DDS) for the treatment of uncomplicated falciparum malaria. **METHODS:** Open-label clinical trial comparing CPG-DDS alone or with artesunate 4, 2, or 1 mg/kg at medical centers in Blantyre, Malawi and Farafenni, The Gambia. The trial was conducted between June 2002 and February 2005, including 116 adults (median age 27 years) and 107 children (median age 38 months) with acute uncomplicated Plasmodium falciparum malaria. Subjects were randomized into 4 groups to receive CPG-DDS alone or plus 4, 2 or 1 mg/kg of artesunate once daily for 3 days. Assessments took place on Days 0-3 in hospital and follow-up on Days 7 and 14 as out-patients. Efficacy was evaluated in the Day 3 per-protocol (PP) population using mean time to reduce baseline parasitemia by 90% (PC90). A number of secondary outcomes were also included. Appropriate artesunate dose was determined using a pre-defined decision matrix based on primary and secondary outcomes. Treatment emergent adverse events were recorded from clinical assessments and blood parameters. Safety was evaluated in the intent to treat (ITT) population. **RESULTS:** In the Day 3 PP population for the adult group (N = 85), mean time to PC90 was 19.1 h in the CPG-DDS group, significantly longer than for the +artesunate 1 mg/kg (12.5 h; treatment difference -6.6 h [95%CI -11.8, -1.5]), 2 mg/kg (10.7 h; -8.4 h [95%CI -13.6, -3.2]) and 4 mg/kg (10.3 h; -8.7 h [95%CI -14.1, -3.2]) groups. For children in the Day 3 PP population (N = 92), mean time to PC90 was 21.1 h in the CPG-DDS group, similar to the +artesunate 1 mg/kg group (17.7 h; -3.3 h [95%CI -8.6, 2.0]), though the +artesunate 2 mg/kg and 4 mg/kg groups had significantly shorter mean times to PC90 versus CPG-DDS; 14.4 h (treatment difference -6.4 h [95%CI -11.7, -1.0]) and 12.8 h (-7.4 h [95%CI -12.9, -1.8]), respectively. An analysis of mean time to PC90 for the Day 14 PP and ITT populations was consistent with the primary analysis. Treatment emergent, drug-related adverse events were experienced in 35.3% (41/116) of adults and 70.1% (75/107) of children; mostly hematological and gastroenterological. The nature and incidence of adverse events was similar between the groups. No dose-related changes in laboratory parameters were observed. Nine serious adverse events due to any cause occurred in five subjects including two cases of hemolysis believed to be associated with drug treatment (one adult, one child). One adult died of anaphylactic shock, not associated with investigational therapy. **CONCLUSIONS:** CPG-DDS plus artesunate demonstrated advantages over CPG-DDS alone for the primary efficacy endpoint (mean time to PC90) except in children for the 1 mg/kg artesunate dose. Based on a pre-defined decision matrix, the primary endpoint in the child group supported an artesunate dose of 4 mg/kg. Secondary endpoints also supported a 4 mg/kg artesunate dose to take forward into the remainder of the development program. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00519467.



Population pharmacokinetics of chloroquine and sulfadoxine and treatment response in children with malaria: suggestions for an improved dose regimen.

[Obua C](#), [Hellgren U](#), [Ntale M](#), [Gustafsson LL](#), [Ogwal-Okeng JW](#), [Gordi T](#), [Jerling M](#).

Department of Pharmacology and Therapeutics, Makerere University, Kampala, Uganda.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT: * Both chloroquine (CQ) and sulfadoxine/ pyrimethamine (SDx/PYR) remain important drugs in the control of malaria. * The available data on CQ, SDx and PYR are summary pharmacokinetic parameters based on classical/traditional methods, mostly in adults. * No study has described the population pharmacokinetics of a fixed-dose CQ + SDx/PYR combination in children with falciparum malaria. WHAT THIS STUDY ADDS: * This study presents population pharmacokinetic data on CQ and SDx in children with uncomplicated falciparum malaria. * The study demonstrates that in age-based fixed-dose regimens with CQ and SDx, drug exposures and outcomes may be correctly predicted, although correlation with body weight is poor. * The study proposes dose modification to improve response with the CQ + SDx/PYR combination. AIMS: To describe the pharmacokinetics of chloroquine (CQ) and sulfadoxine (SDx), and to identify predictors of treatment response in children with malaria given the CQ + SDx and pyrimethamine (PYR) combination. METHODS: Eighty-six Ugandan children with uncomplicated falciparum malaria, 6 months to 5 years old, were randomly treated with prepacked fixed-dose CQ + SDx/PYR. The youngest children (<24 months) received half strength and the older (>24 months) full strength treatment. The reported day 14 failure rates were 48% and 18%, respectively. Capillary blood (100 microl) applied on to filter paper was collected on eight occasions during 28 days of follow up. Concentrations of CQ and SDx were determined. A population approach was used for the pharmacokinetic analysis. RESULTS: A two-compartment model adequately described the data for both CQ and SDx. For CQ, the typical apparent clearance (CL/F) and volume of distribution (V(C)/F) values were estimated to be 2.84 l h⁻¹ and 230 l. The typical CL/F for SDx was 0.023 l h⁻¹, while the factor relating its V(C)/F to normalized body weight was 1.6 l kg⁻¹. Post hoc parameter estimates for both drugs showed lower maximum concentrations (C(max)) and concentration-time curve areas (AUC(0,336 h)) in younger children. The AUC(0,336 h) for SDx and CQ were independently significant factors for prediction of cure. Simulations suggest that giving the higher dose to the youngest children would result in higher CQ and SDx concentrations and improved outcome. CONCLUSIONS: The study results suggest that full-strength combination to all children would improve the cure rate.

PLoS ONE. 2008 Feb 20;3(2):e1630.



Safety and efficacy of methylene blue combined with artesunate or amodiaquine for uncomplicated falciparum malaria: a randomized controlled trial from Burkina Faso.

[Zoungrana A](#), [Coulibaly B](#), [Sié A](#), [Walter-Sack I](#), [Mockenhaupt FP](#), [Kouyaté B](#), [Schirmer RH](#), [Klose C](#), [Mansmann U](#), [Meissner P](#), [Müller O](#).

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Centre de Recherche en Santé de Nouna, Nouna, Burkina Faso.

BACKGROUND: Besides existing artemisinin-based combination therapies, alternative safe, effective and affordable drug combinations against falciparum malaria are needed. Methylene blue (MB) was the first synthetic antimalarial drug ever used, and recent studies have been promising with regard to its revival in malaria therapy. The objective of this study was to assess the safety and efficacy of two MB-based malaria combination therapies, MB-artesunate (AS) and MB-amodiaquine (AQ), compared to the local standard of care, AS-AQ, in Burkina Faso. **METHODS AND FINDINGS:** Open-label randomised controlled phase II study in 180 children aged 6-10 years with uncomplicated falciparum malaria in Nouna, north-western Burkina Faso. Follow-up was for 28 days and analysis by intention-to-treat. The treatment groups were similar in baseline characteristics and there was only one loss to follow-up. No drug-related serious adverse events and no deaths occurred. MB-containing regimens were associated with mild vomiting and dysuria. No early treatment failures were observed. Parasite clearance time differed significantly among groups and was the shortest with MB-AS. By day 14, the rates of adequate clinical and parasitological response after PCR-based correction for recrudescence were 87% for MB-AS, 100% for MB-AQ ($p = 0.004$), and 100% for AS-AQ ($p = 0.003$). By day 28, the respective figure was lowest for MB-AS (62%), intermediate for the standard treatment AS-AQ (82%; $p = 0.015$), and highest for MB-AQ (95%; $p < 0.001$; $p = 0.03$). **CONCLUSIONS:** MB-AQ is a promising alternative drug combination against malaria in Africa. Moreover, MB has the potential to further accelerate the rapid parasite clearance of artemisinin-based combination therapies. More than a century after the antimalarial properties of MB had been described, its role in malaria control deserves closer attention. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00354380.

[PLoS ONE](#). 2008 Feb 13;3(2):e1578.



Sulfadoxine-pyrimethamine-based combinations for malaria: a randomised blinded trial to compare efficacy, safety and selection of resistance in Malawi.

[Bell DJ](#), [Nvirongo SK](#), [Mukaka M](#), [Zijlstra EE](#), [Plowe CV](#), [Molyneux ME](#), [Ward SA](#), [Winstanley PA](#).

Department of Molecular and Biochemical Parasitology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom.

BACKGROUND: In Malawi, there has been a return of *Plasmodium falciparum* sensitivity to chloroquine (CQ) since sulfadoxine-pyrimethamine (SP) replaced CQ as first line treatment for uncomplicated malaria. When used for prophylaxis, Amodiaquine (AQ) was associated with agranulocytosis but is considered safe for treatment and is increasingly being used in Africa. Here we compare the efficacy, safety and selection of resistance using SP or CQ+SP or artesunate (ART)+SP or AQ+SP for the treatment of uncomplicated falciparum malaria. **METHODOLOGY AND FINDINGS:** 455 children aged 1-5 years were recruited into a double-blinded randomised trial comparing SP to the three combination therapies. Using intention to treat analysis with missing outcomes treated as successes, and without adjustment to distinguish

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recrudescence from new infections, the day 28 adequate clinical and parasitological response (ACPR) rate for SP was 25%, inferior to each of the three combination therapies ($p < 0.001$). AQ+SP had an ACPR rate of 97%, higher than CQ+SP (81%) and ART+SP (70%), $p < 0.001$. Nineteen children developed a neutropenia of $\leq 0.5 \times 10^3$ cells/microl by day 14, more commonly after AQ+SP ($p = 0.03$). The mutation pfcr76T, associated with CQ resistance, was detected in none of the pre-treatment or post-treatment parasites. The prevalence of the pfmdr1 86Y mutation was higher after treatment with AQ+SP than after SP, $p = 0.002$.

CONCLUSIONS: The combination AQ+SP was highly efficacious, despite the low efficacy of SP alone; however, we found evidence that AQ may exert selective pressure for resistance associated mutations many weeks after treatment. This study confirms the return of CQ sensitivity in Malawi and importantly, shows no evidence of the re-emergence of pfcr76T after treatment with CQ or AQ. Given the safety record of AQ when used as a prophylaxis, our observations of marked falls in neutrophil counts in the AQ+SP group requires further scrutiny.

TRIAL REGISTRATION: Controlled-Trials.com ISRCTN22075368

[Malar J.](#) 2008 Feb 12;7:31.



Sulphadoxine/pyrimethamine versus amodiaquine for treating uncomplicated childhood malaria in Gabon: a randomized trial to guide national policy.

[Nsimba B](#), [Guiyedi V](#), [Mabika-Mamfoumbi M](#), [Mourou-Mbina JR](#), [Ngoungou E](#), [Bouyou-Akotet M](#), [Loembet R](#), [Durand R](#), [Le Bras J](#), [Kombila M](#).

National Malaria Control Programme - Division for Disease Control, Ministry of Health, Brazzaville, Congo. basilensimba@aol.com

BACKGROUND: In Gabon, following the adoption of amodiaquine/artesunate combination (AQ/AS) as first-line treatment of malaria and of sulphadoxine/pyrimethamine (SP) for preventive intermittent treatment of pregnant women, a clinical trial of SP versus AQ was conducted in a sub-urban area. This is the first study carried out in Gabon following the WHO guidelines. **METHODS:** A random comparison of the efficacy of AQ (10 mg/kg/day x 3 d) and a single dose of SP (25 mg/kg of sulphadoxine/1.25 mg/kg of pyrimethamine) was performed in children under five years of age, with uncomplicated falciparum malaria, using the 28-day WHO therapeutic efficacy test. In addition, molecular genotyping was performed to distinguish recrudescence from reinfection and to determine the frequency of the dhps K540E mutation, as a molecular marker to predict SP-treatment failure. **RESULTS:** The day-28 PCR-adjusted treatment failures for SP and AQ were 11.6% (8/69; 95% IC: 5.5-22.1) and 28.2% (20/71; 95% CI: 17.7-38.7), respectively. This indicated that SP was significantly superior to AQ ($P = 0.019$) in the treatment of uncomplicated childhood malaria and for preventing recurrent infections. Both treatments were safe and well-tolerated, with no serious adverse reactions recorded. The dhps K540E mutation was not found among the 76 parasite isolates tested. **CONCLUSION:** The level of AQ-resistance observed in the present study may compromise efficacy and duration of use of the AQ/AS combination, the new first-line malaria treatment. Gabonese policy-makers need to plan country-wide and close surveillance of AQ/AS efficacy to determine whether, and for how long, these new recommendations for the treatment of uncomplicated malaria remain valid.

[Malar J.](#) 2007 Dec 21;6:170.



Adding artesunate to sulphadoxine-pyrimethamine greatly improves the treatment efficacy in children with uncomplicated falciparum malaria on the coast of Benin, West Africa.

[Nahum A](#), [Erhart A](#), [Gazard D](#), [Agbowai C](#), [Van Overmeir C](#), [van Loen H](#), [Menten J](#), [Akogbeto M](#), [Coosemans M](#), [Massougboji A](#), [D'Alessandro U](#).

Laboratoire de Parasitologie, Centre de Recherches Entomologique de Cotonou, Cotonou, Bénin. nahum_alain@yahoo.fr

BACKGROUND: Benin has recently shifted its national antimalarial drug policy from monotherapies to combinations containing artemisinin derivatives. When this decision was taken, the available information on alternatives to chloroquine and sulphadoxine-pyrimethamine, the first- and second-line treatment, was sparse. **METHODS:** In 2003 - 2005, before the drug policy change, a randomized, open-label, clinical trial was carried out on the efficacy of chloroquine, and sulphadoxine-pyrimethamine alone or combined with artesunate, with the aim of providing policy makers with the information needed to formulate a new antimalarial drug policy. Children between six and 59 months of age, with uncomplicated malaria and living in the lagoon coastal area in southern Benin, were randomly allocated to one of the three study arms and followed up for 28 days. **RESULTS:** Treatment failure (PCR corrected) was significantly lower in the artesunate + sulphadoxine-pyrimethamine group (4/77, 5.3%) than in chloroquine group (51/71, 71.8%) or the sulphadoxine-pyrimethamine alone group (30/70, 44.1%) ($p < 0.001$). Despite high sulphadoxine-pyrimethamine failure, its combination with artesunate greatly improved treatment efficacy. **CONCLUSION:** In Benin, artesunate + sulphadoxine-pyrimethamine is efficacious and could be used when the recommended artemisinin-based combinations (artemether-lumefantrine and amodiaquine-artesunate) are not available. However, because sulphadoxine-pyrimethamine is also used in pregnant women as intermittent preventive treatment, its combination with artesunate should not be widely employed in malaria patients as this may compromise the efficacy of intermittent preventive treatment.

[Trans R Soc Trop Med Hyg.](#) 2008 Feb;102(2):137-42. Epub 2007 Dec 21.

Antimalarial resistance and DHFR/DHPS genotypes of Plasmodium falciparum three years after introduction of sulfadoxine-pyrimethamine and amodiaquine in rural Tanzania.

[Eriksen J](#), [Mwankusye S](#), [Mduma S](#), [Veiga MI](#), [Kitua A](#), [Tomson G](#), [Petzold MG](#), [Swedberg G](#), [Gustafsson LL](#), [Warsame M](#).

Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet at

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Karolinska University Hospital Huddinge, Stockholm, Sweden. jaran.eriksen@ki.se
<jaran.eriksen@ki.se>

We assessed the efficacy of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) and DHFR/DHPS genotypes of *Plasmodium falciparum* in rural Tanzania, 3 years after their introduction as first- and second-line treatments for uncomplicated malaria, respectively. Under five children with uncomplicated malaria were given standard treatments of either SP (n=66) or AQ (n=30) and treatment outcomes after 14 and 28 days were determined. Total treatment failure of 18 and 42.5% was observed for SP on days 14 and 28, respectively. For AQ, total treatment failure of 27 and 53% was found on day 14 and 28, respectively. On day 14, significantly lower SP total treatment failures were observed in 2004 compared with results from a study conducted in 1999 in the same location. No relationship was detected between clinical outcome and DHFR/DHPS genotypes, but the point mutation prevalence in parasites was higher than in 1999. Pre-treatment blood levels of SP were detected in a quarter of the study children: less than expected. We report unacceptably high levels of total treatment failures, both for first- and second-line treatments for uncomplicated malaria in Tanzania 3 years after their introduction, supporting the decision to replace them with artemisinin-based combination therapy.

[Malar J.](#) 2007 Nov 11;6:146.



Efficacy and safety of artemisinin-based antimalarial in the treatment of uncomplicated malaria in children in southern Tanzania.

[Kabanywanyi AM](#), [Mwita A](#), [Sumari D](#), [Mandike R](#), [Mugittu K](#), [Abdulla S](#).

Ifakara Health Research and Development Centre, Tanzania. omulokozi@gmail.com

BACKGROUND: Tanzania switched the antimalarial first line to sulphadoxine-pyrimethamine (SP) in 2001 from ineffective chloroquine (CQ). By 2003 higher levels of SP resistance were recorded, prompting an urgent need for replacing the first line drug with ACT, as currently recommended by the World Health Organization. Despite this recommendation country-specific evidence-based data to support efficacy and safety profile of ACT is still limited. A study on the efficacy and safety of artesunate plus amodiaquine (AS+AQ) and artemether plus lumefantrine (AL)(Coartem) was carried out in 2004 with the view of supporting the National Malaria Control Programme in the review of the policy in mainland Tanzania. **METHODS:** An in vivo efficacy study was conducted at Ipinda and Mlimba health facilities between May and November 2004. The study recruited children aged 6-59 months presenting with symptoms of uncomplicated malaria, history of fever or an axillary temperature ≥ 37.5 degrees C; mono infection with *Plasmodium falciparum* (2,000-200,000 parasites/microl). Patients were randomized to received either SP or amodiaquine monotherapy or treated with standard doses of AS+AQ in Mlimba and Coartem in Kyela and followed-up for 28 days to assess treatment responses. This study reports results of the combination therapies. **RESULTS:** A total of 157 children (76 in Mlimba and 99 in Kyela) who were enrolled in to the study and treated with either AL or AS+AQ were successfully followed-up. Both combinations were tolerated and effected rapid fever and parasite clearance. The crude ACPRs were 80 (87%) and 41 (63%) for

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AL and AS+AQ respectively. However, after PCR adjustments the corresponding figures raised to 100% (n = 86) and 93.8% (n = 45) in AL and AS+AQ groups, respectively. The mean haemoglobin improved moderately from day 0 to day 28 by 1 g/dl in AL and 0.4 g/dl in AS+AQ treatment group and was statistically significant (p < 0.001 both). CONCLUSION: These findings provide substantial evidence that AL is highly efficacious in areas of high resistance of SP and supported the country's decision to switch from SP monotherapy to AL.

[Clin Infect Dis.](#) 2007 Dec 1;45(11):1453-61. Epub 2007 Oct 22.



Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Burkina Faso.

[Zongo I](#), [Dorsey G](#), [Rouamba N](#), [Dokomajilar C](#), [Séré Y](#), [Rosenthal PJ](#), [Ouédraogo JB](#).

Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso.

BACKGROUND: Combination antimalarial therapy is advocated to improve treatment efficacy and limit selection of drug-resistant parasites. We compared the efficacies of 3 combination regimens in Bobo-Dioulasso, Burkina Faso: amodiaquine plus sulfadoxine-pyrimethamine, which was recently shown to be highly efficacious at this site; artemether-lumefantrine, the new national first-line antimalarial regimen; and dihydroartemisinin-piperaquine (DP), a newer regimen. **METHODS:** We enrolled 559 patients ≥ 6 months of age with uncomplicated Plasmodium falciparum malaria and randomized them to the 3 regimens. We analyzed the risk of recurrent parasitemia by day 28 and day 42, both unadjusted and adjusted by PCR methods to distinguish recrudescence and new infection. **RESULTS:** Complete data were available for 517 (92.5%) of the enrolled subjects. Early treatment failures occurred in 5 patients treated with amodiaquine plus sulfadoxine-pyrimethamine and in 2 patients each treated with the other regimens. The day 28 risk of recurrent parasitemia, unadjusted by genotyping, was significantly higher for patients receiving artemether-lumefantrine than for patients receiving amodiaquine plus sulfadoxine-pyrimethamine (20.1% vs. 6.2%; risk difference, 13.8%; 95% confidence interval, 7.0%-20.7%) or dihydroartemisinin-piperaquine (20.1% vs. 2.2%; risk difference, 17.9%; 95% confidence interval, 11.6%-24.1%). Similar differences were seen for children <5 years of age (54% of the study population) and when outcomes were extended to 42 days. Significant differences were not seen between outcomes for patients receiving amodiaquine plus sulfadoxine-pyrimethamine and outcomes for those receiving dihydroartemisinin-piperaquine. Recrudescences were uncommon (occurring in <5% of patients) in all treatment groups. No serious adverse events were noted. **CONCLUSIONS:** All regimens were highly efficacious in clearing infection, but considering the risks of recurrent malaria after therapy, the amodiaquine plus sulfadoxine-pyrimethamine and dihydroartemisinin-piperaquine regimens were more efficacious than the artemether-lumefantrine regimen (the new national regimen in Burkina Faso) for the treatment of uncomplicated P. falciparum malaria.

[Am J Trop Med Hyg.](#) 2007 Oct;77(4):612-6.



Comparison of different artemisinin-based combinations for the treatment of *Plasmodium falciparum* malaria in children in Kigali, Rwanda, an area of resistance to sulfadoxine-pyrimethamine: artesunate plus sulfadoxine/pyrimethamine versus artesunate plus sulfamethoxypyrazine/pyrimethamine.

[Rulisa S.](#), [Gataraviha JP.](#), [Kabarisa T.](#), [Ndavisaba G.](#)

Central University Hospital of Kigali, Kigali, Rwanda. stevenruse@yahoo.com

In view of the changing policy towards artemisinin-based combination therapies (ACTs), the efficacy, tolerance, and degree of re-infection of two ACTs were investigated: artesunate plus sulfadoxine/pyrimethamine (As + SP) and AS plus sulfamethoxypyrazine/pyrimethamine (As + SMP). One hundred three children were assigned to receive As + SP and 109 to receive As + SMP. In spite of the high incidence of resistance to SP, As + SP showed satisfactory results consistent with recent recommendations for ACTs (adequate clinical and parasitologic response on day 28 [ACPR] \geq 90%), but results with As + SMP fulfilled the most stringent criteria (ACPR \geq 95%). The absence of side effects and the low price of these drugs make them it worth to reconsider national therapies in favor of either of these two drug combinations.

[PLoS ONE](#). 2007 Oct 31;2(10):e1101.



A randomised controlled trial to assess the efficacy of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Peru.

[Grande T.](#), [Bernasconi A.](#), [Erhart A.](#), [Gamboa D.](#), [Casapia M.](#), [Delgado C.](#), [Torres K.](#), [Fanello C.](#), [Llanos-Cuentas A.](#), [D'Alessandro U.](#)

Institute of Tropical Medicine-Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru.

