

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

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## Randomised trials in child health in developing countries 2005-6

### SEARCH STRATEGY

Hayne's strategy, Clinical Queries, Pubmed "narrow" search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR 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. In most developing countries access to information through the Internet remains unsatisfactory, so our aim is to provide this booklet in cheap hard-copy and in a form that can be sent by email.

The method of searching for studies to include uses a search engine that is freely available and widely used in most countries throughout the world: Pubmed. 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. Many RCTs are efficacy trials (a test of whether the specific intervention has a specific effect in a trial circumstance). Unfortunately there are fewer effectiveness trials (whether under more real-life circumstances the intervention has an effect). Even more research is needed on how to turn the results of such trials into policy and into implemented, integrated and sustainable programs. Research on health systems improvement is much more difficult to do than (say) a study of two different drugs, but for most countries it is problems in health systems, not the technical content of paediatric treatment recommendations, that are the barriers to improving child health.

As the world approaches 2015, focus is increasingly on Millennium Development Goal No. 4: a reduction in child mortality by 2/3 of what it was in 1990. Therefore studies showing an impact on mortality are of great importance. This year 4 trials were large enough to measure the impact of an intervention on child mortality (marked with \*\*\*). The interventions included zinc supplementation in Bangladesh; and household treatment of drinking water with flocculant-disinfectant in Kenya. Breast feeding (*either* predominant or exclusive again shown to be protective against mortality in Ghana, India and Peru. Conversely routine iron supplementation, when given to all children in a highly malaria endemic area in Zanzibar was associated with higher rates of hospitalization and mortality. This last study underscores the need for large enough trials to evaluate safety as well as efficacy, in various populations.

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Trevor Duke  
August 2006

## Acute respiratory infection

(See also Public Health / Hygiene)

## Micronutrients and pneumonia

Am J Clin Nutr. 2005 Nov;82(5):1090-6.

### **Effects of moderate doses of vitamin A as an adjunct to the treatment of pneumonia in underweight and normal-weight children: a randomized, double-blind, placebo-controlled trial.**

Rodriguez A, Hamer DH, Rivera J, Acosta M, Salgado G, Gordillo M, Cabezas M, Naranjo-Pinto C, Leguisamo J, Gomez D, Fuenmayor G, Jativa E, Guaman G, Estrella B, Sempertegui F.

**BACKGROUND:** Randomized controlled trials have shown inconsistent responses of childhood pneumonia to the use of vitamin A as an adjunct to the standard treatment of pneumonia. **OBJECTIVE:** We evaluated the effect of a moderate dose of vitamin A as an adjunct to standard antimicrobial treatment on the duration of respiratory signs in children with pneumonia. **DESIGN:** **Children, aged 2-59 mo, with pneumonia and weight-for-age <50th percentile who had been admitted to the Baca Ortiz Children's Hospital in Quito, Ecuador, were randomly assigned to receive 50,000 IU (aged 2-12 mo) or 100,000 IU (aged >12-59 mo) vitamin A or a placebo.** **RESULTS:** Of the 287 children enrolled, 145 received vitamin A and 142 received placebo. **No overall differences were observed between the 2 groups in the duration of signs of pneumonia.** Multiple linear regression showed a significant interaction between basal serum retinol concentration and vitamin A group for the time (in h) to remission of respiratory signs ( $\beta = -3.57$ ,  $SE = 1.09$ ,  $P = 0.001$ ). Duration of clinical signs was less in children with basal serum retinol concentrations  $>200$  microg/L who received vitamin A supplements than in children with similar concentrations who received placebo ( $69.9 \pm 49.9$  h compared with  $131.3 \pm 143.9$  h;  $P = 0.049$ ). **CONCLUSIONS:** Overall, we found **no effect of a moderate dose of vitamin A supplementation on the duration of uncomplicated pneumonia in underweight or normal-weight children aged <5 y.** However, a beneficial effect was seen in children with high basal serum retinol concentrations.

Eur J Clin Nutr. 2006 May;60(5):673-80.

### **Antioxidant vitamins E and C as adjunct therapy of severe acute lower-respiratory infection in infants and young children: a randomized controlled trial.**

**Mahalanabis D, Basak M, Paul D, Gupta S, Shaikh S, Wahed MA, Khaled MA.**

**OBJECTIVE:** To evaluate the effect of antioxidant Vitamins E and C as adjunct therapy of severe acute lower respiratory infection (ALRI) in children. **DESIGN:** Randomized double-blind placebo-controlled clinical trial. **SETTING:** A large children's hospital serving the urban

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poor in Kolkata, India. **SUBJECTS:** Children aged 2-35 months admitted with severe ALRI. **INTERVENTION:** In total, 174 children were randomly assigned to receive alpha-tocopherol 200 mg and ascorbic acid 100 mg twice daily or placebo for 5 days. All children received standard treatment for severe ALRI. Outcome measures were: time taken to recover from a very ill status, fever, tachypnoea, and feeding difficulty; and improvement in oxidative stress and immune response indicated by thiobarbituric acid reacting substances (TBARS) and response to skin antigens, respectively. **RESULTS:** Recovery rate ratios (95% CI) using proportional hazards model were 0.89 (0.64-1.25), 1.01 (0.72-1.41), 0.86 (0.57-1.29), and 1.12 (0.77-1.64) for very ill status, feeding difficulty, fever, and tachypnoea, respectively. TBARS values were high and similar in the two groups at admission, discharge, and at 2 weeks follow-up. Serum alpha-tocopherol significantly increased in treated group at discharge. Immune response to skin antigens were very poor at admission and after 2 weeks, in both groups. **CONCLUSION: Infants with severe ALRI failed to benefit from two antioxidant nutrients as adjunct therapy.** Severe ALRI in infants may cause cell-mediated immune dysfunction. We need a better understanding of oxidative processes in growing infants to help us better design interventions with antioxidant therapy.

Am J Clin Nutr. 2006 May;83(5):1089-96; quiz 1207.

### **Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old.**

**Bose A, Coles CL, Gunavathi, John H, Moses P, Raghupathy P, Kirubakaran C, Black RE, Brooks WA, Santosham M.**

**BACKGROUND:** Severe pneumonia remains a leading cause of morbidity and mortality in undernourished young children in developing countries. **OBJECTIVE:** This study evaluated the effect of adjuvant zinc therapy on recovery from severe pneumonia by hospitalized children in southern India who were receiving standard antibiotic therapy. **DESIGN:** This randomized, double-blind, placebo-controlled clinical trial was conducted at the Christian Medical College Hospital, an 1800-bed teaching hospital in Tamilnadu, India. Enrollment and follow-up occurred between September 2003 and August 2004. **Children aged 2-23 mo (n = 299) who were hospitalized with severe pneumonia were randomly assigned to receive 10-mg tablets of zinc sulfate or placebo twice a day during hospitalization, along with standard therapy for severe pneumonia.** All clinical signs and symptoms of pneumonia were assessed and recorded at 8-h intervals. **RESULTS: There were no clinical or statistically significant differences in the duration of tachypnea, hypoxia, chest indrawing, inability to feed, lethargy, severe illness, or hospitalization. Zinc supplementation was associated with a significantly longer duration of pneumonia in the hot season (P = 0.015).** **CONCLUSIONS: Zinc supplementation had no overall effect on the duration of hospitalization or of clinical signs associated with severe infection in young children hospitalized for severe pneumonia in southern India.** This finding differs from the results of 2 previously reported trials wherein zinc supplementation was associated with a shorter period of recovery from severe pneumonia. Given the conflicting results, further research in representative settings is required to help clarify the role of zinc in the treatment of severe pneumonia.

### **Comment**

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*Previous studies of zinc have shown a clinical benefit in the treatment of pneumonia in Bangladesh, showing a reduction in duration of chest indrawing and hypoxaemia. RCTs this year there don't support the theory that zinc or other micronutrients modify the course of severe pneumonia. Trials, involving a total of 760 children of zinc and vitamins A, E and C, showed no differences in outcome. The role of zinc in adjuvant treatment of pneumonia is potentially important, but awaits further research.*

## Asthma

Allergy. 2006 Feb;61(2):191-7.

### **A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients.**

Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, Chen P, Sheng J, Wu A, Zhong N.

**BACKGROUND:** The purpose of this study was to determine if house dust mite immunotherapy with Alutard SQ is effective in improving symptom control and reducing rescue medication use in Chinese patients with mild to moderate allergic asthma. **METHODS:** This is a double-blind, placebo-controlled study involving 132 asthmatic subjects aged 6-45 years recruited from three different regions of Mainland China. Subjects were given a 52-week course of immunotherapy with Dermatophagoides pteronyssinus extract (Alutard Der p, ALK-Abello, Horsholm, Denmark) or placebo while their dose of inhaled corticosteroids (ICS) was maintained. **RESULTS:** 129 subjects (64 in active group) completed the study. **The symptom scores began to diverge at week 29 with the immunotherapy group showing a significantly lower score until week 48 (P = 0.018). Immunotherapy resulted in a significant decline in symptom (P = 0.002) and medication (P = 0.007) scores during the second half of the treatment period. Both groups showed significant improvement in peak flow rate and bronchial hyperresponsiveness. Serum eosinophil cationic protein (ECP) also decreased in both groups of subjects, but peripheral blood eosinophil count remained unchanged.** Skin test response decreased in actively treated subjects only, but Der p-specific immunoglobulin E (IgE) remained unchanged. Immunotherapy resulted in a significantly greater improvement in self-evaluation scores (P < 0.01). **CONCLUSIONS:** One year treatment with Alutard SQ house dust mite immunotherapy significantly reduced symptoms and medication use in asthmatic subjects. This was associated with a greater subjective improvement in asthma control.

J Nurs Res. 2005 Sep;13(3):174-83.

### **Effects of nursing instruction on asthma knowledge and quality of life in schoolchildren with asthma.**

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Yang BH, Chen YC, Chiang BL, Chang YC.

The issue of whether nursing instruction efforts could improve asthma knowledge and quality of life among schoolchildren was investigated using a quasi-experimental design. The key instruments were the Asthmatic Knowledge Questionnaire and the Childhood Asthma Questionnaire-Form B. Asthmatic knowledge increased among children who received instruction from nurses (Meanpre/post=22.20/31.87,  $p<.05$ ). These children also experienced significant improvements in their active quality of life (Meanpre/post=27.53/30.20,  $p<.05$ ), and decreased distress (Meanpre/post=24.04/10.86,  $p<.05$ ) and asthma severity (Meanpre/post=13.27/8.3,  $p<.05$ ). This study finds nursing instruction helpful in improving asthma knowledge. However, in terms of quality of life, elevated knowledge has a marked (negative) correlation only with levels of distress and severity. It shows no detectable relationship with active or passive life quality. Therefore, though nursing instruction can improve schoolchildren's knowledge about asthma, the improvement in knowledge only relates to reducing distress and severity and thus improving quality of life. This result can provide guidance for nursing personnel in developing nursing instruction to improve active quality of life in child patients.

## Diarrhoeal disease

(See also Public Health / Hygiene)

## Water purification

Am J Trop Med Hyg. 2005 Nov;73(5):926-33.

### Effect of home-based water chlorination and safe storage on diarrhea among persons with human immunodeficiency virus in Uganda.

Lule JR, Mermin J, Ekwaru JP, Malamba S, Downing R, Ransom R, Nakanjako D, Wafula W, Hughes P, Bunnell R, Kaharuza F, Coutinho A, Kigozi A, Quick R.

Diarrhea is frequent among persons infected with human immunodeficiency virus (HIV) but few interventions are available for people in Africa. We conducted a randomized controlled trial of a home-based, safe water intervention on the incidence and severity of diarrhea among persons with HIV living in rural Uganda. Between April 2001 and November 2002, households of **509 persons with HIV and 1,521 HIV-negative household members received a closed-mouth plastic container, a dilute chlorine solution, and hygiene education (safe water system [SWS]) or simply hygiene education alone.** After five months, HIV-positive participants received daily cotrimoxazole prophylaxis (160 mg of trimethoprim and 800 mg of sulfamethoxazole) and were followed for an additional 1.5 years. **Persons with HIV using SWS had 25% fewer diarrhea episodes (adjusted incidence rate ratio [IRR] = 0.75, 95% confidence interval [CI] = 0.59-0.94,  $P = 0.015$ ), 33% fewer days with diarrhea (IRR = 0.67, 95% CI = 0.48-0.94,  $P = 0.021$ ), and less visible blood or mucus in stools (28% versus 39%;  $P < 0.0001$ ).** The SWS was equally effective with or without cotrimoxazole prophylaxis ( $P = 0.73$  for interaction), and together they reduced diarrhea episodes by 67% (IRR = 0.33, 95% CI = 0.24-0.46,  $P < 0.0001$ ), days with diarrhea by 54% (IRR = 0.46, 95% CI = 0.32-0.66,  $P < 0.0001$ ), and days of work or school lost due to diarrhea by 47% (IRR = 0.53, 95% CI =

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0.34-0.83,  $P < 0.0056$ ). **A home-based safe water system reduced diarrhea frequency and severity among persons with HIV living in Africa and large scale implementation should be considered.**

\*\*\* BMJ. 2005 Sep 3;331(7515):478. Epub 2005 Jul 26.

### **Household based treatment of drinking water with flocculant-disinfectant for preventing diarrhoea in areas with turbid source water in rural western Kenya: cluster randomised controlled trial.**

**Crump JA, Otieno PO, Slutsker L, Keswick BH, Rosen DH, Hoekstra RM, Vulule JM, Luby SP.**

**OBJECTIVE:** To compare the effect on prevalence of diarrhoea and mortality of household based treatment of drinking water with flocculant-disinfectant, sodium hypochlorite, and standard practices in areas with turbid water source in Africa. **DESIGN:** Cluster randomised controlled trial over 20 weeks. **SETTING:** Family compounds, each containing several houses, in rural western Kenya. **PARTICIPANTS: 6650 people in 605 family compounds.**

**INTERVENTION:** Water treatment: flocculant-disinfectant, sodium hypochlorite, and usual practice (control). **MAIN OUTCOME MEASURES:** Prevalence of diarrhoea and all cause mortality. Escherichia coli concentration, free residual chlorine concentration, and turbidity in household drinking water as surrogates for effectiveness of water treatment. **RESULTS: In children < 2 years old, compared with those in the control compounds, the absolute difference in prevalence of diarrhoea was -25% in the flocculant-disinfectant arm (95% confidence interval -40 to -5) and -17% in the sodium hypochlorite arm (-34 to 4).** In all age groups compared with control, the absolute difference in prevalence was -19% in the flocculant-disinfectant arm (-34 to -2) and -26% in the sodium hypochlorite arm (-39 to -9).

**There were significantly fewer deaths in the intervention compounds than in the control compounds (relative risk of death 0.58,  $P = 0.036$ ).** Fourteen per cent of water samples from control compounds had E coli concentrations < 1 CFU/100 ml compared with 82% in flocculant-disinfectant and 78% in sodium hypochlorite compounds. The mean turbidity of drinking water was 8 nephelometric turbidity units (NTU) in flocculant-disinfectant households, compared with 55 NTU in the two other compounds ( $P < 0.001$ ).

**CONCLUSIONS: In areas of turbid water, flocculant-disinfectant was associated with a significant reduction in diarrhoea among children < 2 years.** This health benefit, combined with a significant reduction in turbidity, suggests that the flocculant-disinfectant is well suited to areas with highly contaminated and turbid water.

Trop Med Int Health. 2006 Apr;11(4):479-89.

### **Combining drinking water treatment and hand washing for diarrhoea prevention, a cluster randomised controlled trial.**



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Luby SP, Agboatwalla M, Painter J, Altaf A, Billhimer W, Keswick B, Hoekstra RM.

**OBJECTIVES:** To evaluate the effectiveness of point of use water treatment with flocculent-disinfectant on reducing diarrhoea and the additional benefit of promoting hand washing with soap. **METHODS:** The study was conducted in squatter settlements of Karachi, Pakistan, where diarrhoea is a leading cause of childhood death. Interventions were randomly assigned to 47 neighbourhoods. **Households in 10 neighbourhoods received diluted bleach and a water vessel; nine neighbourhoods received soap and were encouraged to wash hands; nine neighbourhoods received flocculent-disinfectant water treatment and a water vessel; 10 neighbourhoods received disinfectant-disinfectant water treatment and soap and were encouraged to wash hands; and nine neighbourhoods were followed as controls.** Field workers visited households at least once a week from April to December 2003 to promote use of the interventions and to collect data on diarrhoea. **RESULTS:** Study participants in control neighbourhoods had diarrhoea on 5.2% of days. Compared to controls, participants living in intervention neighbourhoods had a lower prevalence of diarrhoea: 55% (95% CI 17%, 80%) lower in bleach and water vessel neighbourhoods, 51% (95% CI 12%, 76%) lower in hand washing promotion with soap neighbourhoods, 64% lower (95% CI 29%, 90%) in disinfectant-disinfectant neighbourhoods, and 55% (95% CI 18%, 80%) lower in disinfectant-disinfectant plus hand washing with soap neighbourhoods. **CONCLUSIONS: With an intense community-based intervention and supplies provided free of cost, each of the home-based interventions significantly reduced diarrhoea.** There was no benefit by combining hand washing promotion with water treatment.

## Lactobacillus

Am J Clin Nutr. 2005 Nov;82(5):1040-5.

### Effect of Lactobacillus GG on intestinal integrity in Malawian children at risk of tropical enteropathy.

Galpin L, Manary MJ, Fleming K, Ou CN, Ashorn P, Shulman RJ.

**BACKGROUND:** Tropical enteropathy is an asymptomatic villous atrophy of the small bowel that is prevalent in the developing world and is associated with altered intestinal function and integrity. The histology of tropical enteropathy resembles that seen in small-bowel bacterial overgrowth. **OBJECTIVE:** This study tested the hypothesis that treatment of 3-5-y-old Malawian children with the probiotic Lactobacillus GG would improve their intestinal function and integrity. **DESIGN: Clinically healthy children (n = 164) were enrolled in a placebo-controlled, randomized, double-blind trial.** Intestinal function and integrity were measured by using the site-specific sugar-absorption test before and after 30 d of treatment with Lactobacillus GG or placebo. The primary outcomes were the ratios of urinary lactulose to mannitol (L:M) and of urinary sucrose to lactulose (S:L) excretion. **RESULTS: Of the 161 children who completed the study, 119 (73%) had tropical enteropathy on enrollment (L:M > 0.10).** Children receiving Lactobacillus GG did not differ significantly from the placebo group in the excretion (in % of dose administered) of mannitol (mean +/- SD: 8.9 +/- 4.4 and 8.9 +/- 3.9, respectively), lactulose (0.31 +/- 0.20 and 0.33 +/- 0.23, respectively), or sucrose (0.078 +/- 0.058 and 0.082 +/- 0.075, respectively). L:M and S:L also did not differ

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significantly between the Lactobacillus and placebo groups (0.19 +/- 0.13 and 0.20 +/- 0.12, respectively, for L:M; 0.58 +/- 0.46 and 0.65 +/- 0.57, respectively, for S:L). **CONCLUSION: Administration of Lactobacillus GG for 30 d had no effect on the intestinal integrity of 3-5-y-old Malawian children.**

Pediatrics. 2005 Aug;116(2):e221-8. Epub 2005 Jul 1.

## **Lactobacillus paracasei strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh.**

**Sarker SA, Sultana S, Fuchs GJ, Alam NH, Azim T, Brussow H, Hammarstrom L.**

**BACKGROUND:** Previous studies have shown that selected strains of lactobacilli that are administered orally result in a modest reduction of diarrhea duration. However, duration alone is not considered optimal for therapeutic evaluation of any agent in diarrhea. **OBJECTIVE:** To examine the effect of a new probiotic, Lactobacillus paracasei strain ST11 (ST11), in acute childhood diarrhea by using evaluation criteria recommended by the World Health Organization. **METHODS:** **In a randomized, double-blind, placebo-controlled clinical trial, 230 male infants and young children, 4 to 24 months of age, presenting with diarrhea of <2 days' duration** were admitted to the metabolic research ward of the International Centre for Diarrheal Disease Research, Bangladesh, and fed 10(10) colony-forming units of lyophilized ST11 or placebo daily for 5 days. Stool output and frequency, oral rehydration solution intake, and excretion of rotavirus were monitored daily. **RESULTS:** **No effect of ST11 treatment on severe rotavirus diarrhea was observed. However, the probiotic treatment did significantly reduce cumulative stool output (225 +/- 218 vs 381 +/- 240 mL/kg), stool frequency (27.9 +/- 17 vs 42.5 +/- 26), and oral rehydration solution intake (180 +/- 207 vs 331 +/- 236 mL/kg) in children with less-severe nonrotavirus diarrhea compared with those receiving placebo treatment. A significantly higher proportion of nonrotavirus children receiving ST11 had their diarrhea resolve within 6 days of therapy (ST11 versus placebo: 76% vs 49%).** **CONCLUSIONS:** **ST11 has a clinically significant benefit in the management of children with nonrotavirus-induced diarrhea, but it is ineffective in those with rotavirus diarrhea.**

## **Ear disease**

Int J Pediatr Otorhinolaryngol. 2005 Sep;69(9):1225-33.

