

RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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SEARCH STRATEGY

Hayne's strategy, Clinical Queries, Pubmed "narrow" search: (child AND (developing country OR Africa OR India OR Pacific OR South America OR Asia OR Papua New Guinea)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])). Searched for articles published July 1st 2004 to June 30th 2005.

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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.

It is encouraging that there are more RCTs on common child health topics from developing countries this year than in the previous years. The rich research reflected by this booklet demonstrates the major achievements being made by child health researchers in developing countries, and many studies demonstrate the value of appropriate collaboration in addressing problems of child health.

Please feel free to copy this booklet and distribute it to colleagues. A previous edition is available at: http://www.rch.org.au/emplibrary/cich/RCTs_devCountries_child_2004.pdf

Trevor Duke
August 2005

Acute respiratory infection

Lancet. 2004 Sep 25;364(9440):1141-8.

Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study.

Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, MacLeod WB, Maulen I, Patel A, Qazi S, Thea DM, Nguyen NT.

BACKGROUND: Injectable penicillin is the recommended treatment for WHO-defined severe pneumonia (lower chest indrawing). If oral amoxicillin proves equally effective, it could reduce referral, admission, and treatment costs. We aimed to determine whether oral amoxicillin and parenteral penicillin were equivalent in the treatment of severe pneumonia in children aged 3-59 months. **METHODS:** This multicentre, randomised, open-label equivalency study was undertaken at tertiary-care centres in eight developing countries in Africa, Asia, and South America. Children aged 3-59 months with severe pneumonia were admitted for 48 h and, if symptoms improved, were discharged with a 5-day course of oral amoxicillin. 1702 children were randomly allocated to receive either oral amoxicillin (n=857) or parenteral penicillin (n=845) for 48 h. Follow-up assessments were done at 5 and 14 days after enrollment. **Primary outcome was treatment failure (persistence of lower chest indrawing or new danger signs) at 48 h.** Analyses were by intention-to-treat and per protocol. **FINDINGS:** **Treatment failure was 19% in each group (161 patients, penicillin; 167 amoxicillin; risk difference -0.4%; 95% CI -4.2 to 3.3) at 48 h.** Infancy (age 3-11 months; odds ratio 2.72, 95% CI 1.95 to 3.79), very fast breathing (1.94, 1.42 to 2.65), and hypoxia (1.95, 1.34 to 2.82) at baseline predicted treatment failure by multivariate analysis. **INTERPRETATION:** Injectable penicillin and oral amoxicillin are equivalent for severe pneumonia treatment in controlled settings. Potential benefits of oral treatment include decreases in (1) risk of needle-borne infections; (2) need for referral or admission; (3) administration costs; and (4) costs to the family.

Comment

This was a large trial, powered for equivalence. It establishes well that in a tertiary care setting oral amoxicillin is as effective as injectable penicillin for severe pneumonia. To what extent this can be transferred to lower-level health facilities or to be used to support community treatment, as the authors proposed, is not certain. With a 19% failure rate and with failure being associated with hypoxia, the need for hospital admission for WHO-defined severe pneumonia (signs of pneumonia plus chest in-drawing) will still exist. There are issues of adherence to treatment and follow-up that might make the outcomes from the community treatment of severe pneumonia considerably less effective. However it is very encouraging that children with WHO-defined severe pneumonia can be treated very effectively without injections.

Indian J Pediatr. 2004 Nov;71(11):969-72

Comparison of two antibiotic regimens in the empirical treatment of severe childhood pneumonia.

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OBJECTIVE: The diagnosis and the treatment of community-acquired severe pneumonia is still a serious child health problem in developing countries. The aim of this study is to evaluate the effectiveness of two different antibiotic regimens in the empirical treatment of severe childhood pneumonia. **METHODOLOGY:** We enrolled 97 infants (aged 2-24 months) with severe community-acquired pneumonia in a randomized-controlled trial of 10 days of treatment with penicillin G+chloramphenicol (n:46) or ceftriaxone (n:51). We evaluated the effectiveness of treatments with symptoms and some laboratory tests during and at the end of the study. **RESULTS:** The cure rates were similar in both groups and the antibiotic regimens in all patients were found effective ($P < 0.001$). The number of nurse rounds was much more in penicillin plus chloramphenicol group than ceftriaxone group. **CONCLUSION:** Both penicillin G plus chloramphenicol and ceftriaxone are effective in the empirical treatment of severe community pneumonia of young children. In spite of more nurse visits for antibiotic treatment, penicillin G+ chloramphenicol combination may be a cheaper alternative to ceftriaxone in the treatment of childhood pneumonia.

Comment

The problems with the use of ceftriaxone as first-line treatment for community-acquired pneumonia will be cost and increased risk of resistance. Use of cephalosporins as first-line treatment of a very common condition, such as pneumonia, may mean its effective life-span for less common but very important indications, like bacterial meningitis, will be shorter.

Bull World Health Organ. 2005 Jan;83(1):10-9. Epub 2005 Jan 21.

Randomized controlled trial of standard versus double dose cotrimoxazole for childhood pneumonia in Pakistan.

Rasmussen ZA, Bari A, Qazi S, Rehman G, Azam I, Khan S, Aziz F, Rafi S, Roghani MT, Iqbal I, Nagi AG, Hussain W, Bano N, van Latum LJ, Khan M; Pakistan COMET (Cotrimoxazole Multicentre Efficacy) Study Group.

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OBJECTIVE: Increasing concern over bacterial resistance to cotrimoxazole, which is recommended by WHO as a first-line drug for treating non-severe pneumonia, led to the suggestion that this might not be optimal therapy. However, changing to alternative antimicrobial agents, such as amoxicillin, is costly. We compared the clinical efficacy of twice-daily cotrimoxazole in standard versus double dosage for treating non-severe pneumonia in children. **METHODS:** A randomized controlled multicentre trial was implemented in seven hospital outpatient departments and two community health programmes. **A total of 1143 children aged 2-59 months with non-severe pneumonia were randomly allocated to receive 4 mg trimethoprim plus 20 mg sulfamethoxazole/kg of body weight or 8 mg trimethoprim plus 40 mg sulfamethoxazole/kg of body weight orally twice-daily for 5 days.** Treatment failure occurred when a child required a change of therapy, died or was lost to follow-up. Children required a change of therapy if their condition worsened (they developed chest indrawing or danger signs) or if at 48 hours after enrollment, their clinical condition was the same (defined as having a respiratory rate that was 5 breaths/minute higher or lower than at the time of enrollment). **FINDINGS:** The results of 1134 children were analysed: 578 were

assigned to the standard dose of cotrimoxazole and 556 to the double dose. **Treatment failed in 112 children (19.4%) in the standard group and 118 (21.2%) in the double-dose group (relative risk 1.10; 95% confidence interval = 0.87-1.37).** Using multivariate analysis we found that treatment was more likely to fail in children who were not given the medicine correctly ($P = 0.001$), in those younger than 12 months ($P = 0.004$), those who had used antibiotics previously ($P = 0.002$), those whose respiratory rate was $>$ or $=20$ breaths/minute above the age-specific cut-off point ($P = 0.006$), and those from urban areas ($P = 0.042$). **CONCLUSION:** Both standard and double strength cotrimoxazole were equally effective in treating non-severe pneumonia. Close follow-up of patients is essential to prevent worsening of disease. Definitions of clinical failure need to be more specific. Surveillance in both rural and urban areas is essential in the development of treatment policies that are based on clinical outcomes.

Comment

A 20% failure rate from the treatment of non-severe pneumonia emphasizes the need for close follow-up

Anaesthesia

Saudi Med J. 2004 Nov;25(11):1636-9.

Use of dexamethasone to reduce postoperative vomiting and pain after pediatric tonsillectomy procedures.

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OBJECTIVE: The purpose of this study is to determine whether a single dose of dexamethasone 0.5mg/kg administered before surgery could decrease post operative vomiting and pain and improves oral intake in the first 24-hours after pediatric tonsillectomy procedures. **METHODS:** It is a randomized, double blind, placebo controlled study. Sixty children age 2-12-years ASA 1 and 11 were scheduled for tonsillectomy, dexamethasone ($n=29$) and control group ($n=31$) were enrolled in the study. Dexamethasone group received 0.5mg/kg intravenous dexamethasone and control group received saline at the time of induction. The anesthetic regimen and surgical procedures were standardized for all patients. All patients were observed in post anesthesia care unit (PACU) and ward for post operative vomiting, pain, need for rescue antiemetic or analgesia and time for first oral intake for 24-hours. **RESULTS:** Data from 60 patients were analyzed. **The overall incidence of early as well as late vomiting was significantly less in dexamethasone as compared to control group (37% versus 74% $P=0.016$), overall incidence of retching was 29% in control and 3.4% in dexamethasone ($p=0.008$).** Vomiting once or more than once was significantly high in control as compared to dexamethasone group. The need for rescue antiemetic, the time to first oral intake and analgesic requirements did not show any significant difference in both groups. **CONCLUSION:** Dexamethasone is considered safe and there was no adverse effects associated with a single dose of dexamethasone. Although the need for rescue antiemetic, time to oral intake and analgesia requirements in both groups were not significant, however, we found that dexamethasone does have antiemetic properties as overall incidence of retching and

vomiting was significantly less in dexamethasone group as compared to control group in children who underwent tonsillectomy.

Comment

Dexamethasone will be considerably cheaper and more widely available than other highly effective antiemetics (such as ondansetron) in post-operative nausea and vomiting.

Asthma

Indian J Pediatr. 2004 Nov;71(11):961-3.

Comparison of terbutaline and salbutamol inhalation in children with mild or moderate acute exacerbation of asthma.

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OBJECTIVE: To compare the clinical efficacy and side effects of terbutaline and salbutamol administered by metered dose inhaler and holding chamber in the mild to moderate acute exacerbations of asthma in children. **METHODS:** The study subjects were children in the age group of 5- 15 years who presented with a mild or moderate acute exacerbation of asthma. Baseline assessment included clinical parameters and spirometry. The children were then randomized to receive salbutamol or terbutaline. Three puffs each of either 100 mcg salbutamol or 250 mcg of terbutaline were administered using 750 ml holding chamber with valve. Thirty minutes after drug administration, the children were reevaluated for clinical parameters and spirometry. **RESULTS:** Of the total 60 subjects studied, 31 were administered terbutaline and 29 salbutamol. The baseline spirometric parameters were comparable. **After drug administration, all the studied variables showed significant improvement within each group.** However, there were no statistically significant differences when the two groups were compared with each other. There was no significant difference in the side effects between two groups. **CONCLUSION:** Terbutaline and salbutamol, when administered by MDI with holding chamber, are equally efficacious in children with mild or moderate acute exacerbation of asthma.

Cerebral palsy

Pediatr Rehabil. 2005 Jan-Mar;8(1):63-6.

Bedtime diazepam enhances well-being in children with spastic cerebral palsy.

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In work with children with cerebral palsy at Ashirvad, Child Development and Research Centre, Chennai, India, the authors were confronted with fretful children who resisted any

attempt to mobilize their limbs due to hypertonia and muscle spasm. It was found that administering a bedtime dose of diazepam to reduce hypertonia and muscle spasm alongside passive stretching exercises significantly improved the behaviour of the child. There was significant improvement in the well-being of the child during the activities of daily living and this reduced the family's burden of caring for the child. In this double blind, placebo-controlled, randomized clinical trial, each child received a bedtime dose of diazepam or placebo. The bedtime diazepam relaxed the muscles and this made the passive stretching easy and the movements sustained the muscle relaxation during the day. **There were fewer unwarranted crying spells during the day and less wakefulness during the night. The adverse effect of day time sedation was not observed with the use of a single dose of diazepam at bedtime.**

Comment

The management of children with cerebral palsy has not received much attention in many developing countries where rehabilitation services, physiotherapists and occupational therapists are often not available. WHO has produced a manual on how to promote development of children with cerebral palsy, available from WHO for 8.40 Swiss Francs (also available in French):

<http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=93&codcch=52#>

Ear disease

Trop Med Int Health. 2005 Feb;10(2):190-7.

Topical quinolone vs. antiseptic for treating chronic suppurative otitis media: a randomized controlled trial.

Macfadyen C, Gamble C, Garner P, Macharia I, Mackenzie I, Mugwe P, Oburra H, Otvombe K, Taylor S, Williamson P.

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OBJECTIVE: To compare a topical quinolone antibiotic (ciprofloxacin) with a cheaper topical antiseptic (boric acid) for treating chronic suppurative otitis media in children. **DESIGN:** Randomized controlled trial. **SETTING AND PARTICIPANTS:** A total of 427 children with chronic suppurative otitis media enrolled from 141 schools following screening of 39 841 schoolchildren in Kenya. Intervention Topical ciprofloxacin (n = 216) or boric acid in alcohol (n = 211); child-to-child treatment twice daily for 2 weeks. **MAIN OUTCOME MEASURES:** Resolution of discharge (at 2 weeks for primary outcome), healing of the tympanic membrane, and change in hearing threshold from baseline, all at 2 and 4 weeks. **RESULTS:** **At 2 weeks, discharge was resolved in 123 of 207 (59%) children given ciprofloxacin, and in 65 of 204 (32%) given boric acid (relative risk 1.86; 95% CI 1.48-2.35; P < 0.0001). This effect was also significant at 4 weeks, and ciprofloxacin was associated with better hearing at both visits. No difference with respect to tympanic membrane healing was detected. There were significantly fewer adverse events of ear pain, irritation, and bleeding on mopping with ciprofloxacin than boric acid.** **CONCLUSIONS:** Ciprofloxacin performed better than boric acid and alcohol for treating chronic suppurative otitis media in children in Kenya.

Comment

For recommendations on the management of chronic suppurative otitis media, you can also refer to: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/ISBN_92_4_159158_7.htm

Envenomation

BMJ. 2004 Nov 13;329(7475):1129

Crotaline snake bite in the Ecuadorian Amazon: randomised double blind comparative trial of three South American polyspecific antivenoms.

Smalligan R, Cole J, Brito N, Laing GD, Mertz BL, Manock S, Maudlin J, Quist B, Holland G, Nelson S, Laloo DG, Rivadeneira G, Barragan ME, Dolley D, Eddleston M, Warrell DA, Theakston RD.

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OBJECTIVE: To compare the efficacy and safety of three polyspecific antivenoms for bites by pit vipers. **DESIGN:** Randomised double blind comparative trial of three antivenoms. **SETTING:** Shell, Pastaza, southeastern Ecuador. **PARTICIPANTS:** 210 patients with incoagulable blood were recruited from 221 consecutive patients admitted with snake bite between January 1997 and December 2001. **INTERVENTION:** One of three antivenoms manufactured in Brazil, Colombia, and Ecuador, chosen for their preclinical potency against Ecuadorian venoms. **MAIN OUTCOME MEASURES:** Permanent restoration of blood coagulability after 6 and 24 hours. **RESULTS:** The snakes responsible for the bites were identified in 187 cases: 109 patients (58%) were bitten by *Bothrops atrox*, 68 (36%) by *B bilineatus*, and 10 (5%) by *B taeniatus*, *B brazili*, or *Lachesis muta*. Eighty seven patients (41%) received Colombian antivenom, 82 (39%) received Brazilian antivenom, but only 41 (20%) received Ecuadorian antivenom because the supply was exhausted. Two patients died, and 10 developed local necrosis. All antivenoms achieved the primary end point of permanently restoring blood coagulability by 6 or 24 hours after the start of treatment in > 40% of patients. Colombian antivenom, however, was the most effective after initial doses of 20 ml (two vials), < 70 ml, and any initial dose at both 6 and 24 hours. An initial dose of 20 ml of Colombian antivenom permanently restored blood coagulability in 64% (46/72) of patients after 6 hours ($P = 0.054$ compared with the other two antivenoms) and an initial dose of < 70 ml was effective at 6 hours (65%, $P = 0.045$) and 24 hours (99%, $P = 0.06$). **Early anaphylactoid reactions were common (53%, 73%, and 19%, respectively, for Brazilian, Colombian, and Ecuadorian antivenoms, $P < 0.0001$) but only three reactions were severe and none was fatal.** **CONCLUSIONS:** All three antivenoms can be recommended for the treatment of snakebites in this region, though the reactogenicity of Brazilian and Colombian antivenoms is a cause for concern.

Comment

This study highlights the frequency of anaphylactoid reactions from snake antivenom. Another study (Trans R Soc Trop Med Hyg. 1998 Jan-Feb;92(1):69-70) found early anaphylactoid reactions from polyvalent antivenom to be very common, including: generalized urticaria (12; 71%), angio-oedema (18%), bronchospasm (12%), and hypotension (12%). This raises the

issue of the appropriate pre-medication to use. Giving subcutaneous adrenaline routinely, as suggested by Dassanayake AS et al (Ceylon Med J. 2002 Jun;47(2):48-9) in a study in adults may be most effective.

Epilepsy

Child Care Health Dev. 2005 May;31(3):261-3.

Is social support sometimes a mixed blessing?

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BACKGROUND: Child behavioural problems in epilepsy originate from a poorly understood interplay between intrinsic, family and social factors. **METHODS:** We re-analysed data from a randomized controlled trial of antiepileptic treatment in rural India, using regression analysis to find risk factors for behavioural problems. **RESULTS:** Parental satisfaction with social support was positively and independently correlated with child behavioural problems ($P=0.03$). **CONCLUSION:** Our findings suggest parents' interactions within their informal social support network, contrary to expectation, may increase risk for behavioural problems in their children. We suggest a possible explanation for this correlation as well as follow-up studies to investigate the social support-as-risk factor hypothesis.

Eye disease

Br J Ophthalmol. 2004 Dec;88(12):1487-92

A randomised trial of povidone-iodine to reduce visual impairment from corneal ulcers in rural Nepal.

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AIM: To assess whether povidone-iodine provided any benefit over and above a standard regimen of antibiotic therapy for the treatment of corneal ulcers. **METHODS:** All patients diagnosed with corneal ulcers presenting for care at a primary eye care clinic in rural Nepal were randomised to a standard protocol of antibiotic therapy versus standard therapy plus 2.5% povidone-iodine every 2 hours for 2 weeks. The main outcomes were corrected visual acuity and presence, size, and position of corneal scarring in the affected eye at 2-4 months following treatment initiation. **RESULTS:** 358 patients were randomised and 81% were examined at follow up. The two groups were comparable before treatment. **At follow up, 3.9% in the standard therapy and 6.9% in the povidone-iodine group had corrected visual acuity worse than 20/400 (relative risk (RR) 1.77, 95% confidence interval (CI) 0.62 to 5.03). 9.4% in the standard therapy and 13.1% in the povidone-iodine group had corrected visual acuity worse than 20/60 (RR 1.39, 95% CI 0.71 to 2.77), and 17.0% and 18.8% had**

scars in the visual axis in each of these groups, respectively (RR 1.11, 95% CI 0.67 to 1.82). CONCLUSIONS: A small proportion of patients with corneal ulceration treated in this setting had poor visual outcomes. The addition of povidone-iodine to standard antibiotic therapy did not improve visual outcomes, although this design was unable to assess whether povidone-iodine on its own would have resulted in comparable visual outcomes to that of standard therapy.