BACKGROUND: Multi-drug resistant falciparum malaria is an important health problem in the Peruvian Amazon region. We carried out a randomised open label clinical trial comparing mefloquine-artesunate, the current first line treatment in this region, with dihydroartemisinin-piperaquine. **METHODS AND FINDINGS:** Between July 2003 and July 2005, 522 patients with *P. falciparum* uncomplicated malaria were recruited, randomized (260 with mefloquine-artesunate and 262 with dihydroartemisinin-piperaquine), treated and followed up for 63 days. PCR-adjusted adequate clinical and parasitological response, estimated by Kaplan Meier survival and Per Protocol analysis, was extremely high for both drugs (99.6% for mefloquine-artesunate and 98.4% and for dihydroartemisinin-piperaquine) (RR: 0.99, 95% CI [0.97-1.01], Fisher Exact $p = 0.21$). All recrudescences were late parasitological failures. Overall,

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gametocytes were cleared faster in the mefloquine-artesunate group (28 vs 35 days) and new gametocytes tended to appear more frequently in patients treated with dihydroartemisinin-piperaquine (day 7: 8 (3.6%) vs 2 (0.9%), RR: 3.84, 95%CI [0.82-17.87]). Adverse events such as anxiety and insomnia were significantly more frequent in the mefloquine-artesunate group, both in adults and children. CONCLUSION: Dihydroartemisinin-piperaquine is as effective as mefloquine-artesunate in treating uncomplicated *P. falciparum* malaria but it is better tolerated and more affordable than mefloquine-artesunate (US\$1.0 versus US\$18.65 on the local market). Therefore, it should be considered as a potential candidate for the first line treatment of *P. falciparum* malaria in Peru. TRIAL REGISTRATION: ClinicalTrials.gov NCT00373607

[PLoS ONE](#). 2007 Oct 10;2(10):e1023.



Primaquine clears submicroscopic *Plasmodium falciparum* gametocytes that persist after treatment with sulphadoxine-pyrimethamine and artesunate.

[Shekalaghe S](#), [Drakeley C](#), [Gosling R](#), [Ndarro A](#), [van Meegeren M](#), [Enevold A](#), [Alifrangis M](#), [Moshaf F](#), [Sauerwein R](#), [Bousema T](#).

Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

BACKGROUND: *P. falciparum* gametocytes may persist after treatment with sulphadoxine-pyrimethamine (SP) plus artesunate (AS) and contribute considerably to malaria transmission. We determined the efficacy of SP+AS plus a single dose of primaquine (PQ, 0.75 mg/kg) on clearing gametocytaemia measured by molecular methods. **METHODOLOGY:** The study was conducted in Mnyuzi, an area of hyperendemic malaria in north-eastern Tanzania. Children aged 3-15 years with uncomplicated *P. falciparum* malaria with an asexual parasite density between 500-100,000 parasites/microL were randomized to receive treatment with either SP+AS or SP+AS+PQ. *P. falciparum* gametocyte prevalence and density during the 42-day follow-up period were determined by real-time nucleic acid sequence-based amplification (QT-NASBA). Haemoglobin levels (Hb) were determined to address concerns about haemolysis in G6PD-deficient individuals. **RESULTS:** 108 individuals were randomized. Pfs25 QT-NASBA gametocyte prevalence was 88-91% at enrolment and decreased afterwards for both treatment arms. Gametocyte prevalence and density were significantly lower in children treated with SP+AS+PQ. On day 14 after treatment 3.9% (2/51) of the SP+AS+PQ treated children harboured gametocytes compared to 62.7% (32/51) of those treated with SP+AS ($p < 0.001$). Hb levels were reduced in the week following treatment with SP+AS+PQ and this reduction was related to G6PD deficiency. The Hb levels of all patients recovered to pre-treatment levels or greater within one month after treatment. **CONCLUSIONS:** PQ clears submicroscopic gametocytes after treatment with SP+AS and the persisting gametocytes circulated at densities that are unlikely to contribute to malaria transmission. For individuals without severe anaemia, addition of a single dose of PQ to an efficacious antimalarial drug combination is a safe approach to reduce malaria transmission following treatment. TRIAL REGISTRATION: Controlled-Trials.com ISRCTN61534963.

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[Acta Trop.](#) 2008 Jan;105(1):81-6. Epub 2007 Aug 15.

Marked differences in the prevalence of chloroquine resistance between urban and rural communities in Burkina Faso.

[Meissner PE](#), [Mandi G](#), [Mockenhaupt FP](#), [Witte S](#), [Coulibaly B](#), [Mansmann U](#), [Frey C](#), [Merkle H](#), [Burhenne J](#), [Walter-Sack I](#), [Müller O](#).

Department of Tropical Hygiene and Public Health, Ruprecht-Karls-University, Heidelberg, Germany. peter.meissner@urz.uni-heidelberg.de

BACKGROUND: Chloroquine (CQ) resistance has reached high levels in Africa in recent years. Little is known about variations of resistance between urban and rural areas. **OBJECTIVES:** To compare the rates of in vivo resistance to CQ and the prevalences of the main molecular marker for CQ resistance among young children from urban and rural areas in Burkina Faso. **METHODS:** The current analysis used the frame of a randomized controlled trial (ISRCTN27290841) on the combination CQ-methylene blue (MB) (n=177) compared to CQ alone (n=45) in young children with uncomplicated malaria. We examined clinical and parasitological failure rates as well as the prevalence of the Plasmodium falciparum chloroquine resistance transporter gene (pfcr1) T76 mutation. **RESULTS:** Clinical and parasitological failure rates of CQ-MB differed significantly between urban (70%) and rural areas (29%, p<0.0001). Likewise, CQ failure rates were higher in the urban setting. Matching this pattern, pfcr1 T76 was more frequently seen among parasite strains from urban areas (81%) when compared to rural ones (64%, p=0.01). In the presence of parasites exhibiting pfcr1 T76, the odds of overall clinical failure were increased to 2.6-fold ([1.33, 5.16], p(LR)=0.005). CQ was detected at baseline in 21% and 2% of children from the urban and the rural study area, respectively (p(Chi)=0.002). **CONCLUSION:** Even within circumscribed geographical areas, CQ efficacy can vary dramatically. The differences in the prevalence of pfcr1 T76 and in CQ failure rates are probably explained by a higher drug pressure in the urban area compared to the rural study area. This finding has important implications for national malaria policies.

[Antimicrob Agents Chemother.](#) 2008 Jan;52(1):237-43. Epub 2007 Oct 29.



Pharmacokinetics and efficacy of piperazine and chloroquine in Melanesian children with uncomplicated malaria.

[Karunajeewa HA](#), [Ilett KF](#), [Mueller I](#), [Siba P](#), [Law I](#), [Page-Sharp M](#), [Lin E](#), [Lammey J](#), [Batty KT](#), [Davis TM](#).

School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia.

The disposition of chloroquine (CQ) and the related 4-aminoquinoline, piperazine (PQ), were compared in Papua New Guinean children with uncomplicated malaria. Twenty-two children were randomized to 3 days of PQ phosphate at 20 mg/kg/day (12 mg of PQ base/kg/day)

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coformulated with dihydroartemisinin (DHA-PQ), and twenty children were randomized to 3 days of CQ at 10 mg base/kg/day with a single dose of sulfadoxine-pyrimethamine (CQ-SP). After a 42-day intensive sampling protocol, PQ, CQ, and its active metabolite monodesethylchloroquine (DECQ) were assayed in plasma by using high-performance liquid chromatography. A two-compartment model with first-order absorption was fitted to the PQ and CQ data. There were no significant differences in age, gender, body weight, or admission parasitemia between the two groups. The PCR-corrected 42-day adequate clinical and parasitological responses were 100% for DHA-PQ and 94% for CQ-SP, but *P. falciparum* reinfections during follow-up were common (33 and 18%, respectively). For PQ, the median volume of distribution at steady state, allowing for bioavailability (V_{ss}/F), was 431 liters/kg (interquartile range [IQR], 283 to 588 liters/kg), the median clearance (CL/F) was 0.85 liters/h/kg (IQR, 0.67 to 1.06 liters/h/kg), the median distribution half-life ($t_{1/2\alpha}$) was 0.12 h (IQR, 0.05 to 0.66 h), and the median elimination half-life ($t_{1/2\beta}$) was 413 h (IQR, 318 to 516 h). For CQ, the median V_{ss}/F was 154 liters/kg (IQR, 101 to 210 liters/kg), the median CL/F was 0.80 liters/h/kg (IQR, 0.52 to 0.96 liters/h/kg), the median $t_{1/2\alpha}$ was 0.43 h (IQR, 0.05 to 1.82 h), and the median $t_{1/2\beta}$ was 233 h (IQR, 206 to 298 h). The noncompartmentally derived median DECQ $t_{1/2\beta}$ was 290 h (IQR, 236 to 368 h). Combined molar concentrations of DECQ and CQ were higher than those of PQ during the elimination phase. Although PQ has a longer $t_{1/2\beta}$ than CQ, its prompt distribution and lack of active metabolite may limit its posttreatment malaria-suppressive properties.

[Antimicrob Agents Chemother.](#) 2007 Nov;51(11):4090-7. Epub 2007 Sep 10.



Clinical and pharmacological determinants of the therapeutic response to dihydroartemisinin-piperaquine for drug-resistant malaria.

[Price RN](#), [Hasugian AR](#), [Ratcliff A](#), [Siswantoro H](#), [Purba HL](#), [Kenangalem E](#), [Lindegardh N](#), [Penttinen P](#), [Laihad F](#), [Ebsworth EP](#), [Anstey NM](#), [Tjitra E](#).

Information Health Division, Menzies School of Health Research, Charles Darwin University, PO Box 41096, Casuarina, Darwin, NT 0811, Australia. ricprice@doctors.org.uk

Dihydroartemisinin-piperaquine (DHP) is an important new treatment for drug-resistant malaria, although pharmacokinetic studies on the combination are limited. In Papua, Indonesia, we assessed determinants of the therapeutic efficacy of DHP for uncomplicated malaria. Plasma piperaquine concentrations were measured on day 7 and day 28, and the cumulative risk of parasitological failure at day 42 was calculated using survival analysis. Of the 598 patients in the evaluable population 342 had infections with *Plasmodium falciparum*, 83 with *Plasmodium vivax*, and 173 with a mixture of both species. The unadjusted cumulative risks of recurrence were 7.0% (95% confidence interval [CI]: 4.6 to 9.4%) for *P. falciparum* and 8.9% (95% CI: 6.0 to 12%) for *P. vivax*. After correcting for reinfections the risk of recrudescence with *P. falciparum* was 1.1% (95% CI: 0.1 to 2.1%). The major determinant of parasitological failure was the plasma piperaquine concentration. A concentration below 30 ng/ml on day 7 was observed in 38% (21/56) of children less than 15 years old and 22% (31/140) of adults ($P = 0.04$), even though the overall dose (mg per kg of body weight) in children was 9% higher than that in adults ($P < 0.001$). Patients with piperaquine levels below 30 ng/ml were more likely to have a recurrence with *P. falciparum* (hazard ratio [HR] = 6.6 [95% CI: 1.9 to 23]; $P = 0.003$) or

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P. vivax (HR = 9.0 [95% CI: 2.3 to 35]; P = 0.001). The plasma concentration of piperazine on day 7 was the major determinant of the therapeutic response to DHP. Lower plasma piperazine concentrations and higher failure rates in children suggest that dose revision may be warranted in this age group

[Trans R Soc Trop Med Hyg.](#) 2007 Nov;101(11):1081-7. Epub 2007 Aug 17.

Sulfadoxine-pyrimethamine plus artesunate compared with chloroquine for the treatment of vivax malaria in areas co-endemic for Plasmodium falciparum and P. vivax: a randomised non-inferiority trial in eastern Afghanistan.

[Kolaczinski K](#), [Durrani N](#), [Rahim S](#), [Rowland M](#).

HealthNet TPO, P.O. Box 8011, University Town, Peshawar, Pakistan.
k.kolaczinski@malariaconsortium.org

Chloroquine (CQ) is an effective treatment of choice for vivax malaria in most settings, but with the spread of CQ-resistant *Plasmodium falciparum*, many countries now use artemisinin-based combination therapy for treatment of falciparum malaria. In areas co-endemic for falciparum and vivax malaria incorrect differential diagnosis is always a risk. In Afghanistan the adoption of sulfadoxine-pyrimethamine plus artesunate (SP+AS) as first-line falciparum treatment raises the prospect of a significant proportion of vivax malaria being misdiagnosed and treated with the combination. SP is considered to have limited efficacy against vivax malaria, and the efficacy of SP+AS against *Plasmodium vivax* has not been established in areas that are using SP+AS. A randomised, non-inferiority trial comparing SP+AS with CQ monotherapy was undertaken on 190 vivax malaria patients in eastern Afghanistan. Standard WHO procedures for in vivo evaluation of antimalarial drugs were followed. A total of 180 individuals completed the trial to day 42. Using a per protocol analysis, both regimens resulted in > or =96% treatment success at 28 d, but significantly more cases failed in the CQ arm (46%) than in the SP+AS arm (24%) by day 42. In areas where vivax infections might be misdiagnosed as falciparum infections and treated with SP+AS, patient management would be as good, or better than, with the standard CQ treatment.

[Am J Trop Med Hyg.](#) 2007 Aug;77(2):235-41.



Therapeutic efficacy and effects of artemether-lumefantrine and amodiaquine-sulfalene-pyrimethamine on gametocyte carriage in children with uncomplicated Plasmodium falciparum malaria in southwestern Nigeria.

[Sowunmi A](#), [Gbotosho GO](#), [Happi CT](#), [Adedeji AA](#), [Fehintola FA](#), [Folarin OA](#), [Tambo E](#), [Fateye BA](#).

Department of Pharmacology and Therapeutics and Institute for Medical Research and Training, University of Ibadan, Ibadan, Nigeria. akinsowunmi@hotmail.com

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The treatment efficacy and effects of artemether-lumefantrine (AL) and amodiaquine-sulfalene-pyrimethamine (ASP) on gametocyte carriage were evaluated in 181 children ≤ 10 years of age with uncomplicated *Plasmodium falciparum* malaria randomized to receive either drug combination. All children recovered clinically. Fever clearance times were similar. The rate of *P. falciparum* reappearance (recrudescence or re-infection) between two and six weeks after the start of therapy was significantly higher in AL-treated children ($P = 0.01$). Parasite clearance was significantly faster in children treated with AL (mean \pm SD = 1.7 \pm 0.6 days, 95% confidence interval = 1.58 - 1.83, $P = 0.0001$) but the polymerase chain reaction-corrected cure rate (90 of 91 versus 84 of 90) and the rate of resolution of malaria-related anemia two weeks after treatment began (45 of 50 versus 33 of 46) were higher in children treated with ASP. Gametocyte carriage rates were similar. Both regimens were well tolerated. Artemether-lumefantrine clears parasitemia more rapidly than ASP but both combinations are effective in treatment of uncomplicated *P. falciparum* malaria in Nigerian children.

[Trop Med Int Health](#). 2007 Jul;12(7):886-94.



Dramatically decreased therapeutic efficacy of chloroquine and sulfadoxine-pyrimethamine, but not mefloquine, in southern Benin.

[Aubouy A](#), [Fievet N](#), [Bertin G](#), [Sagbo JC](#), [Kossou H](#), [Kinde-Gazard D](#), [Kiniffo R](#), [Massougboji A](#), [Deloron P](#).

Research Unit 010 (UR010), Mother and Child Health in the Tropics, Development Research Institute (IRD), Cotonou, Benin. agnes.aubouy@ird.fr

OBJECTIVE: To evaluate the *in vivo* therapeutic efficacy of chloroquine (CQ), sulfadoxine-pyrimethamine (SP) and mefloquine (MQ) in children presenting with uncomplicated malaria in Benin. **METHODS:** Drug efficacy was tested according to the WHO *in vivo* 28-day protocol. For failures that occurred after 7 days of follow-up, paired pre- and post-treatment blood samples were genotyped at *msp1* and *msp2* loci to distinguish new infections and recrudescence strains. Children enrolled were randomly assigned to a therapeutic group (CQ, $n=14$; SP, $n=42$; MQ, $n=44$). The number of CQ treatment was intentionally restricted after 1 month, as its use was considered to constitute a danger for children. **RESULTS:** Chloroquine and SP showed very high failure rates (85.7% and 50%, respectively), whereas MQ treatment was successful in 97.5%. The molecular tool allowed to re-evaluate two new infections previously considered as failures. **CONCLUSIONS:** Chloroquine should no longer be used to treat children presenting with *Plasmodium falciparum* malaria in Benin.

Treatment of severe or complicated malaria

[Clin Infect Dis](#). 2007 Dec 1;45(11):1446-52. Epub 2007 Oct 22.



Rectal versus intravenous quinine for the treatment of childhood cerebral malaria in Kampala, Uganda: a randomized, double-blind clinical trial.

[Achan J](#), [Byarugaba J](#), [Barennes H](#), [Tumwine JK](#).

Department of Pediatrics and Child Health, Makerere University, Kampala, Uganda.

BACKGROUND: Although artemesinin derivatives are promising for the treatment of severe *Plasmodium falciparum* malaria, intravenous quinine remains the most affordable treatment. However, administration of intravenous quinine is often not feasible in rural areas in Africa because of the lack of simple equipment or trained staff. **We compared the efficacy and safety of intrarectal quinine with those of intravenous quinine in the treatment of childhood cerebral malaria.** **METHODS:** In a randomized, double-blind clinical trial at Mulago Hospital (Kampala, Uganda), Uganda's national referral hospital, **we studied 110 children aged 6 months to 5 years who had cerebral malaria. Patients were randomized to receive either intrarectal or intravenous quinine.** Main outcome measures included parasite clearance time, fever clearance time, coma recovery time, time to sit unsupported, time to begin oral intake, time until oral quinine was tolerated, and death. **RESULTS: Overall, there was no difference in the clinical and parasitological outcomes between the 2 groups (data are mean \pm standard deviation, intrarectal quinine group vs. intravenous quinine group): coma recovery time, 19.4 \pm 18.1 h versus 17.0 \pm 12.1 h; fever clearance time, 26.7 \pm 16.1 h versus 29.9 \pm 18.1 h; and parasite clearance time, 43.2 \pm 14.2 h versus 41.9 \pm 15.2 h. Mortality was similar in both groups; 4 of 56 patients in the intrarectal quinine group died, and 5 of 54 patients in the intravenous quinine group died (odds ratio, 1.3; 95% confidence interval, 0.3-5.2).** Intrarectal quinine was well tolerated, and no major immediate adverse events occurred. **CONCLUSIONS:** Intrarectal quinine is efficacious and could be used as an alternative in the treatment of childhood cerebral malaria, especially in situations in which intravenous therapy is not feasible.

Comment

These results confirm a previous study on the safety and efficacy of quinine given rectally (BMJ. 2006 May 6;332(7549):1055-9) and adds to the evidence on other antimalarials being used in suppository form, including dihydroartemisinin (Am J Trop Med Hyg. 2007 Jan;76(1):1-6.) and artesunate (Antimicrob Agents Chemother. 2006 Mar;50(3):968-74).

[Malar J.](#) 2007 Oct 24;6:138.



Mannitol as adjunct therapy for childhood cerebral malaria in Uganda: a randomized clinical trial.

[Namutangula B](#), [Ndeezi G](#), [Byarugaba JS](#), [Tumwine JK](#).

Randomised trials in child health in developing countries 2007-08

Department of Paediatrics and Child Health, Makerere University Medical School, P O Box 7072 Kampala Uganda. wabwire74@yahoo.com

BACKGROUND: Several reports have suggested that raised intracranial pressure (ICP) is a major contributor to death among children with cerebral malaria. Mannitol, an osmotic diuretic, effectively lowers ICP and is used to treat post-traumatic raised ICP. It is not clear whether intravenous mannitol given to children with cerebral malaria improves clinical outcome. The objective of this study was to determine the effect of mannitol as adjunct therapy on the clinical outcome of children with cerebral malaria. **METHODS:** This randomized double-blind placebo controlled clinical trial was carried out at the Emergency Paediatric ward of Mulago Hospital, Uganda's national referral and teaching hospital. One hundred and fifty six children aged 6 to 60 months with cerebral malaria were randomized to either one dose of mannitol 1 g/kg or placebo, in addition to intravenous quinine. Main outcome measures included coma recovery time; time to sit unsupported, begin oral intake; duration of hospitalization; death and adverse effects. **RESULTS:** Time to regain consciousness ($p = 0.11$), sit unsupported ($p = 0.81$), time to start oral intake ($p = 0.13$) and total coma duration ($p = 0.07$) were similar in both groups. There was no significant difference in the mortality between the placebo (13/80 or 16.3%) and mannitol (10/76 or 13.2%) groups: RR = 1.2 (CI 0.5-2.7). No adverse effects were observed after administration of mannitol. **CONCLUSION:** Mannitol had no significant impact on clinical outcome of cerebral malaria. It is difficult to recommend intravenous mannitol as adjunct therapy for childhood cerebral malaria.

[Cochrane Database Syst Rev.](#) 2007 Oct 17;(4):CD005967.



Artesunate versus quinine for treating severe malaria.

[Jones KL](#), [Donegan S](#), [Lalloo DG](#).

Liverpool School of Tropical Medicine, International Health Group, Pembroke Place, Liverpool, Merseyside, UK, L3 5QA. kats@liv.ac.uk

BACKGROUND: Severe malaria kills over a million people every year. We sought evidence of superiority of artesunate compared with the standard treatment quinine. **OBJECTIVES:** To compare artesunate with quinine for treating severe malaria. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group Specialized Register (January 2007), CENTRAL (The Cochrane Library 2006, Issue 4), MEDLINE (1966 to January 2007), EMBASE (1974 to January 2007), LILACS (1982 to January 2007), ISI Web of Science (1945 to January 2007), the metaRegister of Controlled trials (mRCT), conference proceedings, and reference lists of articles. We contacted researchers and the World Health Organization. **SELECTION CRITERIA:** Randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for treating adults and children with severe malaria who are unable to take medication by mouth. **DATA COLLECTION AND ANALYSIS:** Two authors assessed the eligibility and methodological quality of trials, extracted and analysed data, and drafted the review. The third author contributed to the design and writing of the review. Death was the primary outcome. Dichotomous outcomes were summarized using relative risks and continuous outcomes by mean differences. Where appropriate, we combined

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data in meta-analyses. Heterogeneity was investigated for the primary outcome using subgroup analyses. **MAIN RESULTS:** Six trials enrolling 1938 participants (1664 adults and 274 children) met our inclusion criteria. All six trials were conducted in Asia, and only one small trial enrolled only children. Five trials used intravenous artesunate and one trial intramuscular artesunate; all six used intravenous quinine. Treatment with artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51 to 0.75; 1938 participants, 6 trials), reduced parasite clearance time (WMD 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials), and hypoglycaemia detected by routine monitoring (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials). There was no evidence of a difference in neurological sequelae, coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycaemia. **AUTHORS' CONCLUSIONS: Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia. This review did not identify sufficient data to make firm conclusions about the treatment of children or the effectiveness of intramuscular artesunate. There is an urgent need to compare the effects of artesunate with quinine in African children with severe malaria.** The applicability of these results to Asian children and the ethics of further research are points of debate.

Malnutrition

[Indian J Med Res.](#) 2007 Sep;126(3):199-203.



A pilot study on the effects of curd (dahi) & leaf protein concentrate in children with protein energy malnutrition (PEM).

[Dewan P](#), [Kaur I](#), [Chattopadhyaya D](#), [A Faridi MM](#), [Agarwal KN](#).

Department of Paediatrics, University College of Medical Sciences, New Delhi, India.

BACKGROUND & OBJECTIVE: In protein-energy malnutrition (PEM) there is a significant impairment of immunity, both cell-mediated and humoral, which may be reversed with nutritional rehabilitation. With the use of probiotics like curd (dahi) and micronutrient-rich leaf protein concentrate (LPC), this immune recovery may be hastened. This study was conducted to assess the impact of supplementation of curd and LPC on nutritional status, and immunity as assessed by anthropometry, haemoglobin, ferritin levels, T- cell subpopulation and C-reactive protein (CRP), in children suffering from PEM. **METHODS: Eighty moderate to severely malnourished children (1-5 yr) were randomized to receive either curd or LPC in addition to WHO recommended two-step diet over 15 days. Nutritional, immunological and haematological parameters were measured before and after supplementation and compared within the groups. RESULTS: The change in weight, haemoglobin level and CD4:CD8 T-cell subpopulation was significant in both the groups after supplementation. Response of CRP was blunted in PEM. Serum ferritin decreased significantly after supplementation in both groups. INTERPRETATION & CONCLUSION: Curd and LPC when added to diet of malnourished children, may have therapeutic value by accelerating immune recovery. More studies need to be done on a larger sample to confirm these findings.**

Maternal care and maternal nutrition

[Am J Clin Nutr.](#) 2008 Mar;87(3):704-11.