## **Amoxicillin-sulbactam versus amoxicillin-clavulanic acid for the treatment of non-recurrent-acute otitis media in Argentinean children.**

**Casellas JM Jr, Israele V, Marin M, Ishida MT, Heguilen R, Soutric J, Arenoso H, Sibbald A, Stamboulian D.**

Streptococcus pneumoniae (Sp) and Haemophilus influenzae (Hi) are the leading bacterial

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cause of acute otitis media (AOM), having the nasopharynx (NP) as their reservoir. In October 2001 we began a prospective, multicenter, randomized, evaluator blind study, comparing the efficacy of amoxicillin-sulbactam (Ax/S) and amoxicillin-clavulanic acid (Ax/C) for the treatment of non-recurrent AOM (nr-AOM). Both antimicrobial susceptibility (AS) to Ax/S and Ax/C from Sp and Hi carried by study children (aged 6-48 months with nr-AOM) and, clinical outcome after treatment with high dose of either Ax/C (7:1) or Ax/S (4:1) (amoxicillin dose: 80 mg/(kg day), b.i.d. for 10 days) were assessed. Nasal cultures (NCs) were taken at Day 0. Follow-up NCs, were done only for Sp carriers. **On final analysis 247/289 pts (85.5%) were fully evaluable (120 Ax/S and 127 Ax/C).** NP carriage rate of Hi and Sp at Day 0 was 32.2% (93/289 pts) and 28.7% (83/289 pts), respectively. Persistent Sp carriage was detected only in 2 pts. Hi betalactamase positive rate was 13% (12/93). MICs for Ax/S and Ax/C were identical when tested against Sp and Hi isolates (range  $\leq$  0.016-1.0 and  $\leq$  0.016-0.25 mg/L, respectively). **Clinical efficacy at Days 12-14 and 28-42 were 98.3% (115/117) and 94.2% (97/103) for Ax/S; and 98.3% (115/117) and 95.1% (98/103) for Ax/C, respectively (pNS).** We conclude, that Sp and Hi isolated from NCs of nr-AOM pts were highly sensitive to both drugs and correlated with high clinical efficacy rate.

## Epilepsy

Lancet. 2006 May 13;367(9522):1591-7.

### **Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial.**

Ahmad S, Ellis JC, Kamwendo H, Molyneux E.

**BACKGROUND:** In sub-Saharan Africa, rectal diazepam or intramuscular paraldehyde are commonly used as first-line anticonvulsant agents in the emergency treatment of seizures in children. These treatments can be expensive and sometimes toxic. We aimed to assess a drug and delivery system that is potentially more effective, safer, and easier to administer than those presently in use. **METHODS:** We did an open randomised trial in a paediatric emergency department of a tertiary hospital in Malawi. **160 children aged over 2 months with seizures persisting for more than 5 min were randomly assigned to receive either intranasal lorazepam (100 microg/kg, n=80) or intramuscular paraldehyde (0.2 mL/kg, n=80). The primary outcome measure was whether the presenting seizure stopped with one dose of assigned anticonvulsant agent within 10 min of administration.** The primary analysis was by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00116064. **FINDINGS: Intranasal lorazepam stopped convulsions within 10 min in 60 (75%) episodes treated (absolute risk 0.75, 95% CI 0.64-0.84), and intramuscular paraldehyde in 49 (61.3%; absolute risk 0.61, 95% CI 0.49-0.72).** No clinically important cardiorespiratory events were seen in either group (95% binomial exact CI 0-4.5%), and all children finished the trial. **INTERPRETATION:** Intranasal lorazepam is effective, safe, and provides a less invasive alternative to intramuscular paraldehyde in children with protracted

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convulsions. The ease of use of this drug makes it an attractive and preferable prehospital treatment option.

## Ethics and controlled trials

Bull World Health Organ. 2005 Jul;83(7):511-7.

### International collaboration, funding and association with burden of disease in randomized controlled trials in Africa.

Swingler GH, Pillay V, Pienaar ED, Ioannidis JP.

**OBJECTIVE:** This study aimed to assess whether randomized controlled trials conducted in Africa with collaborators from outside Africa were more closely associated with health conditions that have a burden of disease that is of specific importance to Africa than with conditions of more general global importance or with conditions important to developed countries. We also assessed whether the source of funding influenced a study's relevance to Africa. **METHODS:** We compared randomized controlled trials performed in Africa that looked at diseases specifically relevant to Africa (as determined by burden of disease criteria) with trials classified as looking at diseases of global importance or diseases important to developed countries in order to assess differences in collaboration and funding. **FINDINGS:** **Of 520 trials assessed, 347 studied diseases that are specifically important to Africa; 99 studied globally important diseases and 74 studied diseases that are important to developed countries. The strongest independent predictor of whether a study was of specifically African or global importance was the corresponding author's country of origin: African importance was negatively associated with a corresponding author being from South Africa (odds ratio (OR) = 0.04; 95% confidence interval (CI) = 0.02-0.10) but there was little difference between corresponding authors from other African countries and corresponding authors from countries outside Africa.** The importance of a study to Africa was independently associated with having more non-African authors (OR per author = 1.31; 95% CI = 1.08-1.58), fewer trial sites (OR per site = 0.69; 95% CI = 0.50-0.96), and reporting of funding (OR = 2.14; 95% CI = 1.15-4.00). Similar patterns were present in the comparisons of trials studying diseases important to Africa versus those studying diseases important to developed countries with stronger associations overall. **When funding was reported, private industry funding was negatively associated with African importance compared with global importance (OR = 0.31, P= 0.008 for African importance and OR = 0.51, P= 0.57 for importance for developed countries).** **CONCLUSION:** The relevance to Africa of trials conducted in Africa was not adversely affected by collaboration with non-African researchers but **funding from private industry was associated with a decreased emphasis on diseases relevant to Africa.**

Am J Public Health. 2005 Jul;95(7):1184-9. Epub 2005 Jun 2.

### Quality of parental consent in a Ugandan malaria study.

**Pace C, Talisuna A, Wendler D, Maiso F, Wabwire-Mangen F, Bakyaite N, Okiria E, Garrett-Mayer ES, Emanuel E, Grady C.**

**OBJECTIVES:** We surveyed Ugandan parents who enrolled their children in a randomized pediatric malaria treatment trial to evaluate the parents' levels of understanding about the treatment trial and the quality of the parents' consents to allow their children to participate in the study. **METHODS:** We conducted 347 interviews immediately following enrollment at 4 Ugandan sites. **RESULTS:** A majority (78%) of the parents, most of whom were mothers (86%) had at most a primary school education. Of the participating mothers, a substantial percentage reported that they remembered being told about the study's purpose (77%), the required number of visits (88%), the risks involved (61%), treatment allocation (84%), and their ability to discontinue their children's participation (64%). In addition, most reported knowing the trial's purpose (80%) and the required number of visits (78%); however, only 18% could name possible side effects from the drugs being administered, and only 19% knew that children would not all be administered identical treatments. Ninety-four percent reported that they made the enrollment decision themselves, but 58% said they felt pressure to participate because of their child's illness, and 15% said they felt some type of pressure to participate from others; 41% reported knowing that they did not have to participate. **CONCLUSIONS:** The consent Ugandan parents provided to allow their children to participate in the malaria study was of mixed quality. Parents understood many of the study details, but they were not very aware of the risks involved or of randomization. Many parents felt that they could not have refused to participate because their child was sick and they either did not know or did not believe that their child would receive treatment outside of the study. Our results indicate that further debate is needed about informed consent in treatment studies of emergent illnesses in children.

#### **Comment**

*Although not an RCT, this study has great relevance to all the other trials in this booklet. Parents of sick children are a highly vulnerable group, and many will not fully comprehend the complexities of controlled trials, or their rights to participate or to decline participation. These issues must be taken into account by researchers and ethics committees, so that this vulnerability is not taken advantage of. Every effort should be made to inform parents of the nature of research projects, in local languages and ways they will comprehend. It is perhaps an anomaly of many trials that an ethics committee will review the protocol (including participant information) prior to a study beginning, a DSMB will review safety throughout the trial, but there is rarely an ongoing mechanism for ensuring that participant autonomy is protected during a trial.*

## Helminth infections

Acta Trop. 2005 Nov-Dec;96(2-3):248-54. Epub 2005 Oct 3.

## **School-based interventions to enhance knowledge and improve case management of schistosomiasis: a case study from Hunan, China.**

Yuan LP, Manderson L, Ren MY, Li GP, Yu DB, Fang JC.

This paper discusses an intersectoral health-related intervention, using cartoons and video-recording, print materials and face-to-face educational methods, to increase children's knowledge of schistosomiasis, which in turn might improve the case management of early diagnosis and treatment. The main components of the project were (i) the collaboration between the departments of public health and education and (ii) a randomized, controlled, school-based field trial conducted in the Dongting Lake region, China. **Children in the experimental group (n=604) and their parents participated in the educational programme. Control children (n=527) received a 2 hour lecture about the disease. All participants were pre-tested, and retested five months after the conduct of the educational intervention.** The results show significant changes among children and their parents in the experimental group related to knowledge about schistosomiasis and beliefs towards screening and treatment of the disease. **Children in the experimental group also had better compliance than children in the control group for regular screening for schistosomiasis.** These findings indicate that carefully designed education programmes are useful for providing both children and their families with information about the prevention and treatment of schistosomiasis. Intersectoral collaboration holds promise to deliver research-based interventions for enhanced knowledge of schistosomiasis and improved case management.

## **HIV / AIDS**

J Infect Dis. 2006 Jan 1;193(1):9-15. Epub 2005 Nov 18.

### **Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study.**

Kamya MR, Gasasira AF, Yeka A, Bakyaite N, Nsoby SL, Francis D, Rosenthal PJ, Dorsey G, Havlir D.

**BACKGROUND:** Human immunodeficiency virus (HIV) infection may increase the burden of malaria by increasing susceptibility to infection or by decreasing the response to antimalarial treatment. We investigated the seroprevalence rate of HIV-1 infection and its effect on antimalarial treatment outcomes in adults and children with uncomplicated falciparum malaria in Uganda. **METHODS:** This retrospective study included 1965 patients  $\geq 18$  months old who were randomized to receive 1 of 3 antimalarial regimens at 7 sites in Uganda. HIV-1 testing was performed using 2 enzyme-linked immunosorbent assays and Western blot analysis of stored blood spots. The primary study outcome was clinical treatment failure at 28 days after antimalarial treatment. Molecular genotyping was used to distinguish clinical treatment failures due to new infections from those due to recrudescences. **RESULTS:** The HIV-1 seroprevalence rate was 2.5% in 1802 patients  $< 18$  years old and **31% in 163 patients  $\geq 18$  years old presenting with malaria.** HIV-1 infection was associated with a  $>3$ -fold (hazard ratio [HR], 3.28 [95% confidence interval [CI], 1.25-8.59]) increased risk of clinical treatment failure for

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adults, but there was no increased risk for HIV-1-infected children. Molecular genotyping revealed that clinical treatment failures were due to new infections (HR, 6.35 [95% CI, 1.64-24.5]) rather than to recrudescences (HR, 1.51 [95% CI, 0.27-8.58]). **CONCLUSIONS: The HIV-1 seroprevalence rate was surprisingly high in adults presenting with malaria.** This finding supports the implementation of routine HIV counseling and testing for adults with uncomplicated falciparum malaria. HIV-1 infection increased the susceptibility to new malarial infections but did not increase the risk of recrudescences in adults.

Health Educ Res. 2005 Nov 22; [Epub ahead of print]

## **AIDS education for Tanzanian youth: a mediation analysis.**

**Stigler MH, Kugler KC, Komro KA, Leshabari MT, Klepp KI.**

Mediation analysis is a statistical technique that can be used to identify mechanisms by which intervention programs achieve their effects. This paper presents the results of a mediation analysis of Ngao, an acquired immunodeficiency syndrome (AIDS) education program that was implemented with school children in Grades 6 and 7 in Tanzania in the mid-1990s and evaluated using a controlled, group-randomized trial. The study examined which variables mediated the effect Ngao had in regard to (i) fostering positive attitudes towards people living with AIDS and (ii) decreasing intentions to be sexually active in the near future. Data from students who participated in a baseline and 12-month follow-up survey (n = 814) were analyzed. **Results indicate that increasing exposure to AIDS information and increasing knowledge about human immunodeficiency virus transmission/prevention were significant mediators of the intervention's effect on alleviating the stigma associated with people living with AIDS.** Moreover, encouraging more restrictive social norms about sexual intercourse was a significant mediator of the intervention's effect on decreasing students' intentions to be sexually active in the near future. Implications for future AIDS education programs for school children in this part of Africa designed to achieve similar goals are discussed.

J Infect Dis. 2005 Sep 1;192(5):713-9. Epub 2005 Jul 27.

## **Highly active antiretroviral therapy started during pregnancy or postpartum suppresses HIV-1 RNA, but not DNA, in breast milk.**

**Shapiro RL, Ndung'u T, Lockman S, Smeaton LM, Thior I, Wester C, Stevens L, Sebetso G, Gaseitsiwe S, Peter T, Essex M.**

**BACKGROUND: The ability of highly active antiretroviral therapy (HAART) to reduce human immunodeficiency virus type 1 (HIV-1) RNA and DNA in breast milk has not been described.** **METHODS:** We compared breast-milk HIV-1 RNA and DNA loads of women in Botswana who received HAART (nevirapine, lamivudine, and zidovudine) and women who did not receive HAART. **RESULTS:** Women in the HAART group received treatment for a median of 98 days (range, 67-222 days) at the time of breast-milk sampling; **23**

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**(88%) of 26 had whole breast-milk HIV-1 RNA loads <50 copies/mL, compared with 9 (36%) of 25 women who did not receive HAART (P=.0001).** This finding remained significant in a multivariate logistic-regression model (P = .0006). The whole-milk HIV-1 DNA load was unaffected by HAART. Of women who received HAART, 13 (50%) of 26 had HIV-1 DNA loads <10 copies/10(6) cells, compared with 15 (65%) of 23 who did not receive HAART (P = .39). **CONCLUSIONS: HAART suppressed cell-free HIV-1 RNA in breast milk and may therefore reduce mother-to-child transmission (MTCT) of HIV-1 via breast-feeding. However, HAART initiated during pregnancy or early after delivery had no apparent effect on cell-associated HIV-1 DNA loads in breast milk.** Clinical trials to determine MTCT among breast-feeding women receiving HAART are needed.

## Prevention of mother to child transmission

AIDS. 2005 Aug 12;19(12):1289-97.

### **A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers.**

**Gray GE, Urban M, Chersich MF, Bolton C, van Niekerk R, Violari A, Stevens W, McIntyre JA; for the PEP Study Group.**

**BACKGROUND:** Single-dose nevirapine (NVP) prophylaxis to mother and infant is widely used in resource-constrained settings for preventing mother-to-child transmission (MTCT) of HIV-1. Where women do not access antenatal care or HIV testing, postexposure prophylaxis to the infant may be an important preventative strategy. **METHODS:** This multicentre, randomized, open-label clinical trial (October 2000 to September 2002) in South Africa compared **single-dose NVP with 6 weeks of zidovudine (ZDV), commenced within 24 h of delivery among 1051 infants whose mothers had no prior antiretroviral therapy.** HIV-1 infection rates were ascertained at birth, and at 6 and 12 weeks of age. Kaplan-Meier survival methods were used to estimate HIV-1 infection rates in an intention-to-treat analysis. **RESULTS: Overall, 6 week and 12 week MTCT probability was 12.8% [95% confidence interval (CI),10.5-15.0] and 16.3% (95% CI,13.4-19.2), respectively. At 12 weeks, among infants who were not infected at birth, 24 (7.9%) infections occurred in the NVP arm and 41 (13.1%) in the ZDV arm (log rank P = 0.06).** Using multivariate analysis, factors associated with infection following birth were ZDV use [odds ratio (OR), 1.8; 95% CI,1.1-3.2; P = 0.032], maternal CD4 cell count < 500 x 10(6) cells/l (OR, 2.5; 95% CI,1.3-5.0; P = 0.007), maternal viral load > 50 000 copies/ml (OR, 3.6; 95% CI,2.0-6.2; P < 0.0001) and breastfeeding (OR, 2.2; 95% CI,1.3-3.8; P = 0.006). **CONCLUSION: A single-dose of NVP given to infants offers protection against HIV-1 infection and should be a strategy used in infants of mothers with untreated HIV infection.**

Pediatr Infect Dis J. 2006 Apr;25(4):325-32.



**Growth of human immunodeficiency virus-uninfected children exposed to perinatal zidovudine for the prevention of mother-to-child human immunodeficiency virus transmission.**

**Briand N, Le Coeur S, Traisathit P, Karnchanamayul V, Hansudewechakul R, Ngampiyasakul C, Bhakeecheep S, Ithisukanan J, Hongsiwon S, McIntosh K, Lallemand M.**

BACKGROUND: Perinatal human immunodeficiency virus (HIV) prevention programs have been implemented in several countries, and many children have been or will be exposed to antiretrovirals in utero and during their first weeks of life. Although reducing substantially the number of infected children, the potential adverse consequences of these treatments on the health of HIV-uninfected children need to be assessed. OBJECTIVE: To investigate the impact of in utero and postnatal zidovudine exposure on the growth of HIV-uninfected children born to HIV-infected women. METHODS: We used data prospectively collected in 1408 live born children participating in a clinical trial **comparing zidovudine regimens of different durations to prevent perinatal transmission in Thailand (PHPT-1)**. We used a linear mixed model to analyze the anthropometric measurements (weight for age, height for age and weight for height Z-scores) until 18 months of age according to zidovudine treatment duration (mothers, <7.5 weeks versus more; infants, 3 days versus >4 weeks). RESULTS: **Children exposed in utero for >7.5 weeks had a slightly lower birth weight (Z-score difference, 0.08; P = 0.003). However, zidovudine exposure had no effect on the evolution of Z-scores from 6 weeks to 18 months of age.** CONCLUSIONS: Although a longer in utero zidovudine exposure may have had a negative impact on birth weight, the magnitude of this effect was small and faded over time. Neither the total nor the postnatal duration of exposure was associated with changes in infant Z-scores from 6 weeks to 18 months of age.

AIDS. 2006 Jun 12;20(9):1313-1321.

**A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission.**

**Taha TE, Brown ER, Hoffman IF, Fawzi W, Read JS, Sinkala M, Martinson FE, Kafulafula G, Msamanga G, Emel L, Adeniyi-Jones S, Goldenberg R; the HPTN 024 Team.**

OBJECTIVE:: A multisite study was conducted in Africa to assess the efficacy of antibiotics to reduce mother-to-child transmission (MTCT) of HIV-1. DESIGN:: A randomized, double-blinded, placebo-controlled, phase III clinical trial. METHODS:: **HIV-1-infected women were randomly assigned at 20-24 weeks' gestation to receive either antibiotics (metronidazole plus erythromycin antenatally and metronidazole plus ampicillin intrapartum) or placebo.** Maternal study procedures were performed at 20-24, 26-30, and 36 weeks antenatally, and at labor/delivery. Infants were seen at birth, 4-6 weeks, and 3, 6, 9 and 12 months. The primary efficacy endpoints were overall infant HIV-1 infection and HIV-1-free survival at 4-6 weeks. All women and infants received single-dose nevirapine prophylaxis in this study. RESULTS:: A total of 1510 live-born infants were included in the primary analysis. **The proportions of HIV-1-infected infants at birth were similar (antibiotics 7.1%; placebo**

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**8.3%; P = 0.41**). Likewise, there were no statistically significant differences at 4-6 weeks in the overall risk of MTCT of HIV-1 (antibiotics 16.2%; placebo 15.8%; P = 0.89) or HIV-1-free survival (79.4% in each study arm). Post-randomization, the proportion of women with bacterial vaginosis at the second antenatal visit was significantly lower in the antibiotics arm compared with the placebo arm (23.8 versus 39.7%; P < 0.001), **but the frequency of histological chorioamnionitis was not different (antibiotics 36.9%; placebo 39.7%; P = 0.30)**. Adverse events in mothers and their infants did not differ by randomization arm.  
**CONCLUSION:: This simple antepartum and peripartum antibiotic regimen did not reduce the risk of MTCT of HIV-1.**

## **Nutrition and development in children with HIV**

J Trop Pediatr. 2006 Feb;52(1):34-8. Epub 2005 Jul 13.

### **Features of whey protein concentrate supplementation in children with rapidly progressive HIV infection.**

**Moreno YF, Sgarbieri VC, da Silva MN, Toro AA, Vilela MM.**

HIV infection is associated with subnormal GSH levels. An increase in glutathione levels has been observed in HIV-infected adults under oral whey protein supplementation. We studied the features associated with a whey protein concentrate supplementation in children with rapidly progressive AIDS. A prospective double-blind clinical trial was carried out for 4 months with 18 vertically HIV-infected children (1.98-6.37 years), under antiretroviral therapy, who had received whey protein, maltodextrin (placebo) or none. Erythrocyte glutathione concentration, T lymphocyte counts (CD4+ and CD8+) and occurrence of associated co-infections were evaluated. Wilcoxon's and Fischer's Exact tests were used to assess differences between whey protein-supplemented and control (placebo and non-supplemented) groups. A significant median increase of 16.14 mg/dl (p = 0.018) in erythrocyte glutathione levels was observed in the whey protein-supplemented group; the TCD4/CD8 lymphocyte ratio showed a non significant increase and lower occurrence of associated co-infections was also observed. In conclusion, whey protein concentrate supplementation can stimulate glutathione synthesis and, possibly, decrease the occurrence of associated co-infections.

Pediatrics. 2006 Feb;117(2):e216-25.

### **Effect of maternal multivitamin supplementation on the mental and psychomotor development of children who are born to HIV-1-infected mothers in Tanzania.**

**McGrath N, Bellinger D, Robins J, Msamanga GI, Tronick E, Fawzi WW.**

**OBJECTIVES:** To determine the association between maternal multivitamin supplementation and the mental and psychomotor development of children who are born to HIV-1-infected mothers in Tanzania, as secondary endpoints in a randomized trial that investigated the effect

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of maternal multivitamin supplementation on HIV-1 vertical transmission and progression. METHODS: The Bayley Scales of Infant Development, 2nd Edition, were administered at 6, 12, and 18 months of age to a subset of children (N = 327). We assessed the effect of vitamin A and multivitamin (vitamins B, C, and E) supplementation using linear regression models and Cox proportional hazard models for the Mental Development Index, the Psychomotor Development Index, and raw scores separately. RESULTS: Multivitamin supplementation was associated significantly with a mean increase in Psychomotor Development Index score of 2.6 (95% confidence interval: 0.1-5.1). Multivitamins were also significantly protective against the risk for developmental delay on the motor scale (relative risk: 0.4; 95% confidence interval: 0.2-0.7) but not on the Mental Development Index. Vitamin A supplementation had no significant effect on these outcomes. CONCLUSIONS: Maternal multivitamin supplements provide a low-cost intervention to reduce the risk for developmental delays among infants who are born to HIV-positive mothers in developing countries.