Filariasis

Trans R Soc Trop Med Hyg. 2004 Aug;98(8):462-72.

The effect of single dose ivermectin alone or in combination with albendazole on Wuchereria bancrofti infection in primary school children in Tanzania.

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Examination of 1829 children from 6 primary schools in coastal Tanzania revealed overall *Wuchereria bancrofti* microfilaria (mf) and circulating filarial antigen (CFA) prevalences of 17.3% and 43.7%, respectively. **A randomized double-blind field trial with a single dose of ivermectin (150-200 microg/kg body weight) alone or in combination with albendazole (400 mg) was subsequently carried out among these children.** Both treatment regimens resulted in a considerable decrease in mean mf intensities, with overall reductions being slightly but statistically significantly higher for the combination than for ivermectin alone. The difference in effect between the two treatment regimens was most pronounced at 6 months, whereas it was minor at 12 months after treatment. The relative effect of treatment on mean CFA units was less pronounced than on mf. For both treatment regimens, reductions in CFA intensity appeared to be higher in children who were both CFA and mf positive before treatment, which may suggest that treatment mainly affected the survival and/or production of mf, rather than the survival of adult worms. **New cases of infection appeared after treatment with both regimens among the pre-treatment mf and CFA negative children. Adverse reactions were few and mild in both groups,** and mainly reported from pre-treatment mf and CFA positive children. The alarmingly high prevalence of *W. bancrofti* infection in primary school children highlights the importance of also determining the reversibility of already acquired early lesions, and the development of new measures and strategies to specifically protect children from later developing clinical disease.

Health education

Indian J Med Sci. 2004 Jul;58(7):289-96.

A school-based intervention to teach 3-4 grades children about healthy heart; the Persian Gulf healthy heart project.

Nabipour I, Imami SR, Mohammadi MM, Heidari G, Bahramian F, Azizi F, Khosravizadegan Z, Pazoki R, Soltanian AR, Ramazanzadeh M, Emadi A, Arab J,

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BACKGROUND: Cardiovascular health promotion in children has the potential to reduce the risk of atherosclerosis in both the individual child and the population at large. It thus seems eminently reasonable to initiate healthful lifestyle training in childhood to promote improved cardiovascular health in adult life. **AIMS:** To test the hypothesis that a year long, classroom-based education for the third and fourth graders could change their knowledge scores about healthy heart. **SETTINGS AND DESIGN:** A randomized, controlled trial in elementary schools of Bushehr/Iran. **METHODS AND MATERIALS:** A total of 14 elementary schools, categorized by socioeconomic types and male and female setting were selected and randomized into control or intervention groups. Subjects were 1128 third and fourth graders, aged 9 to 10 years (49.1% boys and 50.9% girls). **Over a course of 8 weeks, health educators and sport teachers of the elementary schools presented two hours sessions per week on heart function, nutrition, and exercise for healthy heart and living tobacco free for the intervention group.** The education program was based on HeartPower! Program, an American Heart Association program. **STATISTICAL ANALYSIS:** Mann-Whitney U test and Wilcoxon matched-pairs signed rank test and Bonferroni correction for the two pair wise comparisons were used. **RESULTS: Total heart knowledge at posttest was 25% correct higher in the intervention than in the control group (p< 0.001).** Difference in means of total healthy heart knowledge scores between control and intervention group increased from 1.43 points in baseline to 4.02 points in posttest (p< 0.001). **CONCLUSION:** It can be concluded that the classroom-based cardiovascular health promotion had a significant effect on the heart healthy knowledge. Therefore, schools provide an excellent setting for introducing comprehensive healthy heart education and promotion of cardiovascular health to the general population.

Int J Vitam Nutr Res. 2004 Jul;74(4):264-8.

Effect of nutrition education and diet modification in iron depleted preschool children in nurseries in Tehran: a pilot study.

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In view of the high prevalence of iron deficiency in preschool children and its consequences, this study was carried out to examine the effect of nutrition education and dietary modification on 438 two- to six-year-old nursery school children in Tehran in 1999. Sixty-two children who were judged anemic, iron-depleted, or having low iron stores were randomly allocated to "control," "dietary modification" (consuming one additional citrus fruit after lunch), and "nutrition education" (teaching the mothers proper eating patterns based on the food pyramid) groups. Food habits were surveyed, including 24-hour dietary recall and food frequency, as well as timing of consumption of special items; this survey was carried out for each child before and after intervention. After three months, blood samples were taken from the subjects. The prevalence of anemia, iron depletion, and low iron stores was 11.4, 62.8, and 15.1% respectively, with no significant differences observed in hemoglobin and percent transferrin

saturation (%TS) between the groups. **Mean \pm -SD serum ferritin concentrations in "control," "diet modification," and "nutrition education" groups were 8.9 \pm -3.1, 9.5 \pm -3.7, and 6.9 \pm -2.3 microg/dL. The same figures at the end of intervention were 6.9 \pm -3.5, 11.2 \pm -5, and 10.7 \pm -5.9 microg/dL, respectively.** Analysis of variance showed ferritin concentrations to be significantly different, in that there was a reduction in the control and elevation in the nutrition education groups. There was no significant difference in %TS before and after the intervention. **During three months of intervention, changes in frequency of fruit and fruit juice intake after the meals in nutrition education and diet modification groups were significantly correlated to serum ferritin alteration. Frequency of fruit juice intake (rich in vitamin C) after meals (at least five times a week) can significantly increase serum ferritin within three months.** Therefore, educating mothers of iron-deficient children while increasing the iron stores in children can prevent the recurrence of iron deficiency and result in general child well-being.

Bull World Health Organ. 2005 Jan;83(1):27-33. Epub 2005 Jan 21.

Helping northern Ethiopian communities reduce childhood mortality: population-based intervention trial.

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OBJECTIVE: More than 10 million children die each year mostly from preventable causes and particularly in developing countries. WHO guidelines for the Integrated Management of Childhood Illness (IMCI) are intended to reduce childhood mortality and are being implemented in Ethiopia. As well as specific clinical interventions, the role of the community in understanding and acting on childhood sickness is an important factor in improving survival. This trial sought to assess the effect on survival of community-based health promotion activities. **METHODS:** Two districts in northern Ethiopia were studied, each with a random sample of more than 4000 children less than 5 years old. Regular six-monthly visits were made to document deaths among children. **After the first year, communities in one district were educated about issues of good childcare and caring for sick children while the other district received this information only after the trial ended.** **FINDINGS:** **Although overall mortality was higher in the post-intervention period, most of the increase was seen in the control area. A Cox proportional hazards model gave an adjusted hazard ratio of 0.66 (95% confidence interval = 0.46-0.95) for the intervention area compared with the control area in the post-intervention period, with no significant pre-intervention difference.** Significant survival advantages were found for females, children of younger fathers, those with married parents, those living in larger households, and those whose nearest health facility was a health centre. For all of the children who died, only 44% of parents or caregivers had sought health care before the child's death. **CONCLUSION:** **This non-specific community-based public health intervention, as an addition to IMCI strategies in local health facilities, appears to have significantly reduced childhood mortality in these communities. The possibility that such interventions may not effectively reach certain social groups (for example single parents) is an important consideration for implementation of similar strategies in future. The synergy between community awareness and the availability of effective peripheral health services is also an issue that needs further exploration.**

Helminth infections

S Afr Med J. 2004 Dec;94(12):972-6.

Efficacy of albendazole against the whipworm trichuris trichiura--a randomised, controlled trial.

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OBJECTIVES AND DESIGN: To test the efficacy of albendazole against the whipworm *Trichuris trichiura* for school-based deworming in the south-western Cape, South Africa. **Children infected with *Trichuris* were randomised to 3 doses of albendazole (400, 800 or 1200 mg), each repeated 4 times.** The boy/girl ratio was 1. A group not infected with worms was treated with placebo, creating a negative control. **SUBJECTS AND SETTING:** Pupils at a primary school serving a wine-producing area approximately 90 km east of Cape Town. **OUTCOME MEASURES:** *Trichuris* cure rates and reduction in the number of eggs/g in faeces, as well as the infection dynamics of *Trichuris* and *Ascaris* during treatment with placebo. **RESULTS:** **Albendazole treatment was associated with *Trichuris* cure rates of 23% (400 mg), 56% (800 mg) and 67% (1200 mg) after the final treatment.** The corresponding reductions in the number of eggs/g of faeces were 96.8%, 99.3% and 99.7%. Environmental pollution by human faeces was confirmed because worm egg-negative children in the placebo group became egg-positive while the study was in progress. **CONCLUSION:** **The 400 mg stat dose had a low *Trichuris* cure rate.** To repeat the dose on 2 or 3 days would increase cost, reduce compliance and complicate management. Albendazole cannot be used in deworming programmes in South Africa because it is a Schedule 4 prescription medicine. De-scheduling is needed urgently, particularly because of high efficacy against hookworm in KwaZulu-Natal and neighbouring countries.

Comment

Although 400mg doses have poor efficacy against whipworm they are highly effective in deworming programs against hookworm (see Trans R Soc Trop Med Hyg. 2005 99:261-7, below)

Am J Trop Med Hyg. 2005 Feb;72(2):119-23.

Efficacy of mirazid in comparison with praziquantel in Egyptian *Schistosoma mansoni*-infected school children and households.

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This trial investigated the anti-schistosomal activity of mirazid in comparison with that of praziquantel in *Schistosoma mansoni*-infected Egyptian patients. The sample population was composed of 1,131 individuals (459 school children and 672 household members). Screening for *S. mansoni* was conducted using the standard Kato Katz technique. Four slides from a single stool sample were examined before treatment, and four slides per sample from stool samples obtained on three consecutive days were examined post-treatment. **All positive eligible subjects were randomly assigned into two groups, the first received mirazid at a dose of 300 mg/day for three consecutive days, and the second received praziquantel at a single dose of 40 mg/kg.** All treated subjects were examined 4-6 weeks post-treatment. **Mirazid showed low cure rates of 9.1% and 8.9% in *S. mansoni*-infected school children and household members, respectively, compared with cure rates of 62.5% and 79.7%, respectively, in those treated with praziquantel.** Therefore, we do not recommend mirazid as an agent to control schistosomiasis.

Trans R Soc Trop Med Hyg. 2005 Apr;99(4):261-7.

Periodic deworming with albendazole and its impact on growth status and diarrhoeal incidence among children in an urban slum of India.

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This study was undertaken to measure the impact of periodic deworming with albendazole on growth status and incidence of diarrhoea in children aged 2-5 years in an urban setting in India and to assess the feasibility of local health workers implementing the procedures involved. This was a double-blind, placebo-controlled, randomized, community-based intervention trial with 702 children randomly allocated to receive either albendazole or placebo. **The two study groups received two doses of albendazole (400 mg) or placebo six months apart. Mean weight increased significantly in the albendazole group compared to the control group at three months, six months and nine months following treatment ($P<0.01$, $P<0.01$ and $P<0.001$ respectively). The albendazole group also experienced fewer episodes of diarrhoea than their control counterparts (relative risk 1.3, 95% CI 1.07-1.53) with a 28% reduction.** The health workers administered the correct dosage satisfactorily and there were no adverse effects. Thus, periodic mass deworming with albendazole would seem to be a safe and effective method that could be adopted at the community level or as an integral part of school health services and could be expected to improve growth and reduce the incidence of diarrhoea in children.

Comment

Many countries are adopting deworming as a major public health strategy. There is evidence that deworming of women in pregnancy improves maternal health, increases birth-weight and reduces infant mortality. Deworming of children improves health by reducing diarrhoea. Deworming can be effectively added to other programs, such as vitamin A to reduce delivery costs and enable remote communities (most at risk of vitamin A deficiency and worm infestation) exist. To read more about deworming go to:

http://whqlibdoc.who.int/hq/2005/WHO_CDS_CPE_PVC_2005.14.pdf

HIV / AIDS

Control Clin Trials. 2004 Aug;25(4):353-65.

Issues in the design of a clinical trial with a behavioral intervention--the Zambia exclusive breast-feeding study.

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PURPOSE: We present the rationale and design of the Zambian Exclusive Breast-feeding Study (ZEBS), a randomized trial evaluating the efficacy of short-duration exclusive breast-feeding (EBF) as a strategy to reduce postnatal human immunodeficiency virus (HIV) transmission while preserving the other health benefits of this important mode of infant feeding. **METHODS:** One thousand two hundred HIV-positive pregnant women were recruited in Lusaka, Zambia, and followed with their infants for 24 months. In addition to Nevirapine (NVP), all women received intensive and frequent clinic- and home-based counseling to support exclusive breast-feeding. **When the infant was 1 week of age, half of the women were randomly assigned to a group encouraged to abruptly (<24 h) cease all breast-feeding at 4 months. The primary outcome of the experimental (randomized) comparison is HIV-free survival at 24 months.** The design is also observational and will compare HIV transmission rates between those who do and do not adhere to the counseling intervention promoting exclusive breast-feeding. **CONCLUSION:** Our study aims to quantify the benefit-risk ratio of early cessation of exclusive breast-feeding to interrupt mother-to-child transmission of HIV with an intensive behavioral intervention and has both observational and experimental analytic approaches. Our study design assesses efficacy and also has a prominent applied component that if the intervention is effective, it will permit rapid and sustainable adoption within low-resource communities.

JAMA. 2004 Jul 14;292(2):202-9

Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial.

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CONTEXT: Antenatal counseling and human immunodeficiency virus (HIV) testing are not universal in Africa; thus, women often present in labor with unknown HIV status without receiving the HIVNET 012 nevirapine (NVP) regimen (a single oral dose of NVP to the mother at the start of labor and to the infant within 72 hours of birth). **OBJECTIVE:** **To determine risk of mother-to-child transmission of HIV when either standard use of NVP alone or in combination with zidovudine (ZDV) was administered to infants of women tested at delivery.** **DESIGN, SETTING, AND PARTICIPANTS:** A randomized, open-label, phase 3 trial conducted between April 1, 2000, and March 15, 2003, at 6 clinics in Blantyre, Malawi, Africa. The trial included all infants born to 894 women who were HIV positive,

received NVP intrapartum, and were previously antiretroviral treatment-naïve. Infants were randomly assigned to NVP (n = 448) and NVP plus ZDV (n = 446). Infants were enrolled at birth, observed at 6 to 8 weeks, and followed up through 3 to 18 months. The HIV status of 90% of all infants was established at 6 to 8 weeks. INTERVENTION: **Mothers received a 200-mg single oral dose of NVP intrapartum and infants received either 2-mg/kg oral dose of NVP or NVP (same dose) plus 4 mg/kg of ZDV twice per day for a week.** MAIN OUTCOME MEASURES: HIV infection of infant at birth and 6 to 8 weeks, and adverse events. RESULTS: **The mother-to-child transmission of HIV at birth was 8.1% (36/445) in infants administered NVP only and 10.1% (45/444) in those administered NVP plus ZDV (P =.30). A life table estimate of transmission at 6 to 8 weeks was 14.1% (95% confidence interval [CI], 10.7%-17.4%) in infants who received NVP and 16.3% (95% CI, 12.7%-19.8%) in those who received NVP plus ZDV (P =.36).** For infants not infected at birth and retested at 6 to 8 weeks, transmission was 6.5% (23/353) in those who received NVP only and 6.9% (25/363) in those who received NVP plus ZDV (P =.88). Almost all infants (99%-100%) were breastfed at 1 week and 6 to 8 weeks. Grades 3 and 4 adverse events were comparable; 4.9% (22/448) and 5.4% (24/446) in infants receiving NVP only and NVP plus ZDV, respectively (P =.76). CONCLUSIONS: The frequency of mother-to-child HIV transmission at 6 to 8 weeks in our 2 study groups was comparable with that observed for other perinatal HIV intervention studies among breastfeeding women in Africa. The safety of the regimen containing neonatal ZDV was similar to that of a standard NVP regimen.

N Engl J Med. 2004 Jul 15;351(3):217-28

Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand.

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BACKGROUND: Although zidovudine prophylaxis decreases the rate of transmission of the human immunodeficiency virus (HIV) type 1 substantially, a large number of infants still become infected. We hypothesized that the administration, in addition to zidovudine, of a single dose of oral nevirapine to mothers during labor and to neonates would further reduce transmission of HIV. METHODS: We conducted a randomized, double-blind trial of three treatment regimens in Thai women who were receiving zidovudine therapy during the third trimester of pregnancy. **In one group, mothers and infants received a single dose of nevirapine (nevirapine-nevirapine regimen); in another, mothers and infants received nevirapine and placebo, respectively (nevirapine-placebo regimen); and in the last, mothers and infants received placebo (placebo-placebo regimen).** The infants also received one week of zidovudine therapy and were formula-fed. The end point of the study was infection with HIV in the infants, established by virologic testing. RESULTS: Between January 15, 2001, and February 28, 2003, a total of 1844 Thai women were enrolled. At the first interim analysis, the independent data monitoring committee stopped enrollment in the placebo-placebo group. **Among women who delivered before the interim analysis, the as-randomized Kaplan-Meier estimates of the transmission rates were 1.1 percent (95 percent confidence interval, 0.3 to 2.2) in the nevirapine-nevirapine group and 6.3**

percent (95 percent confidence interval, 3.8 to 8.9) in the placebo-placebo group ($P < 0.001$). The final per-protocol transmission rate in the nevirapine-nevirapine group, 1.9 percent (95 percent confidence interval, 0.9 to 3.0), was not significantly inferior to the rate in the nevirapine-placebo group (2.8 percent; 95 percent confidence interval, 1.5 to 4.1). Nevirapine had an effect within subgroups defined by known risk factors such as viral load and CD4 count. No serious adverse effects were associated with nevirapine therapy. **CONCLUSIONS: A single dose of nevirapine to the mother, with or without a dose of nevirapine to the infant, added to oral zidovudine prophylaxis starting at 28 weeks' gestation, is highly effective in reducing mother-to-child transmission of HIV.**

J Acquir Immune Defic Syndr. 2005 Mar 1;38(3):283-8.

Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1.

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OBJECTIVE: To determine nevirapine (NVP) plasma levels during the postpartum period after a single intrapartum NVP dose for the prevention of mother-to-child transmission.