Effects of prenatal food and micronutrient supplementation on infant development: a randomized trial from the Maternal and Infant Nutrition Interventions, Matlab (MINIMat) study.

[Tofail F](#), [Persson LA](#), [El Arifeen S](#), [Hamadani JD](#), [Mehrin F](#), [Ridout D](#), [Ekström EC](#), [Huda SN](#), [Grantham-McGregor SM](#).

International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh.
ftofail@icddr.org

BACKGROUND: Few data exist for the effects of multiple micronutrient (MM) or food supplementation to undernourished pregnant women on their offsprings' development. **OBJECTIVE:** We aimed to compare the effects on infant development of early (8-10 wk gestation) or usual (approximately 17 wk gestation) supplementation with food and MM, 30 mg Fe + 400 microg folate, or 60 mg Fe + 400 microg folate. **DESIGN:** A large, randomized, controlled trial of pregnancy supplementation was conducted in Bangladesh. A subsample of infants (n = 2853) were assessed on 2 problem-solving tests (support and cover tests), the motor index of the Bayley Scales of Infant Development, and Wolke's behavior ratings at 7 mo of age. **RESULTS:** There were no significant effects of any intervention in the group as a whole. However, infants of undernourished mothers [body mass index (BMI; in kg/m²) < 18.5] who received early food supplementation performed slightly but significantly (P = 0.035) better on the support test than did infants of mothers who received usual food supplementation (z score: 0.17; 95% CI: 0.01, 0.33). There were no benefits in infants of higher-BMI mothers (P = 0.024 for BMI x food interaction). Children of low-BMI mothers who received MMs had slightly better motor scores (z score: 0.28; 95% CI: 0.08, 0.48) and activity ratings (z score: 0.24; 95% CI: 0.037, 0.45) than did those who received 30 mg Fe + 400 microg folate, whereas other children did not benefit (P = 0.05 for both motor scores and BMI x micronutrients and for activity and BMI x micronutrients). **CONCLUSIONS:** **Small benefits from early food and MM supplementation were found in infants of low-BMI but not of high-BMI mothers.** However, the benefits were of doubtful functional importance, and longer follow-up is required to determine programmatic implications.

[Lancet.](#) 2008 Feb 9;371(9611):492-9.



Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial.

[Vaidya A](#), [Saville N](#), [Shrestha BP](#), [Costello AM](#), [Manandhar DS](#), [Osrin D](#).

Randomised trials in child health in developing countries 2007-08

Mother and Infant Research Activities (MIRA), Kathmandu, Nepal.

BACKGROUND: The negative effects of low birthweight on the later health of children in developing countries have been well studied. However, undertaking programmes to address this issue can be difficult since there is no simple correlation between increasing birthweight and improving child health. In 2005, we published results of a randomised controlled trial in Nepal, in which 1200 women received either iron and folic acid or a supplement that provided the recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Here, we report on 2-3 years' follow-up of children born during the trial.

METHODS: We visited children at home and obtained data for the primary outcomes of weight and height, for childhood illnesses, and maternal blood haemoglobin. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

FINDINGS: **Between December, 2005, and December, 2006, we assessed 917 children (455 controls, 462 intervention) at a mean age of 2.5 years. Mean birthweight had been 77 g (95% CI 24-130) greater in the micronutrient group than in controls. At 2.5 years old, controls weighed a mean of 10.7 kg (SD 1.38), and those in the intervention group 10.9 kg (SD 1.54). Children of women who had taken multiple micronutrient supplements during pregnancy were a mean 204 g (95% CI 27-381) heavier than controls. They also had greater measurements than controls in the circumference of the head (2.4 mm [95% CI 0.6-4.3]), chest (3.2 mm [0.4-6.0]), and mid-upper arm (2.4 mm [1.1-3.7]), and in triceps skinfold thickness (2.0 mm [0.0-0.4]). Systolic blood pressure was slightly lower in the intervention group (2.5 mm Hg [0.5-4.6]).** **INTERPRETATION:** **In a poor population, the effects of maternal multiple micronutrient supplementation on the fetus persisted into childhood, with increases in both weight and body size.** These increases were small, however, since those exposed to micronutrients had an average of 2% higher weight than controls. The public-health implications of changes in weight and blood pressure need to be clarified through further follow-up.

Comment

This study from Nepal provides some of the first evidence that maternal micronutrient supplementation may have beneficial effects on growth in early childhood. The study further above from Bangladesh (Am J Clin Nutr. 2008 Mar;87(3):704-11) showed small benefits of maternal micronutrient supplementation in the children of specific subgroups of mothers.

[Food Nutr Bull.](#) 2008 Mar;29(1):67-75.

Impact of pilot project of Rural Maintenance Programme (RMP) on destitute women: CARE, Bangladesh.

[Roy SK](#), [Bilkes F](#), [Islam K](#), [Ara G](#), [Tanner P](#), [Wosk I](#), [Rahman AS](#), [Chakraborty B](#), [Jolly SP](#), [Khatun W](#).

International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh. skroy@icddr.org

BACKGROUND: The rate of malnutrition among women in Bangladesh is high, but

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historically there has not been a specific program focusing on the improvement of the nutritional status of Bangladeshi women. **OBJECTIVE:** To observe changes in the nutritional status of destitute women of the Rural Maintenance Programme (RMP) by incorporating a health and nutrition intervention package with RMP ongoing activities. **METHODS:** An intervention study involving 1,275 poor destitute women was conducted from July 2004 to June 2005 in 17 districts in Bangladesh under two field offices, Mymensingh and Jessore, covering 8 and 9 districts, respectively. The respondents were divided into intervention, comparison, and control groups. All participants in the intervention and comparison groups were paid as part of the RMP and received weekly 30-minute nutrition interventions for 7 weeks in addition to routine training. The comparison group also received RMP training. The control group consisted of women with similar demographic characteristics to the intervention and comparison groups who did not receive pay or any intervention. The intervention was a unique combination of the three components of the UNICEF triangle model (food security, caring practices, and disease control). Data on socioeconomic and anthropometric characteristics, immunization, and vitamin A capsule intake were also collected with the use of a structured questionnaire. **RESULTS:** **After the intervention, the mean body weight had significantly increased by 1,333 g in the intervention group and had decreased by 277 g in the control group and 147 g in the comparison group.** The body mass index of women in the intervention group had also significantly increased at the end of the study ($p < .001$). There was a significant increase in the intake of iodized salt in the intervention group as well as increased immunization coverage in all groups. Intake of the first vitamin A capsule by children increased (from 60% to 97%) in the intervention group only. **CONCLUSIONS:** The nutrition pilot intervention was highly effective in improving the nutritional status of women in the RMP.

[Lancet](#). 2007 Nov 10;370(9599):1629-37.



Treatment of postnatal depression in low-income mothers in primary-care clinics in Santiago, Chile: a randomised controlled trial.

[Rojas G](#), [Fritsch R](#), [Solis J](#), [Jadresic E](#), [Castillo C](#), [González M](#), [Guajardo V](#), [Lewis G](#), [Peters TJ](#), [Araya R](#).

Hospital Clínico, Facultad de Medicina, Universidad de Chile, Santiago, Chile.

BACKGROUND: The optimum way to improve the recognition and treatment of postnatal depression in developing countries is uncertain. We compared the effectiveness of a multicomponent intervention with usual care to treat postnatal depression in low-income mothers in primary-care clinics in Santiago, Chile. **METHODS:** 230 mothers with major depression attending postnatal clinics were randomly allocated to either a multicomponent intervention (n=114) or usual care (n=116). The multicomponent intervention involved a psychoeducational group, treatment adherence support, and pharmacotherapy if needed. Usual care included all services normally available in the clinics, including antidepressant drugs, brief psychotherapeutic interventions, medical consultations, or external referral for specialty treatment. The primary outcome measure was the Edinburgh postnatal depression scale (EPDS)

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score at 3 and 6 months after randomisation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00518830. FINDINGS: 208 (90%) of women randomly assigned to treatment groups completed assessments. The crude mean EPDS score was lower for the multicomponent intervention group than for the usual care group at 3 months (8.5 [95% CI 7.2-9.7] vs 12.8 [11.3-14.1]). Although these differences between groups decreased by 6 months, EPDS score remained better in multicomponent intervention group than in usual care group (10.9 [9.6-12.2] vs 12.5 [11.1-13.8]). The adjusted difference in mean EPDS between the two groups at 3 months was -4.5 (95% CI -6.3 to -2.7; $p < 0.0001$). The decrease in the number of women taking antidepressants after 3 months was greater in the intervention group than in the usual care group (multicomponent intervention from 60/101 [59%; 95% CI 49-69%] to 38/106 [36%; 27-46%]; usual care from 18/108 [17%; 10-25%] to 11/102 [11%; 6-19%]). INTERPRETATION: Our findings suggest that low-income mothers with depression and who have newly born children could be effectively helped, even in low-income settings, through multicomponent interventions. Further refinements to this intervention are needed to ensure treatment compliance after the acute phase.

[Obstet Gynecol](#). 2007 Nov;110(5):989-97.



Predictors of stillbirth in sub-saharan Africa.

[Chi BH](#), [Wang L](#), [Read JS](#), [Taha TE](#), [Sinkala M](#), [Brown ER](#), [Valentine M](#), [Martinson F](#), [Goldenberg RL](#).

Centre for Infectious Disease Research in Zambia, Lusaka, Zambia. bchi@cidrz.org

OBJECTIVE: To describe the incidence and predictors of stillbirth in a predominantly human immunodeficiency virus (HIV)-infected African cohort. METHODS: Human Immunodeficiency Virus (HIV) Prevention Trials Network (HPTN) 024 was a randomized controlled trial of empiric antibiotics to reduce chorioamnionitis-related perinatal HIV transmission. A proportion of HIV-uninfected individuals were enrolled to reduce community-based stigma surrounding the trial. For this analysis, only women who gave birth to singleton infants were included. RESULTS: Of 2,659 women enrolled, 2,434 (92%) mother-child pairs met inclusion criteria. Of these, 2,099 (86%) infants were born to HIV-infected women, and 335 (14%) were born to HIV-uninfected women. The overall stillbirth rate was 32.9 per 1,000 deliveries (95% confidence interval [CI] 26.1-40.7). **In univariable analyses, predictors for stillbirth included previous stillbirth (odds ratio [OR] 2.3, 95% CI 1.2-4.3), antenatal hemorrhage (OR 14.4, 95% CI 4.3-47.9), clinical chorioamnionitis (OR 20.9, 95% CI 5.1-86.2), and marked polymorphonuclear infiltration on placental histology (OR 2.9, 95% CI 1.7-5.2).** When compared with pregnancies longer than 37 weeks, those at 34-37 weeks (OR 1.7, 95% CI 0.8-3.4) and those at less than 34 weeks (OR 22.8, 95% CI 13.6-38.2) appeared more likely to result in stillborn delivery. Human immunodeficiency virus infection was not associated with a greater risk for stillbirth in either univariable (OR 1.5, 95% CI 0.7-3.0) or multivariable (adjusted OR 1.11, 95% CI 0.38-3.26) analysis. Among HIV-infected women, however, decreasing CD4 cell count was inversely related to stillbirth risk ($P = .009$). CONCLUSION: In this large cohort, HIV infection was not associated with increased stillbirth risk. **Further work is needed to elucidate**

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the relationship between chorioamnionitis and stillbirth in African populations.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00021671 LEVEL OF EVIDENCE: II.

[Obstet Gynecol.](#) 2007 Nov;110(5):977-85.



Chlorhexidine vaginal and neonatal wipes in home births in Pakistan: a randomized controlled trial.

[Saleem S](#), [Reza T](#), [McClure EM](#), [Pasha O](#), [Moss N](#), [Rouse DJ](#), [Bartz J](#), [Goldenberg RL](#).

Aga Khan University, Karachi, Pakistan.

OBJECTIVE: To assess tolerance and safety of 0.6% chlorhexidine vaginal and neonatal wipes to improve perinatal outcomes in home deliveries in Pakistan and the ability of traditional birth attendants and project staff to perform a randomized trial of this intervention. **METHODS:** Focus groups of pregnant and nonpregnant women and in-depth interviews of traditional birth attendants explored barriers to the use of chlorhexidine wipes. Then, a study was performed of women delivering at home attended by traditional birth attendants. Consenting women were randomly assigned to receive either 0.6% chlorhexidine or saline vaginal and neonatal wipes. Women and their infants were followed up on postpartum days 7, 14, and 28. Acceptability and tolerance of vaginal and neonatal wipes, as well as maternal and neonatal outcomes, were assessed. **RESULTS:** The focus groups and interviews indicated that the chlorhexidine intervention would be acceptable to women and their providers. Of the 213 eligible pregnant women approached, 203 (95%) gave informed consent and were enrolled and allocated to groups. Traditional birth attendants had no difficulty administering chlorhexidine vaginal and neonatal wipes in a home setting. Of the 203 births, 103 (51%) of whom received 0.6% chlorhexidine, there were no allergic reactions, vaginal itching, burning, or requests for study termination. Follow-up at 28 days postpartum was more than 95%. Although this study was not powered to show significant differences in neonatal outcomes between treatment groups, the lower rates of some neonatal adverse clinical outcomes in the chlorhexidine group were encouraging. **CONCLUSION:** Use of 0.6% chlorhexidine vaginal and neonatal wipes for the prevention of neonatal infection is well-tolerated and seems safe. A trial of this intervention by traditional birth attendants in a home-delivery setting is feasible. **CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00121394 **LEVEL OF EVIDENCE:** I.

[BJOG.](#) 2007 Jul;114(7):802-11.



Randomised controlled trial of two antenatal care models in rural Zimbabwe.

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[Majoko F](#), [Munjanja SP](#), [Nyström L](#), [Mason E](#), [Lindmark G](#).

Department of Women's & Children's Health, Section for International Maternal & Child Health, Uppsala University, Uppsala, Sweden. majokof215@doctors.org.uk

OBJECTIVE: To compare a five-visit antenatal care (ANC) model with specified goals with the standard model in a rural area in Zimbabwe. **DESIGN:** Cluster randomised controlled trial with the clinic as the randomisation unit. **SETTING:** Primary care setting in a developing country where care was provided by nurse-midwives. **POPULATION:** Women booking for ANC in the clinics were eligible. **MAIN OUTCOME MEASURES:** Number of antenatal visits, antepartum and intrapartum referrals, utilization of health centre for delivery and perinatal outcomes. **METHODS:** Twenty-three rural health centres were stratified prior to random allocation to the new (n = 11) or standard (n = 12) model of care. **RESULTS:** We recruited 13,517 women (new, n = 6897 and standard, n = 6620) in the study, and 78% (10,572) of their pregnancy records were retrieved. There was no difference in median maternal age, parity and gestational age at booking between women in the standard model and those in the new model. The median number of visits was four for both models. The proportion of women with five or less visits was 77% in the new and 69% in the standard model (OR 1.5; 95% CI 1.08-2.2). The likelihood of haemoglobin testing was higher in the new model (OR 2.4; 95% CI 1.0-5.7) but unchanged for syphilis testing. There were fewer intrapartum transfers (5.4 versus 7.9% [OR 0.66; 95% CI 0.44-0.98]) in the new model but no difference in antepartum or postpartum transfers. There was no difference in rates of preterm delivery or low birthweight. The perinatal mortality was 25/1000 in standard model and 28/1000 in new model. **CONCLUSION:** In Gutu district, a focused five-visit schedule did not change the number of contacts but was more effective as expressed by increased adherence to procedures and better use of institutional health care.

Measles

[Cochrane Database Syst Rev](#). 2008 Jul 16;(3):CD001477.

Antibiotics for preventing complications in children with measles.

[Kabra SK](#), [Lodha R](#), [Hilton DJ](#).

Pediatric Pulmonology Division, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India, 110029.

BACKGROUND: Measles is the leading killer among vaccine-preventable diseases, responsible for an estimated 44% of the 1.7 million vaccine-preventable deaths among children annually.

OBJECTIVES: To assess the effects of antibiotics given to children with measles to prevent complications and reduce pneumonia, other morbidities and mortality. **SEARCH STRATEGY:**

In this 2008 update we searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, Issue 1) MEDLINE (1966 to January week 1, 2008), EMBASE (1980 to December 2007) and the National Research Register (Issue 3, 2007). **SELECTION**

CRITERIA: Randomized controlled trials (RCTs) and quasi-RCTs comparing antibiotics with placebo or no treatment to prevent complications in children with measles. **DATA**

COLLECTION AND ANALYSIS: Two review authors independently extracted data and assessed trial quality. **MAIN RESULTS:** Seven trials with 1385 children were included. Pooled

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study data showed that the incidence of pneumonia was lower in the treatment group compared to the control group. **However, the difference was not statistically significant. In children who received antibiotics, 1.9% developed pneumonia, while in the control group 6% developed pneumonia (OR 0.28; 95% CI 0.06 to 1.25).** The one trial that showed an increase in the rate of pneumonia with antibiotics was conducted in 1942 and compared oral sulfathiazole with symptomatic treatment. **If the results of this trial are removed from the meta-analysis, and the remaining six studies are combined, there is a statistically significant reduction in the incidence of pneumonia in children receiving antibiotics (OR 0.17; 95% CI 0.05 to 0.65).** The number needed to treat to prevent one episode of pneumonia is 24 patients. The incidence of other complications was significantly lower in children receiving antibiotics: purulent otitis media (OR 0.34; 95% CI 0.16 to 0.73) and tonsillitis (OR 0.08; 95% CI 0.01 to 0.72). There was no difference in the incidence of conjunctivitis (OR 0.39; 95% CI 0.15 to 1.0), diarrhea (OR 0.53; 95% CI 0.23 to 1.22) or croup (OR 0.16; 95% CI 0.01 to 4.06). **AUTHORS' CONCLUSIONS: This review suggests a beneficial effect of antibiotics in preventing complications such as pneumonia, purulent otitis media and tonsillitis in children with measles.** On the basis of this review, it is not possible to give definitive guidelines on the type of antibiotic, duration, or the day of initiation. Use of penicillin or co-trimoxazole may be considered. There is a need to generate more evidence by well planned RCTs to answer these questions.

Neonatal care

[Lancet](#). 2008 Jun 7;371(9628):1936-44.***



Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial.

[Baqui AH](#), [El-Arifeen S](#), [Darmstadt GL](#), [Ahmed S](#), [Williams EK](#), [Seraji HR](#), [Mannan I](#), [Rahman SM](#), [Shah R](#), [Saha SK](#), [Syed U](#), [Winch PJ](#), [Lefevre A](#), [Santosham M](#), [Black RE](#); [Projahnmo Study Group](#). Collaborators (22)

[Ahmed J](#), [Alam A](#), [Ali NA](#), [Al-Kabir A](#), [Al-Mahmud AB](#), [Al-Sabir A](#), [Anwar T](#), [Begum N](#), [Chowdhury AI](#), [Chowdhury M](#), [Chowdhury S](#), [Das MK](#), [Hakim ZA](#), [Haque AK](#), [Hasan Q](#), [Hossain D](#), [Khatun S](#), [Law P](#), [Rahman QS](#), [Siddik A](#), [Waters H](#), [Zaman K](#).

Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. abaqui@jhsph.edu

BACKGROUND: Neonatal mortality accounts for a high proportion of deaths in children under the age of 5 years in Bangladesh. Therefore the project for advancing the health of newborns and mothers (Projahnmo) implemented a community-based intervention package through government and non-government organisation infrastructures to reduce neonatal mortality.

METHODS: In Sylhet district, 24 clusters (with a population of about 20 000 each) were randomly assigned in equal numbers to one of two intervention arms or to the comparison arm. Because of the study design, masking was not feasible. All married women of reproductive age (15-49 years) were eligible to participate. **In the home-care arm, female community**

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health workers (one per 4000 population) identified pregnant women, made two antenatal home visits to promote birth and newborn-care preparedness, made postnatal home visits to assess newborns on the first, third, and seventh days of birth, and referred or treated sick neonates. In the community-care arm, birth and newborn-care preparedness and careseeking from qualified providers were promoted solely through group sessions held by female and male community mobilisers. The primary outcome was reduction in neonatal mortality. Analysis was by intention to treat. The study is registered with ClinicalTrials.gov, number 00198705. FINDINGS: The number of clusters per arm was eight. The number of participants was 36059, 40159, and 37598 in the home-care, community-care, and comparison arms, respectively, with 14 769, 16 325, and 15 350 livebirths, respectively. **In the last 6 months of the 30-month intervention, neonatal mortality rates were 29.2 per 1000, 45.2 per 1000, and 43.5 per 1000 in the home-care, community-care, and comparison arms, respectively. Neonatal mortality was reduced in the home-care arm by 34% (adjusted relative risk 0.66; 95% CI 0.47-0.93) during the last 6 months versus that in the comparison arm. No mortality reduction was noted in the community-care arm (0.95; 0.69-1.31).** INTERPRETATION: A home-care strategy to promote an integrated package of preventive and curative newborn care is effective in reducing neonatal mortality in communities with a weak health system, low health-care use, and high neonatal mortality.

Comment

This important study shows that provision of a package of home-based antenatal care and care in the week after birth reduces neonatal mortality. In the home-based arm of this trial community health workers (CHWs) had 6 weeks training in communication, provision of essential newborn care, clinical assessment of neonates, and management of sick neonates with an algorithm adapted from IMCI. The CHWs identified pregnancies during visits to each household every 2 months, and provided 2 antenatal and 3 early postnatal home visits, and gave iron and folic acid supplements. The CHWs identified very sick newborns and gave IM antibiotics and referred babies on. Such models of home based care have been successful in other countries; India and Nepal particularly.

[J Health Popul Nutr.](#) 2007 Jun;25(2):236-40.

Acceptability of massage with skin barrier-enhancing emollients in young neonates in Bangladesh.

[Ahmed AS](#), [Saha SK](#), [Chowdhury MA](#), [Law PA](#), [Black RE](#), [Santosham M](#), [Darmstadt GL](#).

Department of Neonatology, Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh.

Oil massage of newborns has been practised for generations in the Indian sub-continent; however, oils may vary from potentially beneficial, e.g. sunflower seed oil, to potentially toxic, e.g. mustard oil. The study was carried out to gain insights into oil-massage practices and acceptability of skin barrier-enhancing emollients in young, preterm Bangladeshi neonates. Preterm infants of <33 weeks gestational age were randomized to high-linoleate sunflower seed oil, Aquaphor Original Emollient Ointment, or the comparison group (usual care). A survey was administered at admission to assess routine skin-care practices prior to admission and at discharge to assess acceptability of emollient therapy during hospitalization. Oil massage was given to 83 (21%) of 405 babies before hospital admission, 86% (71/83) of whom were

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delivered at home. Application of oil, most commonly mustard oil (88%, 73/83), was started within one hour of birth in 51 cases (61%) and was applied all over the body (89%, 74/83) one to six (mean 2.2) times before admission. Of infants who received emollient therapy in the hospital, 42% (n=32) of mothers reported that the emollient applied in the hospital was better than that available at home, and only 29% would use the same oil (i.e. mustard oil) in the future as used previously at home. No problems resulted from use of emollient in the hospital. Topical therapy with sunflower seed oil or Aquaphor was perceived by many families to be superior to mustard oil. If caregivers and health professionals can be motivated to use inexpensive, available emollients, such as sunflower seed oil that are beneficial, emollient therapy could have substantial public-health benefit.

