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## 1. ABOUT IMCI

Heiby JR

### **Quality improvement and the integrated management of childhood illness: lessons from developed countries.**

*The Joint Commission Journal on Quality Improvement*, 1998 May, 24(5): 264-79

BACKGROUND: The World Health Organization (WHO) and the United Nations Children's Fund have launched a global initiative to reform the health care received by sick children in developing countries. The core of this initiative, known as Integrated Management of Childhood Illness (IMCI), is a clinical practice guideline. The guideline addresses the case management of clinically ill children under the conditions typical of peripheral facilities, focusing on the most common serious conditions, such as pneumonia and malaria. WHO estimates that up to 70% of childhood deaths in developing countries are attributable to conditions addressed by IMCI. About 40 developing countries have made commitments to implementing IMCI in public-sector programs. QUALITY IMPROVEMENT STRATEGIES AND GUIDELINES IN DEVELOPING COUNTRIES: Like other clinical guidelines, which are increasingly accepted in developing countries' health programs, IMCI raises difficult quality issues. High levels of guideline compliance are needed for IMCI to be effective. However, many developing countries have achieved relatively low levels of compliance with far simpler guidelines, such as those for diarrhoea case management. Despite obvious differences, the experience of developed countries in quality improvement (QI) offers a wide range of promising strategies for IMCI, including (1) developing standards, (2) communicating those standards to providers, (3) monitoring quality and providing feedback, (4) team-based QI problem solving, (5) designing processes conducive to high levels of quality, and (6) regulating providers and institutions. MORE LESSONS FROM DEVELOPED COUNTRIES FOR IMCI: Only recently have QI strategies been adapted for use in developing countries, and virtually none of the early experience has dealt with IMCI. Indirect evidence suggests that a wide range of QI approaches will prove suitable for IMCI. However, it will be important to carefully evaluate the cost-effectiveness of early applications. The experience of developed countries also provides useful models for important issues that have not yet been addressed by the IMCI initiative. These issues include (1) the review and possible modification of the current guideline, (2) extending IMCI into the private sector through regulatory strategies, and (3) institutionalising QI.

Publication Types: Review, Review, tutorial

Lejneve I, Bailey R

### **Integrated management of childhood illness (IMCI): A challenge for both health professionals and teaching institutions**

*Towards Unity for Health*, April 2000 p 18-19

The WHO Department of Child and Adolescent Health and Development, together with its partners, is working to develop and introduce approaches to combat childhood illness and to promote healthy growth and development of children. These efforts have resulted in the Integrated Management of Childhood Illness (IMCI) strategy that focuses on the child as a whole, rather than on a single disease or condition. Action is being taken to introduce the teaching of IMCI in medical schools to ensure that future doctors know proven methods for preventing and managing major childhood illnesses and have the skills to apply them.

Among the numerous challenges that must be overcome in a country before health professionals and teaching institutions are able to practice and teach the IMCI are: reaching consensus on health priorities in the country, strengthening the health system to allow graduates to practise newly acquired skills, reshaping the way paediatrics is taught including giving priority to interactive and skill-oriented teaching, and ensuring co-ordination between disease specific programmes and between different teaching units.

Nicoll A

**Integrated management of childhood illness in resource-poor countries: an initiative from the World Health Organization.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000 Jan-Feb; 94(1): 9-11

It is estimated that each year around 12 million children aged < 5 years die in resource-poor countries and that 70% of these deaths are due to communicable diseases and/or malnutrition. The same conditions are responsible for an even higher percentage of childhood illness. Since the mid-1990s the World Health Organization has been leading the development of an integrated approach to care for ill children at the primary care level, a programme known as Integrated Management of Childhood Illness (IMCI). The approach essentially combines improved management of childhood illness with aspects of nutrition, immunization and maternal health. IMCI replaces or complements a number of 'vertical' child health programmes aimed at specific groups of conditions including control of diarrhoeal diseases (CDD), acute respiratory infections (ARI) and the Expanded Programme on Immunization (EPI). As of late 1998 the programme, at various stages of development, had been introduced to 51 countries: Introduction (19 countries), Early Implementation (29 countries) or Expansion (9). The approach has many advantages not least that it is well accepted by tropical country paediatricians because it conforms to practice in secondary care. In some countries paediatricians are playing a greater leadership role than they did with previous specific programmes. Many problems remain: programmatic issues, probable over-diagnosis of malaria, relationships with other specific initiatives ('Roll Back Malaria' and new-born care) and how to integrate HIV infection into the diagnosis and care 'package'. However the initiative deserves support by paediatricians and public health specialists in industrialized countries.

Tulloch J

**Integrated approach to child health in developing countries.**

*Lancet* 1999 Sep;354 Suppl 2:SII16-20

Publication Types: Review, Review, tutorial

The integrated approach to child health embodied in IMCI focuses on the diseases of childhood that cause the greatest global burden, while allowing for the content to be adapted to an individual country's needs. An integrated approach is justified by good clinical practice; it is important to treat the child as a whole and not simply his or her most obvious disease. The strategy involves not only curative care but also interventions to promote healthy growth and development and to prevent diseases. Often, these too are aimed at more than one disease. In health facilities, the IMCI strategy promotes the accurate identification of childhood illness in outpatient settings, ensures appropriate combined treatment of all major illnesses, strengthens the counselling of caretakers and the provision of preventive services, and speeds up the referral of severely ill children. The strategy also aims to improve the quality of care of sick children at the referral level. In the home settings, it promotes appropriate early home care and care seeking, improved nutrition and prevention, and the correct implementation of prescribed care. Through improving co-ordination and quality of services provided by existing child health and other programmes, the IMCI strategy will increase the effectiveness of care and should in time reduce recurrent costs. It offers a model for improving one aspect of service delivery that could be applied to other parts of health care. It can contribute to the achievement of the goals of major global initiatives such as the "Roll Back Malaria" movement. Integrated approaches, in child health or in other health domains, if well founded, deserve support at a level that recognizes the magnitude and scope of the problems being addressed. They should not be seen, automatically, as a convenient way of reducing expenditure.

Wolfheim C

**From disease control to child health and development.**

*World Health Forum* 1998;19(2):174-81

The control of diarrhoeal diseases, acute respiratory infections and other childhood killers—such as measles, malaria and malnutrition—is now combined in WHO's Division of Child Health and Development. The need for integrated management of childhood illness is shown in its historical context.

World Health Organization

**Information sheets on Integrated Management of Childhood Illness (IMCI).**

[http://whqlibdoc.who.int/hq/1998/WHO\\_CHS\\_CAH\\_98.1\\_\(A-M\)\\_REV.1\\_1999.pdf](http://whqlibdoc.who.int/hq/1998/WHO_CHS_CAH_98.1_(A-M)_REV.1_1999.pdf)

*Management of Childhood Illness in developing countries: Rationale for an integrated strategy.*  
WHO/CHS/CAH/98.1A REV.1 1999

*Integrated Management of Childhood Illness: Global status of implementation*  
WHO/CHS/CAH/98.1B REV.1 1999

*Planning national implementation of IMCI*  
WHO/CHS/CAH/98.1C REV.1 1999

*Adaptation of the IMCI technical guidelines and training materials*  
WHO/CHS/CAH/98.1D REV.1 1999

*IMCI training course for first-level health workers: Linking integrated care and prevention*  
WHO/CHS/CAH/98.1E REV.1 1999

*Follow-up after training: Reinforcing the IMCI skills of first level health workers*  
WHO/CHS/CAH/98.1F REV.1 1999

*The role of IMCI in improving family and community practices to support child health and development*  
WHO/CHS/CAH/98.1G REV.1 1999

*Update on development projects to support IMCI*  
WHO/CHS/CAH/98.1H REV.1 1999

*IMCI research priorities: Investigating methods to prevent and manage childhood illness*  
WHO/CHS/CAH/98.1I REV.1 1999

*Introducing IMCI into pre-service training for health professionals*  
WHO/CHS/CAH/98.1J REV.1 1999

*IMCI indicators, monitoring and evaluation*  
WHO/CHS/CAH/98.1K REV.1 1999

*Integrated Management of Childhood Illness and health sector reform*  
WHO/CHS/CAH/98.1L REV.1 1999

*Building partnership for child health*  
WHO/CHS/CAH/98.1M REV.1 1999

World Health Organization, Division of Child Health and Development

***Improving Child Health. IMCI: the integrated approach.***

Geneva, World Health Organization, 1997, 20 p. (unpublished document WHO/CHD/97.12 Rev 2 available on request from the Division of Child and Adolescent Health and Development (CAH))  
[http://whqlibdoc.who.int/hq/1997/WHO\\_CHD\\_97.12\\_Rev.2.pdf](http://whqlibdoc.who.int/hq/1997/WHO_CHD_97.12_Rev.2.pdf)

The document gives an overview of the integrated management of childhood illness (IMCI) and its components as a new approach to treating sick children. It explains the rationale for an integrated approach to childhood illness and briefly describes the importance of major conditions included into IMCI: pneumonia, diarrhoea, malaria, measles and malnutrition.

World Health Organization, Regional Office for South-East Asia  
***Towards Better Child Health and Development. IMCI: Integrated Management of Childhood Illness.***  
World Health Organization, Regional Office for South-East Asia, New Delhi, 2001, 38 p.

The publication of the WHO Regional Office for South-East Asia, is designed for decision, policy and opinion-makers in South-East Asia to help to upscale the implementation of IMCI strategy. It includes 11 chapters: Message from the Regional Director, Introduction, Why IMCI?, IMCI works!, Components of IMCI, IMCI tools, Common misconceptions about IMCI, Linkages of IMCI to other priority health programmes, Adaptations of IMCI, Conclusions, and WHO offices in the South-East Asia region. The chapters will describe the IMCI topics suggested by their titles in the context of South East Asia.

## 2. GENERAL DANGER SIGNS

### 2.1. CONVULSIONS

#### Articles

#### Treatment

Choonara IA

**Giving drugs per rectum for systemic effect.**

*Archives of Disease in Childhood*, 1987, 62(8):771-772.

The paper discusses the acceptability and indications of giving drugs per rectum and the physiology of absorption of drugs from the rectum. Anticonvulsants are among the specific drugs discussed. Solution of diazepam given rectally is effective for treating convulsions in children, therapeutic plasma concentrations being obtained within 4 minutes. There is a considerable delay in the achievement of a therapeutic plasma concentration of diazepam after the use of suppositories. Major indications for the use of diazepam solution rectally in children are by parents at home for children who suffer from febrile convulsions or poorly controlled epilepsy or by a doctor when immediate intravenous access is not technically possible. It is preferable to give diazepam intravenously as therapeutic plasma concentrations are more readily achieved by this route. A therapeutic plasma concentration of clonazepam administered rectally is achieved after 20 minutes. Rectal absorption of paraldehyde is considerably slower than if it is given either intramuscularly or orally and it is therefore unsuitable for treating epilepsy. Paraldehyde can also irritate the rectum and large intestine, and decomposed paraldehyde has caused perforation of the large bowel. CONCLUSIONS: Solution of diazepam given rectally is effective for treating convulsions in children.

Dieckmann RA

**Rectal diazepam for prehospital paediatric status epilepticus.**

*Annals of Emergency Medicine*, 1994, 23(2):216-224.

STUDY OBJECTIVES: To compare the feasibility, effectiveness, and safety of rectal diazepam and intravenous diazepam in the treatment of paediatric prehospital status epilepticus. DESIGN AND SETTING: Retrospective analysis of a 30-month consecutive sample of ambulance-transported children in a large urban emergency medical service region. TYPE OF PARTICIPANTS: Study group included 324 patients with seizure who were less than 18 years of age; 36 had status epilepticus, of whom 16 received rectal diazepam and 15 received IV diazepam. INTERVENTIONS: For children with status epilepticus, paramedics administered the 5-mg/mL IV solution of diazepam by one of two routes: rectally either through a 5F feeding tube with an attached syringe or by lubricated tuberculin syringe inserted 4 to 5 cm into the rectum at a one-time dose of 0.2 to 0.5 mg/kg or intravenously using a one-time dose of 0.1 to 0.3 mg/kg. Cardiopulmonary status was carefully monitored in the field and emergency department. MEASUREMENTS AND MAIN RESULTS: Thirteen of 16 children (81%) who received rectal diazepam stopped seizing after a single dose ranging from 0.16 to 0.57 mg/kg. Convulsions recurred before arrival at the ED in four of the 13 (30.8%). All of three patients who did not respond to rectal diazepam initially were 3 to 5 years old and had serious underlying comorbidity; two required endotracheal intubation in the ED and multiple anticonvulsants to terminate the seizure. No child treated with rectal diazepam required prehospital endotracheal intubation. All children who received IV diazepam stopped seizing after one dose ranging from 0.04 to 0.33 mg/kg. Convulsions recurred before arrival at the ED in nine of 15 children (60%); two required prehospital endotracheal intubation for profound respiratory depression. CONCLUSIONS: Rectal diazepam is a simple, effective, and safe method of prehospital management of paediatric status epilepticus. Compared with IV diazepam, rectal diazepam is easier to administer, especially in infants and toddlers; is equally efficacious; and is less likely to produce respiratory depression. Although respiratory depression is rare with rectal diazepam, prehospital personnel must be

prepared to provide definitive respiratory support. Short duration of action is an important limitation of both treatments.

Hoppu K, Santavuori P

**Diazepam rectal solution for home treatment of acute seizures in children.**

*Acta Paediatrica Scandinavica*, 1981, 70(3):369-372.

To gain clinical experience of treating acute convulsions in children with diazepam rectal solution, 17 epileptic children with prolonged convulsions were treated at home. The drug was used 65 times. On 2/3 of all occasions the seizure was interrupted in less than 15 min. A starting dose of 0.5 mg/kg is recommended, with a maximum of 20 mg per single dose. One patient had respiratory difficulties, one dizziness and two skin reactions.

Publication Types: Clinical trial

Kalra A, Chaturvedi N, Vashishtha VM, Dube KN, Kalra K

**Per rectal diazepam therapy in convulsive disorders.**

*Indian Pediatrics*, 1992, 8:975-978.

One hundred and twenty children with persistent convulsions (lasting > or = 10 min) were treated with per rectal diazepam (dosage: 0.2 to 0.7 mg/kg/dose). Another group of 100 age matched children with convulsions, along with those who did not respond to rectal therapy were given intravenous diazepam in a dosage of 0.2 to 0.3 mg/kg/dose. Rectal treatment was effective in 80.83% cases while intravenous diazepam was effective in 90% cases which is statistically just significant ( $p < 0.05$ ). No significant difference was observed in the efficacy of two routes of administration in controlling convulsions of different clinical types and various etiological groups ( $p < 0.05$ ), except for primary generalised type where intravenous route was more effective than the rectal one ( $p < 0.05$ ). No significant side effect was observed with rectal therapy. Among the 23 (19.17%) children in whom rectal therapy failed, 12 (10%) responded to intravenous diazepam while the remaining 11 (9.17%) cases were resistant to both routes of administration.

Knudsen FU

**Plasma diazepam in infants after rectal administration in solution and by suppository.**

*Acta Paediatrica Scandinavica*, 1977, 66:563-567.

Twenty infants aged 1-2 years who had previously had one attack of febrile convulsions were randomly given a single dose of diazepam rectally, either as a solution (0.7 mg/kg) or by suppository (5 mg). Plasma-diazepam levels were determined repeatedly during the first hour using gas chromatography. Rectal administration of diazepam in solution resulted in anticonvulsant plasma values within 4 +/- 1 min. Similar plasma levels were obtained only after 20-30 min in the group treated with suppositories. Diazepam in solution given rectally may therefore be useful in the acute treatment of febrile convulsions, while treatment by suppository would seem to be of little value in this respect. Moreover, diazepam in solution given rectally seems suitable for use at home in case of recurrent febrile convulsions. This treatment, however, cannot be recommended until the anticonvulsant effect and side-effects have been elucidated further.

Publication Types: Clinical trial, Randomised controlled trial

## **Documents and publications**

Advanced Life Support Group

### **Convulsions (status epilepticus).**

In: Advanced paediatric life support. The Practical Approach. *BMJ Publishing Group*, 1993, 1997.

Chapter 12 of the book describes pathophysiology of status epilepticus, primary assessment and resuscitation, secondary assessment and emergency treatment, and lists mandatory and optional investigations.





### 3. COUGH OR DIFFICULT BREATHING

#### Articles

#### Importance

Duke T, Michael A

**Increase in sepsis due to multi-resistant enteric gram-negative bacilli in Papua New Guinea.**

*Lancet*, 1999, 26:353:2210-1

OBJECTIVE: Prospective study to determine the incidence of antibiotic-resistant gram-negative sepsis and their effect on mortality in children at Goroka hospital, Papua New Guinea. METHODS: In 54 children with severe sepsis, and in those who deteriorated despite a standard antibiotic treatment, cultures of blood, cerebrospinal fluid (CSF), lung aspirate, and other suspected infected sites were done over 16 months period beginning in mid 1997. RESULTS: Sixty-one isolates of non-typhoid enteric gram-negative bacilli were grown from 54 children with sepsis. The median age of the children was 5 months, 39 of the children were 2 months of age or older. Only 12 (24%) children survived; 38 (70%) children died from gram-negative sepsis, four died of other causes. Only 6 (9.8%) of the 61 isolates were sensitive to chloramphenicol, 22 (33.9%) were sensitive to gentamicin, 4 (6.5%) were sensitive to cotrimoxazole and 2 (3.3%) were sensitive to ampicillin/amoxycillin. Forty-six (78%) of 59 isolates tested were sensitive to ceftriaxone. In 1984, from the same hospital, a series of lung aspirate and blood cultures on 83 children with severe pneumonia isolated only two enteric gram-negative bacilli, both of them were sensitive to chloramphenicol and to gentamicin. Infections due to multiresistant gram-negative bacilli are now a fairly common cause of death in the highlands of Papua New Guinea. Apart from intrinsic resistance expected for some bacteria uncontrolled dispensing of amoxycillin, cotrimoxazole and oral chloramphenicol is likely to be the cause.

Forge IM, O'Neill KP, Lloyd-Evans N, Leinonen M, Campbell H, Whittle HC, Greenwood BM

**Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital.**

*The Pediatric Infectious Disease Journal* 1991 Jan;10(1):42-7

Seventy-four children ages 1 to 9 years hospitalised because of severe pneumonia were investigated using blood cultures, lung aspirates, nasopharyngeal aspirates, serology and antigen detection procedures. A bacterial infection was identified in 57 (77%), a viral infection was seen in 25 (34%) and 18 (24%) had mixed viral-bacterial infections. The bacterial pathogens most frequently identified were *Streptococcus pneumoniae* and *Haemophilus influenzae* found in 61 and 15% of patients, respectively. The viral pathogen most frequently recovered was respiratory syncytial virus (12%). Evidence of *Chlamydia pneumoniae* strain TWAR and *Mycoplasma pneumoniae* infection was found in 12 and 4% of cases, respectively. Overall a potential pathogen was identified in 60 (81%) children, with evidence of polymicrobial infection in 30 cases (40.5%). The study provides information on the relative role of different infectious agents in the etiology of severe pneumonia in children in a developing country.

Garenne M, Ronsmans C, Campbell H

**The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries.**

*World Health Statistics Quarterly* 1992;45(2-3):180-91

This article reviews the available evidence of mortality from acute respiratory infections (ARI) among children aged under 5 years in contemporary developing countries and compares the findings with European populations before 1965. In European populations before 1965, the level of mortality was found to be a determinant of the proportion of deaths due to ARI. There were marked differences according to

regional patterns of mortality. Deaths from ARI played a smaller role after 1950, when the use of antibiotics became generalised. In developing countries, the role of ARI mortality seems to be similar to the European experience. The age pattern is very marked. In absolute values, ARI mortality is highest in the neonatal period and decreases with age. In relative values, ARI mortality is highest in the postneonatal period. ARI, mainly pneumonia, accounts for about 18% of underlying causes of death in developing countries. Pneumonia and other ARI are frequent complications of measles and pertussis; ARI is also commonly found after other infections and in association with severe malnutrition. Virtually no data are available in developing countries to provide final estimates of the role of ARI in mortality of children aged under 5 years. However, the WHO figure of 1 out of 3 deaths due to—or associated with—ARI may be close to the real range of the ARI-proportional mortality in children of developing countries. Results are discussed in light of the definitions of ARI used in various studies, the difficulties in ascertaining and coding multiple causes of death and the quality of data from some sources.

Mulholland EK, Ogunlesi OO, Adegbola RA, Weber M, Sam BE, Palmer A, Manary MJ, Secka O, Aidoo M, Hazlett D, Whittle H, Greenwood BM

**Etiology of serious infections in young Gambian infants.**

*Paediatric Infectious Diseases Journal* 1999 Oct;18(10 Suppl):S35-41

**BACKGROUND:** Despite improvements in infant mortality rates in many developing countries including The Gambia, neonatal mortality remains high and many neonatal deaths are caused by infection. The study described in this paper was conducted to determine the bacterial and viral etiology of serious infections in Gambian infants younger than 91 days old. **METHODS:** At a first level health facility 497 infants with symptoms that could indicate serious infection were enrolled, of whom 239 with 1 or more signs of serious infection and 55 with no signs were investigated, yielding 17 cases with positive bacterial cultures of blood and/or cerebrospinal fluid. At a nearby paediatric referral hospital 198 infants were seen and 182 were investigated, yielding 35 positive bacterial cultures. **RESULTS:** There were 15 culture positive cases of meningitis caused by *Streptococcus pneumoniae* (7), *Streptococcus pyogenes* (2), *Enterobacter cloacae* (2), *Escherichia coli* (1), *Haemophilus influenzae* type b (1), *Streptococcus agalactiae* (1) and *Salmonella* spp. (1). Six of these children died. Thirty-three infants without meningitis had positive blood cultures for *Staphylococcus aureus* (17), *S. pneumoniae* (3), *Salmonella* spp. (5), *E. coli* (3), other enterobacteria (4) and *S. agalactiae* (1), of whom 14 died. Nasopharyngeal aspirates from 438 children were investigated for common respiratory viruses. Respiratory syncytial virus was found in 51, influenza A in 46, influenza B in 22, parainfluenza in 26 and adenovirus in 16. Respiratory syncytial virus and influenza A isolates were found most frequently toward the end of the wet season. Nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae* was studied in 320 infants recruited during the first year. Of these 184 (58%) were positive for *S. pneumoniae* and 141 (44%) were positive for *H. influenzae*, 18 of which were type b. Infants with a bacterial isolate from blood or cerebrospinal fluid were more likely than the rest to die, whereas those with a viral isolate were less likely to die.

**CONCLUSIONS:** The most important causes of serious infections in young Gambian infants are *Staphylococcus aureus*, *S. pneumoniae* and *Salmonella* spp.

Publication Types: Multicenter study

(see also other articles on the young infant in chapter Young infant)

Shann F

**Etiology of severe pneumonia in children in developing countries.**

*Pediatric Infectious Disease* 1986 Mar-Apr;5(2):247-52

The results of bacterial culture of lung aspirates from children in developing countries, and lung aspiration studies and postmortem studies in children in developed countries in the preantimicrobial era, provide strong evidence that most children dying from pneumonia in developing countries have bacterial pneumonia. In the studies in developing countries bacteria were isolated from 640 (62%) of 1029 lung aspirates from children with pneumonia who had not received antibiotics, while evidence of viral infection could be found in only 281 (23%) of 1212 children with pneumonia. The lung aspiration studies demonstrate that at least 2/3 of the children who die from pneumonia have bacterial infection. Clinical studies in children with pneumonia have shown that patients treated with antibiotics have less than half the mortality of untreated patients. The use of simple, cheap, standardized regimens for the antibiotic

management of pneumonia might therefore be expected to make a substantial impact on the high mortality of children in developing countries.

Simoes EA

**Respiratory syncytial virus and subsequent lower respiratory tract infections in developing countries: A new twist to an old virus.**

*The Journal of Pediatrics*, 1999, 135(6):657-61

Most early studies examining whether respiratory syncytial virus (RSV) is a predisposing factor to or a marker for the development of atopic asthma relied on hospital-based identification of infants and children with RSV lower respiratory infection (LRI) and their subsequent follow-up. However, almost all children have experienced RSV by 3 years of age, and although <1% of them are hospitalised, a much larger number (about 30%) of children see a physician for treatment of a wheezing disease or asthma in their first 5 years of age. The results of subsequent community based studies in developed countries suggested that there are 2 distinct groups of patients with asthma in early childhood. Transient wheezing occurs in infants and young children with prior diminished lung function and no family history of asthma, no atopy, and normal concentration of serum IgE. Persistent wheezing occurs in those with prior normal lungs but with a family history of asthma, atopy, and high concentrations of IgE. Because airway growth is for the most part completed in utero, prenatal factors and prematurity can be expected to influence development of the airways. The first community study from a developing country has shown that in the 3 years after RSV LRI, infants and children in The Gambia are 8 times more likely to have a wheezing LRI and 4 times more likely to have a non-wheezing RLI. After severe RSV disease, recurrent LRI occurred in the first 2 years after infection but disappeared by the third year. Pneumonia occurred about 4 times more commonly than wheezing LRI. The prevention of RSV LRI could possibly prevent 2/3 of recurrent acute RLI in this group. RSV is by far the most important cause of viral acute RLI in both developed and developing countries. Thus, although a strong case can be made for using the currently available vaccines against H. influenzae and S. pneumoniae to reduce pneumonia-related mortality rates in developing countries, an RSV vaccine would be equally important in reducing acute morbidity, mortality rates, and the number of subsequent RLI in developing countries. Currently no vaccines are available for use in infancy and childhood.

Weber MW, Dackour R, Usen S, Schneider G, Adegbola RA, Cane P, Jaffar S, Milligan P, Greenwood BM, Whittle H, Mulholland EK

**The clinical spectrum of respiratory syncytial virus disease in The Gambia.**

*The Pediatric Infectious Disease Journal* 1998 Mar;17(3):224-30

**BACKGROUND:** Respiratory syncytial virus (RSV) is a well-recognized cause of lower respiratory tract infections in early childhood in industrialized countries, but less is known about RSV infection in developing countries. **METHODS:** Four outbreaks of RSV infection that occurred between 1993 and 1996 in The Gambia, West Africa, were studied. RSV was sought by immunofluorescent staining of nasopharyngeal aspirate samples among young children who presented with respiratory infections at three hospitals in the Western Region of the country. **RESULTS:** Five hundred seventy-four children with RSV infection were identified. The median ages of children seen in 1993 through 1996 were 3, 7, 8 and 5 months, respectively. Sixty-two percents of children <6 months old were boys. Thirteen children (2.4%) had conditions considered to increase the risk of severe RSV infection. On physical examination crepitations were heard in 80% of the children admitted to hospital, whereas wheezes were heard in only 39%. Eighty (16%) children received oxygen because of hypoxemia. Nine of 255 blood cultures (3.5%) were positive: 4 *Streptococcus pneumoniae*; 2 *Haemophilus influenzae* type b; 2 *Staphylococcus aureus*; and 1 *Enterobacter agglomerans*. Thirteen children died (2.4%). During the 4 study years 90, 25, 75 and 95% of isolates typed were RSV Subgroup A, respectively.

**CONCLUSIONS:** RSV is a significant cause of lower respiratory tract infection in young children in The Gambia, causing epidemics of bronchiolitis. It poses a significant burden on the health system, especially through the demand for supplementary oxygen. The clinical spectrum of RSV disease in The Gambia is similar to that seen in developed countries; concomitant bacterial infections are uncommon.

Weber MW, Milligan P, Giadom B, Pate MA, Kwara A, Sadiq AD, Chanayireh M, Whittle H, Greenwood BM, Mulholland K

**Respiratory illness after severe respiratory syncytial virus disease in infancy in The Gambia.**

*The Journal of Pediatrics* 1999 Dec;135(6):683-8

**OBJECTIVE:** To determine the frequency of later respiratory tract morbidity after respiratory syncytial virus (RSV) disease in infancy. **DESIGN:** Cohort study with passive, clinic-based surveillance. **SETTING:** Outpatient department in The Gambia. **SUBJECTS:** One hundred five children admitted to the hospital with severe RSV disease (case cohort), 105 control children matched for age not admitted to the hospital during the previous RSV season (control cohort 1), and 102 control children born after the RSV season (control cohort 2). **Main outcome measures:** Frequencies of pneumonia, wheezing, and hospital admission with acute lower respiratory tract infection. **RESULTS:** Pneumonia was more common in case children than in both control groups (adjusted incidence rate ratio [IRR, 95% CI]: 3.80 [2.73, 6.10]), as was wheezing (IRR 7.33 [3.10, 17.54]), pneumonia or wheezing (IRR 3.96 [2.60, 6.04]), and admission with pneumonia or wheezing (IRR 3.40 [1.87, 6.15]). The incidence rate per 100 child-years for pneumonia in the dry season for 12-month-old children was 27 for case patients, 8.1 for control cohort 1, and 6.51 for control cohort 2. By 3 years of age, the rates had fallen to low levels in all groups.

**CONCLUSIONS:** Pneumonia and wheezing are significantly more common in children after RSV-associated lower respiratory tract disease than in control subjects, but the incidence declines rapidly with increasing age.

Comment in: *J Pediatr* 1999 Dec;135(6):657-61; *J Pediatr* 1999 Dec;135(6):661-4

Weber MW, Milligan P, Hilton S, Lahai G, Whittle H, Mulholland EK, Greenwood BM

**Risk factors for severe respiratory syncytial virus infection leading to hospital admission in children in the Western Region of The Gambia.**

*International Journal of Epidemiology* 1999 Feb;28(1):157-62

**BACKGROUND:** Acute lower respiratory tract infections (ALRI) are the major cause of mortality and morbidity in young children worldwide. Respiratory syncytial virus (RSV) infection is the most important viral cause of severe ALRI but only a small proportion of children infected with this virus develop severe disease. To identify possible risk factors for severe RSV infection leading to hospital admission we have carried out a case-control study of Gambian children with RSV infection admitted to hospital. **METHODS:** In all, 277 children admitted to three hospitals in the Western Region of The Gambia with lower respiratory tract infection due to RSV were compared with 364 control children matched for age and location of residence who had not been admitted to hospital with an ALRI during the RSV season. A detailed questionnaire covering a wide range of potential social, environmental and nutritional risk factors was administered to the child's guardian. **RESULTS:** Cases came from larger or more crowded compounds than controls; increased risk was particularly associated with greater numbers of children in the age group 3-5 years living in the compound (odds ratio [OR] for > or =2 children in the age group 3-5 years = 9.1, 95% CI: 3.7-28). Cases were more likely to have a sibling who had died (OR = 3.4, 95% CI: 1.7-7). Controls were more likely to have been exposed to smoke from cooking fires (OR for the mother of cases cooking at least once daily = 0.31, 95% CI: 0.14-0.7). Other protective factors were father's nationality and some professions. Vegetables were included in the diet of controls more frequently than in that of cases (OR = 0.16, 95% CI: 0.06-0.46). Mothers of cases complained of asthma more frequently than mothers of controls, but the number of asthmatic mothers was small (4.2 versus 0.5%, P = 0.05).

**CONCLUSIONS:** Risk factors for severe RSV infection identified in this study are not amenable to public health interventions. Prevention of severe infection is likely to require the development of an effective vaccine.

Publication Types: Multicenter study

Weber MW, Mulholland EK, Greenwood BM

**Respiratory syncytial virus infection in tropical and developing countries.**

*Tropical Medicine and International Health* 1998 Apr;3(4):268-80

Little is known about the epidemiology of respiratory syncytial virus (RSV) infection in tropical and developing countries; the data currently available have been reviewed. In most studies, RSV was found to be the predominant viral cause of acute lower respiratory tract infections (ALRI) in childhood, being responsible for 27-96% of hospitalised cases (mean 65%) in which a virus was found. RSV infection is seasonal in most countries; outbreaks occur most frequently in the cold season in areas with temperate and Mediterranean climates and in the wet season in tropical countries with seasonal rainfall. The situation on islands and in areas of the inner tropics with perennial high rainfall is less clear-cut. The age group mainly affected by RSV in developing countries is children under 6 months of age (mean 39% of hospital patients with RSV). RSV-ALRI is slightly more common in boys than in girls. Very little information is available about the mortality of children infected with RSV, the frequency of bacterial co-infection, or the incidence of further wheezing after RSV. Further studies on RSV should address these questions in more detail. RSV is an important pathogen in young children in tropical and developing countries and a frequent cause of hospital admission. Prevention of RSV infection by vaccination would have a significant impact on the incidence of ALRI in children in developing countries.

Publication Types: Review, Review, multicase

## **Assessment**

Campbell H, Byass P, Lamont AC, Forgie IM, O'Neill KP, Lloyd-Evans N, Greenwood BM  
**Assessment of clinical criteria for identification of severe acute lower respiratory tract infections in children.**

*Lancet*, 1989, 1(8633):297-299.

This study was undertaken to help define which clinical signs and symptoms would be most predictive of severe pneumonia in a community setting. A cohort of children under 5 years of age in Basse, a rural area of Gambia, was surveyed for one year with weekly visits by trained field workers. The field workers recorded the respiratory rate and temperature and referred children to the project clinician when signs of respiratory distress were recognized. Among 491 children, 222 episodes of ALRI were identified using the criteria of cough with respiratory rate above 50/min, indrawing, wheeze, or stridor at the time of presentation. Chest radiographs, taken in 216 episodes, showed radiological changes consistent with ALRI in 81 episodes (38%) and 25 (12%) showed lobar consolidation. Severe ALRI was considered to be present if there was complete radiological consolidation in one or more lobes. Children with severe ALRI were compared to all other children with ALRI, including those with and without other radiological changes. Refusal to breast-feed and a fever of greater than 38.5°C were the best predictors of severe ALRI in infants. Among children aged 1 to 4 years, bronchial breath sounds, a fever of greater than 38.5°C and a respiratory rate greater than 60/min were the most accurate clinical signs for severe ALRI. For all study children, chest indrawing did not distinguish the presence of lobar consolidation. After adjustment for other factors, only bronchial breath sounds or decreased air entry, and fever above 38.5°C were independently associated with severe disease. Indrawing was extremely prevalent in this study, present in 62% of all children with ALRI, which may reflect the severity of illness seen or the definition and ascertainment of indrawing. Although indrawing was not defined, it is likely that mild degrees of indrawing were included. In addition, radiological consolidation of one or more complete lobes is an imperfect measure of severity, and it is neither inclusive nor specific for bacterial etiology, thus limiting the general applicability of these results for the prediction of severe pneumonia.

Cherian T, John TJ, Simoes E, Steinhoff MC, John M.

**Evaluation of simple clinical signs for the diagnosis of acute lower respiratory tract infection.** *Lancet*, 1988, 2(8603):125-128.

The reliability of clinical signs that might be used by village health workers in distinguishing acute lower respiratory infection (LRI) from upper respiratory infections (URI) in children was evaluated. 142 infants and 108 preschool children with LRI and 151 infants and 281 preschool children with URI, attending hospital, were studied. Respiratory rates of over 50/min in infants and over 40/min in children 12-35 months of age, as well as a history of rapid breathing and the presence of chest retractions in both age groups, were found to be sensitive and specific indicators of LRI. Increased respiratory rates and history of rapid breathing were also sensitive in diagnosis of less severe LRI that did not necessitate admission to the wards, whereas chest retraction was not. All these clinical signs had a low sensitivity in diagnosing LRI in children aged 36 months and over.

Harari M, Shann F, Spooner V, Meisner S, Carney M, de Campo J

**Clinical signs of pneumonia in children.**

*Lancet*, 1991, 338(8772):928-930.

Clinical and chest radiographic findings were recorded prospectively in 185 children with cough who attended an outpatient clinic in Papua New Guinea. Children were studied if they were between 8 weeks and 6 years of age; patients with wheeze, stridor, measles, or pertussis were excluded. 56 children (30%) had radiological evidence of pneumonia. The presence of either a respiratory rate greater than or equal to 50/min or chest indrawing, or of both signs, was a good indication of pneumonia, with a predictive power of 46% for a positive test and 83% for a negative test. A more complex definition of tachypnoea, as a respiratory rate greater than or equal to 40/min in children over 12 months old and greater than or equal to 50/min in infants, showed little additional diagnostic benefit.

Kalter HD, Schillinger JA, Hossain M, Burnham G, Saha S, de Wit V, Khan NZ, Schwartz B, Black RE

**Identifying sick children requiring referral to hospital in Bangladesh.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):65-75.

The object of this study was to evaluate and improve the guidelines for the Integrated Management of Childhood Illness (IMCI) with respect to identifying young infants and children requiring referral to hospital in an area of low malaria prevalence. A total of 234 young infants (aged 1 week to 2 months) and 668 children (aged 2 months to 5 years) were prospectively sampled from patients presenting at a children's hospital in Dhaka, Bangladesh. The study paediatricians obtained a standardized history and carried out a physical examination, including items in the IMCI guidelines developed by WHO and UNICEF. The paediatricians made a provisional diagnosis and judged whether each patient needed hospital admission. Using the paediatrician's assessment of a need for admission as the standard, the sensitivity and specificity of the current and modified IMCI guidelines for correctly referring patients to hospital were examined. The IMCI's sensitivity for a paediatrician's assessment in favour of hospital admission was 84% (95% confidence interval (CI): 75-90) for young infants and 86% (95% CI: 81-90) for children, and the specificity was, respectively, 54% (95% CI: 45-63) and 64% (95% CI: 59-69). One fourth or more in each group had a provisional diagnosis of pneumonia, and the IMCI's specificity was increased without lowering sensitivity by modifying the respiratory signs calling for referral. These results show that the IMCI has good sensitivity for correctly referring young infants and children requiring hospital admission in a developing country setting with a low prevalence of malaria. The guidelines' moderate specificity will result in considerable over-referral of patients not needing admission, thereby decreasing opportunities for successful treatment of patients at first-level health facilities. The impact of the IMCI guidelines on children's health and the health care system must be judged in the light of current treatment practices, health outcomes and referral patterns.

Mulholland EK, Simoes EA, Costales MO, McGrath EJ, Manalac EM, Gove S.

**Standardized diagnosis of pneumonia in developing countries.**

*The Pediatric Infectious Disease Journal*, 1992, 11(2):77-81.

The World Health Organization recommends the use of raised respiratory rate and chest wall indrawing to enable health workers in developing countries to diagnose pneumonia. We evaluated the current World Health Organization guidelines for management of the child with cough or difficult breathing in Manila, Philippines and Mbabane, Swaziland using an identical protocol in both countries. Raised respiratory rate was defined as greater than or equal to 50/minute for children ages 2 to 12 months and greater than or equal to 40/minute for children 12 months to 5 years. Chest wall indrawing was defined as inward movement of the bony structures of the lower chest wall with inspiration. In the Philippines raised respiratory rate or chest wall indrawing, when applied by a paediatrician, was found to have a sensitivity of 0.81 and specificity of 0.77 for predicting pneumonia as determined by a paediatrician with the aid of a chest roentgenogram. In Swaziland the sensitivity was 0.77 and the specificity was 0.80. When applied by health workers the sensitivity was similar but the specificity was lower. The current World Health Organization ARI case management guidelines predicted pneumonia with similar sensitivity and specificity in two very different developing countries, the Philippines and Swaziland.

Mulholland EK, Olinsky A, Shann FA

**Clinical findings and severity of acute bronchiolitis.**

*Lancet* 1990 May 26;335(8700):1259-61

Clinical features on admission of 60 infants with acute bronchiolitis were related to disease severity. Crackles and cyanosis (which are related to oxygen requirements during the hospital stay) most closely correlated with severity, which was assessed by arterial blood gas analysis and pulse oximetry. Respiratory rate on presentation did not predict severity. Transcutaneous haemoglobin oxygen saturation on admission, measured by pulse oximetry, was closely related to cyanosis and maximum oxygen requirements. The best method for initial assessment of bronchiolitis was pulse oximetry.

Perkins BA, Zucker JR, Otieno J, Jafari HS, Paxton L, Redd SC, Nahlen BL, Schwartz B, Oloo AJ, Olango C, Gove S, Campbell CC

**Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):33-42.

(See chapter Effectiveness of IMCI guidelines)

Sazawal S, Black RE

**Meta-analysis of intervention trials on case management of pneumonia in community settings.**

*Lancet*, 1992, 340(8818):528-533.

To appraise the effectiveness of the pneumonia case-management strategy in improving child survival, we have done a meta-analysis of six published intervention trials. The results of a seventh published study and two unpublished studies were also reviewed. The six published studies satisfied our criteria for methodological soundness. The reduction in mortality rate (control group minus intervention group) was estimated for each study, and for all the studies together. For total infant mortality, the overall reduction was 15.9 (95% confidence interval 10.6-21.1) deaths per 1000 live births; infant mortality due to acute lower respiratory infection was reduced by 10.7 (4.8-16.7) deaths/1000 live births. Mortality among children under 5 years was decreased by 36 deaths/1000 live births. The pooled estimates of relative risk are consistent with a 20% reduction in infant mortality and a 25% reduction in under-5 mortality. There was no clear association across the studies between the effect of the pneumonia case-management and extent of co-interventions such as immunisation and oral rehydration therapy. The consistency of findings of all the studies, despite differences in design and methods, shows that the case-management strategy has a substantial effect on infant and under-5 mortality, at least in settings with infant mortality rates of 90/1000 live births or more. It is important to find out the most efficient ways of implementing this strategy and integrating it into primary health care.



Shann F, Barker J, Poore P

**Clinical signs that predict death in children with severe pneumonia.**

*The Pediatric Infectious Disease Journal*, 1989, 8(12):852-855.

It is important to define clinical signs that can be used to identify children who have a high risk of dying from pneumonia so that these children can be given more intensive therapy. We prospectively studied 748 children in Papua New Guinea who had severe pneumonia, as defined by the World Health Organization. There was a very high mortality in children with a prolonged illness, severe roentgenogram changes, cyanosis, leukocytosis, hepatomegaly or inability to feed, and there was a trend toward a higher mortality in children with grunting or severe chest indrawing. Afebrile malnourished children had a particularly high mortality, but afebrile children had an increased mortality only if they were malnourished, and malnourished children had an increased mortality only if they were afebrile. Mortality was not increased in very young children or in children with tachypnoea or tachycardia. The World Health Organization has suggested that most children with pneumonia in developing countries can be treated with penicillin but has recommended that children who are cyanotic or too sick to feed be treated with chloramphenicol because of their high risk of dying; our findings confirm that children who are cyanotic or too sick to feed have a very high risk of dying from pneumonia.

Publication Types: Clinical trial, Multicenter study

Shann F, Hart K, Thomas D

**Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission.**

*Bulletin of the World Health Organization*, 1984, 62(15):749-751.

This study was performed to determine which clinical findings could best predict the outcome or need for antibiotics in lower respiratory tract infections and which signs could most reliably be elicited by primary health workers. Prospectively, 200 children with cough brought to the Goroka Hospital outpatient department, Goroka, Papua New Guinea, 100 age-matched controls without cough, and 50 children admitted to the hospital with pneumonia, were studied. Of the 200 outpatients, 106 (53%) were under 12 months of age and of the 50 inpatients, 36 (72%) were under 12 months of age. For children under 12 months of age, the mean respiratory rate for those with crepitations was 63 and for those without crepitations 45. For children aged 12 months or more, those with crepitations had a mean of 54 and those without crepitations 37. For all children, the sensitivity for the presence of crepitations was higher for a respiratory rate  $>40/\text{min}$  (90%) than for a respiratory rate  $>50/\text{min}$  (72%), while an age-specific cut-off (respiratory rate  $>50/\text{min}$  for children under 12 months of age and  $>40/\text{min}$  for children 12 months or older) had an intermediate sensitivity (78%). The specificities for these cut-offs were 59%, 81%, and 73%, respectively. In both age groups, the children with cough but no crepitations had a similar respiratory rate to those with no cough. Although breathlessness, as reported by the mother, identified almost two-thirds of children with crepitations, the combination of breathlessness with respiratory rate performed no better than respiratory rate alone. Chest indrawing was found in 4 (2%) of the children brought to the outpatient department with cough. Of the children admitted to hospital, all had chest indrawing and crepitations (chest indrawing was used as a criterion for admission), 96% had a respiratory rate  $>40/\text{min}$ , 90% were breathless according to the mother, 86% had a respiratory rate  $>50/\text{min}$ , and 60% had a temperature over  $37.5^{\circ}\text{C}$ . The authors noted that the choice of a respiratory rate cut-off involves trade-offs: a lower rate of  $40/\text{min}$  detects almost all children with crepitations but significantly overtreats children who do not need antibiotics, while a higher rate of  $50/\text{min}$  results in fewer incorrect treatments overall but misses a higher proportion of children who might benefit from antibiotics. The choice of an age-specific cut-off, as above, produces an intermediate result in this setting.