METHODS: Plasma samples at delivery and during days 8 to 45 postpartum were obtained from HIV-infected Thai women who received an intrapartum NVP dose in the Perinatal HIV Prevention Clinical Trial-2 (PHPT-2) for the prevention of perinatal HIV transmission. These data were combined with NVP concentration data from 2 phase 1 studies of NVP for a population analysis. **RESULTS: The median NVP level fell to 68 ng/mL (range: <50-228, n = 43) 8 to 14 days after dosing and to 51 ng/mL (range: <50-166, n = 25) between 15 and 21 days. During the second and third weeks postpartum, NVP levels were below the limit of quantitation in 23% and 44% of samples, respectively. Between 21 and 45 days, no sample had a quantifiable NVP concentration. A simulation derived from the population analysis predicts that NVP concentration falls to less than 10 ng/mL in 5% of women by 11 days, in 50% of women by 17.5 days, and in 95% of women by 28 days. CONCLUSIONS: Significant NVP concentrations remained for up to 20 days in these Thai women. To ensure that coverage is maintained until NVP concentrations fall to nonsuppressive levels, 1 month of additional antiretroviral treatment after delivery should be considered to prevent the emergence of resistant viruses.**

Lancet. 2004 Nov 20;364(9448):1865-71

Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial.

Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, Farrelly L, Kaganson N, Zumla A, Gillespie SH, Nunn AJ, Gibb DM; CHAP trial team.

University Teaching Hospital, Lusaka, Zambia.

BACKGROUND: No trials of co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis for HIV-infected adults or children have been done in areas with high levels of bacterial resistance to this antibiotic. We aimed to assess the efficacy of daily co-trimoxazole in such an area. **METHODS:** We did a double-blind randomised placebo-controlled trial in children aged 1-14 years with clinical features of HIV infection in Zambia. Primary outcomes were mortality and adverse events possibly related to treatment. Analysis was by intention to treat. **FINDINGS:** In October, 2003, the data and safety monitoring committee recommended early stopping of the trial. 541 children had been randomly assigned; seven were subsequently identified as HIV negative and excluded. **After median follow-up of 19 months, 74 (28%) children in the co-trimoxazole group and 112 (42%) in the placebo group had died (hazard ratio [HR] 0.57 [95% CI 0.43-0.77], p=0.0002).** This benefit applied in children followed up beyond 12 months (n=320, HR 0.48 [0.27-0.84], test for heterogeneity p=0.60) and across all ages (test for heterogeneity p=0.82) and baseline CD4 counts (test for heterogeneity p=0.36). 16 (6%) children in the co-trimoxazole group had grade 3 or 4 adverse events compared with 18 (7%) in the placebo group. These events included rash (one placebo), and a neutrophil count on one occasion less than $0.5 \times 10^9/L$ (16 [6%] co-trimoxazole vs seven [3%] placebo, p=0.06). *Pneumocystis carinii* was identified by immunofluorescence in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia. **INTERPRETATION:** Our results suggest that children of all ages with clinical features of HIV infection should receive co-trimoxazole prophylaxis in resource-poor settings, irrespective of local resistance to this drug.

Comment

This is a very important trial demonstrating the importance of cotrimoxazole prophylaxis in children of all ages with HIV. Given that this trial mostly involved children commonly thought to be out of the age range at which PCP is a major risk, one wonders if cotrimoxazole prevented other intercurrent infections (such as bacterial pneumonia), or whether PCP is major pathogen across all age groups with HIV

IMCI

BMJ. 2004 Jul 31;329(7460):266

Impact of counselling on careseeking behaviour in families with sick children: cluster randomised trial in rural India.

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OBJECTIVE: To assess whether training doctors in counselling improves careseeking behaviour in families with sick children. **DESIGN:** Pair matched, community randomised trial conducted in 12 primary health centres (six pairs). **Doctors in intervention centres were trained in counselling, communication, and clinical skills, using the integrated management of childhood illness approach.** **SETTING:** Rural district in Rajasthan, India. **PARTICIPANTS:** Children aged under 5 years presenting for curative care and their mothers were recruited and visited monthly at home for six months. A total of 2460 children were recruited (1248 intervention, 1212 control). **MAIN OUTCOME MEASURES:** Careseeking

behaviour of mothers for sick children; mothers' knowledge and perceptions of seeking care; counselling performance of doctors. RESULTS: For episodes of illness with at least one reported danger sign, 15% of intervention group mothers and 10% of control group mothers reported having sought care from an appropriate provider promptly; this difference was not statistically significant (relative risk reduction 5%, 95% confidence interval -0.4% to 11%; $P = 0.07$). **One month after training, intervention site doctors counselled more effectively than control group doctors, but at six months their performance had declined.** A greater proportion of mothers in the intervention group than in the control group recalled having had at least one danger sign explained (45% v 8%; $P = 0.02$). CONCLUSIONS: Mothers' appreciation of the need to seek prompt and appropriate care for severe episodes of childhood illness increased, but their careseeking behaviour did not improve significantly.

Comment

A study that demonstrates that some effects of IMCI training will be limited. It underlines the importance of long-term follow up studies. Immediately after training there will be enhanced knowledge and performance, but without reinforcement, incentive, and counselling being part of the health culture, performance may wane over a relatively short time. Perhaps nurses would be better at providing counselling than doctors? Another RCT this year (Patient Educ Couns. 2004 Jul;54(1):35-44, see below) highlights the need for counselling education and practice to be done in local language where possible.

Lancet. 2004 Oct 30;364(9445):1595-602.

Integrated Management of Childhood Illness (IMCI) in Bangladesh: early findings from a cluster-randomised study.

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BACKGROUND: We report the preliminary findings from a continuing cluster randomised evaluation of the Integrated Management of Childhood Illness (IMCI) strategy in Bangladesh. METHODS: **20 first-level outpatient facilities in the Matlab sub-district and their catchment areas were randomised to either IMCI or standard care.** Surveys were done in households and in health facilities at baseline and were repeated about 2 years after implementation. Data on use of health facilities were recorded. IMCI implementation included health worker training, health systems support, and community level activities guided by formative research. FINDINGS: 94% of health workers in the intervention facilities were trained in IMCI. Health systems supports were generally available, but implementation of the community activities was slow. **The mean index of correct treatment for sick children was 54 in IMCI facilities compared with 9 in comparison facilities (range 0-100). Use of the IMCI facilities increased from 0.6 visits per child per year at baseline to 1.9 visits per child per year about 21 months after IMCI introduction. 19% of sick children in the IMCI area were taken to a health worker compared with 9% in the non-IMCI area.** INTERPRETATION: 2 years into the assessment, the results show improvements in the quality of care in health facilities, increases in use of facilities, and gains in the proportion of sick children taken to an appropriate health care provider. These findings are being used to strengthen child health care nationwide. They suggest that low levels of use of health facilities

could be improved by investing in quality of care and health systems support.

Patient Educ Couns. 2004 Jul;54(1):35-44

Impact of IMCI training and language used by provider on quality of counseling provided to parents of sick children in Bougouni District, Mali.

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This study evaluates the impact of the Integrated Management Of Childhood Illness (IMCI) training on quality of counseling provided to caregivers about administration of antimalarials to their children. Ten community health centers in southern Mali were randomized to either training or comparison arms of the study, and health providers' consultations with caregivers were observed. Out of a 10-point counseling scale (Cronbach's alpha=0.77), IMCI-trained providers completed an average of 1.47 (95% CI, -0.25, 3.2) more tasks than did providers who had not received IMCI training in a linear regression analysis that accounted for intra-provider correlations. Drug consultations done in both French and the local language, Bambara, had higher scores than those conducted exclusively in Bambara. The effect of providers receiving IMCI training was more pronounced in bilingual consultations, with an average increase of 2.49 (95% CI, 0.76, 4.22) in IMCI, bilingual consultations, and average increase of 0.87 (95% CI, -0.95, 2.69) in IMCI monolingual (Bambara) consultations as compared to non-IMCI-trained providers in monolingual consultations. IMCI training showed a non-significant trend overall in improving drug counseling provided to caregivers, with significant improvements in bilingual consultations. The IMCI program in Mali should consider strategies such as role-playing of counseling in Bambara or other local languages during training to improve patient-provider communication. Similar problems related to counseling by health workers in local languages are likely to be present throughout Africa, and warrant further study.

Trop Med Int Health. 2005 May;10(5):471-7.

Primary care nurses using guidelines in Thailand: a randomized controlled trial.

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BACKGROUND: Nurses run primary health centres in Thailand. We examined whether clinical guidelines improved the quality of the care they provide. **METHODS:** Eighteen nurse-led health centres randomized to (a) guidelines, receiving a training workshop plus educational outreach visit, with guidelines for children (acute respiratory tract infection and diarrhoea) and adults (diazepam prescribing and diabetes management) or (b) usual care. Outcomes were changes at 6 months in antibiotic use, diazepam prescribing, drug costs per patient, and a composite process index for diabetes care. **RESULTS:** Baseline prescribing was high for antibiotics (37% of all attendees), and no difference between intervention and control sites was

detected at follow-up for this variable. **In children (0-5 years old), antibiotics were widely used for acute respiratory tract infection (34%), and fell with guidelines (intervention: 42% at baseline to 27% at follow-up; control: 27-30%, P=0.022), with an associated fall in drug costs per patient. Antibiotics were widely prescribed for diarrhoea in children (91%), but no change was detected with guidelines.** In adults, diazepam prescribing at baseline was high (17%), and fell in the guidelines group (intervention: 17-10%; control 21-18%; P=0.029). Diabetes care was generally good, and changed little with guidelines. **CONCLUSION:** Staff at primary health centres over-prescribe antibiotics in children and tranquilizer in adults. Clinical guidelines implemented with workshops and educational outreach visits improved some but not all aspects of prescribing in the short-term.

Iron deficiency anaemia

Am J Trop Med Hyg. 2004 Oct;71(4):428-33

A randomized comparison of two anemia treatment regimens in Tanzanian children.

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We used a prospective, open-label randomized trial to evaluate two treatment regimens in Tanzanian children two months to four years of age presenting to a hospital with a packed cell volume (PCV) < 25%. **Treatment was either standard (14 days of ferrous sulfate and an antimalarial) or extended (three months of ferrous sulfate and three antimalarial treatments).** The prevalence of anemia was measured two weeks after completion of treatment and six months after recruitment. Two weeks after completing treatment, the prevalence of PCV < 33% was 58% in the standard treatment arm and 44% in the extended treatment group (P = 0.04), and the mean PCV was significantly higher in the extended treatment arm (32.1%, SD = 4.5% versus 30.8%, SD = 4.9%; P = 0.031). However, there was no difference in the prevalence of PCV < 25% in the first survey, and **the benefits of extended therapy were only apparent six months after recruitment in children compliant with the extended treatment (odds ratio of PCV < 25% = 0.16, P = 0.06).** Compliance was satisfactory in only 39% (82 of 209) of the children in the first week of treatment. Extending the duration of therapy and improving compliance may have health benefits for anemic children in malaria-endemic settings.

J Nutr. 2005 Apr;135(4):850-5.

Mother-infant interactions and infant development are altered by maternal iron deficiency anemia.

Perez EM, Hendricks MK, Beard JL, Murray-Kolb LE, Berg A, Tomlinson M, Irlam J, Isaacs W, Njengele T, Sive A, Vernon-Feagans L.

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The aim of this study was to determine whether iron deficiency anemia (IDA) in young South African mothers alters mother-infant interactions and the infant's development. The study was a prospective, randomized, controlled intervention trial with 3 groups of mothers: nonanemic controls and anemic mothers administered either placebo (25 mg ascorbic acid and 10 microg folate) or daily iron treatment (125 mg FeSO₄ plus ascorbate and folate). Mothers of full-term, normal birth weight infants (n = 81) were followed from 10 wk to 9 mo postpartum. Maternal iron status, socioeconomic level, mother-infant interaction [Parent/Caregiver Involvement Scale (PCIS scale)], and infant development (Griffiths scale) were assessed. At baseline, anemic mothers tended (P < 0.10) to be less responsive to, and more controlling of, their infants. Infants of anemic mothers were developmentally delayed at 10 wk in hand-eye movement and overall quotient. Despite normalization of maternal iron status with supplementation in some mothers, the developmental delays were not diminished at 9 mo. **At 9 mo, anemic mothers were significantly more "negative" towards their babies, engaged less in goal setting, and were less "responsive" than control mothers. In contrast, the behavior of anemic mothers given iron treatment toward their children was similar to that of the control mothers on all 11 scales of the PCIS.** In conclusion, IDA altered mother-child interactions at both 10 wk and 9 mo postpartum. Additionally, infants whose mothers were anemic in the early postpartum scored worse on developmental tests at 10 wk and 9 mo of age.

J Nutr. 2005 Feb;135(2):267-72.

Maternal iron deficiency anemia affects postpartum emotions and cognition.

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The aim of this study was to determine whether iron deficiency anemia (IDA) in mothers alters their maternal cognitive and behavioral performance, the mother-infant interaction, and the infant's development. This article focuses on the relation between IDA and cognition as well as behavioral affect in the young mothers. This prospective, randomized, controlled, intervention trial was conducted in South Africa among 3 groups of mothers: nonanemic controls and anemic mothers receiving either placebo (10 microg folate and 25 mg vitamin C) or daily iron (125 mg FeSO₄, 10 microg folate, 25 mg vitamin C). Mothers of full-term normal birth weight babies were followed from 10 wk to 9 mo postpartum (n = 81). Maternal hematologic and iron status, socioeconomic, cognitive, and emotional status, mother-infant interaction, and the development of the infants were assessed at 10 wk and 9 mo postpartum. Behavioral and cognitive variables at baseline did not differ between iron-deficient anemic mothers and nonanemic mothers. However, iron treatment resulted in a 25% improvement (P < 0.05) in previously iron-deficient mothers' depression and stress scales as well as in the Raven's Progressive Matrices test. Anemic mothers administered placebo did not improve in behavioral measures. Multivariate analysis showed a strong association between iron status variables (hemoglobin, mean corpuscular volume, and transferrin saturation) and cognitive variables (Digit Symbol) as well as behavioral variables (anxiety, stress, depression). **This study demonstrates that there is a strong relation between iron status and depression, stress,**

and cognitive functioning in poor African mothers during the postpartum period. There are likely ramifications of this poorer "functioning" on mother-child interactions and infant development, but the constraints around this relation will have to be defined in larger studies.

Comment

These two studies show the great importance of maternal iron status in child development and maternal mental health. While most studies of iron supplementation have focused on changes in Hb and cognitive development in older children, the impact on infant development of maternal depression due to iron deficiency has not been well recognized.

J Trop Pediatr. 2004 Oct;50(5):276-8

Efficacy of daily vs. weekly supplementation of iron in schoolchildren with low iron status.

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Iron deficiency anemia (IDA) is still a major nutritional and public health problem in developing countries. The prevalence among young children and pregnant women is particularly high. Daily oral supplementation with medicinal iron is considered an effective strategy for reducing the incidence of IDA but non-compliance is a major problem with this strategy. We undertook this study to compare the results of **once-weekly vs. daily oral iron supplementation in schoolchildren**. Sixty children ranging between 5 and 10 years with iron deficiency anemia were selected from a school in Karachi, Pakistan and were divided into two equal groups, i.e., daily and weekly supplementation groups. Hemoglobin (Hb), hematocrit (Hct), serum iron, total iron binding capacity (TIBC), and serum ferritin were determined before the start of the study. Ferrous sulfate (200 mg) was given daily to the daily supplementation group and once-weekly to the weekly supplementation group for 2 months. When post-supplementation values of the above-mentioned parameters were determined, a significant improvement was observed in all parameters in both groups. **It is concluded that once-weekly iron supplementation is as effective as daily supplementation for the treatment of iron deficiency anemia.** Moreover, weekly iron supplementation is cost effective and has no or fewer side-effects.

J Nutr. 2004 Nov;134(11):3037-41

Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children.

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Conflicting evidence exists on the possible role of iron supplementation in the predisposition to malaria infection or the enhancement of its clinical severity. Where anemia prevalence is >40%, current guidelines are to provide low-dose daily iron to young children for up to 18 mo. Earlier studies used doses higher than the current guidelines, intermittent doses, or have supplemented for durations < or = 4 mo. **We aimed to assess the effect of low-dose, long-term iron supplementation on malaria infection** using a double-blind, placebo-controlled, randomized design, and to examine possible subgroup effects by season and child age. The study was conducted in Pemba Island, Zanzibar, where Plasmodium falciparum malaria has year-round high transmission. A community-based sample of 614 children 4-71 mo old was randomly allocated to 10 mg/d iron or placebo for 12 mo. Outcome measures were the prevalence and density of malaria infection, which was assessed by blood films at monthly intervals. **At baseline, 94.4% were anemic (hemoglobin < 110 g/L), 48.1% were stunted (height-for-age Z-score less than -2) and >80% had malaria-positive blood films. No significant differences in malariometric indices were observed between children in the iron-supplemented and placebo groups. Parasite density was higher in certain months and in younger children, but iron supplementation was not associated with any malarial infection outcome in any season or age subgroup.** We conclude that in this environment of high malaria transmission, daily oral low-dose supplementation of iron for 12 mo did not affect the prevalence of malaria infection or parasite density.

Trop Med Int Health. 2004 Aug;9(8):904-9

Weekly iron supplements given by teachers sustain the haemoglobin concentration of schoolchildren in the Philippines.

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OBJECTIVES: To examine the effectiveness of weekly iron supplements given for 10 weeks by teachers to children in rural schools in the Philippines. **METHODS:** Forty-nine rural primary schools took part in the study and were randomly assigned to two groups: **children in 25 schools received a weekly tablet providing 108 mg iron while children in 24 schools acted as controls.** All children were dewormed before the start of the iron supplementation. The haemoglobin concentration of a systematic sample of one in three children in two classes in each school was estimated before and 5-17 weeks after the end of the iron supplementation. **RESULTS:** A total of 1510 children aged 7-12 years were studied at both surveys. **The mean haemoglobin concentration of children in the intervention group did not change significantly; in the untreated group it fell by 3.8 g/l and the prevalence of anaemia rose from 14.3% to 25.6%.** The difference between study groups was significantly larger amongst the younger children (7-8 years), and was observed in both anaemic and non-anaemic children. **CONCLUSION:** Even where anaemia is only a mild public health problem, weekly iron supplements given by teachers may prevent a fall in the haemoglobin concentration, and can benefit both anaemic and non-anaemic children.

J Nutr. 2004 Sep;134(9):2349-54

Once-weekly and 5-days a week iron supplementation differentially affect cognitive function but not school performance in Thai children.