## Hypoglycaemia

Pediatrics. 2005 Nov;116(5):e648-53.

### **Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycemia among children in the tropics.**

**Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E.**

BACKGROUND: Hypoglycemia is a common determining factor of poor prognosis for children with severe malaria in sub-Saharan Africa. Intravenous dextrose administration is rarely available. Oral mucosal delivery may be an alternative to parenteral administration. A randomized, clinical trial was performed in Burkina Faso among moderately hypoglycemic children, comparing sublingual sugar administration with oral water, oral sugar, and dextrose infusion administrations. METHODS: **Sixty-nine children with glucose concentrations of < 0.8 g/L were assigned randomly to 1 of 4 methods of administration, 1 with 3 different doses of sugar, as follows: oral group (OG) (n = 15): 2.5 g of sugar; sublingual group (SG) (n = 27): 2.5 g of sugar under the tongue, with 3 treatment subgroups, ie, 0.1 g/kg, 0.15 g/kg, and 0.2 g/kg; intravenous group (IG) (n = 8): 8 mL of 30% dextrose in a single bolus; water group (n = 11).** Eight children received sublingual sugar twice, ie, 0.1 g/kg at baseline and 20 minutes later. Blood glucose concentrations were measured every 20 minutes for 80 minutes. Treatment failures, peak glucose concentrations, times to glucose concentration normalization, and kinetic profiles were evaluated. RESULTS: No treatment failures were observed in the SG and IG, compared with 8 (53%) and 9 (81.8%) failures in the OG and water group, respectively. SG children exhibited glucose kinetic profiles and bioavailabilities (77%, 99%, and 81% in the 3 SG groups) similar to those of IG children. Bioavailabilities were 84% and 38% in the SG and OG, respectively. **Children > 7 years of age required repeated sublingual administrations to maintain normoglycemia.** CONCLUSIONS: **The sublingual administration of sugar proved to be effective among moderately hypoglycemic children.** It is a simple and promising method to control hypoglycemia among children in both

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developing and developed countries. This pediatric practice should be investigated in more detail among children with severe malaria.

## **IMCI**

Health Policy Plan. 2005 Dec;20 Suppl 1:i69-i76.

### **Improving quality and efficiency of facility-based child health care through Integrated Management of Childhood Illness in Tanzania.**

**Bryce J, Gouws E, Adam T, Black RE, Schellenberg JA, Manzi F, Victora CG, Habicht JP.**

**OBJECTIVES:** To assess the effect of Integrated Management of Childhood Illness (IMCI) relative to routine care on the quality and efficiency of providing care for sick children in first-level health facilities in Tanzania, and to disseminate the results for use in health sector decision-making. Design: **Non-randomized controlled trial** to compare child health care quality and economic costs in two intervention (>90% of health care workers trained in IMCI) and two comparison districts in rural Tanzania. Participants: For quality measures, all sick children presenting for care at random samples of first-level health facilities; for costs, all national, district, facility and household costs associated with child health care, taking a societal perspective. **RESULTS: IMCI training is associated with significantly better child health care in facilities at no additional cost to districts. The cost per child visit managed correctly was lower in IMCI than in routine care settings: \$4.02 versus \$25.70, respectively, in 1999 US dollars and after standardization for variations in population size.** **CONCLUSION:** IMCI improved the quality and efficiency of child health care relative to routine child health care in the study districts. Previous study results indicated that the introduction of IMCI in these Tanzanian districts was associated with mortality levels that were 13% lower than in comparison districts. We can therefore conclude that **IMCI is also more cost-effective than routine care for improving child health outcomes.** The dissemination strategy for these results led to adoption of IMCI for nationwide implementation within 12 months of study completion.

## **Iron deficiency**

(See also Vitamin A and Malaria)

Am J Clin Nutr. 2005 Nov;82(5):1032-9.

### **Effect of a fortified maize-meal porridge on anemia, micronutrient status, and motor development of infants.**

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Faber M, Kvalsvig JD, Lombard CJ, Benade AJ.

**BACKGROUND:** Maize-meal porridge is used for infant feeding in many African countries, including South Africa. A low-cost, finely milled, maize-meal porridge was fortified with beta-carotene, iron, and zinc (100% of recommended dietary allowance), as well as ascorbic acid, copper, selenium, riboflavin, vitamin B-6, vitamin B-12, and vitamin E. **OBJECTIVE:** We assessed whether the fortified porridge could reduce anemia and improve the micronutrient status and motor development of infants. **DESIGN:** **Infants aged 6-12 mo (n = 361) were randomly assigned to receive either the fortified or unfortified porridge for 6 mo.** Primary outcomes were hemoglobin and serum retinol, zinc, and ferritin concentrations and motor development. Growth was assessed as a secondary outcome. Primary and secondary outcomes were assessed at baseline and 6 mo. **RESULTS:** Two hundred ninety-two infants completed the study. The fortified-porridge group had an intervention effect of 9.4 microg/L (95% CI: 3.6, 15.1 microg/L) for serum ferritin and 9 g/L (95% CI: 6, 12 g/L) for hemoglobin concentrations. **The proportion of infants with anemia decreased from 45% to 17% in the fortified-porridge group, whereas it remained >40% in the control group. The fortified-porridge group achieved on average 15.5 of the 25 motor development score items, whereas the control group achieved 14.4 items (P = 0.007). Serum retinol concentration showed an inconsistent effect, and no intervention effect was observed for serum zinc concentrations.** **CONCLUSIONS:** This low-cost fortified porridge can potentially have a significant effect in reducing anemia and improving iron status and motor development of infants in poor settings. The formulation needs some adjustment in terms of zinc fortification.

Pediatrics. 2006 Jun;117(6):2014-21.

## Iron fortification reduces blood lead levels in children in Bangalore, India.

Zimmermann MB, Muthayya S, Moretti D, Kurpad A, Hurrell RF.

**OBJECTIVE:** Chronic lead poisoning and iron deficiency are concentrated in urban children from lower socioeconomic strata, and both impair neurocognitive development. Our study objective was to determine if iron fortification reduces blood lead levels in urban, lead-exposed, iron-deficient children in Bangalore, India. **DESIGN, SETTING, AND PARTICIPANTS:** A randomized, double-blind, controlled school-based feeding trial was done in 5- to 13-year-old iron-deficient children (n = 186). At baseline, a high prevalence of lead poisoning was found in the younger children. Subsequently, all 5- to 9-year-old children participating in the trial (n = 134) were followed to determine if iron fortification would affect their blood lead levels. **INTERVENTION:** Children were dewormed and fed 6 days/week for 16 weeks either an iron-fortified rice meal (approximately 15 mg of iron per day as ferric pyrophosphate) or an identical control meal without added iron. Feeding was directly supervised and compliance monitored. **OUTCOME MEASURES:** Hemoglobin, serum ferritin, C-reactive protein, transferrin receptor, zinc protoporphyrin, and blood lead concentrations were measured. **RESULTS:** **The prevalence of iron deficiency was significantly reduced in the iron group (from 70% to 28%) compared with the control group (76% to 55%). There was a significant decrease in median blood lead concentration in the iron group compared with the control group. The prevalence of blood lead levels > or =10 microg/dL was significantly reduced in the iron group (from 65% to 29%) compared with the control group (68% to 55%).** **CONCLUSIONS:** Our findings suggest providing iron in a

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fortified food to lead-exposed children may reduce chronic lead intoxication. Iron fortification may be an effective and sustainable strategy to accompany environmental lead abatement.

Lancet. 2006 Jan 14;367(9505):144-52.

### **Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial.**

**Tielsch JM, Khattry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, Mullany LC, Shrestha S, Black RE.**

**INTRODUCTION:** Iron deficiency is widespread in the developing world and is especially common in young children who live on the Indian subcontinent. Supplementation with iron and folic acid alleviates severe anaemia and enhances neurodevelopment in deficient populations, but little is known about the risks of mortality and morbidity associated with supplementation. **METHODS:** We did a community-based, cluster-randomised, double-masked, placebo-controlled, 2x2 factorial trial in children aged 1-36 months and residing in southern Nepal. We randomly assigned children daily oral supplementation to age 36 months with: **iron (12.5 mg) and folic acid (50 microg; n=8337), zinc alone (10 mg), iron, folic acid, and zinc (n=9230), or placebo (n=8683); children aged 1-11 months received half the dose.** Our primary outcome measure was all-cause mortality, and our secondary outcome measures included cause-specific mortality and incidence and severity of diarrhoea, dysentery, and acute respiratory illness. Analyses were by intention to treat. This study is registered at , number NCT00109551. **FINDINGS:** The iron and folic acid-containing groups of the study were stopped early in November, 2003, on the recommendation of the data and safety monitoring board; mortality in these groups did not differ from placebo and there was low power to detect positive or negative effects by the time enrollment was completed. We continued to enroll children to the placebo and zinc alone groups. 25,490 children participated and analyses are based on 29,097.3 person-years of follow-up. There was no difference in mortality between the groups who took iron and folic acid without or with zinc when compared with placebo (HR 1.03, 95% CI 0.78-1.37, and 1.00, 0.74-1.34, respectively). **There were no significant differences in the attack rates for diarrhoea, dysentery, or respiratory infections between groups, although all the relative risks except one indicated modest, non-significant protective effects.** **INTERPRETATION:** Daily supplementation of young children in southern Nepal with iron and folic acid with or without zinc has no effect on their risk of death, but might protect against diarrhoea, dysentery, and acute respiratory illness.

\*\*\* Lancet. 2006 Jan 14;367(9505):133-43.

### **Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial.**

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Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, Kabole FM.

**BACKGROUND:** Anaemia caused by iron deficiency is common in children younger than age 5 years in eastern Africa. However, there is concern that universal supplementation of children with iron and folic acid in areas of high malaria transmission might be harmful. **METHODS:** We did a randomised, placebo-controlled trial, of children aged 1-35 months and living in Pemba, Zanzibar. We assigned children to **daily oral supplementation with: iron (12.5 mg) and folic acid (50 µg; n=7950), iron, folic acid, and zinc (n=8120), or placebo (n=8006); children aged 1-11 months received half the dose.** Our primary endpoints were all-cause mortality and admission to hospital. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN59549825. **FINDINGS:** **The iron and folic acid-containing groups of the trial were stopped early** on Aug 19, 2003, on the recommendation of the data and safety monitoring board. To this date, 24 076 children contributed a follow-up of 25,524 child-years. **Those who received iron and folic acid with or without zinc were 12% (95% CI 2-23, p=0.02) more likely to die or need treatment in hospital for an adverse event and 11% (1-23%, p=0.03) more likely to be admitted to hospital; there were also 15% (-7 to 41, p=0.19) more deaths in these groups.** **INTERPRETATION:** **Routine supplementation with iron and folic acid in preschool children in a population with high rates of malaria can result in an increased risk of severe illness and death.** In the presence of an active programme to detect and treat malaria and other infections, iron-deficient and anaemic children can benefit from supplementation. However, supplementation of those who are not iron deficient might be harmful. As such, current guidelines for universal supplementation with iron and folic acid should be revised.

### *Comment*

*This is an important study that has modified WHO's recommendations for iron supplementation in areas where malaria is common. While previous studies have shown that various combinations and methods of delivery of iron supplementation (for example weekly and through school programs) reduce the incidence of iron deficiency anaemia, this very large study found there was an increased risk of serious illness or death in the iron and folic acid supplemented groups. How to provide supplementation for those children who need it, but avoid supplementation for children who are not iron deficient should be the focus of further research. The logistics and cost-effectiveness of haemoglobin testing prior to supplementation should be explored*

Food Nutr Bull. 2005 Sep;26(3):259-65.

## **Effect of fortification of drinking water with iron plus ascorbic acid or with ascorbic acid alone on hemoglobin values and anthropometric indicators in preschool children in day-care centers in Southeast Brazil.**

de Almeida CA, Dutra-De-Oliveira JE, Crott GC, Cantolini A, Ricco RG, Del Ciampo LA, Baptista ME.

**BACKGROUND:** Iron-deficiency anemia currently is the most frequently occurring nutritional disorder world-wide. Previous Brazilian studies have demonstrated that drinking water fortified

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with iron and ascorbic acid is an adequate vehicle for improving the iron supply for children frequenting day-care centers. **OBJECTIVE:** The objective of this study was to clarify the role of ascorbic acid as a vehicle for improving iron intake in children in day-care centers in Brazil. **METHODS:** A six-month study was conducted on 150 children frequenting six day-care centers divided into two groups of three day-care centers by drawing lots: **the iron-C group (3 day-care centers, n = 74), which used water fortified with 10 mg elemental iron and 100 mg ascorbic acid per liter, and the comparison group (3 day-care centers, n = 76), which used water containing only 100 mg ascorbic acid per liter.** Anthropometric measurements and determinations of capillary hemoglobin were performed at the beginning of the study and after six months of intervention. The food offered at the day-care centers was also analyzed. **RESULTS:** The food offered at the day-care center was found to be deficient in ascorbic acid, poor in heme iron, and adequate in non-heme iron. **Supplementation with fortified drinking water resulted in a decrease in the prevalence of anemia and an increase in mean hemoglobin levels associated with height gain in both groups.** **CONCLUSIONS:** Fortification of drinking water with iron has previously demonstrated effectiveness in increasing iron supplies. This simple strategy was confirmed in the present study. The present study also demonstrated that for populations receiving an abundant supply of non-heme iron, it is possible to control anemia in a simple, safe, and inexpensive manner by adding ascorbic acid to drinking water.

## Leishmaniasis

Am J Trop Med Hyg. 2005 Nov;73(5):871-6.

### **A phase II dose-increasing study of sitamaquine for the treatment of visceral leishmaniasis in Kenya.**

**Wasunna MK, Rashid JR, Mbui J, Kirigi G, Kinoti D, Lodenyo H, Felton JM, Sabin AJ, Albert MJ, Horton J.**

Sitamaquine (WR6026) is an 8-aminoquinoline in development for the oral treatment of visceral leishmaniasis (VL). This was an open-label, dose-increasing study to determine the dose-response and safety profile for sitamaquine in Kenyan patients with VL caused by *Leishmania donovani*. Patients (mean age 15.9 [range = 5-47] years) received sitamaquine daily for 28 days at one of four doses: 1.75 (n = 12), 2.0 (n = 61), 2.5 (n = 12), or 3.0 (n = 12) mg/kg/day. The primary efficacy outcome was cure (absence of parasites on splenic aspirate) in the intent-to-treat population at day 180. Cure was achieved in 79 (83%) of 95 patients overall, and in 11 (92%) of 12, 49 (80%) of 61, 9 (82%) of 11, and 10 (91%) of 11 patients at sitamaquine doses of 1.75, 2.0, 2.5, or 3.0 mg/kg/day, respectively. The most frequent adverse events during active treatment were abdominal pain (12 [12%] of 97) and headache (11 [11%] of 97), and one patient in each of the 2.5 mg/kg/day and 3.0 mg/kg/day dose groups had a severe renal adverse event. The effects of sitamaquine on the kidney need further investigation. Sitamaquine was efficacious and generally well tolerated in Kenyan patients with VL.



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Am J Trop Med Hyg. 2005 Dec;73(6):1005-11.

### **A phase II dose-ranging study of sitamaquine for the treatment of visceral leishmaniasis in India.**

**Jha TK, Sundar S, Thakur CP, Felton JM, Sabin AJ, Horton J.**

This randomized, open label, multicenter study assessed the dose-response and safety profile for oral sitamaquine in 120 Indian subjects with visceral leishmaniasis (VL). Patients aged 5-64 years (mean age 21.2 years) received one of four sitamaquine doses (1.5, 1.75, 2.0, or 2.5 mg kg<sup>-1</sup> day<sup>-1</sup>) daily for 28 days. **At Day 180 in the intent-to-treat population, final cure (primary efficacy outcome) was achieved in 92 of 106 (87%) patients overall and 25 of 31 (81%), 24 of 27 (89%), 23 of 23 (100%), and 20 of 25 (80%) patients at doses of 1.5, 1.75, 2.0, or 2.5 mg kg<sup>-1</sup> day<sup>-1</sup> sitamaquine, respectively.** Sitamaquine was generally well tolerated. The most common adverse events during the active treatment phase were vomiting (8% [10 of 120]), dyspepsia (8% [9 of 120]) and cyanosis (3% [4 of 120]). Nephrotic syndrome (3% [3 of 120]) and glomerulonephritis (2% [2 of 120]) were also reported and require further investigation. Oral sitamaquine demonstrated efficacy in Indian VL and was well tolerated.

## **Malaria**

### **Malaria vaccine**

Lancet. 2005 Dec 10;366(9502):2012-8.

### **Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial.**

**Alonso PL, Sacarlal J, Aponte JJ, Leach A, Macete E, Aide P, Sigauque B, Milman J, Mandomando I, Bassat Q, Guinovart C, Espasa M, Corachan S, Lievens M, Navia MM, Dubois MC, Menendez C, Dubovsky F, Cohen J, Thompson R, Ballou WR.**

**BACKGROUND:** RTS,S/AS02A is a pre-erythrocytic stage malaria vaccine that provides partial protection against infection in malaria-naïve adult volunteers and hyperimmune adults. A previous report showed that this vaccine reduced risk of clinical malaria, delayed time to new infection, and reduced episodes of severe malaria over 6 months in African children. An important remaining issue is the durability of protection against clinical disease in these children. **METHODS:** We did a **randomised, controlled, phase IIb trial of RTS,S/AS02A given at 0, 1, and 2 months in 2022 Mozambican children aged 1-4 years.** We previously determined vaccine efficacy (VE) against clinical malaria in a double-blind phase that included study months 2.5-8.5 (VE(2.5-8.5)). We now report VE in a single-blind phase up to month 21

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(VE(8.5-21)). **The primary endpoint was time to first or only clinical episode of Plasmodium falciparum malaria (axillary temperature 37.5 degrees C and P falciparum asexual parasitaemia >2500 per microL) detected through a passive case detection system.** We also determined VE for other case definitions and for episodes of severe malaria. This study is registered with the ClinicalTrials.gov identifier NCT00197041. **FINDINGS: During the single-blind phase, VE(8.5-21) was 28.9% (95% CI 8.4-44.8; p=0.008). At month 21, prevalence of P falciparum infection was 29% lower in the RTS,S/AS02A group than in the control (p=0.017).** Considering the entire study period, VE(2.5-21) was 35.3% (95% CI 21.6-46.6; p<0.0001) and VE(2.5-21) for severe malaria was 48.6% (95% CI 12.3-71.0; p=0.02). **INTERPRETATION:** These results show that RTS,S/AS02A confers partial protection in African children aged 1-4 years living in rural endemic areas against a range of clinical disease caused by P falciparum for at least 18 months, and confirm the potential of malaria vaccines to become credible control tools for public-health use.

Vaccine. 2005 Jul 14;23(32):4148-57. Epub 2005 Apr 15.

### **Safety and immunogenicity of RTS,S/AS02A candidate malaria vaccine in Gambian children.**

**Bojang KA, Olodude F, Pinder M, Ofori-Anyinam O, Vigneron L, Fitzpatrick S, Njie F, Kassanga A, Leach A, Milman J, Rabinovich R, McAdam KP, Kester KE, Heppner DG, Cohen JD, Tornieporth N, Milligan PJ.**

RTS,S/AS02A is a pre-erythrocytic malaria vaccine candidate in which a portion of the circumsporozoite surface protein (CSP) of Plasmodium falciparum is genetically linked to hepatitis B surface antigen (HBsAg) coexpressed in yeast with unfused HBsAg. The resulting particulate antigen is formulated with the adjuvant system AS02A. We have initiated the paediatric clinical development of this vaccine by conducting two sequential Phase I studies in children: a study in older children (6--11 years), followed by a second study in younger children (1--5 years). **In each study, a double-blind, randomised controlled, staggered, dose-escalation design was used to evaluate 10 microg RTS,S dose (10 microg RTS,S in 0.1mL AS02A), 25 microg dose (25 microg RTS,S in 0.25mL AS02A) and finally a 50 microg dose (50 microg RTS,S in 0.5mL AS02A) of the RTS,S/AS02A candidate malaria vaccine administered according to a 0-, 1- and 3-month vaccination schedule. Safety and reactogenicity were evaluated before moving to a higher dose level. The RTS,S/AS02A vaccine was safe at all dose levels, in both age groups.** No serious adverse events related to vaccination were reported. The frequency of local Grade 3 symptoms was low but tended to increase with increasing dose level. Grade 3 general adverse events in the RTS,S/AS02A groups were infrequent and of short duration. The majority of local and general Grade 3 symptoms resolved or decreased in intensity within 48h. The pattern and intensity of reactogenicity seen in these studies are similar to those of previous studies with RTS,S/AS02A. **All doses were highly immunogenic for anti-CSP and anti-HBsAg antibodies. The pooled anti-CSP antibody data from the two studies showed that the 25 microg dose and 50 microg dose anti-CSP antibody response were similar at both dose levels. However, the immunogenicity of the 10 microg dose anti-CSP response was significantly lower than that of either the 50 microg or 25 microg dose. The 25 microg dose was selected for future studies of RTS,S/AS02A in paediatric populations.**

## **Intermittent presumptive treatment**

BMJ. 2005 Oct 1;331(7519):727-33.