CONCLUSIONS: The authors concluded that the respiratory rate can be used to decide which children presenting with a cough should be treated with antibiotics.

Simoes EA, Desta T, Tessema T, Gerbresellassie T, Dagne M, Gove S  
**Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia.**  
*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):43-53.  
(See chapter Effectiveness of IMCI guidelines)

Simoes EA, McGrath EJ  
**Recognition of pneumonia by primary health care workers in Swaziland with a simple clinical algorithm.**  
*Lancet* 1992 Dec 19-26;340(8834-8835):1502-3

In developing countries primary health care workers are being trained to manage and treat acute respiratory infections with a protocol developed by the WHO. We tested the ability of nurses and nursing assistants in Swaziland to recognise the signs and symptoms of pneumonia; with the results of a paediatrician's examination as "gold standard", sensitivities and specificities were calculated. Danger signs of stridor and abnormal sleepiness were poorly recognised (sensitivity 0-50%) by the health care workers, as was audible wheeze. Severe undernutrition, tachypnoea, and chest wall indrawing were well recognised. Overall, the recognition of pneumonia was good (sensitivity 71-83%, specificity 84-85%). These findings highlight topics for emphasis in training.

Usen S, Weber M, Mulholland K, Jaffar S, Oparaugo A, Omosigho C, Adegbola R, Greenwood B  
**Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study.**  
*British Medical Journal* 1999 Jan 9;318(7176):86-91

**OBJECTIVES:** To determine clinical correlates and outcome of hypoxaemia in children admitted to hospital with an acute lower respiratory tract infection. **DESIGN:** Prospective cohort study. **SETTING:** Paediatric wards of the Royal Victoria Hospital and the hospital of the Medical Research Council's hospital in Banjul, the Gambia. **SUBJECTS:** 1072 of 42 848 children, aged 2 to 33 months, who were enrolled in a randomised trial of a Haemophilus influenzae type b vaccine in the western region of the Gambia, and who were admitted with an acute lower respiratory tract infection to two of three hospitals. **MAIN OUTCOME MEASURES:** Prevalence of hypoxaemia, defined as an arterial oxygen saturation <90% recorded by pulse oximetry, and the relation between hypoxaemia and etiological agents. **RESULTS:** 1072 children aged 2-33 months were enrolled. Sixty three (5.9%) had an arterial oxygen saturation <90%. A logistic regression model showed that cyanosis, a rapid respiratory rate, grunting, head nodding, an absence of a history of fever, and no spontaneous movement during examination were the best independent predictors of hypoxaemia. The presence of an inability to cry, head nodding, or a respiratory rate  $\geq 90$  breaths/min formed the best predictors of hypoxaemia (sensitivity 70%, specificity 79%). Hypoxaemic children were five times more likely to die than non-hypoxaemic children. The presence of malaria parasitaemia had no effect on the prevalence of hypoxaemia or on its association with respiratory rate. **CONCLUSION:** In children with an acute lower respiratory tract infection, simple physical signs that require minimal expertise to recognise can be used to determine oxygen therapy and to aid in screening for referral. The association between hypoxaemia and death highlights the need for early recognition of the condition and the potential benefit of treatment.  
Publication Types: Clinical trial, Randomised controlled trial  
Comment in: *BMJ* 1999 Jul 3;319(7201):58

Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM

**Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):25-32.

(See chapter Effectiveness of IMCI guidelines)

World Health Organization, Division of Child Health and Development and the World Health Organization Regional Office for Africa. **Integrated management of childhood illness: field test of the WHO/UNICEF training course in Arusha, United Republic of Tanzania.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):55-64.

(See chapter Effectiveness of IMCI guidelines)

## **Treatment and prevention**

This section is further divided into parts:

- Treatment - antibiotics
- Treatment – chloramphenicol
- Treatment - oxygen
- Treatment – wheezing
- Prevention

### **Treatment – antibiotics**

Arroll B, Kenealy T

**Antibiotics for the common cold (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.

**BACKGROUND:** The common cold is caused by viruses, which cannot be helped by antibiotics.

**OBJECTIVES:** The objective of this review was to assess the effects of antibiotics for the common cold.

**SEARCH STRATEGY:** We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, the Family Medicine Database, and reference lists of articles, and we contacted principal investigators. The most recent search was in December 1998.

**SELECTION CRITERIA:** Randomised trials comparing any antibiotic therapy with placebo in acute upper respiratory tract infections.

**DATA COLLECTION AND ANALYSIS:** Both reviewers independently assessed trial quality and extracted data.

**MAIN RESULTS:** Seven trials involving 2056 people aged between six months and 49 years were included. The overall quality of the included trials was variable. People receiving antibiotics did not do better in terms of cure or improvement than those on placebo (odds ratio 0.95, 95% confidence interval 0.70 to 1.28 fixed effects model).

One study found a significant benefit for antibiotics compared with placebo for runny nose (clear or purulent). The only other study to evaluate purulent nasal discharge found no significant benefit for antibiotics.

Only one study reported work time lost with 22% of those on antibiotic treatment and 25% of those on placebo but this was not significant. Patients treated with antibiotics had a significant increase in side effects (odds ratio 2.72, 95% confidence interval 1.02 to 7.27, random effects model).

**CONCLUSIONS:** Antibiotics appear to have no benefit in the treatment of acute upper respiratory tract infections. The implications for practice are that prescription of antibiotics should not be given in the first instance as they will not improve the symptoms and some patients will get adverse effects.

Campbell H, Byass P, Forgie IM, O'Neill KP, Lloyd-Evans N, Greenwood BM

**Trial of cotrimoxazole versus procaine penicillin with ampicillin in treatment of community-acquired pneumonia in young Gambian children.**

*Lancet* 1988 Nov 19;2(8621):1182-4

134 Gambian children under 5 years of age with severe pneumonia (as defined by the World Health Organisation classification of acute respiratory infections) were given either oral cotrimoxazole for 5 days, or a single intramuscular dose of fortified procaine penicillin and 5 days of oral ampicillin. At 2 weeks, there was no significant difference in outcome between the two groups. Cotrimoxazole is much less expensive than ampicillin or procaine penicillin, requires only twice-daily administration, and can be given by health-care staff with little training.

CONCLUSIONS: The results support the use of cotrimoxazole as the antibiotic of first choice in outpatient management of young children with pneumonia in developing countries.

Publication Types: Clinical trial, Controlled clinical trial

Comment in: *Lancet* 1989 Feb 11;1(8633):336-7

Congeni B

**The use of ceftriaxone for bacterial pneumonia in paediatric patients.**

*Clinical Pediatrics*, 1990, 29(11):640-641.

*Streptococcus pneumoniae* and *H. influenzae* type b are the major pathogens responsible for bacterial pneumonia in children beyond the neonatal period. ceftriaxone, an injectable third generation cephalosporin, when given in a single daily injection was effective for paediatric patients presumed to have bacterial pneumonia and a variety of paediatric infections including meningitis and musculo-skeletal infections. It does not follow however, that this drug is the therapy of choice for bacterial pneumonia. Some specific circumstances where ceftriaxone alone would not be adequate therapy for bacterial pneumonia include infection in neonates, caused most often by other pathogens and the presence of certain clinical features suggesting other pathogens. Also lack of favorable clinical response may be due to several factors other than having selected a drug that is not active against the specific organism. Although ceftriaxone has the safety profile of a cephalosporin, diarrhoea, usually not necessitating discontinuation of the drug, is seen in 20% or more patients. Ceftriaxone has also been rarely associated with sludging in the biliary tract and its use in neonates presents the theoretical possibility of bilirubin displacement. For many paediatric infections including pneumonia a consensus does not exist as to what specific drug should be used initially, and for how long and by what route.

Types of publication: Editorial

Gutman LT

**The use of trimethoprim-sulfamethoxazole in children: a review of adverse reactions and indications.**

*The Pediatric Infectious Disease Journal*, 1984, 3(4):349-357.

The review describes studies, which reveal the incidence of adverse reactions to trimethoprim-sulfamethoxazole (TMP-SMX) in all ages, incidence in children, types of adverse reactions in children, pharmacokinetics of TMP-SMX in children and indications for the administration of TMP-SMX in children.

Publication Types: Review

Jick SS, Jick H, Habakangas JA, Dinan BJ

**Co-trimoxazole toxicity in children.**

*Lancet*, 1984, 2:631.

Publication Types: Letter

To evaluate possible adverse effects of cotrimoxazole we have done a follow up study of 4,828 children under the age of 10 years who received the drug as outpatients between 1979 and 1981. None among the recipients was subsequently admitted to hospital for any blood disorder or leukaemia. We also reviewed

the outpatient records of a subset of 2,622 unselected children. Among the recipients of cotrimoxazole there were 66 (2.5%) in whom an adverse event was attributed to the drug. Of these events, 46 (70%) were rashes and 15 (23%) were episodes of vomiting and/or diarrhoea. The remaining reactions were 1 each of the following: dizziness, headache, swollen lips, blue lips and hands and constipation.

**CONCLUSIONS:** Our follow-up study of 2622 children using cotrimoxazole did not reveal any serious adverse reactions that could be attributed to the drug. In particular, there were no reported blood disorders, nor any hospital admission secondary to drug toxicity. The study provides considerable reassurance that serious adverse reactions to cotrimoxazole in children are uncommon.

Qazi SA, Rehman GN, Khan MA

**Standard management of acute respiratory infections in a children's hospital in Pakistan: impact on antibiotic use and case fatality.**

*Bulletin of the World Health Organization*, 1996, 74(5):501-507.

Acute respiratory infections (ARI) are a leading cause of childhood morbidity and mortality in Pakistan. The National ARI Control Programme was launched in 1989 in order to reduce the mortality attributed to pneumonia, and rationalize the use of drugs in the management of patients with ARI. WHO's standard ARI case management guidelines were adopted to achieve these objectives. The medical staff at the Children's Hospital, Islamabad, were trained in such management in early 1990; further training sessions were conducted when new staff arrived. Data on outpatients were obtained from special ARI abstract registers, which have been maintained in the outpatient department since January 1990. Details on inpatients who were admitted with ARI were obtained from hospital registers. During the period 1989-92, the use of antibiotics in the outpatient department decreased from 54.6% to 22.9% ( $P < 0.0001$ ). The case fatality rate (CFR) in children admitted with ARI fell from 9.9% to 4.9% ( $P < 0.0001$ ), while the overall case fatality rate fell from 8.7% to 6.2%.

**CONCLUSIONS:** Our results from a tertiary health care facility show that standard ARI case management reduced both antibiotic use and expenditure on drugs. Although the ARI case management criteria, which are more sensitive than the conventional diagnostic criteria of auscultation and radiography, led to more admissions, we believe that this strategy contributed to a significant reduction in the ARI case fatality rate.

Rowe AK, Deming MS, Schwartz B, Wasas A, Rolka D, Rolka H, Ndoyo J, Klugman KP

**Antimicrobial resistance of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children in the Central African Republic.**

*The Pediatric Infectious Disease Journal* 2000 May;19(5):438-44

**BACKGROUND:** To assist the Central African Republic (CAR) develop national guidelines for treating children with pneumonia, a survey was conducted to determine antimicrobial resistance rates of nasopharyngeal isolates of *Streptococcus pneumoniae* (SP) and *Haemophilus influenzae* (HI). Secondary purposes of the survey were to identify risk factors associated with carriage of a resistant isolate and to compare the survey methods of including only children with pneumonia vs. including all ill children.

**METHODS:** A cross-sectional survey of 371 ill children was conducted at 2 outpatient clinics in Bangui, CAR. **RESULTS:** In all 272 SP isolates and 73 HI isolates were cultured. SP resistance rates to penicillin, trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline and chloramphenicol were 8.8, 6.3, 42.3 and 9.2%, respectively. All penicillin-resistant SP isolates were intermediately resistant. HI resistance rates to ampicillin, TMP-SMX and chloramphenicol were 1.4, 12.3 and 0%, respectively. The most common SP serotypes/groups were 19, 14, 6 and 1; 49% of HI isolates were type b. History of antimicrobial use in the previous 7 days was the only factor associated with carriage of a resistant isolate. Resistance rates were similar among ill children regardless of whether they had pneumonia.

**CONCLUSIONS:** Resistance rates were low for antimicrobials recommended by the World Health Organization for children with pneumonia. We recommended TMP-SMX as the first line treatment for pneumonia in CAR because of its low cost, ease of dosing and activity against malaria.

Shann F, Linnemann V, Gratten M

**Serum concentrations of penicillin after intramuscular administration of procaine, benzyl, and benethamine penicillin in children with pneumonia.**

*The Journal of Pediatrics* 1987 Feb;110(2):299-302

Serum concentrations of penicillin were measured in 37 children with pneumonia. The mean serum concentration of penicillin was greater than 1.0 microgram/mL for 11 hours after intramuscular administration of 48,000 U/kg benethamine penicillin compound (nine children), for 26 hours after 48,000 U/kg aqueous procaine penicillin (10 children), and for 40 hours after 79,000 U/kg aqueous procaine penicillin (seven children). After intramuscular administration of 35,000 U/kg benzyl penicillin in 11 children, the serum concentration was 13.3 +/- 7.4 micrograms/mL (mean +/- SD) 30 minutes after the injection, and 4.9 +/- 3.2 micrograms/mL after 3 hours.

**CONCLUSIONS:** Our findings lend support to the World Health Organization recommendation that children with mild pneumonia in developing countries be given daily intramuscular injections of 50,000 U/kg aqueous procaine penicillin.

Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B

**Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxycillin for pneumonia among children in Pakistan: randomised controlled trial.**

Pakistan Co-trimoxazole Study Group. *Lancet*, 1998 Jul 25, 352(9124):270-4

**BACKGROUND:** Co-trimoxazole is widely used in treatment of paediatric pneumonia in developing countries, but drug resistance may decrease its effectiveness. We studied the effectiveness of co-trimoxazole compared with that of amoxycillin in pneumonia therapy, and assessed the clinical impact of co-trimoxazole resistance. **METHODS:** We recruited 595 children, aged 2-59 months, with non-severe or severe pneumonia (WHO criteria) diagnosed in the outpatient wards of two urban Pakistan hospitals. Patients were randomly assigned on a 2:1 basis co-trimoxazole (n=398) or amoxycillin (n=197) in standard WHO doses and dosing schedules, and were monitored in study wards. The primary outcome was inpatient therapy failure (clinical criteria) or clinical evidence of pneumonia at outpatient follow-up examination. **FINDINGS:** There were 92 (23%) therapy failures in the co-trimoxazole group and 30 (15%) in the amoxycillin group (p=0.03)-26 (13%) versus 12 (12%) among children with non-severe pneumonia (p=0.856) and 66 (33%) versus 18 (18%) among those with severe pneumonia (p=0.009). For patients with severe pneumonia, age under 1 year (p=0.056) and positive chest radiographs (p=0.005) also predicted therapy failure. There was no significant association between antimicrobial minimum inhibitory concentration and outcome among bacteraemic children treated with co-trimoxazole.

**INTERPRETATION:** Co-trimoxazole provided effective therapy in non-severe pneumonia. For severe, life-threatening pneumonia, however, co-trimoxazole is less likely than amoxycillin to be effective.

Publication Types: Clinical trial, Multicenter study Randomised controlled trial

Turnidge JD

**A reappraisal of co-trimoxazole.**

*Medical Journal of Australia*, 1988, 148(6): 296-305.

This study was performed to determine which clinical findings could best predict the outcome or need for antibiotics in lower respiratory tract infections and which signs could most reliably be elicited by primary health workers. Prospectively, 200 children with cough brought to the Goroka Hospital outpatient department, Goroka, Papua New Guinea, 100 age-matched controls without cough, and ~ 50 children admitted to the hospital with pneumonia, were studied. Of the 200 outpatients, 106 (53%) were under 12 months of age and of the 50 inpatients, 36 (72%) were under 12 months of age. For children under 12 months of age, the mean respiratory rate for those with crepitations was 63 and for those without crepitations 45. For children aged 12 months or more, those with crepitations had a mean of 54 and those without crepitations 37. For all children, the sensitivity for the presence of crepitations was higher for a respiratory rate >40/min (90%) than for a respiratory rate >50/min (72%), while an age-specific cut-off (respiratory rate > 50/min for children under 12 months of age and > 40 /min for children 12 months or older) had an intermediate sensitivity (78%). The specificities for these cut-offs were 59%, 81%, and 73%, respectively. In both age groups, the children with cough but no crepitations had a similar respiratory rate

to those with no cough. Although breathlessness, as reported by the mother, identified almost two-thirds of children with crepitations, the combination of breathlessness with respiratory rate performed no better than respiratory rate alone. Chest indrawing was found in 4 (2%) of the children brought to the outpatient department with cough. Of the children admitted to hospital, all had chest indrawing and crepitations (chest indrawing was used as a criterion for admission), 96% had a respiratory rate >40/min, 90% were breathless according to the mother, 86% had a respiratory rate >50/min, and 60% had a temperature over 37.5\* C.

The authors noted that the choice of a respiratory rate cut-off involves trade-offs: a lower rate of 40/min detects almost all children with crepitations but significantly overtreats children who do not need antibiotics, while a higher rate of 50/min results in fewer incorrect treatments overall but misses a higher proportion of children who might benefit from antibiotics. The choice of an age-specific cut-off, as above, produces an intermediate result in this setting.

**CONCLUSIONS:** The respiratory rate can be used to decide which children presenting with a cough should be treated with antibiotics.

Published erratum appears in Med J Aust 1989 Sep 18;151(6):355

Publication Types: Review, Review, tutorial

## **Treatment – chloramphenicol**

Feder HM Jr, Osier C, Maderazo EG

**Chloramphenicol: A Review of Its Use in Clinical Practice.**

*Reviews of Infectious Diseases*, 1981, 3:3:479-491.

Chloramphenicol has certain notable characteristics: it penetrates reliably into the central nervous system; it is usually bacteriostatic, but is bactericidal for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*; it is metabolized in the liver, and levels of drug in serum need to be monitored in patients with liver disease and in neonates. Potential toxicity limits the use of this drug. It has been estimated that death from aplastic anaemia occurs in one of 24,500-40,800 courses of treatment. The incidence of aplastic anaemia after parenteral therapy is unknown; however, only a few cases have been reported. The gray baby syndrome occurred in premature and newborn infants receiving high or unmodified doses of chloramphenicol. This condition can be avoided by reduction of dosage and by monitoring levels of drug in the serum of these infants. The most common toxicity is a reversible, dose-related bone marrow suppression, which is identified by serial monitoring of reticulocyte and complete blood cell counts. Many of the indications for use of this drug are still controversial because studies comparing the toxicity and efficacy of chloramphenicol and of alternative antibiotics have not been done.

Publication Types: Review

Feder HM Jr.

**Current Concepts in Therapy. Chloramphenicol: What We Have Learned in the Last Decade.**

*Southern Medical Journal*, 1986, 79:9:1129-1134.

Chloramphenicol is a unique antibiotic. The kinetics and efficacy of the oral and intravenous preparations are comparable. Chloramphenicol is usually bacteriostatic but is bactericidal against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, and chloramphenicol's clinical efficacy against these meningeal pathogens is well established. Chloramphenicol can be used to treat serious paediatric infections when *Haemophilus influenzae* is a likely pathogen, as well as typhoid fever, anaerobic infections, bacterial meningitis in patients allergic to penicillin, brain abscesses, and rickettsial infections. The use of chloramphenicol is limited because of its toxicity. Aplastic anaemia is very rare but can occur after either oral or intravenous administration. The gray syndrome can be eliminated and marrow suppression minimized by using chloramphenicol at the recommended doses and monitoring levels. During the last decade the increased use of chloramphenicol has not resulted in increased resistance or in frequent reports of toxicity. Thus, chloramphenicol remains an important inpatient antibiotic that can be invaluable for treating certain life-threatening infections.

Publication Types: Review

Kumana CR, Li KY, Chau PY

**Worldwide Variation in Chloramphenicol Utilization: Should It Cause Concern?**

*Journal of Clinical Pharmacology*, 1988, 28:1071-1075

Per capita sales of chloramphenicol in Hong Kong (which presumably reflect adult and paediatric consumption in the community) are between about 11 to 442 fold greater than in several western countries and Australia. Despite such relatively excessive exposure to a potentially marrow-damaging drug, the certified death rate from aplastic anaemia in Hong Kong was only 0.4 per 1000 deaths compared with 1.0 per 1000 in England and Wales. Nor was there any other evidence to indicate that Hong Kong residents suffered an excessive incidence of aplastic anaemia. Wherever chloramphenicol use is widespread, prospective investigations should be undertaken in the local population to evaluate the alleged high risks of producing aplastic anaemia.

Shann F, Linnemann V, Mackenzie A, Barker J, Gratten M, Crinis N

**Absorption of chloramphenicol sodium succinate after intramuscular administration in children.**

*New England Journal of Medicine*, 1985, 313(7):410-414.

Because it is thought that chloramphenicol is poorly absorbed after intramuscular administration, we compared blood levels of chloramphenicol after intramuscular administration with those after intravenous administration in children with a variety of diagnoses. Fifty-seven children were studied on 62 occasions while they were receiving chloramphenicol sodium succinate (25 mg of chloramphenicol per kilogram of body weight) intramuscularly every six hours. The peak level of chloramphenicol was 19.5 +/- 5.99 micrograms per milliliter (mean +/- S.D.) in 11 children after the first dose and 31.4 +/- 12.99 micrograms per milliliter in 51 children after two or more doses. The lowest peak level after intramuscular administration was 13 micrograms per milliliter, which is in the therapeutic range of 10 to 30 micrograms per milliliter. Thirteen children were studied on 17 occasions while they were receiving chloramphenicol sodium succinate (25 mg of chloramphenicol per kilogram) intravenously every six hours. The peak level of chloramphenicol was 19.4 +/- 6.37 micrograms per milliliter in eight children after the first dose and 28.2 +/- 11.09 micrograms per milliliter in nine children after two or more doses. The area under the serum level curve was not significantly different after intramuscular and intravenous administration. We conclude that chloramphenicol sodium succinate is well absorbed after intramuscular administration. This route is cheaper, it demands less staff time, and it does not carry the risks of sepsis and overhydration associated with intravenous therapy.

Shann F, Barker J, Poore P

**Chloramphenicol alone versus chloramphenicol plus penicillin for severe pneumonia in children.**

*Lancet* 1985 Sep 28;2(8457):684-6

748 children with severe pneumonia in three hospitals in Papua New Guinea were randomised to receive intramuscular injections of either chloramphenicol alone or chloramphenicol plus penicillin. Sequential analysis showed no difference between the two treatments. 48 (13%) of the 377 children in the chloramphenicol alone group died, and 3 (0.8%) were changed to different treatment. 62 (17%) of the 371 children in the chloramphenicol-plus-penicillin group died, and 6 (1.6%) were changed to different treatment. The difference in failure rates (death or withdrawal for change of treatment) was 4.8% +/- 5.2% (+/- 95% confidence limits). In children with severe pneumonia, treatment with chloramphenicol alone is as effective as treatment with chloramphenicol plus penicillin.

Publication Types: Clinical trial, Randomised controlled trial



Vincent PC

**Drug-Induced Aplastic Anaemia and Agranulocytosis. Incidence and Mechanisms.**

*Drugs*, 1986, 31:52-63.

Aplastic anaemia and agranulocytosis are uncommon but serious adverse effects of drug therapy. They result from an adverse interaction between the drug and the haemopoietic pathway in certain susceptible individuals. The nature of this idiosyncratic interaction differs for different drugs and possibly for different individuals. In some instances an immune mechanism might be implicated, in others the patient's cells might carry a genetic susceptibility to the drug, while yet other patients might metabolise the drug abnormally. The idiosyncratic nature of these effects has made their investigation difficult, but experimental studies have allowed some progress in our understanding. In a practical sense, however, responsibility for preventing these problems will remain with clinicians, who should be alert to the risks and revise their prescribing habits accordingly.

## **Treatment - oxygen**

Dobson M, Peel D, Khallaf N

**Field trial of oxygen concentrators in upper Egypt.**

*Lancet* 1996 Jun 8;347(9015):1597-9

Technical problems in developing countries often require more than just technological solutions. Many small hospitals in rural areas are without a reliable oxygen supply; small oxygen concentrators offer a solution, but simply sending out machines is ineffective. This account details the setting up and first year's operation of a project to test oxygen concentrations in a developing country. A co-ordinated strategy has been developed to include machines, supplies, education, training, and feedback. Initial results are encouraging, and support the idea that suitably installed and maintained concentrations can have a valuable role in bringing oxygen therapy to patients and hospitals in countries which have so far been denied it.

Kumar RM, Kabra SK, Singh M

**Efficacy and acceptability of different modes of oxygen administration in children: implications for a community hospital.**

*Journal of Tropical Pediatrics* 1997 Feb;43(1):47-9

Eighty under-five children admitted in the paediatric ward with acute respiratory distress requiring oxygen inhalation were prospectively studied. Oxygen was administered to all the children by head box, face mask, nasopharyngeal catheter, and twin-holed prenasal catheter in a predetermined sequence. Oxygen was delivered at a flow rate of 4 l/min in the head box and by face mask and at a rate of 1 l/min for nasopharyngeal catheter and twin-holed prenasal catheter. There was a significant rise in  $paO_2$  and  $SaO_2$  values with all the oxygen delivery methods. The number of children who achieved  $paO_2$  of  $> 90$  mmHg with oxygen delivered by head box was 53 (69 per cent), with face mask 37 (57 per cent), with nasopharyngeal catheter 13 (26 per cent), and with twin-holed prenasal catheter 18 (25 per cent). In view of high acceptability of twin-holed prenasal catheter, a further pilot study involving 10 children was carried out to compare the efficacy of head box and twin-holed prenasal catheter at an identical oxygen flow rate of 4 l/min. The number of children achieving  $paO_2$  of  $> 90$  mmHg were comparable, i.e. seven (70 per cent) and eight (80 per cent) when the oxygen was delivered by head box and twin-holed prenasal catheter, respectively.

**CONCLUSIONS:** Both, head box and twin-holed prenasal catheter are equally effective, acceptable and safe methods for administration of oxygen to children with acute respiratory disorders. In view of the cost-effectiveness, and easy availability and affordability of twin-holed prenasal catheter, it should be popularized in the small hospitals in the community, while head box should be reserved for use in the referral hospitals.

Muhe L, Degefu H, Worku B, Oljira B, Mulholland EK

**Oxygen administration to hypoxic children in Ethiopia: a randomised controlled study comparing complications in the use of nasal prongs with nasopharyngeal catheters.**

*Annals of Tropical Paediatrics* 1997 Sep;17(3):273-81

Oxygen administration is one of the most important therapeutic interventions for a child with severe acute lower respiratory tract infection (ALRI). Inexpensive and efficient methods of oxygen administration are highly desirable in hospitals in developing countries. The objectives of this study were to compare the frequency and nature of complications when nasopharyngeal catheters or nasal prongs are used to deliver oxygen. One hundred and twenty-one children between the ages of 2 weeks and 5 years with hypoxia due to ALRI were randomised to receive oxygen via a catheter (61 children) or via nasal prongs (60 children).

The two groups were similar in terms of diagnoses, clinical severity, oxygen saturation on admission and case fatality rates. There was no difference in the incidence of hypoxaemic episodes between the two groups. The oxygen flow rates required on the day of admission for adequate oxygenation ( $\text{SaO}_2 > 90\%$ ) ranged from 0.8 litres per minute to 1.2 litres per minute. The required oxygen flow rate decreased during the course of treatment. Mucus production was more of a problem in the catheter group, and nasal blockage, intolerance of the method of oxygen administration and nursing effort were generally higher amongst the catheter group, but none of these differences was significant. Ulceration or bleeding of the nose was significantly more common in the catheter group (19.7% vs 6.7%,  $p < 0.05$ ). Abdominal distension and nasal perforation were not seen in either group. **CONCLUSIONS:** This study suggests that nasal prongs are safer, more comfortable and require less nursing expertise than nasopharyngeal catheters for administration of oxygen to children.

Publication Types: Clinical trial, Randomised controlled trial

Weber MW, Palmer A, Jaffar S, Mulholland EK

**Humidification of oxygen with unheated humidifiers in tropical climates.**

*Paediatric Pulmonology* 1996 Aug;22(2):125-8

In developing countries, oxygen therapy in hospitals is frequently humidified with unheated bubble-through humidifiers. We assessed the efficacy of humidification under such circumstances. The water temperature in the humidifier and the ambient air temperature were measured and compared to the oxygen flow rate. It was calculated that oxygen was cooled in the humidifier by 6.12 degrees C (95% CI: 5.88; 6.35) per litre of flow for flow rates up to 2 l/min. Using the average temperatures on the hospital ward in January and August, and the WHO-recommended flow rates of 0.5 l/min and 1 l/min, the relative humidity of the oxygen delivered to a child was estimated to be between 34% and 56%. We conclude that unheated bubble-through humidifiers achieve low humidity in oxygen in tropical climates. Some of the complications associated with the use of nasopharyngeal catheters for the delivery of oxygen might be explained by this, as oxygen of low humidity and temperature is delivered directly into the posterior nasopharynx.

Weber MW, Palmer A, Oparaugo A, Mulholland EK

**Comparison of nasal prongs and nasopharyngeal catheter for the delivery of oxygen in children with hypoxemia because of a lower respiratory tract infection.**

*Journal of Pediatrics* 1995 Sep;127(3):378-83

**OBJECTIVE:** To determine the best method of oxygen delivery for children in developing countries who have hypoxemia caused by acute lower respiratory tract infection. **METHODS:** One hundred eighteen children between 7 days and 5 years of age with a lower respiratory tract infection and arterial haemoglobin oxygen saturation ( $\text{Sao}_2$ ) less than 90% were randomly selected to receive oxygen by nasopharyngeal (NP) catheter ( $n = 56$ ) or nasal prongs ( $n = 62$ ). A crossover study to determine the flow rate necessary to achieve an  $\text{Sao}_2$  of 95% was performed in 60 children. **RESULTS:** One hundred twelve children could be oxygenated by the allocated method; in six oxygenation was poor with either method. The mean duration of therapy was 87.5 hours for the prongs and 94.9 hours for the NP catheter (not significant). The median oxygen consumption was 2142 L for prongs and 1692 L for the NP catheter (not significant). In the crossover study the prongs needed, on average, 26% higher oxygen flow rates than the NP catheter to obtain an  $\text{Sao}_2$  of 95% ( $p = 0.003$ ). Complete nasal obstruction was observed in 24 of the children (44%)

in the NP catheter group and in 8 (13%) in the prongs group ( $p < 0.001$ ). Eighteen children died, 11 with NP catheter and 7 with prongs (not significant).

**CONCLUSIONS:** Because nasal prongs are less prone to complications, and oxygenation in children is equally effective, they are a more appropriate method than the NP catheter for oxygen delivery to children in developing countries with acute lower respiratory tract infections.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *J Pediatr* 1995 Sep;127(3):427-8; *J Pediatr* 1996 Jul;129(1):185; discussion 186

## Treatment - wheezing

Kellner JD, Ohlsson A, Gadomski AM, Wang EE

### **Efficacy of bronchodilator therapy in bronchiolitis. A meta-analysis.**

*Archives of Paediatric and Adolescent Medicine* 1996 Nov;150(11):1166-72

**OBJECTIVE:** To determine if bronchodilators are efficacious in treating bronchiolitis. **DATA SOURCES:** A search of bibliographic databases (MEDLINE, Excerpta Medica, and Reference Update) for bronchiolitis and albuterol or ipratropium bromide, or adrenergic agents or bronchodilator agents. Reference lists were also used. **STUDY SELECTION:** Randomised, placebo-controlled trials of bronchodilator treatment in bronchiolitis were selected by 2 investigators. Fifteen of 89 identified publications met the selection criteria. **DATA EXTRACTION:** Investigators independently abstracted data for 3 outcomes: clinical score, oxygen saturation, and hospitalisation. Clinical score was measured as a dichotomous variable (score +/- improved) or continuous variable (average score). **DATA SYNTHESIS:** For primary analysis, data were pooled from 8 trials of children with first-time wheezing. The effect size for average score was -0.32 (95% confidence interval [CI], -0.54 to -0.11;  $P < .01$ ), favoring treatment; the relative risk for score +/- improved was 0.76 (95% CI, 0.60 to 0.95;  $P = .02$ ), favoring treatment. Bronchodilators had no effect on hospitalisation (relative risk, 0.85; 95% CI, 0.47 to 1.53;  $P = .58$ ), but co-interventions may have been administered prior to this outcome. The results for oxygen saturation were too varied to allow pooling of the results. Secondary analyses were performed on 4 outpatient trials of children with first-time wheezing, 7 trials in which only nebulized beta-agonists were used, and on all 15 trials identified. The results were similar, but the data varied more.

**CONCLUSIONS:** Bronchodilators produce modest short-term improvement in clinical features of mild or moderately severe bronchiolitis.

Publication Types: Clinical trial, Meta-analysis, Randomised controlled trial

Comment in: *Arch Pediatr Adolesc Med* 1996 Nov;150(11):1120-1; *Arch Pediatr Adolesc Med* 1999 Apr;153(4):430

Von Mutius E

### **Presentation of new GINA guidelines for paediatrics. The Global Initiative on Asthma.**

*Clinical and Experimental Allergy* 2000 Jun;30 Suppl 1:6-10.

The Global Initiative on Asthma (GINA) has provided guidelines for the management of children with asthma. For a step-wise approach to therapy, asthma is divided into four categories based on severity of symptoms: intermittent, mild persistent, moderate persistent, and severe persistent asthma. Long-term preventive therapy is distinguished from quick relief therapy in each group. Although these guidelines are clear and simple there have been few studies on asthma therapy for infants. Moreover, the existence of different wheezing phenotypes with varying pathogenic mechanisms hampers the interpretation of these studies. Transient wheezers have stopped wheezing by the age of 3 years and there is no relationship to atopy or a family history of asthma. In contrast, persistent wheezers continue to wheeze from the first year of life throughout school-age and have a high risk of atopy. Although they have normal lung function at birth, persistent wheezers develop significant decrements in lung function by the age of 6 years. Whether these impairments are amenable to prevention by early initiation of anti-inflammatory therapy remains to be seen. At present, there are no disease markers to identify the different wheezing phenotypes in infancy, although eosinophil counts and measurements of eosinophil cationic protein in serum may prove to be helpful in distinguishing these conditions.

## Prevention

Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK

### **Zinc Supplementation Reduces the Incidence of Acute Lower Respiratory Infections in Infants and preschool Children: A Double-blind Controlled Trial.**

*Pediatrics*, 1998, 102(1): 1-5.

**BACKGROUND:** Increased acute lower respiratory infection incidence, severity, and mortality are associated with malnutrition, and reduced immunological competence may be a mechanism for this association. Because zinc deficiency results in impaired immunocompetence and zinc supplementation improves immune status, we hypothesized that zinc deficiency is associated with increased incidence and severity of acute lower respiratory infection. **METHODS:** We evaluated the effect of daily supplementation with 10 mg of elemental zinc on the incidence and prevalence of acute lower respiratory infection in a double-blind, randomised, controlled trial in 609 children (zinc, n = 298; control, n = 311) 6 to 35 months of age. Supplementation and morbidity surveillance were done for 6 months. **RESULTS:** After 120 days of supplementation, the percentage of children with plasma zinc concentrations <60 microg/dL decreased from 35.6% to 11.6% in the zinc group, whereas in the control group it increased from 36.8% to 43.6%. Zinc-supplemented children had 0.19 acute lower respiratory infection episodes/child/year compared with 0.35 episodes/child/year in the control children. After correction for correlation of data using generalized estimating equation regression methods, there was a reduction of 45% (95% confidence interval, 10% to 67%) in the incidence of acute lower respiratory infections in zinc-supplemented children.

**CONCLUSIONS:** A dietary zinc supplement resulted in a significant reduction in respiratory morbidity in preschool children. These findings suggest that interventions to improve zinc intake will improve the health and survival of children in developing countries.

Publication Types: Clinical trial, Randomised controlled trial

Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A

### **Prevention of diarrhoea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomised controlled trials.**

Zinc Investigators' Collaborative Group. *Journal of Pediatrics* 1999 Dec;135(6):689-97

**OBJECTIVES:** This study assessed the effects of zinc supplementation in the prevention of diarrhoea and pneumonia with the use of a pooled analysis of randomised controlled trials in children in developing countries. **STUDY DESIGN:** Trials included were those that provided oral supplements containing at least one half of the United States Recommended Daily Allowance (RDA) of zinc in children <5 years old and evaluated the prevention of serious infectious morbidity through household visits. Analysis included 7 "continuous" trials providing 1 to 2 RDA of elemental zinc 5 to 7 times per week throughout the period of morbidity surveillance and 3 "short-course" trials providing 2 to 4 RDA daily for 2 weeks followed by 2 to 3 months of morbidity surveillance. The effects on diarrhoea and pneumonia were analyzed overall and in subgroups defined by age, baseline plasma zinc concentration, nutritional status, and sex. The analysis used random effects hierarchical models to calculate odds ratios (OR) and 95% CIs. **RESULTS:** For the zinc-supplemented children compared with the control group in the continuous trials, the pooled ORs for diarrhoeal incidence and prevalence were 0.82 (95% CI 0.72 to 0.93) and 0.75 (95% CI 0.63 to 0.88), respectively. Zinc-supplemented children had an OR of 0.59 (95% CI 0.41 to 0.83) for pneumonia. No significant differences were seen in the effects of the zinc supplement between the subgroups examined for either diarrhoea or pneumonia. In the short-course trials the OR for the effects of zinc on diarrhoeal incidence (OR 0.89, 95% CI 0.62 to 1.28) and prevalence (OR 0.66, 95% CI 0.52 to 0.83) and pneumonia incidence (OR 0.74, 95% CI 0.40 to 1.37) were similar to those in the continuous trials.

**CONCLUSIONS:** Zinc supplementation in children in developing countries is associated with substantial reductions in the rates of diarrhoea and pneumonia, the 2 leading causes of death in these settings.

Publication Types: Meta-analysis

Comment in: *J Pediatr* 1999 Dec;135(6):657-61; *J Pediatr* 1999 Dec;135(6):661-4

## **Documents and publications**

Maher D, Chaulet P, Spinaci S, Harries A

### ***Treatment of Tuberculosis. Guidelines for National Programmes***

Second edition WHO, Geneva 1997, 77 pages [E]

WHO/TB/97.220 Rev 1

Sw.fr. 12.-/US \$10.80; in developing countries: Sw.fr. 8.40

Order no. 1930109

Provides expert practical guidelines for the treatment and control of tuberculosis within the context of national TB programmes. Now in its second edition, the manual has been revised to reflect considerable experience, since 1993, in the use of WHO recommended control strategies. These advocate standardized short-course chemotherapy regimens, applied under proper case management conditions, and make the identification and cure of smear-positive pulmonary TB the first priority of any national programme. With the effectiveness of these strategies now firmly established, the manual gives programme managers, policy-makers, and clinicians a clear - and proven - approach to TB control that relies on precise case definitions, distinct treatment categories, and standardized treatment regimens using essential anti-TB drugs. Since 95% of the global TB burden occurs in low- and middle-income countries, issues of cost-effectiveness are also repeatedly addressed. The manual has eight concise chapters. Background information is provided in the first, which presents basic facts about the global TB epidemic and explains how control can be achieved through universal application of the WHO recommended DOTS (directly-observed treatment, short course) strategy. Further details about the DOTS strategy are presented in chapter two, which elaborates a framework for TB control and describes the components, targets, and policies of effective national programmes. Against this background, the main part of the manual provides a didactic guide to the diagnosis and clinical management of cases. Chapter three, on case definitions, explains how to diagnose TB, define the type of case, and then match the case definition to one of four treatment categories. Standardized treatment regimens are covered in the next chapter, which describes the essential anti-TB drugs, presents the rationale for standardized treatment regimens, and discusses recommended and alternative regimens for each of the four treatment categories. Treatment regimens in special situations, such as pregnancy, lactation, and liver or renal disorders, are also described. Chapter five explains how to monitor and record the response to treatment, especially in sputum smear-positive TB patients, and how to monitor and manage drug-induced toxicity. The vital importance of treatment adherence is addressed in chapter six, which includes practical examples of ways to ensure direct observation of treatment under different local circumstances. The remaining chapters offer guidance for the treatment of HIV-infected TB patients and explain what the managers of national programmes can do to ensure both the regular supply of essential drugs and their appropriate use. The important issues of drug quality and the bioavailability of fixed-dose drug combinations are also considered.

World Health Organization

### ***Cough and Cold Remedies in the Treatment of Acute Respiratory Infections in Young Children.***

Geneva, World Health Organization, 1998, 38 p. (draft document WHO/CHD).

The document reviews the efficacy and safety of cough and cold remedies in children under 5 years of age suffering from acute respiratory infections. It gives an overview of the pathophysiology of the common cold, curative or prophylactic and symptomatic treatment of the common cold. Discussed are centrally acting cough suppressants, antihistamines, soothing remedies, remedies to clear thick sputum, remedies to relief nasal congestion and other cold symptoms, remedies to relief sore throat, use of combination drugs, and traditional cough and cold remedies. The paper is concluded by the recommendations for the management of a simple cough or cold or sore throat.

World Health Organization

***Bronchodilators and other medications for the treatment of wheeze-associated illnesses in young children.***

Geneva, World Health Organization, 1993, 37 p. (unpublished document WHO/ARI/93.29; available on request from the Division of Child Health and Development (CHD)).

[http://whqlibdoc.who.int/hq/1993/WHO\\_ARI\\_93.29.pdf](http://whqlibdoc.who.int/hq/1993/WHO_ARI_93.29.pdf)

The WHO Programme for the Control of Acute Respiratory Infections (ARI) has focused on the case management of pneumonia in an attempt to reduce mortality from acute lower respiratory infections. The WHO ARI Programme also recognizes that the clinical presentation of wheeze has considerable overlap with that of pneumonia. There is a need to identify children with pneumonia, to ensure that they will receive antibiotic therapy and to identify children with wheeze whose drug treatment will include a bronchodilator. This background document deals with common causes of wheeze, with the pathogenesis and pathophysiology of asthma and bronchiolitis and with the drugs that are available for the treatment of wheeze. Presentation and dosage of bronchodilators and other drugs for the treatment of wheeze are summarized in an annex.

World Health Organization

***Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities.***

Geneva, World Health Organization, 1991, 24 p. (unpublished document WHO/ARI/91.20; available on request from the Division of Child Health and Development (CHD)).

[http://whqlibdoc.who.int/hq/1991/WHO\\_ARI\\_91.20.pdf](http://whqlibdoc.who.int/hq/1991/WHO_ARI_91.20.pdf)

The document presents an overview of etiological studies of pneumonia and the efficacy of its antimicrobial treatment. It describes the effectiveness of the standard case management of acute respiratory infections in seven WHO sponsored intervention studies. These studies had a substantial impact on pneumonia-specific mortality rates in children, which was also reflected in a reduction of overall childhood mortality. In separate sections the document describes the rationale for empirical treatment of pneumonia, classification of acute respiratory infections, standard plan for case management and action at household level.