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Many studies have reported comparable hemoglobin response in subjects given intermittent and daily iron supplements. However, the effect of intermittent iron supplementation on impaired cognitive function, one of the serious consequences of iron deficiency among children, has not been studied. We investigated the effects of 1 d/wk (weekly) and 5 d/wk (daily) iron supplementation on changes in results of intelligence quotient (IQ), Thai language, and mathematics tests among Thai primary schoolchildren. A double-blind, randomized, placebo-controlled trial was conducted. **Primary schoolchildren (n = 397) were randomly assigned to receive iron supplements daily or weekly or placebo.** Ferrous sulfate (300 mg) or placebo tablets were given under direct observation by the researcher for 16 wk. Changes in IQ, and Thai language and mathematics scores were then compared. **The increases in hemoglobin concentration were comparable in the weekly and daily iron supplementation groups but serum ferritin increased more in the children supplemented daily.** Children receiving daily iron supplements, however, had a significantly lower increase in IQ (3 +/- 12 points) than those receiving the supplement weekly (6 +/- 12 points) or placebo (6 +/- 12 points), whereas the last-mentioned two groups did not differ. Z-scores of Thai language and mathematics test results did not differ among the groups. We conclude that weekly iron supplementation is the regimen of choice in this study community.

Comment

Much has been learnt from RCTs about iron supplementation this year: iron supplementation for anaemic mothers reduces maternal depression and improves infant development; increasing fruit juice intake increases serum ferritin concentrations; a long-term effect on Hb requires extended therapy (i.e. 3 months); and once weekly iron supplementation does not appear to increase the risk of malaria, is effective in preventing anaemia in children at risk, and can be given as part of a school health program.

Leprosy

Lepr Rev. 2004 Dec;75(4):376-88

A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: design, methodology and recruitment findings of COLEP.

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In this article, we describe the design, methodology and recruitment findings of the COLEP

study. The objectives of this study were to determine the effectiveness of chemoprophylaxis with a single dose of rifampicin in the prevention of leprosy among close contacts of leprosy patients, and to find characteristics of contact groups most at risk to develop clinical leprosy. These characteristics should be usable by routine leprosy control programmes. COLEP consists of a cluster randomized, double-blind and placebo-controlled trial, **a cohort study to determine risk factors characterizing the sub-groups most at risk within the total contact group of a patient, and a cohort study using a reference group from the general population to determine the prevalence and incidence of leprosy in the total population of the study area.** The follow-up period will be 4 years. A coding system was developed describing the physical and genetic distance of the contact person to the patient. This study in Bangladesh includes 1037 newly diagnosed and previously untreated leprosy patients and their 21,867 contacts. The prevalence of leprosy among contacts was 7.3 per 1000. A total of 21,708 contacts without signs and symptoms of clinical leprosy are included in a trial of chemoprophylaxis with single dose rifampicin, and randomized at contact group level in treatment and placebo arms. The results of this large field trial will become available in the years to come.

Malaria

Trop Med Int Health. 2005 Jun;10(6):521-9.

Efficacy of combination therapy with artesunate plus amodiaquine compared to monotherapy with chloroquine, amodiaquine or sulfadoxine-pyrimethamine for treatment of uncomplicated Plasmodium falciparum in Afghanistan.

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INTRODUCTION: In South and Central Asia resistance to chloroquine (CQ) has reached unmanageable levels, and resistance to sulfadoxine-pyrimethamine (SP) is emerging. Amodiaquine (AQ) is widely used in the region, and elsewhere shows only partial resistance to CQ. In Afghanistan, one option for slowing the spread of resistance and improving treatment outcomes is the use of artemisinin combination therapy (ACT). **METHODS:** The efficacy of CQ, AQ, SP and amodiaquine plus artesunate (AQ/AS) in the treatment of uncomplicated falciparum malaria was investigated using standard World Health Organization (WHO) procedures. Malaria patients were randomized to four treatment groups: 268 were enrolled and 240 completed the trial. **RESULTS:** **There was a high level of cross-resistance between CQ and AQ resistance: adequate clinical and parasitological response by day 42 was 11% after CQ treatment and 9% after AQ treatment. The trend of treatment failure between AQ and CQ was almost identical. Cure rates were considerably improved by the addition of artesunate to AQ or by use of SP; adequate clinical and parasitological response being 72% for AQ/AS and 92% for SP.** The combination of AS/AQ substantially reduced the odds of treatment failure relative to AQ monotherapy by day 42 [odds ratio (OR) = 0.03, 95% confidence interval (CI) 0.01-0.1] in addition to reducing the proportion of patients with gametocytes throughout the 42-day period. Gametocyte carriage rate was only marginally higher in the SP than in the CQ- and AQ-treated groups. **CONCLUSION:** The therapeutic and parasitological cure rates with AS/AQ were inadequate, and the criteria for deploying ACT - namely to prevent further selection of drug resistance from a position of low frequency - was not met in the region. An alternative drug combination to AQ/AS is required for Afghanistan.

Comment

Note that several other RCTs published this year have shown that resistance between amodiaquine and chloroquine is not always concordant, as found in this study.

J Trop Pediatr. 2005 Feb;51(1):17-24. Epub 2004 Dec 15.

A randomized open label clinical trial to compare the efficacy and safety of intravenous quinine followed by oral malarone vs. intravenous quinine followed by oral quinine in the treatment of severe malaria.

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The treatment of patients with severe malaria in sub-Saharan Africa has become a challenge to clinicians due to poor compliance to quinine and the increasing multidrug resistance to antimalarials by the *P. falciparum* parasite. **The aim of this study was to compare the efficacy and safety profile of two truncated antimalarial regimens of intravenous quinine followed by oral Malarone (Malarone arm) with intravenous quinine followed by oral quinine (quinine arm) in the treatment of severe *P. falciparum* malaria.** The outcome measures were parasite clearance time, fever clearance time, efficacy, and adverse events profile. Consecutive patients aged 1-60 years, with a diagnosis of severe malaria with positive blood smears for *P. falciparum* parasites and admitted to the Moi Teaching and Referral Hospital were randomized into the two study arms. Of the 360 patients studied 167 and 193 cases were randomized into the Malarone and quinine arms, respectively. Of the five (1.4 per cent) patients who died, three came from the quinine arm. **The frequency of adverse reactions was higher in the oral quinine group (31.6 per cent) than in the Malarone group (25.7 per cent). The mean parasite clearance time was 120 h and 108 h for the quinine and Malarone arms of the study, respectively, and the mean fever clearance times were 84 h and 72 h for the quinine and Malarone arms, respectively (p=0.1). Truncated therapeutic regimen using malarone after intravenous quinine is safer and as effective as conventional intravenous quinine followed by oral quinine in the treatment of severe malaria.** The *P. falciparum* recrudescence rate was lower with the use of Malarone than for quinine.

Am J Trop Med Hyg. 2004 Aug;71(2):160-6

Artesunate with mefloquine at various intervals for non-severe Plasmodium falciparum malaria.

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To study the efficacy, tolerance, population pharmacokinetics and pharmacodynamics of artesunate followed by mefloquine at various intervals, **360 patients with Plasmodium falciparum malaria received 4 mg/kg of artesunate and thereafter 15 mg/kg of mefloquine simultaneously (group A), after 8 hours (after group B), and after 24 hours (group C).** Three dosages were completed with placebo. Follow-up was 28 days. All patients recovered rapidly except one case of failure within the first 24 hours. Mefloquine pharmacokinetics was similar in the three regimens. **Parasites reappeared in 26%, 26%, and 33% of the patients in groups A, B, and C, respectively.** Early recrudescence was associated with high initial parasite density, slow parasite clearance, and rapid mefloquine clearance and low plasma concentrations at day 28. Mefloquine plasma concentrations all reached therapeutic ranges, suggesting reduced parasite sensitivity. In conclusion, there is no interaction between artesunate and mefloquine with respect to tolerance, efficacy, and pharmacokinetics. Single-dose combination therapy with artemisinin drugs and 15 mg/kg of mefloquine does not completely prevent parasite recurrence and may not prevent mefloquine resistance.

Trop Med Int Health. 2004 Sep;9(9):975-80

Efficacy of chloroquine, sulphadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated Plasmodium falciparum malaria in Kajo Keji county, Sudan.

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To provide advice on the rational use of antimalarial drugs, Medecins Sans Frontieres conducted a randomized, an open label efficacy study in Kajo Keji, an area of high transmission of malaria in southern Sudan. **The efficacy of chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ) were measured in a 28-day in vivo study,** with results corrected by PCR genotyping. Of 2010 children screened, 115 children aged 6-59 months with uncomplicated Plasmodium falciparum malaria were randomized into each group to receive a supervised course of treatment. Of these, 114, 103 and 111 were analysed in the CQ, SP and AQ groups, respectively. **The overall parasitological failure rates at day 28 were 93.9% [95% confidence interval (CI) 87.3-97.3] for CQ, 69.9% (95% CI 60.0-78.3) for SP, and 25.2% (95% CI 17.7-34.5) for AQ.** These results provide important missing data on antimalarial drug efficacy in southern Sudan. They indicate that none of the drugs could be used in monotherapy and suggest that even in combination with artemisinin, cure rates might not be efficacious enough. We recommend a combination of artemether and lumefantrine as first-line treatment for uncomplicated P. falciparum malaria cases in Kajo Keji county.

Parasite. 2004 Sep;11(3):317-23

Plasmodium falciparum hyperparasitaemia in children. Risk factors, treatment outcomes, and gametocytaemia following treatment.

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The risk factors associated with hyperparasitemia at presentation and after treatment with different antimalarial drug regimens were evaluated in 1,048 children enrolled prospectively in seven antimalarial drug trials between July 1996 and September 2003 in a hyperendemic area of southwestern Nigeria. The outcomes of treatment of hyperparasitaemia, and gametocyte carriage following treatment were also evaluated. The children were assigned to one of seven treatment groups: **chloroquine (CQ) only; pyrimethamine-sulfadoxine (PS) only; amodiaquine (AQ) only; CQ plus chlorpheniramine (CQCP); PS combined with CQ or AQ (COM); PS combined with probenecid (PPS); and halofantrine (HF).**

Hyperparasitaemia was found in 100 (9.5%) of the 1,048 children at enrolment (day 0). Following oral therapy, 1.2% of all patients (i.e. 13 patients) became hyperparasitaemic, which developed in all patients by day 1 of follow-up. In a multiple regression model, age \leq 5 years, and a core temperature (oral or rectal) \geq 39.5 degrees C were found to be independent risk factors for hyperparasitaemia at enrolment. **Following therapy, the cure rate on day 14 was significantly lower in those treated with CQ compared to other treatment groups. Severe resistance (RIII) response to treatment occurred significantly more frequently in those with hyperparasitaemia at enrolment than in those without, and was seen in five and one child with hyperparasitaemia who were treated with CQ and CQCP, respectively.** Gametocyte carriage was insignificantly lower at enrolment and at all times following treatment in children with hyperparasitaemia than in age- and gender-matched children without hyperparasitaemia who received the same treatment. The results are discussed in the light of management of uncomplicated hyperparasitaemia in children in endemic settings.

Trop Med Int Health. 2004 Oct;9(10):1091-8

Is amodiaquine failing in Rwanda? Efficacy of amodiaquine alone and combined with artesunate in children with uncomplicated malaria.

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We investigated the safety and efficacy of amodiaquine alone (AQ) and combined with artesunate (AQ + AS) in 308 Rwandan children 6-59 months old with uncomplicated Plasmodium falciparum malaria attending three sentinel sites. The two treatment regimes were well tolerated and no serious adverse events were recorded. After excluding new infections, **children treated with AQ + AS had fewer clinical failures at day 28 after treatment than those treated with AQ alone: OR = 0.20 [95% CI: 0.06-0.57 (P = 0.001)].** Total (parasitological and clinical) failure was also significantly less frequent in the AQ + AS group: OR = 0.34 [95% CI: 0.17-0.67 (P = 0.001)]. When adjusting for study site, the hazard ratio for treatment failure was 0.37 [95% CI: 0.20-0.68 (P = 0.001)]. Combining AQ with AS increases the efficacy of the treatment but the apparent increase of AQ resistance observed in just a 1-

year period is worrying and casts doubts on the suitability of implementing AQ + AS as first-line treatment in Rwanda. Alternative treatments should be identified and tested.

Trop Med Int Health. 2004 Nov;9(11):1175-83

Therapeutic efficacy of artemether-lumefantrine and artesunate-mefloquine for treatment of uncomplicated Plasmodium falciparum malaria in Luang Namtha Province, Lao People's Democratic Republic.

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The efficacy of the six-dose regimen of artemether-lumefantrine was compared with the combination of artesunate and mefloquine in a randomised, comparative trial in Luang Namtha Province, Northern Laos. Of 1033 screened patients, 201 were positive for Plasmodium falciparum; 108 patients of all age groups (2-66 years) with acute, uncomplicated P. falciparum malaria were enrolled in the study, 100 of whom were followed-up for 42 days. Fifty-three patients received artemether-lumefantrine and 55 received artesunate-mefloquine. Both drug combinations induced rapid clearance of parasites and malaria symptoms; there was no significant difference in the initial therapeutic response parameters. **Both regimes were well tolerated. After 42 days, cure rates were 93.6% (95% CI = 82.5-98.7%; 44 of 47 patients) for artemether-lumefantrine and 100% (95% CI = 93.3-100.0%; 53 of 53 patients) for artesunate-mefloquine.** The results show the excellent efficacy and tolerability of both artemether-lumefantrine and artesunate-mefloquine in Northern Laos.

Trop Med Int Health. 2004 Nov;9(11):1184-90

Comparison of chloroquine, sulfadoxine/pyrimethamine, mefloquine and mefloquine-artesunate for the treatment of falciparum malaria in Kachin State, North Myanmar.

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Multi-drug resistant falciparum malaria is widespread in Asia. In Thailand, Cambodia and Vietnam the national protocols have changed largely to artesunate combined treatment regimens but elsewhere in East and South Asia chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) are still widely recommended by national malaria control programmes. In Kachin State, northern Myanmar, an area of low seasonal malaria transmission, the efficacy of CQ (25 mg base/kg) and SP (1.25/25 mg/kg), the nationally recommended treatments at the time, were compared with mefloquine alone (M; 15 mg base/kg) and mefloquine combined with artesunate (MA; 15:4 mg/kg). An open randomized controlled trial enrolled 316 patients with uncomplicated Plasmodium falciparum malaria, stratified prospectively into three age-groups. Early treatment failures (ETF) occurred in 41% (32/78) of CQ treated patients and in

24% of patients treated with SP (18/75). In young children the ETF rates were 87% after CQ and 35% after SP. Four children (two CQ, two SP) developed symptoms of cerebral malaria within 3 days after treatment. **By day 42, failure rates (uncorrected for reinfections) had increased to 79% for CQ and 81% for SP. ETF rates were 2.5% after treatment with M and 3.9% after treatment with MA (P > 0.2).** Overall uncorrected treatment failure rates at day 42 following M and MA were 23% and 21%, respectively. **Chloroquine and SP are completely ineffective for the treatment of falciparum malaria in northern Myanmar.** Mefloquine treatment is much more effective, but three day combination regimens with artesunate will be needed for optimum efficacy and protection against resistance.

Cochrane Database Syst Rev. 2004;(2):CD000363

Insecticide-treated bed nets and curtains for preventing malaria.

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BACKGROUND: Malaria is an important cause of illness and death in many parts of the world, especially in sub-Saharan Africa. There has been a renewed emphasis on preventive measures at community and individual levels. Insecticide-treated nets (ITNs) are the most prominent malaria preventive measure for large-scale deployment in highly endemic areas. **OBJECTIVES:** To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates. **SEARCH STRATEGY:** I searched the Cochrane Infectious Diseases Group trials register (January 2003), CENTRAL (The Cochrane Library, Issue 1, 2003), MEDLINE (1966 to October 2003), EMBASE (1974 to November 2002), LILACS (1982 to January 2003), and reference lists of reviews, books, and trials. I handsearched journals, contacted researchers, funding agencies, and net and insecticide manufacturers. **SELECTION CRITERIA:** Individual and cluster randomized controlled trials of insecticide-treated bed nets or curtains compared to nets without insecticide or no nets. Trials including only pregnant women were excluded. **DATA COLLECTION AND ANALYSIS:** The reviewer and two independent assessors reviewed trials for inclusion. The reviewer assessed trial methodological quality and extracted and analysed data. **MAIN RESULTS: Fourteen cluster randomized and eight individually randomized controlled trials met the inclusion criteria. Five trials measured child mortality: ITNs provided 17% protective efficacy (PE) compared to no nets (relative rate 0.83, 95% confidence interval (CI) 0.76 to 0.90), and 23% PE compared to untreated nets (relative rate 0.77, 95% CI 0.63 to 0.95). About 5.5 lives (95% CI 3.39 to 7.67) can be saved each year for every 1000 children protected with ITNs.** In areas with stable malaria, ITNs reduced the incidence of uncomplicated malarial episodes in areas of stable malaria by 50% compared to no nets, and 39% compared to untreated nets; and in areas of unstable malaria: by 62% for compared to no nets and 43% compared to untreated nets for *Plasmodium falciparum* episodes, and by 52% compared to no nets and 11% compared to untreated nets for *P. vivax* episodes. When compared to no nets and in areas of stable malaria, ITNs also had an impact on severe malaria (45% PE, 95% CI 20 to 63), parasite prevalence (13% PE), high parasitaemia (29% PE), splenomegaly (30% PE), and their use improved the average haemoglobin level in children by 1.7% packed cell volume. **REVIEWERS' CONCLUSIONS: ITNs are highly effective in reducing childhood mortality and morbidity from malaria.** Widespread access to ITNs is currently being advocated by Roll Back Malaria, but universal deployment will require major financial, technical, and operational inputs.

Lancet. 2004 Nov 27;364(9449):1950-7

Combination treatments for uncomplicated falciparum malaria in Kampala, Uganda: randomised clinical trial.