### **Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana.**

**Chandramohan D, Owusu-Agyei S, Carneiro I, Awine T, Amponsa-Achiano K, Mensah N, Jaffar S, Baiden R, Hodgson A, Binka F, Greenwood B.**

**OBJECTIVE:** To evaluate the effects of intermittent preventive treatment for malaria in infants (IPTi) with sulfadoxine-pyrimethamine in an area of intense, seasonal transmission. **DESIGN:** Cluster randomised placebo controlled trial, with 96 clusters allocated randomly to sulfadoxine-pyrimethamine or placebo in blocks of eight. **INTERVENTIONS:** Children received sulfadoxine-pyrimethamine or placebo and one month of iron supplementation when they received DPT-2, DPT-3, or measles vaccinations and at 12 months of age. **MAIN OUTCOME MEASURES:** Incidence of malaria and of anaemia determined through passive case detection. **RESULTS:** 89% (1103/1242) of children in the placebo group and 88% (1088/1243) in the IPTi group completed follow-up to 24 months of age. The protective efficacy of IPTi against all episodes of malaria was 24.8% (95% confidence interval 14.3% to 34.0%) up to 15 months of age. IPTi had no protective effect against malaria between 16 and 24 months of age (protective efficacy -4.9%, -21.3% to 9.3%). The incidence of high parasite density malaria (> or = 5000 parasites/mul) was higher in the IPTi group than in the placebo group between 16 and 24 months of age (protective efficacy -19.5%, -39.8% to -2.2%). IPTi reduced hospital admissions with anaemia by 35.1% (10.5% to 52.9%) up to 15 months of age. IPTi had no significant effect on anaemia between 16 and 24 months of age (protective efficacy -6.4%, -76.8% to 35.9%). The relative risk of death up to 15 months of age in the IPTi group was 1.26 (95% confidence interval 0.81 to 1.96; P = 0.31), and from 16 to 24 months it was 1.28 (0.77 to 2.14; P = 0.35). **CONCLUSIONS:** Intermittent preventive treatment for malaria with sulfadoxine-pyrimethamine can reduce malaria and anaemia in infants even in seasonal, high transmission areas, but concern exists about possible rebound in the incidence of malaria in the second year of life.

Lancet. 2006 Feb 25;367(9511):659-67.

### **Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial.**

**Cisse B, Sokhna C, Boulanger D, Milet J, Ba el H, Richardson K, Hallett R, Sutherland C, Simondon K, Simondon F, Alexander N, Gaye O, Targett G, Lines J, Greenwood B, Trape JF.**

**BACKGROUND:** In the Sahel and sub-Saharan regions of Africa, malaria transmission is highly seasonal. During a short period of high malaria transmission, mortality and morbidity

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are high in children under age 5 years. We assessed the efficacy of seasonal intermittent preventive treatment—a full dose of antimalarial treatment given at defined times without previous testing for malaria infection. **METHODS:** We did a randomised, placebo-controlled, double-blind trial of the effect of intermittent preventive treatment on morbidity from malaria in three health-care centres in Niakhar, a rural area of Senegal. **1136 children aged 2-59 months received either one dose of artesunate plus one dose of sulfadoxine-pyrimethamine or two placebos on three occasions during the malaria transmission season.** The primary outcome was a first or single episode of clinical malaria detected through active or passive case detection. Primary analysis was by intention-to-treat. This study is registered with, number NCT00132561. **FINDINGS: During 13 weeks of follow-up, the intervention led to an 86% (95% CI 80-90) reduction in the occurrence of clinical episodes of malaria. With passive case detection, protective efficacy against malaria was 86% (77-92), and when detected actively was 86% (78-91).** The incidence of malaria in children on active drugs was 308 episodes per 1000 person-years at risk, whereas in those on placebo it was 2250 episodes per 1000 person-years at risk. 13 children were not included in the intention-to-treat analysis, which was restricted to children who received a first dose of antimalarial or placebo. **There was an increase in vomiting in children who received the active drugs, but generally the intervention was well tolerated.** **INTERPRETATION:** Intermittent preventive treatment could be highly effective for prevention of malaria in children under 5 years of age living in areas of seasonal malaria infection.

Am J Trop Med Hyg. 2006 Mar;74(3):386-93.

## A randomized, double-blind, placebo-controlled, clinical trial of the impact of malaria prevention on the educational attainment of school children.

**Fernando D, de Silva D, Carter R, Mendis KN, Wickremasinghe R.**

A double-blind, placebo-controlled trial of nine months duration was carried out to investigate the impact of malaria and its prevention on the educational attainment of school children in a malaria-endemic area in southern Sri Lanka where both *Plasmodium falciparum* and *P. vivax* infections are prevalent. **A total of 587 children attending grades 1-5 in four schools and resident in the area were randomly allocated to chloroquine (n = 295) and placebo (n = 292) arms.** Language and mathematics scores of end-of-term school examinations for 1998 and 1999 and number of days absent and reasons for absenteeism during seven months pre-intervention and nine months of the intervention were recorded. The results indicate that there were no differences in language (95% confidence interval [CI] = 48.44-53.78 in chloroquine group and 50.43-55.81 in placebo group) and mathematics (95% CI = 49.24-54.38 in chloroquine group and 51.12-56.38 in placebo group) scores between the two groups prior to the intervention. During the intervention, the malaria incidence rate decreased by 55% (95% CI = 49-61%) and school absenteeism due to malaria was reduced by 62.5% (95% CI = 57-68%) in children who received chloroquine compared with the placebo group. **Post-intervention, children who received chloroquine scored approximately 26% higher in both language (95% CI = 21-31%) and mathematics (95% CI = 23-33%) than children who received placebo.** In a multivariate model, educational attainment was significantly associated with taking chloroquine prophylaxis and absenteeism due to malaria ( $P < 0.001$  for both) but not due to health causes other than malaria or non-health causes. Language scores were associated with number of malaria attacks ( $P < 0.022$ ). Educational attainment was significantly better

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among children whose compliance to chloroquine prophylaxis was higher ( $P < 0.001$ ). **The data suggest that malarial attacks have an adverse impact on the educational attainment of the school child and prevention of these attacks significantly improves educational attainment of children living in malaria-endemic areas.**

### **Comment**

*This is an important study, demonstrating the major impact of malaria in endemic areas on educational progress. The effect of preventing malaria is not just on health morbidity, but on educational and vocational achievement. This provides a strong economic argument for malaria prevention.*

## **Insecticide treated materials**

Bull World Health Organ. 2006 Feb;84(2):120-6. Epub 2006 Feb 23.

### **Effects of insecticide-treated bednets during early infancy in an African area of intense malaria transmission: a randomized controlled trial.**

**Muller O, Traore C, Kouyate B, Ye Y, Frey C, Coulibaly B, Becher H.**

**OBJECTIVE:** Insecticide-impregnated bednets and curtains have been shown by many studies to be effective against malaria. However, because of possible interactions with immunity development, treated bednets may cause no effect at all or even an increase in malaria morbidity and mortality in areas of high transmission. To clarify this issue, we did a randomized controlled trial to assess the long-term effects of bednet protection during early infancy. **METHODS:** A total of 3387 neonates from 41 villages in rural Burkina Faso were individually randomized to receive either bednet protection from birth (group A) or from age 6 months (group B). Primary outcomes were all-cause mortality in all study children and incidence of falciparum malaria in a representative subsample of the study population. **FINDINGS:** After a mean follow-up of 27 months, there were 129 deaths in group A and 128 deaths in group B rate ratio (RR) 1.0 (95% confidence interval (CI): 0.78-1.27)). Falciparum malaria incidence was lower in group A than in group B, during early (0-5 months) and late infancy (6-12 months) (RR 3.1, 95% CI: 2.0-4.9; RR 1.3, 95% CI: 1.1-1.6) and rates of moderate to severe anaemia were significantly lower during late infancy (11.5% vs 23.3%,  $P = 0.008$ ), but there were no differences between groups in these parameters in children older than 12 months. **CONCLUSION:** The findings from this study provide additional evidence for the efficacy of insecticide-treated nets in young children living in areas of intense malaria transmission.

Am J Trop Med Hyg. 2005 Nov;73(5):859-64.

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### **Protective efficacy of lambda-cyhalothrin treated nets in *Anopheles gambiae* pyrethroid resistance areas of Cote d'Ivoire.**

**Henry MC, Assi SB, Rogier C, Dossou-Yovo J, Chandre F, Guillet P, Carnevale P.**

The efficacy of nets treated with lambda-cyhalothrin, a pyrethroid insecticide, on malaria infection and disease was assessed for the first time at the community level in *Anopheles gambiae* pyrethroid resistance areas. The study was carried out in northern Cote d'Ivoire, which is an area of kdr resistance. **Four pairs of villages were selected and matched according to demographic, sociological, and ecological criteria. Among each pair, a village was randomly allocated to receive mosquito nets. More than 80% of beds were covered with nets treated with lambda-cyhalothrin and retreated after 6 months.** In each village, 54 children aged 0-59 months were randomly selected and clinically monitored for 8 periods of 7 days throughout the year. **Results showed that the efficacy of treated nets was maintained with a reduction of the prevalence of asymptomatic malaria infection by 12% and an estimated protective efficacy against malaria disease of 56%.**

### **Treatment of severe malaria**

\*\*\* Lancet. 2005 Aug 27-Sep 2;366(9487):717-25.

### **Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial.**

**Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group.**

**BACKGROUND:** In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain. **METHODS:** We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2.4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2-8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat. **FINDINGS:** We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (95% CI 18.5-47.6%; p=0.0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3-7.8; p=0.009). **INTERPRETATION:** Artesunate should become the treatment of choice for severe falciparum malaria in adults.

BMJ. 2006 May 6;332(7549):1055-9.

**Safety and efficacy of rectal compared with intramuscular quinine for the early treatment of moderately severe malaria in children: randomised clinical trial.**

**Barennes H, Balima-Koussoube T, Nagot N, Charpentier JC, Pussard E.**

**OBJECTIVE:** To compare the safety and efficacy of quinine given by the rectal route with quinine given by the intramuscular route in children with moderately severe *Plasmodium falciparum* malaria. **DESIGN:** Randomised, open, clinical trial. **SETTING:** Health centre in Burkina Faso. **PARTICIPANTS:** 898 children with moderately severe *P falciparum* malaria who were unable to take oral treatment. **INTERVENTION:** Rectal quinine (20 mg/kg diluted to 30 mg/ml in water solution) or intramuscular quinine (12.5 mg/kg) every 12 hours until oral quinine could be taken. **MAIN OUTCOME MEASURES:** Primary safety outcome was the presence of blood in stools and secondary safety outcome was diarrhoea. Primary efficacy outcome was early treatment failure and secondary efficacy outcomes were late clinical and parasitological failures, fever clearance time, and time to oral intake. **RESULTS:** Blood in stools and diarrhoea were more common in children given quinine by the rectal route than by the intramuscular route (blood in stools: 5% v 1%, absolute difference 3.9%, 95% confidence interval 1.8% to 6.1%; diarrhoea: 5% v 1%, 3.5%, 1.3% to 5.7%). On anoscopy, inflammatory lesions (9/248, 3%) were associated with bloody striations in stools. Side effects of rectal quinine were rare and transitory. Local pain (90%), inflammation (79%), and transient impairment of mobility (15%) were observed with intramuscular quinine. Early treatment failure was higher in the rectal group (6% v 3%, absolute difference 3.0%, 95% confidence interval 0.2% to 5.9%). All except two children in each group had negative blood slide results at day 5. Fever recurrence at day 7 was higher in the intramuscular group (37/375 v 18/395, absolute difference 5.3%, 1.6% to 8.9%). Other efficacy outcomes (late clinical failure, late parasitological failure, fever clearance time, time to starting oral intake and rate of deterioration to severe malaria) did not differ. **CONCLUSION:** Quinine given by the rectal route has an acceptable safety profile and could be used in the early management of moderately severe malaria in children in sub-Saharan Africa, halting progression to severe disease.

**Treatment of uncomplicated malaria**

Clin Infect Dis. 2005 Aug 15;41(4):425-32. Epub 2005 Jul 15.

**A randomized, controlled study of a simple, once-daily regimen of dihydroartemisinin-piperaquine for the treatment of uncomplicated, multidrug-resistant falciparum malaria.**

**Ashley EA, McGready R, Hutagalung R, Phaiphun L, Slight T, Proux S, Thwai KL, Barends M, Looareesuwan S, White NJ, Nosten F.**

**BACKGROUND:** Dihydroartemisinin-piperaquine (DP) is a fixed-combination antimalarial drug increasingly deployed in Southeast Asia. The current regimen involves 4 doses given over 3 days. Simplification of the dose regimen should facilitate treatment adherence and thereby increase effectiveness. **METHODS:** In a randomized, controlled, 3-arm trial conducted along the northwestern border of Thailand, **the standard 4-dose course of DP (DP4) was compared**

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to an equivalent dose given as a once-daily regimen (DP3) and to the standard treatment of mefloquine-artesunate (MAS3). RESULTS: A total of 499 patients were included in the study. Times to fever and parasite clearance were similar in all groups. **The PCR genotyping-adjusted cure rates at day 63 after treatment initiation were 95.7% (95% confidence interval [95% CI], 92.2%-98.9%) for MAS3, 100% for DP4, and 99.4% (95% CI, 98.1%-100%) for DP3. The DP4 and DP3 cure rates were significantly higher than that for MAS3 (P=.008 and P=.03, respectively).** All regimens were well tolerated. There were 3 deaths (1 in the MAS3 group and 2 in the DP3 group), all of which were considered to be unrelated to treatment. Rates of other adverse events were comparable between the groups, except for diarrhea, which was more common in the DP4 group (P=.05 vs. the MAS3 group). CONCLUSIONS: A once-daily, 3-dose regimen of DP is a highly efficacious treatment for multidrug-resistant falciparum malaria. This simple, safe, and relatively inexpensive fixed combination could become the treatment of choice for falciparum malaria.

Am J Trop Med Hyg. 2005 Nov;73(5):826-32.

### **Amodiaquine, sulfadoxine-pyrimethamine, and combination therapy for uncomplicated falciparum malaria: a randomized controlled trial from Burkina Faso.**

**Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Lankoande M, Ouedraogo JB, Rosenthal PJ.**

Increasing resistance to chloroquine necessitates the evaluation of other antimalarial therapies in Africa. **We compared the efficacies of amodiaquine (AQ), sulfadoxine-pyrimethamine (SP), and AQ + SP for the treatment of uncomplicated falciparum malaria in a randomized trial of patients 6 months of age or older in Bobo-Dioulasso, Burkina Faso.** Of the 944 patients enrolled, 829 (88%; 53% under 5 years of age) were assigned 28-day efficacy outcomes. For all regimens, early treatment failures were uncommon (< 2%). Considering all treatment failures based on WHO criteria, **AQ + SP was most efficacious (failures in 4.2%), followed by SP (9.1%) and AQ (17.9%; P < 0.02 for all pairwise comparisons).** Considering only clinical failures, relative efficacies were similar (failures in 2.1% with AQ + SP, 6.5% with SP, and 13.2% with AQ; P < 0.02 for all pairwise comparisons). The risk of recrudescence was lower with AQ + SP (2.1%) compared with SP (6.1%, P = 0.02) and AQ (8.1%, P = 0.001). Risks of new infection were lower with AQ + SP (2.1%) and SP (2.4%) compared with AQ (9.1%, P < 0.001 for both comparisons). No serious adverse events were seen. **AQ + SP appears to offer a highly effective, inexpensive, and available therapy for the treatment of uncomplicated malaria in Burkina Faso.**

Trans R Soc Trop Med Hyg. 2006 Feb;100(2):108-18. Epub 2005 Nov 14.

### **A randomized trial comparing the efficacy of four treatment regimens for uncomplicated falciparum malaria in Assam state, India.**



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**Campbell P, Baruah S, Narain K, Rogers CC.**

A four-arm drug sensitivity study compared chloroquine, sulfadoxine-pyrimethamine (SP), mefloquine and mefloquine-artesunate in Sonitpur and Karbi Anglong districts in Assam state, India. Two criteria were used to ascertain outcome: success of clinical treatment and parasitologic cure. In Sonitpur, at 14 days, there were 36/56 early and late treatment failures plus late parasitologic failures to chloroquine and 16/56 for SP. In Karbi Anglong, combined treatment failure at 14 days was 16/56 to chloroquine and 8/60 to SP. Mefloquine and mefloquine-artesunate demonstrated 93.9% and 93.6% sustained responses respectively at 42 days. High failure rates to both chloroquine and SP preclude the use of these drugs as first-line treatment for uncomplicated falciparum malaria in this region. A mefloquine-artesunate combination presents an effective alternative utilizing the currently recommended higher dose of mefloquine.

Ann Trop Med Parasitol. 2005 Jul;99(5):449-55.

### **A comparison of the efficacy of artesunate plus sulfadoxine-pyrimethamine with that of sulfadoxine-pyrimethamine alone, in the treatment of uncomplicated, Plasmodium falciparum malaria in eastern Sudan.**

**Adam I, A-Elbasit IE, Idris SM, Malik EM, Elbashir MI.**

In an open, randomized, clinical trial, conducted in New Halfa, eastern Sudan, in September-October 2004, the **efficacies and adverse effects of artesunate plus sulfadoxine-pyrimethamine (SP), in the treatment of uncomplicated, Plasmodium falciparum malaria, were compared with those of SP alone. Patients were randomized to receive either artesunate (4 mg/kg. day) on days 0-2 plus SP (25 mg sulfadoxine/kg) on day 0 or the SP alone, and then followed-up for 28 days.** Sixty patients completed follow-up. Compared with the 30 given artesunate plus SP (ASP), the 30 given SP alone were much more likely to be febrile (30% v. 3.3%;  $P=0.006$ ) and parasitaemic (50% v. 6.7%;  $P<0.0001$ ) on day 1. By day 3, 16.7% of the patients given SP alone were still febrile and 6.7% of them were still parasitaemic, although all the patients given ASP were then afebrile ( $P=0.02$ ) and aparasitaemic ( $P=0.1$ ). **Five (16.7%) of the patients treated with SP alone but none of those given ASP appeared to be treatment failures ( $P<0.05$ ).** Parasite genotyping revealed that four of the five apparent treatment failures were true recrudescences but the other represented a re-infection detected on day 28. The true frequencies of cure by day 28 were therefore 100% for ASP and 86.7% for SP alone ( $P=0.02$ ). Adverse effects of treatment (nausea, itching and giddiness) were observed with similar frequencies in the two treatment arms (10.0% of the patients given ASP v. 13.3% of the patients given SP alone;  $P>0.05$ ). **The frequencies of gametocytaemia during follow-up were, however, much lower in the ASP arm than in the SP-only (0.0% v. 23.3%;  $P=0.005$ ).** Thus, although the problems posed by adverse effects were similar in the two treatment arms, ASP appeared markedly better, in terms of fever- and parasite-clearance times and the prevalence of post-treatment gametocytaemia, than SP alone.

Antimicrob Agents Chemother. 2006 Mar;50(3):968-74.

**Artesunate suppositories versus intramuscular artemether for treatment of severe malaria in children in Papua New Guinea.**

**Karunajeewa HA, Reeder J, Lorry K, Dabod E, Hamzah J, Page-Sharp M, Chiswell GM, Ilett KF, Davis TM.**

Drug treatment of severe malaria must be rapidly effective. Suppositories may be valuable for childhood malaria when circumstances prevent oral or parenteral therapy. **We compared artesunate suppositories (n = 41; 8 to 16 mg/kg of body weight at 0 and 12 h and then daily) with intramuscular (i.m.) artemether (n = 38; 3.2 mg/kg at 0 h and then 1.6 mg/kg daily) in an open-label, randomized trial with children with severe Plasmodium falciparum malaria in Papua New Guinea (PNG).** Parasite density and temperature were measured every 6 h for > or = 72 h. Primary endpoints included times to 50% and 90% parasite clearance (PCT50 and PCT90) and the time to per os status. In a subset of 29 patients, plasma levels of artemether, artesunate, and their common active metabolite dihydroartemisinin were measured during the first 12 h. One suppository-treated patient with multiple complications died within 2 h of admission, but the remaining 78 recovered uneventfully. **Compared to the artemether-treated children, those receiving artesunate suppositories had a significantly earlier mean PCT50 (9.1 versus 13.8 h; P = 0.008) and PCT90 (15.6 versus 20.4 h; P = 0.011).** Mean time to per os status was similar for each group. **Plasma concentrations of primary drug plus active metabolite were significantly higher in the artesunate suppository group at 2 h postdose.** The earlier initial fall in parasitemia with artesunate is clinically advantageous and mirrors higher initial plasma concentrations of active drug/metabolite. **In severely ill children with malaria in PNG, artesunate suppositories were at least as effective as i.m. artemether and may, therefore, be useful in settings where parenteral therapy cannot be given.**

**Comment**

*This study is important not just for areas where parenteral therapy cannot be given, but all health facilities where unnecessary injections are to be avoided when other routes of administration of drugs are safe and effective. A review of artemisinin derivatives in the treatment of malaria can be found at [www.ichrc.org](http://www.ichrc.org).*

Trop Med Int Health. 2005 Nov;10(11):1161-70.

**Open randomized study of artesunate-amodiaquine vs. chloroquine-pyrimethamine-sulfadoxine for the treatment of uncomplicated Plasmodium falciparum malaria in Nigerian children.**

**Sowunmi A, Fehintola FA, Adedeji AA, Gbotosho GO, Tambo E, Fateye BA, Happi TC, Oduola AM.**

BACKGROUND: Artemisinin-based combination antimalarials are currently considered effective alternatives for the treatment of malaria in Africa, but there are few studies of such combinations in Nigerian children. We assessed the safety, treatment efficacy and effects on gametocyte carriage of the combination of artesunate plus amodiaquine and chloroquine plus

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pyrimethamine-sulfadoxine in children. **METHODS:** We evaluated 153 children who were aged 12 years or younger who had uncomplicated *Plasmodium falciparum* malaria. **Patients were randomly assigned a combination of artesunate (4 mg/kg of body weight daily for 3 days) plus amodiaquine (30 mg/kg over 3 days), or chloroquine (25 mg/kg over 3 days) plus pyrimethamine-sulfadoxine (25 mg/kg of the sulfadoxine component at presentation).** The primary endpoints were the proportions of children with adequate clinical and parasitological response, late parasitological failure, late clinical failure and early treatment failure. The parasitological cure rates on days 14-28 were also used as the primary endpoints. **RESULTS:** Both regimens were well tolerated; no child was withdrawn because of drug intolerance. All children treated with artesunate plus amodiaquine had adequate clinical and parasitological response (ACPR), while all but five children treated with chloroquine plus pyrimethamine-sulfadoxine had similar response. Fever clearance times were similar in the two treatment groups. However, the proportion of patients whose parasitaemia cleared by day 2 was significantly higher (100 vs. 50%,  $P = 0.00001$ ) and parasite clearance was significantly faster ( $1.7 \pm 0.4$  vs.  $2.5 \pm 0.8$  days,  $P = 0.0001$ ) in children treated with artesunate plus amodiaquine. The cure rates on days 21 (100% vs. 94%,  $P = 0.03$ ) and 28 (100% vs. 90%,  $P = 0.003$ ) were also significantly higher in children treated with artesunate plus amodiaquine than in those treated with chloroquine plus pyrimethamine-sulfadoxine. Overall, a significantly higher proportion of children treated with chloroquine plus pyrimethamine-sulfadoxine carried gametocytes at least once during follow-up compared with those treated with artesunate plus amodiaquine [5 of 50 (10%) vs. 1 of 103 (0.97%),  $P = 0.01$ ]. **CONCLUSION:** The combination of artesunate plus amodiaquine is therapeutically superior to a combination of chloroquine plus pyrimethamine-sulfadoxine, and significantly reduced gametocyte carriage following treatment.