World Health Organization

***Antibiotics in the treatment of acute respiratory infections in young children.***

Geneva, World Health Organization, 1990, 22 p. (unpublished document WHO/ARI/90.10; available on request from the Division of Child Health and Development (CHD)).

[http://whqlibdoc.who.int/hq/1990/WHO\\_ARI\\_90.10.pdf](http://whqlibdoc.who.int/hq/1990/WHO_ARI_90.10.pdf)

The WHO ARI Programme recommends four first-line antibiotics for the outpatient treatment of pneumonia in children 2 months up to 5 years of age: cotrimoxazole, amoxycillin, ampicillin, and procain penicillin. Benzathine penicillin and phenoxymethylpenicillin are not recommended for the treatment of pneumonia. A further group of antibiotics are recommended for the initial treatment of severe or very severe pneumonia: benzylpenicillin, chloramphenicol, oxacillin or (flu)cloxacillin, and gentamicin. The antimicrobial activity, pharmacology, mode of administration, dosage, toxicity, and clinical use of these antibiotics in the treatment of ARI are considered in detail in this document. Also included is erythromycin because it is specifically indicated in the treatment of pertussis. The spectrum of activity of each antibiotic and the recommended dosage schedules are summarized and presented in annexes.



## 4. DIARRHOEA

### Articles

#### Importance

Bern C, Martines J, de Zoysa I, Glass RI

**The magnitude of the global problem of diarrhoeal disease: a ten-year update.**

*Bulletin of the World Health Organization* 1992;70(6):705-14

In order to update global estimates of diarrhoeal morbidity and mortality in developing countries, we carried out a review of articles published from 1980 to the present and calculated median estimates for the incidence of diarrhoea and diarrhoeal mortality among under-5-year-olds. The incidence of diarrhoea obtained (2.6 episodes per child per year) was virtually the same as that estimated by Snyder & Merson in 1982, while the global mortality estimate was lower (3.3 million deaths per year; range, 1.5-5.1 million). The mortality estimate is based on a small number of active surveillance and prospective studies, and thus associated with a large degree of uncertainty, reflecting the weakness of the global database. However, many surveys reporting reductions in mortality in several locations are consistent with a decreased estimate for mortality. More accurate execution of WHO survey methods, including population-based sampling in representative locations, and repeat surveys every 5 years, are needed to monitor the progress of diarrhoeal disease control programmes and trends in diarrhoeal morbidity and mortality over time.

Publication Types: Review, Review, tutorial

Bhan MK, Bhandari N, Bhatnagar S, Bahl R

**Epidemiology & management of persistent diarrhoea in children of developing countries.**

*Indian Journal of Medical Research* 1996 Jul;104:103-14

Diarrhoea that begins acutely but lasts longer than two weeks is defined to be persistent. Revised estimates in developing countries including India showed that acute diarrhoea accounts for 35 per cent, dysentery 20 per cent and non-dysenteric persistent diarrhoea (PD) for 45 per cent of total diarrhoeal deaths. PD also often changes marginal malnutrition to more severe forms. Factors that increase the risk of acute diarrhoea becoming persistent have been identified in India and other developing countries. These include antecedent malnutrition, micronutrient deficiency particularly for zinc and vitamin A, transient impairment in cell mediated immunity, infection with entero aggregative *Escherichia coli* and *cryptosporidium*, sequential infection with different pathogens and lack of exclusive breast feeding during the initial four months of life particularly use of bovine milk. Several issues regarding the management of persistent diarrhoea in hospitalised children in India have been resolved. Diets providing modest amounts of milk mixed with cereals are well tolerated. In those who fail on such diets providing carbohydrate as a mixture of cereals and glucose or sucrose hasten recovery. The role of antimicrobial agents and individual micronutrients in PD is currently being investigated. A management algorithm appropriate for India and other developing countries has been developed and found to substantially reduce case fatality in hospital settings to about 2-3 per cent. Recent epidemiological and clinical research related to persistent diarrhoea is also reviewed.

Publication Types: Review, Review, tutorial



Black RE

**Persistent diarrhoea in children in developing countries.**

*The Pediatric Infectious Disease Journal*, 1993, 12:751-761.

A WHO meeting in 1987 recommended that persistent diarrhoea be operationally defined as an episode that begins acutely and lasts for at least 14 days. Recent studies largely adopted this definition. Among 8 studies conducted in 5 countries in Asia and Latin America 3 to 23 % of all episodes of diarrhoea persisted for longer than 2 weeks. Information from 4 countries (India, Bangladesh, Brazil and Senegal) indicates that 45% diarrhoea-associated deaths in these studies were associated with persistent nondysenteric diarrhoea (45%) and 20% with dysentery of any duration. The studies available to date seem to lead to the conclusion that acute and persistent diarrhoea can each be initiated by any of the wide array of enteric pathogens, even if some organisms, such as enteroadherent *E. coli* or cryptosporidium have an association with persistent diarrhoea in some settings. The frequency of enteric infections and the likelihood of simultaneous or sequential infections in a short time period may all contribute to the incidence of persistent diarrhoea. Nutritional status, prior illness, immunocompetence and specific management of acute diarrhoea are discussed as risk factors for persistent diarrhoea. Mucosal injury, small bowel bacterial overgrowth are discussed as possible factors in the pathogenesis of persistent diarrhoea. The role of antibiotics and other drugs, fluids and dietary management of persistent diarrhoea is described and selected research topics recommended.

Publication Types: Review, Review, tutorial

Hambidge KM

**Zinc and diarrhoea.**

*Acta Paediatrica* Suppl 1992 Sep;381:82-6

Malnutrition is a major factor in the aetiology, management and prognosis of persistent diarrhoea in young children. Apart from inadequate energy intake, deficiencies of several specific nutrients have been implicated. Zinc is a micronutrient that appears to be of special interest, at least in some communities. Zinc deficiency has been documented in otherwise normal children. The risk of deficiency, however, is enhanced by diarrhoea which is associated with variable but sometimes gross increases in zinc losses in the feces. These losses could contribute to a vicious circle, as there is now evidence that mild as well as severe zinc deficiency states can contribute to the duration and severity of diarrhoeal disease. During rehabilitation, impaired zinc nutriture could be responsible for slow growth, especially if the rehabilitation diet is high in phytate, a recognized inhibitor of zinc absorption. Research should be directed to a better understanding of zinc metabolism and homeostasis during diarrhoea disease, to the consequences of zinc deficiency and to the benefits to be derived from zinc supplementation programs.

Publication Types: Review, Review, tutorial

Koo D, Aragon A, Moscoso V, Gudiel M, Bietti L, Carrillo N, Chojoj J, Gordillo B, Cano F, Cameron DN, Wells JG, Bean NH, Tauxe RV

**Epidemic cholera in Guatemala, 1993: transmission of a newly introduced epidemic strain by street vendors.**

*Epidemiology and Infection*, 1996, 116:121-126.

Epidemic cholera reached Guatemala in July 1991. By mid-1993, Guatemala ranked third in the hemisphere in reported cases of cholera. We conducted a case-control study with two age-, sex-, and neighbourhood-matched controls per patient in periurban Guatemala City. Twenty-six patients hospitalised for cholera and 52 controls were enrolled. Seven (47%) of 15 stool cultures obtained after admission yielded toxigenic *Vibrio cholerae* O1. All seven were resistant to furazolidone, sulfisoxazole, and streptomycin, and differed substantially by pulsed-field gel electrophoresis from the Latin American epidemic strain dominant in the hemisphere since 1991. In univariate analysis, illness was associated with consumption of left-over rice (odds ratio [OR] = 7.0, 95% confidence interval [CI] = 1.4-36), flavored ices (-helados) (OR = 3.6, CI = 1.1 - 12), and street-vended non-carbonated beverages (OR = 3.8, CI = 1.2-12) and food items (OR = 11.0, CI = 2.3-54). Street-vended food items remained significantly associated with illness in multivariate analysis (OR = 6.5, CI = 1.4-31). Illness was not associated with drinking municipal

tap water. Maintaining water safety is important, but slowing the epidemic in Guatemala City and elsewhere may also require improvement in street vendor food handling and hygiene.

## Treatment and prevention

Bhan MK, Bhandari N, Bhatnagar S, Bahl R

### **Epidemiology & management of persistent diarrhoea in children of developing countries.**

*Indian Journal of Medical Research* 1996 Jul;104:103-14

(See this chapter section Importance)

Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A

### **Prevention of diarrhoea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomised controlled trials.**

Zinc Investigators' Collaborative Group. *Journal of Pediatrics* 1999 Dec;135(6):689-97

(See chapter Cough or difficult breathing)

Black RE

### **Persistent diarrhoea in children in developing countries.**

*The Pediatric Infectious Disease Journal*, 1993, 12:751-761.

(See this chapter, section Importance)

International Working Group on Persistent Diarrhoea

### **Evaluation of an algorithm for the treatment of persistent diarrhoea: a multicentre study.**

*Bulletin of the World Health Organization*, 1996, 74(5):479-89.

Described are the findings of a multicentre cohort study to test an algorithm for the treatment of persistent diarrhoea relying on the use of locally available, inexpensive foods, vitamin and mineral supplementation, and the selective use of antibiotics to treat associated infections. The initial diet (A) contained cereals, vegetable oil, and animal milk or yoghurt. The diet (B) offered when the patient did not improve with the initial regimen was lactose free, and the energy from cereals was partially replaced by simple sugars. A total of 460 children with persistent diarrhoea, aged 4-36 months, were enrolled at study centres in Bangladesh, India, Mexico, Pakistan, Peru, and Viet Nam. The study population was young (11.5 +/- 5.7 months) and malnourished (mean weight-for-age Z-score, -3.03 +/- 0.86), and severe associated conditions were common (45% required rehydration or treatment of severe infections on admission). The overall success rate of the treatment algorithm was 80% (95% CI, 76-84%). The recovery rate among all children with only diet A was 65% (95% CI, 61-70%), and was 71% (95% CI, 62-81%) for those evaluated after receiving diet B. The children at the greatest risk for treatment failure were those who had acute associated illnesses (including cholera, septicaemia, and urinary tract infections), required intravenous antibiotics, and had the highest initial purging rates.

**CONCLUSIONS:** Our results indicate that the short-term treatment of persistent diarrhoea can be accomplished safely and effectively, in the majority of patients, using an algorithm relying primarily on locally available foods and simple clinical guidelines. This study should help establish rational and effective treatment for persistent diarrhoea.

Publication Types: Clinical trial, Controlled clinical trial, Multicenter study

CHOICE Study Group

**Multicentre randomised double blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration solution in children with acute watery diarrhoea.**

*Pediatrics* Vol. 107 No. 4 April 2001, pp. 613-618

**OBJECTIVE.** To compare the efficacy of a reduced osmolarity oral rehydration salts (ORS) solution (75 mmol/L of sodium [Na], 20 mmol/L of potassium [K], 65 mmol/L of chloride, 10 mmol/L of citrate, and 75 mmol/L of glucose; osmolarity, 245 mosm/L) with that of the standard World Health Organization (WHO) ORS solution. **DESIGN** A multicenter, double-blind, randomized, controlled clinical trial conducted in children with acute diarrhea in 5 developing countries to measure mean stool output in the 24 hours after randomization, proportion of children who required unscheduled intravenous therapy, proportion of children who vomited in the first 24 hours, and diarrhea duration after randomization. **Results.** A total of 675 children who ranged in age from 1 to 24 months and who had acute diarrhea and dehydration were enrolled in the trial; 341 were randomized to receive reduced osmolarity ORS solution, and 334 were randomized to receive the WHO ORS solution. The mean (SE) stool output (g/kg) in the first 24 hours (reduced osmolarity ORS solution vs WHO ORS solution = 114 [4] vs 125 [5]) and during the total study period (reduced osmolarity ORS solution vs WHO ORS solution = 320 [18] vs 331 [18]) were comparable. The proportion of children who vomited in the first 24 hours (reduced osmolarity ORS solution vs WHO ORS solution = 58% vs 62%) and the diarrhea duration in the 2 treatment groups, compared by log rank test, were similar. The proportion of children who required unscheduled intravenous therapy was significantly lower in children who received reduced osmolarity ORS solution (10%) as compared with those who received the WHO ORS solution (15%; odds ratio = 0.6, 95% confidence interval = 0.4-1.0). There was no significant difference in the incidence of hyponatremia (serum Na <130 mmol/L) at 24 hours between the 2 treatment groups (11% in reduced osmolarity ORS solution group vs 9% in the WHO ORS solution group; odds ratio = 1.3; 95% confidence interval = 0.8-2.2). The frequency of patients with serum Na <125 mmol/L at 24 hours was 13 of 341 (4%) in children who were treated with reduced osmolarity ORS solution versus 7 of 334 (2%) in children who received the WHO ORS solution.

**CONCLUSIONS.** Treatment with reduced osmolarity ORS solution was associated with a 33% reduction in the need for unscheduled intravenous therapy and had no apparent effect on stool output and illness duration when compared with treatment with the standard WHO ORS solution. Children with acute diarrhea, therefore, may benefit from a reduced osmolarity ORS solution. The results of trials that examine the efficacy and safety of reduced osmolarity ORS solution in adult patients with cholera have to be taken into consideration before consensus on composition of oral rehydration formulation can be reached.

Fontaine O, Gore SM, Pierce NF

**Rice based oral rehydration solution for treating diarrhoea** (Cochrane Review).

In: *The Cochrane Library*, Issue 1,2001. Oxford: Update Software.

**BACKGROUND:** Oral rehydration therapy is used to treat dehydration caused by diarrhoea. However the rehydration solution does not reduce stool loss or length of illness. A solution able to do this may lessen the use of ineffective diarrhoea treatments as well as improve morbidity and mortality related to diarrhoea.

**OBJECTIVES:** The objective of this review was to assess the effects of rice-based oral rehydration salts solution compared with glucose-based oral rehydration salts solution on reduction of stool output and duration of diarrhoea in patients with acute watery diarrhoea. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Embase, Lilacs and the reference lists of relevant articles. We also contacted researchers in the field.

**SELECTION CRITERIA:** Randomised trials comparing standard World Health Organization oral rehydration solution with an experimental oral rehydration salts solution in which glucose (20 grams per litre) was replaced by 50-80 grams per litre of rice powder, with the electrolytes remaining unchanged. **Data collection and analysis:** Data were extracted independently by a statistician and a clinician. **Main results:** Twenty-two trials were included. Concealment of allocation was adequate in 15 of these trials. Irrespective of age, people with cholera who were given rice oral rehydration salts solution had substantially lower rates of stool loss than those given oral rehydration salts solution in the first 24 hours. Mean stool outputs in the first 24 hours were lower by 67 millilitres/kg of body weight (weighted mean difference -67.4, 95% confidence interval -94.3 to -41.0) in children, and by 51 millilitres/kg of body weight (weighted mean difference -51.1, 95% confidence interval -65.9 to -36.3) in adults. The rate of stool

loss in infants and children with acute non-cholera diarrhoea was reduced by only four millilitres/kg of body weight (weighted mean difference -4.3, 95% confidence interval -9.3 to 0.8).

CONCLUSIONS: Rice-based oral rehydration appears to be effective in reducing stool output in people with cholera. This effect was not apparent in infants and children with non-cholera diarrhoea.

Garg P, Chakraborty S, Basu I, Datta S, Rajendran K, Bhattacharya T, Yamasaki S, Bhattacharya SK, Takeda Y, Nair GB, Ramamurthy

**Expanding multiple antibiotic resistance among clinical strains of *Vibrio cholerae* isolated from 1992-7 in Calcutta, India.**

*Epidemiology and Infection* 2000 Jun;124(3):393-9

Antimicrobial susceptibilities of *Vibrio cholerae* strains isolated from cholera patients admitted to the Infectious Diseases Hospital, Calcutta, India for 6 years were analysed to determine the changing trends; 840 *V. cholerae* strains isolated in 1992-1997 were included in this study. Among *V. cholerae* serogroup O1 and O139, ampicillin resistance increased from 1992 (35 and 70%, respectively) to 1997 (both serogroups 100%). Resistance to furazolidone and streptomycin was constantly high among *V. cholerae* O1 strains with gradual increase in resistance to other drugs such as ciprofloxacin, co-trimoxazole, neomycin and nalidixic acid. *V. cholerae* O139 strains exhibited susceptibilities to furazolidone and streptomycin comparable with those of O1 strains. However, after initial increase in resistance to chloramphenicol and co-trimoxazole, all the *V. cholerae* O139 strains became susceptible to these two drugs from 1995 onwards. Both *V. cholerae* O1 and O139 remained largely susceptible to gentamicin and tetracycline. *V. cholerae* non-O1, non-O139 strains, in contrast, exhibited high levels of resistance to virtually every class of antimicrobial agents tested in this study especially from 1995. Kruskal-Wallis one-way analysis showed that *V. cholerae* O1 Ogawa serogroup exhibited significant yearly increase in resistance to nine antibiotics followed by non-O1 non-O139 and O139 strains to six antibiotics and two antibiotics respectively. Interesting observation encountered in this study was the dissipation of some of the resistant patterns commonly found among *V. cholerae* non-O1 non-O139 or O1 serogroups to the O139 serogroup and vice versa during the succeeding years.

Hahn S, Kim Y, Garner P

**Low osmolarity oral rehydration solution for treating children with diarrhoea: a systematic review.**

Submitted for publication. In: *The Cochrane Library*.

Koo D, Aragon A, Moscoso V, Gudiel M, Biatti L, Carrillo N, Chojoj J, Gordillo B, Cano F, Cameron DN, Wells JG, Bean NH, Tauxe RV

**Epidemic cholera in Guatemala, 1993: transmission of a newly introduced epidemic strain by street vendors.**

*Epidemiology and Infection*, 1996, 116:121-126.

(See this chapter, section Importance)

Materu SF, Lema OE, Mukunza HM, Adhiambo CG, Carter JY

**Antibiotic resistance pattern of *Vibrio cholerae* and *Shigella* causing diarrhoea outbreaks in the eastern Africa region: 1994-96.**

*East African Medical Journal*, 1997, 74:193-197.

Between March 1994 and December 1996, 1797 rectal swabs were transported to the AMREF laboratory from sites in six countries in the eastern Africa region: 1749 were cultured for *Vibrio cholerae* and 48 for *Shigella*/*Salmonella*. Culture, isolation, identification and antibiotic susceptibility testing were performed using standardized techniques. The isolates were categorised as sensitive or resistant based on standardized zones of inhibition. The rate of isolation of *V. cholerae* from rectal swabs increased progressively from less than 20% to more than 45% between 1994 and 1996, 80-100% of isolates of *V. cholerae* from Kenya and south Sudan, and 65-90% from Somalia were sensitive to tetracycline, although in 1995 isolates from Mogadishu showed only 44% sensitivity. All isolates from Tanzania and Rwanda were 100% resistant to

tetracycline. In Kenya and Somalia, the percentage of isolates sensitive to chloramphenicol and cotrimoxazole reduced markedly from 85% in 1994 to < 10% in 1996. 100% of isolates from Rwanda and Tanzania were resistant to chloramphenicol and cotrimoxazole while in south Sudan > 70% of isolates were sensitive. Nalidixic acid and erythromycin retained > 75% sensitivity in all areas. *Shigella dysenteriae* and *Shigella flexneri* were recovered from dysentery specimens in northern Kenya. Both species showed similar antibiotic sensitivity patterns and were sensitive only to nalidixic acid and furazolidone. Due to variations of resistance patterns within countries in the region, antibiotic sensitivity testing should be performed at the start of an outbreak, and antibiotic use should be restricted to severe cases of *V. cholerae* and *Shigella* infection.

Publication Types: Review, Review, tutorial

Comment in: *East Afr Med J* 1997 Mar;74(3):121-3

Ramamurthy T, Rajendran K, Garg P, Shimada T, Basu A, Chowdhury NR, Nandy RK, Yamasaki S, Bhattacharya SK, Takeda Y, Nair GB

**Cluster-analysis & patterns of dissemination of multidrug resistance among clinical strains of *Vibrio cholerae* in Calcutta, India.**

*Indian Journal of Medical Research* 2000 Sep;112:78-85

**BACKGROUND & OBJECTIVES:** Antimicrobial resistance among *Vibrio cholerae* has been monitored for several years in Calcutta. To investigate the changing trends in multidrug resistance (MDR) among different serogroups of *V. cholerae* and to perform software assisted cluster analysis the current study was undertaken. **METHODS:** Strains isolated from patients with cholera and "cholera-like" diarrhoea admitted in the Infectious Diseases Hospital, Calcutta were analysed. Eight hundred and forty *V. cholerae* strains isolated from 1992 through 1997 were tested for susceptibility to 11 antibiotics. Cluster analysis was done using SPSS software. **RESULTS:** Most of the strains exhibited MDR with fluctuating trends as the resistance profile diverged each year. A total of 119 different resistance profiles exhibited by *V. cholerae* O1, O139 and non-O1, non-O139 serogroups were analysed by cluster combination method. During 1993 and 1994, 53 per cent of *V. cholerae* O139 and 82 per cent of *V. cholerae* O1 serogroups, respectively, exhibited maximal number of new resistance patterns. The frequency of new resistance patterns among *V. cholerae* non-O1, non-O139 was constantly high (33-47%) during 1995 to 1997.

**INTERPRETATION & CONCLUSIONS:** With a few exceptions, preponderance of the resistance profiles was generally not confined to any serogroup. The cluster analysis depicted dissemination of some of the resistance patterns commonly found among *V. cholerae* non-O1, non-O139 belonging to different serogroups to the O139 serogroup in the succeeding years. In this study we have shown that the *V. cholerae* strains are resistant to several antibiotics with constant change in the MDR profiles. It is imperative to define the susceptibility pattern of the strains to determine the effective drug of choice for the treatment of cholera.

Salam MA, Bennis ML

**Antimicrobial therapy for shigellosis.**

*Journal of Antimicrobial Chemotherapy*, 1992, 30:243-247.

In controlled clinical trials, which were first performed with use of the sulfonamides, antimicrobial agents have been shown to shorten the duration of symptoms and lessen the excretion of pathogens during episodes of shigellosis. Not all antimicrobial agents that are active in vitro against *Shigella* are effective in vivo, and efficacy of an agent can only be assessed by properly conducted clinical trials. Resistance to both ampicillin and trimethoprim-sulfamethoxazole, the drugs of choice for the treatment of shigellosis, is now common among *Shigella dysenteriae* type I isolates in Africa and Asia and is increasing among isolates of other *Shigella* species, including *Shigella sonnei* in the United States. Nalidixic acid, the newer quinolones, and ammidocillin pivoxil are additional agents that have been found to be effective in controlled clinical trials. There is a need, however, for more data on the safety of the quinolones before they can be routinely administered to children. Newer agents that deserve evaluation include the orally administered second- and third-generation cephalosporins, which are highly active in vitro against most strains of *Shigella*.

Publication Types: Review, Review, tutorial

Salam MA, Dhar U, Khan WA, Bennish ML

**Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis.**

*Lancet* 1998 Aug 15;352(9127):522-7

**BACKGROUND:** Infections caused by multiply resistant *Shigella* species are a major cause of childhood morbidity and mortality in Third World countries. The fluoroquinolone agent ciprofloxacin is active in vitro against these strains of bacteria, but has not been routinely used to treat acute childhood infections because of concern that quinolones may cause arthropathy in children. We undertook a randomised double-blind study to test the effects of ciprofloxacin treatment in children with shigella dysentery. **METHODS:** We compared the efficacy and toxic effects of ciprofloxacin suspension (10 mg/kg every 12 h for 5 days, maximum individual dose 500 mg) with those of pivmecillinam tablets (15-20 mg/kg every 8 h for 5 days, maximum individual dose 300 mg). We enrolled 143 children aged 2-15 years with dysentery of 72 h or less duration. Patients stayed in hospital for 6 days, and were followed up 7, 30, and 180 days after hospital discharge. Joint symptoms and function were assessed daily for 6 days. Clinical success was defined as the absence of frank dysentery on day 3, and on day 5 no bloody-mucoid stools, one or no watery stool, six or fewer total stools, and no fever. If no shigella were isolated from faecal samples on day 3 or thereafter, treatment was judged bacteriologically successful. **FINDINGS:** 13 patients were excluded since they did not meet eligibility criteria; 10 withdrew before day 5. Thus 120 patients (60 in each group) completed the study. Treatment was clinically successful in 48 (80%) of 60 patients who received ciprofloxacin and in 39 (65%) of 60 patients who received pivmecillinam ( $p=0.10$ ). Treatment was bacteriologically successful in all of the patients receiving ciprofloxacin, and in 54 (90%) of the patients receiving pivmecillinam ( $p=0.03$ ). Joint pain after treatment began in 13 (18%) of 71 patients who received ciprofloxacin and 16 (22%) of 72 patients who received pivmecillinam ( $p>0.2$ ), and no patient had signs of arthritis. **INTERPRETATION:** In our trial, ciprofloxacin suspension and pivmecillinam had the same clinical efficacy. Ciprofloxacin had greater bacteriological efficacy and was not associated with the development of arthropathy.

**CONCLUSIONS:** Ciprofloxacin is an effective and safe drug for use in multiply resistant childhood shigellosis.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *Lancet* 1998 Oct 17;352(9136):1313

Sirinavin S, Garner P

**Antibiotics for treating salmonella gut infections (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.

**BACKGROUND:** Antibiotic treatment of salmonella infections aims to shorten illness and prevent serious complications. There are also concerns about increasing antibiotic drug resistance.

**OBJECTIVES:** The objective of this review was to assess the effects of antibiotics in adults and children with diarrhoea who have salmonella. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Science Citation Index, African Index Medicus, Lilacs, Extra Med and reference lists of relevant articles. We also contacted experts in the field. **SELECTION CRITERIA:** Randomised and quasi-randomised trials comparing antibiotic therapy with placebo or no antibiotic therapy for salmonella infections in symptomatic or asymptomatic adults or children. Typhoid and paratyphoid salmonella infections were excluded. **DATA COLLECTION AND ANALYSIS:** Trial quality assessment and data were extracted independently by two reviewers. **MAIN RESULTS:** Twelve trials involving 778 participants (with at least 258 infants and children) were included. There were no significant differences in length of illness, diarrhoea or fever between any antibiotic regimen and placebo. The weighted mean difference for length of illness was -0.07 days, 95% confidence interval -0.55 to 0.40; diarrhoea -0.03 days, 95% confidence interval -0.53 to 0.48; fever -0.45 days, 95% confidence interval -0.98 to 0.08. Antibiotic regimens resulted in more negative cultures during the first week of treatment. Relapses were more frequent in those receiving antibiotics, and there were more cases with positive cultures in the antibiotic groups after three weeks. Adverse drug reactions were more common in the antibiotic groups (odds ratio 1.67, 95% confidence interval 1.05 to 2.67).

**CONCLUSIONS:** There appears to be no evidence of a clinical benefit of antibiotic therapy in otherwise healthy children and adults with non-severe salmonella diarrhoea. Antibiotics appear to increase adverse effects and they also tend to prolong salmonella detection in stools.

Vinh H, Wain J, Chinh MT, Tam CT, Trang PT, Nga D, Echeverria P, Diep TS, White NJ, Parry CM

**Treatment of bacillary dysentery in Vietnamese children: two doses of ofloxacin versus 5-days nalidixic acid.**

*Transactions of Royal Society of Tropical Medicine and Hygiene* 2000 May-Jun;94(3):323-6

Nalidixic acid (NA: 55 mg/kg daily for 5 days) is the recommended treatment for uncomplicated bacillary dysentery in areas where multidrug-resistant *Shigella* are prevalent. An open randomised comparison of this NA regimen with 2 doses of ofloxacin (total 15 mg/kg) was conducted in 1995/96 in 135 Vietnamese children with fever and bloody diarrhoea. Sixty-six children with a bacterial pathogen isolated were eligible for analysis. Of the 63 *Shigella* isolates, 39 (62%) were resistant to multiple antibiotics. Resolution times for fever and diarrhoea were similar in the 2 groups, but excretion time of stool pathogen was significantly longer in the NA recipients [median (range) days 1 (1-9) vs 1 (1-2),  $P = 0.001$ ]. There were 9 (25%) treatment failures in the NA regimen and 3 (10%) in the ofloxacin group;  $P = 0.1$ . Two patients had NA-resistant *Shigella flexneri*. One of these isolates was selected during NA treatment.

CONCLUSIONS: From a clinical and public health standpoint a 2-dose regimen of ofloxacin is preferable to nalidixic acid in the treatment of bacillary dysentery.

Publication Types: Clinical trial, Randomised controlled trial

## **Documents and publications**

World Health Organization

***Management of severe malnutrition - A manual for physicians and other senior health workers.*** Geneva, World Health Organization 1999, 60p ISBN 9241545119

(See Chapter Nutritional status, nutrition and breastfeeding counselling, section Nutrition counselling)

World Health Organization, Division of Child Health and Development, Family and Reproductive Health  
***Persistent diarrhoea and breastfeeding.***

Geneva, World Health Organization, 1997, 14 p. (unpublished document WHO/CHD/97.8; available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1997/WHO\\_CHD\\_97.8.pdf](http://whqlibdoc.who.int/hq/1997/WHO_CHD_97.8.pdf)

(See Chapter Nutritional status, nutrition and breastfeeding counselling, section Breastfeeding counselling)

World Health Organization

***Guidelines for the control of epidemics due to Shigella dysenteriae type 1.***

Geneva, World Health Organization, 1995, 42 p. (unpublished document WHO/CDR/95.5; available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1995/WHO\\_CDR\\_95.4.pdf](http://whqlibdoc.who.int/hq/1995/WHO_CDR_95.4.pdf)

The guidelines are intended to assist national health authorities, public health officers and health care providers in their efforts to prevent and/or treat *Shigella dysenteriae* type 1 disease (Sd1). The text describes the epidemiology, clinical features and management of disease caused by Sd1, and interventions that can reduce both the incidence of Sd1 infections and mortality due to Sd1 disease.

World Health Organization

***The treatment of diarrhoea: A manual for physicians and other senior health workers.***

Geneva, World Health Organization, 1995 (unpublished document WHO/CDR/95.3; available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1995/WHO\\_CDR\\_95.3.pdf](http://whqlibdoc.who.int/hq/1995/WHO_CDR_95.3.pdf)

The manual describes the principles and practices of treating infectious diarrhoea, especially in young children. It is intended for physicians and other senior-level health workers. This third revision of the manual reflects recent clinical experience and research findings in diarrhoea case management. It provides details on the management of bloody diarrhoea (dysentery) and cholera, and includes guidelines on the management of children with persistent diarrhoea and diarrhoea with severe malnutrition. Guidelines in the manual are based on the WHO chart: Management of the patient with diarrhoea revised in 1992, which is reproduced in the manual.

World Health Organization

***The management of bloody diarrhoea in young children.***

Geneva, World Health Organization, 1994, 17 p. (unpublished document WHO/CDD/94.49; available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1994/WHO\\_CDD\\_94.49.pdf](http://whqlibdoc.who.int/hq/1994/WHO_CDD_94.49.pdf)

The document describes simple and effective guidelines, and their rationale, for the management of bloody diarrhoea in children below age 5 years, especially among outpatients. These guidelines are based on case management guidelines outlined in the WHO chart, Management of the patient with diarrhoea (1992 version), and in other WHO documents and publications.

World Health Organization

***The selection of fluids and food for home therapy to prevent dehydration from diarrhoea: Guidelines for developing a national policy.***

Geneva, World Health Organization, 1993 (unpublished document WHO/CDD/93.44; available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1993/WHO\\_CDD\\_93.44.pdf](http://whqlibdoc.who.int/hq/1993/WHO_CDD_93.44.pdf)

The text describes a simple, logical process for selecting the fluids and foods to be promoted for preventing dehydration in children with diarrhoea. It also shows how to include the selected fluids and foods in national guidelines for home therapy of diarrhoea. The document is intended for the managers of national diarrhoeal disease control programmes to provide them with a tool to identify the most appropriate home fluids and foods for use during home therapy of diarrhoea in their countries.

This document replaces the WHO CDD document entitled “A decision Process for Establishing a Policy on Fluids for Home Therapy of Diarrhoea” (WHO/CDD/SER/87.10)

World Health Organization

***Management of the patient with cholera.***

Geneva, World Health Organization, 1992, 8 p. (unpublished document WHO/CDD/SER/92.16; available on request from the Child and Adolescent Health and Development (CAH) Department).

[http://whqlibdoc.who.int/hq/1991/WHO\\_CDD\\_SER\\_91.15\\_REV.1.pdf](http://whqlibdoc.who.int/hq/1991/WHO_CDD_SER_91.15_REV.1.pdf)

The text concisely describes the steps in the management of suspected cholera: (1) Assess for dehydration, (2) Rehydrate the patient, and monitor frequently; then reassess hydration status, (3) Maintain hydration, (4) Give oral antibiotic to the patient with severe dehydration, (5) Feed the patient.



World Health Organization

***Readings on diarrhoea: Student manual.***

Geneva, World Health Organization, 1992.

1992, vii + 147 pages [C, E, F; S from PAHO]

ISBN 92 4 154444 9

Sw.fr. 20.-/US \$18.00; in developing countries: Sw.fr. 14.-

Order no. 1150386

A collection of eight teaching units conveying essential information about the pathophysiology, clinical features, diagnosis, epidemiology, treatment and prevention of diarrhoea in children. Addressed to medical students undergoing clinical training in paediatrics, the manual aims to equip students with all the knowledge needed to assess patients, plan treatment, and prevent deaths through proper case management. Information, which is specific to conditions in developing countries, ranges from an explanation of the clinical features seen in different forms of dehydration, through advice on how to communicate with mothers, to a discussion of the role of feeding in the management of diarrhoea. Recommended lines of action draw their authority from published research and extensive WHO experience in programmes for the treatment and prevention of diarrhoea. The first two teaching units provide fundamental information about the epidemiology, clinical types of diarrhoea, causative agents, modes of transmission, pathophysiology, and implications for treatment. Subsequent units explain how the clinical assessment of patients should be performed and interpreted, discuss ways of teaching mothers to treat diarrhoea at home, describe clinical measures for the treatment of dehydrated patients, and discuss the special procedures to be followed during the treatment of dysentery, persistent diarrhoea, and diarrhoea associated with other illnesses. The remaining units cover the nutritional management of diarrhoea in children, including those suffering from severe malnutrition, and explain how physicians can promote prevention, particularly through the education of mothers and other family members. Each unit concludes with a list of exercises. Further practical information is presented in a series of annexes, which include illustrated, step-by-step instructions for intravenous rehydration and nasogastric rehydration.

World Health Organization

***The Rational Use of Drugs in the Management of Acute Diarrhoea in Children.***

Geneva, World Health Organization, 1990, iv + 71 pages [C, E, F, S from PAHO]

ISBN 92 4 156142 4

Sw.fr. 14.-/US \$12.60; in developing countries: Sw.fr. 9.80

Order no. 1150355

Provides authoritative information essential to those concerned with improving the rational use of drugs in the management of acute diarrhoea in infants and young children and with tackling the immense problems posed by the prescribing of clinically useless and potentially dangerous drugs. The book gathers the information needed to argue against the widespread use of medicines that have no established clinical benefits, are frequently harmful, and may delay or replace effective treatment measures.

Drugs judged effective are dealt with concisely in a table listing four first-choice antimicrobials, and six alternatives, useful in the management of cholera, shigella dysentery, amoebiasis, and giardiasis. Apart from these cases of specific aetiology, readers are informed that antidiarrhoeal drugs and antiemetics should never be used for children, as none has any proven practical value and some are frankly dangerous. This statement is substantiated through a review of data on eleven antidiarrhoeal drugs widely used in paediatric practice. The book concludes that none of these preparations has any documented benefits, some actually prolong diarrhoea, and others have been shown to produce severe and sometimes fatal side-effects. The book further concludes that the continued production, promotion, and sale of these preparations for paediatric practice cannot be justified.

## 5. FEVER

### 5.1. DETECTING FEVER AND CHOICE OF ANTIPYRETIC

#### Articles

#### Importance

Tomlinson WA

**High fever. Experience in private practice.**

*American Journal of Diseases in Childhood*, 1975, 129:693-696.

Experience with confirmed high fever, 40 C (104 F) or more, in a private practice during 14 years is presented. The records of 1,500 patients covering 8,000 patient years disclosed only 108 confirmed episodes of high fever. Eleven diagnostic categories included 149 diagnoses. Fourteen of 43 roentgenographic examinations yielded positive findings, including two cases of pneumonia not detected on physical examination. Two of six stool cultures yielded specific enteric pathogens. Convulsions occurred in 12 of the 108 episodes of high fever, and recurred only once in one child. There were no deaths in this series of children with high fevers. Only one diagnosis, pneumonia, was significantly more frequent in confirmed high fever than in unconfirmed high fever. Lastly, the ability of a group of mothers to read thermometers set at three different temperatures proved to be surprisingly good.

#### Assessment

Banco L, Veltri D

**Ability of mothers to subjectively assess the presence of fever in their children.**

*American Journal of Diseases in Childhood*, 1984, 138:976-978.

We assessed the ability of mothers to subjectively determine the presence or absence of fever in their children when compared with simultaneous temperature determination obtained by thermometer. Mothers who said their children were febrile were correct 52.3% of the time; those who said their children were afebrile were correct 93.9% of the time. The sensitivity was 73.9% of the specificity was 85.6%. Ninety percent of children aged 2 years or younger with temperatures of 38.9 degrees C or higher were correctly identified as febrile. Administration of antipyretics to both febrile and afebrile children was greater among those whose temperature was determined at home by thermometer than among those whose temperature was determined by subjective criteria.

CONCLUSIONS: Maternal subjective fever assessment criteria are useful as a screening method to rule out the presence of fever at all ages and that mothers can identify high fevers in most young children without the use of a thermometer.

Ogren JM

**The inaccuracy of axillary temperatures measured with an electronic thermometer.**

*American Journal of Diseases in Childhood*, 1990, 144:109-111.

Temperatures were measured using an electronic thermometer in an emergency department to determine the relationship between oral or rectal and axillary measurements. A total of 164 data pairs were obtained--95 in afebrile children, and 69 in febrile children. The correlation coefficient was .74 for oral-axillary pairs, and .70 for rectal-axillary pairs. The mean difference between oral and axillary temperatures was 1.17 degrees C +/- 0.72 degrees C, and between rectal and axillary temperatures was 1.81 degrees C +/- 0.97 degrees C. Using 37.4 degrees C (greater than or equal to 2 SDs) axillary as the upper limit of normal, the sensitivity, specificity, and positive and negative predictive values were calculated for detecting a fever. The sensitivity was 46%; specificity, 99%; positive predictive value, 97%; and negative predictive value, 72% for combined oral-axillary and rectal-axillary data. It was concluded that axillary temperatures are not sensitive enough to determine a fever when measured with an electronic thermometer. Electronic thermometers should be used to determine oral or rectal temperatures; axillary temperatures may be misleading and should be abandoned in the outpatient setting.

Perkins BA, Zucker JR, Otieno J, Jafari HS, Paxton L, Redd SC, Nahlen BL, Schwartz B, Oloo AJ, Olango C, Gove S, Campbell CC

**Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1): 33-42.

(see chapter Efficiency of IMCI guidelines).

Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM

**Evaluation of an algorithm for integrated management of childhood illness in an area with seasonal malaria in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1): 25-32.

(see chapter Efficiency of IMCI guidelines).

## Treatment

Casey R, McMahon F, McCormick MC, Pasquariello PS Jr, Zavod W, King FH Jr

**Fever therapy: an educational intervention for parents.**

*Paediatrics*, 1984, 73: 600-605.

Fever in children is a common problem, but one which often alarms parents. Parental misconceptions often lead them to unnecessarily aggressive and inappropriate management of fever in their children. A prospective controlled trial of an educational intervention to improve parental understanding and management of fever, involving the parents of 108 children, aged 6 months to 4 years, was performed in a private group practice. Although the majority of these patients were well educated, most were found to be misinformed about many aspects of the seriousness of fever and its management. Parents in the intervention group received a standardized interview in which the management of fever was discussed, demonstrated, and practiced. In addition, they received a printed information sheet for reinforcement 2 months after the initial interview. Parents in both the control group and intervention group revealed an increase in knowledge about fever over time, but only in the intervention group were inappropriate physician contacts and medication errors reduced. The effectiveness of an active learning approach to anticipatory guidance for the management of transient febrile illness was documented and it is suggested that extension of this approach to other common problems in the private practice setting be examined.

Publication Types: Clinical trial, Controlled clinical trial

## Documents and publications

***The management of fever in young children with acute respiratory infections in developing countries.***

Geneva, World Health Organization, 1993 (unpublished document WHO/ARI/93.30; available on request from the Division of Child and Adolescent Health and Development (CAH)).

[http://whqlibdoc.who.int/hq/1993/WHO\\_ARI\\_93.30.pdf](http://whqlibdoc.who.int/hq/1993/WHO_ARI_93.30.pdf)

Up till a century ago fever was considered a healthy response to disease. At present an overly aggressive treatment is common. A review of the available scientific evidence presented in this material may be helpful in developing a more rational approach to management of children with fever. Data from laboratory immunological studies and a limited number of animal studies suggest that a moderate rise in body temperature may improve defence against infection and may therefore be desirable. Harmful effects of fever alone are rare and are found mainly in very ill and compromised children or in children with very high fever (above 42<sup>0</sup>C). High fevers or rapid rise in temperature in young children are associated with febrile convulsions but these generally resolve spontaneously and are not associated with long-term neurological complications. There is no evidence that they can be prevented with antipyretic treatment.

Reduction of fever should be oriented towards relieving the child's discomfort and in most circumstances there is no indication to give antipyretic treatment for fever below 39<sup>0</sup>C (rectal). The safest and most effective treatment for fever in young children is paracetamol in a dose 10-15 mg/kg 6 hourly. Supportive care with additional fluids, appropriate clothing and environmental conditions should be emphasized.



## 5.2. MALARIA

### Articles

#### Importance

Menendez C, Fleming AF, Alonso PL

##### **Malaria-related anaemia**

*Parasitology Today* 2000 Nov;16(11):469-76

(see chapter Anaemia, intestinal parasites)

Rooth IB, Bjorkman A

##### **Suppression of Plasmodium falciparum infections during concomitant measles or influenza, but not during pertussis.**

*American Journal of Tropical Medicine and Hygiene*, 1992, 47(5):675-681.

In tropical countries, concomitant infections are a continuous problem. In the Rufiji Delta, an area of Tanzania that is holoendemic for malaria, there were outbreaks of influenza A, measles, and pertussis in 1986 and 1987. Significantly lower parasitic prevalences and mean densities of malaria parasites were found in children up to nine years of age who had measles or influenza than in asymptomatic control children. In contrast, children with pertussis had a higher prevalence and mean density than controls. The clinical courses of measles, influenza, or pertussis infections did not appear to be significantly affected by concomitant malaria infections. The reasons for the suppression of Plasmodium falciparum parasitemia during these viral infections are unclear. This effect could not be explained by the presence of fever.

#### Assessment

English M, Punt J, Mwangi I, McHugh K, Marsh K

##### **Clinical overlap between malaria and severe pneumonia in African children in hospital.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, 90(6):658-662.

Data collected from 200 children admitted to a hospital on the Kenyan coast who met a broad definition of severe acute respiratory infection (ARI) indicated that simple clinical signs alone are unable absolutely to distinguish severe ARI and severe malaria. However, laboratory data showed that marked differences exist in the pathophysiology of unequivocal malaria and unequivocal ARI. Children in the former group had a higher mean oxygen saturation (97 vs. 94,  $P < 0.001$ ), mean blood urea level (5.3 vs. 1.9 mmol/L,  $P < 0.001$ ) and geometric mean lactate level (4.5 vs. 2.1 mmol/L,  $P < 0.001$ ), and lower mean haemoglobin level (5.3 vs. 9.0 g/dL,  $P < 0.001$ ) and base excess (-9.4 vs. -2.6,  $P < 0.001$ ) than those in the latter group. Using these discriminatory variables it was estimated that up to 45% of children admitted with respiratory signs indicative of severe ARI probably had malaria as the primary diagnosis. Radiological examination supported this conclusion, indicating that pneumonia characterised by consolidation was uncommon in children with respiratory signs and a high malarial parasitaemia ( $> \text{ or } = 10,000/\text{microliters}$ ). There is no specific radiological sign of severe malaria.