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BACKGROUND: Plasmodium falciparum resistance has rendered chloroquine monotherapy ineffective in much of Africa, but data on alternative regimens are limited. **We compared chloroquine+sulfadoxine-pyrimethamine, amodiaquine+sulfadoxine-pyrimethamine, and amodiaquine+artesunate for treatment of uncomplicated malaria in Kampala, Uganda.** **METHODS:** Of 1017 consecutive patients aged 6 months to 10 years with uncomplicated malaria who were screened, 418 were randomised to receive: chloroquine (25 mg/kg over 3 days) and sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine, 1.25 mg/kg pyrimethamine, single dose); amodiaquine (25 mg/kg over 3 days) and sulfadoxine-pyrimethamine; or amodiaquine and artesunate (4 mg/kg daily for 3 days). Primary efficacy outcomes were 28-day clinical failure risks, adjusted and unadjusted by genotyping to distinguish new infection and recrudescence. The primary safety endpoint was incidence of serious adverse events during follow-up. Analysis was intention to treat and per protocol. **FINDINGS:** 18 patients were excluded before enrollment. Of those enrolled, 384 of 400 (96%) were assigned an efficacy outcome and 396 (99%) were assessed for safety. **Risk of 28-day clinical treatment failure was significantly higher with chloroquine+sulfadoxine-pyrimethamine (44/125 [35%]) than with amodiaquine+sulfadoxine-pyrimethamine (12/129 [9%]; risk difference 26% [95% CI 16-36]; p<0.0001) or amodiaquine+artesunate (3/130 [2%]; 33% [24-42]; p<0.0001).** The greater risk of clinical treatment failure with amodiaquine+sulfadoxine-pyrimethamine was balanced by a lower risk of new infection, resulting in a similar need for retreatment over 28 days for amodiaquine+sulfadoxine-pyrimethamine (17/129 [13%]) and amodiaquine+artesunate (16/130 [12%]; p=0.854). Serious adverse events were uncommon with all regimens. **INTERPRETATION: Risk of treatment failure with chloroquine+sulfadoxine-pyrimethamine was unacceptably high. Combinations of amodiaquine and sulfadoxine-pyrimethamine or artesunate were significantly more efficacious,** and each regimen could be an appropriate alternative for treatment of uncomplicated malaria in Africa.

J Infect Dis. 2004 Nov 15;190(10):1773-82

Randomized, controlled dose-optimization studies of dihydroartemisinin-piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand.

Ashley EA, Krudsood S, Phaiphun L, Srivilairit S, McGready R, Leowattana W, Hutagalung R, Wilairatana P, Brockman A, Looareesuwan S, Nosten F, White NJ.

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BACKGROUND: Dihydroartemisinin-piperaquine (DP) is a new and relatively inexpensive artemisinin-containing fixed-combination antimalarial treatment. An adult treatment course contained 6.4 mg/kg dihydroartemisinin (DHA), which is >40% lower than the level in most artemisinin-containing combinations. This raised the possibility that the efficacy of the current coformulation may not be optimal in the treatment of multidrug-resistant falciparum malaria. **METHODS:** In 2 large randomized, controlled studies in Thailand, the recommended dose of DP was compared with a regimen with additional artemisinin derivative (12 mg/kg; DP+) and with mefloquine plus artesunate (MAS3). **RESULTS:** A total of 731 patients were included: 201 in a hospital-based study and 530 in a community study. **Day-28 cure rates in the hospital-based study were 100% (95% confidence interval [CI], 93.9%-100%) in the MAS3 and DP+ groups and 98.3% (95% CI, 91%-99.7%) in the DP group, with a single recrudescence on day 21. In the community study, polymerase chain reaction genotyping-adjusted cure rates on day 63 were 96.1% (95% CI, 92.6%-99.7%) in the DP group, 98.3% (95% CI, 96.1%-100%) in the DP+ group, and 94.9% (95% CI, 91.2%-98.6%) in the MAS3 group (P=.2).** Adverse events were few, with an excess of mild abdominal pain in the DP group. **CONCLUSIONS:** The current dosage of DP (6.4 mg/kg DHA and 51.2 mg/kg piperaquine phosphate) given over the course of 48 h is highly effective, safe, and well tolerated for the treatment of multidrug-resistant falciparum malaria, and its efficacy is not improved by the addition of more DHA.

Am J Trop Med Hyg. 2005 May;72(5):573-80.

Sulfadoxine-pyrimethamine plus chloroquine or amodiaquine for uncomplicated falciparum malaria: a randomized, multisite trial to guide national policy in Uganda.

Bakyaita N, Dorsey G, Yeka A, Banek K, Staedke SG, Kamya MR, Talisuna A, Kironde F, Nsobya S, Kilian A, Reingold A, Rosenthal PJ, Wabwire-Mangen F.

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The use of combinations of inexpensive drugs for the treatment of malaria in Africa has been proposed as an interim policy while awaiting the widespread availability of more effective regimens. **We compared sulfadoxine-pyrimethamine plus chloroquine or amodiaquine in three districts in Uganda.** Patients aged 6 months or greater with uncomplicated falciparum malaria were enrolled and randomized to therapy. Safety, tolerability, and efficacy outcomes, adjusted by genotyping, were assessed over 28 days. Of 1,105 patients enrolled, 1,057 (96%) completed follow-up. **For children less than 5 years old, the risk of clinical treatment failure adjusted by genotyping at the three sites ranged from 34% to 67% with chloroquine plus sulfadoxine-pyrimethamine and from 13% to 35% with amodiaquine plus sulfadoxine-pyrimethamine (risk differences 21-32%, P < 0.0001 at all sites).** Serious adverse events were uncommon with both regimens. The risk of treatment failure with chloroquine plus sulfadoxine-pyrimethamine, the current standard in Uganda, was unacceptably high. **Amodiaquine plus sulfadoxine-pyrimethamine was significantly more efficacious; however, existing levels of resistance raises concern about the useful therapeutic life-span of this regimen.**

Am J Trop Med Hyg. 2005 May;72(5):568-72.

Efficacy and tolerability of artesunate plus sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine alone for the treatment of uncomplicated Plasmodium falciparum malaria in Peru.

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To assist the Peruvian Ministry of Health in modifying the malaria treatment policy for their north Pacific coastal region, we conducted an in vivo efficacy trial of sulfadoxine-pyrimethamine (SP) and SP plus artesunate (SP-AS) for the treatment for uncomplicated Plasmodium falciparum infections. **A total of 197 patients were randomized to therapy with either SP (25 mg/kg of the sulfadoxine component in a single dose on day 0) or a combination of SP plus AS (4 mg/kg on days 0, 1, and 2) and were followed for 28 days for symptoms and recurrence of parasitemia.** No statistically significant differences between the two groups were observed on enrollment with respect to age, sex, history of malaria, or geometric mean parasite density. A total of 185 subjects completed the 28-day follow-up. **Of the 91 subjects treated with SP alone, two had recurrences of parasitemia on day 7 and one on day 21. Of the 94 subjects treated with SP-AS, one had a recurrence of parasitemia on day 21. Fever and asexual parasite density decreased significantly more rapidly and the proportion of patients with gametocytemia on days 3-28 was significantly lower in subjects treated with combination therapy than in those who received SP alone.** No severe adverse drug reactions were observed; however, self-limited rash and pruritis were significantly more common and an exacerbation of nausea, vomiting, and abdominal pain were observed significantly more frequently among patients who had received SP-AS. These results have contributed to a National Malaria Control Program decision to change to SP-AS combination therapy as the first-line treatment for uncomplicated P. falciparum malaria in northern coastal Peru in November 2001, making Peru the first country in the Americas to recommend this combination therapy.

Lancet. 2005 Apr 23-29;365(9469):1474-80.

Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial.

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BACKGROUND: Many countries in Africa are considering a change to combination treatment for falciparum malaria because of the increase in drug resistance. However, there are few effectiveness data for these combinations. Our aim was to study the effectiveness of three drug combinations that have proven efficacious in east Africa compared with amodiaquine

monotherapy. **METHODS:** We undertook a randomised trial of antimalarial drug combinations for children (aged 4-59 months) with uncomplicated malaria in Muheza, Tanzania, an area with a high prevalence of resistance to sulfadoxine-pyrimethamine and chloroquine. **Children were randomly allocated 3 days of amodiaquine (n=270), amodiaquine+sulfadoxine-pyrimethamine (n=507), or amodiaquine+artesunate (n=515), or a 3-day six-dose regimen of artemether-lumefantrine (n=519).** Drugs were taken orally, at home, unobserved by medical staff. The primary endpoint was parasitological failure by day 14 assessed blind to treatment allocation. Secondary endpoints included day 28 follow-up and gametocyte carriage. Analysis was by intention to treat. **FINDINGS:** Of 3158 children screened, 1811 were randomly assigned treatment and 1717 (95%) reached the 14-day follow-up. **The amodiaquine group was stopped early by the data and safety monitoring board. By day 14, the parasitological failure rates were 103 of 248 (42%) for amodiaquine, 97 of 476 (20%) for amodiaquine+sulfadoxine-pyrimethamine, 54 of 491 (11%) for amodiaquine+artesunate, and seven of 502 (1%) for artemether-lumefantrine. By day 28, the parasitological failure rates were 182 of 239 (76%), 282 of 476 (61%), 193 of 472 (40%), and 103 of 485 (21%), respectively.** The difference between individual treatment groups and the next best treatment combination was significant ($p<0.001$) in every case. Recrudescence rates by day 28, after correction by genotyping, were 48.4%, 34.5%, 11.2%, and 2.8%, respectively. **INTERPRETATION: The study shows how few the options are for treating malaria where there is already a high level of resistance to sulfadoxine-pyrimethamine and amodiaquine.** The WHO-packaged six-dose regimen of artemether-lumefantrine is effective taken unsupervised, although cost is a major limitation.

Lancet. 2005 Apr 23-29;365(9469):1467-73.

Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomised trial.

Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor W, Checchi F, Guthmann JP.

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BACKGROUND: The six-dose regimen of artemether-lumefantrine is effective and is among combination therapies prioritised to replace antimalarials that no longer work in Africa. However, its effectiveness has not been assessed in the field, and could be compromised by poor adherence, incorrect timing of doses, and insufficient intake of fatty foods with every dose. Our aim, therefore, was to assess the effectiveness of artemether-lumefantrine prescribed under routine outpatient conditions, compared with its efficacy when given under supervision to inpatients with acute uncomplicated falciparum malaria. **METHODS:** We did a randomised trial to compare the efficacy, safety, and pharmacokinetics of artemether-lumefantrine when given in a supervised (all doses observed with fatty-food intake; n=313) or unsupervised (first dose supervised followed by outpatient treatment with nutritional advice; n=644) setting to patients of all ages (weight >10 kg) with acute, uncomplicated falciparum malaria in Mbarara, Uganda. Our primary endpoint was 28 day, PCR-adjusted, parasitological cure rate. Analysis was by intention to treat and evaluability analysis. **FINDINGS:** 38 patients were lost to follow-up and one withdrew consent. **Day-28 cure rates were 97.7% (296 of 303) and 98.0% (603 of 615) in the supervised and unsupervised groups, respectively. We recorded 15 non-**

severe, drug-related adverse events, all of which resolved. INTERPRETATION:

Artemether-lumefantrine has a high cure rate irrespective of whether given under supervision with food or under conditions of routine clinic practice. If used as first-line treatment, artemether-lumefantrine could make a substantial contribution to malaria control in Africa, though cost is an issue.

Ann Trop Med Parasitol. 2005 Mar;99(2):111-7.

Efficacies of mefloquine alone and of artesunate followed by mefloquine, for the treatment of uncomplicated, Plasmodium falciparum malaria in eastern Sudan.

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In late 2003, **the efficacies of mefloquine monotherapy and of an artesunate-mefloquine combination, for the oral treatment of uncomplicated, Plasmodium falciparum malaria, were investigated and compared in New Halfa, in eastern Sudan.** Of the patients who completed the 28 days of follow-up, 40 were treated only with single-dose mefloquine (at a dose of 25 mg/kg), and 38 with artesunate (at 4 mg/kg. day) for 3 days followed by single-dose mefloquine (at 15 mg/kg), given on the third day. Compared with those given the combination, the patients given mefloquine alone were more likely to suffer nausea, vomiting and dizziness (25.0% v. 2.6%; P=0.005) and to be found gametocytaemic (12.5% v. 0%; P=0.02) after treatment, and more likely to be found febrile (i.e. with a temperature >37.5 degrees C) on day 2 (25.0% v. 2.6%; P=0.005), although no patients were found febrile on day 3. Six of the patients--three (7.5%) of those given mefloquine only and three (7.9%) of those given the combination (P>0.05)--appeared to be treatment failures. Parasite genotyping indicated, however, that, although five of these six patients had true recrudescences, one (who had been treated with the combination) had been re-infected during the follow-up. **The true frequencies of cure were therefore 92.5% after mefloquine alone and 94.7% after the combination (P>0.05).** Thus, although the treatments appeared equally effective in clearing parasitaemias, the combination was better at clearing gametocytaemias and was less likely to cause adverse side-effects. It remains unclear why mefloquine given alone was almost 10-fold more likely to trigger adverse effects than treatment with a combination that contained the same drug. This may be a reflection of the different mefloquine doses and, for the patients given the combination, of the use of artesunate before the mefloquine treatment.

Trop Med Int Health. 2005 Mar;10(3):279-84.

A randomized comparative study of chloroquine, amodiaquine and sulphadoxine-pyrimethamine for the treatment of uncomplicated malaria in Ghana.

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The study examined the efficacy of chloroquine (CQ), amodiaquine (AQ) and sulphadoxine-pyrimethamine (SP) for the treatment of uncomplicated Plasmodium falciparum malaria in Ghana. A total of 351 children were randomized to receive either of the three study drugs. Patients were evaluated using the WHO 14-day in vivo antimalarial testing guidelines. **The 14-day adequate clinical and parasitological response analysis revealed that CQ, 46.7% (95% CI 37.5, 56.0) has the least efficacy compared with AQ, 86.1% (95% CI 78.3, 91.8) and SP, 77.6% (95% CI 68.9, 84.8).** Late parasite failures were also lower and similar in the AQ and SP (9.6% and 10.3%) than in the CQ (32.5%) group. However, CQ and AQ groups showed better fever clearance compared with SP throughout except for day 7 and after when possibly due to its significant late clinical failures, clearance by CQ was lower. **Our findings suggest that CQ is no longer useful in Ghana and should be replaced as a first-line treatment of malaria.** Replacement of CQ preferably with AQ combination treatment will be an effective and an affordable alternative for the treatment of uncomplicated malaria.

BMJ. 2005 Feb 12;330(7487):334.

Rectal artemether versus intravenous quinine for the treatment of cerebral malaria in children in Uganda: randomised clinical trial.

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OBJECTIVE: To compare the efficacy and safety of rectal artemether with intravenous quinine in the treatment of cerebral malaria in children. **DESIGN:** Randomised, single blind, clinical trial. **SETTING:** Acute care unit at Mulago Hospital, Uganda's national referral and teaching hospital in Kampala. **PARTICIPANTS:** 103 children aged 6 months to 5 years with cerebral malaria. **INTERVENTION:** Patients were randomised to either intravenous quinine or rectal artemether for seven days. **MAIN OUTCOME MEASURES:** Time to clearance of parasites and fever; time to regaining consciousness, starting oral intake, and sitting unaided; and adverse effects. **RESULTS:** **The difference in parasitological and clinical outcomes between rectal artemether and intravenous quinine did not reach significance (parasite clearance time 54.2 (SD 33.6) hours v 55.0 (SD 24.3) hours, P = 0.90; fever clearance time 33.2 (SD 21.9) hours v 24.1 (SD 18.9) hours, P = 0.08; time to regaining consciousness 30.1 (SD 24.1) hours v 22.67 (SD 18.5) hours, P = 0.10; time to starting oral intake 37.9 (SD 27.0) hours v 30.3 (SD 21.1) hours, P = 0.14).** Mortality was higher in the quinine group than in the artemether group (10/52 v 6/51; relative risk 1.29, 95% confidence interval 0.84 to 2.01). No serious immediate adverse effects occurred. **CONCLUSION:** Rectal artemether is effective and well tolerated and could be used as treatment for cerebral malaria.

Trop Med Int Health. 2005 Feb;10(2):139-45.

Efficacy and effectiveness of the combination of sulfadoxine/pyrimethamine and a 3-day course of artesunate for the treatment of uncomplicated falciparum malaria in a refugee settlement in Zambia.

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In the Maheba Refugee Settlement, in the clinics supported by Medecins Sans Frontieres, all children aged up to 5 years with a confirmed diagnosis of uncomplicated falciparum malaria are treated with the combination of sulfadoxine/pyrimethamine (SP) and artesunate (AS). We compared the treatment's efficacy and effectiveness. Patients were randomized in order to receive the treatment supervised (efficacy) or unsupervised (effectiveness). Therapeutic response was determined after 28 days of follow up. The difference between recrudescence and re-infection was ascertained by polymerase chain reaction (PCR). We also assessed genetic markers associated to SP resistance (dhfr and dhps). **Eighty-five patients received treatment under supervision and 84 received it unsupervised. On day 28, and after PCR adjustment, efficacy was found to be 83.5% (95% CI: 74.1-90.5), and effectiveness 63.4% (95% CI: 52.6-73.3) (P < 0.01).** Point mutations on dhfr (108) and dhps (437) were found for 92.0% and 44.2% respectively of the PCR samples analysed. **The significant difference in therapeutic response after supervised and unsupervised treatment intake can only be explained by insufficient patient adherence.** When implementing new malaria treatment policies, serious investment in ensuring patient adherence is essential to ascertain the effectiveness of the new treatment schedules.

Br J Haematol. 2005 Feb;128(3):393-400.

Pre-transfusion management of children with severe malarial anaemia: a randomised controlled trial of intravascular volume expansion.

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Symptomatic severe malarial anaemia (SMA) has a high fatality rate of 30-40%; most deaths occur in children awaiting blood transfusion. Blood transfusion services in most of Africa are not capable of delivering adequate supplies of safe blood in a timely manner to critically ill children with SMA. Contrary to widely held belief, hypovolaemia, rather than heart failure, has emerged as a common complication in such children. We examined the safety of pre-transfusion management (PTM) by volume expansion, aimed at stabilizing children and obviating the urgency for blood transfusion. Kenyan children with severe falciparum anaemia (haemoglobin <5 g/dl) and respiratory distress were randomly assigned to 20 ml/kg of 4.5% albumin or 0.9% saline or maintenance only (control) while awaiting blood transfusion. PTM was apparently safe since it did not lead to the development of pulmonary oedema or other adverse events. There was no significant difference in the primary outcome [mean percentage reduction in base excess between admission and 8 h (95% confidence interval)] between the control group 42% (19-66%) albumin group 44% (32-57%) and saline group 36% (16-57%); adjusted analysis of variance $F=0.31$, $P=0.7$. However, the number of children requiring emergency interventions was significantly greater in the control group, four of 18 (22%) than the saline group 0 of 20 ($P=0.03$). We have established the safety of this PTM in children with SMA whilst awaiting blood transfusion at a hospital with an adequate blood-banking program.

The impact on mortality should be assessed where blood transfusion services are unable to supply emergency transfusions.

Comment

In RCTs this year it has been clearly shown that chloroquine is ineffective in the management of uncomplicated malaria, alone or in combination, in Afghanistan, Sudan, Nigeria, Myanmar and Ghana. In Afghanistan and Tanzania amodiaquine was also ineffective. However amodiaquine was effective in Sudan, Ghana, Uganda, especially when combined with sulphadoxine/pyrimethamine or artesunate.