Trans R Soc Trop Med Hyg. 2005 Jul;99(7):548-54.

### **Malaria in the Nuba Mountains of Sudan: baseline genotypic resistance and efficacy of the artesunate plus sulfadoxine-pyrimethamine and artesunate plus amodiaquine combinations.**

**Hamour S, Melaku Y, Keus K, Wambugu J, Atkin S, Montgomery J, Ford N, Hook C, Checchi F.**

Both northern and southern Sudan are deploying artemisinin-based combinations against uncomplicated *Plasmodium falciparum* malaria (artesunate+sulfadoxine-pyrimethamine [AS+SP] in the north, artesunate+amodiaquine [AS+AQ] in the south). In 2003, we tested the efficacy of 3 day AS+SP and AS+AQ regimens in vivo in the isolated, seasonally endemic Nuba Mountains region (the first study of AS combinations in southern Sudan). We also analysed pre-treatment blood samples for mutations at the *P. falciparum* chloroquine transporter (Pfcrt) gene (associated with CQ resistance), and at the dihydrofolate reductase (Dhfr) gene (associated with pyrimethamine resistance). **Among 161 randomized children under 5 years, PCR-corrected cure rates after 28 days were 91.2% (52/57, 95% CI 80.7-97.1) for AS+SP and 92.7% (51/55, 95% CI 82.4-98.0) for AS+AQ, with equally rapid parasite and fever clearance.** The Pfcrt K76T mutation occurred in 90.0% (144/160) of infections, suggesting CQ would work poorly in this region. Overall, 82.5% (132/160) carried mutations at Dhfr (N51I, C59R or S108N, but not I164L), but triple mutants (more predictive of in vivo SP failure) were rare (3.1%). CQ use should be rapidly discontinued in this region.

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SP resistance may propagate rapidly, and AS+AQ is likely to be a better long-term option, provided AQ use is limited to the combination.

Clin Infect Dis. 2005 Jun 15;40(12):1777-84. Epub 2005 May 3.

### **Artesunate-clindamycin versus quinine-clindamycin in the treatment of Plasmodium falciparum malaria: a randomized controlled trial.**

**Ramharter M, Oyakhirome S, Klouwenberg PK, Adegnika AA, Agnandji ST, Missinou MA, Matsiegui PB, Mordmuller B, Borrmann S, Kun JF, Lell B, Krishna S, Graninger W, Issifou S, Kremsner PG.**

**BACKGROUND:** Artemisinin-based drug combinations are the mainstay in the fight against drug-resistant malaria in Africa. Currently available antimalarial drug combinations that include artemisinins are pharmacokinetically unmatched and are therefore potentially increasing the risk of selection of resistant mutants in areas in which the rate of transmission of malaria is high. We tested the potential value of artemisinin-based combination therapy with a short elimination half-life for the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. **METHODS:** We conducted an open-label, randomized, controlled clinical trial to evaluate the efficacy and tolerability of oral artesunate-clindamycin therapy given twice daily for 3 days (artesunate, 2 mg/kg, and clindamycin, 7 mg/kg, per dose), compared with a standard quinine-clindamycin regimen given twice daily for 3 days (quinine, 15 mg/kg, and clindamycin, 7 mg/kg, per dose), for the treatment of uncomplicated falciparum malaria in 100 Gabonese children aged 3-12 years. The primary end point of the study was the polymerase chain reaction-corrected cure rate for the per-protocol population. **RESULTS:** The activity of artesunate-clindamycin was comparable to that of quinine-clindamycin in the per-protocol analysis of cure rates at day 28 of follow-up (87% versus 94%). No serious adverse events were reported, and tolerability was good and was similar in both groups. Times to clearance of fever and clearance of parasites were significantly shorter in the artesunate-clindamycin group. **CONCLUSIONS:** Artesunate-clindamycin and other matching artemisinin-based combinations with a short plasma half-life merit further attention for use in regions in which the rate of transmission of malaria is high.

Acta Trop. 2005 Sep;95(3):194-203.

### **Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana.**

**Koram KA, Abuaku B, Duah N, Quashie N.**

The emergence and spread of Plasmodium falciparum resistance to commonly used antimalarials such as chloroquine and sulphadoxine/pyrimethamine poses major challenges to malaria control in sub-Saharan Africa. We undertook a study on the efficacy of some antimalarial drugs in 2003 with the view of supporting the National Malaria Control Programme in the review of the antimalarial drug treatment policy in Ghana. **Children aged 6-59 months with signs/symptoms of uncomplicated malaria including axillary temperature > or =37.5 degrees C; mono infection with P. falciparum; and parent's willingness to give**

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**consent, were randomized into four treatment groups and followed up for a maximum of 28 days.** The treatment groups were chloroquine (CHQ), sulphadoxine/pyrimethamine (SP), amodiaquine+artesunate (ADQ+ART) combination, and artemether+lumefantrine (Coartem) combination. **Clinical evaluation of 168 children studied showed that cumulative per-corrected cure rates on day 28 were 100% for ADQ+ART; 97.5% for coartem, 60% for SP and 25% for CHQ.** The artemisinin-based combinations effected rapid fever and parasite clearance. Prevalence of gametocytaemia was highest in the SP group whilst the CHQ group did not show any significant changes in haemoglobin levels during the follow-up period. The findings are in agreement with current recommendations for using artemisinin-based combinations for treating uncomplicated malaria in areas of high CHQ failure such as Ghana.

### *Comment*

*Studies again this year confirm the central importance of artemisinin-based combinations for the treatment of malaria. However, as for many interventions, ideal strategies (such as conjugate pneumococcal vaccine) are out of reach of many of the people who need it most. As demonstrated in Tanzania (see below), the cost of artemisinin-based combination therapy for malaria will need to be reduced before universal access to effective antimalarials is achieved.*

Bull World Health Organ. 2005 Nov;83(11):845-52. Epub 2005 Nov 10.

## **Differences in willingness to pay for artemisinin-based combinations or monotherapy: experiences from the United Republic of Tanzania.**

**Wiseman V, Onwujekwe O, Matovu F, Mutabingwa TK, Whitty CJ.**

**OBJECTIVE:** The cost of combination treatment is thought to be one of the greatest barriers to their deployment, but this has not been tested directly. Estimates of willingness to pay were compared across four drug combinations used to treat Tanzanian children with uncomplicated malaria. The reasons behind respondents' valuations and the effect of socioeconomic status on willingness to pay were explored. **METHODS:** One hundred and eighty mothers whose children had been recruited into a recently completed randomized effectiveness trial of amodiaquine + artesunate (AQ+AS), amodiaquine + sulfadoxine-pyrimethamine (AQ+SP), artemether-lumefantrine (coartemether) and amodiaquine monotherapy (AQ) were interviewed about their willingness to pay for these drugs two weeks after treatment. Estimates of willingness to pay were elicited with the bidding game technique. **FINDINGS:** A significant difference was detected in the mean amounts respondents were willing to pay, with those who received AQ+AS willing to pay the most, followed by co-artemether, AQ+SP and finally AQ. **The amounts patients' mothers were willing to pay for the artemisinin-based combinations, however, fell well short of the market costs.** Socioeconomic status was not found to have a statistically significant effect on mean willingness to pay scores for any treatment group. **CONCLUSION: This study shows that families who live in an area in which drug resistance to monotherapy is very high are willing to pay more for more effective artemisinin-based combination therapies. These amounts, however, are nowhere near the real costs of delivering the new drugs.** Only with subsidies will artemisinin-based combination therapies realistically have any impact.

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Am J Trop Med Hyg. 2005 Sep;73(3):609-15.

### **Efficacy of trimethoprim-sulfamethoxazole compared with sulfadoxine-pyrimethamine plus erythromycin for the treatment of uncomplicated malaria in children with integrated management of childhood illness dual classifications of malaria and pneumonia.**

**Hamel MJ, Holtz T, Mkandala C, Kaimila N, Chizani N, Bloland P, Kublin J, Kazembe P, Steketee R.**

In Malawi, trimethoprim-sulfamethoxazole (TS) is the recommended first-line treatment for children with Integrated Management of Childhood Illness dual classifications of malaria and pneumonia, and sulfadoxine-pyrimethamine (SP) plus five days of treatment with erythromycin (SP plus E) is the recommended second-line treatment. **Using a 14-day, modified World Health Organization protocol, children with dual IMCI classifications of malaria and pneumonia with Plasmodium falciparum parasitemia were randomized to receive TS or SP plus E.** Clinical and parasitologic responses and gametocytemia prevalence were obtained. A total of 87.2% of children receiving TS and 80.0% receiving SP plus E reached adequate clinical and parasitologic responses (ACPRs) ( $P = 0.19$ ). Severely malnourished children were less likely to achieve ACPRs than those better nourished (relative risk = 3.34,  $P = 0.03$ ). Day 7 gametocyte prevalence was 55% and 64% among children receiving TS and SP plus E, respectively ( $P = 0.19$ ). Thus, TS and SP plus E remain efficacious treatment of *P. falciparum* malaria in this setting. However, patient adherence and effectiveness of five days of treatment with TS is unknown.

Bull Soc Pathol Exot. 2005 Sep;98(3):193-6.

### **Evaluation of the therapeutic efficacy of amodiaquine versus chloroquine in the treatment of uncomplicated malaria in Abie, Cote-d'Ivoire**

**Adjetei TA, Affoumou GB, Loukou DD, Nebavi NG, Barro-Kiki P, Menan EI, Yavo W, Kone M.**

The WHO 14-days' test and an in vitro survey were carried out to study the efficacy of amodiaquine versus chloroquine in Abie, a hyperendemic village in the southern forest area of Cote-d'Ivoire. **One hundred and nineteen children less than 15 years old suffering from uncomplicated malaria were randomised. Among these, 62 were given amodiaquine treatment and 57 chloroquine treatment.** Both 4-aminoquinolines were administered at the same dose of 30 mg/kg spread over three days by 10 mg/kg/day. Before the drug was administered, parasites were taken from some patients of each group and were evaluated in vitro to both drugs. In vivo, **the amodiaquine treatment shows 95% of clinical success, 2% of early clinical failures and 3% of late clinical failures. For the chloroquine treatment, the rates are respectively. 79%, 7% and 14%.** However, some patients still had a level of parasitaemia for both treatments but were asymptomatic. These parasites were found to be resistant in vitro. The authors recommend that the treatment to be used in Abie must be firstly

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amodiaquine followed by sulfadoxine-pyrimethamine in cases where there is persistent asymptomatic parasitemia.

J Infect Dis. 2006 Apr 1;193(7):978-86. Epub 2006 Mar 1.

### **Geographic differences in antimalarial drug efficacy in Uganda are explained by differences in endemicity and not by known molecular markers of drug resistance.**

**Francis D, Nsobya SL, Talisuna A, Yeka A, Kanya MR, Machekano R, Dokomajilar C, Rosenthal PJ, Dorsey G.**

**BACKGROUND:** Recent clinical trials from Uganda have shown that the risk of failure following antimalarial therapy varies geographically. We tested the hypothesis that geographic differences in the response to therapy could be explained by differences in the prevalence of known molecular markers of drug resistance. **METHODS:** Samples from 2084 patients treated with chloroquine (CQ) plus sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) plus SP were tested for the presence of known molecular markers of resistance. Differences in the risk of treatment failure across 6 sites were compared, and age and complexity of infection were controlled for. **RESULTS:** The prevalence of molecular markers of drug resistance was high at all of the sites: 61%-91% of patients were infected with parasites containing the pfcr1 Thr-76 mutation and dhfr/dhps quintuple mutation. The risk of treatment failure decreased with increasing transmission intensity for both CQ plus SP (73% to 19%) and AQ plus SP (38% to 2%). Restricting the analyses to patients infected with parasites containing all 6 mutations of interest did not affect these trends. **CONCLUSIONS:** The risk of treatment failure was inversely proportional to transmission intensity and was not explained by differences in molecular markers of antimalarial drug resistance. Our findings strongly suggest that geographic differences in response to antimalarial therapy in Uganda are primarily mediated by acquired immunity associated with malaria transmission intensity, rather than by parasite factors.

Acta Trop. 2006 Apr;98(1):6-14. Epub 2006 Mar 2.

### **Predictors of the failure of treatment with pyrimethamine-sulfadoxine in children with uncomplicated falciparum malaria.**

**Sowunmi A, Fateye BA, Adedeji AA, Gbotosho GO, Happi TC, Bamgboye AE, Bolaji OM, Oduola AM.**

The prevalence of pyrimethamine-sulfadoxine (PS)-resistant *Plasmodium falciparum* malaria has been increasing in sub-Saharan Africa or other parts of the world in the last one or two decades. The factors that identify children at risk of treatment failure after being given PS were evaluated in 291 children with acute, symptomatic, uncomplicated, *P. falciparum* malaria. The children took part in four antimalarial drug trials between July 1996 and July 2004 in a hyperendemic area of southwestern Nigeria. Following treatment, 64 (22%) of 291 children

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failed treatment by day 7 or 14. In a multivariate analysis, an age  $\leq 1.5$  years (AOR=2.9, 95% CI 1.3-6.4,  $P = 0.009$ ) and presence of fever (AOR = 3.3, 95% CI 1.28-7.14,  $P = 0.01$ ) were independent predictors of the failure of treatment with PS at presentation. Following treatment, delay in parasite clearance  $>3$  days (AOR = 2.56, CI 1.19-5.56,  $P = 0.016$ ) was an independent predictor of the failure of treatment with PS. In addition, **compared with the children who had no fever then, children with fever three or more days after starting treatment were more likely to be treatment failures.** These findings may have implications for malaria control efforts in some sub-Saharan African countries where treatment of malaria disease depends almost entirely on PS monotherapy, and for programmes employing PS or PS-based combination therapy.

J Infect Dis. 2005 Nov 15;192(10):1823-9. Epub 2005 Oct 13.

## Impact of trimethoprim-sulfamethoxazole prophylaxis on falciparum malaria infection and disease.

**Thera MA, Sehdev PS, Coulibaly D, Traore K, Garba MN, Cissoko Y, Kone A, Guindo A, Dicko A, Beavogui AH, Djimde AA, Lyke KE, Diallo DA, Doumbo OK, Plowe CV.**

**BACKGROUND:** Trimethoprim-sulfamethoxazole (TS) prophylaxis is recommended for persons living with human immunodeficiency virus infection and acquired immunodeficiency syndrome in Africa. TS and the antimalarial combination sulfadoxine-pyrimethamine (SP) share mechanisms of action and resistance patterns, and concerns about the impact of TS resistance on SP efficacy have contributed to reluctance to implement TS prophylaxis in Africa. **METHODS:** To determine whether TS prophylaxis impairs SP efficacy for treatment of uncomplicated falciparum malaria, we conducted a randomized, controlled, open-label study of TS prophylaxis. **Two hundred and forty children 5-15 years old were randomized in a 2 : 1 fashion to receive either thrice-weekly TS for 12 weeks or no prophylaxis and were treated with SP for subsequent episodes of malaria.** The incidence of malaria, SP efficacy, and the prevalence of parasite mutations that confer antifolate drug resistance were measured. **RESULTS.** TS prophylaxis had a 99.5% protective efficacy against episodes of clinical malaria, with 97% efficacy against infection. Four SP treatment failures occurred in the control group, and none occurred in the TS group. No evidence was seen for selection by TS of antifolate resistance-conferring mutations in parasite dihydrofolate reductase or dihydropteroate synthase during subclinical infections. **CONCLUSIONS.** In this setting of low antifolate resistance, TS was highly effective in preventing falciparum malaria infection and disease and did not appear to select for SP-resistant parasites.

Trans R Soc Trop Med Hyg. 2005 Oct;99(10):727-35.

## Efficacy of chloroquine + sulfadoxine--pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat Plasmodium



### **falciparum malaria in the Chittagong Hill Tracts, Bangladesh.**

**van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, Rahman M, Rahman MR, Bangali AM, Das S, Barends M, Faiz AM.**

Bangladesh faces growing levels of *Plasmodium falciparum* resistance to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP). Alternative antimalarial therapies, particularly combination regimens, need to be considered. Therefore, the efficacy of three antimalarial combination therapies was assessed in Chittagong Hill Tracts. A total of 364 *P. falciparum* patients were recruited and randomly assigned to either CQ + SP, mefloquine + artesunate (MQ + AS) or lumefantrine + artemether (Coartem). Results showed that CQ + SP therapy was less effective than the two artemisinin-based combination therapies. The day 42 PCR-corrected efficacy rate was 62.4% for CQ + SP, 100% for MQ + AS and 97.1% for Coartem. Failures occurred at a shorter interval after CQ + SP treatment than after Coartem. The artemisinin-based therapies effectively prevented development of gametocytes, whereas CQ + SP did not. All three therapies were well tolerated, although reports of mild complaints during treatment appeared higher with MQ + AS. We conclude that CQ + SP is not a viable option for replacing CQ monotherapy as first-line *P. falciparum* treatment in this area of Bangladesh. A change to artemisinin-based combination therapy is recommended. Both Coartem and MQ + AS appear to be good options, effective in curing *P. falciparum* malaria and in preventing recrudescences following treatment.

Malar J. 2005 Sep 22;4:45.

### **Safety of the methylene blue plus chloroquine combination in the treatment of uncomplicated falciparum malaria in young children of Burkina Faso [ISRCTN27290841].**

**Meissner PE, Mandi G, Witte S, Coulibaly B, Mansmann U, Rengelshausen J, Schiek W, Jahn A, Sanon M, Tapsoba T, Walter-Sack I, Mikus G, Burhenne J, Riedel KD, Schirmer H, Kouyate B, Muller O.**

**BACKGROUND:** Safe, effective and affordable drug combinations against *falciparum* malaria are urgently needed for the poor populations in malaria endemic countries. **Methylene blue (MB) combined with chloroquine (CQ) has been considered as one promising new regimen.** **OBJECTIVES:** The primary objective of this study was to evaluate the safety of CQ-MB in African children with uncomplicated *falciparum* malaria. Secondary objectives were to assess the efficacy and the acceptance of CQ-MB in a rural population of West Africa. **METHODS:** In this hospital-based randomized controlled trial, **226 children (6-59 months) with uncomplicated falciparum malaria were treated in Burkina Faso. The children were 4:1 randomized to CQ-MB (n = 181; 25 mg/kg CQ and 12 mg/kg MB over three days) or CQ (n = 45; 25 mg/kg over three days) respectively.** The primary outcome was the incidence of severe haemolysis or other serious adverse events (SAEs). Efficacy outcomes were defined according to the WHO 2003 classification system. Patients were hospitalized for four days and followed up until day 14. **RESULTS: No differences in the incidence of SAEs and other adverse events were observed between children treated with CQ-MB (including 24 cases of G6PD deficiency) compared to children treated with CQ.** There was no case of severe haemolysis and also no significant difference in mean haemoglobin between study groups.

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**Treatment failure rates were 53.7% (95% CI [37.4%; 69.3%]) in the CQ group compared to 44.0% (95% CI [36.3%; 51.9%]) in the CQ-MB group.** CONCLUSION: MB is safe for the treatment of uncomplicated falciparum malaria, even in G6PD deficient African children. However, the efficacy of the CQ-MB combination has not been sufficient at the MB dose used in this study. Future studies need to assess the efficacy of MB at higher doses and in combination with appropriate partner drugs.

Am J Trop Med Hyg. 2005 Oct;73(4):681-5.

### **Therapeutic efficacy of sulfadoxine-pyrimethamine and amodiaquine among children with uncomplicated Plasmodium falciparum malaria in Zanzibar, Tanzania.**

**Lemnge MM, Ali AS, Malecela EK, Sambu E, Abdulla R, Juma MS, Fakih K, Abdulla KH, Njau RJ.**

The efficacy of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) was assessed at Kivunge and Micheweni in Zanzibar, Tanzania, in 2001. The main objective was to obtain baseline data after observations of high levels of chloroquine treatment failures. Children (6-59 months) were randomized to receive either drug. At Kivunge, SP and AQ were given to 64 and 63 cases, while for Micheweni, 61 and 70 cases were treated. Main findings were overall high rates (> 90%) of adequate clinical response (ACR) with AQ. A lower ACR was seen in the SP group at Kivunge (87.1%) compared with Micheweni (94.8%). Furthermore, in the ACR group, 16.7% AQ parasitological resistance (RI-RIII) was encountered at Kivunge. Most of the cases of SP parasitological resistance (14.5%; RI/RII) were seen at Micheweni. Notwithstanding this, **the overall treatment failure was only 9.2% with SP and 5.5% with AQ.** The Zanzibar Ministry of Health has since reviewed its antimalarial drug policy.

Am J Trop Med Hyg. 2005 Aug;73(2):267-8.