[Pediatrics](#). 2008 Mar;121(3):522-9.***

PEDIATRICS
FINAL VERSION

Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial.

[Darmstadt GL](#), [Saha SK](#), [Ahmed AS](#), [Ahmed S](#), [Chowdhury MA](#), [Law PA](#), [Rosenberg RE](#), [Black RE](#), [Santosham M](#).

Department of International Health E8153, Bloomberg School of Public Health, Johns Hopkins University, 615 North Wolfe St, Baltimore, MD 21205, USA. gdarmsta@jhsph.edu

OBJECTIVE: Skin barrier therapy during the neonatal period, when the skin barrier is most highly compromised and the risk of death is greatest, has been shown to have a number of potential benefits, including reduced risk of nosocomial sepsis. Topical application of emollients that augment skin barrier function was evaluated as a strategy for improving survival rates among hospitalized preterm infants in Bangladesh. **METHODS:** A prospective, randomized, controlled, clinical trial was conducted in the special care nursery at Dhaka Shishu (Children) Hospital, the largest tertiary care children's hospital in Bangladesh. **Preterm infants (gestational age: < or = 33 weeks; N = 497) received daily topical applications of sunflower seed oil or Aquaphor ointment. Neonatal mortality rates were compared in an intent-to-treat analysis with a control group that did not receive emollient therapy. RESULTS:** Treatment with sunflower seed oil resulted in a statistically significant 26% reduction in mortality rates, compared with infants not receiving topical emollient therapy. Aquaphor therapy also significantly reduced mortality rates, by 32%. **CONCLUSIONS:** Topical therapy with skin barrier-enhancing emollients improved survival rates among preterm hospitalized infants in Bangladesh. This study provides strong evidence for the implementation of topical therapy for high-risk preterm neonates in developing countries.

Comment

In this study emollient was applied to the entire body surface, except for the scalp and face, 3 times per day for the first 14 days and then 2 times per day until discharge from hospital. The overall mortality rate among all neonates enrolled in the trial was very high (64%), but was significantly lower in the subjects who received the emollient. This was an unblinded trial, and it is possible that there were other differences, such as better hand-washing prior to touching babies (which was emphasized to the study nurses applying the emollient), or even the effect of massage. Nevertheless it is an important study, showing that, under the right conditions,

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sunflower oil as a skin emollient may reduce neonatal case fatality rates in nurseries where resources are limited and case fatality rates are high.

[Trop Med Int Health](#). 2008 Jan;13(1):123-8.



Beyond symptom recognition: care-seeking for ill newborns in rural Ghana.

[Bazzano AN](#), [Kirkwood BR](#), [Tawiah-Agyemang C](#), [Owusu-Agyei S](#), [Adongo PB](#).

London School of Hygiene and Tropical Medicine, University of London, London, UK, and College of Health Sciences, Touro University, Vallejo, CA, USA.

OBJECTIVES: To assess newborn care-seeking practices in a rural area of Ghana where most births take place at home in order to inform potential strategies for reducing newborn mortality. **METHODS:** Qualitative, ethnographic study with quantitative data from a birth cohort collected as part of the surveillance system of an ongoing randomized controlled trial. Data collected comprised 84 h of participant observation (including following an ill newborn through a hospital visit), 14 in-depth interviews with key informants (older mothers and grandmothers), 45 semistructured interviews with mothers, 28 case histories from women who had recently given birth and 32 expert interviews with local health providers. Thirteen focus groups were held with men and women, and narrative histories of newborn deaths were taken from eight women. Birth cohort data came from 2878 singletons born alive in the study district within the year July 2003-June 2004. **RESULTS: Significant delays in care seeking for ill newborns occur in Kintampo District, Ghana. 2.1% of 2878 newborns in the birth cohort had a serious illness during the first 4 weeks of life, but care was only sought outside the home for 61% of those and from a doctor or hospital for 39%. Barriers to prompt allopathic care seeking include sequential care-seeking practices, with often exclusive use of traditional medicine as first-line treatment for 7 days, previous negative experiences with health service facilities, financial constraints and remoteness from health facilities.** **CONCLUSIONS:** Improvements in care seeking are urgently needed. Families should be urged to seek medical care for any symptom of illness in a newborn; financial and socio-cultural barriers to care seeking for newborns must be addressed in order to improve neonatal survival.

Comment

Useful information on knowledge, attitudes and practices can be derived from effectiveness trials. This trial describes important barriers to seeking care for sick newborns, which will be common to many poor regions, and are crucial to address if newborns are to access known effective interventions, and if neonatal mortality rates in the poorest regions of the world are to be reduced.

[Indian Pediatr](#). 2008 Jan;45(1):17-23.



Kangaroo mother care for low birth weight infants: a randomized controlled trial.

[Suman RP](#), [Udani R](#), [Nanavati R](#).

Department of Neonatology, Seth GS Medical College and KEM Hospital, Mumbai, India.
raosumanv@rediffmail.com

OBJECTIVE: To compare the effect of Kangaroo mother care (KMC) and conventional methods of care (CMC) on growth in LBW babies (<2000 g). **STUDY DESIGN:** Randomized controlled trial. **SETTING:** Level III NICU of a teaching institution in western India. **SUBJECTS:** 206 neonates with birth weight < 2000 g. **INTERVENTION:** The subjects were randomized into two groups: the intervention group (KMC-103) received Kangaroo mother care. The control group (CMC: 103) received conventional care. **OUTCOME MEASURES:** Growth, as measured by average daily weight gain and by other anthropometrical parameters at 40 weeks postmenstrual age in preterm babies and at 2500 g in term SGA infants was assessed. **RESULTS:** **The KMC babies had better average weight gain per day (KMC: 23.99 g vs CMC: 15.58 g, P < 0.0001). The weekly increments in head circumference (KMC: 0.75 cm vs CMC: 0.49 cm, P = 0.02) and length (KMC: 0.99 cm vs CMC: 0.7 cm, P = 0.008) were higher in the KMC group. A significantly higher number of babies in the CMC group suffered from hypothermia, hypoglycemia, and sepsis.** There was no effect on time to discharge. More KMC babies were exclusively breastfed at the end of the study (98% vs 76%). KMC was acceptable to most mothers and families at home. **CONCLUSION:** Kangaroo mother care improves growth and reduces morbidities in low birth weight infants. It is simple, acceptable to mothers and can be continued at home.

[Indian J Pediatr.](#) 2008 Jan;75(1):43-7.

KMC facilitates mother baby attachment in low birth weight infants.

[Gathwala G](#), [Singh B](#), [Balhara B](#).

Division of Neonatal Services, Department of Pediatrics, Pt. B.D. Sharma PGIMS, Rohtak, India. g_gathwala@hotmail.com

OBJECTIVE: To determine whether Kangaroo mother care (KMC) facilitates mother baby attachment in low birth weight infants. **METHODS:** Over 16 month period 110 neonates were randomized into kangaroo mother care group and control group using a random number table. The kangaroo group was subjected to Kangaroo mother care for at least 6 hours per day. The babies also received kangaroo care after shifting out from NICU and at home. The control group received standard care (incubator or open care system). After 3 months followup, structured maternal interview was conducted to assess attachment between mothers and their babies. **RESULTS:** Mean birth weight was 1.69 +/- 0.11 Kg in KMC group compared to 1.690 +/- 0.12 Kg in control group (p>0.05). Mean gestational age was 35.48 +/- 1.20 week in KMC group and 35.04 +/- 1.09 week in the control group (p>0.05). KMC was initiated at a mean age of 1.72 +/- 0.45 days. The duration of KMC in first month was 10.21 +/- 1.50 hour, in the 2nd month was 10.03 +/- 1.57 hour and in the 3rd month was 8.97 +/- 1.37 hours. The duration of hospital stay

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was significantly shorter in the KMC group (3.56+/-0.57 days) compared to control group (6.80+/-1.30 days). The total attachment score (24.46+/-1.64) in the KMC group was significantly higher than that obtained in control group (18.22+/-1.79, $p < 0.001$). In KMC group, mother was more often the main caretaker of the baby. Mothers were significantly more involved in care taking activities like bathing, diapering, sleeping with their babies and spent more time beyond usual care taking. They went out without their babies less often and only for unavoidable reasons. They derived greater pleasure from their babies. **CONCLUSION:** KMC facilitates mother baby attachment in low birth weight infants.

Comment

The two studies above on Kangaroo Mother Care (KMC) in low birth weight babies show its value in: higher weight gain, head growth, more breast feeding, and fewer complications of sepsis, hypothermia and hypoglycaemia. Most studies of KMC have been done in relatively low-risk populations of babies, where the neonatal mortality rate is much less than, for example that reported in the Skin Emollient study from Bangladesh (above). The role of KMC is certain for low-risk babies, but needs to be further evaluated in babies at high risk of mortality in resource limited settings. The study below suggests that in VLBW babies, even short-term skin to skin contact has benefits.

[J Paediatr Child Health](#). 2007 Dec;43(12):831-6. Epub 2007 Sep 4.



Short duration of skin-to-skin contact: effects on growth and breastfeeding.

[Boo NY](#), [Jamli FM](#).

Department of Paediatrics, Faculty of Medicine, Hospital Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia. nemyun_boo@imu.edu.my

AIM: To compare weight gain and head growth in very-low-birthweight (VLBW, <1501 g) infants with or without exposure to short duration of skin-to-skin contact (STSC) during their stay in a neonatal intensive care unit. **METHODS:** Stable VLBW infants were randomised into either STSC or control group. Parents of the STSC group were encouraged to provide STSC for at least 1 h daily. **RESULTS: One hundred and forty-six infants were randomised, but only 126 were enrolled (STSC group: n = 64; Controls: n = 62). Infants in the STSC group had better mean weekly increase in head circumference (1.0 cm (SD = 0.3) vs. 0.7 cm (SD = 0.3); $P < 0.0001$) and higher breastfeeding rate at discharge (29.7% vs. 14.5%; $P = 0.04$).** Although the mean duration of maternal education was longer in STSC (13.0 vs. 12.1 years; $P = 0.04$) than in controls, linear regression analysis showed that the significant predictors associated with weekly head growth were exposure to STSC (unstandardised coefficient: 0.2; 95% confidence intervals (CI): 0.1, 0.3; $P < 0.0001$) and head circumference of infants at the time of enrollment (unstandardised coefficient: -0.05; 95% CI: -0.08, -0.03; $P < 0.0001$); the number of years of maternal education was not a significant predictor. Logistic regression analysis showed that the only significant predictors of successful breastfeeding at discharge were receiving expressed breast milk at enrollment (adjusted OR: 4.1; 95% CI: 1.4, 11.7; $P = 0.009$) and receiving expressed breast milk during intervention period (adjusted OR: 8.3; 95%

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CI: 2.8, 24.4; $P < 0.0001$); exposure to STSC and maternal education were not significant predictors. CONCLUSION: Exposure to short duration of STSC may promote head growth in VLBW infants.

Neurology

[J Child Neurol](#). 2007 Jul;22(7):829-35.



Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial.

[Lakshmi CV](#), [Singhi P](#), [Malhi P](#), [Ray M](#).

Department of Pediatrics, Advanced Pediatric Center, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Several large, randomized controlled trials have demonstrated the efficacy of topiramate in migraine prophylaxis in adults. However, there are limited data about the use of topiramate in migraine prophylaxis in children. We conducted this single-center, double-blind, placebo-controlled trial to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine in children. **A total of 44 children with migraine were randomized using random number tables to receive topiramate (n = 22) or placebo (n = 22). The total duration of treatment was 4 months**, including a baseline period of 1 month during which topiramate was titrated weekly in 25-mg increments to 100 mg/d in 2 divided doses or to the maximum tolerated dose. The titration was followed by a 12-week maintenance phase during which topiramate was given in 2 divided doses. The primary outcome measures were the reduction in the mean migraine frequency and severity of headache. Secondary outcome measures included the number of times analgesics were required for a month for acute attacks and functional disability. Functional disability was measured by comparing school absenteeism and Pediatric Migraine Disability Assessment Scale (PedMIDAS). **The decrease in mean (+/-SD) monthly migraine frequency from 16.14 (+/-9.35) at baseline to 4.27 (+/-1.95) at the end of the study in the topiramate group was significantly greater as compared with a decrease from 13.38 (+/-7.78) to 7.48 (+/-5.94) at the end of the study in the placebo group (P = .025).** The difference in number of rescue medications used for topiramate and placebo was not statistically significant (P = .059). There was a statistically significant decrease in the PedMIDAS score from 50.66 (+/-32.1) to 10.42 (+/-6.39) at the end of the study in the topiramate group compared with a decrease from 42.66 (+/-27.5) to 23.7 (+/-19.1) at the end of 4 months in the placebo group (P = .003). The decrease in school absenteeism was significant with topiramate compared with placebo (P = .002). Weight loss, decreased concentration in school, sedation, and parasthesias were important side effects with topiramate. Most of these side effects were mild to moderate and were not significant enough to cause dropout from the study.

[Jpn J Infect Dis.](#) 2008 Jan;61(1):18-24.



Clinical application of reverse-transcription polymerase chain reaction and intravenous immunoglobulin for enterovirus encephalitis.

[Cheng MF](#), [Chen BC](#), [Huang TS](#), [Hsieh KS](#), [Chen SN](#), [Liu YC](#).

Department of Pediatrics, Veterans General Hospital-Kaohsiung, Kaohsiung, Taiwan.

Although polymerase chain reaction (PCR) is a highly sensitive procedure for the diagnosis of enteroviruses, it has never been systemically applied to the treatment of enteroviral encephalitis using intravenous immunoglobulin (IVIg). We conducted a 2-year randomized, controlled comparison of reverse transcription (RT)-PCR of cerebrospinal fluid (CSF) with traditional viral isolation to guide IVIg treatment. Seventy-five patients were enrolled and classified into three groups: one group with clinical manifestations of enteroviral infections and two without. The latter two groups were separated on the basis of whether IVIg treatment was guided by RT-PCR or virus culture assay. CSF specimens from the 18 confirmed cases of enteroviral encephalitis were RT-PCR positive for enterovirus in all but one case. Of the remaining 57 cases of nonenteroviral encephalitis, only 4 were positive for enterovirus RT-PCR. One patient in the group of IVIg treatment guided by viral isolation subsequently displayed a sequel of epilepsy. No patients in the IVIg treatment groups guided by RT-PCR had any neurological sequelae. In conclusion, the use of RT-PCR allowed rapid, sensitive, and specific detection of enteroviral RNA in CSF. When used to guide IVIg treatment, RT-PCR may shorten hospitalization and improve outcomes of patients with enteroviral encephalitis.

Neurocysticercosis

[J Assoc Physicians India.](#) 2007 Jun;55:419-24.

Short course of oral prednisolone on disappearance of lesion and seizure recurrence in patients of solitary cysticercal granuloma with single small enhancing CT lesion: an open label randomized prospective study.

[Kishore D](#), [Misra S](#).

Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, India.

OBJECTIVE: To evaluate the effect of a short course of oral prednisolone on disappearance of lesion and seizure recurrence in newly diagnosed patients with single small enhancing CT lesion. **METHODS:** In this open-label, randomized, prospective follow-up study, **100 patients of new-onset seizures and a cysticercus granuloma presenting as single enhancing computed tomography detected lesion were randomly divided in two groups to receive either antiepileptic monotherapy (Group A) or antiepileptic drugs with oral prednisolone in a dose of 1 mg/kg body weight for 7 days and tapering off dose in next 3 days (Group B).**

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Repeat CT scan was performed on 8th-12th week to know radiological state of lesion. The patients were followed up for 1 year for seizure recurrence. **RESULTS:** The majority of patients were in second decade. Male: female ratio 1.56:1. Mean number of seizure episodes was 4.33 +/- 3.50 in group A and 4.23 +/- 3.97 in group B. Partial seizure were the most common presentation (85%). 72% patients presented with single seizure or seizure in cluster. Solitary ring lesion was the commonest (69%) CT finding, most of them were located in parietal lobe (52%). **Follow up CT scan showed complete resolution of lesion in 60.86% of total [group A (n = 47), 32 patients, 68.08%; group B (n = 45), 24 patients, 53.33%]. Significant difference in group A and B regarding lesion resolution was observed (chi2 = 5.926, d.f. = 1) p < 0.05.** Clinical follow up showed seizure recurrence in group A - 5 patients (10.63%), in group B - 12 patients (26.66%). Statistically significant higher number of seizure recurrences were noted in group B as compared to group A (chi2 = 3.93, d.f. = 1) p < 0.05. **CONCLUSIONS: Short-term oral prednisolone along with antiepileptic drugs helps in rapid resolution of single small enhancing lesions in patient with newly diagnosed seizure disorder with good clinical outcome.**

Comment

Steroids are useful for something else! A review of the role of steroids in many other infectious diseases was also published this year: Arch Int Med 2008;169(10):1034-1046

Nutrition, micronutrients and breast feeding

(see also sections on Maternal care and nutrition, Malnutrition, Anaemia, Vitamin A and Zinc)

[J Nutr.](#) 2008 Apr;138(4):782-6.



Fortifying brown bread with sodium iron EDTA, ferrous fumarate, or electrolytic iron does not affect iron status in South African schoolchildren.

[van Stuijvenberg ME](#), [Smuts CM](#), [Lombard CJ](#), [Dhansay MA](#).

Nutritional Intervention Research Unit, Medical Research Council, Cape Town, South Africa.
lize.van.stuijvenberg@mrc.ac.za

The choice of iron fortificant usually represents a balance between bioavailability of the compound and its tendency to cause organoleptic problems. The aim of this study was to evaluate the efficacy of sodium iron EDTA (NaFeEDTA) and ferrous fumarate at levels compatible with South African brown bread (10 mg/kg flour for NaFeEDTA and 20 mg/kg flour for ferrous fumarate) in a randomized controlled trial; electrolytic iron was evaluated at the level currently used in South Africa (35 mg/kg flour). **Schoolchildren (n = 361), aged 6-11 y, from a low socioeconomic community with hemoglobin (Hb) < or = 125 g/L were randomly assigned to 1 of 4 groups that received 4 slices of brown bread supplying either: 1) no fortification iron 2) 2.35 mg iron as NaFeEDTA; 3) 4.70 mg iron as ferrous fumarate; and 4) 8.30 mg iron as electrolytic iron per intervention day.** These amounts simulated a bread intake of 6 slices per day over the 34-wk study period at fortification levels of 0, 10, 20, and 35 mg/kg flour, respectively. Hb concentration and iron status were assessed at baseline and after 34 wk of intervention. The iron interventions did not affect Hb concentration, transferrin

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saturation, or serum ferritin, iron, or transferrin receptor concentrations relative to the control group. **Our results suggest that electrolytic iron at the level currently used in South Africa is not effective in improving iron or Hb status. Neither do NaFeEDTA or ferrous fumarate appear to be suitable alternatives for the fortification of wheat flour when included at levels that do not cause color changes.**

[East Afr Med J](#). 2007 Oct;84(10):473-80

Dual fortification of salt with iron and iodine in women and children in rural Ghana.

[Asibey-Berko E](#), [Zlotkin SH](#), [Yeung GS](#), [Nti-Nimako W](#), [Ahunu B](#), [Kvei-Faried S](#), [Johnston JL](#), [Tondeur MC](#), [Mannar V](#).

Department of Nutrition and Food Science, University of Ghana,

OBJECTIVE: To test the efficacy of double-fortified salt (DFS) on the anaemia and iodine deficiency (ID) status of women and their children. **DESIGN:** Double-blind randomised controlled trial. **SETTING:** Sekyere West District of Ghana. **SUBJECTS:** In this eight-month trial, **mildly anaemic or non-anaemic, non-pregnant, non-lactating women were randomised into three groups receiving: DFS plus weekly placebo (n = 61); iodised salt plus weekly 70 mg iron supplement (n = 65); or iodised salt (IS) plus weekly placebo (control group, n = 58).** Correspondingly, their mildly anaemic and non-anaemic children aged 1-5 years were randomised into two groups receiving either the DFS (n = 23) or IS alone (control group, n = 59). **RESULTS:** At the end of the intervention, **prevalence of anaemia in women remained unchanged in the DFS or IS plus weekly iron supplement group, but significantly increased by 19.5% in the control group (P = 0.039).** In children, prevalence of anaemia in the DFS group significantly decreased by 21.7% (P = 0.025) while no change was observed in the control group. ID decreased significantly in all groups of women (P < 0.001) and children (P < 0.05), with no difference among groups of women and children. **CONCLUSION:** **While the use of DFS prevented anaemia in women, it had a significant role in both the prevention and treatment of anaemia in children. Both the DFS and IS significantly reduced ID in women and children to a similar degree.**

[Biol Trace Elem Res](#). 2008 Mar;121(3):193-204. Epub 2008 Jan 8.

Apparent efficacy of food-based calcium supplementation in preventing rickets in Bangladesh.

[Combs GF Jr](#), [Hassan N](#), [Dellagana N](#), [Staab D](#), [Fischer P](#), [Hunt C](#), [Watts J](#).

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853, USA.
gerald.combs@ars.usda.gov

To determine whether increased Ca intakes can prevent rickets in a susceptible group of children living in a rickets-endemic area of Bangladesh, we conducted a 13-month long, **double-blind**,

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clinical trial with 1-to 5-year-old children who did not present with rickets but ranked in the upper decile of plasma alkaline phosphatase (AP) activity of a screening cohort of 1,749 children. A total of 158 children were randomized to a milk-powder-based dietary supplement given daily, 6 days/week, and providing either 50, 250, or 500 mg Ca, or 500 mg Ca plus multivitamins, iron, and zinc. Upon initial screening, 194 healthy children presented with no rachitic leg signs and had serum AP in the upper decile (>260 u/dl) of the cohort. When 183 of those subjects were re-screened after a 7-month pre-trial period, 23 (12.6%) had developed rachitic leg signs, suggesting an annual risk of 21.5% in this cohort. Of those still not presenting with leg signs and completing 13 months of dietary intervention, none showed rachitic leg signs, none showed significant radiological evidence of active rickets, and all showed carpal ossification normal for age after that intervention. **These results are consistent with even the lowest amount of supplemental Ca (50 mg/day) being useful in supporting normal bone development in this high-risk population.**

[Indian Pediatr.](#) 2007 Nov 7;44(11):823-829.



Effect of Consumption of Micronutrient Fortified Candies on the Iron and Vitamin A Status of Children Aged 3-6 years in Rural Haryana.

[Anand K](#), [Lakshmy R](#), [Janakarajan VN](#), [Ritvik A](#), [Misra P](#), [Pandey RM](#), [Kapoor SK](#), [Sankar R](#), [Bulusu S](#).

All India Institute of Medical Sciences, New Delhi; Global Alliance for Improved Nutrition; and The Micronutrient Initiative -India Office; India. Correspondence to: Dr K. Anand, Associate Professor, Center for Community Medicine, AIIMS, New Delhi 110 029, India. kanandiyer@yahoo.com.