Malnutrition

Am J Clin Nutr. 2005 Apr;81(4):864-70.

Comparison of home-based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial.

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BACKGROUND: Childhood malnutrition is common in Malawi, and the standard treatment, which follows international guidelines, results in poor recovery rates. Higher recovery rates have been seen in pilot studies of home-based therapy with ready-to-use therapeutic food (RUTF). **OBJECTIVE:** **The objective was to compare the recovery rates among children with moderate and severe wasting, kwashiorkor, or both receiving either home-based therapy with RUTF or standard inpatient therapy.** **DESIGN:** A controlled, comparative, clinical effectiveness trial was conducted in southern Malawi with **1178 malnourished children. Children were systematically allocated to either standard therapy (186 children) or home-based therapy with RUTF (992 children) according to a stepped wedge design to control for bias introduced by the season of the year. Recovery, defined as reaching a weight-for-height z score > -2, and relapse or death were the primary outcomes.** The rate of weight gain and the prevalence of fever, cough, and diarrhea were the secondary outcomes. **RESULTS:** **Children who received home-based therapy with RUTF were more likely to achieve a weight-for-height z score > -2 than were those who received standard therapy (79% compared with 46%; P < 0.001) and were less likely to relapse or die (8.7% compared with 16.7%; P < 0.001). Children who received home-based therapy with RUTF had greater rates of weight gain (3.5 compared with 2.0 g . kg(-1) . d(-1); difference: 1.5; 95% CI: 1.0, 2.0 g . kg(-1) . d(-1)) and a lower prevalence of fever, cough, and diarrhea than did children who received standard therapy.** **CONCLUSION:** Home-based therapy with RUTF is associated with better outcomes for childhood malnutrition than is standard therapy.

BMJ. 2005 May 14;330(7500):1109. Epub 2005 Apr 25.

Antioxidant supplementation for the prevention of kwashiorkor in Malawian children: randomised, double blind, placebo controlled trial.

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OBJECTIVE: To evaluate the efficacy of antioxidant supplementation in preventing kwashiorkor in a population of Malawian children at high risk of developing kwashiorkor. **DESIGN:** Prospective, double blind, placebo controlled trial randomised by household. **SETTING:** 8 villages in rural southern Malawi. **PARTICIPANTS:** 2372 children in 2156 households aged 1-4 years were enrolled; 2332 completed the trial. **INTERVENTION:** **Daily supplementation with an antioxidant powder containing riboflavin, vitamin E, selenium, and N-acetylcysteine in a dose that provided about three times the recommended dietary allowance of each nutrient or placebo for 20 weeks.** **MAIN OUTCOME MEASURES:** The primary outcome was the incidence of oedema. Secondary outcomes were the rates of change for weight and length and the number of days of infectious symptoms. **RESULTS:** **62 children developed kwashiorkor (defined by the presence of oedema); 39/1184 (3.3%) were in the antioxidant group and 23/1188 (1.9%) were in the placebo group (relative risk 1.70, 95% confidence interval 0.98 to 2.42).** The two groups did not differ in rates of weight or height gain. Children who received antioxidant supplementation did not experience less fever, cough, or diarrhoea. **CONCLUSIONS:** Antioxidant supplementation at the dose provided did not prevent the onset of kwashiorkor. This finding does not support the hypothesis that depletion of vitamin E, selenium, cysteine, or riboflavin has a role in the development of kwashiorkor.

Neonatal care

BMC Pediatr. 2004 Aug 7;4(1):15

Treatment of retinopathy of prematurity with topical ketorolac tromethamine: a preliminary study.

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BACKGROUND: Retinopathy of Prematurity (ROP) is a common retinal neovascular disorder of premature infants. It is of variable severity, usually heals with mild or no sequelae, but may progress to blindness from retinal detachments or severe retinal scar formation. This is a preliminary report of the effectiveness and safety of a new and original use of topical ketorolac in preterm newborn to prevent the progression of ROP to the more severe forms of this disease. **METHODS:** From January 2001 to December 2002, all fifty nine preterm newborns with birthweight less than 1250 grams or gestational age less than 30 weeks of gestational age admitted to neonatal intensive care were eligible for treatment with topical ketorolac (0.25 milligrams every 8 hours in each eye). The historical comparison group included all 53 preterm newborns, with the same inclusion criteria, admitted between January 1999 and December 2000. **RESULTS:** Groups were comparable in terms of weight distribution, Apgar score at 5 minutes, incidence of sepsis, intraventricular hemorrhage and necrotizing enterocolitis. The duration of oxygen therapy was significantly longer in the control group. **In the ketorolac group, among 43 children that were alive at discharge, one (2.3%) developed threshold**

ROP and cryotherapy was necessary. In the comparison group 35 children survived, and six child (17%) needed cryotherapy (Relative Risk 0.14, 95%CI 0.00 to 0.80, p = 0.041). Adjusting by duration of oxygen therapy did not significantly change these results. Adverse effects attributable to ketorolac were not detected. **CONCLUSIONS:** This preliminary report suggests that ketorolac in the form of an ophthalmic solution can reduce the risk of developing severe ROP in very preterm newborns, without producing significant adverse side effects. These results, although promising, should be interpreted with caution because of the weakness of the study design. This is an inexpensive and simple intervention that might ameliorate the progression of a disease with devastating consequences for children and their families. We believe that next logical step would be to assess the effectiveness of this intervention in a randomized controlled trial of adequate sample size.

Nutrition

J Nutr. 2004 Sep;134(9):2342-8

An educational intervention to promote appropriate complementary feeding practices and physical growth in infants and young children in rural Haryana, India.

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Complementary feeding practices are often inadequate in developing countries, resulting in a significant nutritional decline between 6 and 18 mo of age. We assessed the effectiveness of an educational intervention to promote adequate complementary feeding practices that would be feasible to sustain with existing resources. The study was a cluster randomized controlled trial in communities in the state of Haryana in India. We developed the intervention through formative research. Eight communities were pair matched on their baseline characteristics; one of each pair was randomly assigned to receive the intervention and the other to no specific feeding intervention. Health and nutrition workers in the intervention communities were trained to counsel on locally developed feeding recommendations. Newborns were enrolled in all of the communities (552 in the intervention and 473 in the control) and followed up every 3 mo to the age of 18 mo. The main outcome measures were weights and lengths at 6, 9, 12, and 18 mo and complementary feeding practices at 9 and 18 mo. All analyses were by intent to treat. In the overall analyses, **there was a small but significant effect on length gain in the intervention group (difference in means 0.32 cm, 95% CI, 0.03, 0.61). The effect was greater in the subgroup of male infants (difference in mean length gain 0.51 cm, 95% CI 0.03, 0.98).** Weight gain was not affected. Energy intakes from complementary foods overall were significantly higher in the intervention group children at 9 mo (mean +/- SD: 1556 +/- 1109 vs. 1025 +/- 866 kJ; P < 0.001) and 18 mo (3807 +/- 1527 vs. 2577 +/- 1058 kJ; P < 0.001). Improving complementary feeding practices through existing services is feasible but the effect on physical growth is limited. Factors that limit physical growth in such settings must be better understood to plan more effective nutrition programs.

Am J Clin Nutr. 2004 Oct;80(4):952-9

Dual fortification of salt with iodine and micronized ferric pyrophosphate: a

randomized, double-blind, controlled trial.

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BACKGROUND: In many developing countries, children are at high risk for both goiter and anemia. In areas of subsistence farming in rural Africa, salt is one of the few regularly purchased food items and could be a good fortification vehicle for iodine and iron, provided that a stable yet bioavailable iron fortificant is used. **OBJECTIVE:** We tested the efficacy of salt dual-fortified with iodine and micronized ferric pyrophosphate for reducing the prevalence of iodine and iron deficiencies in children. **DESIGN:** In rural northern Morocco, we fortified local salt with 25 microg I (as potassium iodate)/g salt and 2 mg Fe (as micronized ferric pyrophosphate; mean particle size = 2.5 microm)/g salt. After storage and acceptability trials, we compared the efficacy of the dual-fortified salt (DFS) with that of iodized salt in a 10-mo, randomized, double-blind trial in iodine-deficient 6-15-y-old children (n = 158) with a high prevalence of anemia. **RESULTS:** After storage for 6 mo, there were no significant differences in iodine content or color lightness between the DFS and iodized salt. During the efficacy trial, the DFS provided approximately 18 mg Fe/d; iron absorption was estimated to be approximately 2%. **After 10 mo of treatment in the DFS group, mean hemoglobin increased by 16 g/L (P < 0.01), iron status and body iron stores increased significantly (P < 0.01), and the prevalence of iron deficiency anemia decreased from 30% at baseline to 5% (P < 0.001). In both groups, urinary iodine (P < 0.001) and thyroid volume (P < 0.01) improved significantly from baseline.** **CONCLUSION:** A DFS containing iodine and micronized ferric pyrophosphate can be an effective fortification strategy in rural Africa.

Am J Clin Nutr. 2004 Oct;80(4):973-81

Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3-6 y.

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BACKGROUND: Multiple micronutrient deficiencies are often the basic causative factor in stunting and anemia, 2 conditions that affect entire generations of children in deprived populations. No generally accepted recommendations for micronutrient intakes for recovery from stunting are available. **OBJECTIVE:** The objective was to assess the effect of a highly nutrient-dense spread fortified with vitamins and minerals, with or without antiparasitic metronidazole treatment, in correcting retarded linear growth and reducing anemia in stunted children. **DESIGN:** Saharawi refugee children (n = 374) aged 3-6 y with initial height-for-age z scores <-2 were assigned to 1 of 5 groups: fortified spread (FS), fortified spread plus metronidazole (FS+M), unfortified spread (US), unfortified spread plus metronidazole (US+M), or control. Supervised supplementation was given daily for 6 mo. Weight, height, knee-heel length, hematologic indexes, parasitic infections, and morbidity were assessed at 0,

3, and 6 mo. RESULTS: **Linear growth of children fed FS was 30% faster at 3 mo than in US and control groups, after which height-for-age z scores increased only slightly in the FS group and remained unchanged in the other groups. No additional benefits from metronidazole were observed. Increase in hemoglobin concentrations in the FS group at 6 mo was twofold that in the US and control groups (37 +/- 40, 19 +/- 15, and 16 +/- 17 g/L, respectively; P < 0.0001), and anemia was reduced by nearly 90%. CONCLUSIONS: FS, and not US, induces catch-up growth in stunted children whose diets are poor in micronutrients. Our trial provides support for delivering multiple micronutrients to reverse stunting and reduce anemia in children up to age 6 y.**

J Nutr. 2004 Nov;134(11):3031-6

Na₂EDTA enhances the absorption of iron and zinc from fortified rice flour in Sri Lankan children.

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Rice flour was proposed as a vehicle for iron and zinc fortification in Sri Lanka. Although widely consumed, rice flour has not been evaluated as a fortified food, and the absorption of minerals including iron and zinc from this flour is unknown. Determination of the bioavailability of these nutrients is a critical step before commencing a fortification program. We randomly divided 53 Sri Lankan schoolchildren ages 6-10 y into 4 groups that consumed a local dish prepared with 25 g of fortified rice flour labeled with one of the following: 1) (58)FeSO₄ 2) (58)FeSO₄ + Na₂EDTA 3) (58)FeSO₄ + (67)ZnO or, 4) (58)FeSO₄ + Na₂EDTA + (67)ZnO. The levels of iron and zinc were 60 mg/kg; the rice flour also contained folate at 2 mg/kg in each group. Na₂EDTA was added at a Fe:Na₂EDTA, 1:1 molar ratio. A total of 48 children completed the trial. **Absorption of (58)Fe from a meal was significantly greater (P < 0.01) in the groups administered FeSO₄ + Na₂EDTA (4.7 +/- 3.6%) than in those administered FeSO₄ without Na₂EDTA (2.2 +/- 1.3%). Fractional absorption of zinc was 13.5 +/- 6.0% in the FeSO₄ + Na₂EDTA group and 8.8 +/- 2.0% in the FeSO₄ group (P = 0.037). Although zinc absorption was low, our results demonstrated a benefit in using Na₂EDTA to improve both iron and zinc absorption.** We conclude that the fortification of rice flour is feasible, although additional strategies such as dephytinization or an increase in the level of iron and zinc fortification should be considered to obtain a higher proportion of the daily requirement of total absorbed iron and zinc.

Adv Exp Med Biol. 2004;554:63-77.

The optimal duration of exclusive breastfeeding: a systematic review.

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Although the health benefits of breastfeeding are acknowledged widely, opinions and recommendations are divided on the optimal duration of exclusive breastfeeding. We

systematically reviewed available evidence concerning the effects on child health, growth, and development and on maternal health of exclusive breastfeeding for 6 months vs. exclusive breastfeeding for 3-4 months followed by mixed breastfeeding (introduction of complementary liquid or solid foods with continued breastfeeding) to 6 months. Two independent literature searches were conducted, together comprising the following databases: MEDLINE (as of 1966), Index Medicus (prior to 1966), CINAHL, HealthSTAR, BIOSIS, CAB Abstracts, EMBASE-Medicine, EMBASE-Psychology, Econlit, Index Medicus for the WHO Eastern Mediterranean Region, African Index Medicus, Lilacs (Latin American and Caribbean literature), EBM Reviews-Best Evidence, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register. No language restrictions were imposed. The two searches yielded a total of 2,668 unique citations. Contacts with experts in the field yielded additional published and unpublished studies. Studies were stratified according to study design (controlled trials vs. observational studies) and provenance (developing vs. developed countries). The main outcome measures were weight and length gain, weight-for-age and length-for-age z-scores, head circumference, iron status, gastrointestinal and respiratory infectious morbidity, atopic eczema, asthma, neuromotor development, duration of lactational amenorrhea, and maternal postpartum weight loss. **Twenty independent studies meeting the selection criteria were identified by the literature search: 9 from developing countries (2 of which were controlled trials in Honduras) and 11 from developed countries (all observational studies). Neither the trials nor the observational studies suggest that infants who continue to be exclusively breastfed for 6 months show deficits in weight or length gain, although larger sample sizes would be required to rule out modest increases in the risk of undernutrition.** The data are conflicting with respect to iron status but suggest that, at least in developing-country settings, where iron stores of newborn infants may be suboptimal, exclusive breastfeeding without iron supplementation through 6 months of age may compromise hematologic status. Based primarily on an observational analysis of a large randomized trial in Belarus, infants who continue exclusive breastfeeding for 6 months or more appear to have a significantly reduced risk of one or more episodes of gastrointestinal tract infection. No significant reduction in risk of atopic eczema, asthma, or other atopic outcomes has been demonstrated in studies from Finland, Australia, and Belarus. Data from the two Honduran trials suggest that exclusive breastfeeding through 6 months of age is associated with delayed resumption of menses and more rapid postpartum weight loss in the mother. **Infants who are breastfed exclusively for 6 months experience less morbidity from gastrointestinal tract infection than infants who were mixed breastfed as of 3 or 4 months of age.** No deficits have been demonstrated in growth among infants from either developing or developed countries who are exclusively breastfed for 6 months or longer. Moreover, the mothers of such infants have more prolonged lactational amenorrhea and faster postpartum weight loss. **Based on the results of this review, the World Health Assembly adopted a resolution to recommend exclusive breastfeeding for 6 months to its member countries.** Large randomized trials are recommended in both developed and developing countries to ensure that exclusive breastfeeding for 6 months does not increase the risk of undernutrition (growth faltering), to confirm the health benefits reported thus far, and to investigate other potential effects on health and development, especially over the long term.

Br J Nutr. 2004 Jul;92(1):159-68.

School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing.

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A 2-year milk intervention trial was carried out with 757 girls, aged 10 years, from nine primary schools in Beijing (April 1999 - March 2001). Schools were randomised into three groups: group 1, 238 girls consumed a carton of 330 ml milk fortified with Ca on school days over the study period; group 2, 260 girls received the same quantity of milk additionally fortified with 5 or 8 microg cholecalciferol; group 3, 259 control girls. Anthropometric and bone mineralisation measurements, as well as dietary, health and physical-activity data, were collected at baseline and after 12 and 24 months of the trial. **Over the 2-year period the consumption of this milk, with or without added cholecalciferol, led to significant increases in the changes in height (> or =0.6 %), sitting height (> or =0.8 %), body weight (> or 2.9 %), and (size-adjusted) total-body bone mineral content (> or =1.2 %) and bone mineral density (> or =3.2 %).** Those subjects receiving additional cholecalciferol compared with those receiving the milk without added 25-hydroxycholecalciferol had significantly greater increases in the change in (size-adjusted) total-body bone mineral content (2.4 v. 1.2 %) and bone mineral density (5.5 v. 3.2 %). The milk fortified with cholecalciferol significantly improved vitamin D status at the end of the trial compared with the milk alone or control groups. It is concluded that an increase in milk consumption, e.g. by means of school milk programmes, would improve bone growth during adolescence, particularly when Ca intake and vitamin D status are low.

Am J Clin Nutr. 2005 May;81(5):1168-75.

Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10-12 y in Beijing.

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BACKGROUND: We previously reported that increased milk consumption enhances growth and bone mineral accretion in Chinese girls aged 10-12 y. **OBJECTIVE:** Our objective was to evaluate the effects of milk supplementation on cortical bone accretion and to study the physiologic mechanisms underlying the observed changes in bone. **DESIGN:** Chinese girls aged 10 y were randomly assigned into calcium-fortified milk (Ca milk), calcium and vitamin D-fortified milk (CaD milk), and control groups according to their schools in a 24-mo school milk intervention trial. Periosteal and medullary diameters of metacarpal bone were measured at baseline and 24 mo in the Ca milk (n = 177), CaD milk (n = 210), and control (n = 219) groups. Insulin-like growth factor I (IGF-I), parathyroid hormone (PTH), bone alkaline phosphatase (BAP), osteocalcin, and deoxypyridinoline concentrations were measured at baseline and at 12 and 24 mo in the Ca milk (n = 43), CaD milk (n = 44), and control (n = 41) groups. **RESULTS:** **After adjustment for pubertal status and clustering by school, 24-mo supplementation led to greater increases in periosteal diameter (1.2%) and cortical thickness (5.7%) and to smaller gains in medullary diameter (6.7%) than did the control (P < 0.05).** The CaD milk group had lower serum BAP at 12 mo (19.9%) and lower serum PTH at 12 (46.2%) and 24 (16.4%) mo than did the control group (P < 0.05). The effect of milk

supplementation on increasing IGF-I concentrations at 24 mo (16.7-23.3%) was significant in individual analyses but not after adjustment for clustering by school. **CONCLUSIONS:** Milk supplementation showed positive effects on periosteal and endosteal apposition of cortical bone.