### **Short report: no evidence of cardiotoxicity of atovaquone-proguanil alone or in combination with artesunate.**

**Gupta RK, Van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, Nosten F.**

Combinations are set to become the mainstay in treatment and prophylaxis of malaria due to Plasmodium falciparum. Various antimalarials have been implicated in cardiotoxicity via prolongation of the QTc interval. Atovaquone-proguanil is an effective and increasingly popular antimalarial choice when used alone or with artesunate in areas of drug resistance. We report the results of an investigation carried out on the Thai-Burmese border in **42 patients randomized to receive either atovaquone-proguanil or atovaquone-proguanil-artesunate for three days.** Electrocardiographic recordings were made at baseline and one hour after each dose. **There was no statistically significant change in QTc interval between baseline and any subsequent readings in either treatment group or the cohort as a whole.** We conclude

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that atovaquone-proguanil shows no evidence of cardiotoxicity either alone or when combined with artesunate.

## Malnutrition

J Health Popul Nutr. 2005 Dec;23(4):320-30.

### **Intensive nutrition education with or without supplementary feeding improves the nutritional status of moderately-malnourished children in Bangladesh.**

**Roy SK, Fuchs GJ, Mahmud Z, Ara G, Islam S, Shafique S, Akter SS, Chakraborty B.**

This prospective randomized trial was carried out to test the efficacy of a specific intervention for reducing the extent of their malnutrition and to change behaviour of mothers relating to child-feeding practices, care-giving, and health-seeking practices under the Bangladesh Integrated Nutrition Project (BINP). **The study was conducted in rural Bangladesh among 282 moderately-malnourished (weight-for-age between 61% and 75% of median of the National Center for Health Statistics standard) children aged 6-24 months. Mothers of the first intervention group received intensive nutrition education (INE group) twice a week for three months. The second intervention group received the same nutrition education, and their children received additional supplementary feeding (INE+SF group). The comparison group received nutrition education from the community nutrition promoters twice a month according to the standard routine service of BINP.** The children were observed for a further six months. After three months of interventions, a significantly higher proportion of children in the INE and INE+SF groups improved (37% and 47% respectively) from moderate to mild or normal nutrition compared to the comparison group (18%) ( $p < 0.001$ ). **At the end of six months of observation, the nutritional status of children in the intervention groups improved further from moderate to mild or normal nutrition compared to the comparison group (59% and 86% vs 30%,  $p < 0.0001$ ).** As the intensive nutrition education and supplementation given were highly effective, more children improved from moderate malnutrition to mild or normal nutritional status despite a higher incidence of morbidity. The frequency of child feeding and home-based complementary feeding improved significantly ( $p < 0.001$ ) in both the intervention groups after three months of interventions and six months of observation. Body-weight gain was positively associated with age, length-for-age, weight-for-length, frequency of feeding of khichuri, egg, and potato ( $p < 0.05$ ). Ability of mothers to identify malnutrition improved from 15% to 99% in the INE group and from 15% to 100% in the INE+SF group, but reduced from 24% to 21% in the comparison group. Use of separate feed pots, frequency of feeding, and cooking of additional complementary feeds improved significantly in the INE and INE+SF groups compared to the comparison group after three months of interventions and six months of observation. **It can be concluded from the findings of the study that intensive nutrition education significantly improves the status of moderately-malnourished children with or without supplementary feeding.**

## Randomised trials in child health in developing countries 2005-6

Food Nutr Bull. 2005 Dec;26(4):323-9.

### **Increased food intake after the addition of amylase-rich flour to supplementary food for malnourished children in rural communities of Bangladesh.**

Hossain MI, Wahed MA, Ahmed S.

International Centre for Diarrhoeal Disease Research, Bangladesh, Centre for Health and Population Research, Mohakhali, Dhaka, Bangladesh. ihossain@icddr.org

**BACKGROUND:** In Bangladesh, as in other developing countries, protein-energy malnutrition is most prevalent among children during weaning. After weaning, children are often fed cereal-based diluted low-calorie porridge, resulting in growth-faltering. **OBJECTIVE:** To assess the effect on food intake of adding amylase-rich flour (ARF) from germinated wheat to supplementary food among children in nine rural Community Nutrition Centers under the Bangladesh Integrated Nutrition Project (BINP). **METHODS:** A total of 166 malnourished children of either sex, aged 6 to 24 months, received one of three diets randomly allocated to the Community Nutrition Centers. The composition of the diets was the same; however, the consistency and calorie density were altered by adding either ARF or water. **Thirty-five children received the standard supplementary food of the BINP (S-SF), 65 received supplementary food with added ARF (ARF-SF), and 66 received supplementary food with added water (W-SF).** The children were studied for six weeks. **Results.** The mean +/- SD intake of supplementary food from a single meal by children completing six weeks on the diets was higher for children receiving ARF-SF (33.91 +/- 8.25 g) than for those receiving S-SF (25.66 +/- 6.73 g) or W-SF (30.26 +/- 8.39g) ( $p < .05$  for both comparisons). The weight of vomited food was significantly higher for children receiving W-SF than for children in the other two groups. **Weight gain and increments in length and weight-for-height were higher for children who received ARF-SF than for children in the other two groups, but the differences were not statistically significant.** The acceptability of ARF-SF was higher than that of the two other diets. The additional cost of adding 2 g of ARF to the diet was about Taka 0.25 (U.S. dollar 1 = Taka 48). **CONCLUSIONS:** Addition of ARF to existing standard supplementary food, as used under the BINP program, is a simple and effective means to increase the intake of food by changing its consistency, thus making it easier for malnourished children to ingest.

## Meningitis

Lancet. 2005 Jul 23-29;366(9482):308-13.

**Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study.**

## Randomised trials in child health in developing countries 2005-6

Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty JF, Guillerm M, Alberti KP, Pinoges L, Guerin PJ, Legros D.

**BACKGROUND:** In sub-Saharan Africa in the 1990s, more than 600,000 people had epidemic meningococcal meningitis, of whom 10% died. The current recommended treatment by WHO is short-course long-acting oily chloramphenicol. Continuation of the production of this drug is uncertain, so simple alternatives need to be found. We assessed whether the efficacy of **single-dose treatment of ceftriaxone was non-inferior to that of oily chloramphenicol for epidemic meningococcal meningitis.** **METHODS:** In 2003, we undertook a randomised, open-label, non-inferiority trial in nine health-care facilities in Niger. Participants with suspected disease who were older than 2 months were randomly assigned to receive either chloramphenicol or ceftriaxone. Primary outcome was treatment failure (defined as death or clinical failure) at 72 h, measured with intention-to-treat and per-protocol analyses. **FINDINGS:** Of 510 individuals with suspected disease, 247 received ceftriaxone, 256 received chloramphenicol, and seven were lost to follow-up. **The treatment failure rate at 72 h for the intention-to-treat analysis was 9% (22 patients) for both drug groups (risk difference 0.3%, 90% CI -3.8 to 4.5). Case fatality rates and clinical failure rates were equivalent in both treatment groups (14 [6%] ceftriaxone vs 12 [5%] chloramphenicol).** Results were also similar for both treatment groups in individuals with confirmed meningitis caused by *Neisseria meningitidis*. No adverse side-effects were reported. **INTERPRETATION: Single-dose ceftriaxone provides an alternative treatment for epidemic meningococcal meningitis--its efficacy, ease of use, and low cost favour its use.** National and international health partners should consider ceftriaxone as an alternative first-line treatment to chloramphenicol for epidemic meningococcal meningitis.

### Comment

Currently WHO's recommendation for the management of epidemic meningococcal meningitis is oily chloramphenicol (WHO Pocketbook of Hospital Care for Children: [http://www.who.int/child-adolescent-health/publications/CHILD\\_HEALTH/PB.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm)). This study shows the efficacy and, perhaps surprisingly, the relative cost effectiveness of single-dose ceftriaxone.

## Neonatal care

Acta Paediatr. 2005 Aug;94(8):1109-15.

### Postnatal peer counselling on exclusive breastfeeding of low-birthweight infants: a randomized, controlled trial.

Agrasada GV, Gustafsson J, Kylberg E, Ewald U.

**AIM:** Exclusive breastfeeding increases survival and optimizes growth of low-birthweight (LBW) infants. If supported, mothers can overcome the unique difficulties associated with breastfeeding from birth to 6 mo. We tested the efficacy of postnatal peer counselling among first-time mothers that aimed to increase exclusive breastfeeding of term LBW infants.

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**METHODS:** In a Manila hospital, **204 mothers were randomized into three groups. Two intervention groups receiving home-based counselling visits, one by counsellors trained in breastfeeding counselling (n=68), the other by counsellors trained in general childcare (n=67), were compared with a control group of mothers (n=69) who did not receive counselling.** **RESULTS:** Eighty-eight per cent of the participating pairs completed the trial. **At 6 mo, 44% of the breastfeeding counselled mothers, 7% childcare-counselled mothers and none of the mothers in the control group were exclusively breastfeeding.** More mothers in the breastfeeding counselled group than in the other groups were still breastfeeding at 6 mo. Twenty-four infants who were exclusively breastfed for 6 mo did not have any diarrhoea. All groups had improved mean weight-for-age Z-scores at 6 mo. **CONCLUSION:** This study has provided fundamental evidence of successful intervention to achieve 6 mo of exclusive breastfeeding among term LBW infants. By improving health outcomes, enhanced breastfeeding offers a distinct possibility of disrupting the intergenerational cycle of undernourished women giving birth to LBW infants.

## Nutrition

(See also Neonatal care, Vitamin A)

\*\*\* Bull World Health Organ. 2005 Jun;83(6):418-26. Epub 2005 Jun 17.

### **Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study.**

**Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, Arthur P.**

**OBJECTIVE:** To determine the association of different feeding patterns for infants (exclusive breastfeeding, predominant breastfeeding, partial breastfeeding and no breastfeeding) with mortality and hospital admissions during the first half of infancy. **METHODS:** This paper is based on a secondary analysis of data from a multicentre randomized controlled trial on immunization-linked vitamin A supplementation. **Altogether, 9424 infants and their mothers (2919 in Ghana, 4000 in India and 2505 in Peru) were enrolled when infants were 18-42 days old in two urban slums in New Delhi, India, a periurban shanty town in Lima, Peru, and 37 villages in the Kintampo district of Ghana.** Mother-infant pairs were visited at home every 4 weeks from the time the infant received the first dose of oral polio vaccine and diphtheria-pertussis-tetanus at the age of 6 weeks in Ghana and India and at the age of 10 weeks in Peru. At each visit, mothers were queried about what they had offered their infant to eat or drink during the past week. Information was also collected on hospital admissions and deaths occurring between the ages of 6 weeks and 6 months. The main outcome measures were all-cause mortality, diarrhoea-specific mortality, mortality caused by acute lower respiratory infections, and hospital admissions. **FINDINGS:** There was no significant difference in the risk of death between children who were exclusively breastfed and those who were predominantly breastfed (adjusted hazard ratio (HR) = 1.46; 95% confidence interval (CI) = 0.75-2.86). **Non-breastfed infants had a higher risk of dying when compared with those who had been predominantly breastfed (HR = 10.5; 95% CI = 5.0-22.0; P < 0.001) as did partially breastfed infants (HR = 2.46; 95% CI = 1.44-4.18; P = 0.001).** **CONCLUSION:** There are two major implications of these findings. **First, the extremely high risks of infant mortality associated with not being breastfed need to be taken into account when informing HIV-**

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**infected mothers about options for feeding their infants. Second, our finding that the risks of death are similar for infants who are predominantly breastfed and those who are exclusively breastfed suggests that in settings where rates of predominant breastfeeding are already high, promotion efforts should focus on sustaining these high rates rather than on attempting to achieve a shift from predominant breastfeeding to exclusive breastfeeding.**

### Comment

*This study is a counterpoint to previous findings that mixed breast milk and artificial formula feeding may carry a higher risk of HIV transmission than exclusive artificial feeding.*

*Predominant breast feeding will confer survival benefits similar to exclusive breast feeding, so we shouldn't be focused too much on exclusivity of breast feeding, but rather encourage as many mothers to breast feed as much as possible. Specific interventions should be targeted towards mothers who are unlikely to breast feed at all, and several community-based RCTs this year have shown the benefits of education at every opportunity on rates of breast feeding and better infant feeding practices.*

Public Health Nutr. 2005 Aug;8(5):461-7.

## **Fortification of maize meal improved the nutritional status of 1-3-year-old African children.**

**Nesamvuni AE, Vorster HH, Margetts BM, Kruger A.**

**OBJECTIVE:** To evaluate the effectiveness of a vitamin-fortified maize meal to improve the nutritional status of 1-3-year-old malnourished African children. **DESIGN:** A randomised parallel intervention study was used in **which 21 experimental children and their families received maize meal fortified with vitamin A, thiamine, riboflavin and pyridoxine, while 23 control children and their families received unfortified maize meal. The maize meal was provided for 12 months** to replace the maize meal habitually consumed by these households. **METHODS:** Sixty undernourished African children with height-for-age or weight-for-age below the 5th percentile of the National Center for Health Statistics' criteria and aged 1-3 years were randomly assigned to an experimental or control group. Baseline measurements included demographic, socio-economic and dietary data, as well as height, weight, haemoglobin, haematocrit, serum retinol and retinol-binding protein (RBP). Anthropometric, blood and serum variables were measured again after 12 months of intervention. Complete baseline measurements were available for 44 children and end data for only 36. Changes in these variables from baseline to end within and between groups were assessed for significance with paired t-tests, t-tests and analysis of variances using the SPSS program, controlling for expected weight gain in this age group over 12 months. Relationships between changes in variables were examined by calculating correlation coefficients. **RESULTS: The children in the experimental group had a significantly ( $P < \text{or} = 0.05$ ) higher increase in body weight than control children (4.6 kg vs. 2.0 kg) and both groups had significant ( $P < \text{or} = 0.05$ ) but similar increases in height.** The children in the experimental group showed non-significant increases in haemoglobin and serum retinol, **while the control children had a significant ( $P = 0.007$ ) decrease in RBP.** The change in serum retinol showed a significant correlation with baseline retinol ( $P = 0.014$ ), RBP ( $P = 0.007$ ) and weight ( $P = 0.029$ ), as well as with changes in haemoglobin ( $P = 0.029$ ). **CONCLUSION:** Despite a small sample size, **this**

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**study showed positive effects of a vitamin-fortified maize meal on weight gain and some variables of vitamin A status in 1-3-year-old African children.** The study confirmed the relationship between vitamin A and iron status. The results suggest that fortification of maize meal would be an effective strategy to address micronutrient deficiencies in small children in South Africa.

Eur J Clin Nutr. 2006 Feb;60(2):265-71.

### **Early short-term infant food supplementation, maternal weight loss and duration of breast-feeding: a randomised controlled trial in rural Senegal.**

**Ly CT, Diallo A, Simondon F, Simondon KB.**

**OBJECTIVE:** Early supplementation of breastfed infants may have consequences both for the mother and the child. We hypothesised that it would result in decreased maternal weight loss and in shorter durations of breastfeeding and birth intervals. **DESIGN:** Controlled randomised population-based trial. **SETTING:** Six villages in the Sine area of Senegal, West Africa. **Subjects:** Healthy breastfed infants and their mothers, 68 controls and 66 supplemented infants at randomization. **INTERVENTION:** **Supplementation with high-energy, nutrient dense food from 4 to 7 months of age, twice daily under supervision of field workers.** Both controls and supplemented infants were free to eat other complementary foods. Maternal weight was measured monthly. Dates of breastfeeding cessation and of subsequent births were collected prospectively through weekly demographic surveillance, and were analysed using Cox's regression models and 'intent-to-supplement' approach. **RESULTS:** Mean maternal weight gain from 4 to 7 months postpartum tended to be greater in the supplemented group (+0.25 kg/months, 95% confidence interval (CI): -0.07, +0.57). Supplemented infants were breastfed for significantly longer durations than controls (medians: 24.9 and 23.7 months, respectively, P: 0.034). Their adjusted hazard ratio (HR) for breastfeeding cessation was 0.59 (95% CI: 0.40, 0.89). Their mothers had a lower risk of a new birth than mothers of controls (adjusted HR: 0.57, 95% CI: 0.36, 0.92). **CONCLUSIONS:** **Early short-term infant supplementation tended to decrease maternal postpartum weight loss, but it increased, rather than shortened, the duration of breastfeeding and birth interval.** **SPONSORSHIP:** This study was supported by a grant from the French Ministry of Research (Grant 92L0623).

Appetite. 2005 Dec;45(3):279-86. Epub 2005 Aug 26.

### **Effects of the duration of the habituation period on energy intakes from low and high energy density gruels by Burkinabe infants living in free conditions.**

**Traore T, Vieu MC, Alfred TS, Serge T.**

The present study was carried out in Ouagadougou (Burkina Faso) with the aim of determining if the duration of the habituation period (1, 5 or 10 days) to low and high energy density gruels affected the amounts consumed or the energy intakes from gruels consumed by 6-9-month-old infants. Thirty infants were chosen randomly among the eligible children in the study area and



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randomly assigned to two groups (S1 and S2). Each infant was given successively for 10 consecutive days two experimental gruels, each type of gruel being fed twice a day. The 15 infants in group S1 received low energy density gruel (G1) in the first period and high energy density gruel (G2) in the second, and the 15 infants in group S2 received G2 in the first period and G1 in the second. The two periods of 10 days were separated by 4 days during which the infant received his or her usual foods. The intakes of experimental gruels and other complementary foods were measured on days 1, 5 and 10 of each period. Whatever the type of gruel, the 10-day period of habituation did not result in an increase in the amounts consumed or in the energy intakes from these gruels. The amounts of G1 consumed on day 5 were significantly higher than those of G2 (9.0 vs 6.8 g/kg/meal;  $p = 0.044$ ). Energy intakes from G2 were significantly higher than those from G1 on days 1 (28.8 vs 18.0 kJ/kg/meal;  $p = 0.0002$ ), 5 (28.8 vs 19.2 kJ/kg/meal;  $p = 0.002$ ) and 10 (25.9 vs 15.5 kJ/kg/meal;  $p = 0.0004$ ). Daily frequencies of breastfeeding (approximately 5.6), water drinking (approximately 3.7) and meals with foods other than experimental gruels were relatively high and did not vary with the duration of the habituation period or the type of gruels. Whatever the type of gruel, the increase in the duration of the habituation period did not increase the amount consumed or energy intakes. The study confirmed that consumption of high energy density gruels led to a 60% increase in energy intakes in comparison with the consumption of low energy density gruels.

Health Policy Plan. 2005 Sep;20(5):328-36.

## Use of multiple opportunities for improving feeding practices in under-twos within child health programmes.

**Bhandari N, Mazumder S, Bahl R, Martines J, Black RE, Bhan MK; Infant Feeding Study Group.**

**OBJECTIVES:** In a community randomized trial, we aimed to promote exclusive breastfeeding and appropriate complementary feeding practices in under-twos to ascertain the feasibility of using available channels for nutrition counselling, their relative performance and the relationship between intensity of counselling and behaviour change. We also assessed whether using multiple opportunities to impart nutrition education adversely affected routine activities. **METHODS:** We conducted a community randomized, controlled effectiveness trial in rural Haryana, India, with four intervention and four control communities. We trained health and nutrition workers in the intervention communities to counsel mothers at multiple contacts on breastfeeding exclusively for 6 months and on appropriate complementary feeding practices thereafter. The intervention was not just training health and nutrition workers in counselling but included community and health worker mobilization. **FINDINGS:** In the intervention group, about 32% of caregivers were counselled by traditional birth attendants at birth. **The most frequent sources of counselling from birth to 3 months were immunization sessions (45.1%) and home visits (32.1%), followed closely by weighing sessions (25.5%); from 7 to 12 months, home visits (42.6%) became more important than the other two.** An increase in the number of channels through which caregivers were counselled was positively associated with exclusive breastfeeding prevalence at 3 months ( $p = 0.002$ ), consumption of milk/cereal gruel or mix use at 9 months ( $p = 0.004$ ) and 18 months ( $p = 0.003$ ), undiluted milk at 9 months ( $p < 0.0001$ ) and 24 hour non-breast-milk energy intakes at 18 months ( $p = 0.023$ ), after controlling for potential confounding factors. Intervention areas,

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compared with the control, had higher coverage for vitamin A (45% vs. 11.5%) and iron folic acid (45% vs. 0.4%) supplementation. **CONCLUSIONS:** Using multiple available opportunities and workers for counselling caregivers was feasible, resulted in high coverage and impact, and instead of disrupting ongoing services, resulted in their improvement.

Am J Clin Nutr. 2006 Mar;83(3):714-21.

### **Growth, bone mass, and vitamin D status of Chinese adolescent girls 3 y after withdrawal of milk supplementation.**

**Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H.**

**BACKGROUND:** A 2-y school milk intervention trial showed that 330 mL of a dietary milk supplement (fortified with calcium alone or with both calcium and vitamin D) enhanced the growth and bone mineral accretion of Chinese girls aged 10 y at baseline. Girls who received milk fortified with both calcium and vitamin D also had better vitamin D status than did girls who received nothing or girls who received milk fortified only with calcium. **OBJECTIVE:** **The aim was to evaluate whether these effects were sustained 3 y after supplement withdrawal.** **DESIGN:** Anthropometric measures and dietary intake were reassessed in 501 of the 698 girls whose data had been studied at the end of the intervention. As in the intervention phase, total-body bone mineral content and bone mineral density and serum 25-hydroxyvitamin D concentrations were measured in half of these subjects. **RESULTS:** At follow-up, 99% of girls had reached menarche, at a mean (+/-SD) menarcheal age of 12.1 +/- 1.1 y. No significant differences in the timing of menarche were observed between the 3 groups ( $P = 0.6$ ). No significant differences in the changes of total-body bone mineral content and bone mineral density since baseline were observed between the groups. The group receiving calcium-fortified milk had significantly greater gains in sitting height ( $0.9 \pm 0.3\%$ ;  $P = 0.02$ ) than did the control group. The group that received calcium- and vitamin D-fortified milk had  $17.1 \pm 6.7\%$  lower serum 25-hydroxyvitamin D concentrations than did the control group ( $P = 0.04$ ), but the difference was attenuated by additional adjustment for physical activity level ( $14.2 \pm 6.7\%$ ;  $P = 0.08$ ). **CONCLUSION:** **Milk supplementation during early puberty does not have long-lasting effects on bone mineral accretion.**

J Clin Endocrinol Metab. 2006 Feb;91(2):405-12. Epub 2005 Nov 8.