**CONCLUSIONS:** In practice, all children with respiratory signs warranting hospital admission in a malaria endemic area should be treated for both malaria and ARI unless blood film examination excludes malaria. In those with malaria and clinical evidence of acidosis, but no crackles, antibiotics may be withheld while appropriate treatment for dehydration and anaemia is given. However, if clinical improvement is not rapid, antibiotics should be started.

English M, Waruiru C, Amukoye E, Murphy S, Crawley J, Mwangi I, Peshu N, Marsh K  
**Deep breathing in children with severe malaria: indicator of metabolic acidosis and poor outcome.**

*American Journal of Tropical Medicine and Hygiene*, 1996, 55(5):521-524.

Despite the frequent association of respiratory symptoms and signs with malarial morbidity and mortality in sub-Saharan Africa, the value of individual symptoms and signs has rarely been assessed. We have prospectively examined the association of individual clinical findings with the summary diagnosis of respiratory distress, outcome, and the presence of metabolic acidosis in children admitted with severe malaria to a Kenyan district hospital. Respiratory distress was present in 119 of the 350 children included in the study and in 23 of the 30 deaths (relative risk = 6.5, 95% confidence interval = 2.8-14.4). The features of a history of dyspnea, nasal flaring, and indrawing or deep breathing (Kussmaul's respiration) were individually most closely associated with the summary diagnosis of respiratory distress. Of these, deep breathing, which was sensitive (91%) and specific (83%) for the presence of severe metabolic acidosis (base excess < or = -12), is the best candidate sign to represent the prognostically important syndrome of malarial respiratory distress. Therefore, it warrants further prospective evaluation in different clinical settings and areas of different malaria endemicity.

Gomes M, Espino FE, Abaquin J, Realon C, Salazar NP

**Symptomatic identification of malaria in the home and in the primary health care clinic.**

*Bulletin of the World Health Organization*, 1994, 72(3):383-390.

In endemic areas in the absence of microscopy, the WHO case definition of malaria is the presence or a history of fever without other obvious cause. Yet there is little empirical evidence on the accuracy, predictability and reliability of clinical signs and symptoms for diagnosing malaria within different endemic settings. Studying patients in endemic communities in the Philippines, we found that fever alone did not discriminate well for malaria. In contrast, a sequential occurrence of fever, chills and/or sweating, or a combination of all three symptoms was a good general predictor of the disease. However, the place of diagnosis and observation (home or clinic), age, and season affected the positive predictive values obtained. Specificities and positive predictive values were greatest (over 80%) for those at most risk—children under 9 years of age in highly endemic communities—and were most reliable when the diagnosis was made at home. Predictive values were also greatest during the season when childhood acute lower respiratory infections in the study area increase.

CONCLUSIONS: The good predictability of clinical signs and symptoms for high-risk groups suggests that simple protocols can be developed for the management of malaria in endemic areas of the Philippines.

Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, Newton C,  
Winstanley P, Warn P, Peshu N, et al

**Indicators of life-threatening malaria in African children.**

*New England Journal of Medicine*, 1995, 332(21):1399-1404.

BACKGROUND. About 90 percent of the deaths from malaria are in African children, but criteria to guide the recognition and management of severe malaria have not been validated in them. METHODS. We conducted a prospective study of all children admitted to the paediatric ward of a Kenyan district hospital with a primary diagnosis of malaria. We calculated the frequency and mortality rate for each of the clinical and laboratory criteria in the current World Health Organization (WHO) definition of severe malaria, and then used logistic-regression analysis to identify the variables with the greatest prognostic value. RESULTS. We studied 1844 children (mean age, 26.4 months) with a primary diagnosis of malaria. Not included were 18 children who died on arrival and 4 who died of other causes. The mortality rate was 3.5 percent (95 percent confidence interval, 2.7 to 4.3 percent), and 84 percent of the deaths occurred within 24 hours of admission. Logistic-regression analysis identified four key prognostic indicators: impaired consciousness (relative risk, 3.3; 95 percent confidence interval, 1.6 to 7.0), respiratory distress (relative risk, 3.9; 95 percent confidence interval, 2.0 to 7.7), hypoglycemia (relative risk, 3.3; 95 percent confidence interval, 1.6 to 6.7), and jaundice (relative risk, 2.6; 95 percent confidence interval, 1.1 to 6.3). Of the 64 children who died, 54 were among those with impaired consciousness (n = 336; case fatality rate, 11.9

percent) or respiratory distress (n = 251; case fatality rate, 13.9 percent), or both. Hence, this simple bedside index identified 84.4 percent of the fatal cases, as compared with the 79.7 percent identified by the current WHO criteria.

**CONCLUSIONS.** In African children with malaria, the presence of impaired consciousness or respiratory distress can identify those at high risk for death.

Comments: N Engl J Med 1995 May 25;332(21):1441-2; N Engl J Med 1995 Oct 12;333(15):1011; discussion 1012; N Engl J Med 1995 Oct 12;333(15):1011-2

O'Dempsey TJ, McArdle TF, Laurence BE, Lamont AC, Todd JE, Greenwood BM

**Overlap in the clinical features of pneumonia and malaria in African children.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, 87(6):662-665.

Pneumonia and malaria are common causes of childhood morbidity and mortality in many developing countries and simple guidelines have been proposed to facilitate their diagnosis by relatively unskilled health workers. We have studied children in The Gambia attending out-patient and under-five clinics with clinically suspected pneumonia (cough or difficulty in breathing and a raised respiratory rate) during periods of high or low malaria transmission. During a period of high malaria transmission, 33% of these children had radiological evidence of pneumonia (with or without malaria parasitaemia) compared to 38% who had malaria parasitaemia, no radiological evidence of pneumonia and no other obvious cause of fever. Corresponding figures during a period of low malaria transmission were 48% and 6% respectively.

**CONCLUSIONS:** The clinical overlap between pneumonia and malaria has important implications for case management strategies and evaluation of disease-specific interventions in regions in which both pneumonia and malaria are prevalent.

Rooth IB, Bjorkman A

**Fever episodes in a holoendemic malaria area of Tanzania: parasitological and clinical findings and diagnostic aspects related to malaria.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1992, 86(5):479-482.

All episodes of acute illness, in children aged 0-9 years, were registered during 3 years in a health clinic in a village of about 500 inhabitants in a malaria holoendemic area on the Tanzanian coast. Of 668 clinical episodes, 395 were diagnosed as malaria. There was no death. Only 5% of the children with malaria episodes came to the clinic after more than 3 d of symptoms. All 11 severe anaemias occurred among these children. Fever was reported in 98%, vomiting in 15%, and diarrhoea in 8% of the malaria episodes. Intermittent fever was reported in 98% of the malaria patients with more than one day of fever, compared to 4% of those with other febrile illnesses. Parasite densities  $\geq 10,000$ /microliters were found in 48% of the malaria episodes. Densities  $\geq 400$ /microliters were found in 96% of the malaria episodes and in only 8% of the other febrile illnesses. The 16 malaria episodes (4%) with densities below that level were all in children under one year of age. The ability of the rural medical aid or the doctor to differentiate malaria episodes from other febrile illnesses without microscopical examination was limited. Although very few malaria episodes were missed, substantial over-diagnosis resulted in specificity values of only 13% and 52% for their respective malaria diagnoses.

**CONCLUSIONS:** Intermittent fever was strongly associated with malaria, but a high accuracy of malaria diagnosis in febrile children requires microscopical examination.

Simoes EA, Desta T, Tessema T, Gerbresellassie T, Dagnaw M, Gove S

**Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia.**

(See in chapter Effectiveness of IMCI guidelines)



Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM

**Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement1):25-32.

(See chapter Effectiveness of IMCI guidelines).

## Treatment

Bjorkman A, Phillips-Howard PA

**Adverse reactions to sulfa drugs: implications for malaria chemotherapy.**

*Bulletin of the World Health Organization*, 1991, 69(3):297-304.

Department of Infectious Diseases, Roslagstull Hospital, Stockholm, Sweden.

National adverse drug reaction registers in Sweden and the United Kingdom provided data on the type, severity and frequency of reported adverse reactions attributed to sulfa drugs. Reactions to the ten principal drugs were examined in terms of their half-lives and usual indications for use. Of 8339 reactions reported between 1968 and 1988, 1272 (15%) were blood dyscrasias, 3737 (45%) were skin disorders, and 578 (7%) involved the liver. These side-effects occurred with all types of sulfa drugs investigated, although at different relative rates, and 3525 (42%) of them were classified as serious. The overall case fatality rate (CFR) was 1:15 serious reactions, and was highest in patients with white blood cell dyscrasias (1:7). Drugs with longer elimination half-lives had higher CFRs, particularly for fatalities after skin reactions. In Sweden, the estimated incidences of serious reactions were between 9 and 33 per 100,000 short-term users of sulfa drugs (two weeks), between 53 and 111 among those on malaria prophylaxis, and between 1744 and 2031 in patients on continuous therapy. For dapsone, the incidence appeared to increase with higher doses.

CONSLUSIONS: Our results indicate that sulfa drugs with short elimination half-lives deserve to be considered for use in combination with proguanil or chlorproguanil for malaria chemotherapy and possibly prophylaxis. The smaller risk of adverse reactions associated with lower-dose dapsone suggests that it should also be evaluated as a potentially safe alternative.

Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC

**Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa.**

*Journal of Infectious Diseases*, 1993, 167(4):932-937.

Emphasis on retaining chloroquine as the first-line therapy for *Plasmodium falciparum* infections in most of sub-Saharan Africa for as long as it remains effective has resulted in widespread reliance on chloroquine in areas where it can have little effect on *P. falciparum* parasitemia. To address this issue, clinical, parasitologic, and hematologic responses to chloroquine or pyrimethamine/sulfadoxine treatment were assessed among very young children in Malawi (n = 153) and Kenya (n = 73). The median time to resumption of clinical symptoms in chloroquine-treated children was 13.5 days in Malawi and 9.5 days in Kenya. Children treated with pyrimethamine/sulfadoxine maintained clinical improvement and had greater increases in their haemoglobin concentration during the follow-up period than did children treated with chloroquine. Treatment with chloroquine failed to produce either a durable clinical improvement or optimal hematologic recovery.

CONCLUSIONS: Chloroquine can no longer be considered adequately effective therapy of clinical *P. falciparum* malaria in very young children in Malawi and Kenya.

Publication Types: Clinical trial, Randomised controlled trial

Bloland PB, Redd SC, Kazembe P, Tembenu R, Wirima JJ, Campbell CC  
**Co-trimoxazole for childhood febrile illness in malaria-endemic regions.**  
*Lancet*, 1991, 337(8740):518-520.

The efficacy of co-trimoxazole for the treatment of *Plasmodium falciparum* parasitaemia in children younger than 5 years of age was evaluated in Malawi. 46 children with *P falciparum* parasitaemia, 37% of whom also met clinical criteria for a diagnosis of acute lower respiratory tract infection, were treated with 20 mg/kg co-trimoxazole twice daily for five days. Parasitaemia (mean clearance time 2.7 days) and symptoms were rapidly abolished and improvement was maintained during follow-up for 14 days.  
CONCLUSIONS: Co-trimoxazole may be an effective single treatment for febrile illness in young children in areas where malaria is endemic, resources are few, and diagnosis must rely on clinical findings alone.  
Publication Types: Clinical trial

Daramola OO, Alonso PL, O'Dempsey TJ, Twumasi P, McArdle TF, Greenwood BM  
**Sensitivity of *Plasmodium falciparum* in the Gambia to co-trimoxazole.**  
*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1991, 85(3):345-348.

In The Gambia co-trimoxazole is used widely to treat children with an acute respiratory infection (ARI). Because malaria may sometimes be mistaken for ARI, some children with malaria are treated with co-trimoxazole. Therefore, we investigated the sensitivity of Gambian isolates of *Plasmodium falciparum* to this drug. Six days after the start of treatment with co-trimoxazole 3.3% of blood films of 65 asymptomatic subjects were positive, and 7.7% were positive after 21 d. One of 10 patients with ARI and malaria treated with co-trimoxazole had a positive blood film 3 d after the start of treatment but was negative thereafter. All 10 patients recovered satisfactorily. Thirty 'wild' isolates of *P. falciparum* were tested in vitro against co-trimoxazole at a ration of 5 parts sulphamethoxazole (SMZ) to 1 part trimethoprim (TMP). The mean EC<sub>50</sub>s, using a 36 h assay, were  $1.2 \times 10^{-7}$  and  $2.5 \times 10^{-8}$  M for SMZ and TMP respectively. When a [<sup>3</sup>H]hypoxanthine incorporation assay was employed, values of  $5.7 \times 10^{-7}$  M for SMZ and  $1.2 \times 10^{-7}$  M for TMP were obtained. These values are well below the peak plasma concentration.  
CONCLUSIONS: Our findings suggest that co-trimoxazole is effective against *falciparum* malaria in The Gambia. However, if it were to be used widely, the parasite would be likely to develop resistance to this and other dihydrofolate reductase inhibitor antimalarials.

Kilian AH, Jelinek T, Prislín I, Kabagambe G, Byamukama W, Mpigika G, Korte R, von Sonnenburg F  
**Resistance in vivo of *Plasmodium falciparum* to co-trimoxazole in western Uganda.**  
*Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998 Mar-Apr;92(2):197-200

In the context of the 'integrated management of childhood illnesses' (IMCI) programme the World Health Organization recommends treating children in malarious areas presenting with fever and respiratory symptoms with co-trimoxazole. In order to verify its effectiveness in uncomplicated *Plasmodium falciparum* malaria we carried out a study in vivo in western Uganda: 180 children under 5 years old were enrolled and treated with 40/8 mg/kg/d co-trimoxazole over 5 d, and 159 could be followed on days 3, 7 and 14. Effectiveness of treatment was found to be significantly different in various parts of the study area. In Bundibugyo District, bordering République Democratique du Congo (Zaire), 59.1% (39/66) of children were clinically cured after 14 d and 56.1% were parasitologically cured. In the east of Kabarole District (43 children), the figures were 76.7% and 65.1%, respectively. In western Kabarole (50 children) the rates were 96.0% and 90.0%, respectively. We conclude that, in view of the high level of clinical failures in parts of the study area, co-trimoxazole should not be used in the IMCI programme for combined treatment of malaria and pneumonia in the region. Assessment of therapeutic effectiveness of antimalarial drugs needs to consider the microepidemiology of resistance.

McIntosh HM, Olliaro P

**Artemisinin derivatives for treating severe malaria (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.



**BACKGROUND:** Artemisinin derivatives may have advantages over quinoline drugs for treating severe malaria since they are fast acting and effective against quinine resistant malaria parasites. **OBJECTIVES:** The objective of this review was to assess the effects of artemisinin drugs for severe and complicated falciparum malaria in adults and children. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group trials register, Cochrane Controlled Trials Register, Medline, Embase, Science Citation Index, Lilacs, African Index Medicus, conference abstracts and reference lists of articles. We contacted organisations, researchers in the field and drug companies. **SELECTION CRITERIA:** Randomised and pseudo-randomised trials comparing artemisinin drugs (rectal, intramuscular or intravenous) with standard treatment, or comparisons between artemisinin derivatives in adults or children with severe or complicated falciparum malaria. **DATA COLLECTION AND ANALYSIS:** Eligibility, trial quality assessment and data extraction were done independently by two reviewers. Study authors were contacted for additional information. **MAIN RESULTS:** Twenty three trials are included, allocation concealment was adequate in nine. Sixteen trials compared artemisinin drugs with quinine in 2653 patients. Artemisinin drugs were associated with better survival (mortality odds ratio 0.61, 95% confidence interval 0.46 to 0.82, random effects model). In trials where concealment of allocation was adequate (2261 patients), this was barely statistically significant (odds ratio 0.72, 95% CI 0.54 to 0.96, random effects model). In 1939 patients with cerebral malaria, mortality was also lower with artemisinin drugs overall (odds ratio 0.63, 95% CI 0.44 to 0.88, random effects model). The difference was not significant however when only trials reporting adequate concealment of allocation were analysed (odds ratio 0.78, 95% CI 0.55 to 1.10, random effects model) based on 1607 patients. No difference in neurological sequelae was shown. Compared with quinine, artemisinin drugs showed faster parasite clearance from the blood and similar adverse effects. **CONCLUSIONS:** Artemisinin drugs are no worse than quinine in preventing death from severe malaria. Aggregate data suggests that at best one more life could be saved in every 25 patients (95% CI 16 to 65) treated with an artemisinin drug compared with quinine, however, this has to be interpreted with caution because of the heterogeneity between studies. Additional supportive care might be more essential to survival than the antimalarial drug in patients with complications of severe malaria, including cerebral malaria. There is no evidence yet to suggest that early treatment in rural areas with suppositories is inappropriate, being more convenient than parenteral quinolines, whilst patients are being transferred to a higher grade health facility. There is a need to determine whether the superiority of artemisinin drugs over quinine is a reflection of reduced sensitivity to quinine. Combination with a longer-acting antimalarial drug such as mefloquine or sulfadoxine-pyrimethamine does reduce the rate of recrudescence according to the available evidence, and could possibly slow development of resistance to artemisinin derivatives. However, the risk of enhanced neurological reactions with mefloquine following severe malaria needs to be considered (NJ White, personal communication). The best derivative, route of administration, dose and treatment regimen has not been established in randomised controlled trials.

McIntosh HM, Olliaro P

**Artemisinin derivatives for treating uncomplicated malaria (Cochrane Review)**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.



A substantive amendment to this systematic review was last made on 18 February 1999. Cochrane reviews are regularly checked and updated if necessary. **BACKGROUND:** Artemisinin derivatives are a relatively new group of drugs with antimalarial properties. As resistance to other antimalarial drugs continues to increase, artemisinin drugs may be useful alternatives. **OBJECTIVES:** The objective of this review was to assess the effects of artemisinin drugs for treating uncomplicated falciparum malaria. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Embase, Science Citation Index, Lilacs, African Index Medicus; conference abstracts and reference lists of relevant articles. We contacted organisations, researchers in the field and drug companies. **SELECTION CRITERIA:** Randomised and quasi-randomised trials of artemisinin derivatives, alone or in combination with other antimalarials, compared with standard antimalarial treatments, in adults or children with uncomplicated falciparum malaria. Only trials where treatment was given by mouth or suppository were included. Comparisons between different artemisinin derivatives and treatment regimens were also included. **DATA COLLECTION AND ANALYSIS:** Eligibility and trial

quality were assessed and data were extracted independently by the two reviewers. MAIN RESULTS: Forty-one trials involving over 5000 patients were included. Variation in study design and quality made synthesis of the data problematic. Allocation concealment was adequate in only two trials. Most data were from areas of multidrug resistant falciparum malaria in South East Asia. Compared with standard antimalarial treatments, artemisinin drugs showed fast parasite clearance and high cure rates at follow-up, provided the duration of treatment with artemisinin drugs was adequate. Combination with mefloquine improved sustained parasite clearance and was effective in multidrug resistant areas. When doses were adequate, the combination shortened the duration of treatment. We found no evidence that artemisinin drugs are more harmful than standard treatment drugs over a typical trial period of 28 days.

CONCLUSIONS Artemisinin drugs clear parasitaemia more effectively than standard treatment with chloroquine or sulfadoxine-pyrimethamine in Africa. In South East Asia and Brazil, there is no difference in sustained parasite clearance between artemisinin drugs used alone and standard treatment with quinine or mefloquine. Single-agent treatment with artemisinin drugs is well tolerated. Dizziness in particular is less common than with mefloquine and quinine. Data from Tanzania and Nigeria show that artemisinin drugs clear parasitaemia more effectively than standard treatment with chloroquine or sulfadoxine-pyrimethamine in areas where resistance to those drugs is increasing. Most data are from areas of multidrug resistant falciparum malaria in South East Asia and Brazil. When used alone, even at WHO recommended doses, artemisinin derivatives do not improve sustained parasite clearance compared with quinine or mefloquine standard treatment in these areas. Parasite clearance and fever clearance is achieved earlier if mefloquine is combined with an artemisinin drug compared with mefloquine alone. In areas of mefloquine resistance the combination improves sustained parasite clearance compared with either drug alone. Neuropsychiatric adverse effects have not been reported in patients given only artemisinin derivatives, but have been reported in patients given mefloquine and artemisinin drug combination treatment. Severe vomiting might be less likely with combination treatment compared with mefloquine alone. There are few data on combination treatment with longer-acting antimalarial drugs other than mefloquine. There is no evidence from randomised trials that any artemisinin derivative is better than the others. Most data apply to artesunate and artemether, fewer to artemisinin and very few to dihydroartemisinin. A wide variety of treatment regimens has been tested in randomised trials. The rationale is often not explained in terms of previous clinical or pharmacokinetic findings. Treatment regimens reported as having a comparative advantage in some studies achieve inadequate cure rates. Overall, it appears that if artemisinin drugs are given alone at least 7 days treatment is needed to reliably achieve adequate cure rates; if they are combined with mefloquine at least 3 days treatment is needed with a dose of 1250mg mefloquine in mefloquine-resistant areas. The treatment regimens recommended in WHO guidelines from 1996 may be inadequate and should be revised as a matter of priority.

McIntosh HM

**Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.

BACKGROUND: Amodiaquine and chloroquine give fast relief from malaria symptoms, particularly fever. When used alone in areas where there is some parasite resistance they do not completely clear parasites from the blood in all cases, and so not all patients are cured of infection. The major disadvantage of using sulfadoxine-pyrimethamine alone is that it takes a relatively long time to relieve fever. OBJECTIVES: To assess the effectiveness of chloroquine or amodiaquine given with sulfadoxine-pyrimethamine to treat uncomplicated falciparum malaria. SEARCH STRATEGY: The Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Science Citation Index, African Index Medicus and LILACS were searched. Experts in the field and drug companies were contacted. SELECTION CRITERIA: Randomised and quasi-randomised trials of chloroquine or amodiaquine given with sulfadoxine-pyrimethamine compared with either drug alone in adults or children with confirmed uncomplicated falciparum malaria. DATA COLLECTION AND ANALYSIS: Two people independently applied the inclusion criteria. Data were extracted by the reviewer and checked independently by another person. MAIN RESULTS: Five trials were included. Fever clearance time was reduced by combination therapy compared with sulfadoxine-pyrimethamine alone. Parasite clearance at day seven follow-up was not significantly different for chloroquine or amodiaquine treatment with or without sulfadoxine-pyrimethamine. Parasite clearance at day 28 was better with combination therapy compared with chloroquine or amodiaquine alone (odds ratio 14.28, 95% confidence

interval 6.76 to 30.19), but not significantly better than sulfadoxine-pyrimethamine alone (odds ratio 3.17, 95% confidence interval 0.96 to 10.43). There was no evidence from the included trials of serious side effects with combination treatment.

**CONCLUSIONS:** In areas where chloroquine or amodiaquine are still effective, despite some degree of resistance, using these drugs in combination with sulfadoxine-pyrimethamine, rather than sulfadoxine-pyrimethamine alone, may make people feel better faster and improve sustained parasites clearance.

von Seidlein L, Milligan P, Pinder M, Bojang K, Anyalebechi C, Gosling R, Coleman R, Ude JI, Sadiq A, Duraisingh M, Warhurst D, Allouche A, Targett G, McAdam K, Greenwood B, Walraven G, Olliaro P, Doherty T

**Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial.**

*Lancet* 2000 Jan 29;355(9201):352-7

**BACKGROUND:** Resistance to cheap effective antimalarial drugs, especially to pyrimethaminesulphadoxine (Fansidar), is likely to have a striking impact on childhood mortality in sub-Saharan Africa. The use of artesunate (artesunic acid) [corrected] in combination with pyrimethamine-sulphadoxine may delay or prevent resistance. We investigated the efficacy, safety, and tolerability of this combined treatment. **METHODS:** We did a double-blind, randomised, placebo-controlled trial in The Gambia. 600 children with acute uncomplicated *Plasmodium falciparum* malaria, aged 6 months to 10 years, at five health centres were randomly assigned pyrimethaminesulphadoxine (25 mg/500 mg) with placebo; pyrimethamine-sulphadoxine plus one dose of artesunate (4mg/kg bodyweight); or pyrimethamine-sulphadoxine plus one dose 4 mg/kg bodyweight artesunate daily for 3 days. Children were visited at home each day after the start of treatment until parasitaemia had cleared. **FINDINGS:** The combined treatment was well tolerated. No adverse reactions attributable to treatment were recorded. By day 1, only 178 (47%) of 381 children treated with artesunate were still parasitaemic, compared with 157 (81%) of 195 children in the pyrimethamine-sulphadoxine alone group (relative risk 1.7 [95% CI 1.5-2.0],  $p < 0.001$ ). Treatment-failure rates at day 14 were 3.1% in the pyrimethamine sulphadoxine alone group, and 3.7% in the one-dose artesunate group (risk difference -0.6% [-4.2 to 3.0]) and 1.6% in the three-dose group (1.5 [1.5-4.5],  $p = 0.048$ ). Symptoms resolved faster in children who received artesunate, but there was no additional benefit for three doses of artesunate over one dose. Children given artesunate were less likely to be gametocytaemic after treatment.

**INTERPRETATION:** The combined treatment was safe, well tolerated, and effective. The addition of artesunate to malaria treatment regimens in Africa results in lower gametocyte rates and may lower transmission rates.

Publication Types: Clinical trial, Multicenter study, Randomised controlled trial

Published erratum appears in *Lancet* 2000 Jun 10;355(9220):2080

World Health Organization Division of Child Health and Development and the World Health Organization Regional Office for Africa

**Integrated management of childhood illness: field test of the WHO/UNICEF training course in Arusha, United Republic of Tanzania.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):55-64.

(see chapter Effectiveness of IMCI guidelines)

World Health Organization, Division of Control of Tropical Diseases

**Severe falciparum malaria.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94(Supplement 1):1-90.

This publication is based on an informal technical meeting sponsored by WHO held in 1995 with the objective to review the latest scientific evidence for, and practical experience in, the clinical management of severe malaria in children, adults and pregnant women. The publication gives a comprehensive overview of classification, clinical features and prognostic indices of severe falciparum malaria in children, clinical features and prognostic indices of severe falciparum malaria in adults, and clinical features of severe falciparum malaria in pregnant women. It describes the pathophysiology and pathology of severe

falciparum malaria, diagnosis of malaria and specific drugs in the chemotherapy of severe malaria. Further it describes supportive and ancillary treatment, management of specific problems in severe falciparum malaria with special parts devoted to children and pregnant women. It also gives an overview of common errors in the management of severe falciparum malaria.

Zucker JR, Lackritz EM, Ruebush TK, Hightower AW, Adungosi JE, Were JB, Metchock B, Patrick E, Campbell CC

**Childhood mortality during and after hospitalisation in western Kenya: effect of malaria treatment regimens.**

*American Journal of Tropical Medicine and Hygiene*, 1996, 55(6):655-660.

Plasmodium falciparum infection is an important cause of the high childhood mortality rates in sub-Saharan Africa. Increasingly, the contribution of P. falciparum-associated severe anaemia to paediatric mortality is being recognized while the impact of chloroquine resistance on mortality has not been evaluated. To address the issues of paediatric mortality, causes of death among hospitalised children less than five years of age in western Kenya were identified using standardized clinical examinations and laboratory evaluations. Follow-up examinations were conducted to determine the child's clinical status post hospitalisation. Of the 1,223 children admitted to Siaya District Hospital from March to September 1991, 293 (24%) were severely anaemic (haemoglobin level < 5.0 g/dL). There were 265 (22%) deaths. 121 (10%) occurred in-hospital and 144 (13%) occurred out-of-hospital within eight weeks after admission; 32% of all deaths were associated with malaria. Treatment for malaria with chloroquine was associated with a 33% case fatality rate compared with 11% for children treated with more effective regimens (pyrimethamine/sulfa, quinine, or trimethoprim/sulfamethoxazole for five days). The risk of dying was associated with younger age ( $P < 0.0001$ ) and severe anaemia (relative risk [RRI] = 1.52. 95% confidence interval [CI] = 1.22. 1.90), and was decreased by treatment with an effective antimalarial drug (RR = 0.33, 95% CI = 0.19, 0.65). Effective drug therapy for P. falciparum with regimens that are parasitocidal in areas with a high prevalence of severe anaemia and chloroquine resistance can significantly improve the survival of children in Africa.

## **Documents and publications**

Bosman A, Cattani, JA

***Clinical diagnosis of uncomplicated malaria.***

Informal consultation on the management of uncomplicated malaria and the use of drugs for the protection of travellers convened by WHO in Geneva 18-21 September 1995. Geneva, World Health Organization, 1995, 11 p. (unpublished paper WHO/MAL/IC/WP.95.1; available on request from Division of Control of Tropical Diseases (CTD)).

The paper describes the clinical presentation of malaria, discusses the need for appropriate clinical diagnosis and minimal criteria for clinical assessment and provides the WHO malaria case-definition to guide the management of fever with its rationale.

***Malaria prevention and treatment.***

The Prescriber Published by UNICEF's Programme Division in cooperation with the World Health Organization. 2000, 18: 1-18

The issue covers following topics: The new global Roll Back Malaria partnership. The Global Malaria Burden. Strategies to prevent and control malaria. New risks and new opportunities in the control of malaria. What malaria mosquitoes look like and how they live. How to diagnose malaria. Malaria drug resistance patterns. Treatment of mild and severe malaria. Special concerns for pregnant women and young children. Chemoprophylaxis against malaria. Personal protection and selective vector control measures. How to treat mosquito nets with insecticide.

Schapira A

***A standard protocol for assessing the proportion of children presenting with febrile disease who suffer from malarial disease.***

Geneva, World Health Organization, 1994, 5 p. (unpublished document WHO/MAL/94.1069; available on request from Division of Control of Tropical Diseases (CTD)).  
[http://whqlibdoc.who.int/hq/1994/WHO\\_MAL\\_94.1069.pdf](http://whqlibdoc.who.int/hq/1994/WHO_MAL_94.1069.pdf)

This short document provides a protocol for assessing, in different seasons, the proportion of children aged 2 – 59 months - and/or other groups - presenting to a health facility with febrile disease who suffer from malarial disease.

World Health Organization

***The use of antimalarial drugs: policy implications for the prevention of malaria and the treatment of uncomplicated malaria. Report of a WHO informal consultation, Geneva 13-17 November 2000.***

Geneva, World Health Organization, (unpublished document, in press)

This document updates the document “Management on uncomplicated malaria and the use of antimalarial drugs for the protection of travelers” WHO/MAL/96.1075 Rev 1, 1997 (see this section) with respect to the management of uncomplicated malaria by evaluating current approaches for malaria diagnosis, providing guidelines on the principles of therapy and ancillary treatment, evaluating the roles of currently used antimalarial drugs, and providing recommendations and regimens for the use of antimalarial drugs with special reference to special target groups. In addition, the use of antimalarial drugs currently recommended for chemoprophylaxis is evaluated with special reference to age and population groups, toxicity and interaction with other drugs.

World Health Organization

***Malaria diagnosis. New perspectives. Report of a joint WHO/USAID informal consultation 25 – 27 October 1999.***

Geneva, World Health Organization, 2000, 57 p. (unpublished document WHO/CDS/RBM/2000.14.pdf; available on request from Communication Diseases Cluster, Roll Back Malaria Department)  
[http://whqlibdoc.who.int/hq/2000/WHO\\_CDS\\_RBM\\_2000.14.pdf](http://whqlibdoc.who.int/hq/2000/WHO_CDS_RBM_2000.14.pdf)



Rapid diagnostic tests (RDTs) have introduced a new dimension to the diagnosis and treatment of malaria. They now permit, among other things, on-the—spot confirmatory diagnosis of malaria at the periphery of the health care system by health workers with minimal training. The rational use of RDTs as a complement to microscopy might give substantial health benefits a) through earlier treatment and consequent reduction in morbidity and mortality, b) by targeting expensive drugs and drug combinations to high risk populations in multidrug resistant areas and c) through a more rational use of drugs that might effectively reduce drug pressure and possibly delay the progress of drug resistance. Nevertheless, RDTs are unlikely to be widely adopted until their detection capacities have been improved, their potential benefits have been confirmed, and their cost has come closer to what most malaria control programmes can afford. Addressing these issues, and ensuring the optimal use of RDTs as a key tool in malaria control, will require a coordinated effort among users, control programmes, manufacturers and international agencies.

World Health Organization

***Management of severe malaria: a practical handbook.***

*Second edition.* World Health Organization, Geneva, 2000, vii + 70 pages

ISBN 92 4 154523 2

Sw.fr. 15.–/US \$13.50; in developing countries: Sw.fr. 10.50

Order no. 1152368

The second revised edition of a pocket-sized guide to the rapid diagnosis and management of severe *P. falciparum* malaria. In view of the complexities of management, the need for speed, and the severe consequences of errors, the book adopts a highly didactic approach, offering an at-a-glance reference to the signs to look for, the tests to perform, the actions to take immediately and later, and the nursing care required. Special problems addressed throughout the book include the tendency of malaria to mimic many other diseases, the difficulty of diagnosis in cases of self-medication, the spread of parasite resistance to chloroquine and other drugs, and the need for special precautions in areas where blood may be contaminated with the human immunodeficiency virus (HIV). Addressed to doctors and other medical staff, the book is designed to facilitate rapid decisions and immediate action. Fold-out flaps on the inside and back covers guide the correct selection, dosage, and administration of antimalarial drugs, provide a map showing the global status of chloroquine resistance, and summarize the immediate steps to follow when confronted with thirteen specific complications. Coloured tab dividers make it possible to flip to the appropriate section containing full details on the clinical features and management of a given complication, the general principles of management and nursing care that apply to all patients, and the special protocols to follow when treating children and pregnant women.

World Health Organization

***Expert Committee on Malaria: Twentieth Report***

*Technical Report Series*, No. 892, 2000, v + 71 pages [E, F\*, S\*]

ISBN 92 4 120892 9

Sw.fr. 14.–/US \$12.60; in developing countries: Sw.fr. 9.80

Order no. 1100892



Reports the recommendations and conclusions of an expert committee convened to assess progress in implementation of the Global Malaria Control Strategy, adopted in 1992. Issued at a time when malaria control is one of the highest priorities at WHO, the report offers expert advice on the full range of questions – from the best measures for ensuring early diagnosis and prompt treatment to strategies for the prevention of drug resistance – that can help countries strengthen programmes for control. The report opens with fact, figures, and maps profiling the current global malaria situation, including trends in the spread and intensification of parasite resistance to antimalarial drugs. Section two considers the extent to which each of four technical elements of the global strategy has been implemented over the past decade. The relationship of malaria control programmes to health sector reforms is explored in the next section, which focuses on the impact of health system decentralizations, reforms in health-care financing, and the growth of partnerships with communities and the private sector. Against this background, the components of proper disease management are presented and discussed in terms of their relevance to control programmes. Topics covered include the advantages and disadvantages of diagnosis based on clinical observations, the role of microscopical and other tests for parasite detection, and the factors to consider when deciding on treatment objectives and recommended drugs. The difficult question of drug supply in the absence of formal health services is also considered. Subsequent sections offer advice on techniques for monitoring drug resistance and therapeutic efficacy, strategies for the containment of parasite drug resistance, and methods for the prediction and control of malaria epidemics. A section on the prevention of malaria describes various approaches to vector control, including the use of insecticide-treated bednets and other materials, the management of malaria in development projects, and the current status of drugs used for chemoprophylaxis. The remaining sections discuss information systems and operational research, and describe WHO's new Roll Back Malaria initiative.



World Health Organization

***Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission.***

Geneva, World Health Organization, 1996, 101 p. (unpublished document WHO/MAL/96.1077; available on request from Division of Control of Tropical Diseases (CTD)).

[http://whqlibdoc.who.int/hq/1996/WHO\\_MAL\\_96.1077.pdf](http://whqlibdoc.who.int/hq/1996/WHO_MAL_96.1077.pdf)

This document presents a standard protocol that has been developed specifically for the testing of the therapeutic efficacy of antimalarial drugs against clinically manifest infections with *Plasmodium falciparum* in infants and young children in areas of intense transmission. In the development of this protocol, due note has been taken of earlier work towards the same objective as reflected in WHO document WHO/MAL/94.1070 Antimalarial drug policies (see in this section). The standard protocol takes into account clinical and parasitological response, the need for an efficient technique that provides accurate, reliable and representative results. In the described form the test is simple and feasible, provides the essential information, and requires only modest resources in terms of staff and material. The therapeutic efficacy protocol has in purpose of determining the practical efficacy of a particular drug regimen, with the ultimate objective of ascertaining its continued usefulness or the need for replacing it in the routine treatment of uncomplicated falciparum malaria. This protocol should be applied wherever a drug policy needs to be developed or revised with the intention of effective implementation and evaluation. It has been prepared with particular emphasis on areas with intensive malaria transmission and it requires adaptation for areas with moderate or low endemicity.

World Health Organization

***Management of uncomplicated malaria and the use of antimalarial drugs for the protection of travellers. Report of an informal consultation, Geneva, 18-21 September 1995.*** Geneva, World Health Organization, 1997 (unpublished document WHO/MAL/96.1075 Rev 1 1997; available on request from Division of Control of Tropical Diseases (CTD)).

[http://whqlibdoc.who.int/hq/1996/WHO\\_MAL\\_96.1075.pdf](http://whqlibdoc.who.int/hq/1996/WHO_MAL_96.1075.pdf)

This document complements the document Antimalarial drug policies (WHO/MAL/94.1070) (see this section) with respect to the management of uncomplicated malaria by evaluating current approaches for malaria diagnosis, providing guidelines on the principles of therapy and ancillary treatment, evaluating the roles of currently used antimalarial drugs, and providing recommendations and regimens for the use of antimalarial drugs with special reference to special target groups. In addition, the use of antimalarial drugs currently recommended for chemoprophylaxis is evaluated with special reference to age and population groups, toxicity and interaction with other drugs.

World Health Organization

***Antimalarial drug policies: data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy. Report of an informal consultation, Geneva, 14-18 March 1994.***

Geneva, World Health Organization, 1994, 67 p. (unpublished document WHO/MAL/94.1070; available on request from Division of Control of Tropical Diseases (CTD)).

[http://whqlibdoc.who.int/hq/1994/WHO\\_MAL\\_94.1070.pdf](http://whqlibdoc.who.int/hq/1994/WHO_MAL_94.1070.pdf)

The worsening problems of drug resistance in many parts of the world have led to increasing difficulties for decision-making on the use of antimalarial drugs. This informal consultation was convened to address the broad aspects of the development of national antimalarial drug policies as well as three selected topics essential to this development: (a) treatment of uncomplicated malaria, (b) treatment and prophylaxis of malaria in pregnancy, and (c) monitoring and assessment of efficacy and effectiveness of antimalarial treatments, patient compliance with treatment, antimalarial drug utilization and adverse reactions. The document is divided into 6 chapters. After the Introduction, Chapter 2 describes the current situation concerning drug resistance and drug policies, Chapter 3 defines a national antimalarial policy, its purposes and its essential components, responsibilities and implementation. Chapter 4 deals with the updating of a policy for treatment of uncomplicated malaria. Chapter 5 discusses epidemiological considerations concerning malaria and pregnancy, treatment of acute uncomplicated malaria in pregnancy, control of placental infection and control of maternal anaemia. Chapter 6 reviews methodology for monitoring and

assessment. In annexes are summarized antimalarial drug regimens for the first- or second –line treatment of uncomplicated malaria and the status of antimalarial drugs under development.

World Health Organization

***The overlap in the clinical presentation and treatment of malaria and pneumonia in children. Report of an informal consultation, Geneva, 8 April 1991.***

Geneva, World Health Organization, 1992 (unpublished document WHO/ARI/92.23 and WHO/MAL/92.1065; available on request from Division of Child and Adolescent Health and Development (CAH) and from Division of Control of Tropical Diseases (CTD)).

[http://whqlibdoc.who.int/hq/1992/WHO\\_ARI\\_92.23.pdf](http://whqlibdoc.who.int/hq/1992/WHO_ARI_92.23.pdf)

The consultation discusses the extent of overlap in clinical presentation between pneumonia and malaria in young children based on the current clinical guidelines of the Acute Respiratory Infections Programme, the clinical guidelines of the Malaria Action Programme and studies conducted in Malawi, Gambia and Mozambique. The document provides an overview of current global status of *P. falciparum* resistance to chloroquine and sulfadoxine/pyrimethamine, the current knowledge concerning cotrimoxazole as an antimalarial and cotrimoxazole and sulfadoxine/pyrimethamine interactions as a technical justification of its conclusions. Priorities for further research are outlined.

**CONCLUSIONS:** The meeting concluded that cotrimoxazole for 5 days is an effective antimalarial in children and that, where laboratory facilities are not available, there is sufficient evidence to suggest that the recommendation to treat with both an antibiotic and an antimalarial (in children in malarious areas with fast breathing and fever) should be changed. Cotrimoxazole can be recommended as a single treatment for these children. A policy involving the use of cotrimoxazole as dual therapy for clinically-diagnosed pneumonia and malaria is relevant only to those areas where malaria is moderately to highly endemic, the predominant malaria parasite being transmitted is *P. falciparum*; and *P. falciparum* remains sensitive to sulfadoxine/pyrimethamine.



## 5.3. MEASLES AND VITAMIN A SUPPLEMENTATION

### 5.3.1. MEASLES

#### Documents and publications

World Health Organization

***Clinical research on treatment of measles: report of a meeting.***

Banjul, Gambia, 3-5 November 1993. Geneva, World Health Organization, 1995, 47 p. (unpublished document WHO/CDR/95.15 and WHO/EPI/GEN/95.07; available on request from the Expanded Programme on Immunisation (EPI) and the Division of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1995/WHO\\_CDR\\_95.15.pdf](http://whqlibdoc.who.int/hq/1995/WHO_CDR_95.15.pdf)

**OBJECTIVE:** The objective of the meeting was to examine the current state of knowledge on the clinical case management and treatment of complications of measles, to identify areas of lack of or deficient knowledge on the clinical case management and treatment of measles, its complications, and to plan studies in clinical research which would provide the missing information.

**CONCLUSIONS:** The literature review has highlighted that measles is a major cause of childhood morbidity and mortality. However, most of the data referring to complications are from hospital-based studies and most of them focus on three of the major complications, i.e. pneumonia, croup and diarrhoea. Other complications such as encephalitis, otitis media and stomatitis are not discussed in depth. Of particular concern is the fact that data on the inpatient and outpatient management of measles and its complications are virtually non-existent. This review has highlighted the urgent need for community and hospital studies that address issues such as the natural history of measles and its complications, the aetiology of complications and intervention strategies relating to more effective measles case management.

World Health Organization

***Technical basis for the case management of measles.***

Geneva, World Health Organization, 1995, 28 p. (unpublished document WHO/EPI/95 and WHO/CDR/95; available on request from the Expanded Programme on Immunisation (EPI) and the Division of Child and Adolescent Health and Development (CAH)).

The document outlines the common complications of measles and reviews the various therapeutic options, with a view to improving the understanding of the principles of measles case management. Antibiotic therapy is clearly appropriate when cases of measles are complicated by pneumonia, otitis media, mastoiditis, bacterial tracheitis or dysentery. For children with uncomplicated measles the role of prophylactic antibiotic therapy is less clear. There is thus urgent need for controlled clinical trials to resolve this issue. However, since children with severe malnutrition and HIV infection are at an exceptionally high risk for severe measles disease, they should be given antibiotics to prevent overwhelming bacterial infections. Vitamin A therapy reduces morbidity and mortality in children with measles. Vitamin A should be administered to children with measles according to WHO recommendations. Vitamin A prophylaxis should be provided to children in vitamin A-deficient areas. In case of diarrhoea, the prevention and treatment of dehydration by oral rehydration solution is recommended. Attention to nutritional support in the acute and recuperative stages is essential. As there is significantly increased morbidity and mortality following measles in the months after the acute illness, parents should be encouraged to return to the clinic at regular intervals.