Osteoporos Int. 2004 Aug;15(8):654-8. Epub 2004 Apr 17

Benefits of milk powder supplementation on bone accretion in Chinese children.

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Low dietary calcium intake has been demonstrated to be a risk factor for hip and vertebral fractures in studies conducted among Hong Kong Chinese. Few studies have demonstrated the effect of milk supplementation in bone accretion in Chinese children. The aim was to examine the effects of milk powder supplementation in enhancing bone accretion in Chinese children. Three hundred and forty-four children, aged 9-10 years old, were randomized to receive milk powder equivalent to 1300 mg and 650 mg calcium, and to a control group, respectively. Bone mineral density (BMD) at the proximal femur, lumbar spine and total body were measured at 6 months, 12 months and 18 months. The treatment effects were modeled using linear mixed effect models and compared using linear contrast F-tests, by intention-to-treat. **Subjects randomized to milk powder equivalent to 1300 mg calcium had significantly higher increase in BMD at both the total hip (7.4 +/- 0.4% in treatment group versus 6.3 +/- 0.4% in the control) and the spine (8.4 +/- 0.5% in the treatment group versus 7.0 +/- 0.5% in the control group).** Subjects randomized to milk powder equivalent to 650 mg calcium had smaller increases in BMD at the total hip and spine, although the increase in BMD at the total body was significantly higher (3.1 +/- 0.3% in treatment group versus 2.4 +/- 0.2% in controls). It is concluded that supplementing the diet of Chinese children with milk powder was effective in enhancing bone accretion.

Am J Clin Nutr. 2004 Nov;80(5):1283-90

Triple fortification of salt with microcapsules of iodine, iron, and vitamin A.

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BACKGROUND: In many developing countries, children are at high risk of goiter, vitamin A deficiency, and iron deficiency anemia. **OBJECTIVE:** We aimed to develop a stable, efficacious salt fortified with iodine, iron, and vitamin A. **DESIGN:** A novel spray-cooling technique was used with hydrogenated palm oil to package potassium iodate, micronized ferric pyrophosphate, and retinyl palmitate into microcapsules (mean particle size: 100 µm). We used the microcapsules to create **triple-fortified salt (TFS) with 30 µg I, 2 mg Fe, and 60**

mug vitamin A/g salt. After storage trials, we compared the efficacy of TFS with that of iodized salt in a 10-mo, randomized, double-blind trial in goitrous schoolchildren (n = 157) who had a high prevalence of vitamin A deficiency and iron deficiency anemia. RESULTS: After storage for 6 mo, losses of iodine and vitamin A from the TFS were approximately 12-15%, and color was stable. In the TFS group, mean hemoglobin increased by 15 g/L at 10 mo ($P < 0.01$), iron status indexes and body iron stores improved significantly ($P < 0.05$), and mean serum retinol, retinol-binding protein, and the ratio of retinol-binding protein to prealbumin increased significantly ($P < 0.01$). **At 10 mo, prevalences of vitamin A deficiency and iron deficiency anemia were significantly lower in the TFS group than in the iodized salt group ($P < 0.001$).** CONCLUSION: Newly developed microcapsules containing iodine, iron, and vitamin A are highly stable when added to local African salt. TFS was efficacious in reducing the prevalence of iron, iodine, and vitamin A deficiencies in school-age children.

Oncology

Eur J Oncol Nurs. 2004 Dec;8(4):341-9

Children's acceptance and tolerance of chlorhexidine and benzydamine oral rinses in the treatment of chemotherapy-induced oropharyngeal mucositis.

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Oral care is of great importance in the prevention of chemotherapy-induced oropharyngeal mucositis. Although considerable attention has been given in improving oral care practices, patients' acceptance and tolerance of oral rinses is a continuing problem in oral care. A randomized crossover design was used to determine the relative acceptability and tolerability of chlorhexidine and benzydamine oral rinse agents in children receiving chemotherapy. At the end of the study, each subject was asked to compare these two agents in relation to stinging and taste, as well as his/her perception in reducing mucositis. Thirty-four children aged 6-17 years completed two courses of chemotherapy during which they alternately practiced oral care using chlorhexidine then benzydamine or benzydamine then chlorhexidine. All of the children tolerated the agents well and continued with rinsing throughout the study. Only a few children had to resort to diluting the agents with normal saline or water. Fifty-nine percent of children reported that the stinging associated with benzydamine was more accepted than chlorhexidine. The taste of both these agents was accepted by 50% of children. Approximately 60% of children reported that chlorhexidine was more helpful than benzydamine in reducing mucositis. About 47% and 50% of them preferred chlorhexidine and benzydamine in their subsequent chemotherapy, respectively. In conclusion, chlorhexidine and benzydamine are acceptable and well-tolerated by children over the age 6 years old.

Public Health / health systems

Lancet. 2004 Dec 4;364(9450):2030-7.

Monetary incentives in primary health care and effects on use and coverage of preventive health care interventions in rural Honduras: cluster randomised

trial.

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BACKGROUND: Scaling-up of effective preventive interventions in child and maternal health is constrained in many developing countries by lack of demand. In Latin America, some governments have been trying to increase demand for health interventions by making direct payments to poor households contingent on them keeping up-to-date with preventive health services. We undertook a public health programme effectiveness trial in Honduras to assess this approach, contrasting it with a direct transfer of resources to local health teams.

METHODS: **70 municipalities were selected because they had the country's highest prevalence of malnutrition. They were allocated at random to four groups: money to households; resources to local health teams combined with a community-based nutrition intervention; both packages; and neither.** Evaluation surveys of about 5600 households were undertaken at baseline and roughly 2 years later. Pregnant women and mothers of children younger than 3 years old were asked about use of health services (primary outcome) and coverage of interventions such as immunisation and growth monitoring (secondary outcome). Reports were supplemented with data from children's health cards and government service utilisation data. Analysis was by mixed effects regression, accounting for the municipality-level randomisation. **FINDINGS:** **The household-level intervention had a large impact (15-20 percentage points; $p < 0.01$) on the reported coverage of antenatal care and well-child check-ups. Childhood immunisation series could thus be started more opportunely, and the coverage of growth monitoring was markedly increased (15-21 percentage points; $p < 0.01$. Measles and tetanus toxoid immunisation were not affected. The transfer of resources to local health teams could not be implemented properly because of legal complications.** **INTERPRETATION:** Conditional payments to households increase the use and coverage of preventive health care interventions.

Skin disease

Isr Med Assoc J. 2004 Dec;6(12):756-9

Repellency of citronella for head lice: double-blind randomized trial of efficacy and safety.

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BACKGROUND: Head lice move easily from head to head. The lack of safe, effective repellents leads to reinfestation. **OBJECTIVES:** **To test the efficacy of a slow-release citronella formulation as a repellent against the head louse.** **METHODS:** During 4 months in 2003 a randomized, placebo-controlled double-blind clinical study was conducted in four elementary schools; 103 children were treated with the test formulation and 95 with a placebo.

RESULTS: A significant difference was observed during the second examination 2 months later, when 12.0% of the children treated with the test repellent and 50.5% of those treated with placebo were infested with lice. A significant difference was also observed at the third examination 2 months later, when 12.4% of the children treated with the test repellent and 33.7% treated with placebo were infested. **Overall, there were significant differences between those treated with the repellent and those treated with the placebo (15.4% and 55.1% respectively, $P < 0.0001$).** Side effects were observed in 4.4% of children who disliked the odor of the formulation, and an additional 1.0% who complained of a slight itching and burning sensation. CONCLUSIONS: Use of an effective repellent could significantly lower the incidence of reinfestations, which would lower expenditure on lice control, including pediculicides, combs and products for nit removal, and the time spent on treatment and removal of the nits.

Surgical problems

J Neurosurg. 2005 May;102(4 Suppl):358-62.

Comparison of 1-year outcomes for the Chhabra and Codman-Hakim Micro Precision shunt systems in Uganda: a prospective study in 195 children.

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OBJECT: The author investigated the 1-year outcomes for shunt treatment of hydrocephalic children in Uganda, comparing the results using the inexpensive Chhabra shunt (\$35 US dollars), widely used in East Africa, with those using the Codman-Hakim Micro Precision Valve shunt (\$650). METHODS: The results in 195 consecutive children (mostly infants) in whom shunts were placed were studied prospectively. **In Group 1, 90 patients randomly received either the Chhabra or Codman shunt as primary treatment for hydrocephalus.** In Group 2, 105 patients received the Chhabra shunt when endoscopic third ventriculostomy could not be performed or had failed. The end points of the study were shunt malfunction, shunt migration, wound complication, death, or no problem at 1 year. Of all patients, 9.7% were lost to follow up and 15.9% died before 1 year. The occurrence of complications in all patients were infection (9.7%), migration/disconnection (6.3%), wound complication (5.7%), valve malfunction (3.4%), ventricular catheter obstruction (2.8%), and peritoneal catheter obstruction (1.1%). **There was no statistically significant difference in any outcome category for patients receiving the Codman or Chhabra shunt ($p = 0.2463-1.0000$).** CONCLUSIONS: Ventriculoperitoneal shunt insertion for treatment of hydrocephalus can be performed in a developing country with results similar to those reported in developed countries. No difference in outcome was noted between the two shunt types. No advantage was found in using a shunt system that, in this setting, is prohibitively expensive.

Tuberculosis

QJM. 2004 Aug;97(8):525-35

Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up.

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BACKGROUND: Tuberculous pericarditis is common in Transkei (Eastern Cape). Two randomized trials showed benefits at two years for prednisolone in patients with constrictive pericarditis, and open drainage plus prednisolone in patients with pericardial effusion. **AIM:** To see whether the advantages of prednisolone and open drainage were maintained up to 10 years. **DESIGN:** Follow-up of randomized, double-blind, placebo-controlled trials. **METHODS:** All 383 patients (143 constriction, 240 effusion) received the same anti-tuberculosis chemotherapy. They were randomized to prednisolone or placebo for the first 11 weeks, and were followed-up over 10 years. Among the 240 with effusion, 122 were also randomized to immediate open surgical drainage of pericardial fluid versus pericardiocentesis as required. Adverse outcomes were: death from pericarditis, pericardiectomy, repeat pericardiocentesis, and subsequent open drainage. **RESULTS:** The 10-year follow-up rate was 96%. In constriction patients, adverse outcomes occurred in 19/70 (27%) prednisolone vs. 28/73 (38%) placebo ($p = 0.15$), deaths from pericarditis being 2 (3%) vs. 8 (11%), respectively ($p = 0.098$, Fisher's exact test). **In effusion patients, adverse outcomes occurred in 14/27 (52%) with neither drainage nor prednisolone, vs. 4/29 (14%) drainage and prednisolone, 4/35 (11%) drainage and placebo, and 6/31 (19%) prednisolone and no drainage ($p = 0.08$ for interaction).** Drainage eliminated the need for repeat pericardiocentesis. **In the 176 with effusion and no drainage, adverse outcomes occurred in 17/88 (19%) prednisolone vs. 35/88 (40%) placebo patients ($p = 0.003$), with repeat pericardiocentesis 20 (23%) placebo vs. 9 (10%) prednisolone ($p = 0.025$).** **In a multivariate survival analysis (stratified by type of pericarditis), prednisolone reduced the overall death rate after adjusting for age and sex ($p = 0.044$), and substantially reduced the risk of death from pericarditis ($p = 0.004$).** At 10 years, the great majority of surviving patients in all treatment groups were either fully active or out and about, even if activity was restricted. **DISCUSSION:** In the absence of a clear contraindication, a corticosteroid should be used in addition to antituberculosis chemotherapy in the management of patients with tuberculous pericarditis.

Comment

The benefits of steroids as adjuvant therapy have also been shown in RCTs this year in adolescents and adults with tuberculous meningitis (N Engl J Med. 2004 Oct 21;351(17):1741-51), but are cannot be recommended in for pulmonary TB in patients with HIV (J Infect Dis. 2004 Sep 1;190(5):869-78. Epub 2004 Jul 29, J Infect Dis. 2005 Mar 15;191(6):856-65. Epub 2005 Feb 8.) Although prednisolone therapy was associated with a more rapid clearance of Mycobacterium tuberculosis from the sputum, it was also associated with a transient increase in HIV RNA levels, which receded when prednisolone therapy was discontinued. The intervention worsened underlying hypertension and caused fluid retention and hyperglycemia.

Typhoid

Infect Immun. 2004 Nov;72(11):6586-8

Effect of dosage on immunogenicity of a Vi conjugate vaccine injected twice into 2- to 5-year-old Vietnamese children.

Canh do G, Lin FY, Thiem VD, Trach DD, Trong ND, Mao ND, Hunt S, Schneerson R, Robbins JB, Chu C, Shiloach J, Bryla DA, Bonnet MC, Schulz D, Szu SC.

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In a double-blind, randomized, and placebo-controlled previous trial, the efficacy of Vi-rEPA for typhoid fever in 2- to 5-year-olds was 89.0% for 46 months. Vi-rEPA contained 25 microg of Vi and induced a greater-than-eightfold rise in immunoglobulin G (IgG) anti-Vi in all of the vaccinees tested. In this investigation, we conducted a dosage-immunogenicity study of 5, 12.5, and 25 microg of Vi-rEPA in this age group. Two doses of Vi-rEPA were injected 6 weeks apart. Blood samples were taken before and at 10 weeks (4 weeks after the second injection) and 1 year later. All postimmunization geometric mean (GM) levels were higher than the preimmune levels ($P < 0.0001$). At 10 weeks, the GM IgG anti-Vi level elicited by 25 microg (102 EU/ml) was higher than those elicited by 12.5 microg (74.7 EU/ml) and 5 microg (43 EU/ml) ($P < 0.004$): all of the children had ≥ 3.52 EU/ml (estimated minimum protective level). One year later, the levels declined about sevenfold (13.3 and 11.3 versus 6.43 EU/ml, $P < 0.0001$) but remained significantly higher than the preimmune levels ($P < 0.0001$), and $>96\%$ of the children had a greater-than-eightfold rise. This study also confirmed the safety and consistent immunogenicity of the four lots of Vi-rEPA used in this and previous trials.

Ann Trop Paediatr. 2005 Mar;25(1):17-22.

Comparative trial of short-course ofloxacin for uncomplicated typhoid fever in Vietnamese children.

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An open, randomised comparison of 2 or 3 days of oral ofloxacin (10 mg/kg/day) for uncomplicated typhoid fever was conducted in 235 Vietnamese children. Multi-drug-resistant *Salmonella typhi* was isolated from 182/202 (90%) children and 5/166 (3%) tested isolates were nalidixic acid-resistant (Na(R)). Eighty-nine of 116 children randomised to 2 days and 107/119 randomised to 3 days were blood culture-positive and eligible for analysis. **There were 12 (13.5%) failures in the 2-day group (six clinical failures, four blood culture-positive post treatment, two relapses) compared with eight (7.5%) failures in the 3-day group (four clinical failures, one blood culture-positive post treatment, three relapses)** (OR 1.9, 95% CI 0.7-5.5, $p = 0.17$). There were no significant differences in the mean (95% confidence interval) fever clearance times (h) [92 (82-102) vs 101 (93-110), $p = 0.18$] or duration of hospitalisation (d) [7.6 (7.2-8.1) vs 8.0 (7.6-8.4), $p = 0.19$] between the two groups. There was one failure in the four eligible children infected with an Na(R) isolate of *S. typhi*. No adverse events were attributable to the ofloxacin. These results extend previous observations on the efficacy of short courses of ofloxacin for children with uncomplicated multi-drug-resistant typhoid fever.

Comment

The wide confidence intervals (OR 1.9, 95% CI 0.7-5.5) suggest that little conclusion can be made as to what the most appropriate duration of treatment is. While it is unlikely that 2 days is sufficient, the optimal duration can not be ascertained from this study.

Vaccines

Infect Immun. 2005 May;73(5):2932-9.

Serologic responses to ACYW135 polysaccharide meningococcal vaccine in Saudi children under 5 years of age.

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An immunization campaign with meningococcal ACYW135 polysaccharide vaccine was conducted in 2003 by the Saudi Arabian Ministry of Health and included a study to evaluate the immune responses in children under 5 years of age in the Al Qassim region of Saudi Arabia. Children who were ≥ 24 months old were given one dose of tetravalent polysaccharide vaccine, while younger children were given two doses with an interval of 2 to 3 months. Blood samples were collected prevaccination and 1 month after the second dose for children younger than 24 months old and 1 month after the single dose for older children. Serogroup-specific antibody responses were determined by serum bactericidal antibody (SBA) assays and a tetraplex immunoglobulin G (IgG) bead assay. Significant increases in the proportions of individuals who were ≥ 24 months old with SBA titers of ≥ 8 were observed pre- to postvaccination for all serogroups. Age-dependent increases in the percentage of individuals with SBA titers of ≥ 8 1 month postvaccination were observed for each serogroup. Age-dependent increases in postvaccination IgG levels were observed for serogroup A (menA), serogroup W135 (menW), and serogroup Y (menY) but not for serogroup C (menC). Two doses of tetravalent polysaccharide vaccine in individuals who were ≤ 18 months old were poorly immunogenic for menC, menW, and menY. However, for menA, 42% of the children who were 18 months old were putatively protected with SBA titers of ≥ 8 . A high percentage of subjects who were ≥ 2 years of age were putatively protected for menA; a similar level was observed for menY for children who were 4 years of age but not for younger children. However, for menC and menW poor levels of putative protection were still evident at 4 years of age.

Clin Infect Dis. 2005 May 15;40(10):1511-8. Epub 2005 Apr 7.

The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children.

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INTRODUCTION: Pneumococcal conjugate vaccine (PnCV) may be used as a probe to define the burden of pneumococcal disease and better characterize the clinical presentation of pneumococcal pneumonia. **METHODS:** This study used a 9-valent PnCV to define different end points of vaccine efficacy and the preventable burden of pneumococcal pneumonia in 39,836 children who were randomized in a double-blind, placebo-controlled trial in South Africa. **RESULTS:** Whereas the point-estimate of vaccine efficacy was greatest when measured against the outcome of vaccine-serotype specific pneumococcal bacteremic pneumonia (61%; $P = .01$), the sensitivity of blood culture to measure the burden of pneumococcal pneumonia prevented by vaccination was only 2.6% in human immunodeficiency virus (HIV)-uninfected children and 18.8% in HIV-infected children. Only 37.8% of cases of pneumococcal pneumonia prevented by PnCV were detected by means of chest radiographs showing alveolar consolidation. **A clinical diagnosis of pneumonia provided the best estimate of the burden of pneumococcal pneumonia prevented through vaccination in HIV-uninfected children (267 cases prevented per 100,000 child-years) and HIV-infected children (2573 cases prevented per 100,000 child-years).** **CONCLUSION:** Although outcome measures with high specificity, such as bacteremic pneumococcal pneumonia, provide a better estimate as to vaccine efficacy, the burden of disease prevented by vaccination is best evaluated using outcome measures with high sensitivity, such as a clinical diagnosis of pneumonia.