OBJECTIVE: To assess the efficacy of micronutrient fortified sugar candies in improving the iron and vitamin A status in children aged 3 to 6 years. **DESIGN:** Triple blind randomized controlled trial. **SETTINGS:** Anganwadis and preparatory schools in rural Haryana. **METHODS:** 410 children were randomized in four groups. One group received full dose candy (vitamin A 1000 IU and 14 mg elemental iron) daily, the second group received full dose candy for 3 days a week, the third group received half dose candy (vitamin A 500 IU and 7 mg elemental iron) daily and the fourth received placebo. The candies were provided to children under supervision of field workers. Hemoglobin, S. ferritin, S. retinol and S. retinol binding protein levels were estimated at baseline and after 13 weeks of intervention. **RESULTS:** **The increase in hemoglobin was least in the placebo group (0.3 g/dL) as compared to the two full dose groups (1.15-1.18 g/dL, P < 0.001).** Among anemic children, the increase in hemoglobin was about 2 g/dL in the full dose group and 0.7g/dL in the placebo group (P < 0.001). S. ferritin levels increased significantly only in the full dose daily group (p < 0.05). The prevalence of anemia decreased from around 50% at baseline to 9.6% in the full dose daily group (p < 0.01). Based on the S. retinol levels, the study area was not vitamin A deficient and the intervention did not result in a significant improvement in the vitamin A status of the children. **CONCLUSION:** **Micronutrient fortified candies were effective in improving the hemoglobin level and decreasing anemia prevalence.** It could serve as a suitable vehicle for micronutrient supplementation in children and other target groups.

[Acta Paediatr.](#) 2008 Jan;97(1):68-75. Epub 2007 Dec 3.



Promotion of exclusive breastfeeding is not likely to be cost effective in West Africa. A randomized intervention study from Guinea-Bissau.

[Jakobsen MS](#), [Sodemann M](#), [Biai S](#), [Nielsen J](#), [Aaby P](#).

Bandim Health Project, Indepth Network, Danish Epidemiology Science Centre, Apartado 861, Bissau, Guinea-Bissau. mariann.jakobsen@dadlnet.dk

AIM: To evaluate the impact of promotion of exclusive breastfeeding on infant health in Guinea-Bissau, West Africa, where mortality rates are high, breastfeeding is widely practiced but exclusive breastfeeding is rare. METHOD: At the Bandim Health Project in Guinea Bissau, West Africa, a birth cohort of **1721 infants were randomized to receive health education: promotion of exclusive breastfeeding for the first 4-6 months of life according to WHO recommendations at the time of the study. All children were followed from birth to 6 months of age.** RESULTS: **Introduction of both water and weaning food was significantly delayed in the intervention group. However we found no beneficial health effects of the intervention; there was no reduction in mortality in the intervention group compared with the control group (mortality rate ratio: 1.86 (0.79-4.39)), weight at 4-6 months of age was significantly lower in the intervention group (7.10 kg vs. 7.25 kg; Wilcoxon two-sample test: p=0.03).** There was no difference in diarrhoea morbidity and hospitalization rates. CONCLUSION: Although mothers were sensitive to follow new breastfeeding recommendations, it had no beneficial impact on infant health in this society with traditional, intensive breastfeeding. There seems to be little reason to discourage local practices as long as there are no strong data justifying such a change.

[Br J Nutr.](#) 2008 Mar;99(3):581-97. Epub 2007 Oct 10.



Effect of consumption of the nutrient-dense, freshwater small fish *Amblypharyngodon mola* on biochemical indicators of vitamin A status in Bangladeshi children: a randomised, controlled study of efficacy.

[Kongsbak K](#), [Thilsted SH](#), [Wahed MA](#).

Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Rolighedsvej 30, 1958 Frederiksberg C, Denmark. katjakongsbak@yahoo.dk

In Bangladesh, some commonly consumed, indigenous, freshwater small fish species (eaten whole with bone, head and eyes) such as mola (*Amblypharyngodon mola*) are nutrient-dense,

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containing preformed vitamin A as retinol and especially 3,4-dehydroretinol. The objective of the present randomised, controlled efficacy study was to evaluate the effects of mola on biochemical indicators of vitamin A status. **Children (n 196), aged 3-7 years, with serum retinol 0.36-0.75 micromol/l, were randomly allocated to one of three treatment groups to receive a daily test meal (6 d/week for 9 weeks) of rice and vegetable curry (no vitamin A) ad libitum and 50 g fish curry consisting of: (1) mola, 600 retinol activity equivalents (RAE) (using 40 % biological activity of 3,4-dehydroretinol isomers) (experimental group, n 66); (2) rui (Labeo rohita), a large fish (no vitamin A), with added retinyl palmitate, 600 RAE (positive control group, n 65); or (3) rui, 0 RAE (negative control group, n 65). The nutrient compositions of the dishes were analysed. After 9 weeks, no significant treatment effects were observed for serum retinol (P = 0.52) and retinol-binding protein (P = 0.81) in the experimental group compared with the negative control, whereas the positive control improved significantly (P < 0.001). The present results do not suggest conversion of the large amount of 3,4-dehydroretinol in mola curry to retinol. Further research on the functional effect of mola in humans is needed. Mola is a nutrient-dense animal-source food, rich in haem Fe, Zn and especially Ca, thus consumption of mola in Bangladesh should continue to be encouraged.**

[Am J Clin Nutr.](#) 2007 Oct;86(4):1094-103.



Fortified complementary foods with or without alpha-amylase treatment increase hemoglobin but do not reduce breast milk intake of 9-mo-old Zambian infants.

[Owino VO](#), [Kasonka LM](#), [Sinkala MM](#), [Wells JK](#), [Eaton S](#), [Darch T](#), [Coward A](#), [Tomkins AM](#), [Filteau SM](#).

Center for International Child Health, Institute of Child Health, London, United Kingdom.
vowino@hotmail.com

BACKGROUND: Malnutrition in late infancy in developing countries may result from poor-quality complementary foods that displace breast milk. **OBJECTIVE:** The objective of the study was to assess the effects of fortified complementary blends of different energy densities on growth, hemoglobin concentrations, and breast milk intake of 9-mo-old Zambian infants. **DESIGN:** **Infants were randomly assigned at 6 mo of age to receive for 3 mo a fortified blend of maize, beans, bambaranuts, and groundnuts [Chilenje Baby Mix (CBM); energy density: 68 kcal/100 g; n = 37] or a similar blend with alpha-amylase (CBMA; energy density: 106 kcal/100 g; n = 44).** Cross-sectional data were obtained at 9 mo for a control group of infants (n = 69) not given the diets. Breast milk intake was measured by using the dose-to-the-mother deuterium dilution technique. **RESULTS:** **No differences in weight or length z scores, all of which were within normal ranges, were seen between groups at 9 mo. Percentage fat mass was significantly (P = 0.01) greater in the infants in both the CBM (23.2 +/- 2.7%) and CBMA (23.4 +/- 2.5%) groups than in the control group (21.6 +/- 2.6%). Hemoglobin concentrations were significantly (P = 0.03) greater in both intervention groups (CBM group: 104 +/- 12 g/L; CBMA group: 103 +/- 12 g/L) than in the control group (98 +/- 14 g/L). Breast milk intake was not significantly (P = 0.87) different**

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between groups (CBM group: 614 +/- 271 g/d; CBMA group: 635 +/- 193 g/d; control group: 653 +/- 221 g/d). **CONCLUSIONS: The study foods improved hemoglobin concentrations without reducing breast milk intake and may be used to improve the nutritional status of infants in developing countries.**

[Am J Clin Nutr.](#) 2007 Oct;86(4):1082-93.



Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia.

[Osendarp SJ](#), [Baghurst KI](#), [Bryan J](#), [Calvaresi E](#), [Hughes D](#), [Hussaini M](#), [Karyadi SJ](#), [van Klinken BJ](#), [van der Knaap HC](#), [Lukito W](#), [Mikarsa W](#), [Transler C](#), [Wilson C](#); [NEMO Study Group](#).

Unilever Food and Health Research Institute (UFHRI), Unilever R&D, Olivier van Noortlaan 120, 3133 AT Vlaardingen, Netherlands. saskia.osendarp@unilever.com

BACKGROUND: Little is known about the combined effect of micronutrients and essential fatty acids on cognitive function in school-aged children. **OBJECTIVE:** We assessed the effect of micronutrients, long-chain n-3 fatty acids, or both on indicators of cognitive performance in well-nourished and marginally nourished school-aged children. **DESIGN:** Two 2-by-2 factorial randomized controlled double-blind trials were performed home-based in Adelaide, South Australia, and at 6 primary schools in Jakarta, Indonesia. A total of 396 children (aged 6-10 y) in Australia and 384 children in Indonesia were randomly allocated to receive a drink with a micronutrient mix (iron, zinc, folate, and vitamins A, B-6, B-12, and C), with docosahexanoic acid (DHA, 88 mg/d) and eicosapentaenoic acid (EPA, 22 mg/d), or with both or placebo 6 d/wk for 12 mo. Biochemical indicators were determined at baseline and 12 mo. Cognitive performance was measured at baseline, 6 mo, and 12 mo. **RESULTS:** The micronutrient treatment significantly improved plasma micronutrient concentrations in Australian and Indonesian children. DHA+EPA treatment increased plasma DHA and total plasma n-3 fatty acids in both countries. The micronutrient treatment resulted in significant increases in scores on tests representing verbal learning and memory in Australia (estimated effect size: 0.23; 95% CI: 0.01, 0.46). A similar effect was observed among Indonesian girls (estimated effect size: 0.32; 95% CI: -0.01, 0.64). No effects were found on tests measuring general intelligence or attention. No effects of DHA+EPA on the factors of cognitive tests were observed. **CONCLUSION:** In well-nourished school-aged children, fortification with multiple micronutrients can result in improvements in verbal learning and memory.

[Child Care Health Dev.](#) 2007 Sep;33(5):641-6.



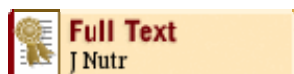
The effects of a 3-year obesity intervention in schoolchildren in Beijing.

[Jiang J](#), [Xia X](#), [Greiner T](#), [Wu G](#), [Lian G](#), [Rosenqvist U](#).

National Center for Women's and Children's Health, China CDC, Beijing 100013, China.
jiangjingxiong@chinawch.org.cn

BACKGROUND: Childhood obesity has become a health problem in urban areas in China. Intervention to reduce childhood obesity should be of high priority. School-based intervention programmes are needed to deal with the growing prevalence of childhood obesity in China. **METHODS:** Five primary schools were selected randomly for this study in the Beijing urban area in China; two were allocated to the intervention group and three to the control group. A total of 2425 children (1029 children in intervention schools and 1396 children in control schools) took part in the study for 3 years. **In the intervention group, children and their parents were involved in a programme of nutrition education and physical activity.** Control school students followed their usual health and physical education curriculum with no extra intervention. **RESULTS: After the 3-year intervention, the prevalence of overweight and obesity were significantly lower in the intervention schools than in the control schools (overweight: 9.8% vs. 14.4%, $P < 0.01$; obesity: 7.9% vs. 13.3%, $P < 0.01$). The prevalence of overweight and obesity decreased by 26.3% and 32.5% in intervention schools respectively after intervention.** The prevalence of overweight and obesity increased in control schools. There was also significant difference in body mass index between intervention and control schools (18.2 +/- 2.6 vs. 20.3 +/- 3.4, $P < 0.01$) after intervention. More non-obese children became obese in the control schools (7.0%) than in the intervention schools (2.4%) at end line ($P < 0.01$). Among the children who were obese at baseline, 49.2% remained obese at end line in intervention schools while 61.9% remained obese in control schools ($P < 0.01$). **CONCLUSIONS:** Our study showed that an intervention programme could be feasible in schools in Beijing, China. The prevalence of overweight and obesity was reduced in schoolchildren in Beijing through an intervention focused on nutrition education and physical activity. Overweight and obesity children as well as normal weight children and their parents should be involved in such an intervention programme.

[J Nutr](#). 2007 Sep;137(9):2147-53.



A multiple-micronutrient-fortified beverage affects hemoglobin, iron, and vitamin A status and growth in adolescent girls in rural Bangladesh.

[Hyder SM](#), [Haseen F](#), [Khan M](#), [Schaetzel T](#), [Jalal CS](#), [Rahman M](#), [Lönnerdal B](#), [Mannar V](#), [Mehansho H](#).

Department of Public Health Sciences, University of Toronto and Research Institute, the Hospital for Sick Children, Toronto, Canada M5G 1X8. ziauddin.hyder@sickkids.ca

Adolescent girls have high nutrient needs and are susceptible to micronutrient deficiencies. The objective of this study was to test the effect of a multiple-micronutrient-fortified beverage on

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hemoglobin (Hb) concentrations, micronutrient status, and growth among adolescent girls in rural Bangladesh. **A total of 1125 girls (Hb > or = 70 g/L) enrolled in a randomized, double-blind, placebo-controlled trial and were allocated to either a fortified or nonfortified beverage of similar taste and appearance.** The beverage was provided at schools 6 d/wk for 12 mo. Concentrations of Hb and serum ferritin (sFt), retinol, zinc, and C-reactive protein were measured in venous blood samples at baseline, 6 mo, and 12 mo. In addition, weight, height, and mid-upper arm circumference (MUAC) measurements were taken. **The fortified beverage increased the Hb and sFt and retinol concentrations at 6 mo (P < 0.01). Adolescent girls in the nonfortified beverage group were more likely to suffer from anemia (Hb <120 g/L), iron deficiency (sFt <12 microg/L), and low serum retinol concentrations (serum retinol <0.70 micromol/L) (OR = 2.04, 5.38, and 5.47, respectively; P < 0.01). The fortified beverage group had greater increases in weight, MUAC, and BMI over 6 mo (P < 0.01).** Consuming the beverage for an additional 6 mo did not further improve the Hb concentration, but the sFt level continued to increase (P = 0.01). The use of multiple-micronutrient-fortified beverage can contribute to the reduction of anemia and improvement of micronutrient status and growth in adolescent girls in rural Bangladesh

[Asia Pac J Clin Nutr.](#) 2007;16(3):505-11.

Multiple micronutrient fortification of salt and its effect on cognition in Chennai school children.

[Kumar MV](#), [Rajagopalan S](#).

Sundar Serendipity Foundation, 6G century plaza, 560-562 Anna Salai, Teynampet, Chennai, 600018, India. vinodkumar_m_k@hotmail.com

AIM: To test the efficacy of a multiple micronutrient fortified salt in improving the micronutrient status and health of school children and its effect on cognition. METHODS: A salt fortified with multiple micronutrients was developed containing chelated ferrous sulphate, microencapsulated vitamin A, B1, B2, B6, B12, folic acid, niacin, calcium pantothenate and iodine. The efficacy of the fortified salt was assessed in 7-11 year old school children in Chennai, India. **In the experimental group (N=63), the food in the school kitchen was cooked with the fortified salt for a period of one year. The control group (N=66) consisted of day scholars who did not eat at the school.** Hemoglobin, red blood cell count, hematocrit, serum vitamin A, urinary iodine and prevalence of angular stomatitis were measured at baseline and at the end of the study after one year. A battery of 7 memory tests (The personal information test, the Mann-Suiter Visual memory screen for objects, The digit span forward test, The digit span backward test, The delayed response test, The Benton Visual Retention Test and The Cattells retentivity test), one test for attention and concentration (Letter cancellation test) and one test for intelligence (Raven's coloured progressive matrices) were administered to all the children at baseline and endline. RESULTS: **There was a significant (p<0.05) improvement in the experimental group in hemoglobin, red cell count, urinary iodine and serum vitamin A whereas in the control group there was a statistically significant decline (p<0.05) in hemoglobin, hematocrit, red cell count and urinary iodine. Angular stomatitis was eliminated from baseline 30.4% in the experimental group whereas it increased from 3.25% to 25.5% in the control group.** In 4 tests out of the 7 memory tests and in the letter cancellation test for attention, the mean increment in scores in the experimental group is significantly more (p<0.05) than the control group. There was no significant improvement in overall intelligence as seen in the Ravens progressive matrices between the experimental and

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control groups. CONCLUSION: The study shows that the multiple micronutrient fortified salt is effective in improving multiple micronutrient status and cognition in children

[J Pediatr \(Rio J\)](#). 2007 Jul-Aug;83(4):363-9. Epub 2007 Jul 17.



Randomized clinical trial of the impact of a nutritional supplement "multimixture" on the nutritional status of children enrolled at preschools.

[Gigante DP](#), [Buchweitz M](#), [Helbig E](#), [Almeida AS](#), [Araújo CL](#), [Neumann NA](#), [Victoria C](#).

Universidade Federal de Pelotas (UFPel), Pelotas, RS, Brazil. denise@epidemiologia-ufpel.org.br

OBJECTIVE: To evaluate the effect of adding a nutritional supplement "multimixture" to school meals on the nutritional status of children enrolled at municipal preschools. **METHODS:** Longitudinal, controlled intervention study of 24 preschools which were compared before and after an intervention. The control and intervention groups were defined by drawing lots to choose schools that had previously been paired for nutritional status. The intervention consisted of the addition of 10 g of multimixture to the meals provided to children attending the 12 schools in the intervention group. Outcome measures include changes in z scores for the three nutritional indices and hemoglobin values over the 6-month period during which the supplement was added. A multilevel model was used for analyses. **RESULTS:** Mean z scores for weight for age at the end of follow-up were 0.40 (+/-1.34) and 0.31 (+/-1.32), for the intervention and control groups respectively. The multilevel analysis demonstrated non-significant differences in favor of the intervention in mean z scores for weight for age (beta 0.05; 95% CI -0.03 to 0.12) and height for age (beta 0.02; 95% CI -0.06 to 0.09). Mean change in hemoglobin was against the intervention, but this was also without significance (beta -0.01; 95% CI -0.36 to 0.34). **CONCLUSIONS:** Supplementation with 10 g of multimixture did not have a significant effect on any of the nutritional indices or measurements of the municipal preschool pupils studied here.

Oral health

[J Indian Soc Pedod Prev Dent](#). 2007 Jul-Sep;25(3):126-9.



A comparative study of two mouthrinses on plaque and gingivitis in school children in the age group of 13-16 years in Bangalore city.

[Jayaprakash K](#), [Veerasha KL](#), [Hiremath SS](#).

Department of Preventive and Community Dentistry, Rama Dental College and Hospital,

Randomised trials in child health in developing countries 2007-08

Kanpur - 208 024, India. jpdentdoc@gmail.com

Research and clinical evidence indicate that most forms of plaque associated periodontal disease start as inflammatory lesions of the gingiva which if left untreated, may progress and eventually involve and compromise the entire periodontal attachment apparatus of the affected teeth. A study was conducted to assess the effect of a mouthrinse containing chlorhexidine and sodium fluoride on plaque accumulation and gingivitis in comparison with a chlorhexidine mouthrinse alone in a group of school children aged 13-16 years in Bangalore city. This combination along with the well established effect of fluoride in the prevention of caries presents an important contribution to dental public health. The results suggest that the chlorhexidine-sodium fluoride mouthrinse potentially possesses a significant effect on inhibition of plaque accumulation and gingivitis. This combination along with the well-established effect of fluoride in the prevention of caries, presents an important contribution to dental public health.

Ophthalmology

[Trop Med Int Health](#). 2008 Apr;13(4):556-65. Epub 2008 Feb 14.



Risk factors for active trachoma and Chlamydia trachomatis infection in rural Ethiopia after mass treatment with azithromycin.

[Edwards T](#), [Harding-Esch EM](#), [Hailu G](#), [Andreason A](#), [Mabey DC](#), [Todd J](#), [Cumberland P](#).

London School of Hygiene and Tropical Medicine, London, UK. tansy.edwards@lshtm.ac.uk

OBJECTIVES: To investigate risk factors for ocular Chlamydia trachomatis infection and active trachoma, comparing communities receiving or not receiving an intervention programme of community-wide azithromycin treatment and health education. **METHODS:** In a 3-year post-intervention follow-up survey, 1722 children aged 3-9 years, from randomly selected households in 37 communities, were examined for signs of active trachoma and had samples taken to test for ocular C. trachomatis by polymerase chain reaction. Multivariate random effects logistic regression analyses considered interventions at community level, adjusting for other independent risk factors as appropriate. **RESULTS:** Younger age, ocular discharge and flies on eyes were risk factors for active trachoma in communities with and without antibiotic treatment. After azithromycin treatment, odds of active trachoma were lower in children aged 6-9 years than in children aged 3-5 years (OR 0.48, 95% CI: 0.36-0.66) and higher for children with ocular discharge (OR 4.5, 95% CI: 2.6-7.7) or flies on their eyes (OR 2.5, 95% CI: 1.6-3.7). Odds of C. trachomatis infection were lower in children aged 6-9 years than in younger children (OR 0.47, 95% CI: 0.23-0.96); and in children who received 2 or 3 doses rather than 1 (OR 0.26, 95% CI: 0.08-0.88). **CONCLUSIONS:** In communities that received or did not receive the mass antibiotic treatment, the same risk factors for C. trachomatis and active trachoma were identified. Education and environmental improvements need to supplement antibiotic campaigns in order to positively impact on these remaining child level risk factors.

[Br J Ophthalmol](#). 2008 Jan;92(1):19-24.



Two strategies for correcting refractive errors in school students in Tanzania: randomised comparison, with implications for screening programmes.

[Wedner S](#), [Masanja H](#), [Bowman R](#), [Todd J](#), [Bowman R](#), [Gilbert C](#).

International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, UK. susanne.wedner@gmx.net

PURPOSE: To compare whether free spectacles or only a prescription for spectacles influences wearing rates among Tanzanian students with un/undercorrected refractive error (RE). **METHODS:** DESIGN: Cluster randomised trial. SETTING: 37 secondary schools in Dar es Salaam, Tanzania. PARTICIPANTS: Distance visual acuity was measured in 6,904 year-1 students (90.2% response rate; median age 14 years; range 11-25 years) using a Snellen E-chart. 135 had RE requiring correction. INTERVENTIONS: Schools were randomly allocated to free spectacles (arm A) or prescription only (arm B). Primary outcome: Spectacle use at 3 months. RESULTS: The prevalence of un/undercorrected RE was 1.8% (95% CI: 1.5 to 2.2%). At 3 months, 27/58 (47%) students in arm A were wearing spectacles or had them at school compared with 13/50 (26%) in arm B (adjusted OR 2.4, 95% CI 1.0 to 6.7). Free spectacles and myopia were independently associated with spectacle use. CONCLUSIONS: The low prevalence of un/undercorrected RE and poor uptake of spectacles, even when provided free, raises doubts about the value of vision-screening programmes in Tanzanian secondary schools. Policy decisions on school vision screening in middle- and low-income countries should take account of the cost-effectiveness as well as competing demands for scarce resources.

Quality of care

[BMJ](#). 2007 Oct 27;335(7625):862. Epub 2007 Oct 22.***



Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomised trial.

[Biai S](#), [Rodrigues A](#), [Gomes M](#), [Ribeiro I](#), [Sodemann M](#), [Alves F](#), [Aaby P](#).

Projecto de Saúde de Bandim, INDEPTH Network, Bissau Codex 1004, Guinea-Bissau. sidubiai@hotmail.com

OBJECTIVE: To test whether strict implementation of a standardised protocol for the management of malaria and provision of a financial incentive for health workers reduced mortality. **DESIGN:** Randomised controlled intervention trial. **SETTING:** Paediatric ward at the

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national hospital in Guinea-Bissau. All children admitted to hospital with severe malaria received free drug kits. PARTICIPANTS: 951 children aged 3 months to 5 years admitted to hospital with a diagnosis of malaria randomised to normal or intervention wards. INTERVENTIONS: Before the start of the study, all personnel were trained in the use of the standardised guidelines for the management of malaria, including strict follow-up procedures. Nurses and doctors were randomised to work on intervention or control wards. Personnel in the intervention ward received a small financial incentive (\$50 (25 pounds sterling; 35 euros)/month for nurses and \$160 for doctors) and their compliance with standard case management was closely monitored. MAIN OUTCOME MEASURES: In-hospital mortality and cumulative mortality within 4 weeks of hospital admission. RESULTS: In-hospital mortality was 5% for the intervention group and 10% in the control group (risk ratio 0.48, 95% confidence interval 0.29 to 0.79). The effect may have been stronger in patients with positive malaria slides (0.36, 0.16 to 0.80). Cumulative mortality 4 weeks after discharge was also lower in the intervention group (0.61, 0.40 to 0.95). CONCLUSIONS: Supervising healthcare workers to adhere to a standardised treatment protocol was associated with greatly reduced in-hospital mortality. Financial incentives may be important for the dedication and compliance of staff members. TRIAL REGISTRATION: Clinical Trials NCT00465777 [ClinicalTrials.gov]

Comment

This is an important study, as it showed a reduction in mortality rate from malaria in paediatric wards where there was training, availability of free drugs and treatment kits, and “modest” financial incentives to staff. On the one hand, this study calls for much better remuneration and support for health workers. On the other hand, the way the study was conducted raised some important issues of inequality. Important comments on this study were made in: BMJ. 2007 Nov 10;335(7627):954. “There was no mention of how the unequal hospital environment created by the study may itself have contributed to the results. It would have been useful to hear from the nurses and doctors themselves. How did it feel to be in the control group, to receive no extra money, and to have to continue moonlighting to pay for food and rent, while colleagues (working in a similar children's ward in the same building) enjoyed a monthly bonus (\$50 and \$160 a month for nurses and doctors respectively)?”