**CONCLUSIONS:** A major aim of the measles control initiative is to reduce measles deaths. This requires, in addition to increasing measles vaccine coverage, proper case management and aggressive treatment of complications. While this document describes WHO's policy on treating cases of measles, it is stressed that primary prevention of measles by immunisation remains the strategy of choice against the disease.

World Health Organization

***Treating measles in children.***

Geneva, World Health Organization, 1997, 56 p. (unpublished document WHO/EPI/TRAM/97.02; available on request from the Global Programme on Vaccines and Immunisation (GPV/EPI)).

The booklet and a set of 35 slides are aimed at health workers, particularly those involved in primary health care initiatives such as immunisation, nutrition, education or maternal and child health, and their corresponding educational institutions. They will also help health workers in treatment centres and hospitals. The material is intended for the training of health workers in measles case management, with emphasis on how to identify, assess and classify a case, prevent, recognize, treat and manage complications.

## 5.3.2. VITAMIN A SUPPLEMENTATION

### Articles

Barclay AJ, Foster A, Sommer A

**Vitamin A supplementation and mortality related to measles: a randomised clinical trial.**

*British Medical Journal Clinical Research Ed.*, 1987, 294(6567):294-296.

One hundred and eighty children admitted with measles were randomly allocated to receive routine treatment alone or with additional large doses of vitamin A (200,000 IU orally immediately and again the next day). Baseline characteristics of the two groups were virtually identical for age, severity of measles, and vitamin A and general nutritional states. In 91% of the children serum vitamin A concentrations were less than 0.56  $\mu\text{mol/l}$ . Of the 88 subjects given vitamin A supplements, six (7%) died; of the 92 controls, 12 (13%) died ( $p = 0.13$ ). This difference in mortality was most obvious for children aged under 2 years (one death out of 46 children receiving supplements versus seven deaths out of 42 controls;  $p$  less than 0.05) and for cases complicated by croup or laryngotracheobronchitis. Mortality was several times higher in marasmic than in better nourished children, regardless of study allocation ( $p$  less than 0.01).

Publication Types: Clinical trial, Randomised controlled trial

Barreto ML, Santos LM, Assis AM, Araujo MP, Farenzena GG, Santos PA, Fiaccone RL

**Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil.**

*Lancet*, 1994, 344(8917):228-231.

A beneficial effect of periodic vitamin A supplementation on childhood mortality has been demonstrated, but the effect on morbidity is less clear. We investigated the effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections (ALRI) in children from north-eastern Brazil in a randomised, double-blind, placebo-controlled community trial. 1240 children aged 6-48 months were assigned vitamin A or placebo every 4 months for 1 year. They were followed up at home three times a week, and data about the occurrence and severity of diarrhoea and ALRI were collected. Any child with cough and respiratory rate above 40 breaths per min was visited by a paediatrician. The overall incidence of diarrhoea episodes was significantly lower in the vitamin-A-supplemented group than in the placebo group (18.42 vs 19.58  $\times 10^{-3}$  child-days; rate ratio 0.94 [95% CI 0.90-0.98]). The benefit of supplementation was greater as regards severe episodes of diarrhoea; the incidence was 20% lower in the vitamin A group than in the placebo group (rate ratio 0.80 [0.65-0.98]). With the standard definition of diarrhoea ( $>$  or = 3 liquid or semi-liquid stools in 24 h) the effect of vitamin A on mean daily prevalence did not reach significance, but as the definition of diarrhoea was made more stringent (increasing number of stools per day), a significant benefit became apparent, reaching for diarrhoea with 6 or more liquid or semi-liquid stools in 24 h a 23% lower prevalence. We found no effect of vitamin A supplementation on the incidence of ALRI. The reduction in severity of diarrhoea may be the most important factor in the lowering of mortality by vitamin A supplementation.

Publication Types: Clinical trial, Randomised controlled trial

Beaton GH et al.

**Vitamin A supplementation and child morbidity and mortality in developing countries.**

*Food and Nutrition Bulletin*, 1994, 15:282-289.

A meta-analysis of eight mortality trials indicates that improving the vitamin A status of children aged six months to five years reduced mortality rates by about 23% in populations with at least low prevalence of clinical signs of vitamin A deficiency. The observed effect of supplementation, described in terms of relative risk (RR), was  $RR = 0.77$  (95% confidence interval 0.68-0.88;  $p < .001$ ) and did not differ by sex

or age. However, the number of lives saved was greater at younger ages because of higher mortality. A significant RR was shown for deaths attributed to diarrhoea and measles, but not for respiratory infection. Variability among the trials in effects was apparent, but attempts to explain it by descriptors of the population (baseline anthropometric status, prevalence of xerophthalmia, age profile, baseline mortality) were unsuccessful. Owing to the lack of data, firm conclusions could not be reached about effectiveness in children less than 6 months and in settings where biochemical but not clinical evidence of vitamin A deficiency exists.

**CONCLUSIONS:** Information about morbidity outcomes from about two dozen studies was reviewed. No consistent effects on frequency or prevalence of diarrhoeal and respiratory infections were found. Improvement in vitamin A status did appear to reduce severe morbidity, particularly in children with measles.

Benn CS, Aaby P, Bale C, Olsen J, Michaelsen KF, George E, Whittle H

**Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, west Africa.**

*Lancet*, 1997, 350(9071):101-105.

**BACKGROUND:** WHO has recommended vitamin A supplementation for children aged 6 months or older in developing countries at the same time as immunisation. One study has reported significantly lower seroconversion ratios among children who have received vitamin A supplements with measles vaccine at age 6 months. The aim of our study was to assess the effect of vitamin A supplementation on antibody response to measles vaccination at age 9 months, which is the more common age for immunisation in developing countries. **METHODS:** In an urban community in Guinea-Bissau, we did a randomised, double-blind, placebo-controlled study of the effect of simultaneous vaccination and vitamin A supplementation in 462 children who received either a two-dose schedule of measles vaccine at the ages of 6 months and 9 months (150 infants) or one dose of measles vaccine at age 9 months (312 infants). Children were followed up to the age of 18 months and a blood sample was then collected to assess the antibody response. **FINDINGS:** 397 (86%) of the children took part in the follow-up (52 [11%] had moved and 13 [3%] had died). Among children who received a two-dose vaccine schedule, seroconversion was 98%. There was no difference in seroconversion or geometric mean titre (GMT) for children receiving vitamin A compared with children receiving no supplement. Among children receiving only one dose of measles vaccine at age 9 months, seroconversion was 95%. The GMT was significantly higher in children receiving vitamin A than in those receiving no supplement (3704 vs 2439 mIU; GMT ratio 1.52 [1.22-1.88]). The effect on plasma antibody concentration in the blood was stronger for boys (3902 vs 1916 mIU; GMT ratio 2.04 [1.53-2.72]) than for girls (3502 vs 3017 mIU; GMT ratio 1.16 [0.85-1.58]) who had received vitamin A with measles vaccine. In a multivariate analysis of variance adjusted for sex, vitamin A supplementation was associated with higher antibody titres ( $p < 0.001$ ). There was a significant interaction between vitamin A supplementation and sex ( $p = 0.02$ ).

**INTERPRETATION:** There is no indication that simultaneous administration of measles vaccine and vitamin A supplements has a negative effect on measles immunity. Among the children who had received two doses of measles vaccine at the ages of 6 months and 9 months, supplements of vitamin A had no significant effect. Among children only receiving one dose of measles vaccine at age 9 months, 100,000 IU vitamin A increased antibody concentrations, especially for boys.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *Lancet* 1997 Jul 12;350(9071):81-2; *Lancet* 1997 Oct 4;350(9083):1031-2

Bhandari N, Bahl R, Sazawal S, Bhan MK

**Breast-feeding status alters the effect of Vitamin A treatment during acute diarrhoea in children.**

*Journal of Nutrition*, 1997, 127(1):59-63.

Vitamin A administration in children reduces the incidence of severe diarrhoea during the subsequent few months. We therefore examined the effect of treatment with vitamin A during acute diarrhoea on the episode duration and severity. In a double-blind controlled field trial, 900 children 1 to 5 y of age with acute diarrhoea of  $<$  or  $=$  7 d duration were randomly assigned to receive vitamin A (60 mg) or a placebo. Children were followed up at home every alternate day until they recovered from the diarrhoeal episode.

In all study children, those treated with vitamin A had a significantly lower risk of persistent diarrhoea [odds ratio (OR) 0.30, 95% confidence interval (CI) 0.07-0.97], but there was no effect on the mean diarrhoeal duration or the mean stool frequency, in the subgroup of children who were not breast-fed, the mean diarrhoeal duration [ratio of geometric means (GM) 0.84, 95% CI 0.72-0.97], mean number of stools passed after the intervention (ratio of GM 0.73, 95% CI 0.56-0.95), the proportion of episodes lasting  $\geq$  14 d ( $P = 0.002$ ) and the percentage of children who passed watery stools on any study day (OR 0.40, 95% CI 0.21-0.77) were significantly lower in those treated with vitamin A.

**CONCLUSIONS:** Administration of vitamin A during acute diarrhoea may reduce the severity of the episode and the risk of persistent diarrhoea in non-breast-fed children. Similar benefit was not seen in breast-fed children.

Publication Types: Clinical trial, Randomised controlled trial

Bhandari N, Bhan MK, Sazawal S

**Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity.**

*British Medical Journal*, 1994, 309(6966):1404-1407.

**OBJECTIVE--**To assess the impact of vitamin A supplementation on morbidity from acute respiratory tract infections and diarrhoea. **DESIGN--**Double blind randomised placebo controlled field trial. **SETTING--**An urban slum area in New Delhi, India. **SUBJECTS--**900 children aged 12-60 months attending a local health facility for acute diarrhoea of less than seven days' duration randomly allocated to receive vitamin A 200,000 IU or placebo. **MAIN OUTCOME MEASURES--**Incidence and prevalence of acute lower respiratory tract infections and diarrhoea during the 90 days after termination of the enrolment diarrhoeal episode measured by twice weekly household surveillance. **RESULTS--**The incidence (relative risk 1.07; 95% confidence interval 0.92 to 1.26) and average number of days spent with acute lower respiratory tract infections were similar in the vitamin A supplementation and placebo groups. Among children aged 23 months or less there was a significant reduction in the incidence of measles (relative risk 0.06; 95% confidence interval 0.01 to 0.48). The incidence of diarrhoea was also similar (relative risk 0.95; 0.86 to 1.05) in the two groups. There was a 36% reduction in the mean daily prevalence of diarrhoea associated with fever in the vitamin A supplemented children older than 23 months.

**CONCLUSIONS:** Results were consistent with a lack of impact on acute lower respiratory tract related mortality after vitamin A supplementation noted in other trials and a possible reduction in the severity of diarrhoea.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *BMJ* 1995 Feb 25;310(6978):530

Hussey GD, Klein M

**A randomised, controlled trial of vitamin A in children with severe measles.**

*New England Journal of Medicine*, 1990, 323(3):160-164.

**BACKGROUND.** Measles kills about 2 million children annually, and there is no specific therapy for the disease. It has been suggested that vitamin A may be of benefit in the treatment of measles. **METHODS.** We conducted a randomised, double-blind trial involving 189 children who were hospitalised at a regional centre in South Africa because of measles complicated by pneumonia, diarrhoea, or croup. The children (median age, 10 months) were assigned to receive either vitamin A (total dose, 400,000 IU of retinyl palmitate, given orally;  $n = 92$ ) or placebo ( $n = 97$ ), beginning within five days of the onset of the rash. At base line, the characteristics of the two groups were similar. **RESULTS.** Although clinically apparent vitamin A deficiency is rare in this population, the children's serum retinol levels were markedly depressed (mean [ $\pm$  SEM], 0.405  $\pm$  0.021  $\mu$ mol per liter [11.6  $\pm$  0.6 micrograms per deciliter]), and 92 percent of them had hyporetinemia (serum retinol level less than 0.7  $\mu$ mol per liter [20 micrograms per deciliter]). Serum concentrations of retinol-binding protein (mean, 30.1  $\pm$  2.0 mg per liter) and albumin (mean, 33.4  $\pm$  0.5 g per liter) were also low. As compared with the placebo group, the children who received vitamin A recovered more rapidly from pneumonia (mean, 6.3 vs. 12.4 days, respectively;  $P$  less than 0.001) and diarrhoea (mean, 5.6 vs. 8.5 days;  $P$  less than 0.001), had less croup (13 vs. 27 cases;  $P = 0.03$ ), and spent fewer days in the hospital (mean, 10.6 vs. 14.8 days;  $P = 0.01$ ). Of the 12 children who



died, 10 were among those given placebo ( $P = 0.05$ ). For the group treated with vitamin A, the risk of death or a major complication during the hospital stay was half that of the control group (relative risk, 0.51; 95 percent confidence interval, 0.35 to 0.74).

**CONCLUSIONS:** Treatment with vitamin A reduces morbidity and mortality in measles, and all children with severe measles should be given vitamin A supplements, whether or not they are thought to have a nutritional deficiency.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *N Engl J Med* 1990 Dec 20;323(25):1774-5

Ross DA, Cutts FT

**Vindication of policy of vitamin A with measles vaccination.**

*Lancet*, 1997, 350(9071):81-82.

WHO has recommended vitamin A supplementation for children aged 6 months or older in developing countries at the same time as immunisation. One study has reported significantly lower seroconversion ratios among children who have received vitamin A supplements with measles vaccine at age 6 months. Benn and colleagues conducted a study in Guinea-Bissau with the aim to assess the effect of simultaneous vaccination and vitamin A supplementation in 462 children who received either a two-dose schedule of measles vaccine at the ages of 6 months and 9 months or one dose of measles vaccine at age 9 months. Children were followed up to the age of 18 months and a blood sample was then collected to assess the antibody response.

**CONCLUSIONS:** The most important finding for public health programmes in developing countries is that high-dose vitamin A supplements can be given safely alongside measles vaccination, whether administered in a single dose at 9 months of age or in a two dose measles vaccination regimen. The policy of administration of vitamin A to 6 – 59 month-old children at opportunities such as during visits for immunisation should be actively implemented.

Types of publication: Comment

The Vitamin A and Pneumonia Working Group

**Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality.**

*Bulletin of the World Health Organization*, 1995, 73(5):609-619.

Reported are the results of a meta-analysis (12 large-scale field trials in seven countries) of the impact of vitamin A supplementation on pneumonia morbidity and mortality, undertaken as part of a wider review process of a range of possible potential interventions for the prevention of childhood pneumonia. The summary estimate of the relative risk for the impact of vitamin A supplementation on pneumonia incidence was 0.95 (95% confidence interval (CI) = 0.89, 1.01), and for pneumonia mortality, 0.98 (95% CI = 0.75, 1.28). This is in marked contrast to the substantial impact of vitamin A supplementation on all-cause mortality (combined rate ratio (RR) = 0.77, 95% CI = 0.71, 0.84), and on diarrhoea-specific and measles-specific mortality. There was no evidence for a differential impact on pneumonia mortality by age. Since the majority of pneumonia deaths occur in the first year of life, we complemented the paucity of data on pneumonia-specific mortality among this age group with a detailed examination of all-cause mortality among infants. The mortality reduction in the 6-11 month age group was consistent with that observed for older age groups (RR = 0.69; 95% CI = 0.54, 0.90), but there was no reduction for 0-5 month-olds (RR = 0.97; 95% CI = 0.73, 1.29).

Publication Types: Meta-analysis

West KP Jr, Katz J, Khattry SK, LeClerq SC, Pradhan EK, Shrestha SR, Connor PB, Dali SM, Christian P, Pokhrel RP, Sommer A

**Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal.** The NNIPS-2 Study  
*British Medical Journal* 1999, 318(7183):570-5

**OBJECTIVE:** To assess the impact on mortality related to pregnancy of supplementing women of reproductive age each week with a recommended dietary allowance of vitamin A, either preformed or as beta carotene. **DESIGN:** Double blind, cluster randomised, placebo controlled field trial. **SETTING:** Rural south-east central plains of Nepal (Sarlahi district). **SUBJECTS:** 44 646 married women, of whom 20 119 became pregnant 22 189 times. **INTERVENTION:** 270 wards randomised to 3 groups of 90 each for women to receive weekly a single oral supplement of placebo, vitamin A (7000 micrograms retinol equivalents) or beta carotene (42 mg, or 7000 micrograms retinol equivalents) for over 3 1/2 years. **MAIN OUTCOME MEASURES:** All cause mortality in women during pregnancy up to 12 weeks post partum (pregnancy related mortality) and mortality during pregnancy to 6 weeks postpartum, excluding deaths apparently related to injury (maternal mortality). **RESULTS:** Mortality related to pregnancy in the placebo, vitamin A, and beta carotene groups was 704, 426, and 361 deaths per 100 000 pregnancies, yielding relative risks (95% confidence intervals) of 0.60 (0.37 to 0.97) and 0.51 (0.30 to 0.86). This represented reductions of 40% (P<0.04) and 49% (P<0.01) among those who received vitamin A and beta carotene. Combined, vitamin A or beta carotene lowered mortality by 44% (0.56 (0.37 to 0.84), P<0.005) and reduced the maternal mortality ratio from 645 to 385 deaths per 100 000 live births, or by 40% (P<0.02). Differences in cause of death could not be reliably distinguished between supplemented and placebo groups. **CONCLUSIONS:** Supplementation of women with either vitamin A or beta carotene at recommended dietary amounts during childbearing years can lower mortality related to pregnancy in rural, undernourished populations of south Asia.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *BMJ* 1999 Feb 27;318(7183):551-2; *BMJ* 1999 Oct 30;319(7218):1201-2; discussion 1203; *BMJ* 1999 Oct 30;319(7218):1202; discussion 1203; *BMJ* 1999 Oct 30;319(7218):1202-3

WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group

**Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy.**

*Lancet* 1998 Oct 17;352(9136):1257-63

**BACKGROUND:** The benefits and safety of vitamin A supplementation linked to immunisation in infancy need to be assessed before it can be widely recommended. We assessed the safety and benefits of maternal postpartum and infant vitamin A supplementation administered with each of the three diphtheria-tetanus-pertussis (DPT) and poliomyelitis immunisations and with a fourth dose with measles immunisation. **METHODS:** From January, 1995, we enrolled 9424 mother-infant pairs from Ghana, India, and Peru in this randomised, double-blind, placebo-controlled trial. 4716 mothers of infants in the vitamin A group received 200000 IU vitamin A, and their infants were given 25000 IU vitamin A with each of the first three doses of DPT/poliomyelitis immunisation at 6, 10, and 14 weeks. In the control group, 4708 mothers and their infants received placebo at the same times. At 9 months, with measles immunisation, infants in the vitamin A group were given a further dose of 25000 IU and those in the control group received 100000 IU vitamin A. Infants were followed up to age 12 months. The primary outcome measures were vitamin A status, signs of acute toxic effects, anthropometric indicators, and severe morbidity. Analysis was by intention to treat. **FINDINGS:** 3933 (93%) of the eligible 4212 infants on vitamin A and 3938 (93%) of the eligible 4227 controls received all four study doses. At the 6-month follow-up, there was a small decrease in vitamin A deficiency in the vitamin A group compared with controls (serum retinol < or =0.70 micromol/L 101 [29.9%] vs 122 [37.1%; 95% CI of the difference -14.3% to -0.2%]). This effect was no longer apparent at 9 and 12 months. There were no significant between-group differences in mortality throughout the study. The rate ratio to compare all deaths up to age 9 months in the two groups was 0.96 (95% CI 0.73 to 1.27). Fewer than 1% of the infants had bulging fontanel. The intervention had no effect on anthropometric status, or on overall or severe morbidity.

**INTERPRETATION:** The trial confirmed the safety of the intervention, but shows no sustained benefits in terms of vitamin A status beyond age 6 months or infant morbidity

## **Documents and publications**

Global Programme for Vaccines and Immunisation, Expanded Programme on Immunisation  
***Integration of vitamin A supplementation with immunisation: policy and programme implications.***  
Report of a meeting, 12-13 January 1998, UNICEF, New York. World Health Organization, Geneva 1998  
20 p. (Unpublished document WHO/EPI/GE/98.07)

There is a wide range of possible ways how children could receive adequate vitamin A supplementation. Immunisation services often provide the only reliable routine contacts with health services for mothers and their infants. The risk of vitamin A deficiency associated mortality is highest in the group of children from 6 to 36 months of age, and this group should receive priority, although efforts should also cover children up to five years of age. Increasingly, countries are choosing to give additional doses of vaccine in their routine immunisation schedule after one year of age. These extra contacts with immunisation services may provide opportunities to give age-specific doses of vitamin A supplements as well. Data concerning seroconversion of measles and polio vaccines when given simultaneously with vitamin A indicate no significant reduction in seroconversion rates. It is anticipated that recommendations will soon also include those visits for DPT, hepatitis B, HiB and yellow fever vaccine as suitable for simultaneous administration of vitamin A. Additional information is being collected to support this before any recommendation is finalized. The document provides target groups, potential immunisation contact and recommended vitamin A doses for vitamin A supplementation.

WHO/UNICEF/IVACG Task Force.

***Vitamin A supplements: A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.***

2nd ed. Geneva, World Health Organization, 1997, vi + 28 pages [E, F\*, S\*]

ISBN 92 4 154506 2, Sw.fr. 14.-/US \$12.60; in developing countries: Sw.fr. 9.80

Order no. 1152303

Provides concise, authoritative advice on the use of high-dose vitamin A supplements for the control of vitamin A deficiency and the emergency treatment of xerophthalmia and other conditions in high-risk groups. Now in its second edition, the guide has been updated and expanded to reflect the latest scientific knowledge, particularly concerning the safety and effectiveness of different dose schedules in different age and population groups. Recommended lines of action also draw on practical experiences gained in the recent international drive to eliminate vitamin A deficiency as a public health problem by the year 2000.

The guide is addressed to programme managers and administrators and aims to answer all practical questions concerning how much vitamin A should be given to different age and population groups, how often, and in what form. Details range from an alert to conditions that should be treated as medical emergencies, through advice on how to calculate procurement requirements, to the simple warning that oil-based preparations should never be injected.

The guide has five sections. The first explains the role of high-dose vitamin A supplements as a proven strategy for controlling xerophthalmia, preventing nutritional blindness and, among deficient populations, reducing the severity and case-fatality rate of certain childhood infections, particularly measles and diarrhoea. Factors influencing the choice of target populations, distribution schemes, and overall programme strategies are also briefly discussed.

Section two presents schedules, for universal and targeted distribution, for the prevention of vitamin A deficiency, xerophthalmia, and nutritional blindness in infants and young children. Questions about safety, side effects, and the potential hazards of overdosing are addressed and clearly answered. Subsequent sections give treatment schedules for xerophthalmia in all age groups and in the special case of pregnant women, and summarize the rationale for supplementation during measles.

Operational issues are discussed in the final and most extensive section, which includes information on the practical and technical advantages of different vitamin A preparations, sources of supplies and their costs,

steps to follow in procurement planning, and various options for channelling delivery through existing health care services.

The guide concludes with a list of countries categorised according to the significance of vitamin A deficiency as a public health problem, a summary of the scientific rationale for vitamin A supplementation, and detailed information on the potency retention, at different storage temperatures, of commonly used vitamin A preparations.

(3<sup>rd</sup> edition is expected early in 2001)



## 5.4. DENGUE

### Articles

Gubler DJ, Meltzer M

**Impact of dengue/dengue haemorrhagic fever on the developing world.**

*Advances in Virus Research* 1999;53:35-70

Publication Types: Historical article, Review, Review, tutorial

The material reviews the changing epidemiology of dengue/dengue haemorrhage fever (DEN/DHF), estimates the global growth in the number of cases of DEN/DHF from 1955 to 1996 and uses these incidence data to estimate the global economic impact of this disease. The disease pattern associated with dengue-like illness from 1780 to a 1940 was characterised by relatively infrequent but often large epidemics. In the years following World War II the frequency of dengue epidemics increased. In every country where the disease emerged as a major public health problem first appeared sporadic cases of DHF occurring for several years, ultimately culminating in a major epidemic. Following the first epidemic a pattern was established with progressively larger epidemics occurring every 3 to 5 years. The reasons for the dramatic resurgence of epidemic DEN/DHF in the waning years of the 20th century are complex and most likely associated with demographic and societal changes. We calculated the average DALYs lost per million population over a 5-year period (1988 – 1992). The annual average DALYs lost to DEN/DHF ranged from 44 per million population in India, to 848 per million in south-east Asia, to 1463 per million in the Chinese province of Guangxi, Guangdong, and Hong Kong. The average over south-east Asia, Western Pacific, Latin America and Caribbean is 621 DALYs per million population. The estimates do not include estimates of DEN/DHF from Africa. Although cases of DEN have been reported in Africa, there are no data sets of reported cases that would allow to estimate actual number of cases. The development of effective therapy and prevention technologies such as vaccines could be the best hope for effectively reducing the number of DEN/DHF cases.

Pinheiro FP, Corber SJ

**Global situation of dengue and dengue haemorrhage fever, and its emergence in the Americas.**

*World Health Statistics Quarterly* 1997;50(3-4):161-9

About two-thirds of the world's population live in areas infested with dengue vectors, mainly *Aedes aegypti*. All four dengue viruses are circulating, sometimes simultaneously, in most of these areas. It is estimated that up to 80 million persons become infected annually although marked underreporting results in the notification of much smaller figures. Currently dengue is endemic in all continents except Europe and epidemic dengue haemorrhage fever (DHF) occurs in Asia, the Americas and some Pacific islands. The incidence of DHF is much greater in the Asian countries than in other regions. In Asian countries the disease continues to affect children predominantly although a marked increase in the number of DHF cases in people over 15 years old has been observed in the Philippines and Malaysia during recent years. In the 1990's DHF has continued to show a higher incidence in south-east Asia, particularly in Viet Nam and Thailand which together account for more than two-thirds of the DHF cases reported in Asia. However, an increase in the number of reported cases has been noted in the Philippines, Lao People's Democratic Republic, Cambodia, Myanmar, Malaysia, India, Singapore and Sri Lanka during the period 1991-1995 as compared to the preceding 5-year period. In the Americas, the emergence of epidemic DHF occurred in 1981 almost 30 years after its appearance in Asia, and its incidence is showing a marked upward trend. In 1981 Cuba reported the first major outbreak of DHF in the Americas, during which a total of 344,203 cases of dengue were notified, including 10,312 severe cases and 158 deaths. The DHF Cuban epidemic was associated with a strain of dengue-2 virus and it occurred four years after dengue-1 had been introduced in the island causing epidemics of dengue fever. Prior to this event suspected cases of DHF or fatal dengue cases had been reported by five countries but only a few of them fulfilled the WHO criteria

for diagnosis of DHF. The outbreak in Cuba is the most important event in the history of dengue in the Americas. Subsequently to it, in every year except 1983, confirmed or suspected cases of DHF have been reported in the Region. The second major outbreak in the Americas occurred in Venezuela in 1989 and since then this country has suffered epidemics of DHF every year. Between 1981 and 1996 a total of 42,246 cases of DHF and 582 deaths were reported by 25 countries in the Americas, 53% of which originated from Venezuela and 24% from Cuba. Colombia, Nicaragua and Mexico have each reported over 1,000 cases during the period 1992-1996. About 74% of the Colombian cases and 97% of the Mexican cases were reported during 1995-1996. A main cause of the emergence of DHF in the Americas was the failure of the hemispheric campaign to eradicate *Aedes aegypti*. Following a successful period that resulted in the elimination of the mosquito from 18 countries by 1962, the programme began to decline and as a result there was a progressive dissemination of the vector so that by 1997 with the exception of Canada, Chile and Bermuda, all countries in the Americas are infested. Other factors contributing to the emergence/re-emergence of dengue/DHF include the rapid growth and urbanisation of populations in Latin America and the Caribbean, and increased travel of persons which facilitates dissemination of dengue viruses. Presently, all four dengue serotypes are circulating in the Americas, thus increasing the risk for DHF in this region.

Publication Types: Review, Review,

Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV

**Dengue and dengue haemorrhage fever.**

*Lancet* 1998 Sep 19;352(9132):971-7

The incidence and geographical distribution of dengue have greatly increased in recent years. Dengue is an acute mosquito-transmitted viral disease characterised by fever, headache, muscle and joint pains, rash, nausea, and vomiting. Some infections result in dengue haemorrhage fever (DHF), a syndrome that in its most severe form can threaten the patient's life, primarily through increased vascular permeability and shock. The case fatality rate in patients with dengue shock syndrome can be as high as 44%. For decades, two distinct hypotheses to explain the mechanism of DHF have been debated-secondary infection or viral virulence. However, a combination of both now seems to be the plausible explanation. The geographical expansion of DHF presents the need for well-documented clinical, epidemiological, and virological descriptions of the syndrome in the Americas. Biological and social research are essential to develop effective mosquito control, medications to reduce capillary leakage, and a safe tetravalent vaccine.

Publication Types: Review, Review, tutorial

Comment in: *Lancet* 1998 Nov 21;352(9141):1712; Comment in: *Lancet* 1999 Mar 27;353(9158):1100-1

Simoes EA

**Dengue haemorrhage fever: reassessment of the current guidelines for clinical recognition of DHF and DSS (early 2001: in preparation)**

## **Documents and publications**

World Health Organization Regional Office for south-east Asia

***Guidelines for the Treatment of Dengue Fever/Dengue Haemorrhage Fever in Small Hospitals***

World Health Organization Regional Office for south-east Asia, 1999, 29p.

The presented guidelines on treatment of dengue/dengue haemorrhage fever (DF/DHF) were adapted from the WHO publication "Dengue Haemorrhage Fever. Diagnosis, Treatment, Prevention and Control" second edition published in 1997. These guidelines are intended to help the staff working in small hospitals to treat uncomplicated cases of DF/DHF. The material provides information on recognition of DF/DHF, disease course and grading of severity of dengue infection. Treatment of DF/DHF is described in details. These guidelines do not address details of prevention and do not include detailed instructions on intensive care. A handout for patients with dengue fever and information on personal protection against DF/DHF is provided in the annexes.

World Health Organization

**Dengue Haemorrhage Fever. Diagnosis, Treatment, Prevention and Control**

*Second edition. WHO Geneva 1997, viii + 84 pages [E, F\*]*

ISBN 92 4 154500 3

Sw.fr. 26.-/US \$23.40; in developing countries: Sw.fr. 18.20

Order no. 1152249

Online edition: <http://www.who.int/emc/diseases/ebola/Denguepublication/index.html>

A practical guide to the diagnosis, treatment, prevention and control of dengue and dengue haemorrhage fever. Now in its second edition, the book has been revised to reflect considerable recent gains in knowledge, particularly concerning methods of laboratory diagnosis and strategies for vector surveillance and control. All dimensions of the global dengue problem - from the characteristics of epidemics to the complexities of diagnosis - are addressed in this concise, yet comprehensive guide.

The book has seven chapters. Background information is provided in the first, which uses findings from recent outbreaks to describe epidemiological patterns, the transmission chain, the pathology and pathogenesis of dengue haemorrhage fever and dengue shock syndrome, and current knowledge about the virus and its vectors. Against this background, clinical chapters set out authoritative recommendations for diagnosis and treatment. Information includes case definitions, criteria for grading the severity of infection, and step-by-step instructions for treatment. A chapter on laboratory diagnosis offers an expert comparative assessment of all methods - whether currently in use or undergoing development - for the laboratory confirmation of diagnosis. Each technique is evaluated in terms of its strengths and weaknesses, speed, reliability, and costs, and the facilities and skills required.

The remaining chapters describe current recommendations for vector surveillance and control, outline activities for disease surveillance and outbreak prevention and control, and discuss the role of primary health care in case detection, patient management, and vector control. Additional practical tools are included in a series of annexes, which contain a number of checklists, flow charts, and model record sheets and reporting forms.





## 5.5. MENINGITIS

### Articles

Gratten M, Barker J, Shann F, Gerega G, Montgomery J, Kajoi M, Lupiwa T

**The aetiology of purulent meningitis in highland children: a bacteriological study.**

*Papua New Guinea Medical Journal* 1985 Dec;28(4):233-40

Of 155 highlands children with purulent culture-positive meningitis studied from March 1980 to September 1984, 84% were aged twelve months or less and 92% were infected with either *Haemophilus influenzae*, *Streptococcus pneumoniae* or both organisms. Other pathogens were *Neisseria meningitidis* (8 isolations), *Streptococcus pyogenes* (2 isolations) and *Streptococcus agalactiae* and *Klebsiella* species (1 of each). Among *H. influenzae* isolates, serotype b strains predominated (83%) and most (96%) belonged to biotype I or II. Infections due to non-b haemophili included serotype a (9 strains), serotype f (1 strain) and non-serotypable variants (3 strains). Of 67 *S. pneumoniae* strains 22% were resistant to benzylpenicillin, with minimal inhibitory concentrations of 0.1-1.0 micrograms/ml. The commonest serotypes were types 5 (11 isolates), type 7 (9 isolates) and types 2, 6 and 46 (6 of each). No resistance to chloramphenicol was detected in either *H. influenzae* or *S. pneumoniae* and only one of 56 strains of *H. influenzae* was insensitive to betalactam antibiotics. The known case fatality rate in this study was 37%. More children with pneumococcal infection died (46%) than those with haemophilus infection (30%), though the difference was not statistically significant; 79% of all deaths occurred in children aged less than twelve months. There is an urgent need for *H. influenzae* and *S. pneumoniae* vaccines that are effective in young children.

Shann F, Barker J, Poore P

**Chloramphenicol alone versus chloramphenicol plus penicillin for bacterial meningitis in children.**

*Lancet* 1985 Sep 28;2(8457):681-4

367 children with cerebrospinal-fluid findings suggestive of bacterial meningitis were randomised to receive either chloramphenicol alone by intramuscular injection, or chloramphenicol plus penicillin by intravenous injection. Sequential analysis showed no difference in mortality between the two treatments. 48 (26%) of the 183 children in the chloramphenicol alone group died, and 49 (27%) of the 184 children in the chloramphenicol plus penicillin group died. In children with bacterial meningitis chloramphenicol alone given by intramuscular injection is as effective as chloramphenicol plus penicillin given intravenously.

Publication Types: Clinical trial, Randomised controlled trial

### Documents and publications

***Antimicrobial and support therapy for bacterial meningitis in Children: Report of the meeting of June 18-20, 1997 held at the World Health Organization, Geneva.*** Geneva, World Health Organization, 1998, 25 p. (unpublished document WHO/CHD/98.6 and WHO/EMC/BAC/98.2; available on request from the Division of Child and Adolescent Health and Development (CAH)).

[http://whqlibdoc.who.int/hq/1998/WHO\\_EMC\\_BAC\\_98.2.pdf](http://whqlibdoc.who.int/hq/1998/WHO_EMC_BAC_98.2.pdf)

The meeting reviewed current practices of the management of meningitis and provides recommendations concerning the antimicrobial therapy for bacterial meningitis, use of chloramphenicol, role of dexamethasone and fluid therapy in the management of meningitis in children in developing countries. It also provides recommendations concerning the testing of cerebrospinal fluid for diagnostic and surveillance purposes. Recommendations for future research are listed.



## 5.6. RELAPSING FEVER, JARISCH HERXHEIMER REACTION

### Articles

#### Importance

Sundnes KO, Haimanot AT

**Epidemic of louse-borne relapsing fever in Ethiopia.**

*Lancet*, 1993, 342:12131215.

During summer 1991 an outbreak of louse-borne relapsing fever occurred simultaneously in two transit camps established for prisoners of war being returned from Eritrea at the end of the Ethiopian civil war. Only antibiotic treatment was given at the Bahr Dar camp where the frequency of cases increased for 20 days. Vector control by delousing in addition to antibiotics was given at Mekele camp where the frequency of cases fell over a similar period. This difference was significant ( $p < 0.001$ ). Furthermore, there was a significant correlation between the decreasing proportion of camp inhabitants that had not been deloused at Mekele camp each day and the numbers of patients with fever ( $r = 0.89$ ,  $p < 0.001$ ).

CONCLUSION: These results confirm that effective control of an epidemic of louse-borne relapsing fever is dependent on efficient vector control in addition to antibiotic treatment.

Published erratum appears in *Lancet* 1994 Jan 22;334(8891):244

Comment in: *Lancet* 1993 Nov 13;342(8881):1192; *Lancet* 1994 Jan 22;343(8891):242

Nordstrand A, Barbour AG, Bergstrom S

**Borrelia pathogenesis research in the post-genomic and post-vaccine era.**

*Current Opinions on Microbiology* 2000 Feb;3(1):86-92

In the two years after publication of the genome sequence of *Borrelia burgdorferi* and reports on human field trials of a vaccine against Lyme borreliosis, there has been further progress in understanding of host-parasite interactions during Lyme borreliosis and relapsing fever. Some mechanisms that *Borrelia* spirochetes use to avoid elimination and to persist in the host are novel. In addition, the recent discovery of antigenic variation in the Lyme disease agent *B. burgdorferi* adds to the complexity of the possible virulence properties of this human pathogen.

Publication Types: Review, Review, tutorial

Raoult D, Roux V

**The body louse as a vector of re-emerging human diseases.**

*Clinical Infectious Diseases* 1999 Oct;29(4):888-911

The body louse, *Pediculus humanus*, is a strict human parasite, living and multiplying in clothing. Louse infestation is associated with cold weather and a lack of hygiene. Three pathogenic bacteria are transmitted by the body louse. *Borrelia recurrentis* is a spirochete, the agent of relapsing fever, recently cultured on axenic medium. Historically, massive outbreaks have occurred in Eurasia and Africa, but currently the disease is found only in Ethiopia and neighbouring countries. *Bartonella quintana* is now recognized as an agent of bacillary angiomatosis bacteraemia, trench fever, endocarditis, and chronic lymphadenopathy among the homeless. *Rickettsia prowazekii* is the agent of epidemic typhus. The most recent outbreak (and the largest since World War II) was observed in Burundi. A small outbreak was also reported in Russia in 1997. Louse infestation appears to become more prevalent worldwide, associated with a decline in social and hygienic conditions provoked by civil unrest and economic instability.

Publication Types: Review, Review,

## Assessment

Borgnolo G, Denku B, Chiabrera F, Hailu B.

**Louse-borne relapsing fever in Ethiopian children: A clinical study.**

*Annals of Tropical Paediatrics*, 1993, 13(2):165-171.

An outbreak of louse-borne relapsing fever, caused by the return to their original recruitment areas of soldiers at the end of 30 years of fighting in northern Ethiopia, was reported in the Arsi region. We studied 103 infants and children with louse-borne relapsing fever who were admitted to Asella Hospital between 1 May 1991 and 30 April 1992. Twenty-one per cent of the patients had a clear history of contact with sick ex-soldiers; 42% were students admitted to the hospital following the re-opening of schools after the summer vacation. The common clinical features of the disease were fever in 100%, headache in 84.5%, chills in 74%, abdominal pain in 51%, epistaxis in 20%, hepatomegaly in 26%, splenomegaly in 14%, petechial rash in 34% and jaundice in 10%. Differences in symptoms and signs according to age are described. Observed complications were pneumonia in 14% and central nervous system involvement in 10%. Four children went into deep coma, and two of them died. Severe disease was associated with a high density of spirochetes in blood smears. Patients were treated with two low doses of penicillin or one dose of penicillin followed by, according to age, chloramphenicol or tetracycline, and with intravenous fluids. The case fatality rate was 1.9%. Jarisch-Herxheimer reactions occurred in 61% of patients. There were relapses in 2.9% of treated patients.

Borgnolo G, Hailu B, Ciancarelli A, Almaviva M, Woldemariam T.

**Louse-borne relapsing fever. A clinical and an epidemiological study of 389 patients in Asella Hospital, Ethiopia.**

*Tropical and Geographical Medicine*, 1993, 45(2): 66-69.

An outbreak of louse-borne relapsing fever, due to the return of soldiers to their original recruitment areas, after the end of thirty years of fighting in northern Ethiopia, was reported in Arsi region, southern Ethiopia. The epidemic spread to different members of the community and eventually the schools. We studied 389 patients affected by the epidemic and who were admitted to Asella Hospital between June 1991 and May 1992. Twenty-seven per cent of the patients were ex-soldiers; 28% were students, who were admitted to the hospital since the schools were opened after the summer vacations. The common clinical features of the disease were fever (99%), headache (92%), hepatosplenomegaly (66%), myalgia (55%), arthralgia (51%), petechial rash (43%), epistaxis (24%) and jaundice (23%). Observed complications were pneumonia (10%), pulmonary oedema (6%), myocarditis (3%) and 6 abortions in 15 pregnancies. Patients were treated with low dose penicillin and i.v. fluids. The in-hospital case fatality rate was 3.6%. Jarisch-Herxheimer reaction occurred in 43% of the patients. 1.8% of the patients had relapses after treatment. Comment in: *Trop Geogr Med* 1994;46(3):192

## Treatment

Beutler B, Munford RS

**Tumour necrosis factor and the Jarisch-Herxheimer reaction.**

*New England Journal of Medicine*, 1996, 335:347-8

Inflammatory host response after the first dose of an effective antimicrobial drug (Jarisch-Herxheimer reaction - JHR) is most often observed when diseases caused by spirochetes are treated with penicillin or tetracycline. In louse-born relapsing fever caused by *Borrelia recurrentis* the JHR is very common, often severe and fatal in some 5% of cases. Fekade and colleagues report that the JHR can be prevented or attenuated by pretreatment with antibodies against tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) These investigators are the first to establish that passive immunization against TNF- $\alpha$  can block the development of a shock-like illness in humans. Also they have validated in humans the long-held assumption that intervention in the septic response is more likely to succeed if instituted early.

Prophylactic use of TNF- $\alpha$  could be considered in other spirochetal infections and perhaps in some bacterial infections as well. In the effort to prevent or treat sepsis, TNF- $\alpha$  remains an attractive therapeutic target.

Borgnolo G, Denku B, Chiabrera F, Hailu B.

**Louse-borne relapsing fever in Ethiopian children: A clinical study.**

*Annals of Tropical Paediatrics*, 1993, 13(2):165-171.

(See this chapter Assessment)

Borgnolo G, Hailu B, Ciancarelli A, Almaviva M, Woldemariam T

**Louse-borne relapsing fever. A clinical and an epidemiological study of 389 patients in Asella Hospital, Ethiopia.**

*Tropical and Geographical Medicine*, 1993, 45(2): 66-69.

(See this chapter Assessment)

Bryceson AD

**Clinical pathology of the Jarisch-Herxheimer reaction.**

*The Journal of Infectious Diseases*, 1976, 133(6):696-704.

The Jarisch-Herxheimer reaction is a complication that can follow treatment of several infectious diseases. Its most severe form is in louse-borne relapsing fever; in this syndrome the reaction can cause death. Information from studies in Ethiopia during the past eight years is presented, and clinical, physiological, pathological, and immunological features of the reaction are described. Possible causative mechanisms of the reaction are discussed, especially in relation to the role of endotoxin, and an attempt is made to consider this reaction in relation to other endotoxin-associated states.

Gebrehiwot T, Fiseha A

**Tetracycline versus penicillin in the treatment of louse-borne relapsing fever.**

*Ethiopian Medical Journal* 1992 Jul;30(3):175-81

A prospective study of 120 louse-borne relapsing fever (LBRF) patient admitted to Mekele Regional Hospital, Tigray, Ethiopia from September to November 1991 was done. The patients were assigned systematically to a single dose of either tetracycline or procaine penicillin (sixty each). Doses given were oral tetracycline 250 mg or intramuscular procaine penicillin 200,000 units for children ages 12 years or less, and 500 mg or 600,000 IU for adults, respectively. The aim of this study was to compare the clinical effectiveness of tetracycline to that of procaine penicillin. Both drugs induced a Jarisch-Herxheimer (JH) like reaction, which was clinically similar in the two treatment groups, but peaked later and was more prolonged in the patients treated with procaine penicillin. Spirochetes cleared more slowly and relapses were noticed only in the procaine penicillin treated group. Thus, tetracycline is recommended as first choice therapy and a single dose is sufficient for treatment of LBRF patients.