### **Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial.**

**El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, Choucair M, Arabi A, Vieth R.**

**BACKGROUND:** Despite the high prevalence of hypovitaminosis D in children and adolescents worldwide, the impact of vitamin D deficiency on skeletal health is unclear.

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**METHODS:** One hundred seventy-nine girls, ages 10-17 yr, were randomly assigned to receive weekly oral vitamin D doses of 1,400 IU (equivalent to 200 IU/d) or 14,000 IU (equivalent to 2,000 IU/d) in a double-blind, placebo-controlled, 1-yr protocol. Areal bone mineral density (BMD) and bone mineral content (BMC) at the lumbar spine, hip, forearm, total body, and body composition were measured at baseline and 1 yr. Serum calcium, phosphorus, alkaline phosphatase, and vitamin D metabolites were measured during the study. **RESULTS:** In the overall group of girls, lean mass increased significantly in both treatment groups ( $P < \text{or} = 0.05$ ); bone area and total hip BMC increased in the high-dose group ( $P < 0.02$ ). In premenarcheal girls, lean mass increased significantly in both treatment groups, and there were consistent trends for increments in BMD and/or BMC at several skeletal sites, reaching significance at lumbar spine BMD in the low-dose group and at the trochanter BMC in both treatment groups. There was no significant change in lean mass, BMD, or BMC in postmenarcheal girls. **CONCLUSIONS:** Vitamin D replacement had a positive impact on musculoskeletal parameters in girls, especially during the premenarcheal period.

J Nutr. 2006 Jun;136(6):1617-23.

### **A multimicronutrient-fortified seasoning powder enhances the hemoglobin, zinc, and iodine status of primary school children in North East Thailand: a randomized controlled trial of efficacy.**

**Winichagoon P, McKenzie JE, Chavasit V, Pongcharoen T, Gowachirapant S, Boonpradern A, Manger MS, Bailey KB, Wasantwisut E, Gibson RS.**

Anemia and co-existing deficiencies of zinc, iron, iodine, and vitamin A occur among children in many developing countries including NE Thailand, probably contributing to impairments in growth, immune competence, and cognition. Sustainable strategies are urgently required to combat these deficiencies. We assessed the efficacy of a micronutrient-fortified seasoning powder served with a school lunch on reducing anemia and improving the micronutrient status of rural NE Thai children. **Children (n = 569) aged 5.5-13.4y from 10 schools were randomly assigned to receive a seasoning powder either unfortified or fortified with zinc (5 mg), iron (5 mg), vitamin A (270 microg), and iodine (50 microg) (per serving) and incorporated into a school lunch prepared centrally and delivered 5 d/wk for 31 wk.** Teachers monitored school lunch consumption. Baseline and final micronutrient status, hemoglobinopathies, and infection or inflammation were assessed from blood and urine samples. **For the primary outcome, anemia (based on hemoglobin), no intervention effect was apparent (odds ratio: 1.02 95% CI: 0.69, 1.51) after adjustment for design strata. The odds of zinc (based on serum zinc) and urinary iodine deficiency in the fortified group were 0.63 (0.42, 0.94) and 0.52 (0.38, 0.71) times those in the unfortified group, respectively.** Fortification had no effect on serum retinol (0.61: 0.25, 1.51), ferritin (1.12: 0.43, 2.96), or mean red cell volume (1.16: 0.82, 1.64). Therefore, a micronutrient-fortified seasoning powder is a promising vehicle for improving zinc, iodine, and hemoglobin status, and its potential for incorporation into lunch programs in day care centers and schools in NE Thailand warrants investigation.

Eur J Clin Nutr. 2005 Aug;59(8):960-8.

**Effect of vitamin supplementation to HIV-infected pregnant women on the micronutrient status of their infants.**

**Baylin A, Villamor E, Rifai N, Msamanga G, Fawzi WW.**

**OBJECTIVE:** We examined whether supplementation with vitamin A and/or vitamins B, C, and E to HIV-infected women during pregnancy and lactation is related to increased concentrations of vitamins A, B12, and E in their infants during the first 6 months of life. **DESIGN:** We carried out a randomized clinical trial among 716 mother-infant pairs in Dar-es-Salaam, Tanzania. Women were randomly allocated to receive a daily oral dose of one of four regimens: vitamin A, multivitamins (B, C, and E), multivitamins including A, or placebo. Supplementation started at first prenatal visit and continued after delivery throughout the breastfeeding period. The serum concentration of vitamins A, E and B12 was measured in infants at 6 weeks and 6 months postpartum. **RESULTS: Maternal vitamin A supplementation increased serum retinol in the infants at 6 weeks (mean difference=0.09 micromol/l, P<0.0001) and 6 months (mean difference=0.06 micromol/l, P=0.0002), and decreased the prevalence of vitamin A deficiency, but had no impact on serum vitamins E or B12.** Multivitamins increased serum vitamin B12 at 6 weeks and 6 months (mean differences=176 pmol/l, P<0.0001 and 127 pmol/l, P<0.0001, respectively) and vitamin E (mean differences=1.8 micromol/l, P=0.0008 and 1.1 micromol/l, P=0.004, respectively) and decreased the prevalence of vitamin B12 deficiency. **CONCLUSIONS:** Vitamin supplementation to HIV-1-infected women is effective in improving the vitamin status of infants during the first 6 months of age.

## **Oral health**

Community Dent Health. 2005 Dec;22(4):253-9.

**The process and outcome of a programme for preventing early childhood caries in Thailand.**

**Vachirarojpisan T, Shinada K, Kawaguchi Y.**

**OBJECTIVE:** To evaluate the process and outcomes of a participatory dental health education (DHE) programme for preventing early childhood caries (ECC). **DESIGN:** A one-year intervention programme. **SETTING:** 21 health centres. **PARTICIPANTS:** 520 mothers/caregivers of 6-19 month-old children who lived in a rural area of Thailand. **INTERVENTION:** Small group discussion with active involvement in the intervention group and the national teaching DHE programme in the control group. **MAIN OUTCOME MEASURES:** Health centre staff impact evaluation, children's dental cavitated carious increment and stated changes in oral health behaviour. **RESULTS:** After one-year, the percent of subjects using a toothbrush and tooth brushing with fluoride toothpaste was 93% and 87% respectively in the intervention group, significantly higher (p<0.01) than the control group (73% and 58% respectively). Night time bottle-feeding, falling asleep with a bottle and sweet

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snack diet behaviour appeared the same in both groups. The net cavitated carious increment was 3.5 (SD=3.4) teeth in the intervention and 3.2(SD=3.5) in the control group. Health centre staff were very supportive of the programme and suggested extending the participatory format to other child health topics. CONCLUSIONS: The participatory dental health education model was shown to be a practical and effective method for increasing oral hygiene practice, but was not sufficient to prevent the development of ECC. This single intervention in the short term is not seen as sufficient to prevent the development of ECC.

Int J Dent Hyg. 2006 Feb;4(1):30-4.

### **The efficacy of a school-based caries preventive program: a 4-year study.**

**Al-Jundi SH, Hammad M, Alwaeli H.**

This longitudinal study aimed at testing the efficacy of a school-based caries preventive program, by comparing dental caries status of two groups, a study group (436 children) and a control group (420 children) over a period of 4 years. The study group received a preventive program which consisted of **intensive oral hygiene instructions sessions, and supervised daily tooth brushing using fluoridated tooth paste in schools**. The control group received only oral hygiene instructions sessions. Annual dental examination to record dental caries status, using Decayed Missed Filled Teeth Index (DMFT) and deft, was conducted for both groups over a period of 4 years. At the end of the fourth year the efficacy of the program was tested by comparing the DMFT and deft indices for the two groups using Pearson chi-square test and Cochran-Mantel-Haenzele test. The level of significance was set at  $P < 0.05$ . The results after 4 years showed that the caries status of the children in the study group was better than that of the control group. The difference was statistically significant ( $P$ -value 0.001). The estimates of relative risk values also showed that children in **the control group are 3.1 and 6.4 times at higher risk of having dental caries than those in the study group** for age group 12 and 6 respectively. This study proves that supervised daily tooth brushing using fluoridated toothpaste is successful in controlling dental caries in children.

## Public Health / hygiene

Lancet. 2005 Jul 16-22;366(9481):225-33.

### **Effect of handwashing on child health: a randomised controlled trial.**

**Luby SP, Agboatwalla M, Feikin DR, Painter J, Billhimer W, Altaf A, Hoekstra RM.**

BACKGROUND: More than 3.5 million children aged less than 5 years die from diarrhoea and acute lower respiratory-tract infection every year. We undertook a randomised controlled trial to assess the effect of handwashing promotion with soap on the incidence of acute respiratory infection, impetigo, and diarrhoea. METHODS: In adjoining squatter settlements in Karachi, Pakistan, we **randomly assigned 25 neighbourhoods to handwashing promotion; 11**

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**neighbourhoods (306 households) were randomised as controls.** In neighbourhoods with handwashing promotion, **300 households each were assigned to antibacterial soap containing 1.2% triclocarban and to plain soap.** Fieldworkers visited households weekly for 1 year to encourage handwashing by residents in soap households and to record symptoms in all households. Primary study outcomes were diarrhoea, impetigo, and acute respiratory-tract infections (ie, the number of new episodes of illness per person-weeks at risk). Pneumonia was defined according to the WHO clinical case definition. Analysis was by intention to treat. **FINDINGS: Children younger than 5 years in households that received plain soap and handwashing promotion had a 50% lower incidence of pneumonia than controls (95% CI (-65% to -34%).** Also compared with controls, **children younger than 15 years in households with plain soap had a 53% lower incidence of diarrhoea (-65% to -41%) and a 34% lower incidence of impetigo (-52% to -16%).** Incidence of disease did not differ significantly between households given plain soap compared with those given antibacterial soap. **INTERPRETATION: Handwashing with soap prevents the two clinical syndromes that cause the largest number of childhood deaths globally-namely, diarrhoea and acute lower respiratory infections.** Handwashing with daily bathing also prevents impetigo.

## School health

Prev Med. 2006 Jan;42(1):27-32. Epub 2005 Nov 21.

### **Can a handwashing intervention make a difference? Results from a randomized controlled trial in Jerusalem preschools.**

**Rosen L, Manor O, Engelhard D, Brody D, Rosen B, Peleg H, Meir M, Zucker D.**

**BACKGROUND:** Preschools are often focal points for the spread of illness among young children. The objective of this preschool intervention trial was to determine whether a hygiene program can promote handwashing and thereby reduce illness absenteeism. **METHODS:** This cluster randomized trial included 40 Jerusalem preschools with 1029 children for 6 baseline days and 66 study days, yielding 73,779 child days. The main outcomes were rates of handwashing and illness absenteeism. **The intervention included an educational program and environmental changes.** A simultaneous subtrial was run to test a home component. **RESULTS:** This multi-site intervention program produced sustained behavioral and environmental changes over a 6-month period. **An approximately threefold increase in handwashing with soap was observed among preschool children exposed to the intervention.** Neither the preschool nor the home intervention program reduced illness absenteeism or overall absenteeism. **CONCLUSIONS:** This trial illuminates the potential of the preschool as a promising venue for health promotion activities leading to sustained behavioral change, yet suggests the need for enhanced approaches for reducing illness absenteeism.

## Surgical problems

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Trop Doct. 2006 Jan;36(1):42-4.

### **Use of prophylactic antibiotics in a paediatric day-case surgery at NAUTH, Nnewi, Nigeria: a randomized double-blinded study.**

**Osuigwe AN, Ekwunife CN, Ihekowba CH.**

This was a randomized double-blinded study to assess the need for prophylactic antibiotics in paediatric day-case surgery, as well as the cost implication. Group A received preoperative intravenous ampiclox and vitamin B complex in doses appropriate for weight and age, while group B received only vitamin B complex as a placebo. The study was completed by 138 (95.2%) patients in group A, and by 140 (97.2%) patients in group B. **Wound infection was seen in seven (5%) patients in group A and six (4.3%) patients in group B.** The average cost of hernia repair in group A was US 43 dollars and US 31.1 dollars in group B.

## Tuberculosis

Int J Tuberc Lung Dis. 2005 Oct;9(10):1171-3.

### **Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil.**

**Barreto ML, Cunha SS, Pereira SM, Genser B, Hijjar MA, Yury Ichihara M, de Brito SC, Dourado I, Cruz A, Santa'Ana C, Rodrigues LC.**

Bacille Calmette-Guerin (BCG) efficacy against pulmonary disease is highly variable; until very recently there was no evidence of protection after 10 years. **In the control arm of a trial of efficacy of revaccination of schoolchildren in Brazil we found substantial protection (39%; 95%CI 9-58) of neonatal BCG against all forms of tuberculosis (TB) 15-20 years after vaccination, much longer than previously believed.** This confirms recent findings from an earlier trial, and must be considered in the design of trials of new TB vaccines and in policy decisions based on assumed lack of neonatal BCG protection with time.

Indian J Med Res. 2006 Feb;123(2):119-24.

### **Influence of sex, age & nontuberculous infection at intake on the efficacy of BCG: re-analysis of 15-year data from a double-blind randomized control trial in South India.**

**Narayanan PR.**

**BACKGROUND & OBJECTIVE:** To estimate the efficacy of BCG in preventing tuberculosis over a 15-year period, and also to assess the impact of infection with nontuberculous

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environmental mycobacteria in a rural community in Chingleput district in Tamil Nadu in south India. We re-analysed the 15-year follow up data of a large randomized trial conducted earlier. **METHODS: A double-blind randomized control trial was initiated in 1968, in which over 100,000 uninfected subjects with a normal radiograph were allocated to placebo, BCG in low dose (0.01 mg) or BCG in high dose (1.0 mg); two widely used strains of BCG were employed, each in one half of the vaccinated subjects. Sensitivity to purified protein derivative (PPD-B) was also determined. The study population was followed for 15 yr by radiographic surveys of the total population once every 2.5 yr, selective case finding in suspects once in 10 months, and investigation of those reporting voluntarily with chest symptoms.** **RESULTS:** Coverage by radiography was of the order of 80 per cent throughout, while coverage by sputum examination of suspects was usually 90 per cent or above. **The annual incidence of culture-positive tuberculosis (irrespective of smear) was estimated to be 55 per 100,000, and neither strain of BCG had any effect.** The failure to protect was seen in both males and females, and in children and adults. However, in a subset of over 40,000 subjects who were also nonreactors to PPD-B, **BCG had a low level of protection, i.e., 32 per cent (95% CI=3-52%), 29 per cent with the Danish strain and 34 per cent with the French strain.** **INTERPRETATION & CONCLUSION:** Our findings reaffirm that BCG was of little value in preventing sputum-positive cases of pulmonary tuberculosis.

### Comment

*The above two trials reinforce previous research that the protective efficacy of BCG is highly variable, being highly dependent on the strain used and the population studied.*

Trop Med Int Health. 2005 Nov;10(11):1090-8.

## Treatment of lymph node tuberculosis--a randomized clinical trial of two 6-month regimens.

**Jawahar MS, Rajaram K, Sivasubramanian S, Paramasivan CN, Chandrasekar K, Kamaludeen MN, Thirithuvathas AJ, Ananthalakshmi V, Prabhakar R.**

**OBJECTIVE:** The currently recommended treatment for lymph node tuberculosis is 6 months of rifampicin and isoniazid plus pyrazinamide for the first 2 months, given either daily or thrice weekly. The objective of this study was to assess the efficacy of a 6-month twice-weekly regimen and a daily two-drug regimen. **METHODS:** Patients with biopsy confirmed superficial lymph node tuberculosis were randomly allocated to receive either a daily self-administered 6-month regimen of rifampicin and isoniazid, or a twice-weekly, directly observed, 6-month regimen of rifampicin and isoniazid plus pyrazinamide for the first 2 months, in Madurai, South India. Patients were followed up for 36 months after completing treatment. **RESULTS:** **Of 277 enrolled patients, data was available for analysis in 268. At the end of treatment, 116 of 134 [87%; 95% confidence interval (CI) 81-93%] patients in each treatment group had a favourable clinical response; 14 (11%; 95% CI 6-16%) and 17 (13%; 95% CI 7-19%) patients had a doubtful response, and 4 (3%; 95% CI 0-6%) and 1 (1%; 95% CI 0-2%) patients had an unfavourable response among those treated with the daily and twice-weekly regimen, respectively.** During 36 months after completion of treatment, five patients [2 (2%; 95% CI 1-3%) and 3 (2%; 95% CI 1-3%) patients treated with the daily and twice-weekly regimen, respectively] had relapse of lymph node tuberculosis, of 260 assessed. Adverse reactions probably attributable to the treatment regimens occurred in 1% of the



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patients treated daily and in 11% of those treated twice-weekly ( $P < 0.001$ ). At the end of 36 months after treatment, 126 of 134 (94%; 95% CI 90-98%) and 129 of 134 (96%; 95% CI 94-98%) of the patients treated with the daily and twice-weekly regimen, respectively, had a successful outcome. **CONCLUSION: Both the self-administered daily regimen and the fully observed twice-weekly regimen were highly efficacious for treating patients with lymph node tuberculosis and may be considered as alternative options to the recommended regimens.**

## Typhoid

Trop Med Int Health. 2005 Dec;10(12):1219-28.

### **A multi-country cluster randomized controlled effectiveness evaluation to accelerate the introduction of Vi polysaccharide typhoid vaccine in developing countries in Asia: rationale and design.**

Acosta CJ, Galindo CM, Ali M, Elyazeed RA, Ochiai RL, Danovaro-Holliday MC, Page AL, Thiem VD, Jin Y, Park JK, Lee H, Puri MK, Ivanoff B, Agtini MD, Soeharno R, Simanjuntak CH, Punjabi NH, Canh do G, Sur D, Nizami Q, Manna B, Bai-qing D, Anh DD, Honghui Y, Bhattacharya SK, Bhutta Z, Trach DD, Xu ZY, Pang T, Donner A, Clemens JD.

Phase-III vaccine efficacy trials typically employ individually randomized designs intended to ensure that measurements of vaccine protective efficacy reflect only direct vaccine effects. As a result, decisions about introducing newly licensed vaccines into public health programmes often fail to consider the substantially greater protection that may occur when a vaccine is deployed in public health programmes, due to the combination of direct plus indirect vaccine protective effects. Vaccine total protection can be better evaluated with cluster randomized trials. Such a design was considered to generate policy relevant data to accelerate the rationale introduction of the licensed typhoid fever Vi polysaccharide (PS) vaccine in Asia by the Diseases of the Most Impoverished (DOMI) typhoid fever programme. The DOMI's programme multi-country study is one of the largest cluster randomized vaccine trials ever mounted in Asia, which includes approximately 200,000 individuals. Its main objective is to determine the effectiveness of a licensed Vi PS vaccine. The rationale and design of this study are discussed. Preliminary results are presented that determined the final planning of the trial before immunization. Important methodological and practical issues regarding vaccine cluster randomized designs are illustrated.

## Vaccines

(See also malaria, typhoid)

Vaccine. 2005 Dec 30;23(50):5792-7. Epub 2005 Jul 6.

**Immunogenicity of a recombinant, yeast-derived, anti-hepatitis-B vaccine after alternative dosage and schedule vaccination in Pakistani children.**

**Akram DS, Maqbool S, Khan DS, Jafri R, Randhawa S, Valenzuela-Silva C, Lopez-Saura P.**

A controlled, randomized trial was conducted in urban areas of Karachi and Lahore with the aim to look for ways to improve the cost-effectiveness of hepatitis B vaccination. Children under 15 years old (including neonates) were selected and screened for immunization by three regimens according to the frequency and doses of the recombinant vaccine used (Heberbiovac HB, Heber Biotec, Havana). Group A received 10 microg at 0, 1 months; group B (control) received 10 microg at 0, 1 and 2 months (standard regime), and group C received 5 microg at 0, 1 and 2 months. Antibody levels were titrated 2 months after the last dose. Cut-off for seroprotection and hyperresponse were taken as 10 and 100 IU/L, respectively. Nine hundred and ninety children were included and evaluated after discarding those positive for serological hepatitis virus infection markers. Seroprotection rates were 100, 99.7 and 99.7%, and hyperresponse was achieved by 92.7, 99.4, and 97% of the vaccinees in groups A, B, and C, respectively. The same good result was obtained in extreme ages subgroups (< or =1 year and > or =10 years old). The 1-year follow up of the children from Karachi showed good persistence of seroprotection (98, 100, and 99.4%) and hyperresponse (79.7, 96.7, and 87.4%). It is concluded that it is feasible to improve the cost-benefit ratio and compliance of hepatitis B vaccination by means of a two-shots or reduced dose schedule of the vaccine employed in the trial.

J Infect Dis. 2005 Sep 1;192 Suppl 1:S6-S16.

**Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants.**

**Phua KB, Quak SH, Lee BW, Emmanuel SC, Goh P, Han HH, De Vos B, Bock HL.**

**BACKGROUND:** At present, no rotavirus vaccine is commercially available for use worldwide. Hence, a live, attenuated monovalent vaccine was developed with human strain RIX4414 (G1P1A P[8] specificity). Vaccination trials involving infants are ongoing in developed and developing countries. **METHODS:** This study was **a randomized, double-blind, placebo-controlled trial conducted at pediatric hospitals and polyclinics in Singapore for the evaluation of the immunogenicity, reactogenicity, and efficacy of 2 oral doses of RIX4414.** In total, 2464 healthy infants (who were 11-17 weeks old when the first dose was administered, which is in accordance with the local immunization schedule) were enrolled to receive RIX4414 at 3 concentrations of virus (10(4.7), 10(5.2), or 10(6.1) focus-forming units) or placebo at 1-month intervals, concomitantly with routinely administered infant vaccines. **RESULTS:** **The RIX4414 vaccine was highly immunogenic, and virtually all vaccine recipients (98%-100%) experienced "vaccine take" (i.e., a combined immunogenicity end point based on seroconversion and/or shedding of RIX4414 in postvaccination stool samples) after receipt of 2 doses at all 3 dosage levels.** Depending on the virus concentration, the anti-rotavirus IgA seroconversion rate varied from 76% (95% confidence interval [CI], 68%-83%) to 91% (95% CI, 85%-95%). Two doses of RIX4414 were

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well tolerated, with no increase in high fever, severe diarrhea, or vomiting after either dose or with increased viral concentration, compared with placebo. There was no observed interference with routine vaccinations of infants when RIX4414 was coadministered. **The calculated efficacy of RIX4414 against rotavirus gastroenteritis was 82% (P = .046); however, this result was considered to be of limited conclusive value because of the low number of rotavirus gastroenteritis episodes identified during the follow-up period.**

CONCLUSIONS: The live, attenuated rotavirus vaccine (RIX4414) was well tolerated and highly immunogenic in Singaporean infants. The immunogenicity of routinely administered infant vaccines was not impaired by concomitant administration of RIX4414 vaccine.