Lancet. 2005 Mar 26-Apr 1;365(9465):1139-46.

Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial.

Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, Oluwalana C, Vaughan A, Obaro SK, Leach A, McAdam KP, Biney E, Saaka M, Onwuchekwa U, Yallop F, Pierce NF, Greenwood BM, Adegbola RA; Gambian Pneumococcal Vaccine Trial Group.

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BACKGROUND: Pneumonia is estimated to cause 2 million deaths every year in children. *Streptococcus pneumoniae* is the most important cause of severe pneumonia. We aimed to assess the efficacy of a nine-valent pneumococcal conjugate vaccine in children. **METHODS:** We undertook a randomised, placebo-controlled, double-blind trial in eastern Gambia. Children age 6-51 weeks were randomly allocated three doses of either pneumococcal conjugate vaccine ($n=8718$) or placebo (8719), with intervals of at least 25 days between doses. Our primary outcome was first episode of radiological pneumonia. Secondary endpoints were clinical or severe clinical pneumonia, invasive pneumococcal disease, and all-cause admissions. Analyses were per protocol and intention to treat. **FINDINGS:** 529 children assigned vaccine and 568 allocated placebo were not included in the per-protocol analysis. Results of per-protocol and intention-to-treat analyses were similar. **By per-protocol analysis, 333 of 8189 children given vaccine had an episode of radiological pneumonia compared with 513 of 8151 who received placebo. Pneumococcal vaccine efficacy was 37% (95% CI 27-45) against first episode of radiological pneumonia.** First episodes of clinical pneumonia were reduced overall by 7% (95% CI 1-12). Efficacy of the conjugate vaccine was 77% (51-90) against invasive pneumococcal disease caused by vaccine serotypes, 50% (21-69) against disease caused by all serotypes, and 15% (7-21) against all-cause admissions. **We also found**

an efficacy of 16% (3-28) against mortality. 110 serious adverse events arose in children given the pneumococcal vaccine compared with 131 in those who received placebo.
 INTERPRETATION: In this rural African setting, pneumococcal conjugate vaccine has high efficacy against radiological pneumonia and invasive pneumococcal disease, and can substantially reduce admissions and improve child survival. Pneumococcal conjugate vaccines should be made available to African infants

Comment

This is one of the most important RCTs of the year, demonstrating the efficacy of conjugate pneumococcal vaccine on mortality in African children. However the most challenging part is yet to come: making this (or similar) vaccines available to children at risk of pneumococcal disease throughout the world. The time from publication of this paper to achieving this implementation of pneumococcal vaccine in developing countries should be seen as something of a measure of global commitment to lowering child mortality. Hopefully the lessons learned from Hib vaccine implementation will speed up and assist the process.

Am J Trop Med Hyg. 2005 Feb;72(2):189-97.

Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru.

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We conducted a randomized, double-blind, phase III yellow fever (YF) vaccine trial among 1,107 healthy children in Sullana in northern Peru. The safety and efficacy (by measurement of geometric mean neutralizing antibody titer responses) were determined for two YF vaccines, ARILVAX (n = 738) and YF-VAX(R) (n = 369). Seroconversion rates were higher (94.9%) in ARILVAX than in YF-VAX (90.6%) recipients. The two-sided 95% confidence interval (YF-VAX-ARILVAX) was (-12.8% to -2.5%), indicating that the higher seroconversion rate for Arilvax was significant. **Post-vaccination (30-day) mean log₁₀ neutralization indices were found to be similar for both products: 1.32 for ARILVAX and 1.26 for YF-VAX (P = 0.1404, by analysis of variance).** A similar number of subjects in each group reported at least one adverse event (AE); 441 (59.8%) for ARILVAX versus 211 (59.9%) for YF-VAX. Most (591; 96.7%) of these were of a mild nature and resolved without treatment. There were no treatment-related serious AEs. This is the first randomized, double-blind comparison of two YF vaccines in a pediatric population; both vaccines were shown to be highly immunogenic and well-tolerated.

Lancet. 2005 Jan 1-7;365(9453):43-52.

Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial.

Gessner BD, Sutanto A, Linehan M, Djelantik IG, Fletcher T, Gerudug IK, Ingerani, Mercer D, Moniaga V, Moulton LH, Moulton LH, Mulholland K, Nelson C, Soemohardjo S, Steinhoff M, Widjaya A, Stoeckel P, Maynard J, Arjoso S.

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BACKGROUND: Most studies of Haemophilus influenzae type b (Hib) disease in Asia have found low rates, and few Asian countries use Hib vaccine in routine immunisation programmes. Whether Hib disease truly is rare or whether many cases remain undetected is unclear. **METHODS:** To estimate incidences of vaccine-preventable Hib pneumonia and meningitis among children younger than 2 years in Lombok, Indonesia, during 1998-2002, we undertook a hamlet-randomised, controlled, double-blind vaccine-probe study (818 hamlets). Children were immunised (WHO schedule) with diphtheria, tetanus, pertussis (DTP) or DTP-PRP-T (Hib conjugate) vaccine. Vaccine-preventable disease incidences were calculated as the difference in rates of clinical outcomes between DTP and DTP-PRP-T groups. Analyses included all children who received at least one vaccine dose. **FINDINGS:** We enrolled 55073 children: 28147 were assigned DTP-PRP-T and 26926 DTP. **The proportion of pneumonia outcomes prevented by vaccine ranged from less than 0 to 4.8%.** Calculated incidences of vaccine-preventable Hib disease (per 10(5) child-years of observation) for outcome categories were: substantial alveolar consolidation or effusion, less than zero (-43 [95% CI -185 to 98]); all severe pneumonia, 264 (95% CI less than zero to 629); all clinical pneumonia, 1561 (270 to 2853); **confirmed Hib meningitis, 16 (1.4 to 31); meningitis with cerebrospinal-fluid findings consistent with a bacterial aetiology, 67 (22 to 112); and admission for suspected meningitis or presenting to a clinic with convulsions, 158 (42 to 273).** **INTERPRETATION:** Hib vaccine did not prevent the great majority of pneumonia cases, including those with alveolar consolidation. These results do not support a major role for Hib vaccine in overall pneumonia-prevention programmes. Nevertheless, the study identified high incidences of Hib meningitis and pneumonia; **inclusion of Hib vaccine in routine infant immunisation programmes in Asia deserves consideration.**

Vitamin A

Eur J Clin Nutr. 2004 Jul;58(7):990-9

Complex interactions with infection and diet may explain seasonal growth responses to vitamin A in preschool aged Indonesian children.

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OBJECTIVE: To explore the potential contribution of respiratory infections and vitamin A intakes to the seasonal effect of vitamin A supplementation on child growth. **METHODS:** **Data from a randomized double-blind placebo-controlled trial, in which a single high dose of vitamin A or placebo was given every 4 months to 1405 children aged 6-48 months were used for the analysis.** In total, 4430 child-treatment cycles were examined, and for each cycle

the children had their dietary intake, weight, and height assessed at the start and end. Linear regression models of the difference in height and weight during each treatment cycle were used and the within-child correlation was adjusted using the generalized estimating equations (GEE). Other covariables in the model included age, sex, percentage of days with acute lower respiratory infection and diarrhea, and cumulative doses of vitamin A. **RESULTS: This study showed that a significant effect of vitamin A supplementation on linear growth was observed in all seasons in children with a low burden of respiratory infections, that is, < 21.5% of days with respiratory illness.** In each season, the highest effect was found in children with a low burden of respiratory infections and low vitamin A intakes, that is, intakes < 400 RE/day. Children with a high burden of respiratory infections or high vitamin A intakes benefited less from vitamin A supplementation for their linear growth than children with a low burden of respiratory infections and low vitamin A intakes. Finally, there was no benefit for linear growth from vitamin A supplementation in children with both a high burden of respiratory infections and high vitamin A intakes regardless of the season. **CONCLUSIONS: The effect of vitamin A supplementation on growth is dependent on season. Respiratory infections and vitamin A intakes are important factors underlying the seasonal effect of vitamin A supplementation on growth.**

Am J Clin Nutr. 2005 Apr;81(4):880-8.

Vitamin supplementation of HIV-infected women improves postnatal child growth.

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BACKGROUND: Linear growth retardation and wasting are common in children born to HIV-infected women. Inexpensive interventions that could improve the postnatal growth pattern of such children are needed. **OBJECTIVE:** The objective was to examine the effect of supplementing HIV-infected women with multivitamins or vitamin A and beta-carotene, during and after pregnancy, on the growth of their children during the first 2 y of life. **DESIGN:** We conducted a randomized placebo-controlled trial in 886 mother-infant pairs in Tanzania. At the first prenatal visit, HIV-infected women were randomly assigned to 1 of 4 daily oral regimens in a 2 x 2 factorial fashion: multivitamins (MV: thiamine, riboflavin, vitamin B-6, niacin, vitamin B-12, vitamin C, vitamin E, and folic acid), preformed vitamin A + beta-carotene (VA/BC), MV including VA/BC, or placebo. Supplementation continued during the first 2 y postpartum and thereafter. Children were weighed and measured monthly, and all received vitamin A supplements after 6 mo of age per the standard of care. **RESULTS: Multivitamins had a significant positive effect on attained weight (459 g; 95% CI: 35, 882; P = 0.03) and on weight-for-age (0.42; 95% CI: 0.07, 0.77; P = 0.02) and weight-for-length (0.38; 95% CI: 0.07, 0.68; P = 0.01) z scores at 24 mo.** VA/BC seemed to reduce the benefits of MV on these outcomes. No significant effects were observed on length, midupper arm circumference, or head circumference. **CONCLUSION:** Supplementation of HIV-infected women with multivitamins (vitamin B complex, vitamin C, and vitamin E) during pregnancy and lactation is an effective intervention for improving ponderal growth in children.

Eur J Clin Nutr. 2004 Sep;58(9):1223-30

Vitamin A status and hemoglobin concentrations are improved in Indonesian children with vitamin A and deworming interventions.

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OBJECTIVE: Anemia is a major public health problem caused by multiple factors. Vitamin A (VA) depletion can affect hemoglobin concentration (Hb). This study investigated the improvement in Hb and VA status in preschool Indonesian children following supplementation with 210 micromol VA and deworming with 400 mg albendazole. **SUBJECTS AND DESIGN:** Indonesian children (n = 131) infected with *Ascaris lumbricoides* and/or *Trichuris trichiura* were enrolled. The children were grouped by length of time since receiving 210 micromol VA through the local health system. Group 1 (VA administered > or = 4 month before baseline) included 51 children with *Ascaris* and 29 children with *Trichuris*. Group 2 had received VA < or = 1 month of baseline from the local health post and included 51 children. **INTERVENTION AND METHODS:** Immediately following baseline Hb and VA status assessment (modified relative dose response (MRDR) test), Group 1 children were given 210 micromol VA and 400 mg albendazole. Group 2 were randomized to be dewormed either 1 week before, at the same time or 1 week after baseline MRDR and Hb measures. Follow-up assessment was 3-4 weeks after baseline. **RESULTS: VA status in Group 1 significantly improved in children with either *Ascaris* (P < 0.0001) or *Trichuris* (P = 0.028). Although the prevalence of anemia declined, the improvement in Hb was not significant (P = 0.08).** In Group 2, improvement in VA status from the VA delivered through the public health system was maintained for more than 1 month. Hb improved (P = 0.0037) and this improvement appeared to be associated with the length of time between deworming and follow-up assessments. **CONCLUSION:** Public health supplementation programs to improve VA status may also increase Hb concentrations and decrease anemia prevalence, especially when linked to deworming.

Health Policy Plan. 2005 Jan;20(1):60-6.

The impact of vitamin A supplementation on mortality inequalities among children in Nepal.

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OBJECTIVE: This paper examines gender, caste and economic differentials in child mortality in the context of a cluster-randomized trial of vitamin A distribution, in order to determine whether or not the intervention narrowed these differentials. **DESIGN:** The study involved secondary analysis of data from a placebo-controlled randomized field trial of vitamin A supplements. The study took place between 1989-1991 in rural Sarlahi District of Nepal, with

30,059 children age 6 to 60 months. The main outcome measures were differences in mortality between boys and girls, between highest Hindu castes and others, and between the poorest quintile and the four other quintiles. **RESULTS: Without vitamin A, girls in rural Nepal experience 26.1 deaths per 1000, which is 8.3 deaths more than the comparison population of boys. With vitamin A the mortality disadvantage of girls is nearly completely attenuated, at only 1.41 additional deaths per 1000 relative to boys.** Vitamin A supplementation also narrowed mortality differentials among Hindu castes, but did not lower the concentration of mortality across quintiles of asset ownership. The vitamin A-related attenuation in mortality disadvantage from gender and caste is statistically significant. **CONCLUSIONS:** We conclude that universal supplementation with vitamin A narrowed differentials in child death across gender and caste in rural Nepal. Assuring high-coverage vitamin A distribution throughout Nepal could help reduce inequalities in child survival in this population.

Nutrition. 2005 Jan;21(1):25-31.

Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: A controlled clinical trial.

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OBJECTIVE: We investigated whether vitamin A supplementation would decrease mortality and morbidity rates in children infected with the human immunodeficiency virus (HIV). **METHODS:** We conducted a randomized, double-blind, placebo-controlled clinical trial at Mulago Hospital, a large hospital that serves the urban and semiurban populations of Kampala, Uganda. One hundred eighty-one HIV-infected children were enrolled at 6 mo and randomized to receive vitamin A supplementation, 60 mg retinol equivalent, or placebo every 3 mo from ages 15 to 36 mo. Morbidity was assessed through a 7-d morbidity history every 3 mo, and vital events were measured. Children received daily trimethoprim-sulfamethoxazole prophylactic therapy. **RESULTS: After age 15 mo, children were followed for a median of 17.8 mo (interquartile range = 11.1 to 21.0 mo). The trial was stopped when there was a new policy to implement a program of mass supplementation of vitamin A in the country. Mortality rates among 87 children in the vitamin A group and 94 children in the control group were 20.6% and 32.9%, respectively, yielding a relative risk of 0.54 (95% confidence interval, 0.30 to 0.98; P = 0.044) after adjusting for baseline weight-for-height Z score. Children who received vitamin A had lower modified point prevalences of persistent cough (odds ratio, 0.47; 95% confidence interval, 0.23 to 0.96; P = 0.038) and chronic diarrhea (odds ratio, 0.48; 95% confidence interval, 0.19 to 1.18; P = 0.11) and a shorter duration of ear discharge (P = 0.03). Vitamin A supplementation had no significant effect on modified point prevalences of fever, ear discharge, bloody stools, or hospitalizations. CONCLUSIONS:** Vitamin A supplementation decreases mortality rate in HIV-infected children and should be considered in the care for these children in developing countries.

Zinc

Am J Clin Nutr. 2004 Nov;80(5):1276-82

Effects of separate delivery of zinc or zinc and vitamin A on hemoglobin response, growth, and diarrhea in young Peruvian children receiving iron therapy for anemia.

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INTRODUCTION: Anemia is the most prevalent nutritional deficiency in the world. Attempts to improve iron indexes are affected by deficiency of and interaction between other micronutrients. **OBJECTIVE:** Our goal was to assess whether zinc added to iron treatment alone or with vitamin A improves iron indexes and affects diarrheal episodes. **DESIGN:** This was a randomized, placebo-controlled, double-blind trial conducted in Peru. **Anemic children aged 6-35 mo were assigned to 3 treatment groups: ferrous sulfate (FS; n = 104), ferrous sulfate and zinc sulfate (FSZn; n = 109), and ferrous sulfate, zinc sulfate, and vitamin A (FSZnA; n = 110).** Vitamin A or its placebo was supplied only once; iron and zinc were provided under supervision ≥ 1 h apart 6 d/wk for 18 wk. **RESULTS:** The prevalence of anemia was 42.97%. **The increase in hemoglobin in the FS group (19.5 g/L) was significantly less than that in the other 2 groups (24.0 and 23.8 g/L in the FSZn and FSZnA groups, respectively).** The increase in serum ferritin in the FS group (24.5 mug/L) was significantly less than that in the other 2 groups (33.0 and 30.8 mug/L in the FSZn and FSZnA groups, respectively). The median duration of diarrhea and the mean number of stools per day was significantly higher in the FS group than in other 2 groups ($P < 0.005$). **CONCLUSION: Adding zinc to iron treatment increases hemoglobin response, improves iron indexes, and has positive effects on diarrhea. No additional effect of vitamin A was found.**

Am J Clin Nutr. 2004 Sep;80(3):729-36

A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development.

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BACKGROUND: Deficiencies of iron and zinc are associated with delayed development, growth faltering, and increased infectious-disease morbidity during infancy and childhood. Combined iron and zinc supplementation may therefore be a logical preventive strategy. **OBJECTIVE:** The objective of the study was to compare the effects of combined iron and zinc supplementation in infancy with the effects of iron and zinc as single micronutrients on growth, psychomotor development, and incidence of infectious disease. **DESIGN: Indonesian infants (n = 680) were randomly assigned to daily supplementation with 10 mg Fe (Fe group), 10 mg Zn (Zn group), 10 mg Fe and 10 mg Zn (Fe+Zn group), or placebo from 6 to 12 mo of age.** Anthropometric indexes, developmental indexes (Bayley Scales of Infant Development; BSID), and morbidity were recorded. **RESULTS:** At 12 mo, two-factor analysis of variance

showed a significant interaction between iron and zinc for weight-for-age z score, knee-heel length, and BSID psychomotor development. Weight-for-age z score was higher in the Zn group than in the placebo and Fe+Zn groups, knee-heel length was higher in the Zn and Fe groups than in the placebo group, and the BSID psychomotor development index was higher in the Fe group than in the placebo group. No significant effect on morbidity was found.

CONCLUSIONS: Single supplementation with zinc significantly improved growth, and single supplementation with iron significantly improved growth and psychomotor development, but combined supplementation with iron and zinc had no significant effect on growth or development. Combined, simultaneous supplementation with iron and zinc to infants cannot be routinely recommended at the iron-to-zinc ratio used in this study.

Comment

The addition of zinc to iron supplementation in anaemic Peruvian children increased Hb more than iron supplementation alone, but supplementing with zinc and iron together in Indonesian infants limited the beneficial effect of zinc on growth and development