Publication Types: Clinical trial, Controlled clinical trial

Griffin GE

**Cytokines involved in human septic shock—the model of the Jarisch-Herxheimer reaction.**

*Journal of Antimicrobial Chemotherapy* 1998 Jan;41 Suppl A:25-9

Studies of the cytokine cascade in animal models of infection and human experiments involving endotoxin infusion have contributed fundamentally to understanding the role of cytokines in human sepsis. The complexity of this cytokine cascade has been difficult to unravel in clinical sepsis. However, the Jarisch-Herxheimer reaction has been identified as a model of the cytokine cascade in human sepsis and has provided an excellent model for experiments involving blocking agents. TNF blocking has been shown to be important for protection in animal models of sepsis, but has been somewhat disappointing in humans because adverse events have generally outweighed benefits.

Knaack RH, Wright LJ, Leithead CS, Kidan TG, Plorde JJ.

**Penicillin vs. tetracycline in the treatment of louse-borne relapsing fever: A preliminary report.**  
*Ethiopian Medical Journal*, 1972, 10(1):15-22.

Twenty five patients with louse-borne relapsing fever were treated with either a single parenteral injection of tetracycline hydrochloride or penicillin aluminium monostearate. The Jarisch-Herxheimer like reaction accompanying therapy was less severe in the penicillin treated patients. There were no deaths and no relapses noted in either treatment group. Penicillin aluminium monostearate is recommended for the treatment of this disease.

Rahlenbeck SI, Gebre-Yohannes A

**Louse-borne relapsing fever and its treatment.**

*Tropical Geographic Medicine* 1995;47(2):49-52

Publication Types: Review, Review, tutorial

This review of published reports on the clinical course and treatment of louse-born relapsing fever has shown that previous studies have often not made the best use of their data. Though several authors and textbooks recommend tetracycline as treatment of choice in adults, one has to bear in mind that this drug will induce a severe Jarisch-Herxheimer (JHR) reaction in all patients. Doxycycline induces JHR at the same rate as other tetracyclines. Erythromycine seems to be a satisfactory alternative and is recommended for pregnant women and children. Less efficient drugs such as penicillin are often followed by a relapse. However, pretreatment with low-dose penicillin to be followed by tetracycline seems to offer a good compromise between minimal side-effects and maximal efficacy. Controlled clinical trials are needed to establish which dose and regimen should be considered the treatment of choice.

Seboxa T, Rahlenbeck SI

**Treatment of louse-borne relapsing fever with low dose penicillin or tetracycline: a clinical trial.**

*Scandinavian Journal of Infectious Diseases*, 1995, 27(1):29-31.

A clinical trial was conducted in order to evaluate the efficacy of procaine penicillin and tetracycline, respectively, in the treatment of louse-borne relapsing fever. 184 patients (160 men, 24 women) admitted to the Gondar hospital during the rainy season 1992 were assigned to 1 of 4 treatment groups: procaine penicillin 100,000 (PP100), 200,000 (PP200) or 400,000 (PP400) international units (IU) intramuscularly (i.m.), or tetracycline 250 mg per os (TTC, p.o.). All drugs were given as single doses. The overall case fatality rate was 3.3%. Frequency of relapses, Jarisch-Herxheimer-like reactions (JHR) and deaths were significantly different between patients treated with TTC and those treated with PP100. Relapses occurred most often in the group receiving the lowest dose of penicillin (46%), and decreased with increasing dosage of penicillin; none of the patients treated with TTC had a relapse. Occurrence of JHR showed the opposite pattern: whilst 2 (5%) patients treated with PP100 developed a JHR, 16 (29%) in the PP200 group, 10 (31%) in the PP400 group, and 27 (47%) in the TTC group developed a JHR. As mortality is linked to severe JHR, and most relapses are clinically mild and easily treated, these results speak in favour of using low-dose penicillin to initiate the treatment of relapsing fever.

Publication Types: Clinical trial, Controlled clinical trial

## 5.7. SORE THROAT, RHEUMATIC FEVER

### Articles

#### Importance

Alpert JJ, Pickering MR, Warren RJ

**Failure to isolate streptococci from children under age 3 with exudative tonsillitis.**

*Pediatrics*, 1966, 38:663-666.

Forty seven children less than 3 years of age with exudative tonsillitis were studied and only 7 (14.6%) were found to have streptococci. Attempts to explain the aetiology of this syndrome by virological study were unsuccessful, although 22% of 27 patients studied did have evidence of virus infection. Children with exudate in this age group do not usually require antimicrobial therapy unless there is a proof by culture of the presence of streptococci or unless there is other clinical indication such as otitis media. The presence of exudate is, in fact, a strong indication that the streptococcus is not the etiologic agent.

Carapetis JR, Currie BJ

**Group A streptococcus, pyoderma, and rheumatic fever.**

*Lancet*, 1996, 347(9010):1271-1272.

Publication Types: Letter

Authors recently described the highest published rates of rheumatic fever in the world in Aboriginal population of northern Australia. Among this population, streptococcal pyoderma is endemic, with up to 70 % of children in some communities being affected. In the same population, throat carriage of group A streptococci (GAS) are extremely low (usually 1 % to 5 %). Recent work from New Zealand has identified many rheumatic fever-associated isolates of GAS as coming from serotypes traditionally associated with pyoderma. In one of Trinidad studies half of all rheumatic fever episodes were not preceded by symptomatic pharyngitis, 38 % of rheumatic fever patients had recent skin infection, and one of the two most common rheumatic fever-associated strains of GAS came from a “pyoderma” serotype. Authors believe that it is important in endemic areas to include major primary prevention efforts where the majority of GAS disease exists – the skin – with community based scabies and pyoderma control programmes.

Ghana Health Assessment Project Team

**A quantitative method of assessing the health impact of different diseases in less developed countries.**

*International Journal of Epidemiology*, 1981, 10(1):73-80.

A method is described for assessing quantitatively the relative importance of different disease problems on the health of a population. The impact of a disease on a community is measured by the number of healthy days of life which are lost through illness, disability and death as a consequence of the disease. The measure is derived by combining information on the incidence rate, the case fatality rate and the extent and duration of disability produced by the disease. In Ghana, it is estimated that malaria, measles, childhood pneumonia, sickle cell disease and severe malnutrition are the 5 most important causes of loss of healthy life and between them they account for 34% of healthy life lost due to all diseases. The methodology may be used to help determine the priorities for the allocation of resources to alternative health improvement procedures by estimating the number of healthy days of life which are likely to be saved by different procedures and by relating these savings to the costs of the procedures.



Martin DR, Voss LM, Walker SJ, Lennon D

**Acute rheumatic fever in Auckland, New Zealand: spectrum of associated group A streptococci different from expected.**

*The Pediatric Infectious Disease Journal*, 1994, 13(4):264-269.

Annual specific rates for acute rheumatic fever (ARF) in Auckland children less than 15 years were 22/100,000 for the years 1980 to 1984. From 1984 to 1992 the rates remained relatively constant with an average of 45 (range, 30 to 70) children annually admitted with ARF to the Auckland Children's Hospital. This study examined retrospectively Group A streptococci identified from hospitalised paediatric patients during these 9 years. The total of 2410 isolates included 32 isolates from well-documented cases of ARF and an additional 6 from siblings of cases. Results of M typing indicated that streptococci associated with ARF are generally different from those described overseas and involved types which cause more skin than throat infections in the community.

Padmavati S

**Present status of rheumatic fever and rheumatic heart disease in India.**

*Indian Heart Journal* 1995 Jul-Aug;47(4):395-8

This paper examines the present status of Rheumatic fever (RF) and Rheumatic heart disease (RHD) in India with reference to both prevalence and incidence, and evaluates the currently available methods of control. Data available over the last 10 years shows that the prevalence of RF/RHD in the most vulnerable group i.e. school children between 5 to 15 years of age is still unacceptably high. RHD is encountered in 1 to 5.4 per 1,000 in large samples of school children and RF in 0.3 to 0.5 per 1,000 children. There appears to be no obvious decline in its prevalence in school children over a 20 year period. Because of preoccupation with adult cardiac diseases specially ischaemic heart disease (IHD), the problem of RF/RHD has been sidelined and studies on prevalence, treatment and prevention receive scant attention. Only exotic palliative methods such as balloon mitral valvotomy (BMV) have become the centre stage. Studies are needed on the lines of WHO recommendations for the regional prevalence of RF/RHD in school children throughout the country to detect regional variations. The most effective method for control is primary prevention by treating streptococcal sore throat and secondary prevention by early detection and continuous penicillin prophylaxis. This could be done most effectively by general physicians (GP's) who need motivation and education and through school health services. The latter needs to be organised on a state-wise basis throughout the country as it is available in only a few cities. Public health education by all available media specially, through video films is also recommended. The lacunae in our knowledge of RF/RHD calls for further research.

Schwartz RH, Wientzen RL, Fleming K, Schweisthal PE

**Streptococcal pharyngitis in infants: a reappraisal of its prevalence.**

*Southern Medical Journal*, 1981, 74:325-326.

The prevalence of group A streptococcal pharyngitis in children under 3 years of age was determined by retrospective review of the results of throat cultures taken from children seen in a middle-class, suburban, private paediatric practice. Of 2,200 throat cultures obtained, 7% (149) were from children in this age group, and 15% (23) of these were positive for group A streptococci. All children had pharyngeal injection and the majority were symptomatic, with fever, rash, or rhinitis. Exudative pharyngitis was rare. This study suggests that pharyngeal infection with this organism in infants and young children is not uncommon, and justifies the need for throat cultures in this population.

Strasser T, Dondog N, El Kholy A, Gharagozloo R, Kalbian VV, Ogunbi O, Padmavati S, Stuart K, Dowd E, Bekessy A

**The community control of rheumatic fever and rheumatic heart disease: report of a WHO international co-operative project.**

*Bulletin of the World Health Organization*, 1981, 59(2):285-294.

The feasibility and effectiveness of a programme for the community control of rheumatic fever and rheumatic heart disease were studied in a co-operative multicentre project initiated and coordinated by the World Health Organization. The programme was carried out in seven centres in various developing countries of Africa, America and Asia according to a common protocol, and is under way in a further eight countries in Latin America. Pilot community programmes were shown to be practicable and effective in reducing the burden of rheumatic heart disease in developing countries and their extension to cover entire populations should be encouraged.

## Assessment

Attia M, Zaoutis T, Eppes S, Klein J, Meier F

**Multivariate predictive models for group A beta-haemolytic streptococcal pharyngitis in children.**

*Academic Emergency Medicine* 1999 Jan;6(1):8-13

**OBJECTIVES:** To create predictive models for the clinical diagnosis of group A beta-haemolytic streptococcal (GABHS) pharyngitis in children. **METHODS:** Patients aged 6 months to 18 years presenting to a paediatric ED with suspected GABHS pharyngitis were prospectively enrolled in the study. Clinicians recorded pertinent clinical information using a standardized form and obtained a throat swab to culture GABHS using a reference standard method. Twelve demographic and clinical features of patients with positive throat cultures were compared with the features of patients with negative throat cultures. Significantly different features were entered in a stepwise logistic regression analysis to create predictive models for the diagnosis. **RESULTS:** Eighty-five patients (29%) were culture-positive and 212 (71%) were culture-negative for GABHS. Respective mean ages were 6.2 years and 6.1 years in the two groups. Univariate chi-square analysis of the 12 features identified six variables that were significantly associated with GABHS. All significant features were initially included in a stepwise logistic regression analysis. In model I, four independent variables were identified: moderate to severe presentation of tonsillar swelling, moderate to severe tenderness and enlargement of cervical lymph nodes, the presence of scarlatiniform rash, and the absence of moderate to severe coryza, yielding a 95% probability for GABHS. Excluding the rare scarlatiniform rash, the remaining variables were used in the second regression analysis. In model II, three independent variables were identified: moderate to severe tonsillar swelling, moderate to severe tenderness and enlargement of cervical lymph nodes, and absence of moderate to severe coryza, yielding a probability of 65% for the diagnosis. A probability of <15% was observed in the absence of scarlatiniform rash, the absence of moderate to severe tenderness and enlargement of cervical lymph nodes, and the presence of moderate to severe coryza.

**CONCLUSIONS:** In children with moderate to severe presentation of tonsillar swelling, tenderness and enlargement of cervical lymph nodes, and the absence of coryza, the probability of a positive throat culture is >65%. Conversely, in the absence of a moderate to severe presentation of tonsillar swelling, enlargement of cervical nodes, and the presence of coryza, the probability of a positive throat culture is <15%. If prospectively validated, these models could be integrated into a consistent treat, test, and no treatment/no testing approach to the clinical management of childhood pharyngitis.

Publication Types: Clinical trial

Gove S, Cardona PN, Tulloch J

**Streptococcal pharyngitis in Egyptian children.**

*Lancet*, 1998, 351:64-65.

Steinhoff and colleagues (see Steinhoff et al. 1997 this section) propose a modification of WHO guidelines for the presumptive treatment of streptococcal pharyngitis. They suggest a modified guideline whereby

pharyngeal exudates or large cervical nodes would indicate antibiotic treatment. The implication of this proposal should be looked at from a broader public health perspective. In various scenarios based on the incidence of symptomatic pharyngitis in the age group investigated (2 –13 years), proportion of streptococcal etiology of the pharyngitis, and the incidence of rheumatic heart disease (the main target of primary prevention) 500 to 2,640 cases of pharyngitis must be treated to prevent one case of rheumatic heart disease.

**CONCLUSIONS:** The extensive antibiotic-based primary prevention strategy for rheumatic heart disease advocated by Steinhoff and colleagues implies substantial financial and human resources, and it may be that a more cost effective use of these resources can be made in other areas of child health.

Publication Types: Comments, letter

Steinhoff MC, Abd el Khalek MK, Khallaf N, Hamza HS, el Ayadi A, Orabi A, Fouad H, Kamel M  
**Effectiveness of clinical guidelines for presumptive treatment of childhood streptococcal pharyngitis in Egyptian children.**  
*Lancet*, 1997, 350(9082):918-921.

**BACKGROUND:** Primary prevention of acute rheumatic fever requires antibiotic treatment of acute streptococcal pharyngitis. In developing countries, clinicians must rely on clinical guidelines for presumptive treatment of streptococcal pharyngitis since bacterial culture and rapid diagnostic tests are not feasible. We evaluated the WHO Acute Respiratory Infection guideline in a large urban paediatric clinic in Egypt. **METHODS:** Children between 2 and 13 years of age who had a sore throat and pharyngeal erythema were enrolled in the study. Clinical, historical, and demographic information was recorded and a throat culture for group A beta-haemolytic streptococci was done. Sensitivity (% of true-positive throat cultures) and specificity (% of true-negative throat cultures) were calculated for each clinical feature. The effect of various guidelines on correct presumptive treatment for throat-culture status was calculated. **FINDINGS:** Of 451 children with pharyngitis, 107 (24%) had group A beta-haemolytic streptococci on throat culture. A purulent exudate was seen in 22% (99/450) of these children and this sign was 31% sensitive and 81% specific for a positive culture. The WHO Acute Respiratory Infections (ARI) guidelines, which suggest treatment for pharyngeal exudate plus enlarged and tender cervical node, were 12% sensitive and 94% specific; 13/107 children with a positive throat culture would correctly receive antibiotics and 323/344 with a negative throat culture would, correctly, not receive antibiotics. Based on our data we propose a modified guideline whereby exudate or large cervical nodes would indicate antibiotic treatment, and this guideline would be 84% sensitive and 40% specific; 90/107 children with a positive throat culture would correctly receive antibiotics and 138/344 with a negative throat culture would, correctly, not receive antibiotics.

**INTERPRETATION:** The WHO ARI clinical guideline has a high specificity but low sensitivity that limits the unnecessary use of antibiotics, but does not treat 88% of children with a positive streptococcal throat culture who are at risk of acute rheumatic fever. A modified guideline may be more useful in this population. Prospective studies of treatment guidelines from many regions are needed to assess their use since the frequency of pharyngitis varies.

Comment in: *Lancet* 1997 Sep 27;350(9082):899-900; *Lancet* 1998 Jan 3;351(9095):64-5

Comment in: *Lancet* 1998 Jan 3;351(9095):64 : see Gove S. in this section

## Treatment

Del Mar CB, Glasziou PP, Spinks AB  
**Antibiotics for sore throat (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.

**BACKGROUND:** Sore throat is a very common reason for people to attend for medical care. Sore throat is a disease that remits spontaneously, that is, 'cure' is not dependant on treatment. Nonetheless primary care doctors commonly prescribe antibiotics for sore throat and other upper respiratory tract infections.

**OBJECTIVES:** To assess the benefits of antibiotics in the management of sore throat. **SEARCH STRATEGY:** Systematic search of the literature from 1945 to 1999, using electronic searches of

MEDLINE (using the keywords, “pharyngitis”, “sore throat” and “tonsillitis”) after 1966, the Cochrane Library, the Cochrane collection of hand-searched trials, and the reference sections of the articles identified. Abstracts of identified articles were used to determine which studies were trials. **SELECTION CRITERIA:** Trials of antibiotic against control with either measures of the typical symptoms (throat soreness, headache or fever), or complications (suppurative and non-suppurative) of sore throat. **DATA COLLECTION AND ANALYSIS:** RevMan 4.0.3 **MAIN RESULTS:** A total number of 10,484 cases of sore throat have been studied. 1. Non-suppurative complications: There was a trend for protection against acute glomerulonephritis by antibiotics, but insufficient cases were recorded to be sure of this effect. Several studies found benefit from antibiotics for acute rheumatic fever, which reduced this complication to less than one third (OR = 0.30; 95% CI = 0.20-0.45). 2. Suppurative complications: Antibiotics reduced the incidence of acute otitis media to about one quarter of that in the placebo group (OR = 0.22; 95% CI = 0.11-0.43) and reduced the incidence of acute sinusitis to about one half of that in the placebo group (OR = 0.46; 95% CI = 0.10-2.05). The incidence of quinsy was also reduced in relation to placebo group (OR = 0.18; 95% CI = 0.08-0.43). 3. Symptoms: Symptoms of headache, throat soreness and fever were reduced by antibiotics to about one half. The greatest time for this to be evident was at about three and a half days (when the symptoms of about 50% of untreated patients had settled). About 90% of treated and untreated patients were symptom-free by one week. 4. Subgroup analyses of symptom reduction Subgroup analysis by age; blind vs unblinded; use of antipyretics; or results of swabs for Streptococcus yielded no significant differences.

**CONCLUSIONS:** Acute rheumatic fever is common among people living in some parts of the world (Australian Aborigines living in poor socioeconomic conditions, for example), and antibiotics may be justified to reduce the complication of acute rheumatic fever in these settings. For other settings where rheumatic fever is rare, there is a balance to be judged between modest symptom reduction and the hazards of antimicrobial therapy. Since ninety percent of patients are symptom free by one week (in both groups), the absolute benefit of antibiotics at this time and beyond is vanishingly small. Assuming a complication rate of five percent for otitis media in untreated children and one percent for adults, and an odds ratio of 0.23 for treatment with antibiotics, then about 30 children and 145 adults with sore throat must be treated with antibiotics to prevent one episode of acute otitis media. Antibiotics have a small beneficial effect on both suppurative and symptom reduction. The effect is so small that clinicians must judge with individual cases whether it is clinically justifiable to employ antibiotics to produce this small effect. In other words their use appears to be discretionary rather than either prohibited or mandatory.

World Health Organization, Cardiovascular Diseases Unit and principal investigators

**WHO programme for the prevention of rheumatic fever/rheumatic heart disease in 16 developing countries: report from Phase I (1986-90).**

*Bulletin of the World Health Organization* 1992;70(2):213-8

The programme was initiated in 1984 by WHO in close collaboration with the International Society and Federation of Cardiology (ISFC). Sixteen countries in five WHO Regions participated: Mali, Zambia and Zimbabwe (in Africa); Bolivia, El Salvador and Jamaica (in the Americas); Egypt, Iraq, Pakistan and Sudan (in the Eastern Mediterranean); India, Sri Lanka and Thailand (in south-east Asia); and China, the Philippines and Tonga (in the Western Pacific). The programme was planned for implementation in three phases: pilot study and control programme in a selected area, control programmes in all the selected communities, and their extension to the whole country. In Phase I, a total of 1,433,710 schoolchildren were screened and 3135 cases of rheumatic fever/rheumatic heart disease (RF/RHD) were found, giving a prevalence of 2.2 per 1000 (higher in the African and Eastern Mediterranean regions); 33,651 recently identified or already known cases were registered; completion of secondary prophylaxis was irregular but averaged 63.2% coverage; percentages of adverse reactions (0.3%) and recurrence of acute RF (0.4%) were very small; 24,398 health personnel and teachers were trained. Health education activities were organised for patients, their relatives, and the general public in hundreds of health education sessions. Thousands of pamphlets, brochures and posters were distributed, and health education programmes were broadcast on radio and television. The quality of care for RF/RHD patients improved under the programme, which has been expanded to other areas.

No authors listed

**Strategy for controlling rheumatic fever/rheumatic heart disease, with emphasis on primary prevention: memorandum from a joint WHO/ISFC meeting.**

*Bulletin of the World Health Organization*, 1995, 73(5):583-7

This memorandum summarizes the report of a meeting held in Geneva on 7-9 September 1994. Experts and representatives from different countries and regions, as well as WHO, the International Society and federation of Cardiology, UNESCO, and the International Council of Nurses evaluated the experience in controlling rheumatic fever/rheumatic heart disease (RF/RHD) and provided an update on the essential components of RF/RHD prevention, including new areas for research in primary prevention. The meeting's recommendations should be applicable in all countries where RF/RHD is a health problem.

## **Documents and publications**

Achutti A, Kaplan EL, Nordet P, Van der Vynckt S

**Streptococcal Sore Throat. Rheumatic Fever. Rheumatic Heart Disease.**

A reference for physicians and paramedical personnel.

*UNESCO, WHO, ISFC*, 15 p.

This informal brochure is designed for use by primary health care physicians and paramedical personnel in countries where rheumatic fever and rheumatic heart disease are of public health concern. The booklet provides an overview of clinical and epidemiological aspects of Group A streptococcal upper respiratory infection, rheumatic fever and rheumatic heart disease, prevention of rheumatic fever, rheumatic heart disease and infective endocarditis.

World Health Organization

***Joint WHO/ISFC Meeting on Rheumatic Fever/Rheumatic Heart Disease Control, with emphasis on Primary Prevention. Geneva, 7-9 September 1994.*** Geneva, World Health Organization, 1994, 52 p.

(unpublished document WHO/CVD/94.1; WHO Cardiovascular Diseases (CVD)).

[http://whqlibdoc.who.int/hq/1994/WHO\\_CVD\\_94.1.pdf](http://whqlibdoc.who.int/hq/1994/WHO_CVD_94.1.pdf)

The report provides conclusions and recommendations on essential components for primary prevention: epidemiology, laboratory aspects of Group A haemolytic Streptococci infections, diagnosis and management of Group A streptococcal pharyngitis, feasibility under different socioeconomic conditions, cost effectiveness, role of physicians, nurses and health workers and health education and information. New areas for research a primary prevention are suggested. Annexed are: presentation "40 Years' experience of RF/RHD prevention" by Dr. P. Nordet, Report on the current WHO Global Programme for the Prevention and Control of RF/RHD supported by AGFUND, Report on the current WHO Global Programme for the Prevention and Control of RF/RHD supported by ISFC and Guideline for a community-based programme WHO/ISFC Global programme for the prevention and control of rheumatic fever/rheumatic heart disease with emphasis on primary prevention.

## 5.8. TYPHOID/PARATYPHOID

### Articles

#### Treatment

Du Pont HL, Hornick RB, Weiss CF, Snyder MJ, Woodward TE

**Evaluation of chloramphenicol acid succinate therapy of induced typhoid fever and rocky mountain spotted fever.**

*New England Journal of Medicine*, 1970, 282(2):53-57.

In volunteers with induced typhoid fever plasma levels of free biologically active chloramphenicol were approximately twice as high in those treated with oral chloramphenicol (4 subjects) as in those treated with the same dose of intramuscular chloramphenicol succinate (4 subjects), apparently owing to the failure of the intramuscularly administered succinate ester to be completely hydrolysed to the active drug. Plasma chloramphenicol levels in 9 volunteers infected with Rocky Mountain spotted fever and treated with chloramphenicol succinate intramuscularly revealed that approximately a third of the administered drug was present in the biologically inactive unhydrolysed form. Although chloramphenicol succinate was effective in controlling the early toxicity of induced typhoid fever and Rocky Mountain spotted fever, the delayed response and high relapse rate made this preparation inadequate as the sole form of therapy given intramuscularly in conventional doses.

Publication Types: Clinical trial

Maheshwari VD, Agarwal SK

**Present status of drug resistance in cases of enteric fever in Rajasthan.**

*Journal of the Association of Physicians of India*, 1996, 44(9):618-619.

Drug Sensitivity of *Salmonella typhi* isolated from 30 blood culture positive cases of typhoid fever who presented between Nov. '93 to Aug. '94 was tested to determine their in vitro susceptibility to various antimicrobials. 56.6% showed resistance to chloramphenicol, 70% to amoxycillin, 50% to amikacin, 43.3% to gentamicin, 40% to ampicillin, 33.3% to cotrimoxazole, 30% to cephalexin and very low resistance (6.6% each) to ceftriaxone and cefotaxime. All the 30 cases were sensitive to ciprofloxacin and ofloxacin. 17 chloramphenicol resistant typhoid cases in whom chloramphenicol was initially started failed to respond to this drug even after 4-5 days therapy, indicating that in vivo response matched with the in vitro sensitivity. Clinical response to ciprofloxacin, whether given initially or following chloramphenicol failure was prompt and satisfactory. Ciprofloxacin thus appears to be a good choice in such cases.

Mirza SH, Beeching NJ, Hart CA

**The prevalence and clinical features of multi-drug resistant *Salmonella typhi* infections in Baluchistan, Pakistan.**

*Annals of Tropical Medicine and Parasitology*, 1995, 89(5):515-519.

Between January and July 1994, a prospective study of bacteraemia in 692 patients with fever without localising signs was undertaken at the Quetta Military Hospital in Baluchistan, Pakistan. *Salmonella* spp. were isolated from 76 (11%) of the patients; 62 had *S. typhi* and 14 had *S. paratyphi* A. Significantly more isolations of *S. typhi* were made in the hot dry months of May and June than in the earlier months. Although multi-drug resistance (to chloramphenicol ampicillin and cotrimoxazole) was detected in 43 (69%) of the *S. typhi* isolates, it was not found in any of the *S. paratyphi* A. Defervescence of patients with chloramphenicol-sensitive *S. typhi* took 7-10 days of chloramphenicol therapy. In contrast, most (91%)

of the patients infected with multi-drug resistant *S. typhi* who were treated with fluoroquinolones achieved defervescence in 1-3 days; the remainder took 4-6 days.

Naqvi SH, Bhutta ZA, and Farooqui BJ.

**Therapy of multidrug resistant typhoid in 58 children.**

*Scandinavian Journal of Infectious Diseases*, 1992, 24(2):175-179.

Treatment of children with infections caused by *Salmonella typhi* strains resistant to the commonly used oral antimicrobials is a special problem. As children cannot be treated with quinolones, there is no form of oral therapy. Third generation cephalosporins, which have been shown to be effective against typhoid caused by ampicillin sensitive strains of *S. typhi* were effective against typhoid caused by ampicillin, chloramphenicol and sulfamethoxazole/trimethoprim-resistant strains. We treated 28 children with ceftriaxone and 8 with cefotaxime. We found ceftriaxone to be more effective than cefotaxime with significantly lower relapse rate. Antibiotic therapy of 19 other children, initially treated in a similar manner, was altered for ease of therapy or due to poor response to therapy. The high cost of this parenteral therapy and the problems in its delivery point to the need for safe, effective oral therapy.

Rajajee S, Anandi TB, Subha S, Vatsala BR

**Patterns of resistant *Salmonella typhi* infection in infants.**

*Journal of Tropical Pediatrics*, 1995, 41(1):52-54.

Culture-proven cases of enteric fever (182) were studied during the period May 1991 to April 1992; 39 per cent of the children were below 3 years. There was male preponderance. Infants presented within first few days of onset of fever with severe systemic manifestation, such as repeated convulsion, puffiness of face and oedema, massive hepatomegaly, and bleeds due to thrombocytopenia. Only 49-52 per cent of the cultures were sensitive to ampicillin, chloramphenicol, and cotrimoxazole. The infants were treated with cephalosporin such as cefotaxime or quinolones as ciprofloxacin, since 100 per cent of the cultures were sensitive to this drug. Three infants had meningitis, two interstitial nephritis, and six had marrow hypoplasia. Two children who had been treated prior to admission with ampicillin or chloramphenicol died within 48 h of admission, one of a liver abscess and peritonitis, and the other due to meningitis. Markedly prolonged hypothermia was seen during recovery in few cases. Forty-six per cent of infants had complications as against 2 per cent in older children. Drug Resistant *Salmonella typhi* infection seems to have a rapidly progressive severe course with multiple organ involvement such as meningitis, liver abscess, nephritis, and marrow hypoplasia. Initiation of appropriate antibiotics depending on local sensitivity pattern is needed early in the disease to avoid mortality and morbidity.

Rathore MH, Bux D, Hasan M

**Multidrug-resistant *Salmonella typhi* in Pakistani children: clinical features and treatment.**

*Southern Medical Journal*, 1996, 89(2):235-237.

Multidrug-resistant *Salmonella typhi* has become a major public health problem. In this study, typhoid fever was diagnosed by isolation of *Salmonella typhi* from blood or by a positive Widal's reaction in 170 Pakistani children. There were 111 boys (65%) and 59 girls (35%). The average age was 6.2 years; 4 (2%) were less than 1 year old, 78 (46%) were 1 to 5 years old, and 88 (52%) were more than 5 years old. All patients were pre-treated with antibiotics. *Salmonella typhi* was detected by culture in 109 cases (64%), by Widal's test in 84 (49%), and by both in 23 (14%). All 79 isolates that were multidrug resistant were sensitive to ofloxacin, cefotaxime, and ceftriaxone. Clinical features of infections due to resistant *S typhi* did not differentiate these from other cases of typhoid. Fifty-five infections (70%) due to resistant *S typhi* were treated with ofloxacin and 24 (30%) with ceftriaxone. Sixteen patients had complications, and all recovered.

Tran TH, Bethell DB, Nguyen TT, Wain J, To SD, Le TP, Bui MC, Nguyen MD, Pham TT, Walsh AL, et al

**Short course of ofloxacin for treatment of multidrug-resistant typhoid.**

*Clinical Infectious Diseases*, 1995, 20(4):917-923.

In recent years, multiresistant strains of *Salmonella typhi* have emerged in many tropical countries. These strains remain highly sensitive to the fluoroquinolone antibiotics, although use of these drugs by children is considered contraindicated because of their reported toxicity in the cartilage of experimental animals. In a paired, open, randomised study during an epidemic of multidrug-resistant typhoid in southern Vietnam, two short-course ofloxacin regimens (15 mg/kg daily for 3 days and 10 mg/kg daily for 5 days) were compared for the treatment of uncomplicated typhoid fever. Of 438 patients enrolled (of whom 286 were  $\leq$  14 years old), 228 had blood cultures positive for *Salmonella* species (*S. typhi*, 207; *S. paratyphi A*, 19; and *S. choleraesuis*, 2). There was one treatment failure in a patient who took only one dose of ofloxacin. Otherwise, both regimens were completely effective; there were no proven carriers, and there was no evidence of toxicity, particularly in children. A 3-day course of ofloxacin proved to be safe and highly effective in the treatment of uncomplicated, multidrug-resistant typhoid fever.

Publication Types: Clinical trial, Randomised controlled trial

Vinh H, Wain J, Vo TN, Cao NN, Mai TC, Bethell D, Nguyen TT, Tu SD, Nguyen MD, White NJ

**Two or three days of ofloxacin treatment for uncomplicated multidrug-resistant typhoid fever in children.**

*Antimicrobial Agents and Chemotherapy*, 1996, 40(4):958-961.

An open randomised comparison of 2 days (Ofx2) versus 3 days (Ofx3) of oral ofloxacin treatment (15 mg/kg/day) was conducted with Vietnamese children between 1 and 15 years of age with suspected typhoid fever. Of 108 children enrolled, 100 were blood culture positive for *Salmonella typhi*, and 86% of the isolates were multidrug resistant. There were no significant adverse effects. The therapeutic responses were similar in both groups, with mean ( $\pm$  standard deviation) fever clearances of 107  $\pm$  60 h in the Ofx3 group and 100  $\pm$  64 h in the Ofx2 group ( $P > 0.2$ ). There were six "clinical" failures in the Ofx2 group and two clinical failures in the Ofx3 group ( $P > 0.2$ ), in which fever and symptoms persisted for more than 1 week after the start of treatment, but only one of these was culture positive (Ofx3). There was one suspected relapse, and one carrier was identified. Short courses of ofloxacin are simple, inexpensive, safe, and effective for the treatment of uncomplicated multidrug-resistant typhoid fever.

Publication Types: Clinical trial, Randomised controlled trial





## 6. EAR INFECTION

### Articles

Berman S

#### **Otitis Media in Developing Countries.**

*Paediatrics*, 1995, 96:712-15

**OBJECTIVE.** This article reviews the available information concerning the disease burden, epidemiology, and aetiology of otitis media in developing countries and the likelihood that case management with appropriate antibiotic therapy can reduce the burden of this disease. **METHODOLOGY.** The available literature was reviewed to determine the extent to which otitis media impacts mortality and morbidity in developing countries. **EPIDEMIOLOGY.** In community studies, perforation was present in 0.4% to 33.3% of children and youth; otorrhea occurred in 0.4% to 6.1%; and mastoiditis occurred in 0.19% to 0.74%. In school surveys, perforation was identified in 1.3% to 6.24% of students, and otorrhea was found in 0.6% to 4.4%. Mastoiditis was diagnosed in 18% of children and youth who presented to a hospital ear, nose, and throat (ENT) clinic in Uganda. The proportion of patients presenting to ENT clinics with mastoiditis regardless of their initial symptoms varied from 1.7% to 5%. Patients presenting to these ENT clinics with mastoiditis often experience severe complications, including subperiosteal abscess, labyrinthitis, facial palsy, meningitis, and brain abscess. Hearing impairment was a major public health problem compromising the quality of life in approximately one third of the population of developing countries. **ETIOLOGY.** The pathogens isolated from ear aspirates in children with acute otitis media and chronic suppurative otitis (CSOM) carried out in developing countries are similar to those isolated in studies carried out in developed countries. **CASE MANAGEMENT.** Historical data supports the effectiveness of antibiotic therapy in reducing the frequencies of mastoiditis and CSOM complicating acute otitis media. In addition, the introduction of primary care services targeted at otitis media for high-risk populations living in developed countries may have reduced the prevalence of mastoiditis and CSOM. However, it is not clear whether there is a causal relationship between these programs and the reduction because of the use of historical controls. **CONCLUSIONS.** International research organisations should support controlled intervention studies to document the impact of case management of otitis in developing countries. In addition, the efficacy of a conjugated pneumococcal vaccine to prevent otitis and its complications should be evaluated in a developing country site. Pending the results of studies, developing countries should develop primary care case management programs to diagnose and treat otitis and its associated complications.

Publication Types: Review, Tutorial

Berman S

#### **Otitis media in children. Current Concepts.**

*New England Journal of Medicine*, 1995, 332(23):1560-1565.

The diagnosis and management of otitis media in children remain challenging and controversial. The differing ability of families to cope with a child with recurrent or persistent otitis media and the lack of data that show a causal relation between conductive hearing impairment and subsequent behaviour problems or delays in language development (or both) require the clinician to solicit and to consider parental preferences in treatment.

Mahoney JL

#### **Mass management of otitis media in Zaire.**

*Laryngoscope*, 1980, 90:1200-1208.

In 1976, 4,281 cases of otitis media with otorrhea were treated in the otorhinolaryngology department at Mama Yemo hospital, the 2,000-bed major medical center in Kinshasa, Zaire. Topical aluminum acetate

(Burow's solution) on ear wicks of cotton was placed against the ear drum into the ear canal and changed daily as an effective method of mass control of this disease without antibiotics. The results were comparable to those from 0.3% topical gentamycin ophthalmic solution (Garamycin), but were obtained with considerably less expense in an area where economic considerations are essential.

Paradise J

**Managing otitis media: A time for change.**

*Pediatrics*, 1995, 96:712-15.

Given the increasing prevalence of multiply resistant pneumococcal infection and the heightened risks associated with antimicrobial usage, antimicrobial treatment of otitis media in children should be restricted generally to the extent possible without compromising individual children's well-being and without subjecting them to risks potentially greater than the risks associated with antimicrobial usage. Not infrequently the decisions required will be difficult and matters of judgment. However, in most cases the indications for initiating or prolonging antimicrobial treatment will be either straightforward, calling for a decision to proceed, or marginal, in which case the decision not to proceed should be clear.

## 6.1. ACUTE OTITIS MEDIA

Froom J, Culpepper L, Grob P, Bartelds A, Bowers P, Bridges-Webb C, Grava-Gubins I, Green L, Lion J, Somaini B, et al

### **Diagnosis and antibiotic treatment of acute otitis media: Report from The International Primary Care Network.**

*British Medical Journal*, 1990, 300:582-586.

**STUDY OBJECTIVE**—The relation between a history of disorders suggestive of acute otitis media, symptoms, and findings of an examination of the tympanic membrane and doctors' certainty of diagnosis. Also, to examine differences in prescribing habits for acute otitis media among doctors from different countries. **DESIGN**—Questionnaires were completed by participating doctors for a maximum of 15 consecutive patients presenting with presumed acute otitis media. **SETTING**—General practices in Australia, Belgium, Great Britain, Israel, The Netherlands, New Zealand, Canada, Switzerland, and the United States. **PATIENTS**—3660 Children divided into the three age groups 0-12 months, 13-30 months, and greater than or equal to 31 months. **MAIN OUTCOME MEASURES**—General practitioners' responses to questions on their diagnostic certainty and resolution of patients' symptoms after two months. **RESULTS**—The diagnostic certainty in patients aged 0-12 months was 58.0%. This increased to 66.0% in those aged 13-30 months and 73.3% in those aged greater than or equal to 31 months. In all age groups diagnostic certainty was positively associated with the finding of a tympanic membrane that was discharging pus or bulging. Redness of the membrane and pain were also associated with certainty in patients aged 13-30 months, and a history of decreased hearing or recent upper respiratory infection was positively associated in patients aged greater than or equal to 31 months. The proportion of patients prescribed antibiotics varied greatly among the countries, from 31.2% in The Netherlands to 98.2% in both Australia and New Zealand, as did the duration of treatment. Patients who did not take antibiotics had a higher rate of recovery than those who did; the rate of recovery did not differ between different types of antibiotic. **CONCLUSIONS**—Doctors' certainty of diagnosis of acute otitis media was linked to patient's age. Improved criteria or techniques for diagnosing acute otitis media, especially in very young children, need to be developed. Antibiotic treatment did not improve the rate of recovery of patients in this study. Publication Types: Clinical trial, Multicenter study

Glasziou PP, Hayem M, Del Mar CB

### **Antibiotics for acute otitis media in children (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.



**BACKGROUND:** Acute otitis media is one of the most common diseases in early infancy and childhood. Antibiotic use for acute otitis media varies from 31% in the Netherlands to 98% in the USA and Australia. **OBJECTIVES:** The objective of this review was to assess the effects of antibiotics for children with acute otitis media. **SEARCH STRATEGY:** We searched the Cochrane Controlled Trials Register, MEDLINE, Index Medicus, Current Contents and reference lists of articles from 1958 to January 1999. **SELECTION CRITERIA:** Randomised trials comparing antimicrobial drugs with placebo in children with acute otitis media. **DATA COLLECTION AND ANALYSIS:** Three reviewers independently assessed trial quality and extracted data. **MAIN RESULTS:** Nine trials were eligible but only six trials, with a total of 1,962 children, included patient-relevant outcomes. The methodological quality of the included trials was generally high. All trials were from developed countries. The trials showed no reduction in pain at 24 hours, but a 34% relative reduction (95% confidence interval 16% to 48%) in pain at two to seven days. Since approximately 85% of patients will have settled spontaneously in this time, this means an absolute reduction of about 5% or that about 20 children must be treated with antibiotics to prevent one child having some pain after two days. There was no effect of antibiotics on deafness, as measured by subsequent tympanometry, other complications, or recurrence. However, audiometry was done in only two studies and incompletely reported, and there were few serious complications seen in these trials: only one case of mastoiditis occurred (in a penicillin treated group). One semi-randomised trial in Sweden in 1954 reported a rate of 17% in the untreated group versus none in the penicillin treated groups.

CONCLUSIONS: Antibiotics provide a small benefit for acute otitis media in children. As most cases will resolve spontaneously, this benefit must be weighed against the possible adverse reactions. Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common. The management should emphasize advice about adequate analgesia and the limited role for antibiotics.

Hendrickse WA, Kusmiesz H, Shelton S, Nelson JD

**Five vs. ten days of therapy for acute otitis media.**

*The Pediatric Infectious Disease Journal*, 1988, 7:14-23.

In a double blind study 175 patients with acute otitis media were randomised into 2 treatment groups: 10 days of therapy with cefaclor or 5 days of therapy followed by 5 days of placebo. The dosage of cefaclor was 40 mg/kg/day administered orally in equally divided doses at 12-hour intervals. Tympanocentesis before treatment yielded specimens that contained *Streptococcus pneumoniae* or *Haemophilus influenzae* or both in 55% of specimens. *Branhamella catarrhalis* was isolated from 21% of specimens. Culture of material from the ear canal of patients with spontaneous perforation of the tympanic membrane of less than 24 hours duration yielded pneumococci or *H. influenzae* or both in 38% of specimens and staphylococci in 31%. Patients were scheduled for follow-up examinations at 5 or 6, 10, 30, 60 and 90 days. Of the 175 children 151 were evaluable at 10 days. There were 123 patients with both tympanic membranes intact at the time of diagnosis. There were 6 (10%) treatment failures of therapy in the 59 patients assigned to 5 days of therapy and 4 (6%) failures and 1 (2%) early relapse in the 64 assigned to 10 days of therapy (difference not significant). There were 28 evaluable patients with spontaneous perforation. There were 8 (53%) failures in the 15 children assigned to 5 days of therapy and only 1 (8%) failure in the 13 children assigned to receive 10 days of therapy ( $P = 0.016$ , Fisher exact test). Rates of reinfection and persistent middle ear effusion at 10, 30, 60 and 90 days follow-up were not significantly different in patients assigned to 5 to 10 days of therapy. In patients with acute otitis media with intact tympanic membranes we have not been able to show any advantage of the standard duration of 10 days of therapy over a shortened course of 5 days. A 5-day course of antibiotic therapy does not appear to be sufficient for children with acute otitis media and spontaneous purulent drainage.

Publication Types: Clinical trial, Randomised controlled trial

Meistrup-Larsen KI, Sorensen H, Johnsen NJ, Thomsen J, Mygind N, Sederberg-Olsen

J

**Two versus seven days penicillin treatment for acute otitis media. A placebo controlled trial in children.**

*Acta Oto-laryngologica*, 1983, 96:99-104.