## Vitamin A

BMJ. 2005 Dec 17;331(7530):1428-32. Epub 2005 Nov 23.

### Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality.

Benn CS, Martins C, Rodrigues A, Jensen H, Lisse IM, Aaby P.

OBJECTIVES: To determine whether the dose of vitamin A currently recommended by the World Health Organization or half this dose gives better protection against childhood morbidity and mortality. DESIGN: Randomised study. SETTING: A combined oral polio vaccine and vitamin A supplementation campaign in Guinea-Bissau, Africa. PARTICIPANTS: 4983 children aged 6 months to 5 years. INTERVENTIONS: One of two doses of vitamin A (recommended and half); oral polio vaccine. MAIN OUTCOME MEASURES: Mortality and morbidity at six and nine months. RESULTS: Mortality was lower in the children who took half the recommended dose of vitamin A compared with the full dose at both six months (mortality rate ratio 0.69, 95% confidence interval 0.36 to 1.35) and nine months (0.62, 0.36 to 1.06) of follow-up. **There was a significant interaction between sex and dose, the lower dose being associated with significantly reduced mortality in girls (0.19, 0.06 to 0.66) but not in boys (1.98, 0.74 to 5.29).** The lower dose of vitamin A was consistently associated with lower hospital case fatality in girls (0.19, 0.02 to 1.45). Paradoxically, in children aged 6-18 months, the low dose was associated with slightly higher morbidity. CONCLUSIONS: **Half the dose of vitamin A currently recommended by WHO may provide equally good or better protection against mortality but not against morbidity.**

J Nutr. 2005 Nov;135(11):2669-73.

### Vitamin a supplementation does not affect infants' immune responses to polio and tetanus vaccines.

Newton S, Cousens S, Owusu-Agyei S, Filteau S, Stanley C, Linsell L, Kirkwood B.

It has been suggested that administering vitamin A with the measles vaccine may reduce the

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vaccine's immunogenicity. This trial examined the effect of supplementing vitamin A during the early months of life on infants' immune responses to tetanus and polio vaccines. **Young infants (n = 1085) were enrolled and individually randomized into 1 of 4 groups in a factorial, double-blind, placebo-controlled trial. Three vitamin A supplementation strategies were investigated: 1) supplementation of breast-feeding mothers with 60 mg retinol equivalent (RE) vitamin A within 4 wk of delivery; 2) Expanded Program on Immunization (EPI)-linked supplementation of infants with 7.5 mg RE vitamin A at 6, 10, and 14 wk; and 3) combined mother and child supplementations. A 4th group in which mother and child were given placebos served as controls.** Blood samples were collected from each child at 6 wk and 6 mo of age to measure antipolio antibody titer, antitetanus toxoid antibodies, and avidity of antibodies to tetanus. Of the infants randomized into the 4 arms of the study, 767 (71%) completed follow-up at 6 mo of age. Follow-up rates were similar in all 4 arms (69-72%,  $P = 0.8$ ). Antibody titers were relatively high in all 4 groups at both 6 wk and 6 mo of age, with no differences among the groups. **We found no evidence that vitamin A supplementation affects infants' antibody responses to tetanus toxoid or oral polio vaccine delivered at EPI contacts.**

Am J Clin Nutr. 2005 Aug;82(2):406-12.

### **Short-term effects of vitamin A and antimalarial treatment on erythropoiesis in severely anemic Zanzibari preschool children.**

**Cusick SE, Tielsch JM, Ramsan M, Jape JK, Sazawal S, Black RE, Stoltzfus RJ.**

**BACKGROUND:** The pathophysiology of anemia in coastal East Africa is complex. Impaired erythropoietin production is one possible mechanism. Plasmodium falciparum malaria has been found to blunt erythropoietin production, whereas vitamin A stimulates erythropoietin production in vitro. **OBJECTIVE:** We investigated the 72-h effects of vitamin A and the antimalarial drug sulfadoxine pyrimethamine (SP) on erythropoietin production in severely anemic (hemoglobin  $\leq 70$  g/L) preschool children in Zanzibar, a region of known vitamin A deficiency. We hypothesized that both treatments would stimulate erythropoietin production directly, within 72 h, before a change in hemoglobin would occur. **DESIGN:** One hundred forty-one severely anemic children were identified during the baseline assessment of a morbidity substudy of a community-based micronutrient supplementation trial. **All severely anemic children were randomly assigned to receive either vitamin A (100,000 or 200,000 IU depending on age) or SP at baseline; 72 h later they received the opposite treatment plus daily hematinic syrup for 90 d.** Erythropoietic and parasitic indicators were assessed at baseline and again after 72 h. **RESULTS:** After 72 h, SP reduced the malaria parasite density (by 5029 parasites/microL;  $P < 0.001$ ), CRP concentrations (by 10.6 mg/L;  $P = 0.001$ ), and the proportion of children infected with malaria (by 32.4%;  $P < 0.001$ ). **Vitamin A reduced CRP (by 9.6 mg/L;  $P = 0.011$ ), serum ferritin (by 18.1 microg/L;  $P = 0.042$ ), and erythropoietin (by 194.7 mIU/mL;  $P = 0.011$ ) concentrations and increased the reticulocyte production index (by 0.40;  $P = 0.041$ ).** **CONCLUSIONS:** Contrary to our hypothesis, **vitamin A significantly decreased erythropoietin concentration.** The most important effect of both vitamin A and SP was the rapid reduction of inflammation. Vitamin A also mobilized iron from stores and stimulated the production of new erythrocytes.

### Zinc

(See also acute respiratory infection)

#### Comment

*In previous years many studies in several developing countries proved that treatment with zinc reduces the duration and severity of diarrhoea, and markedly reduces mortality in severe malnutrition in African children. This year a trial suggests that zinc may not have a major effect on duration or severity of diarrhoea in infants less than 6 months of age (Paradoxically a previous trial showed zinc supplementation reduced the incidence of diarrhoea in the first year of life in low birth weight infants.) Zinc also appeared less effective for the treatment of diarrhoea in Turkish children (and Australian indigenous children in the Northern Territory) than in the many other populations studied. Similarly, while previous studies in Bangladesh suggested zinc reduced the duration of hypoxaemia and respiratory distress in pneumonia, a study this year suggested that zinc may not be as effective adjuvant treatment for pneumonia in India (see Acute Respiratory Infection).*

*The trial below demonstrates that weekly zinc reduces the risk of pneumonia and diarrhoea in young Bangladeshi children. There is a need for effectiveness trials of population-based zinc supplementation, particularly in countries other than Bangladesh. While most countries have now adopted the use of zinc as part of treatment for diarrhoea and malnutrition, the studies below provides powerful evidence that zinc supplementation should be part of disease prevention, and that zinc is safe to administer in children with HIV-1.*

#### Treatment

Arch Dis Child. 2006 Apr;91(4):296-9. Epub 2005 Dec 14.

#### **Impact of zinc supplementation in children with acute diarrhoea in Turkey.**

**Boran P, Tokuc G, Vagas E, Oktem S, Gokduman MK.**

**OBJECTIVE:** Zinc deficiency is prevalent in children in developing countries. Supplemental zinc provides therapeutic benefits in diarrhoea. Our aim was to evaluate the effect of daily zinc supplementation for 14 days on diarrhoea duration, severity, and morbidity in children.

**METHODS:** In a randomised, open label non-placebo controlled trial, we assessed the efficacy of providing zinc sulfate to 6-60 month old children with acute diarrhoea for 2 weeks followed by 3 months of morbidity surveillance. Children were randomly assigned to zinc (n = 150) and control (n = 130) groups and received 15-30 mg elemental zinc daily. **RESULTS:**

Supplemented children had significantly improved plasma zinc levels by day 14 of therapy. Zinc deficiency was observed in 2.6% of the treatment and 3.3% of the control group. The mean duration of diarrhoea after starting supplementation was 3.02 $\pm$ 2 days in the zinc group and 3.67 $\pm$ 3.2 days in the control group. **There was no significant difference in diarrhoea duration by treatment group (p>0.05). The number of stools after starting supplementation was 5.8 $\pm$ 3.7 and 5.1 $\pm$ 3.9 on day 1, 2.9 $\pm$ 1.6 and 3.0 $\pm$ 2.2 on day 2, and 1.8 $\pm$ 1.1 and 1.6 $\pm$ 0.9 on day 3 in the zinc and control groups, respectively. There was no significant difference in diarrhoea severity by treatment group (p>0.05). No**

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significant effect was found on the incidence and prevalence of diarrhoea in the zinc compared with the control group. **CONCLUSION:** Our data indicate that supplementing children with acute diarrhoea in Turkey with 3 RDA of elemental zinc for 14 days improved neither diarrhoea duration nor severity despite significant increments in plasma zinc.

Am J Clin Nutr. 2005 Sep;82(3):605-10.

### **Efficacy of zinc in young infants with acute watery diarrhea.**

**Brooks WA, Santosham M, Roy SK, Faruque AS, Wahed MA, Nahar K, Khan AI, Khan AF, Fuchs GJ, Black RE.**

**BACKGROUND:** Recent studies reported that zinc significantly reduced the duration and volume of acute watery diarrhea in children aged > or = 4 mo, but there were no data specifically on infants aged < 6 mo. **OBJECTIVE:** This study investigated the effect of zinc on the duration of illness and the stool quantity in acute watery diarrhea of infants aged 1-6 mo by comparing a 20 mg Zn/d dose with a 5 mg Zn/d dose. **DESIGN: Infants hospitalized with at least some dehydration (by World Health Organization classification) were enrolled in a double-blind, randomized, placebo-controlled trial. Infants were randomly assigned to receive 20 mg Zn (acetate)/d, 5 mg Zn/d, or placebo for the duration of illness. RESULTS:** Two hundred seventy-five infants were enrolled between 20 September 1998 and 18 December 2000. Neither diarrhea duration nor mean stool volume differed between groups. There were no significant differences in fluid intake, the need for unscheduled intravenous fluid, weight gain, or vomiting rates between the groups. **CONCLUSIONS: Zinc supplementation did not affect diarrhea duration or stool volume in young infants.** Young infants tolerated both zinc doses. A beneficial effect on subsequent illness cannot be ruled out.

J Health Popul Nutr. 2005 Dec;23(4):311-9.

### **Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial.**

**Larson CP, Hoque AB, Larson CP, Khan AM, Saha UR.**

The childhood diarrhoea-management guidelines of the World Health Organization/United Nations Children's Fund (WHO/UNICEF) now include zinc treatment, 20 mg per day for 10 days. To determine if a dispersible zinc sulphate tablet formulation is associated with increased risk of vomiting or regurgitation following the initial, first treatment dose, a double-blind, placebo-controlled randomized clinical trial was carried out in the Dhaka hospital of ICDDR,B: Centre for Health and Population Research (n=800) and in an adjacent NGO outpatient clinic (n=800). **Children were randomized to one of three groups: no treatment, placebo, or zinc sulphate tablet (20 mg).** They were then observed for 60 minutes, and all vomiting or regurgitation episodes were recorded. When compared with placebo, zinc treatment resulted in an attributable risk increase of 14% for vomiting and 5.2% for regurgitation. **The median time to vomiting among those receiving zinc was 9.6 minutes**

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and was limited to one episode in 91.2% of the cases. Overall, the proportion of 60-minute post-treatment vomiting attributable to zinc, placebo, and the illness episode was estimated to be 40%, 26%, and 34% respectively. **The dispersible zinc sulphate tablet formulation at a dose of 20 mg is associated with increased risks of vomiting and regurgitation.** Both are transient side-effects.

## Prevention

\*\*\* Lancet. 2005 Sep 17-23;366(9490):999-1004.

### **Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial.**

**Brooks WA, Santosham M, Naheed A, Goswami D, Wahed MA, Diener-West M, Faruque AS, Black RE.**

**BACKGROUND:** Pneumonia and diarrhoea cause much morbidity and mortality in children younger than 5 years. Most deaths occur during infancy and in developing countries. Daily regimens of zinc have been reported to prevent acute lower respiratory tract infection and diarrhoea, and to reduce child mortality. **We aimed to examine whether giving zinc weekly could prevent clinical pneumonia and diarrhoea in children younger than 2 years.**

**METHODS:** 1665 poor, urban children aged 60 days to 12 months were randomly assigned zinc (70 mg) or placebo orally once weekly for 12 months. Children were assessed every week by field research assistants. Our primary outcomes were the rate of pneumonia and diarrhoea. The rates of other respiratory tract infections were the secondary outcomes. Growth, final serum copper, and final haemoglobin were also measured. Analysis was by intention to treat. **FINDINGS:** 34 children were excluded before random assignment to treatment group because they had tuberculosis. **809 children were assigned zinc, and 812 placebo.** After treatment assignment, 103 children in the treatment group and 44 in the control group withdrew. **There were significantly fewer incidents of pneumonia in the zinc group than the control group (199 vs 286; relative risk 0.83, 95% CI 0.73-0.95), and a small but significant effect on incidence of diarrhoea (1881 cases vs 2407; 0.94, 0.88-0.99). There were two deaths in the zinc group and 14 in the placebo group (p=0.013). There were no pneumonia-related deaths in the zinc group, but ten in the placebo group (p=0.013).** The zinc group had a small gain in height, but not weight at 10 months compared with the placebo group. Serum copper and haemoglobin concentrations were not adversely affected after 10 months of zinc supplementation. **INTERPRETATION: 70 mg of zinc weekly reduces pneumonia and mortality in young children.** However, compliance with weekly intake might be problematic outside a research programme.

J Nutr. 2005 Sep;135(9):2187-91.

### **Weekly iron supplementation does not block increases in serum zinc due to weekly zinc supplementation in Bangladeshi infants.**

**Baqui AH, Walker CL, Zaman K, Arifeen SE, Chowdhury HR, Wahed MA, Black RE, Caulfield LE.**

Because infants and young children in many developing countries are deficient in both iron and zinc, and zinc can affect iron metabolism, **evaluation of optimum strategies to simultaneously supplement iron and zinc is an important public health priority.** This study evaluated the efficacy of weekly supplementation of iron or zinc or both on iron, zinc, and copper status in Bangladeshi infants. In a double-blind, randomized, controlled community trial, **6-mo-old infants were assigned to receive weekly supplements of 1 mg riboflavin (control, n = 82) or 1 mg riboflavin + 20 mg iron (n = 83), 20 mg zinc (n = 83), or both (n = 85) for 6 mo.** Hemoglobin, serum ferritin, transferrin receptor, zinc, and copper concentrations were measured at baseline and at the end of intervention. Serum Zn increased in both groups receiving zinc; the increase was greatest among children with low baseline serum zinc concentration. Iron status indicators did not differ among the groups before or after 6 mo of supplementation. Supplementation with either zinc or iron decreased serum copper after 6 mo. **Joint supplementation did not alter the individual effects of iron or zinc supplementation in these Bangladeshi children. However, the dosing regimen may not have been adequate to achieve the desired biochemical effects.**

#### **Comment**

*This trial showed that iron supplementation can be given with zinc without reduced efficacy of iron on haemoglobin levels, however another trial published this year (see Iron Deficiency) urged caution in using iron routinely in all children where malaria is endemic.*

Lancet. 2005 Nov 26;366(9500):1862-7.

### **Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial.**

**Bobat R, Coovadia H, Stephen C, Naidoo KL, McKerrow N, Black RE, Moss WJ.**

**BACKGROUND:** Zinc deficiency is associated with impaired immune function and an increased risk of infection. Supplementation can decrease the incidence of diarrhoea and pneumonia in children in resource-poor countries. However, in children with HIV-1 infection, the safety of zinc supplementation is uncertain. We aimed **to assess the role of zinc in HIV-1 replication before mass zinc supplementation is recommended in regions of high HIV-1 prevalence.** **METHODS:** We did a randomised double-blind placebo-controlled equivalence trial of zinc supplementation at Grey's Hospital in Pietermaritzburg, South Africa. **96 children with HIV-1 infection were randomly assigned to receive 10 mg of elemental zinc as sulphate or placebo daily for 6 months.** Baseline measurements of plasma HIV-1 viral load and the percentage of CD4+ T lymphocytes were established at two study visits before randomisation, and measurements were repeated 3, 6, and 9 months after the start of supplementation. The primary outcome measure was plasma HIV-1 viral load. Analysis was per protocol. **FINDINGS:** The mean log<sub>10</sub> HIV-1 viral load was 5.4 (SD 0.61) for the



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placebo group and 5.4 (SD 0.66) for the zinc-supplemented group 6 months after supplementation began (difference 0.0002, 95% CI -0.27 to 0.27). 3 months after supplementation ended, the corresponding values were 5.5 (SD 0.77) and 5.4 (SD 0.61), a difference of 0.05 (-0.24 to 0.35). The mean percentage of CD4+ T lymphocytes and median haemoglobin concentrations were also similar between the two groups after zinc supplementation. Two deaths occurred in the zinc supplementation group and seven in the placebo group (p=0.1). Children given zinc supplementation were less likely to get watery diarrhoea than those given placebo. Watery diarrhoea was diagnosed at 30 (7.4%) of 407 clinic visits in the zinc-supplemented group versus 65 (14.5%) of 447 visits in the placebo group (p=0.001). **INTERPRETATION: Zinc supplementation of HIV-1-infected children does not result in an increase in plasma HIV-1 viral load and could reduce morbidity caused by diarrhoea. RELEVANCE TO PRACTICE: Programmes to enhance zinc intake in deficient populations with a high prevalence of HIV-1 infection can be implemented without concern for adverse effects on HIV-1 replication. In view of the reductions in diarrhoea and pneumonia morbidity, zinc supplementation should be used as adjunct therapy for children with HIV-1 infection.**

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## Processing of complementary food does not increase hair zinc levels and growth of infants in Kilosa district, rural Tanzania.

Lachat CK, Van Camp JH, Mamiro PS, Wayua FO, Opsomer AS, Roberfroid DA, Kolsteren PW.

A community-based, randomized, placebo-controlled, double-blind trial was conducted from March 2001 to March 2002 in Kilosa, a rural district of Morogoro Region in Tanzania. One hundred and fifty-eight infants were selected randomly from lists of local Maternal and Child Health Care Centres and received either processed complementary food (PCF) or unprocessed complementary food (UPCF) from age 6 to 12 months. **Processing increased Zn solubility and energy density of the porridge prepared from the complementary food (CF) as determined in vitro.** Phytate:Zn molar ratio of the PCF and UPCF was 25.8 and 47.5, respectively. Under the study conditions, **the processing of CF did not improve Zn status as measured by hair analysis.** No significant correlations were found between hair Zn values and anthropometric measurements. Our findings suggest that processing alone of cereal-based CF may be insufficient to ensure an adequate supply of Zn to improve growth and Zn status of infants. **Dietary modification to tackle Zn deficiencies in similar target groups may therefore only be successful when other Zn-rich foods such as meat and fish are included.**

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## Demonstrating zinc and iron bioavailability from intrinsically labeled microencapsulated ferrous fumarate and zinc gluconate Sprinkles in young children.

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Zlotkin SH, Schauer C, Owusu Agyei S, Wolfson J, Tondeur MC, Asante KP, Newton S, Serfass RE, Sharieff W.

Nutrient-nutrient interactions are an important consideration for any multiple-micronutrient formulation, including Sprinkles, a home-fortification strategy to control anemia. The objectives of this randomized controlled trial were as follows: 1) to compare the absorption of zinc at 2 doses given as Sprinkles; and 2) to examine the effect of zinc and ascorbic acid (AA) on iron absorption from Sprinkles. **Seventy-five children aged 12-24 mo were randomly assigned to the following groups: 1) 5 mg of labeled zinc ( $^{67}\text{Zn}$ ) with 50 mg AA (LoZn group); b) 10 mg of labeled zinc ( $^{67}\text{Zn}$ ) with 50 mg AA (HiZn group); or 3) 5 mg zinc with no AA (control). All groups contained 30 mg of labeled iron ( $^{57}\text{Fe}$ ).** Intravenous infusions labeled with  $^{70}\text{Zn}$  (LoZn and HiZn groups) and  $^{58}\text{Fe}$  (control) were administered. Blood was drawn at baseline, 48 h and 14 d later. The percentage of zinc absorbed did not differ between LoZn (geometric mean = 6.4%; min-max: 1.7-14.6) and HiZn (geometric mean = 7.5%; min-max: 3.3-18.0) groups. However, total zinc absorbed was significantly different between the LoZn (geometric mean = 0.31 mg; min-max: 0.08-0.73) and HiZn (geometric mean = 0.82 mg; min-max: 0.33-1.82) groups ( $P = 0.0004$ ). Geometric mean percentage iron absorption values did not differ between the LoZn (5.9%; min-max: 0.8-21) and HiZn (4.4%; min-max: 0.6-12.3) groups and between the LoZn and control groups (5.0%; min-max: 1.4-24). We conclude that **zinc in the form of Sprinkles has a low bioavailability, yet provides adequate amounts of absorbed zinc in young children, and that there is no effect of zinc or AA on iron absorption from the given formulations of Sprinkles.**