School health

(see also Nutrition)

[Alcohol](#). 2007 Sep;41(6):403-14.

Language and literacy outcomes from a pilot intervention study for children with fetal alcohol spectrum disorders in South Africa.

[Adnams CM](#), [Sorour P](#), [Kalberg WO](#), [Kodituwakku P](#), [Perold MD](#), [Kotze A](#), [September S](#), [Castle B](#), [Gossage J](#), [May PA](#).

Department of Paediatrics, School of Child and Adolescent Health, University of Cape Town, South Africa.

This pilot study investigated the efficacy of a classroom language and literacy intervention in children with fetal alcohol spectrum disorders (FASD) in the Western Cape Province of South Africa. The study forms part of a larger, ongoing study that includes metacognitive and family support interventions in addition to language and literacy training (LLT). For the LLT study, 65

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nine-year-old children identified as either FASD or not prenatally exposed to alcohol, were recruited. Forty children with FASD were randomly assigned to either a LLT intervention group or FASD control group (FASD-C). Twenty-five nonalcohol-exposed children were randomly selected as nonexposed controls (NONEXP-C). Prior to intervention and after nine school-term months of treatment, general scholastic tests, teacher and parent questionnaires, classroom observations and specific language and literacy tests were administered to the participants. The nine months assessment reflects the midpoint and the first assessment stage of the overall study. At initial diagnosis and prior to commencement of the interventions, participants with FASD were significantly weaker than NONEXP-C children in reading, spelling, addition, subtraction, phonological awareness, and other tests of early literacy. Teachers rated a range of adaptive behaviors of children with FASD as significantly worse than NONEXP-C. Mean scholastic and language and literacy scores for all groups showed improvement over baseline scores after 9 months of intervention. The mean test scores of children with FASD remained lower than those of NONEXP-C. Comparison of mean baseline to postintervention score changes between the LLT, FASD-C, and NONEXP-C groups revealed that although there were no significant gains by the LLT intervention group over control groups on the general scholastic assessment battery, significantly greater improvements occurred in the LLT intervention group compared to the FASD-C group in specific categories of language and early literacy. These categories were syllable manipulation, letter sound knowledge, written letters, word reading and nonword reading, and spelling. In spite of cognitive and classroom behavioral difficulties, children with FASD from a vulnerable environment demonstrated significant cognitive improvements in specific areas targeted by classroom interventions. To our knowledge, this is the first report of a systematic classroom intervention and resultant cognitive response in children with FASD.

[J Trauma Stress](#). 2007 Aug;20(4):541-51.



School-based intervention for prevention and treatment of elementary-students' terror-related distress in Israel: a quasi-randomized controlled trial.

[Berger R](#), [Pat-Horenczyk R](#), [Gelkopf M](#).

Israel Trauma Center for the Victims of Terror and War (NATAL), Tel Aviv, Israel.

A school-based intervention for preventing and reducing children's posttraumatic stress-related symptoms, somatic complaints, functional impairment, and anxiety due to exposure to terrorism was evaluated. In a quasi-randomized controlled trial, elementary school students were randomly assigned to an eight-session structured program, "Overshadowing the Threat of Terrorism" or to a waiting list control comparison group. Two months postintervention, the study group reported significant improvement on all measures. The authors conclude that a school-based universal intervention may significantly reduce posttraumatic stress disorder-(PTSD-) related symptoms in children repeatedly exposed to terrorist attacks and propose that it serve as a component of a public mental health approach dealing with children exposed to ongoing terrorism in a country ravaged by war and terrorism.

[Soc Sci Med](#). 2007 Oct;65(7):1397-409. Epub 2007 Jul 2.

Intergenerational interaction, social capital and health: results from a randomised controlled trial in Brazil.

[de Souza EM](#), [Grundy E](#).

Escola Superior em Ciências da Saúde (School of Health Science) Brasília, DF Brazil.
elzadesouza@terra.com.br

Recent years have seen a burgeoning of intergenerational programmes aiming to improve the well being of participants. However, very few programmes have been formally evaluated. In this paper we report results from a randomised controlled trial of a school-based intergenerational intervention undertaken in Brazil. **Randomly selected samples of 253 adolescents and 266 elders aged 60 and over resident in the school's catchment area were administered a questionnaire including questions on cognitive components of social capital, family relationships, and self-rated health. Participants were then randomly allocated to control and intervention groups. The intervention comprised participation in a 4 month programme of intergenerational activities in which the elders shared their memories with the students. At the end of the intervention the questionnaire was re-administered to the samples.** High proportions (85-95%) of both samples completed the questionnaires but compliance with the intervention was low in the elderly group. In the analysis of results from the elderly sample, we therefore compared the control group with the group assigned to the intervention (intention to treat analysis). Results showed that **adolescents in the intervention group were nearly three times more likely to rate their health as good than those in the control group, but also more likely to judge that most people were selfish. In the elderly sample, those from the intervention group were over twice as likely as those from the control group to report positively on the helpfulness of neighbours; judge most people to be honest or consider their family relationships as good.** There were no significant differences between groups on other outcome measures. These results suggest that **structured intergenerational activities may have positive effects on some aspects of social capital for both adolescents and elderly people**, although further research is needed to elucidate the processes involved and the extent to which the findings are context specific. This study is the first to use a controlled trial design to evaluate this type of intervention and is valuable in showing that this design can be used in interventions of this kind, and also the difficulties involved.

Skin disease

[Int J Dermatol](#). 2007 Oct;46 Suppl 2:19-22.



Oral amoxicillin vs. oral erythromycin in the treatment of pyoderma in Bamako, Mali: an open randomized trial.

[Faye O](#), [Hay RJ](#), [Diawara I](#), [Mahé A](#).

Randomised trials in child health in developing countries 2007-08

Center National d'Appui à la lutte contre la Maladie (CNAM), BP 251, Bamako, Mali.

BACKGROUND: Pyoderma (bacterial superficial skin infection) is an extremely common disorder in tropical developing countries. In these settings, *Streptococcus pyogenes* is considered to be the main etiological agent. Apart from epidemics of poststreptococcal glomerulonephritis where mass treatment with intramuscular benzathine-penicillin is recommended, no recommendation exists for the treatment of pyoderma in this setting. The aim of this study was to evaluate the efficacy of oral amoxicillin in the treatment of pyoderma in Mali, by comparison with oral erythromycin. **METHODS:** In Bamako, **132 patients with pyoderma, diagnosed and graded as "severe" on clinical grounds, were randomly assigned to an oral treatment by either amoxicillin (50 mg/kg per day) or erythromycin;** infections of the follicular appendage were excluded. Both drugs were associated with the topical application of povidone iodine. The patients were evaluated openly at the seventh day of treatment for cure or marked improvement of the clinical features, indicating successful treatment. **RESULTS:** Three patients were lost to follow-up. **Treatment was successful in 57 of 64 patients treated with amoxicillin vs. 58 of 65 patients treated with erythromycin (P = 0.00).** **CONCLUSIONS:** Amoxicillin was as efficacious as erythromycin in the treatment of severe pyoderma in Mali. Owing to its efficacy, added to high availability and low cost, this compound should be considered a first-line treatment of this disorder in this country, and perhaps in other countries where this condition presents in a similar way.

Comment

The p-value quoted (p=0.00) may be incorrect, as there was no difference between the two groups. This does not indicate equivalence, just no difference found in the relatively small sample.

[Int J Dermatol.](#) 2007 Oct;46 Suppl 2:23-8.



Efficacy of triclosan soap against superficial dermatomycoses: a double-blind clinical trial in 224 primary school-children in Kilombero District, Morogoro Region, Tanzania.

[Dinkela A.](#), [Ferié J.](#), [Mbata M.](#), [Schmid-Grendelmeier M.](#), [Hatz C.](#)

Department of Medicine and Diagnostics, Swiss Tropical Institute, Basel, Switzerland.

BACKGROUND: Superficial dermatomycoses are a common problem in tropical regions. Due to limited resources, specific antimycotic therapy is often not available. The present study was performed to assess the clinical efficacy of the antimicrobial agent Triclosan in bar soap in comparison with regular soap against selected superficial dermatomycoses in Tanzanian schoolchildren. **METHODS:** 820 primary school children were examined for skin disorders and 224 of these were included in the soap trial. The clinical presentation of dermatomycoses was recorded using a symptom score. Samples were taken for microscopic examination and mycological culture. The study participants received either bar soap containing Triclosan or a placebo for 2 months. They were re-examined at the end of this period. **RESULTS:** The benefit achieved by the addition of Triclosan was not statistically significant. Overall cure rates for Triclosan and placebo groups taken together were 21.8% for tinea versicolor, 58.3% for tinea capitis, 55.5% for tinea corporis and 68.8% for tinea pedis. This was confirmed microscopically.

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For the majority of the children the dermatomycoses improved significantly. **CONCLUSIONS:** The results strongly argue for regular soap use against common dermatomycoses as a low-cost and effective treatment. This promising finding should be considered in settings where dermatophyte infections represent a public health problem and where access to appropriate treatment and financial resources are limited.

Surgical problems

[Acta Anaesthesiol Scand.](#) 2007 Nov;51(10):1350-3. Epub 2007 Aug 15.



A study of blood glucose in paediatric laparoscopy.

[Dave N](#), [Khan MA](#), [Halbe AR](#), [Kadam PP](#), [Oak SN](#), [Parelkar SV](#).

BYL Nair Charitable Hospital, Mumbai, India. nandini_dave@rediffmail.com

BACKGROUND: There are few studies on stress responses to laparoscopic surgery in children. This study was conducted to assess the blood glucose levels in children undergoing laparoscopy. We also studied the effect of two different intravenous (i.v.) solutions on blood glucose in open and laparoscopic procedures. **METHODS:** **One hundred and twenty healthy children, aged 2-12 years, undergoing either open or laparoscopic surgery, were randomized to receive either dextrose normal saline (DS) or Ringer's lactate peri-operatively (RL).** All patients had blood glucose measurements performed immediately after induction but prior to the i.v. infusion of any fluid. **Blood glucose was again measured 1 h after induction in the open cases and 1 h after insufflation in the laparoscopy cases.** **RESULTS:** In the groups, baseline blood glucose values were comparable. In all groups, blood glucose concentrations increased from the immediate post-induction (baseline) values. When RL was infused, the 1-h blood glucose was higher in the laparoscopy group as compared with the open group. However, when DS was infused the difference between the 1-h blood glucose in the open and laparoscopic procedures was not statistically significant. In the laparoscopy group, the 1-h blood glucose value was significantly higher in the patients receiving dextrose solution. **CONCLUSION:** **Laparoscopic procedures in children are associated with a rise in blood glucose levels similar to open surgery. The hyperglycaemic response was more pronounced when dextrose-containing solutions were infused peri-operatively.**

[Int J Surg.](#) 2007 Aug;5(4):234-8. Epub 2006 Aug 28.

Small lateral access--an alternative approach to appendicitis in paediatric patients: a randomised controlled trial.

[Malik AH](#), [Wani RA](#), [Saima BD](#), [Wani MY](#).

Department of General Surgery, Shri Maharaja Hari Singh Hospital, GMC, Srinagar, Kashmir 190005, India. drarshadmalik@hotmail.com <drarshadmalik@hotmail.com>

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BACKGROUND: Conventionally the appendix is removed through a right lower quadrant transverse incision or a gridiron incision approximately 5 cm in length. In this modern era of minimally invasive surgery, there is a lot of emphasis on cosmesis and early recovery. We performed a prospective, double blind, randomised trial to evaluate a new incision for appendectomy to compare with conventional appendectomy. **METHODS:** One hundred and twenty patients, aged between 3 and 18 years, were randomized to receive either small access appendectomy (SAA) (n=60, 53 acute appendicitis and 7 interval appendectomy) or conventional appendectomy (CAP) (n=60, 55 acute appendicitis and 5 interval appendectomy). SAA was performed through an incision in the lateral 1/3 of the spino-umbilical line, lateral to McBurney's point. The caecum along with the appendix could be delivered through this small incision easily as the ileal loops did not interfere with the delivery. All patients suspected of acute appendicitis were evaluated by the modified Alvarado's system to reduce the rate of negative appendectomies. Patients with diffuse peritonitis were excluded. **RESULTS:** The demographic data for the two groups were similar. The SAA group required less analgesics ($p<0.001$), had earlier ambulation and shorter hospital stay ($p<0.001$), and better cosmetic score ($p<0.001$), but the operation took longer ($p<0.001$) compared to the CAP group. **CONCLUSION:** We conclude that SAA can be done safely without the need for any special equipment, with definite advantages over conventional appendectomy.

[Int J Pediatr Otorhinolaryngol.](#) 2007 Oct;71(10):1555-62. Epub 2007 Jul 12.

Prospective, randomized, single-blind, controlled study to compare two methods of performing adenoidectomy.

[Jonas NE](#), [Sayed R](#), [Prescott CA](#).

Division of Otolaryngology, University of Cape Town Medical School, H-53 Old Main Building, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa.

OBJECTIVE: To compare adenoidectomy using suction-diathermy ablation to curettage adenoidectomy with respect to operative time and adenoid regrowth at 6 months after surgery. **STUDY DESIGN:** A prospective, randomized, single-blind, study to compare two methods of performing adenoidectomy. A group of 100 children, undergoing adenoidectomy alone or in combination with tonsillectomy, were randomized into two groups and underwent either suction diathermy or curettage adenoidectomy by a single surgeon. **SETTING:** A tertiary care Paediatric Hospital. **METHOD:** Indication for surgery, adenoidal size, duration of surgery and complications were recorded and compared. Six-month follow-up was conducted and adenoidal size and symptom status were recorded and compared. Statistical analysis was performed using Microsoft Excel. **RESULTS:** One hundred patients participated in this study and underwent adenoidectomy alone or adenotonsillectomy. Ninety-two patients returned for follow-up and 91 patients completed the study. The two treatment groups were well matched for age and gender. The main indications for both groups were snoring, nasal obstruction and obstructive sleep apnoea. For adenoidectomy alone there was no significant difference in duration of surgery between the curette and suction diathermy groups. When performing tonsillectomy and adenoidectomy together suction diathermy took significantly longer to complete than curettage ($P<0.001$). Overall 96% of patients' symptoms had either improved or resolved. The post-operative comparison at 6 months showed a significant difference in the residual adenoidal size between the two groups, the suction diathermy group being generally smaller than the curettage

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group. CONCLUSIONS: Suction diathermy was better at reducing the adenoidal size 6 months after surgery. Although the difference in size was statistically significant it did not seem to be of clinical significance.

Supportive care

[J Infus Nurs.](#) 2008 May-Jun;31(3):182-8.

Peripheral IVs: factors affecting complications and patency--a randomized controlled trial.

[Tripathi S](#), [Kaushik V](#), [Singh V](#).

Department of Pediatrics, Lady Hardinge Medical College, New Delhi, India.
sandeep.tripathi@downstate.edu

Peripheral intravenous access is a common but stressful pediatric procedure. Though in use for some decades now, there is no consensus on factors affecting the duration of patency and complications. The present study is a randomized controlled trial covering all aspects associated with vascular access. This prospective interventional study was conducted over a period of 6 months in a general pediatric ward of Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital. This sample was composed of 88 patients, from neonates to 12-year-olds who were admitted to the pediatric ward, on whom a total of 377 catheters were started. Intravenous cannulations were randomized for heparin flushes (1:100 dilution) and splints. Prospective data were collected regarding duration of patency and complications. Both univariate and multivariate analysis were done. There was a statistically significant increase in the duration of patency with the use of heparin flushes and splints. The incidence of phlebitis increased with heparin flushes. Shorter patency duration and increased complications were associated with younger age, wrist and scalp insertions, and 24-gauge catheters.

[J Spec Pediatr Nurs.](#) 2008 Apr;13(2):63-73.



Effectiveness and appropriateness of therapeutic play intervention in preparing children for surgery: a randomized controlled trial study.

[Li HC](#), [Lopez V](#).

Department of Nursing Studies, University of Hong Kong, Pokfulam, Hong Kong.
william3@hku.hk

PURPOSE: This paper aims to examine the effectiveness and appropriateness of using therapeutic play in preparing children for surgery. DESIGN/METHOD: A randomized controlled trial was employed. Children (7-12 years of age; n = 203) admitted for surgery during a 13-month period were recruited. RESULTS: The results support the effectiveness and

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appropriateness of using therapeutic play in preparing children for surgery. **PRACTICE IMPLICATIONS:** The study results promote awareness in nurses and parents that play is a very important part of children's lives, and heighten the importance of integrating therapeutic play as an essential component of holistic and quality nursing care to prepare children for surgery.

[Zhongguo Zhen Jiu](#). 2007 Nov;27(11):859-61.

Randomized and controlled observation on acupuncture and moxibustion combined with western medicine for treatment of malaria of children in Africa

[Lin GJ](#), [Fat u Camar a](#).

Chengdu City Wenjiang District People's Hospital, Sichuan 611130.

OBJECTIVE: To compare therapeutic effects of acup-moxibustion combined with western medicine and simple western medicine on child malaria in Africa. **METHODS:** One hundred and thirty-two cases were randomly divided into an acup-moxibustion plus western medicine group (n = 67) and a western medication group (n = 65). The western medication group were treated with Quinine and expectant therapy, and the acup-moxibustion plus western medicine group with acup-moxibustion plus the western medicines as those in the western medication group, and the therapeutic course was one week. Main clinical manifestations and lab examinations for malaria were compared. **RESULTS:** The total effective rate was 97.0% in the acup-moxibustion plus western medicine group and 95.4% in the western medication group, with a significant difference between the two groups ($P < 0.05$); the acup-moxibustion plus western medicine group in decreasing fever of the patient and the density of malarial parasite in blood, shorting the duration of illness and recovery time of RBC was significantly better than the western medication group ($P < 0.05$). **CONCLUSION:** Clinical therapeutic effect of acup-moxibustion combined with western medicine is better than that of simple western medicine

[J Trop Pediatr](#). 2008 Feb;54(1):31-5. Epub 2007 Oct 25.



Pain reduction of heel stick in neonates: Yakson compared to non-nutritive sucking.

[Im H](#), [Kim E](#), [Park E](#), [Sung K](#), [Oh W](#).

The Department of Family and Child Nursing, School of Nursing, University of Washington, WA 98195, USA. hsim@u.washington.edu

The purpose of this study was to test the effect of Yakson (i.e. a traditional Korean touching method) and non-nutritive sucking (NNS) on reducing the pain that neonates experience when undergoing the heel stick procedure for blood testing. Ninety-nine healthy neonates were recruited and assigned into three groups: Yakson (n = 33), NNS (n = 33), and control group (n = 33). Each intervention was provided to the Yakson and NNS groups from 1 min before heel stick until the completion of the heel stick. For the Yakson group, a researcher caressed the belly

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of a neonate with one hand while supporting the back with the other hand. For the NNS group, a pacifier packed with sterile gauze was put in the neonate's mouth. The oxygen saturation levels in the Yakson and NNS group neonates were maintained significantly better than in the control group neonates. There was no significant difference between the groups with regard to heart rate and neonatal infant pain, measured using the Neonatal Infant Pain Scale. Findings indicate that Yakson can be used during heel stick to help neonates maintain their oxygen saturation level following the procedure.

Tuberculosis

[Br J Clin Pharmacol](#). 2008 Mar;65(3):423-7. Epub 2007 Dec 17.



Pyrazinamide blood concentrations in children suffering from tuberculosis: a comparative study at two doses.

[Gupta P](#), [Roy V](#), [Sethi GR](#), [Mishra TK](#).

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India.
drgupta.pooja@gmail.com

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT: Pyrazinamide is recommended in doses varying from 15 to 40 mg kg⁻¹. The most commonly used average daily dose is 25 mg kg⁻¹. Its use is associated with dose dependent hepatotoxicity. Lower doses are not used because of lack of pharmacokinetic data especially in children. There is only one detailed study of pyrazinamide in children at a dose of 35 mg kg⁻¹. **WHAT THIS STUDY ADDS:** This is the first study evaluating serum concentrations of pyrazinamide in children at a dose of 15 mg kg⁻¹ which is on the lower side of the recommended dose. The study also compared the serum concentrations and pharmacokinetics achieved with this dose with the widely used dose of 25 mg kg⁻¹ in children suffering from tuberculosis. The pharmacokinetics and pharmacodynamic indices of pyrazinamide were comparable with the 25 and 15 mg kg⁻¹ doses. **AIMS:** To evaluate the pharmacokinetics and pharmacodynamic indices of pyrazinamide at doses of 15 and 25 mg kg⁻¹ in children suffering from tuberculosis. **METHODS:** **Twenty children with tuberculosis received pyrazinamide at a single dose of 25 mg kg⁻¹ (group I) and 15 mg kg⁻¹ (group II).** Serial blood samples were collected and the drug concentrations were analyzed spectrophotometrically. The pharmacokinetic parameters were calculated and the duration of time for which pyrazinamide concentrations in serum remained above the pyrazinamide inhibitory concentrations of 20 microg ml⁻¹ and 25 microg ml⁻¹ was studied. **RESULTS:** The mean peak serum concentration was 42.4 +/- 3.3 microg ml⁻¹ (95% CI +/- 6.5) and 38.6 +/- 3.9 microg ml⁻¹ (95% CI +/- 7.7) in groups I and II, respectively. The elimination half-life was 9.3 +/- 1.3 h and 10.5 +/- 2.3 h (P = 0.6) and clearance was 0.06 +/- 0.01 l h⁻¹ kg⁻¹ and 0.04 +/- 0.01 l h⁻¹ kg⁻¹ (P = 0.08) in groups I and II, respectively. Pharmacokinetic parameters and PKPD indices were comparable with both the doses. **CONCLUSIONS:** **The study indicates that comparable serum concentrations of pyrazinamide are attained with 25 mg kg⁻¹ and 15 mg kg⁻¹ doses in children. The**

elimination half-life was longer and volume of distribution greater in children than in the adult population.

Vaccines

[PLoS ONE](#). 2008 Jun 4;3(6):e2323.



A randomized, placebo-controlled trial of the bivalent killed, whole-cell, oral cholera vaccine in adults and children in a cholera endemic area in Kolkata, India.

[Mahalanabis D](#), [Lopez AL](#), [Sur D](#), [Deen J](#), [Manna B](#), [Kanungo S](#), [von Seidlein L](#), [Carbis R](#), [Han SH](#), [Shin SH](#), [Attridge S](#), [Rao R](#), [Holmgren J](#), [Clemens J](#), [Bhattacharya SK](#).

Society for Applied Studies, Kolkata, India.