103 children between 1 and 10 years of age participated in a double-blind placebo-controlled trial testing the effect of penicillin-V, 55 mg/kg/day, for two days versus seven days in acute otitis media. No significant differences could be demonstrated with regard to earache, healing of the tympanic membrane, tympanometry, fever or common cold symptoms. 76% in the group treated for seven days had a satisfactory course of the disease, compared to 71% in the group treated for two days ( $p$  greater than 0.1). In spite of the relatively small number of patients, it is concluded that the effect of penicillin for additional five days in acute otitis media after the initial treatment for two days, can at most be marginal. The advantages of a shortened treatment period are several; the authors have outlined a new treatment modality, consisting of masterful inactivity for 8-12 hours, penicillin-V for two days, and myringotomy in refractory cases, after a new evaluation by the otologist. We believe hereby to be able to reduce penicillin consumption in children with acute otitis media to about 15% of the previous level, without increasing the risk of serious complications.

Publication Types: Clinical trial, Controlled clinical trial

Niemela M, Uhari M, Jounio-Ervasti K, Luotonen J, Alho OP, Vierimaa E.

**Lack of specific symptomatology in children with acute otitis media.**

*The Pediatric Infectious Disease Journal*, 1994, 13:765-768.

Although the symptoms of the acutely ill child are important both in the diagnosis and follow-up of acute otitis media (AOM), data about them are quite limited. We carried out a prospective survey by collecting information on 354 consecutive children visiting a paediatrician, otolaryngologist or general practitioner because of any kind of acute symptoms to compare symptoms of children with acute otitis media with those of children with other acute infectious diseases. The symptoms and signs observed at home were recorded by the parents before the visit and the findings in the physical examination were recorded later by the physician. AOM was diagnosed in 191 patients (54.0%). The most important symptoms increasing the likelihood of AOM significantly were ear-related symptoms, such as earache (relative risk (RR) 5.4;  $P < 0.001$ ), rubbing of the ear (RR 5.0;  $P < 0.001$ ) and feeling of blocked ear (RR 4.5;  $P < 0.05$ ). However, only 67.7% of children younger than 2 years of age with AOM had any ear-related symptoms. The children with tympanostomy tubes had earache (47.8%) and rubbing of the ear (58.8%) of the same magnitude as did children without tubes. Rhinitis increased the likelihood of AOM (RR 2.3;  $P < 0.001$ ) as did excessive crying in children older than 2 years of age (RR 3.0;  $P < 0.001$ ). Fever, earache or excessive crying was present in 90.1% of patients with AOM but also in 72.4% of patients without AOM.

Ploussard JH

**Evaluation of 5 days of cefaclor vs. ten days of amoxicillin therapy in acute otitis media.**

*Current Therapeutic Research, Clinical and Experimental*, 1984, 36:641-645.

A comparative study of 5-day vs. 10 day antibiotic therapy was undertaken in infants and children with acute otitis media. Results were evaluated in 27 patients who received 5 days of cefaclor (40 mg/kg/day) and in 29 patients who received 10 days of amoxicillin (40 mg/kg/day). There were no therapeutic failures in the 5-day group; there were four in the 10-day group. During the 16-day post therapy follow-up period, recurrence symptoms and reculture of the same organism occurred in one patient in each group and reinfection with a new pathogen occurred in one patient treated in the 5-day group. The only adverse reaction was one case of rash in a child receiving amoxicillin. These results suggest that 5 days of therapy may be sufficient in many cases of otitis media and should produce significant savings in the cost of medical care. Further studies are indicated.



## 6.2. CHRONIC OTITIS MEDIA

Acuin J, Smith A, Mackenzie I

### **Interventions for chronic suppurative otitis media (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.



**BACKGROUND:** Chronic suppurative otitis media (CSOM) is a serious bacterial infection of the middle ear that can follow untreated acute otitis media. **Objectives:** To assess the effects of different treatments for CSOM. **Search strategy:** We searched Medline from 1966 to 1996 and a bibliographic collection of the Hearing Impairment Research Group in Liverpool, UK. We handsearched two otolaryngology journals and contacted members of an international hearing network.

**SELECTION CRITERIA:** Randomised trials of any method of management for patients with eardrum perforation and persistent otorrhea. **DATA COLLECTION AND ANALYSIS:** Three reviewers independently assessed eligibility and trial quality. One reviewer extracted data. We contacted investigators for clarifications. **MAIN RESULTS:** Twenty-four trials involving 1660 people were included. Clinical definitions and severity of CSOM varied, methodological quality was generally low and follow-up was short. Treatment with antibiotics or antiseptics accompanied by aural toilet was more effective in resolving otorrhea than no treatment (two trials, odds ratio 0.37, 95% confidence interval 0.24 to 0.57) or aural toilet alone (six trials, odds ratio 0.31, 95% confidence interval 0.23 to 0.43). Topical treatment with antibiotics or antiseptics was more effective than systemic antibiotics (six trials, odds ratio 0.46, 95% confidence interval 0.30 to 0.69). Combining topical and systemic antibiotics was not more effective than topical antibiotics. Topical quinolones were more effective than non-quinolones (five trials, odds ratio 0.26, 95% confidence interval 0.16 to 0.41). No difference in the effectiveness of topical antibiotics and topical antiseptics was found (three studies, odds ratio 1.34, 95% confidence interval 0.64 to 2.81). Some topical antibiotic combinations may be more effective than others in resolving otorrhea. Rates of adverse drug events were low and equal between groups.

**REVIEWERS' CONCLUSIONS:** Implications for practice. In terms of short-term resolution of otorrhea from active CSOM, antibiotic treatment is better than aural toilet alone. Topical antibiotics with aural toilet is the most effective method of treatment. The effect of treatment on healing of the tympanic perforation is small and still insignificant. Quinolones, whether systemic or topical, seem to be more effective than other types of antibiotics in resolving otorrhea and clearing bacteria from the middle ear. Antiseptics may be just as effective as antibiotics. These conclusions must be regarded with caution, since they are based on short term outcome measures which may have no relevance to the ultimate resolution of CSOM given its natural course. At best, they offer guidance to the temporary management of CSOM given the lack of better evidence. Physicians should administer antibiotics while advising patients on the proper care of their draining ears. However, the current WHO/UNICEF initiative for the Integrated Management of Childhood Illness (Gove 1997) does not recommend antibiotic treatment for 'chronic ear infection'. This recommendation is likely to be reviewed. The cautious use of topical antibiotics instilled into the middle ear while monitoring for adverse effects such as allergic reactions and ototoxicity should be encouraged. However, medical treatment of chronic draining ears should not delay physicians from operating whenever irreversible disease is present, particularly if it threatens life and well-being.

Brook I

### **Management of chronic suppurative otitis media: Superiority of therapy effective against anaerobic bacteria.**

*The Pediatric Infectious Disease Journal*, 1994, 13:188-193.

The aerobic and anaerobic microbiology and management of 69 children who had chronic suppurative otitis media were studied retrospectively. A total of 188 isolates (103 anaerobic and 85 aerobic) were recovered. Anaerobic organisms alone were isolated from 11 (16%), aerobic bacteria only in 21 (30%) and mixed aerobic and anaerobic flora was present in 37 (54%). Forty-five beta-lactamase-producing bacteria were recovered from 60 (58%) patients. The most rapid time for resolution was noticed with clindamycin (8.3 +/- 0.6 days) ( $P < 0.001$ ), as compared with ampicillin (12.0 +/- 0.8 days), erythromycin (16.5 +/- 1.6 days) and cefaclor (14.6 +/- 2.3 days). Resolution of the infection was achieved in 16 of 20 (80%) of those treated with clindamycin, 12 of 24 (50%) treated with ampicillin, 6 of 13 (46%) treated with erythromycin,



and 4 of 12 (33%) treated with cefaclor. Organisms resistant to the antimicrobial used were recovered in 26 of 31 of patients who failed to respond to therapy. These findings indicate the role of resistant aerobic and anaerobic organisms in the polymicrobial aetiology of chronic otitis media in children and illustrate the superiority of therapy effective against anaerobic bacteria.

Eason RJ, Harding E, Nicholson R, Nicholson D, Pada J, Gathercole J

**Chronic suppurative otitis media in the Solomon Islands: A prospective, microbiological, audiometric and therapeutic survey.**

*New Zealand Medical Journal*, 1986, 99:812-815.

Chronic suppurative otitis media affected 3.8% of 3500 Solomon Island children under 15 years (and 6.1% under 5 years) and was the sole cause of conductive hearing loss recorded in 265 children tested audiometrically. It was characterised by early onset (65% under 18 months) male preponderance and large central tubotympanic perforations. Measles, respiratory infections, swimming and malnutrition were identified as aetiological factors amenable to intervention. *Proteus* and *Pseudomonas* were the principle aerobes isolated from ear pus and gentamicin the only antibiotic tested to be effective against them. However although a prospective therapeutic trial demonstrated a significantly improved outcome after aural toilet, no additional benefit was imparted by concurrent ototopical boric acid or aminoglycoside solution or oral antianaerobic clindamycin. Parental tuition in aural cleaning, avoidance of ear water entry, nose blowing and breathing will yield a good result in up to 60% of children in half of whom tympanic healing occurred.

Publication Types: Clinical trial, Controlled clinical trial

Fliss DM, Dagan R, Houry Z, Leiberman A

**Medical management of chronic suppurative otitis media without cholesteatoma in children.**

*The Journal of Pediatrics*, 1990, 116:991-996.

To determine whether systemic administration of antibiotics may eliminate or reduce the need for tympanomastoid surgery in chronic suppurative otitis media without cholesteatoma, we undertook a randomised, prospective study comparing three regimens: (1) daily suction and debridement, with intravenous administration of mezlocillin until 3 days after the discharge stopped, (2) daily suction and debridement, with intravenous use of ceftazidime until 3 days after the discharge stopped, and (3) daily suction and debridement without antibiotics. No topical antimicrobial agents were used during the study.

Fifty-one patients were included, and 48 children completed the study. The duration of discharge from the ear before treatment was 2 to 123 months (median 20 months). In 26 patients (51%), the disease was bilateral. Aerobic cultures, obtained with the Alden-Senturia middle ear aspirator, yielded *Pseudomonas aeruginosa* in 98%, enteric gram-negative bacilli in 33%, staphylococci in 25%, and *Haemophilus influenzae* in 12%. The first 33 patients were randomly assigned to one of the three regimens. In the 21 patients treated with suction and antibiotics (either mezlocillin or ceftazidime), the discharge stopped completely, versus in only 1 (8%) of 12 patients in the suction-only regimen ( $p$  less than 0.01). Therefore the following 18 patients were randomly assigned to one of only two groups, which included the two suction-and-antibiotic regimens. In all patients treated initially with antibiotics, discharge stopped after 4 to 18 days (mean 12.0 days), but 25% needed treatment for greater than 14 days. Amoxicillin prophylaxis was administered to 27 (56%) of the patients after completion of therapy. All patients were followed for 6 months. Drainage recurred in 12 (25%) patients during the first 3 months after the study. The recurrence rate was not affected by the antibiotic regimen, the patient's age, the duration of drainage before initiation of antibiotic therapy, or prophylaxis.

**CONCLUSIONS:** Intravenous wide-spectrum antibiotic therapy in conjunction with daily suction and debridement is efficacious for the treatment of chronic suppurative otitis media without cholesteatoma.

Publication Types: Clinical trial, Randomised controlled trial

Comments: *J Pediatr* 1991 Jul;119(1 Pt 1):160

Okafor BC

**The chronic discharging ear in Nigeria.**

*Journal of Laryngology and Otology*, 1984, 98(2):113-119.

A study of 386 Nigerian patients with chronic suppurative otitis media is presented. The disease usually starts in early life, even though presentation in hospital may be delayed until adult life. The important aetiological factors were found to be essentially socio-economic. Tubo-tympanic disease dominates the clinical picture and the rarity of the attic retraction type of chronic ear disease would suggest exceptionally good eustachian function in the population studied, but further study is required in this respect. It is suggested that complicated tympano-plastic procedures are in general inappropriate in the chronic ear population of this study.

Smith AW, Hatcher J, Mackenzie IJ, Thompson S, Bal I, Macharia I, Mugwe P, Okoth-Olende C, Oburra H, Wanjohi Z

**Randomised controlled trial of chronic suppurative otitis media in Kenyan schoolchildren.**

*Lancet*, 1996, 348:1128-1133.

**BACKGROUND:** The outcomes of treatment of chronic suppurative otitis media (CSOM) are disappointing and uncertain, especially in developing countries. Because CSOM is the commonest cause of hearing impairment in children in these countries, an effective method of management that can be implemented on a wide scale is needed. We report a randomised, controlled trial of treatment of CSOM among children in Kenya; unaffected schoolchildren were taught to administer the interventions. **METHODS:** We enrolled 524 children with CSOM, aged 5-15 years, from 145 primary schools in Kiambu district of Kenya. The schools were randomly assigned treatments in clusters of five in a ratio of two to dry mopping alone (201 children), two to dry mopping with topical and systemic antibiotics and topical steroids (221 children), and one to no specific treatment (102 children). Schools were matched on factors thought to be related to their socioeconomic status. The primary outcome measures were resolution of otorrhoea and healing of tympanic membranes on otoscopy by 8, 12, and 16 weeks after induction. Absence of perforation was confirmed by tympanometry, and hearing levels were assessed by audiometry. 29 children were withdrawn from the trial because they took non-trial antibiotics. There was no evidence of differences in timing of withdrawals between the groups. **FINDINGS:** By the 16-week follow-up visit, otorrhoea had resolved in a weighted mean proportion of 51% (95% CI 42-59) of children who received dry mopping with antibiotics, compared with 22% (14-31) of those who received dry mopping alone and 22% (9-35) of controls. Similar differences were recorded by the 8-week and 12-week visits. The weighted mean proportions of children with healing of the tympanic membranes by 16 weeks were 15% (10-21) in the dry-mopping plus antibiotics group, 13% (5-20) in the dry-mopping alone group, and 13% (3-23) in the control group. The proportion with resolution in the dry-mopping alone group did not differ significantly from that in the control group at any time. Hearing thresholds were significantly better for children with no otorrhoea at 16 weeks than for those who had otorrhoea, and were also significantly better for those whose ears had healed than for those with otorrhoea at all times.

**INTERPRETATION:** Our finding that dry mopping plus topical and systemic antibiotics is superior to dry mopping alone contrasts with that of the only previous community-based trial in a developing country, though it accords with findings of most other trials in developed countries. The potential role of antibiotics needs further investigation. Further, similar trials are needed to identify the most cost-effective and appropriate treatment regimen for CSOM in children in developing countries.

Publication Types: Clinical trial, Comment, Randomised controlled trial

Comment in: *Lancet* 1996 Oct 26;348(9035):1113-4



### 6.3. MASTOIDITIS

Ginsburg CM, Rudoy R, and Nelson JD

**Acute mastoiditis in infants and children.**

*Clinical Pediatrics*, 1980, 19(8):549-553.

During a 25-year period, 57 cases of acute mastoiditis occurred in infants and young children who ranged in age from 2 months to 12 years of age. All patients had abnormalities of the tympanic membrane and most had fever and localized oedema and redness of the overlying skin. Fifty per cent of the infants who were less than one year of age had swelling primarily above the involved ear pushing the pinna out and down. By contrast, older children had swelling of the skin overlying the mastoid process which produced the classical finding of an elevated earlobe. Mastoid roentgenograms were a useful adjunct to diagnosis, revealing concurrent osteomyelitis in 9 patients. A diagnosis of specific bacterial aetiology was made in 80 per cent of the patients in whom cultures were performed. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes* were the bacteria most frequently isolated. Unusual manifestations or serious complications occurred in 53 per cent of the patients, including one death (due to meningitis). These data indicate that the frequency of serious complications from acute mastoiditis has not declined over the past 3 decades.

Nadal D, Herrmann P, Fanconi A

**Acute mastoiditis: Clinical, microbiological, and therapeutic aspects.**

*European Journal of Pediatrics*, 1990, 149:560-564.

The charts of 73 children (31 girls, 42 boys) aged 4 months to 14 years (mean 4.5 years) with acute mastoiditis managed during a 16-year period were reviewed. Of the patients 36% were less than 24 months old. Retro-auricular swelling was described in 63 of the 73 children, tenderness in 59, erythema in 58, and protrusion of the auricle in 45. A pathological tympanic membrane was noted in 33% of the patients and fever in only 29%. Apart from local inflammation, the most frequent complaints and symptoms were otalgia (n = 42), recent upper respiratory tract infections (n = 22), and fever alone (n = 22). A subperiosteal abscess was found in 36 patients, and CNS involvement in 5. Nearly half of the patients (48%) were on antibiotic therapy at admission. The isolation rates in bacterial cultures from subperiosteal aspirated (81%) and from mastoid mucosa (68%) were considerably higher than from blood cultures (14%) and were not influenced by previously administered antibiotics. Pneumococci (9/32) and *Staphylococcus epidermidis* (6/32) were the agents most often isolated. The incidence of the bacteria isolated from patients pre-treated with antibiotics differed from the incidence in patients not previously treated. In 24 patients (33%) the lesion healed with antibiotic therapy without mastoid surgery. Myringotomy and the insertion of a ventilation tube is indicated initially, if acute otitis media with effusion is found. In the absence of a subperiosteal abscess and of CNS involvement, a 48-hour trial of intravenous antibiotic therapy, directed also against staphylococci, is justified before mastoid surgery is considered.

Ogle JW, Lauer BA

**Acute mastoiditis.**

*American Journal of Diseases of Children*, 1986, 140:1178-1182.

Thirty children with acute mastoiditis were identified over a 12-year-period and their hospital records were reviewed retrospectively. All had abnormal tympanic membranes and 26 (87%) had swelling above or posterior to the ear that deviated the pinna. Findings on mastoid roentgenograms included clouding (n = 12) and osteitis (n = 7); six were normal. From 13 patients, bacteria were recovered from normally sterile sites and included *Pneumococcus* (n = 5), group A streptococcus (n = 3), *Haemophilus* (n = 2), and anaerobes (n = 3). Complications occurred in 13 children, including subperiosteal abscess (n = 7), meningitis (n = 4), osteitis (n = 7), facial palsy (n = 1), and subdural empyema and brain abscess (n = 1). Four of the six children with neurological complications had no external signs of acute mastoiditis on physical examination. Overall, 19 (63%) of the children recovered without mastoidectomy. We conclude that children without meningitis or subperiosteal abscess may be treated initially with antimicrobial therapy

plus myringotomy. The need for mastoidectomy should be reassessed in children who fail to respond in 24 to 48 hours.

## 7. NUTRITIONAL STATUS, NUTRITION AND BREASTFEEDING COUNSELLING

### 7.1 NUTRITIONAL STATUS

#### Articles

#### Importance

de Onis M, Frongillo EA, Blossner M

**Is malnutrition declining? An analysis of changes in levels of child malnutrition since 1980.**

*Bulletin of the World Health Organization* 2000;78(10):1222-33

Nutritional status is the best global indicator of well-being in children. Although many surveys of children have been conducted since the 1970s, lack of comparability between them has made it difficult to monitor trends in child malnutrition. Cross-sectional data from 241 nationally representative surveys were analysed in a standard way to produce comparable results of low height-for-age (stunting). Multilevel modelling was applied to estimate regional and global trends from 1980 to 2005. The prevalence of stunting has fallen in developing countries from 47% in 1980 to 33% in 2000 (i.e. by 40 million), although progress has been uneven according to regions. Stunting has increased in Eastern Africa, but decreased in South-eastern Asia, South-central Asia and South America; Northern Africa and the Caribbean show modest improvement; and Western Africa and Central America present very little progress. Despite an overall decrease of stunting in developing countries, child malnutrition still remains a major public health problem in these countries. In some countries rates of stunting are rising, while in many others they remain disturbingly high. The data we have presented provide a baseline for assessing progress and help identify countries and regions in need of populationwide interventions. Approaches to lower child malnutrition should be based on successful nutrition programmes and policies.

Rice AL, Sacco L, Hyder A, Black RE

**Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries.**

*Bulletin of the World Health Organization* 2000;78(10):1207-21

**INTRODUCTION:** Recent estimates suggest that malnutrition (measured as poor anthropometric status) is associated with about 50% of all deaths among children. Although the association between malnutrition and all-cause mortality is well documented, the malnutrition-related risk of death associated with specific diseases is less well described. We reviewed published literature to examine the evidence for a relation between malnutrition and child mortality from diarrhoea, acute respiratory illness, malaria and measles, conditions that account for over 50% of deaths in children worldwide. **METHODS:** MEDLINE was searched for suitable review articles and original reports of community-based and hospital-based studies. Findings from cohort studies and case-control studies were reviewed and summarized. **RESULTS:** The strongest and most consistent relation between malnutrition and an increased risk of death was observed for diarrhoea and acute respiratory infection. The evidence, although limited, also suggests a potentially increased risk for death from malaria. A less consistent association was observed between nutritional status and death from measles. Although some hospital-based studies and case-control studies reported an increased risk of mortality from measles, few community-based studies reported any association. **DISCUSSION:** The risk of malnutrition-related mortality seems to vary for different diseases. These findings have important implications for the evaluation of nutritional intervention programmes and child survival programmes being implemented in settings with different disease profiles.

## Assessment

Bern C, Zucker JR, Perkins BA, Otieno J, Oloo AJ, Yip R

### **Assessment of potential indicators for protein-energy malnutrition in the algorithm for integrated management of childhood illness.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):87-96.

Potential indicators were assessed for the two classifications of protein-energy malnutrition in the guidelines for integrated management of childhood illness: severe malnutrition, which requires immediate referral to hospital, and very low weight, which calls for feeding assessment, nutritional counselling and follow-up. Children aged < 2 years require feeding assessment and counselling as a preventive intervention. For severe malnutrition, we examined 1202 children admitted to a Kenyan hospital for any association of the indicators with mortality within one month. Bipedal oedema indicating kwashiorkor, and two marasmus indicators (visible severe wasting and weight-for-height (WFH) Z-score of < -3) were associated with a significantly increased mortality risk (odds ratios, 3.1-3.9). Very low weight-for-age (WFA) (Z-score of < -4.4) was not associated with an increased risk of mortality. Because first-level health facilities generally lack length-boards, bipedal oedema and visible severe wasting were chosen as indicators of severe malnutrition. To assess potential WFA thresholds for the very low weight classification, our primary source of data came from 1785 Kenyan outpatient children, but we also examined data from surveys in Nepal, Bolivia, and Togo. We examined the performance of WFA at various thresholds to identify children with low WFH and, for children aged < or = 2 years, low height-for-age (HFA). Use of a WFA threshold Z-score of < -2 identified a considerable proportion of children (from 13% in Bolivia to 68% in Nepal) which, in most settings, would pose an enormous burden on the health facility. Among ill children in Kenya, a threshold WFA Z-score of < -3 had a sensitivity of 89-100% to detect children with WFH Z-scores of < -3, and, with an identification rate of 9%, would avoid overburdening the clinics. Potential modifications include use of a more restrictive cut-off in countries with high rates of stunting, or the elimination of the WFA screen in order to concentrate efforts on intervention for all children below the 2-year age cut-off. Key issues in every country include the capacity to provide counselling for many children and linkage to nutritional improvement programmes in the community.

de Onis M, Yip R, and Mei Z

### **The development of MUAC-for-age reference data recommended by a WHO Expert Committee.**

*Bulletin of the World Health Organization*, 1997, 75(1):11-18.

Low mid-upper-arm circumference (MUAC), determined on the basis of a fixed cut-off value, has commonly been used as a proxy for low weight-for-height (wasting). The use of a fixed cut-off value was based on the observation that MUAC showed small age- and sex-specific differences. However, in 1993, a WHO Expert Committee concluded that age independence is not reflected in the true pattern of mid-upper arm growth, recommended the use of MUAC-for-age, and presented age- and sex-specific MUAC reference data developed with observations obtained from a representative sample of children in the USA aged 6-59 months. In this article, we explain the methodology for the development of these data, present age- and sex-specific growth curves and tables and discuss the applications and limitations of MUAC as a nutritional indicator. To develop the reference data, estimates were first obtained for the mean and standard deviation of MUAC for each month of age using 7-month segmental regression equations; a 5th-degree and a 3rd-degree polynomial in age was then used to describe the mean and standard deviation, respectively, of MUAC-for age. These curves show important age-specific differences, and significant sex-specific differences for boys and girls < 24 months of age. Correct interpretation of MUAC with regard to nutritional status requires the use of MUAC-for-age reference data such as those presented here.

Franklin RR, Di Kassa LN, Bertrand WE

**The impact of oedema on anthropometric measurements in nutritional surveys: case study from Zaire.**

*Bulletin of the World Health Organization*, 1984, 62:145-150.

Six surveys for protein-energy malnutrition were carried out in sequence in Bas-Zaire beginning at the end of 1978 at the estimated height of the famine and continuing throughout the recovery period. Utilizing a stratified multi-stage sampling technique, over 1000 children aged 6 months to 6 years were measured anthropometrically and examined for the presence or absence of bilateral pedal oedema in each survey. The proportions of children who were less than 80% of the reference median weight-for-height and who had oedema decreased, respectively, from 12.8% and 14.4 % initially to 2.1% and 1.8% in the final survey. The proportion of oedematous children who were found to be not less than 80% of the reference median weight-for-height was high, varying from  $71.7 \pm 7.0\%$  to  $94.4 \pm 10.6\%$ . The importance of these findings for the interpretation of anthropometric data from nutritional surveys in developing countries is discussed.

George SM, Latham MC, Abel R, Ethirajan N, Frongillo EA Jr

**Evaluation of effectiveness of good growth monitoring in south Indian villages.**

*Lancet*, 1993, 342:348-352.

We conducted a community intervention trial in 12 villages in Tamil Nadu, India to evaluate the benefits of growth monitoring. The villages were divided into 6 "growth-monitoring package" of intervention villages (GMP) and 6 "non-growth-monitoring package" of intervention villages (NGM). A functioning primary health care system was in place in all 12 villages implemented a set of interventions including health and nutritional education. About 550 children under the age of 60 months were studied over 4 years in GMP villages and a similar number of children in NGM villages. The interventions were identical in the two sets of villages except for the use of growth charts in education in the 6 GMP villages. The nutrition worker in the NGM villages had the same contact time as in the GMP villages but advised mothers without the benefit of growth charts. The research team, independently of the nutrition worker, did anthropometric studies on children in all villages every 4 to 5 months. Comparisons were done by calculating monthly gains in stature, and weight, and the significance of differences observed was adjusted for age and sex. After 30 months of interventions, similar improvements in growth were seen in GMP and NGM children. The interventions seemed to have improved the nutritional status of young children in both groups of villages. In view of the lack of additional benefit from growth monitoring over other educational interventions, we question its use as part of child survival programmes in India.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *Lancet* 1993 Aug 7;342(8867):317; *Lancet* 1993 Sep 18;342(8873):749; *Lancet* 1993 Sep 18;342(8873):750

Gerein NM, Ross DA

**Is growth monitoring worthwhile? An evaluation of its use in three child health programmes in Zaire.**

*Social Science and Medicine*, 1991, 32(6):667-675.

Growth monitoring has become a major component of many child health programmes in developing countries over the past two decades. Little research has been carried out on the separate contribution of growth monitoring to the effectiveness of child health programmes, and discussion on the subject frequently take on an exhortative rather than a scientific character. This paper reports some of the results of an evaluation of three child health programmes in rural Zaire as a screening tool for targeting health and nutrition interventions. The monthly sessions to which mothers brought their children were observed, the health workers interviewed, and information obtained on the supervision system in the programmes, in order to determine whether the health workers accurately identified at-risk children and provided appropriate interventions through the use of growth monitoring information. Health staff were observed weighing and consulting a total of 506 mothers and children. Whilst they measured and recorded weights accurately, they did not carry out any further investigation in one-third of children who had experienced growth faltering. Similarly, no counselling was given to one-third of mothers whose children were ill and/or had growth faltering, called collectively 'at-risk children'. Generally, the quality of advice and



referral for illness was more satisfactory than the nutritional advice given to mothers, which consisted of brief, standard directives. The value of individual screening by weighing is questioned, since attendance was infrequent and non-representative, many mothers identified their children as ill and therefore at-risk even before they were weighed, and since nearly two-thirds of children attending the sessions were classified as at-risk.

Martorell R, Khan LK, Schroeder DG

**Reversibility of stunting: epidemiological findings in children from developing countries.**

*European Journal of Clinical Nutrition*, 1994, 48:S45-S57.

The growth literature from developing countries is reviewed to assess the extent to which stunting, a phenomenon of early childhood, can be reversed in later childhood and adolescence. The potential for catch-up growth increases as maturation is delayed and the growth period is prolonged. However, maturational delays in developing countries are usually less than two years, only enough to compensate for a small fraction of the growth retardation of early childhood. Follow-up studies find that subjects who remain in the setting in which they became stunted experience little or no catch-up in growth later in life. Improvements in living conditions, as through food supplementation or through adoption, trigger catch-up growth but do so more effectively in the very young. One study cautions that in older adopted subjects, accelerated growth may accelerate maturation, shorten the growth period and lead to short adult stature. Publication Types: Review, Review, tutorial

Panpanich R, Garner P

**Growth monitoring in children (Cochrane Review).**

In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.

**BACKGROUND:** Growth monitoring is widely accepted and strongly supported by health professionals, and is a standard component of community paediatric services throughout the world. We sought to evaluate research evidence of its impact. This requires definition, consideration of the setting, and discussion of the intended effects of this activity. In this review, we define growth monitoring as the regular recording of a child's weight, coupled with some specified remedial actions if the weight is abnormal in some way. Although the causes of growth faltering and the responses to it may be region specific, the process is the same, and we consider here growth monitoring in both the deprived and richer populations of the world. **OBJECTIVES:** Growth monitoring consists of routine measurements to detect abnormal growth, combined with some action when this is detected. As primary care workers worldwide invest time in this activity, we sought evidence of its benefits and harms. The review objectives are to evaluate the effects of routine growth monitoring on: 1. The child, in relation to preventing death, illness or malnutrition; and referrals for medical care, medical specialist assessment or professional social support follow-up. 2. The mother, in relation to nutritional knowledge, anxiety or reassurance about the child's health, and satisfaction with services. **SEARCH STRATEGY:** Cochrane Controlled Trials Register; MEDLINE; EMBASE; CINAHL; World Health Organization and World Bank publications; specialists in this area; citations in existing reviews and identified studies. Selection criteria: Randomised or quasi-randomised trials comparing routine growth monitoring (regular monitoring of growth, plotting on a chart, combined with referral or intervention when growth is abnormal) with no growth monitoring. Data collection and analysis: Trial quality was assessed, and data abstracted by both reviewers. **MAIN RESULTS:** Two studies included, both conducted in developing countries. In one, the nutritional status at 30 months in 500 children showed no difference between those allocated to growth monitoring and those not. The other study examined whether counselling improved mothers' knowledge of the growth chart, and reported better test scores at four months.

**CONCLUSIONS** At present, there is insufficient reliable information to be confident whether routine growth monitoring is of benefit to child health in both developing and developed country settings. Thus it is not clear to us whether we recommend that health professionals actively pursue children to obtain measures of growth at arbitrarily defined intervals. This includes home visits of children who have not attended clinic at the expected times.

Pelletier DL

**The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research.**

*Journal of Nutrition*, October 1994, 124(10 Supplement):2047S-2081S.

The prevention of child mortality is a commonly stated health goal in developing countries and the target of much international assistance in the health sector. Over the past decade the primary strategy for accelerating the reduction in child mortality has been the dissemination of simple, low-cost technologies, such as immunisation, oral rehydration therapy and antibiotics, that target specific diseases (Huffmann and Steel 1994). This is done despite the knowledge that malnutrition and disease have a synergistic relationship (Scrimshaw et al. 1968) and that the optimal strategy may involve a combination of health and nutrition interventions. In the 1970s, for instance, it was estimated that malnutrition (notably protein-energy malnutrition--PEM) was the underlying or contributing cause of death for roughly half of all deaths to children aged 1-4 years in several Latin American countries (Puffer and Serrano 1973). Apart from this early study, however, there has been little effort to quantify the contribution of malnutrition to child mortality in other regions of the world in ways which are meaningful to policy. This paper reviews the results of 28 community-based, prospective studies, in 12 Asian and Sub-Saharan African countries, which examined the relationship between anthropometric indicators of malnutrition and child mortality. One purpose is to estimate the contribution of malnutrition to child mortality--distinguishing the effects of severe malnutrition from mild-to-moderate malnutrition--and to examine a number of related issues relevant to policy, programs and research in this area. The accumulated results are consistent in showing that the risk of mortality is inversely related to anthropometric indicators of nutritional status and that there is elevated risk even in the mild-to-moderate range of malnutrition. This latter result contradicts the findings from an earlier, landmark study which suggested that mild-to-moderate malnutrition was not associated with an increased risk of mortality (Chen et al. 1980). The present results indicate that somewhere between 20% and 75% of child deaths are statistically attributable to anthropometric deficits, with most estimates falling in the range 25-50%. When taking account of the relative proportions of severe versus mild-to-moderate malnutrition in the population, the results show further than 16-80% of all nutrition-related deaths are associated with mild-to-moderate malnutrition rather than severe malnutrition. In most studies 46-80% of all nutrition-related deaths are in the mild-to-moderate category.

Publication Types: Review, Review, tutorial

Perkins BA, Zucker JR, Otieno J, Jafari HS, Paxton L, Redd SC, Nahlen BL, Schwartz B, Oloo AJ, Olango C, Gove S, Campbell CC

**Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):33-42.

(See chapter Effectiveness of IMCI guidelines)

Schofield C, Ashworth A

**Why have mortality rates for severe malnutrition remained so high?**

*Bulletin of the World Health Organization*, 1996, 74(2):223-229.

A review of the literature that has appeared over the past five decades indicates that the median case fatality from severe malnutrition has remained unchanged over this period and is typically 20-30%, with the highest levels (50-60%) being among those with oedematous malnutrition. A likely cause of this continuing high mortality is faulty case-management. A survey of treatment centres worldwide (n = 79) showed that for acutely ill children, inappropriate diets that are high in protein, energy and sodium and low in micronutrients are commonplace. Practices that could have fatal consequences, such as prescribing diuretics for oedema, were found to be widespread. Evidence of outmoded and conflicting teaching manuals also emerged. Since low mortality levels from malnutrition can be achieved using appropriate treatment regimens, updated treatment guidelines, which are practical and prescriptive rather than descriptive, need to be implemented as part of a comprehensive training programme.

Publication Types: Review Review, tutorial

Simoes EA, Desta T, Tessema T, Gerbresellassie T, Dagne M, Gove S

**Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):43-54. (See chapter Effectiveness of IMCI guidelines).

Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM

**Evaluation of an algorithm for integrated management of childhood illness in an area with seasonal malaria in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):25-32.

(See chapter Effectiveness of IMCI guidelines)

World Health Organization Division of Child Health and Development and WHO Regional Office for Africa

**Integrated management of childhood illness: field test of the WHO/UNICEF training course in Arusha, United Republic of Tanzania.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):55-64. (See chapter Effectiveness of IMCI guidelines).

## 7. 2. Breastfeeding counselling

### Articles

Brahmbhatt H, Gray RH

**Breastfeeding and the prevention of infant mortality.**

*Lancet* 2000 Apr 15;355(9212):1370

The WHO Collaborative Study Team's analysis of the effects of breastfeeding on infant and child mortality is an important contribution to the policy on early weaning to prevent mother-to-child transmission of HIV-1. However we believe that the estimates of the deleterious effects of weaning per se on mortality may be exaggerated because the study team could not establish whether a preceding illness in the infant or mother precipitated termination of breastfeeding. Some data suggest that the possibility of bias due to reverse causality is likely especially in cultures where breastfeeding is the norm, since women who fail to initiate breastfeeding or who wean early are more likely to do so for involuntary reasons such as maternal or infant illness. When estimating the risks and benefits of early weaning, the focus should be on risks of infant deaths attributable to voluntary weaning, after exclusion of the potentially confounded risks due to preceding illness causing interruption of breastfeeding.

Publication Types: Comment, Letter

Clemens JD, Stanton B, Stoll B, Shahid NS, Banu H, Chowdhury AK

**Breast feeding as a determinant of severity in shigellosis. Evidence for protection throughout the first three years of life in Bangladeshi children.**

*American Journal of Epidemiology*, 1986, 123(4):710-720.

Little is known about the effect of breast feeding upon the severity of illness due to specific diarrhoeal pathogens. Using a systematically sampled and evaluated population of children aged less than 3 years, who attended a diarrhoeal disease hospital in Bangladesh, the authors performed a case-control study that assessed whether breast feeding reduces the severity of illness in shigellosis. From 540 children presenting with shigellosis between 1980-1982, they created a group of cases (n = 53) with severe illness and controls (n = 487) with non-severe illness. Overall, the odds ratio relating breast feeding to the severity of shigellosis (0.49, p = 0.01) suggested a substantial mitigating effect of breast feeding upon clinical severity. The high degree of protection against severe shigellosis was evident for breast-fed children up to 35 months of age, as well as for children at high risk for death because of severe malnutrition or measles. Because shigellosis continues to account for substantial morbidity and mortality in children in developing countries, the results support prolonged breast feeding in these settings.

Clemens JD, Sack DA, Harris JR, Khan MR, Chakraborty J, Chowdhury S, Rao MR, van Loon FP, Stanton BF, Yunus M, et al

**Breast feeding and the risk of severe cholera in rural Bangladeshi children.**

*American Journal of Epidemiology*, 1990, 131(3):400-411.

The association between breast feeding and the risk of severe cholera was examined in a case-control study of rural Bangladeshi children under 36 months of age who were studied in 1985-1986 during a field trial of killed oral cholera vaccines. A total of 116 cases who were treated for severe cholera were compared with 464 age-matched community controls without severe cholera. Overall, the odds ratio relating breast feeding to severe cholera (0.30, p less than 0.0001) reflected a 70% reduction in the risk of severe cholera among breast-fed children. The estimated reduction of risk declined with age, but was clearly evident in children up to 30 months of age. Although the association between breast feeding and a reduced risk of severe cholera was not significantly greater in children of mothers who had received cholera vaccine than in children whose mothers had received placebo during the trial, maternal vaccination per se was

suggestively associated with a reduced risk of severe cholera in their nonvaccinated children (odds ratio = 0.53,  $p = 0.05$ ).

**CONCLUSIONS:** The results indicate that breast feeding was associated with a substantial reduction of the risk of severe cholera and raise the possibility that vaccination of mothers may provide protection to their young children in endemic settings.

De Carvalho M, Robertson S, Friedman A, Klaus M

**Effect of frequent breast-feeding on early milk production and infant weight gain.**

*Pediatrics*, 1983, 72(3):307-311.

To investigate the effects of frequency and duration of breast-feeding on infants' milk intake and weight gain, two groups of mother-infant pairs were studied during the first month after delivery. Mothers in the control group ( $n = 24$ ) nursed their infants on a 3- to 4-hour schedule. Those in the experimental group ( $n = 20$ ) were encouraged to nurse frequently. During the first 14 postpartum days, all mothers recorded the length and time of each breast-feeding. On the 15<sup>th</sup> and on the 35<sup>th</sup> postpartum day, milk intake per feeding for 24 hours and infant weight gain from birth were measured. During the first 2 weeks after delivery, mothers in the experimental group nursed more frequently (9.9 v 7.3 feedings per 24 hours;  $P$  less than .0001). On day 15, their infants took more milk (725 v 502 mL/24 h;  $P$  less than .0002), and had gained more weight from birth (561 v 347 g;  $P$  less than .02). On day 35, although mothers in the experimental group were still nursing more frequently (9.8 v 6.8 feedings per 24 hours;  $P$  less than .01), milk intake and weight gain from birth were not significantly different.

de Zoysa I et al

**Why promote breastfeeding in diarrhoeal disease control programmes?**

*Health Policy and Planning*, 1991, 6(4):371-379.

The improvement of case management practices is the cornerstone of national programmes to control childhood diarrhoea and can lead to a rapid reduction in diarrhoeal mortality. There is, however, increasing interest in the development of interventions that can reduce diarrhoeal morbidity, especially in countries where case management activities are well established. The Diarrhoeal Disease Control Programme of the World Health Organization recommends that breastfeeding be promoted as one of the most important measures for preventing diarrhoea. There is now conclusive evidence that breastfeeding confers significant protection against illness and death associated with diarrhoea, and minimizes its adverse nutritional effects. Breastfeeding promotion has been demonstrated to be an efficient measure for preventing diarrhoea, and has many other important social, economic and health benefits. This paper summarizes the evidence and describes the Programme's ongoing and planned activities in support of efforts to promote breastfeeding.

Haider R, Ashworth A, Kabir I, Huttly SR

**Effect of community-based peer counsellors on exclusive breastfeeding practices in Dhaka, Bangladesh: a randomised controlled trial**

*Lancet* 2000 Nov 11;356(9242):1643-7

**BACKGROUND:** Most mothers breastfeed in Bangladesh, but they rarely practise exclusive breastfeeding. Hospital-based strategies for breastfeeding promotion cannot reach them because about 95% have home deliveries. We postulated that with the intervention of trained peer counsellors, mothers could be enabled to breastfeed exclusively for the recommended duration of 5 months. **METHODS:** 40 adjacent zones in Dhaka were randomised to intervention or control groups. Women were enrolled during the last trimester of pregnancy between February and December, 1996. In the intervention group, 15 home-based counselling visits were scheduled, with two visits in the last trimester, three early postpartum (within 48 h, on day 5, between days 10 and 14), and fortnightly thereafter until the infant was 5 months old. Peer counsellors were local mothers who received 10 days' training. **FINDINGS:** 363 women were enrolled in each group. Peer counselling significantly improved breastfeeding practices. For the primary outcome, the prevalence of exclusive breastfeeding at 5 months was 202/228 (70%) for the intervention group and 17/285 (6%) for the control group (difference=64%; 95% CI 57%-71%,  $p > 0.0001$ ). For the secondary outcomes, mothers in the intervention group initiated breastfeeding earlier than control mothers and were

less likely to give prelacteal and postlacteal foods. At day 4, significantly more mothers in the intervention group breastfed exclusively than controls.

INTERPRETATION: Peer counselors can effectively increase the initiation and duration of exclusive breastfeeding. We recommend incorporation of peer counselors in mother and child health programs in developing countries.

Haider R, Islam A, Hamadani J, Amin NJ, Kabir I, Malek MA, Mahalanabis D, Habte D

**Breast-feeding counselling in a diarrhoeal disease hospital.**

*Bulletin of the World Health Organization*, 1996, 74(2):173-179.

Lactation counsellors were trained to advise mothers of partially breast-fed infants who were admitted to hospital because of diarrhoea, so that they could start exclusive breast-feeding during their hospital stay. Infants (n = 250) up to 12 weeks of age were randomised to intervention and control groups. Mothers in the intervention group were individually advised by the counsellors while mothers in the control group received only routine group health education. During follow-up at home by the counsellors a week later, only the mothers in the intervention group were counselled. All the mothers were evaluated for infant feeding practices at home two weeks after discharge. Among the 125 mother-infant pairs in each group, 60% of mothers in the intervention group were breast-feeding exclusively at discharge compared with only 6% in the control group (P < 0.001); two weeks later, these rates rose to 75% and 8% in the intervention and control groups, respectively (P < 0.001). However, 49% of mothers in the control group reverted back to bottle-feeding compared with 12% in the intervention group (P < 0.001).

CONCLUSIONS: Individual counselling had a positive impact on mothers to start exclusive breast-feeding during hospitalisation and to continue the practice at home. Maternal and child health facilities should include lactation counselling as an integral part of their programme to improve infant feeding practices.

Publication Types: Clinical trial, Randomised controlled trial

Klaus MH

**The frequency of suckling. A neglected but essential ingredient of breast-feeding.**

*Obstetrics and Gynaecology Clinics of North America*, 1987, 14(3):623-633.

This article presents data to suggest that an essential ingredient for the success of breast-feeding is feeding frequency. Increasing the frequency of feeding decreases nipple pain and breast tenderness, significantly increases milk output and infant weight gain, decreases the peak serum bilirubin levels, increases the success of lactation, and decreases ovulation, markedly improving the contraceptive effect of breast-feeding.