OBJECTIVES: An effective vaccine against cholera has been used for public health purposes in Vietnam since the 1990s. This vaccine was reformulated to meet WHO requirements. We assessed the safety and immunogenicity of the reformulated bivalent (*Vibrio cholerae* O1 and O139) killed whole cell oral vaccine in a cholera endemic area in Kolkata, India. **DESIGN:** Double-blind, randomized, placebo controlled trial. **SETTING:** The trial was conducted in the clinical trial ward of the Infectious Diseases Hospital in Kolkata, India. **PARTICIPANTS:** The participants were 101 healthy adults (males and non-pregnant females) aged 18-40 years and 100 healthy children (males and non-pregnant females) aged 1-17 years. **INTERVENTIONS:** Participants were randomized to receive either the bivalent killed whole cell oral cholera vaccine or placebo (killed oral *Escherichia coli* K12). **OUTCOME MEASURES:** For safety: proportion of subjects with adverse events during the duration of study participation. For immunogenicity: Proportion of subjects who had a ≥ 4 -fold rise in serum vibriocidal antibody titers 14 days after the second dose of vaccine or placebo. **RESULTS:** Adverse reactions were observed with similar frequency among vaccine and placebo recipients in both age groups. Among adults 4% of vaccine and 8% of placebo recipients and among children 4% of vaccine and 2% of placebo recipients had at least one adverse event within 28 days of the first dose of the vaccine. Following immunization, 53% of adult and 80% of children vaccinees showed a ≥ 4 fold rise in serum *V. cholerae* O1 vibriocidal antibody titers. A less pronounced response to *V. cholerae* O139 vibriocidal antibody titers post-immunization was noted among vaccinees. **CONCLUSIONS:** We found the vaccine to be safe and immunogenic in a cholera-endemic area in India. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00119197.

[PLoS ONE](#). 2008 May 14;3(5):e2159.



A phase II, randomized study on an investigational DTPw-HBV/Hib-MenAC conjugate vaccine administered to infants in Northern Ghana.

[Hodgson A](#), [Forgor AA](#), [Chandramohan D](#), [Reed Z](#), [Binka F](#), [Bevilacqua C](#), [Boutriau D](#), [Greenwood B](#).

Navrongo Health Research Centre, Ministry of Health, Navrongo, Ghana.

BACKGROUND: Combining meningococcal vaccination with routine immunization in infancy may reduce the burden of meningococcal meningitis, especially in the meningitis belt of Africa. We have evaluated the immunogenicity, persistence of immune response, immune memory and safety of an investigational DTPw-HBV/Hib-MenAC conjugate vaccine given to infants in Northern Ghana. **METHODS AND FINDINGS:** In this phase II, double blind, randomized, controlled study, 280 infants were primed with DTPw-HBV/Hib-MenAC or DTPw-HBV/Hib vaccines at 6, 10 and 14 weeks of age. At 12 months of age, children in each group received a challenge dose of serogroup A+C polysaccharides. Antibody responses were assessed pre, and one month-post dose 3 of the priming schedule and pre and 1 month after administration of the challenge dose. One month post-dose 3, 87.8% and 88.2% of subjects in the study group had bactericidal meningococcal serogroup A (SBA-MenA) and meningococcal serogroup C (SBA-MenC) antibody titres \geq 1:8 respectively. Seroprotection/seropositivity rates to the 5 antigens administered in the routine EPI schedule were non-inferior in children in the study group compared to those in the control group. The percentages of subjects in the study group with persisting SBA-MenA titres \geq 1:8 or SBA-MenC titres \geq 1:8 at the age of 12 months prior to challenge were significantly higher than in control group (47.7% vs 25.7% and 56.4% vs 5.1% respectively). The administration of 10 microg of serogroup A polysaccharide increased the SBA-MenA GMT by 14.0-fold in the DTPW-HBV/HibMenAC-group compared to a 3.8 fold increase in the control-group. Corresponding fold-increases in SBA-MenC titres following challenge with 10 microg of group C polysaccharide were 18.8 and 1.9 respectively. Reactogenicity following primary vaccination or the administration of the challenge dose was similar in both groups, except for swelling (Grade 3) after primary vaccination which was more frequent in children in the vaccine than in the control group (23.7%; 95%CI [19.6-28.1] of doses vs 14.1%; 95% CI [10.9-17.8] of doses). Fifty-nine SAEs (including 8 deaths), none of them related to vaccination, were reported during the entire study. **CONCLUSIONS:** Three dose primary vaccination with DTPw-HBV/Hib-MenAC was non-inferior to DTPw-HBV/Hib for the 5 common antigens used in the routine EPI schedule and induced bactericidal antibodies against *Neisseria meningitidis* of serogroups A and C in the majority of infants. Serogroup A and C bactericidal antibody levels had fallen below titres associated with protection in nearly half of the infants by the age of 12 months confirming that a booster dose is required at about that age. An enhanced memory response was shown after polysaccharide challenge. This vaccine could provide protection against 7 important childhood diseases (including meningococcal A and C) and be of particular value in countries of the African meningitis belt. **TRIAL REGISTRATION:** Controlled-Trials.com ISRCTN35754083.

[Hum Vaccin](#). 2008 Mar-Apr;4(2):121-6. Epub 2007 Oct 26.

Evaluation of two yellow fever vaccines for routine immunization programs in Argentina.

[Ripoll C](#), [Ponce A](#), [Wilson MM](#), [Sharif N](#), [Vides JB](#), [Armoni J](#), [Teuwen DE](#).

Randomised trials in child health in developing countries 2007-08

Jefe del Area Epidemiología, Ministerio de Salud, Jujuy, Argentina.

Although highly effective vaccines have been available for almost 70 years, an estimated 200,000 cases of YF, including 30,000 deaths, still occur annually. This study evaluated the safety of two yellow fever (YF) vaccines [Stamaril and Vacina Contra Febre Amarela (VCFA)]. A total of 2,514 subjects were randomized equally to receive Stamaril or VCFA. Immediate reactions occurring within 30 minutes after vaccination, and solicited local and systemic reactions occurring within eight days, were monitored. Unsolicited local, systemic adverse events and serious adverse events (SAE) were recorded for 21 days after vaccination. Solicited local and systemic adverse reactions were reported by 15.3-17.6% and 30.4-31.6% of the Stamaril and VCFA groups, respectively. Only 56 of the 2,514 study subjects (2.2%) reported a severe solicited adverse reaction, 25 in the Stamaril group (1.99%) and 31 in the VCFA group (2.49%), ($p=0.403$). Ten subjects (0.8%) in each group reported at least one severe solicited local reaction ($p = 0.988$). A total of 18 Stamaril subjects (1.43%) and 21 VCFA subjects (1.68%) reported at least one severe solicited systemic reaction ($p = 0.617$). One SAE considered related to vaccination occurred, polymyalgia in the VCFA group. No immediate reactions to vaccination were seen. Vaccine-related unsolicited events were infrequent, 1.4% in the Stamaril group and 2.0% VCFA group, generally of mild or moderate intensity. We conclude that the safety profiles of Stamaril and VCFA support routine vaccination to prevent YF in residents of and travelers to endemic areas of South America and Africa.

[Bull World Health Organ.](#) 2007 Sep;85(9):688-94.

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Hepatitis B vaccination of newborn infants in rural China: evaluation of a village-based, out-of-cold-chain delivery strategy.

[Wang L](#), [Li J](#), [Chen H](#), [Li F](#), [Armstrong GL](#), [Nelson C](#), [Ze W](#), [Shapiro CN](#).

Program for Appropriate Technology in Health, Beijing, China. lixiaawangcn@gmail.com

OBJECTIVE: To prevent perinatal transmission of hepatitis B virus (HBV), WHO recommends that the first dose of hepatitis B (HepB) vaccine be given within 24 hours after birth. This presents a challenge in remote areas with limited cold-chain infrastructure and where many children are born at home. **METHODS:** Rural townships in three counties in China's Hunan Province were randomized into three groups with different strategies for delivery of the first dose of HepB vaccine. In group 1, vaccine was stored within the cold chain and administered in township hospitals. In group 2, vaccine was stored out of the cold chain in villages and administered by village-based health workers to infants at home. Group 3 used the same strategy as group 2, but vaccine was packaged in a prefilled injection device. Training of immunization providers and public communication conveying the importance of the birth dose was performed for all groups. **FINDINGS:** Among children born at home, timely administration (within 24 hours after birth) of the first dose of HepB vaccine increased in all groups after the study: group 1, from 2.4% to 25.2%; group 2, from 2.6% to 51.8%; and group 3, from 0.6% to 66.7%; $P < 0.001$ in each case. No significant difference in antibody response to vaccine was observed between the groups. **CONCLUSION:** Timely administration of the first dose of HepB vaccine

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was improved by communication and training activities, and by out-of-cold-chain storage of vaccine and administration at the village level, especially among children born at home.

Comment

This study adds to previous evidence that hepatitis B vaccine is effective even if the cold chain is not maintained. It has relevance to locations in which hepatitis B vaccine can be given, and how countries with high rates of deliveries outside health facilities can improve the proportion of babies receiving hepatitis B vaccine in the first 24 hours of life. This study showed that administration at a village level in rural China was effective.

[Int J Infect Dis.](#) 2008 May;12(3):270-7. Epub 2007 Nov 7.

Immunogenicity, safety, and interchangeability of two inactivated hepatitis A vaccines in Chilean children.

[Abarca K](#), [Ibáñez I](#), [Perret C](#), [Vial P](#), [Zinsou JA](#).

Centro Médico San Joaquín, Pontificia Universidad Católica de Chile, Marcoleta 391, Santiago, Chile. katia@med.puc.cl

OBJECTIVES: To compare the immunogenicity, safety, and interchangeability of two pediatric hepatitis A vaccines, Avaxim 80U-Pediatric and Havrix 720, in Chilean children. **METHODS:** In this randomized trial, 332 hepatitis A virus (HAV) seronegative children from 1 to 15 years of age received two doses of Avaxim, two doses of Havrix, or Havrix followed by Avaxim, 6 months apart. Anti-HAV antibody titers were measured before and 14 days after the first dose of vaccine, and before and 28 days after the second dose of vaccine. Immediate reactions were monitored; reactogenicity was evaluated from parental reports. **RESULTS:** Seroconversion rates after the first vaccination were 99.4% and 100% for Avaxim and Havrix, respectively. Anti-HAV geometric mean concentrations (GMCs) were 138 mIU/ml for Havrix (95% confidence interval (CI): 120; 159) and 311 mIU/ml for Avaxim (95% CI: 274; 353). GMCs increased to 4008 mIU/ml after two doses of Havrix, 8537 mIU/ml following two doses of Avaxim, and 7144 mIU/ml in children who received Havrix with Avaxim as the second dose. Following the first injection, 36% of subjects given Avaxim and 44% given Havrix reported local reactions; 38% of subjects in the Avaxim group and 40% in the Havrix group reported systemic reactions related to vaccination. Solicited reactions were less frequent after the second dose of Avaxim or Havrix, occurring in 27% to 37% of subjects. **CONCLUSIONS:** No significant difference in seroconversion rates was seen 14 days after a single dose of vaccine. A two-dose schedule with either vaccine or with Havrix/Avaxim provided a strong booster response. Both vaccines were well tolerated and can be recommended for routine vaccination of Chilean children. Avaxim 80 may be used to complete a vaccine schedule begun with Havrix 720.

[Ann Acad Med Singapore.](#) 2007 Oct;36(10):801-6.



Primary vaccination of infants against hepatitis B can be completed using a combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-Haemophilus influenzae type B vaccine.

[Lim FS](#), [Han HH](#), [Jacquet JM](#), [Bock HL](#).

National Health Care Group Polyclinics, Choa Chu Kang, Singapore.
Fong_Seng_LIM@nhgp.com.sg

INTRODUCTION: Children in Singapore receive vaccination against hepatitis B virus (HBV) at 0, 1 and 5 or 6 months of age, and vaccination against pertussis, diphtheria, tetanus, and polio at 3, 4 and 5 months of age. Parents often choose to vaccinate with the combined acellular-pertussis-inactivated polio-Hib vaccine (DTPa-IPV/Hib). We investigated whether a combined hexavalent vaccine, DTPa-HBV-IPV/Hib, could replace the separate administration of DTPa-IPV/Hib and HBV for the final vaccination at 5 months of age (Trial DTPa-HBV-IPV-075). **MATERIALS AND METHODS:** In an open study, 150 children were randomised to complete their vaccination schedule with DTPa-IPV/Hib + HBV or DTPa-HBV-IPV/Hib. **RESULTS:** One month after the final vaccination, there was no difference between groups in seroprotection rates or antibody concentrations against HBV. Seroprotection rates against diphtheria, tetanus, Hib and polio, as well as vaccine response rates to pertussis antigens were also similar between groups. Local and general symptoms occurred at a similar rate after the third dose of either vaccine. **CONCLUSION:** The immunogenicity and reactogenicity of the hexavalent vaccine DTPa-HBV-IPV/Hib (Infanrix hexa, GSK) group is comparable to that of separately administered DTPa-IPV/Hib and HBV vaccines. Combined hexavalent vaccine, DTPa-HBV-IPV/Hib, could replace the separate administration of DTPa-IPV/Hib and HBV for vaccination at 5 months of age, thereby reducing the number of injections required.

[Pediatr Infect Dis J](#). 2007 Nov;26(11):1001-5.

Revaccination with locally-produced vi typhoid polysaccharide vaccine among chinese school-aged children: safety and immunogenicity findings.

[Zhou WZ](#), [Koo HW](#), [Wang XY](#), [Zhang J](#), [Park JK](#), [Zhu F](#), [Deen J](#), [Acosta CJ](#), [Chen Y](#), [Wang H](#), [Galindo CM](#), [Ochiai L](#), [Park T](#), [von Seidlein L](#), [Xu ZY](#), [Clemens JD](#).

Jiangsu Provincial Center for Disease Prevention and Control, Nanjing, China.

OBJECTIVE: To evaluate the safety and immunogenicity of revaccination with locally-produced Vi polysaccharide vaccine 3 years after the first dose in Chinese children aged 9 to 14 years. **METHODS:** A randomized, placebo-controlled trial was conducted in Suzhou, Jiangsu, China. Six hundred and sixty-seven eligible children who had previously received a primary dose of Vi vaccine were randomly assigned to receive 1 dose of 30 mug Vi vaccine or placebo. In addition, 331 eligible children received 1 dose of Vi polysaccharide vaccine as a primary vaccination. Adverse events were followed for 28 days after vaccination. Serum samples were collected from a subgroup of participants on day 0 and day 28, and Vi antibodies were analyzed using a passive hemagglutination method. **RESULTS:** Revaccination was found to be safe and immunogenic. No severe adverse events were observed. A significant increase in antibody titers after vaccination was observed among children who had and had not been previously vaccinated. Twenty-eight days after injection, the seropositive rate was 79% in both

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revaccination and primary injection groups; the geometric mean antibody titer was 1:40 in the primary injection group and 1:29 in the revaccination group ($P = 0.24$). Although the difference of attained geometric mean titers in follow-up sera was not significantly different in these 2 groups, the fold-rise of these titers from baseline was significantly higher in the primary injection group than in the revaccination group (7.7 versus 3.1, $P < 0.001$). **CONCLUSION:** We found that revaccination using the locally produced Vi polysaccharide vaccine among Chinese school-aged children was safe and increased antibody titers. Revaccination can be used to extend the duration of protection provided by Vi polysaccharide vaccine.

[Pediatr Infect Dis J.](#) 2007 Sep;26(9):787-93.

Concomitant administration of a virosome-adjuvanted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial.

[Dagan R](#), [Amir J](#), [Livni G](#), [Greenberg D](#), [Abu-Abed J](#), [Guy L](#), [Ashkenazi S](#), [Foresner G](#), [Tewald F](#), [Schätzl HM](#), [Hoffmann D](#), [Ibanez R](#), [Herzog C](#).

Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel. rdagan@bgu.ac.il

BACKGROUND: The objectives of this trial were to test for noninferiority of a virosomal hepatitis A virus (HAV) vaccine (Epaxal) coadministered with routine childhood vaccines compared with Epaxal given alone and to an alum-adjuvanted HAV vaccine (Havrix Junior) coadministered with routine childhood vaccines. **METHODS:** Healthy children 12- to 15-month-old were randomized to receive either a pediatric dose (0.25 mL) of Epaxal coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine ($n = 109$; group A), or Epaxal given alone ($n = 105$; group B), or Havrix Junior coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine ($n = 108$; group C). A booster dose was given 6 months later. Anti-HAV antibodies were tested before and 1 month after each vaccination. Safety was assessed for 1 month after each vaccination. Solicited adverse events were assessed for 4 days after each vaccination. **RESULTS:** HAV seroprotection rates ($>$ or $=20$ mIU/mL) at 1 and 6 months after first dose were: A: 94.2% and 87.5%, B: 92.6% and 80.0%, C: 78.2% and 71.3%, respectively (A versus C: $P < 0.001$ and $P = 0.017$ at month 1 and 6, respectively). The respective geometric mean concentrations were: A: 51 and 64 mIU/mL, B: 49 and 59 mIU/mL, C: 33 and 37 mIU/mL (A versus C: $P < 0.001$ at both time points). All groups achieved 100% seroprotection after the booster dose. The geometric mean concentrations after the booster dose were 1758, 1662, and 1414, for groups A, B and C, respectively (A versus C: $P = 0.15$). No clinically significant reduction in immune response to all concomitant vaccine antigens was seen. All vaccines were well tolerated. **CONCLUSIONS:** Coadministration of pediatric Epaxal with routine childhood vaccines showed immunogenicity and safety equal to Epaxal alone as well as to Havrix Junior. After first dose, Epaxal was significantly more immunogenic than Havrix Junior.

[J Pediatr.](#) 2007 Aug;151(2):173-7.

Pre-exposure rabies vaccination using purified chick embryo cell rabies vaccine intradermally is immunogenic and safe.

[Kamoltham T](#), [Thinyounyong W](#), [Phongchamnaphai P](#), [Phraisuwan P](#), [Khawplod P](#), [Banzhoff A](#), [Malerczyk C](#).

Provincial Health Office of Phetchabun, Ministry of Health, Phetchabun, Thailand.

OBJECTIVE: To demonstrate the safety and immunogenicity of intradermal rabies pre-exposure prophylaxis with purified chick embryo cell vaccine (PCECV) in schoolchildren age 5 to 8 years in Thailand. **STUDY DESIGN:** In a randomized, open-label, phase II clinical trial, 2 or 3 intradermal doses of 0.1 mL PCECV (Rabipur) were administered to 703 schoolchildren on days 0 and 28 or on days 0, 7, and 28. In 206 children, 2 simulated post-exposure booster doses were given 1 year after the primary vaccination series. Rabies virus- neutralizing antibody (RVNA) titers were determined by the rapid fluorescent focus inhibition test. **RESULTS:** In school-age children in Thailand, a pre-exposure immunization regimen of 3 intradermal doses of PCECV produced adequate immune responses. After primary vaccination, all subjects developed RVNA titers $>$ or $=0.5$ IU/mL and demonstrated a rapid increase in RVNA titer after 2 simulated post-exposure booster immunizations 1 year after the primary vaccination series. No serious adverse drug reactions occurred. **CONCLUSIONS:** Rabies pre-exposure immunization with PCECV is safe and immunogenic, and its implementation could save the lives of many children in rabies-endemic areas.

[Clin Infect Dis.](#) 2007 Jul 15;45 Suppl 1:S24-8.



Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B.

[Levine MM](#), [Ferrecio C](#), [Black RE](#), [Lagos R](#), [San Martin O](#), [Blackwelder WC](#).

Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201, USA. mlevine@medicine.umaryland.edu

In randomized, controlled field trials in Area Norte and Area Occidente of Santiago, Chile, 2 (Norte) or 3 (Occidente) doses of live oral typhoid vaccine Ty21a in enteric-coated capsules conferred protection against confirmed *Salmonella enterica* serovar Typhi disease (53% efficacy in Norte; 67% efficacy in Occidente) during 3 years of follow-up. There was also a trend in each trial showing protection against *S. enterica* serovar Paratyphi B disease (56% efficacy in Norte; 42% efficacy in Occidente). To enhance statistical power, an analysis was performed using pooled data from the 2 trials; this pooling of data was justified by the following facts: epidemiologic surveillance and microbiological methods were identical, the trials overlapped during 22 of the 36 months of follow-up in each trial, the estimates of efficacy against paratyphoid B fever in the 2 trials were roughly similar, and the ratio of follow-up of vaccine recipients to control subjects in both trials was $\sim 1 : 1$. In the pooled analysis, Ty21a conferred

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significant protection against paratyphoid B fever (efficacy, 49%; 95% confidence interval, 8%-73%; P=.019).

[Pediatr Infect Dis J](#). 2007 Jul;26(7):619-28.

Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia.

[Tam JS](#), [Capeding MR](#), [Lum LC](#), [Chotpitayasunondh T](#), [Jiang Z](#), [Huang LM](#), [Lee BW](#), [Qian Y](#), [Samakoses R](#), [Lolekha S](#), [Rajamohanan KP](#), [Narayanan SN](#), [Kirubakaran C](#), [Rappaport R](#), [Razmpour A](#), [Gruber WC](#), [Forrest BD](#); [Pan-Asian CAIV-T Pediatric Efficacy Trial Network](#).

Department of Microbiology and Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong. tamj1@wyeth.com

BACKGROUND: This study was designed to evaluate the efficacy and safety of cold-adapted influenza vaccine, trivalent (CAIV-T) against culture-confirmed influenza in children 12 to <36 months of age during 2 consecutive influenza seasons at multiple sites in Asia. **METHODS:** In year 1, 3174 children 12 to <36 months of age were randomized to receive 2 doses of CAIV-T (n = 1900) or placebo (n = 1274) intranasally > or =28 days apart. In year 2, 2947 subjects were rerandomized to receive 1 dose of CAIV-T or placebo. **RESULTS:** Mean age at enrollment was 23.5 +/- 7.4 months. In year 1, efficacy of CAIV-T compared with placebo was 72.9% [95% confidence interval (CI): 62.8-80.5%] against antigenically similar influenza subtypes, and 70.1% (95% CI: 60.9-77.3%) against any strain. In year 2, revaccination with CAIV-T demonstrated significant efficacy against antigenically similar (84.3%; 95% CI: 70.1-92.4%) and any (64.2%; 95% CI: 44.2-77.3%) influenza strains. In year 1, fever, runny nose/nasal congestion, decreased activity and appetite, and use of fever medication were more frequent with CAIV-T after dose 1. Runny nose/nasal congestion after dose 2 (year 1) and dose 3 (year 2) and use of fever medication after dose 3 (year 2) were the only other events reported significantly more frequently in CAIV-T recipients. **CONCLUSIONS:** CAIV-T was well tolerated and effective in preventing culture-confirmed influenza illness over multiple and complex influenza seasons in young children in Asia.

Vitamin A

[BMJ](#). 2008 Jun 21;336(7658):1416-20. Epub 2008 Jun 16.



Effect of 50,000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial.

[Benn CS](#), [Diness BR](#), [Roth A](#), [Nante E](#), [Fisker AB](#), [Lisse IM](#), [Yazdanbakhsh M](#), [Whittle H](#), [Rodrigues A](#), [Aaby P](#).

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Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark.
cb@ssi.dk

OBJECTIVE: To investigate the effect of high dose vitamin A supplementation given with BCG vaccine at birth in an African setting with high infant mortality. **DESIGN:** Randomised placebo controlled trial. Setting Bandim Health Project's demographic surveillance system in Guinea-Bissau, covering approximately 90,000 inhabitants. Participants 4345 infants due to receive BCG. **INTERVENTION:** Infants were randomised to 50,000 IU vitamin A or placebo and followed until age 12 months. **MAIN OUTCOME MEASURE:** Mortality rate ratios. **RESULTS:** 174 children died during follow-up (mortality=47/1000 person-years). **Vitamin A supplementation was not significantly associated with mortality; the mortality rate ratio was 1.07 (95% confidence interval 0.79 to 1.44). The effect was 1.00 (0.65 to 1.56) during the first four months and 1.13 (0.75 to 1.68) from 4 to 12 months of age.** The mortality rate ratio in boys was 0.84 (0.55 to 1.27) compared with 1.39 (0.90 to 2.14) in girls (P for interaction=0.10). An explorative analysis revealed a strong interaction between vitamin A and season of administration. **CONCLUSIONS: Vitamin A supplementation given with BCG vaccine at birth had no significant benefit in this African setting. Although little doubt exists that vitamin A supplementation reduces mortality in older children, a global recommendation of supplementation for all newborn infants may not contribute to better survival.** **TRIAL REGISTRATION:** Clinical trials NCT00168597.

[Am J Clin Nutr.](#) 2007 Oct;86(4):1032-9.



Effect of vitamin A supplementation with BCG vaccine at birth on vitamin A status at 6 wk and 4 mo of age.

[Fisker AB](#), [Lisse IM](#), [Aaby P](#), [Erhardt JG](#), [Rodrigues A](#), [Bibby BM](#), [Benn CS](#).

Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau. a.fisker@bandim.org

BACKGROUND: The effect of vitamin A supplementation (VAS) at birth on subsequent vitamin A status has not been studied. **OBJECTIVE: The objective was to study the effect of 50,000 IU vitamin A administered with BCG vaccine at birth on vitamin A status in both sexes.** **DESIGN:** Within a randomized placebo-controlled trial of VAS, we obtained blood from 614 children at 6 wk of age and from 369 mother-infant pairs at 4 mo of age. We assessed vitamin A status on the basis of serum retinol-binding protein (RBP) and measured serum C-reactive protein to monitor for concurrent infections. **RESULTS:** RBP concentrations indicated vitamin A deficiency in 32% of the children at age 6 wk and in 16% at age 4 mo. VAS was not associated with higher RBP concentrations overall or in either sex. However, the effect of VAS varied with maternal education (P for interaction = 0.004): At age 6 wk, VAS was associated with higher (9%; 95% CI: 2, 17%) RBP concentrations in children of noneducated mothers but not in children of educated mothers. Overall, RBP concentrations increased between 6 wk and 4 mo of age. The increase correlated inversely with the number of diphtheria-tetanus-pertussis (DTP) vaccines received in the interval (P = 0.009), particularly in girls (P for interaction = 0.01) and in vitamin A recipients (P = 0.01). **CONCLUSIONS: Overall, VAS at birth had no effect on vitamin A status. However VAS may temporarily improve vitamin A status in the**

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subgroup of children of noneducated mothers. In vitamin A recipients, subsequent DTP vaccines affected vitamin A status negatively. The main trial was registered at clinicaltrials.gov as NCT00168597

Comment

There is limited evidence for any benefit of Vitamin A given to neonates. There is more evidence to support maternal supplementation in the post-partum period and encouragement of exclusive breast feeding to increase vitamin A levels in the first 6 months of life. In communicating the results of this study above it will very important to emphasize the value of vitamin A at 6 months of age. Most country programs do not currently give vitamin A for neonates anyway, but give routine supplementation at 6 and 12 months (and some every 6 months up to 5 years). There is very strong evidence of a protective effect against mortality and morbidity when vitamin A is given at 6 and 12 months, and this message should not be lost in discussions of the value of a birth dose of vitamin A.

[J Nutr.](#) 2008 Apr;138(4):787-92.



Maternal night blindness during pregnancy is associated with low birthweight, morbidity, and poor growth in South India.

[Tielsch JM](#), [Rahmathullah L](#), [Katz J](#), [Thulasiraj RD](#), [Coles C](#), [Sheeladevi S](#), [Prakash K](#).

Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA. jtielsch@jhsph.edu

Maternal night blindness is common during pregnancy in many developing countries. Previous studies have demonstrated important consequences of maternal night blindness during pregnancy on the health of the mother and newborn infant. We compared birthweight, 6-mo infant mortality, morbidity, and growth among infants of women who did and did not report a history of night blindness from a community-based, randomized trial of newborn vitamin A supplementation in south India. Birthweight was measured within 72 h of delivery. Infants were followed until 6 mo of age for mortality and morbidity was assessed at household visits every 2 wk. Anthropometry was assessed at 6 mo of age. A total of 12,829 live-born infants were included, 680 of whom were infants of mothers with night blindness during the index pregnancy. Maternal night blindness was associated with an increased risk of low birthweight in a dose-dependent fashion based on birthweight cut-offs: <2500 g, adjusted relative risk (RR) = 1.13 (95% CI = 1.01, 1.26); <2000 g, adjusted RR = 1.70 (95% CI = 1.27, 2.26); <1500 g, adjusted RR = 3.38 (95% CI = 1.18, 6.33); with an increased risk of diarrhea (adjusted RR = 1.16, 95% CI = 1.03, 1.30), dysentery (adjusted RR = 1.25, 95% CI = 1.03, 1.53), acute respiratory illness (adjusted RR = 1.32, 95% CI = 1.21, 1.44), and poor growth at 6 mo; underweight (adjusted RR = 1.14, 95% CI = 1.02, 1.26), stunting (adjusted RR = 1.19, 95% CI = 1.05, 1.34). Maternal night blindness was not associated with 6-mo infant mortality or wasting at 6 mo. This study demonstrates that there are important consequences to the infant of maternal vitamin A deficiency during pregnancy.

[Nutr J.](#) 2008 Jan 31;7:7.



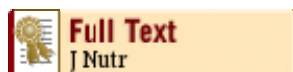
Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomized double blind trial.

[Zeba AN](#), [Sorgho H](#), [Rouamba N](#), [Zongo I](#), [Rouamba J](#), [Guiguemdé RT](#), [Hamer DH](#), [Mokhtar N](#), [Ouedraogo JB](#).

Institut de recherche en sciences de la santé (IRSS), Bobo Dioulasso, Burkina Faso.
nawidzeb@yahoo.fr

BACKGROUND: Vitamin A and zinc are crucial for normal immune function, and may play a synergistic role for reducing the risk of infection including malaria caused by *Plasmodium falciparum*. **METHODS:** A randomized, double-blind, placebo-controlled trial of a single dose of 200 000 IU of vitamin A with daily zinc supplementation was done in children of Sourkoudougou village, Burkina Faso. Children aged from 6 to 72 months were randomized to receive a single dose of 200 000 IU of vitamin A plus 10 mg elemental zinc, six days a week (n = 74) or placebo (n = 74) for a period of six months. Cross-sectional surveys were conducted at the beginning and the end of the study, and children were evaluated daily for fever. Microscopic examination of blood smear was done in the case of fever (temperature ≥ 37.5 degrees C) for malaria parasite detection. **RESULTS:** At the end of the study we observed a significant decrease in the prevalence malaria in the supplemented group (34%) compared to the placebo group (3.5%) ($p < 0.001$). Malaria episodes were lower in the supplemented group ($p = 0.029$), with a 30.2% reduction of malaria cases ($p = 0.025$). Time to first malaria episode was longer in the supplemented group ($p = 0.015$). The supplemented group also had 22% fewer fever episodes than the placebo group ($p = 0.030$). **CONCLUSION:** These results suggest that combined vitamin A plus zinc supplementation reduces the risk of fever and clinical malaria episodes among children, and thus may play a key role in malaria control strategies for children in Africa.

[J Nutr.](#) 2007 Nov;137(11):2470-4.



Newborn vitamin A dosing reduces the case fatality but not incidence of common childhood morbidities in South India.

[Tielsch JM](#), [Rahmathullah L](#), [Thulasiraj RD](#), [Katz J](#), [Coles C](#), [Sheeladevi S](#), [John R](#), [Prakash K](#).

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Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA. jtielsch@jhsph.edu

Vitamin A supplementation reduces mortality in young children in areas of endemic vitamin A deficiency. However, it has no impact on the incidence of common morbidities. This discrepancy has been explained by an impact on case fatality, although with the exception of hospitalized measles cases, there is little direct evidence to support this hypothesis. We assessed the impact of newborn dosing with vitamin A on the incidence and case fatality of common childhood morbidities in early infancy in a community-based, randomized trial in South India. Morbidity for each day in the previous 2 wk was assessed for the first 6 mo of life. A total of 11,619 live-born infants were enrolled and randomized to receive either 48,000 IU (50.4 micromol retinol) of oral vitamin A or placebo following delivery. **There was no difference between treatment groups in the incidence of acute or chronic diarrhea, dysentery, or fever but a small increased incidence of acute respiratory illness (ARI). Case fatality for diarrhea and fever were significantly reduced in the vitamin A group compared with placebo (relative case fatality [95% CI] of 0.50 [0.27, 0.90] and 0.60 [0.40, 0.88], respectively).** There was a trend in reduction of case fatality for various definitions of ARI, but the evidence for this effect was modest. Survival analysis among those with morbid episodes confirmed the case fatality analysis. This trial demonstrated that the reduction in overall mortality due to newborn vitamin A dosing was driven primarily by a reduction in case fatality among infants.

[Am J Clin Nutr.](#) 2007 Oct;86(4):1040-4.



Vitamin A supplementation in iodine-deficient African children decreases thyrotropin stimulation of the thyroid and reduces the goiter rate.

[Zimmermann MB](#), [Jooste PL](#), [Mabapa NS](#), [Schoeman S](#), [Biebinger R](#), [Mushaphi LF](#), [Mbhenyane X](#).

Laboratory for Human Nutrition, Swiss Federal Institute of Technology, Zürich, Switzerland.
michael.zimmermann@ilw.agrl.ethz.ch

BACKGROUND: Vitamin A (VA) deficiency (VAD) and iodine deficiency (ID) often coexist in children in Africa. VAD may affect thyroid function and the response to iodine prophylaxis. **OBJECTIVE:** The aim was to investigate the effects of supplementation with iodine or VA alone, and in combination, in children with concurrent VAD and ID. **DESIGN:** A 6-mo randomized, double-blind, 2 x 2 intervention trial was conducted in 5-14 y-old South African children (n = 404), who, on average, had mild-to-moderate VAD and ID. At baseline and after 3 mo, children received 1) iodine (191 mg I as oral iodized oil) + placebo (IS group), 2) VA (200000 IU VA as retinyl palmitate) + placebo (VAS group), 3) both iodine and VA (IS+VAS group), or 4) placebo. At baseline, 3 mo, and 6 mo, urinary iodine (UI), thyroid volume, thyrotropin (thyroid-stimulating hormone; TSH), total thyroxine (TT(4)), thyroglobulin, serum retinol (SR), and retinol-binding protein (RBP) were measured. **RESULTS:** SR and RBP increased significantly with VA supplementation (P < 0.05). For UI, SR, and RBP, there were no significant treatment interactions between iodine and vitamin A. The 3-factor and all three 2-factor interactions were significant for thyroid volume, TSH, and thyroglobulin (P < 0.001),

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whereas none of these interactions were significant for TT(4). There was a clear effect of VAS without IS on TSH, thyroglobulin, and thyroid volume; all 3 variables decreased significantly ($P < 0.05$). **CONCLUSIONS: Iodine prophylaxis is effective in controlling ID in areas of poor vitamin A status. VA supplements are effective in treating VAD in areas of mild ID and have an additional benefit-through suppression of the pituitary TSHbeta gene, VAS can decrease excess TSH stimulation of the thyroid and thereby reduce the risk of goiter and its sequelae.**

Zinc

(see also: Acute Respiratory Infection, Diarrhoea, Vitamin A)

[Am J Clin Nutr.](#) 2008 Mar;87(3):723-33.



Dose-response trial of prophylactic zinc supplements, with or without copper, in young Ecuadorian children at risk of zinc deficiency.

[Wuehler SE](#), [Sempértegui F](#), [Brown KH](#).

Department of Nutrition, Program in International and Community Nutrition, University of California, Davis, Davis, CA 95616, USA.

BACKGROUND: Multiple studies have shown the benefits of zinc supplementation among young children in high-risk populations. However, the optimal dose and safe upper level of zinc have not been determined. **OBJECTIVES:** The objectives of this study were to measure the effects of different doses of supplemental zinc on the plasma zinc concentration, morbidity, and growth of young children; to detect any adverse effects of 10 mg supplemental Zn on markers of copper or iron status; and to determine whether any adverse effects are alleviated by providing copper with zinc. **DESIGN:** This randomized, double-masked, community-based intervention trial was conducted in 631 Ecuadorian children who were 12-30 mo old at baseline and who had initial length-for-age z scores < -1.3 . Children received 1 of 5 daily supplements for 6 mo: 3, 7, or 10 mg Zn as zinc sulfate, 10 mg Zn + 0.5 mg Cu as copper sulfate, or placebo. **RESULTS:** The change in plasma zinc concentration from baseline was positively related to the zinc dose ($P < 0.001$). Zinc supplementation, including doses as low as 3 mg/d, reduced the incidence of diarrhea by 21-42% ($P < 0.01$). There were no other significant group-wise differences. **CONCLUSIONS:** Zinc supplementation with a dose as low as 3 mg/d increased plasma zinc concentrations and reduced diarrhea incidence in the study population. There were no observed adverse effects of 10 mg Zn/d on indicators of copper or iron status. The current tolerable upper level of zinc recommended by the Institute of Medicine should be reassessed for young children.

[BMJ.](#) 2008 Feb 2;336(7638):266-8. Epub 2008 Jan 8.



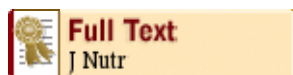
Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial.

[Roy SK](#), [Hossain MJ](#), [Khatun W](#), [Chakraborty B](#), [Chowdhury S](#), [Begum A](#), [Mah-e-Muneer S](#), [Shafique S](#), [Khanam M](#), [Chowdhury R](#).

International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka -1212, Bangladesh. skroy@icddr.org

OBJECTIVE: To investigate the impact of zinc supplementation in children with cholera. **DESIGN:** Double blind, randomised, placebo controlled trial. **SETTING:** Dhaka Hospital, Bangladesh. **PARTICIPANTS:** 179 children aged 3-14 years with watery diarrhoea and stool dark field examination positive for *Vibrio cholerae* and confirmed by stool culture. **INTERVENTION:** Children were randomised to receive 30 mg elemental zinc per day (n=90) or placebo (n=89) until recovery. All children received erythromycin suspension orally in a dose of 12.5 mg/kg every six hours for three days. **MAIN OUTCOME MEASURES:** Duration of diarrhoea and stool output. Results 82 children in each group completed the study. More patients in the zinc group than in the control group recovered by two days (49% v 32%, P=0.032) and by three days (81% v 68%, P=0.03). Zinc supplemented patients had 12% shorter duration of diarrhoea than control patients (64.1 v 72.8 h, P=0.028) and 11% less stool output (1.6 v 1.8 kg/day, P=0.039). **CONCLUSION:** Zinc supplementation significantly reduced the duration of diarrhoea and stool output in children with cholera. Children with cholera should be supplemented with zinc to reduce its duration and severity. **TRIAL REGISTRATION:** Clinical trials NCT00226616.

[J Nutr](#). 2008 Jan;138(1):108-14.



Additional zinc delivered in a liquid supplement, but not in a fortified porridge, increased fat-free mass accrual among young Peruvian children with mild-to-moderate stunting.

[Arsenault JE](#), [López de Romaña D](#), [Penny ME](#), [Van Loan MD](#), [Brown KH](#).

Program in International and Community Nutrition and Department of Nutrition, University of California, Davis, CA 95616, USA.

The exact mechanism whereby zinc influences growth is unknown, although it has been postulated that zinc may stimulate appetite and energy intake or enhance fat-free mass (FFM) accrual directly. We compared energy intake, reported appetite, and body composition of 6- to 8-mo-old Peruvian children with initial length-for-age Z-score (LAZ) < -0.5 SD who were randomly assigned to receive daily for 6 mo: 1) 3 mg/d zinc in a liquid supplement; 2) 3 mg/d zinc in a fortified porridge; or 3) no extra zinc in either the supplement or porridge. There were no group-wise differences in changes in dietary energy intakes or body composition or in the

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prevalence of reported poor appetite. However, among children with an initial LAZ less than the median (-1.1 SD), those who received zinc as a liquid supplement had a 0.41 kg greater increase in FFM than those who did not receive zinc ($P < 0.05$). We concluded that daily provision of 3 mg of supplemental zinc did not affect energy intake or reported appetite. Among children with initial mild-to-moderate stunting, those who received the zinc supplement had a greater increase in FFM than those who did not receive additional zinc. It is possible that the growth-restricted children were more likely to be zinc deficient and that FFM accrual may be an early growth response to supplemental zinc. Zinc supplements may be more efficacious than the same dose of zinc provided in fortified food; therefore, further research is needed on the optimal level of zinc fortification that will result in improved health outcomes in populations with high rates of zinc deficiency

[Am J Clin Nutr.](#) 2007 Oct;86(4):1111-9.



Longitudinal measures of circulating leptin and ghrelin concentrations are associated with the growth of young Peruvian children but are not affected by zinc supplementation.

[Arsenault JE](#), [Havel PJ](#), [López de Romaña D](#), [Penny ME](#), [Van Loan MD](#), [Brown KH](#).

Program in International and Community Nutrition, Department of Nutrition, University of California, Davis, Davis, CA 95616, USA.

BACKGROUND: Leptin, ghrelin, and insulin are hormonal regulators of energy balance and, therefore, may be related to growth during infancy. Zinc is essential for growth, and its growth effects may be mediated through these hormones. **OBJECTIVE:** We examined the effects of supplemental zinc on plasma leptin, ghrelin, and insulin concentrations among young children at risk of zinc deficiency and examined the relations between these hormones and physical growth. **DESIGN:** Children ($n = 142$) aged 6-8 mo were randomly assigned to receive 3 mg Zn/d as a supplement, in a fortified food, or as a placebo for 6 mo. Relations between hormones and anthropometric z scores, body composition, and growth rates were examined at baseline and 3 and 6 mo after the start of the intervention. **RESULTS:** No treatment group-related differences were found in plasma leptin, ghrelin, or glucose concentrations or in anthropometric z scores at 3 or 6 mo after the start of the zinc intervention. Neither plasma leptin nor ghrelin concentrations at baseline or 3 mo were predictive of subsequent changes in growth. However, changes in weight-for-age z scores over the two 3-mo time intervals were positively associated with subsequent leptin concentrations and inversely associated with subsequent plasma ghrelin concentrations. **CONCLUSIONS:** Supplemental zinc did not affect the children's growth, anthropometric indexes, or plasma hormone concentrations in this study population. Our results suggest that plasma leptin and ghrelin concentrations in later infancy are a consequence of previous weight changes rather than predictors of short-term growth.

Randomised trials in child health in developing countries 2007-08

[Lancet](#). 2007 Oct 6;370(9594):1230-9.



Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial.

[Tielsch JM](#), [Khatry SK](#), [Stoltzfus RJ](#), [Katz J](#), [LeClerq SC](#), [Adhikari R](#), [Mullany LC](#), [Black R](#), [Shrestha S](#).

Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205-2013, USA. jtielsch@jhsp.edu

BACKGROUND: Zinc supplementation can reduce subsequent morbidity in children recovering from diarrhoea and respiratory illness in developing countries. However, whether routine supplementation would decrease morbidity and mortality in populations with zinc deficiency is unclear. We assessed the effect of daily zinc supplementation on children in southern Nepal. **METHODS:** We did a community-based, cluster-randomised, double-masked, placebo-controlled, 2x2 factorial trial in children aged 1-35 months. Treatment groups were placebo, iron and folic acid, zinc, and iron and folic acid with zinc, with daily doses of 12.5 mg iron, 50 microg folic acid, and 10 mg zinc. Study staff gave children tablets on 2 days each week and left tablets with caregivers for other days. All children received vitamin A supplementation twice per year. Results of the iron arm of the trial have been reported previously. Between October, 2001, and January, 2006, 41,276 children were enrolled into the placebo (n=20,308) or zinc (n=20,968) groups and were followed-up for 60,636.3 person-years. The primary outcome was child mortality, and analyses were by intention to treat. Daily reports of signs and symptoms of common morbidities in stratified random subsamples of children were assessed every week for 12 months. This study is registered at ClinicalTrials.gov, number NCT00109551. **FINDINGS:** 2505 children refused to continue the trial and 3219 children were lost to follow-up. **There was no significant difference in mortality between the zinc and placebo groups (316 vs 333 deaths; hazard ratio 0.92, 95% CI 0.75-1.12). Zinc had no effect on mortality in children younger than 12 months (181 vs 168 deaths; 1.04, 0.83-1.31); mortality was lower, but not statistically significantly so, in older children receiving zinc (135 vs 165; 0.80, 0.60-1.06). The frequency and duration of diarrhoea, persistent diarrhoea, dysentery, and acute lower respiratory infections did not differ between the groups.** **INTERPRETATION:** Total mortality of children receiving zinc supplementation was not significantly different from that of children receiving placebo. Further data are needed from other populations with endemic zinc deficiency to confirm the potential age-specific effects reported in this study.

[PLoS ONE](#). 2007 Jun 27;2(6):e541.



Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South african children: a randomized controlled trial.

Randomised trials in child health in developing countries 2007-08

[Luabeya KK](#), [Mpontshane N](#), [Mackay M](#), [Ward H](#), [Elson I](#), [Chhagan M](#), [Tomkins A](#), [Van den Broeck J](#), [Bennish ML](#).

Africa Centre for Health and Population Studies, University of KwaZulu Natal, Somkhele, South Africa.

BACKGROUND: Prophylactic zinc supplementation has been shown to reduce diarrhea and respiratory illness in children in many developing countries, but its efficacy in children in Africa is uncertain. **OBJECTIVE:** To determine if zinc, or zinc plus multiple micronutrients, reduces diarrhea and respiratory disease prevalence. **DESIGN:** Randomized, double-blind, controlled trial. **SETTING:** Rural community in South Africa. **PARTICIPANTS:** THREE COHORTS: 32 HIV-infected children; 154 HIV-uninfected children born to HIV-infected mothers; and 187 HIV-uninfected children born to HIV-uninfected mothers. **INTERVENTIONS:** Children received either 1250 IU of vitamin A; vitamin A and 10 mg of zinc; or vitamin A, zinc, vitamins B1, B2, B6, B12, C, D, E, and K and copper, iodine, iron, and niacin starting at 6 months and continuing to 24 months of age. Homes were visited weekly. **OUTCOME MEASURES:** Primary outcome was percentage of days of diarrhea per child by study arm within each of the three cohorts. Secondary outcomes were prevalence of upper respiratory symptoms and percentage of children who ever had pneumonia by maternal report, or confirmed by the field worker. **RESULTS:** Among HIV-uninfected children born to HIV-infected mothers, median percentage of days with diarrhea was 2.3% for 49 children allocated to vitamin A; 2.5% in 47 children allocated to receive vitamin A and zinc; and 2.2% for 46 children allocated to multiple micronutrients ($P = 0.852$). Among HIV-uninfected children born to HIV-uninfected mothers, median percentage of days of diarrhea was 2.4% in 56 children in the vitamin A group; 1.8% in 57 children in the vitamin A and zinc group; and 2.7% in 52 children in the multiple micronutrient group ($P = 0.857$). Only 32 HIV-infected children were enrolled, and there were no differences between treatment arms in the prevalence of diarrhea. **The prevalence of upper respiratory symptoms or incidence of pneumonia did not differ by treatment arms in any of the cohorts.** **CONCLUSION:** When compared with vitamin A alone, supplementation with zinc, or with zinc and multiple micronutrients, did not reduce diarrhea and respiratory morbidity in rural South African children. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00156832.