Publication Types: Review, Review, tutorial

Lang S, Lawrence CJ, Orme RL

**Cup feeding: an alternative method of infant feeding.**

*Archives of Diseases in Childhood*, 1994, 71(4):365-369.

In Exeter neonatal unit more than 500 infants have received cup feeds on one or more occasions since 1989. Cup feeding was found appropriate for breastfed infants nearing discharge whose mothers were not resident on the unit, preterm infants who were to be breastfed but who were not satisfied orally after gastric tube feeds, infants with cleft lip and/or cleft palate whose mothers wished to establish breastfeeding but who were also likely to require an additional method of feeding until surgical repair of the defect was completed, infants with an uncoordinated suck, swallow, and breathing pattern, infants born by caesarean section, if breastfeeding was not possible within the first few hours of surgery and infants at discharge who became tired before they were able to complete a breastfeed.

CONCLUSIONS: In situations where an alternative to bottle and gastric tube feeding is required, cup feeding provides a simple, practical, and effective solution.

Martines JC, Rea M, de Zoysa I

**Breast feeding in the first six months: no need for extra fluids [editorial].**

*British Medical Journal*, 1992, 304(6834):1068-1069.

Infants who receive supplementary fluids have a lower intake of breast milk than if they are exclusively breastfed and are also more likely to be breastfed for shorter periods. The use of these fluids may therefore erode the substantial benefits of breastfeeding in maintaining growth, reducing morbidity and mortality from a range of causes, and increasing birth intervals. The average daily fluid requirement of a healthy infant depends on the concentration of the feeds, energy consumption, and environmental humidity and temperature. Fluids consumption below the requirement will lead to dehydration, which increases serum and urine osmolarity. Six studies have measured the urine osmolarity of 572 healthy, exclusively breastfed infants in setting with high environmental temperatures and varying degrees of humidity. Out of 572 urine samples, 570 had an osmolarity that was within normal limits.

**CONCLUSIONS** The results indicate that healthy infants who consume enough breast milk to satisfy their energy needs receive enough fluid to satisfy their requirements, even in hot and dry environment.

Martines JM, Ashworth A, Kirkwood B.

**Breast-feeding among the urban poor in southern Brazil: reasons for termination in the first 6 months of life.**

*Bulletin of the World Health Organization*, 1989, 67(2):151-161.

A study of breast-feeding practices over the first 6 months of life among a cohort of urban poor infants in southern Brazil indicated that the median duration of breast-feeding was 18 weeks, and at 6 months 41% of the infants were still being breast-fed. The duration of breast-feeding was significantly associated with the following: the infant's sex, mother's colour, type of first feed, timing of the first breast-feed, breast-feeding regimen and frequency of breast-feeding at 1 month, and the use of hormonal contraceptives by the mother. The following were significant risk factors for early termination of breast-feeding: the infant's sex, type of first feed, use of supplementary feeds, frequency of breast-feeding, feeding regimen, weight-for-age, and weight-for-age after controlling for birth weight. Dissatisfaction with their infant's growth rate was the most frequent reason given by mothers for supplementing the diets of infants who were exclusively breast-fed in the first 3 months of life. Also, the mothers' perception that their milk output was inadequate was the most frequent reason expressed for stopping breast-feeding in the first 4 months. The roles of health services and family support in providing favourable conditions for increasing the duration of breast-feeding in the study population are discussed, as well as the possibility of bias being introduced into studies of the relationship between infant feeding and growth by the effect of the infant's rate of growth on the mother's decision to continue breast-feeding.

Nanavati RN, Mondkar JA, Fernandez AR, Raghavan KR

**Lactation management clinic - positive reinforcement to hospital breastfeeding practices.**

*Indian Pediatrics*, 1994, 31(11):1385-1389.

Supportive breastfeeding policies in the hospital constitute the foundation for initiation of successful breastfeeding by mothers, constant reinforcement and support to all lactating mothers is however essential to maintain lactation. The objective, methodology and outcome of the Lactation Management Clinic which constitutes a hospital-based mother support group is described. The study was carried out over a period of 2 ½ years and 519 mothers had attended this clinic. Analysis of the data revealed that at the time of the 1<sup>st</sup> visit to the clinic, 65.9% mothers had already started supplementary top feeds and the commonest reason encountered was mother's own assessment of inadequate milk seen in 73.6% mothers. Two-thirds (66.9%) of babies in our study were roomed in right from the first day of life, 75.3% of babies had received colostrum and 67.1% babies had not received any prelacteal feeds and yet faced problems at lactation. Mother and infant evaluation revealed no complications with 86.5% mothers and with 54.5% babies. Local breast problems were detected in 19.3% mothers. Faulty positioning was observed in 47.2% patients. Psychological support to mothers was the most important form of therapy given. Seventy eight per cent mothers practised exclusive breastfeeding subsequently while 21.2% of mothers were partially successful in lactation. Only 3 mothers had lactation failure.

Prentice AM, Goldberg GR, Prentice A

**Body mass index and lactation performance.**

*European Journal of Clinical Nutrition*, 1994, 48(Supplement 3):S78-S79.

Data from the world literature have been analysed in order to test whether low body mass index (BMI: kg/m<sup>2</sup>) is a useful indicator of functional impairment of lactation performance. Forty-one databases containing 1726 measurements have been identified as having reliable estimates of breast-milk quantity and/or quality. There is no detectable relationship between maternal BMI and the volume of milk produced by mothers when analysed according to the mean BMI of different populations, or of different subgroups stratified by BMI within populations. This conclusion holds even at BMIs < 18.5. The most remarkable feature of the data is the very high milk volumes produced by very thin mothers. It is accepted that the composition of breast milk is relatively unaffected by general undernutrition of the type that would be indicated by a low BMI with the possible exception of milk fat levels and hence the energy content. Analysis of the available data reveals studies in which there are weak, but significant, correlations between maternal BMI and milk fat. However, other studies show no association or even a negative relationship. Inter-country analysis fails to reveal any detectable association between BMI and milk energy. Milk energy levels seem adequate even at BMIs < 18.5.

**CONCLUSIONS:** Human lactation performance is extremely robust and that BMI does not provide a useful indicator of function at the levels studied so far. Lactation performance must become compromised when undernutrition is sufficiently severe, but it appears that this must occur only in famine or near famine conditions.

Rea MF, Venancio SI, Martines JC, Savage F

**Counselling on breastfeeding: Assessing knowledge and skills.**

*Bulletin of the World Health Organization*, 1999, 77(5):

Reported are the results of a randomised controlled trial to assess the effectiveness of the WHO/UNICEF 40-hour course "Breastfeeding counselling: a training course". The course was conducted in a maternity hospital which provides care to a low-income population in a metropolitan area in Sao Paulo, Brazil. Health workers from 60 health units were randomly assigned to be either participants (20) or controls (40), and their breastfeeding knowledge and skills were assessed before and immediately after the course, as well as 3 months later. Immediately after the course the participants' knowledge of breastfeeding had increased significantly compared to controls. Both their clinical and counselling skills also improved significantly. When assessed 3 months later, the scores remained high with only a small decrease. The implementation of the course was also evaluated. The methods used were participatory observation, key interviews and focus group discussion. In the 33 sessions of the course, the average score was 8.43 out of 10. Scores were highest for content and methodology of the theory sessions, and lowest for "use of time", "clinical management of lactation", and "discussion of clinical practice". "Breastfeeding counselling: a training course" therefore effectively increases health workers' knowledge and their clinical and counselling skills for the support of breastfeeding. The course can be conducted adequately using the material and methodology proposed, but could be more satisfactory if the time allocated to exercises and clinical practice sessions were increased.

Publication Types: Clinical trial, Randomised controlled trial

Righard L, Alade MO

**Suckling technique and its effect on success of breastfeeding.**

*Birth*, 1992, 19(4):185-189.

We investigated the prognostic value of sucking technique (faulty vs correct) during the first week after birth in relation to the long-term success of breastfeeding. At discharge from the maternity ward, 82 healthy mother-infant pairs were observed for assessment of breastfeeding technique and followed for four months by regular telephone check-ups. Correct sucking technique was defined as the infant having a wide-open mouth, with the tongue under the areola, and expressing milk from the breast by slow, deep sucks; faulty technique was defined as superficial nipple sucking. The study population was divided into three groups: one in which faulty sucking technique was corrected when observed (n = 29), one with faulty but uncorrected technique (n = 25), and a control group with a correct technique (n = 28). At the four-month



follow-up assessment, the faulty but uncorrected group was characterised by a greater proportion of mothers with breastfeeding problems and early cessation of breastfeeding than the other two groups. Regular use of a pacifier (> 2 hrs/day) was more common among those with breastfeeding problems.

Sachdev HP, Krishna J, Puri RK, Satyanarayana L, Kumar S

**Water supplementation in exclusively breastfed infants during summer in the tropics.**

*Lancet*, 1991, 337(8747):929-933.

This study was designed to determine the need for water supplementation to maintain water homeostasis in exclusively breastfed infants during summer in a tropical country. A prestudy questionnaire revealed that 97% of 34 nurses and 63% of 70 doctors advocated such supplementation. 45 healthy, male, exclusively breastfed babies, aged 1-4 months, were recruited from a well-baby clinic. 9 who had never received supplemental water plus a random selection of 14 others were allocated to group I (breastmilk only); the remaining 22 infants were allocated to group II (breastmilk plus supplemental fluid according to the mother's usual practice). The babies were studied at the hospital for 8 h; breastmilk intake was measured by weighing the infant before and after each feed, water intake by calibrated bottles, and urine output by accurate collection and measurement. The maximum room temperatures were 34-41 degrees C and relative humidities 9-60% (below 50% in all but 3 infants). In group II the mean water intake was 11% (95% confidence interval 7-16%) of the total fluid intake. Both breastmilk intake (274 vs 210 ml) and total fluid intake (274 vs 233 ml) were higher in group I than in group II ( $p = 0.003$ ,  $p = 0.073$ , respectively), after adjustment for age, weight, length, room temperature, and humidity. However, there were no significant differences between the groups in urine output, urine or serum osmolality, weight change, or rectal temperature whether or not the factors adjusted for included total fluid intake.

**CONCLUSIONS:** Exclusively breastfed infants do not need supplemental water to maintain water homeostasis; a reduced breastmilk intake is a potential disadvantage of this practice.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: *Lancet* 1991 Jul 27;338(8761):251

Victoria CG, Behague DP, Barros FC, Olinto MT, Weiderpass E

**Pacifier-use and short breastfeeding duration: cause, consequence or coincidence?**

*Pediatrics*, 1997, 99(3):445-453.

**OBJECTIVES:** Pacifiers are related to a shorter duration of breastfeeding. However, it is unclear whether this association is causal, because confounding, reverse causality, and self-selection of mothers may play a role. These issues were investigated through a combination of epidemiologic and ethnographic research in southern Brazil. **METHODOLOGY:** A population-based cohort of 650 mothers and infants were visited shortly after delivery and at 1, 3, and 6 months. The rate of complete follow-up was 96.8%. A subsample of 80 mothers and infants was selected for the ethnographic study, which included in-depth interviews and participant observations in the age range of 2 to 6 months with a mean of 4.5 visits. **RESULTS:** The epidemiologic study showed that pacifier use was common with 85% of users at 1 month. However, this was a dynamic process, with many infants starting or abandoning the pacifiers in any age range. Children who stopped breastfeeding in a given period were likely to take up the pacifier during that period. Further analyses excluded all infants not breastfed at 1 month of age and those who reportedly had breastfeeding problems, leaving 450 infants with full data. Intense pacifier users at 1 month (children who used the pacifiers during most of the day and at least until falling asleep) were four times more likely to stop breastfeeding by 6 months of age than nonusers. Users also had fewer daily breastfeedings than nonusers. After adjustment for several confounding variables, logistic regression showed that pacifier use was still associated with an odds ratio of 2.5 (95% confidence interval, 1.40 to 4.01) for stopping breastfeeding. The ethnographic analysis showed that pacifier use was widely regarded as a positive behaviour and that mothers often strongly stimulated the infants to accept it. Although few mothers openly admitted that pacifiers might shorten breastfeeding, a considerable group effectively used pacifiers to get their infants off the breast or to increase the interval between feedings. The latter also had rigid breastfeeding styles that increased maternal-infant distance, had important concerns about objective aspects of infant growth and development, and were highly sensitive to infant crying. These behaviours were linked to intense comparison between themselves and other mothers and to a lack of self-confidence. Non-white mothers, those who delivered vaginally, and mothers of infant girls seemed to be more confident and less affected

by these difficulties. The epidemiologic analysis confirmed that pacifier use was more closely associated with breastfeeding duration among non-white mothers and for normally delivered infants.

**CONCLUSIONS:** Pacifiers may be an effective weaning mechanism used by mothers who have explicit or implicit difficulties in breastfeeding, but they are much less likely to affect infants whose mothers are confident about nursing. Breastfeeding promotion campaigns aimed specifically at reducing pacifier use will fail unless they also help women face the challenges of nursing and address their anxieties. The combination of epidemiologic and ethnographic methods was essential for understanding the complex relations between pacifier use and breastfeeding.

World Health Organization Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality

**Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis.**

*Lancet* 2000 Feb 5;355(9202):451-5

Published erratum appears in *Lancet* 2000 Mar 25;355(9209):1104

**BACKGROUND:** The debate on breastfeeding in areas of high HIV prevalence has led to the development of simulation models that attempt to assess the risks and benefits associated with breastfeeding. An essential element of these simulations is the extent to which breastfeeding protects against infant and child mortality; however, few studies are available on this topic. We did a pooled analysis of studies that assessed the effect of not breastfeeding on the risk of death due to infectious diseases. **METHODS:** Studies were identified through consultations with experts in international health, and from a MEDLINE search for 1980-98. Using meta-analytical techniques, we assessed the protective effect of breastfeeding according to the age and sex of the infant, the cause of death, and the educational status of the mother. **FINDINGS:** We identified eight studies, data from six of which were available (from Brazil, The Gambia, Ghana, Pakistan, the Philippines, and Senegal). These studies provided information on 1223 deaths of children under two years of age. In the African studies, virtually all babies were breastfed well into the second year of life, making it impossible to include them in the analyses of infant mortality. On the basis of the other three studies, protection provided by breastmilk declined steadily with age during infancy (pooled odds ratios: 5.8 [95% CI 3.4-9.8] for infants <2 months of age, 4.1 [2.7-6.4] for 2-3-month-olds, 2.6 [1.6-3.9] for 4-5-month-olds, 1.8 [1.2-2.8] for 6-8-month-olds, and 1.4 [0.8-2.6] for 9-11-month-olds). In the first 6 months of life, protection against diarrhoea was substantially greater (odds ratio 6.1 [4.1-9.0]) than against deaths due to acute respiratory infections (2.4 [1.6-3.5]). However, for infants aged 6-11 months, similar levels of protection were observed (1.9 [1.2-3.1] and 2.5 [1.4-4.6], respectively). For second-year deaths, the pooled odds ratios from five studies ranged between 1.6 and 2.1. Protection was highest when maternal education was low.

**INTERPRETATION:** These results may help shape policy decisions about feeding choices in the face of the HIV epidemic. Of particular relevance is the need to account for declining levels of protection with age in infancy, the continued protection afforded during the second year of life, and the question of the safety of breastmilk substitutes in families of low socioeconomic status.

Publication Types: Meta-analysis

Comment in: *Lancet* 2000 Apr 15;355(9212):1370

Woolridge MW

**The 'anatomy' of infant sucking.**

*Midwifery*, 1986, 2(4):164-171.

This paper aims to present a simple account of the mechanisms by which a baby removes milk from the breast, gleaned from past and current literature, to counter the tendency for inaccurate descriptions of the mechanics of infant sucking to be reproduced. The process is described by which milk is expressed from the lactiferous sinuses within the nipple and breast, by compression of the nipple against the palate by rhythmical pulsations of the surface of the tongue. Active in the process of milk transfer are the roles played by negative suction pressure by the infant, and positive ductal pressure due to action of the mother's milk ejection reflex, which interact in making milk available for removal. The reflexes which the newborn possesses to aid feeding are described and suggestions offered as how best to utilise these reflexes in order to fix a baby successfully on the breast. The intention is that armed with an appropriate understanding of

the underlying processes by which milk is transferred from mother to baby a midwife is best equipped to advise a mother regarding the correct technique for achieving trouble-free breast-feeding.

Woolridge MW

**Actiology of sore nipples.**

*Midwifery* 1986 Dec;2(4):172-6

Based upon a description of the mechanics of milk removal contained in the article Woolridge MW : The 'anatomy' of infant sucking (see above), suggestions are made as to the potential physical sources of nipple trauma which can result in sore nipples. The importance of correct fixing and positioning of the baby to the breast is considered as a prime requisite for reducing trauma, and hence the incidence of sore nipples, thus practical recommendations are given for achieving optimal attachment of the baby at the breast. Special emphasis is placed on ensuring physical opposition of the baby's lower jaw and tongue to the underside of the areola so that the baby can effectively strip milk from the lacteal sinuses lying behind the nipple.

## **Documents and publications**

World Health Organization

**Mastitis: Causes and management**

Geneva, World Health Organization, 2000, 45 p. (unpublished document WHO/FCH/CAH/00.13 available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/2000/WHO\\_FCH\\_CAH\\_00.13.pdf](http://whqlibdoc.who.int/hq/2000/WHO_FCH_CAH_00.13.pdf)

This review aims to bring together available information on lactation mastitis and related conditions and their causes, to guide practical management, including the maintenance of breastfeeding.

Mastitis and breast abscess are common and largely preventable conditions, which occur in all populations and which put breastfeeding at risk. They are caused primarily by inefficient removal of breastmilk, but also by bacterial infection, which is probably secondary to milk stasis. Particularly virulent strains of bacteria may cause epidemics of puerperal mastitis in hospitals, when infants are kept in nurseries away from their mothers. Improved breastfeeding practices, including early skin-to-skin contact between mother and infant, rooming-in, skilled help to ensure that an infant is well attached at the breast, and unrestricted and exclusive breastfeeding, are an efficient way to prevent both milk stasis and spread of infection. Whenever possible breastfeeding should continue, both to improve milk removal and to help the condition to resolve, and for the benefit of the infant. If present, bacterial or other infection should be treated with an appropriate antimicrobial agent, but this should be in addition to, and not an alternative to techniques which ensure efficient removal of milk.

World Health Organization, Department of Child and Adolescent Health

**Relactation. A review of experience and recommendations for practice**

Geneva, World Health Organization, 1998, 38 p. (unpublished document WHO/CHS/CAH/98.14 available on request from the Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1998/WHO\\_CHS\\_CAH\\_98.14.pdf](http://whqlibdoc.who.int/hq/1998/WHO_CHS_CAH_98.14.pdf)

In the past relactation and induced lactation were considered exceptional experiences and were not well researched. However there are now sufficient reports to show that most women can relactate if they are motivated and have adequate information and support. Effective techniques have been learned empirically and enough is known to provide practical guidelines to enable mothers to relactate. It is the purpose of this review to make relevant information available to health workers caring for women and children who may be in need of such help.

World Health Organization

***Evidence for the ten steps to successful breastfeeding.***

Geneva, World Health Organization, 1998, 111p. (unpublished document WHO/CHD/98.9; available on request from the Department of Child and Adolescent Health and Development (CAH)).

[http://whqlibdoc.who.int/hq/1998/WHO\\_CHD\\_98.9.pdf](http://whqlibdoc.who.int/hq/1998/WHO_CHD_98.9.pdf)

The purpose of this document is to review the evidence for the efficacy of the “Ten Steps”, and to provide a tool for both advocacy and education.

A literature search was conducted to identify published studies relating to each of the “Ten Steps” and the effect on breastfeeding of their implementation inside health facilities. The information is presented for each step in the following order: (1) the Global Criteria for the step, as defined by the WHO/UNICEF Baby Friendly Hospital Initiative (1992); (2) an introduction describing the background situation; (3) evidence from experimental studies for breastfeeding outcomes; (4) additional supportive evidence from prospective (longitudinal) or cross-sectional studies; (5) experimental or supportive evidence for other outcomes (6) Discussion and conclusions; (7) a comparative table of studies providing supportive evidence; and (8) the information of one study per step is presented graphically.

**CONCLUSIONS:** The basic premise of the baby Friendly Hospital Initiative, which requires all maternity facilities to implement the Ten Steps for Successful Breastfeeding, is valid. However, selective implementation of only some steps may be ineffective and discouraging. Exclusive breastfeeding will be most effectively increased and sustained when agreed policies and adequate practical training of staff are directed at implementing all the ten steps together, including continuing support for mothers in the community, and the restriction of the availability of breast milk substitutes to situations in which there are clearly defined medical reasons.

World Health Organization, Division of Child Health and Development, Family and Reproductive Health

***Persistent diarrhoea and breastfeeding***

Geneva, World Health Organization, 1997, 14 p. (unpublished document WHO/CHD/97.8; available on request Department of Child and Adolescent Health and Development (CAH))

[http://whqlibdoc.who.int/hq/1997/WHO\\_CHD\\_97.8.pdf](http://whqlibdoc.who.int/hq/1997/WHO_CHD_97.8.pdf)

Persistent diarrhoea causes about 35% of diarrhoeal deaths in children, half being of infants under 1 year of age. The typical child at risk is in the first or second year of life, is fed non-human milks, is malnourished, and has had multiple infections.

The mechanism of persistent diarrhoea seems to be mucosal damage, caused by infection, malnutrition, or animal milk proteins, often compounded by delayed mucosal repair. Lactose intolerance may be present, especially in younger malnourished children, but it is rare when breastmilk is the only source of lactose. Optimal infant feeding practices would help to prevent persistent diarrhoea. These include exclusive breastfeeding for at least the first 4 and, if possible, the first 6 months of life, and continued breastfeeding with adequate complementary foods for up to 2 years or beyond. These practices help to prevent acute diarrhoea, and to shorten individual episodes, thus reducing the likelihood of persistent illness. Exposure to sensitising animal milk proteins is minimised.

For the treatment of persistent diarrhoea, breastmilk may be beneficial when fed exclusively, but it is less helpful when part of a mixed diet, even if non-human milk is excluded.

Mothers of infants less than about 6 months of age should be helped to re-establish exclusive breastfeeding and to stop artificial milk feeding, whether or not the infant suffers from persistent diarrhoea. Relactation, which means re-establishing breastfeeding by mothers who have stopped, is now recognised as a feasible intervention, particularly in this age group.

Mothers of older children with persistent diarrhoea should be encouraged to continue and increase breastfeeding; and to reduce or stop giving animal milks, at least temporarily, provided adequate alternative complementary foods are available. The need for specialist and expensive dietary or parenteral treatment could be reduced.

World Health Organization, Division of Diarrhoeal and Acute Respiratory Infections

***Breastfeeding counselling: A training course.***

Geneva, World Health Organization, 1993 (unpublished document WHO/CDR/93.4; available on request from the Department of Child and Adolescent Health and Development (CAH), formerly the Division of Diarrhoeal and Acute Respiratory Disease Control (CDR)).

The training course materials consist of five volumes: Director's Guide, Trainer's guide, Participants manual, Overhead figures, and Answer sheets.

World Health Organization, Division of Child Health and Development

***Indicators for assessing breastfeeding practices.*** Reprinted report of an Informal Meeting 11-12 June 1991, Geneva Switzerland.

Geneva, World Health Organization, 1991 (unpublished document WHO/CDD/SER/91.14; available on request from the Department of Child and Adolescent Health and Development (CAH), formerly Division of Child Health and Development).

[http://whqlibdoc.who.int/hq/1991/WHO\\_CDD\\_SER\\_91.14.pdf](http://whqlibdoc.who.int/hq/1991/WHO_CDD_SER_91.14.pdf)

The purpose of the informal meeting was to reach a consensus on the definitions of key breastfeeding indicators and specific methodologies for their measurement. The report summarizes the discussion and consensus reached on breastfeeding indicators derived from household survey data. It gives precise definitions of indicators and the rationale for their selection and for arriving at the definitions.

## 7.3. BREASTFEEDING AND HIV

See also chapter HIV/AIDS

### Articles

Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM

**Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group.**

*Lancet* 1999 Aug 7;354(9177):471-6

**BACKGROUND:** The observation that mother-to-child transmission of HIV-1 can occur through breastfeeding has resulted in policies that recommend avoidance of breastfeeding by HIV-1-infected women in the developed world and under specific circumstances in developing countries. We compared transmission rates in exclusively breastfed, mixed-fed, and formula-fed (never breastfed) infants to assess whether the pattern of breastfeeding is a critical determinant of early mother-to-child transmission of HIV-1. **METHODS:** We prospectively assessed infant-feeding practices of 549 HIV-1-infected women who were part of a vitamin A intervention trial in Durban, South Africa. The proportions of HIV-1-infected infants at 3 months (estimated by use of Kaplan-Meier life tables) were compared in the three different feeding groups. HIV-1 infection was defined by a positive RNA-PCR test. **FINDINGS:** At 3 months, 18.8% (95% CI 12.6-24.9) of 156 never-breastfed children were estimated to be HIV-1 infected compared with 21.3% (17.2-25.5) of 393 breastfed children ( $p=0.5$ ). The estimated proportion (Kaplan-Meier) of infants HIV-1 infected by 3 months was significantly lower for those exclusively breastfed to 3 months than in those who received mixed feeding before 3 months (14.6% [7.7-21.4] vs 24.1% [19.0-29.2],  $p=0.03$ ). After adjustment for potential confounders (maternal CD4-cell/CD8-cell ratio, syphilis screening test results, and preterm delivery), exclusive breastfeeding carried a significantly lower risk of HIV-1 transmission than mixed feeding (hazard ratio 0.52 [0.28-0.98]) and a similar risk to no breastfeeding (0.85 [0.51-1.42]). **INTERPRETATIONS:** Our findings have important implications for prevention of HIV-1 infection and infant-feeding policies in developing countries and further research is essential. In the meantime, breastfeeding policies for HIV-1-infected women require urgent review. If our findings are confirmed, exclusive breastfeeding may offer HIV-1-infected women in developing countries an affordable, culturally acceptable, and effective means of reducing mother-to-child transmission of HIV-1 while maintaining the overwhelming benefits of breastfeeding.

Comment in: *Lancet* 1999 Aug 7;354(9177):442-3; *Lancet* 1999 Nov 27;354(9193):1901; discussion 1902; *Lancet* 1999 Nov 27;354(9193):1901-2; *Lancet* 1999 Nov 27;354(9193):1903; *Lancet* 1999 Nov 27;354(9193):1903-4

Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, Ndinya-Achola J, Bwayo J, Onyango FE, Hughes J, Kreiss J

**Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomised clinical trial.**

*JAMA* 2000 Mar 1;283(9):1167-74

**CONTEXT:** Transmission of human immunodeficiency virus type 1 (HIV-1) is known to occur through breastfeeding, but the magnitude of risk has not been precisely defined. Whether breast milk HIV-1 transmission risk exceeds the potential risk of formula-associated diarrhoeal mortality in developing countries is unknown. **OBJECTIVES:** To determine the frequency of breast milk transmission of HIV-1 and to compare mortality rates and HIV-1-free survival in breastfed and formula-fed infants. **DESIGN AND SETTING:** Randomised clinical trial conducted from November 1992 to July 1998 in antenatal clinics in Nairobi, Kenya, with a median follow-up period of 24 months. **PARTICIPANTS:** Of 425 HIV-1-seropositive, antiretroviral-naive pregnant women enrolled, 401 mother-infant pairs were included in the analysis of trial end points. **INTERVENTIONS:** Mother-infant pairs were randomised to breastfeeding (n

= 212) vs formula feeding arms (n = 213). MAIN OUTCOME MEASURES: Infant HIV-1 infection and death during the first 2 years of life, compared between the 2 intervention groups. RESULTS: Compliance with the assigned feeding modality was 96% in the breastfeeding arm and 70% in the formula arm (P<.001). Median duration of breastfeeding was 17 months. Of the 401 infants included in the analysis, 94% were followed up to HIV-1 infection or mortality end points: 83% for the HIV-1 infection end point and 93% to the mortality end point. The cumulative probability of HIV-1 infection at 24 months was 36.7% (95% confidence interval [CI], 29.4%-44.0%) in the breastfeeding arm and 20.5% (95% CI, 14.0%-27.0%) in the formula arm (P = .001). The estimated rate of breast milk transmission was 16.2% (95% CI, 6.5%-25.9%). Forty-four percent of HIV-1 infection in the breastfeeding arm was attributable to breast milk. Most breast milk transmission occurred early, with 75% of the risk difference between the 2 arms occurring by 6 months, although transmission continued throughout the duration of exposure. The 2-year mortality rates in both arms were similar (breastfeeding arm, 24.4% [95% CI, 18.2%-30.7%] vs formula feeding arm, 20.0% [95% CI, 14.4%-25.6%]; P = .30). The rate of HIV-1-free survival at 2 years was significantly lower in the breastfeeding arm than in the formula feeding arm (58.0% vs 70.0%, respectively; P = .02). CONCLUSIONS: The frequency of breast milk transmission of HIV-1 was 16.2% in this randomised clinical trial, and the majority of infections occurred early during breastfeeding. The use of breast milk substitutes prevented 44% of infant infections and was associated with significantly improved HIV-1-free survival.

Publication Types: Clinical trial, Randomised controlled trial

Comment in: JAMA 2000 Aug 23-30;284(8):956; discussion 956-7; JAMA 2000 Aug 23-30; 284(8):956-7

Nicoll A, Newell ML, Peckham C, Luo C, Savage F

#### **Infant feeding and HIV-1 infection**

*AIDS* 2000;14 Suppl 3:S57-74

In this paper the authors re-examine the current data relating to infant feeding and HIV infection. They review the possible mechanisms of HIV transmission through breastfeeding, consider approaches to prevention (including feeding options) in different settings and identify research needs. Information was obtained from diverse sources and a systematic review, using computerized literature searches on breastfeeding and HIV, supplemented by consultation with relevant specialists.

Savage DF, Lhotska L

#### **Recommendations on feeding infants of HIV positive mothers. WHO, UNICEF, UNAIDS guidelines.**

In: *Short and Long term Effects of Breast Feeding on Child Health*. B. Koletzko et al. Eds., Kluwer Academic/Plenum Publishers, 2000, p 225 - 230

Also published in *Advances of Experimental Medical Biology* 2000;478:225-30



The second policy statement on HIV and Infant Feeding put forward jointly by WHO, UNICEF and UNAIDS in 1997 (see this section) called for women in all settings to make a fully informed decision about feeding their infants. On the basis of this policy, it became possible to develop *Guidelines for decision-makers* and *Guide for health care managers and supervisors* (both see this section) which sought to clarify the direction for implementation, identify gaps in understanding, and unresolved questions that required further research. There continues to be a concern about issues such as how to provide women with the information necessary to make a fully informed choice, about women's access to adequate fuel, water, necessary utensils and time; and about the risk of misuse and spillover of infant formula among women who are uninfected or whose HIV status is unknown. New evidence has become available that anti-retroviral drugs are effective even if women breastfeed and that exclusive breastfeeding may be less likely to transmit HIV to the infant than mixed feeding. Although it has been suggested that the 1998 guidelines should be revised in the light of the new evidence, it has not been found necessary.

Semba RD, Kumwenda N, Hoover DR, Taha TE, Quinn TC, Mtimavalye L, Biggar RJ, Broadhead R, Miotti PG, Sokoll LJ, van der Hoeven L, Chipangwi JD

**Human immunodeficiency virus load in breast milk, mastitis, and mother-to-child transmission of human immunodeficiency virus type 1.**

*Journal of Infectious Diseases* 1999 Jul;180(1):93-8

Human immunodeficiency virus (HIV) type 1 load in breast milk and mastitis were examined as risk factors for vertical transmission of HIV-1. Six weeks after delivery, HIV-1 load and sodium (an indicator of mastitis) were measured in breast milk from 334 HIV-1-infected women in Malawi. Median breast milk HIV-1 load was 700 copies/mL among women with HIV-1-infected infants versus undetectable (<200 copies/mL) among those with uninfected infants, respectively (P<. 0001). Elevated breast milk sodium levels consistent with mastitis occurred in 16.4% of HIV-1-infected women and were associated with increased vertical transmission of HIV-1 (P<.0001). Median breast milk HIV-1 load was 920 copies/mL among women with versus undetectable among those without elevated breast milk sodium levels, respectively (P<.0001). Mastitis and breast milk HIV-1 load may increase the risk of vertical transmission of HIV-1 through breast-feeding.

Comment in: *J Infect Dis* 2000 Feb;181(2):800-1

## **Documents and publications**

World Health Organization

***HIV and Infant Feeding***

1998, available as a set of three manuals [E]

Sw.fr. 16.–/US \$14.40; in developing countries: Sw.fr. 11.20

Order no. 1930135

[http://whqlibdoc.who.int/hq/1998/WHO\\_FRH\\_NUT\\_CHD\\_98.1.pdf](http://whqlibdoc.who.int/hq/1998/WHO_FRH_NUT_CHD_98.1.pdf)

[http://whqlibdoc.who.int/hq/1998/WHO\\_FRH\\_NUT\\_CHD\\_98.2.pdf](http://whqlibdoc.who.int/hq/1998/WHO_FRH_NUT_CHD_98.2.pdf)

[http://whqlibdoc.who.int/hq/1998/WHO\\_FRH\\_NUT\\_CHD\\_98.3.pdf](http://whqlibdoc.who.int/hq/1998/WHO_FRH_NUT_CHD_98.3.pdf)

*Guidelines for Decision-makers*

1998, 36 pages [E]; WHO/FRH/NUT/CHD 98.1

*A Guide for Health Care Managers and Supervisors*

1998, 36 pages [E]; WHO/FRH/NUT/CHD 98.2

*A Review of HIV Transmission through Breastfeeding*

1998, 28 pages [E]; WHO/FRH/NUT/CHD 98.3

This set of three manuals offers the latest expert advice, from WHO, UNICEF, and UNAIDS, on recommended safe practices for infant feeding when the mother is infected with HIV. Citing firm evidence that HIV can be transmitted through breast milk, the manuals respond to the urgent need for guidance when advising infected mothers as well as formulating sound public health policies. With this need in mind, the manuals identify the wide range of precautions and policy options needed to reduce the risk of HIV transmission through breast milk while ensuring that the nutritional requirements of infants born to HIV-infected mothers are adequately met.

Although recommendations and advice have universal relevance, particular attention is given to options for infant feeding in resource-poor settings where infectious diseases and malnutrition are the leading causes of infant mortality and where artificial feeding may be hazardous as well as prohibitively expensive. The manuals also offer abundant advice on ways of ensuring that breast-milk substitutes reach only those infants who are at risk of HIV infection and thus do not undermine the unique advantages of breastfeeding for the majority of women and infants. Other key messages include the vital importance of confidential counselling, the right of every mother to decide how she wishes to feed her child, and the need to protect infected mothers from stigmatization and discrimination.

The first manual aims to help decision-makers formulate sound public health policies that are appropriate to both local resources and the stage of the HIV/AIDS epidemic. Drawing on the latest scientific



knowledge, the manual explains how mother-to-child transmission occurs, identifies factors that influence the risk of transmission, and discusses the advantages and disadvantages of specific preventive measures – from artificial feeding to the use of wet-nurses or modified cow’s milk – in terms of their costs as well as their safety in different resource settings.

The second manual, addressed to health care managers and supervisors, offers a step-by-step guide to safe feeding practices for infants of HIV-infected mothers. Details range from instructions for feeding infants from a cup, through advice on when to give vitamin supplements, to the warning that provision of free or subsidized breast-milk substitutes to mothers may label them as HIV-infected and lead to discrimination. The final manual provides an expert review of what is known – and unknown – about HIV transmission and breastfeeding. Findings from over 130 recent studies are critically assessed.

UNAIDS

***HIV and Infant Feeding: A policy statement Developed collaboratively by UNAIDS, WHO and UNICEF.***

Joint United Nations Programme on HIV/AIDS, 1997, 2p.

The statement provides policy-makers with a number of key elements for the formulation of a policy on HIV infection and infant feeding such as the human rights perspective and need for reducing women’s vulnerability to HIV infection. Basic elements for establishing a policy on HIV and infant feeding are: supporting breastfeeding, improving access to HIV counselling and testing, ensuring informed choice of the infant feeding method and preventing commercial pressures for artificial feeding.

## 7.4. NUTRITION COUNSELLING

### Articles

Allen LH

**An analytical approach for exploring the importance of dietary quality versus quantity in the growth of Mexican children.**

*Food and Nutrition Bulletin*, 1991, 13:95-104.

The average annual intake of specific nutrients, foods, food groups, and proxies for nutrient bioavailability of 87 Mexican preschoolers and 110 schoolchildren were compared with their anthropometry. Median intakes of energy, protein, thiamine, and iron were adequate; calcium and zinc were low; and other nutrients were very inadequate. Anaemia and low serum retinol were common. Intake of individual nutrients failed to predict size. Correlation matrices, median traces, and principal-components analysis illustrated a dietary continuum ranging from a high dependence on tortillas to more animal products and fruit. Children consuming a lower proportion of tortillas and legumes and more animal products were taller and heavier. Even though the high-tortilla dietary pattern provided more of most nutrients, these were less available. In conclusion, children's size was predicted by dietary quality not quantity - measured either as a high intake of animal products or as a lower intake of factors inhibiting nutrient bioavailability.

Bhatnagar S, Bhan MK, Singh KD, Saxena SK, Shariff M

**Efficacy of Milk-based Diets in Persistent Diarrhoea: A Randomised, Controlled Trial.**

*Pediatrics*, 1996, 98(6):1122-1126.

**OBJECTIVE:** Previous studies have shown increased stool output when children with persistent diarrhoea (PD) received milk as the predominant source of nutrition. **METHODS:** We evaluated the efficacy of milk given in modest amounts as a part of a mixed diet in children with PD. One hundred sixteen children 3 to 24 months of age with diarrhoea for between 14 days and 12 weeks were allocated to milk-based (n = 60) or milk-free (n = 56) cereal dietary regimens. The two diets were isocaloric (86.9 calories/100 g for < or = 9 months; 95.6 cal/100 g for > 9 months) consisting of puffed rice cereal, sugar, and oil differing in only their source of protein, which was either milk or egg white, respectively. An average of 30% of the calories were constituted by milk in the milk-cereal diet. Both diets were offered at the rate of 150 kcal/kg per day. Children receiving milk-cereal consumed an average of 1.9 g/kg lactose per day. **RESULTS:** The baseline characteristics in the two groups were similar. Comparable amounts of diet were consumed in both groups. The milk-cereal group did not have higher median (range) stool output (g/kg/h) compared with the milk-free group during a 0- to 48-hour (milk-cereal, 1.7 [0.2 to 8.7]; milk-free, 1.5 [0.1 to 6.6]) or 0-to 120-hour (milk-cereal, 1.6 [0.4 to 7.2]; milk-free, 1.3 [0.1 to 7.6]) period. The percentage of weight gain was similar in the two groups, and there were no significant differences in the duration of diarrhoea. Overall, 23 children had treatment failures, 10 (17%) in the milk-cereal and 13 (23.6%) in the milk-free groups. **CONCLUSIONS:** Our findings suggest that modest intakes of milk are well tolerated as a part of mixed diet during PD.

Publication Types: Clinical trial, Randomised controlled trial

Black RE, Lopez de Romana G, Brown KH, Bravo N, Bazalar OG, Kanashiro HC

**Incidence and aetiology of infantile diarrhoea and major routes of transmission in Huascar, Peru.**

*American Journal of Epidemiology*, 1989, 129(4):785-799.

Community-based studies of diarrhoea aetiology and epidemiology were carried out from July 1982-June 1984 in 153 infants residing in a poor peri-urban community near Lima, Peru. Study infants had nearly 10 episodes of diarrhoea in their first year of life. Diarrhoea episodes were associated with organisms such as *Campylobacter jejuni*, enterotoxigenic and enteropathogenic *Escherichia coli*, *Shigella*, rotavirus, and

Cryptosporidium. These organisms appeared to be transmitted to infants in the home through animal feces, through contaminated water and food, and by direct person-to-person contact. A particularly important route of transmission may have been weaning foods, which were often contaminated because of improper preparation and inadequate cleaning of utensils.

**CONCLUSIONS:** Improved feeding practices, along with avoidance of animal feces and improved personal and domestic hygiene, should be considered important interventions in reducing the high incidence of diarrhoea in infants in developing countries.

Brown KH, Creed-Kanashiro H, Dewey KG

**Optimal complementary feeding practices to prevent childhood malnutrition in developing countries.**

*Food and Nutrition Bulletin*, 1995, 16:320-338.

Optimal nutritional care of young children requires application of feeding guidelines based on scientific knowledge of children's nutrient requirements and the ability of breastmilk and other foods to satisfy these nutritional needs. This paper reviews recent information on the appropriate duration of exclusive breastfeeding and timing of introduction of complementary foods; the relationship between frequency of feeding, dietary energy density, and total daily energy consumption; and the importance of nutrient composition and selected organoleptic characteristics of complementary foods as determinants of dietary intake. The role of child appetite is also discussed. Finally, programmatic options for the promotion of enhanced complementary feeding and relevant practical experiences in Peru are reviewed.

Brown KH, Stallings RY, de Kanashiro HC, Lopez de Romana G, Black RE

**Effects of common illnesses on infants' energy intakes from breast milk and other foods during longitudinal community-based study in Huascar (Lima), Peru.**

*American Journal of Clinical Nutrition*, 1990, 52(6):1005-1013.

To assess the effects of common infections on dietary intake, 131 Peruvian infants were observed longitudinally. Home surveillance for illness symptoms was completed thrice weekly, and food and breast-milk consumption was measured during 1615 full-day observations. Mean (+/- SD) energy intakes on symptom-free days were 557 +/- 128 kcal/d (92.4 +/- 26.5 kcal.kg-1.d-1) for infants aged less than 181 d and 638 +/- 193 kcal/d (77.7 +/- 25.7 kcal.kg-1.d-1) for infants aged greater than 180 d. Statistical models controlling for infant age, season of the year, and individual showed significant 5-6% decreases in total energy intake during diarrhoea or fever. There were no changes with illness in the frequency of breastfeeding, total suckling time, or amount of breast-milk energy consumed. By contrast, energy intake from non-breast-milk sources decreased by 20-30% during diarrhoea and fever, and the small decrements in total energy consumption during illness were explained entirely by reduced consumption of non-breast-milk foods.

Brown KH, Sanchez-Grinan M, Perez F, Peerson JM, Ganoza L, Stern JS

**Effects of dietary energy density and feeding frequency on total daily energy intakes of recovering malnourished children.**

*American Journal of Clinical Nutrition*, 1995, 62(1):13-18.

To develop recommendations for the design of special foods for young children, we measured total daily energy consumption from semisolid food mixtures with energy densities of 1.67, 2.93, 4.18, or 6.28 kJ/g (0.4, 0.7, 1.0, or 1.5 kcal/g) and that were fed ad libitum three, four, or five times per day to 18 fully weaned children from 6 to 18 mo of age who were recovering in the hospital from malnutrition. The diets were generally indistinguishable by sensory qualities, and were fed in a randomised sequence. The mean amounts consumed (g.kg body wt-1.d-1) were significantly less with successively greater energy density of the diet ( $P < 0.001$ ). The total daily consumption was approximately 16% more when the number of meals was increased from three to four per day, with energy density controlled for ( $P < 0.001$ ), and 7% more when the feeding frequency rose from four to five meals per day ( $P = 0.005$ ). The total daily energy intakes (kJ.kg body wt-1.d-1) increased significantly with the more concentrated diets ( $P < 0.001$ ) and varied positively in relation to feeding frequency ( $P < 0.001$ ). Approximately 15-20 min were required per

meal for the children to reach satiety. The total amount of time required to feed the children each day was related to the number of meals served ( $P < 0.001$ ) and not to energy density. Implications for child feeding are discussed.

Publication Types: Clinical trial, Randomised controlled trial

Elegbe IA, Ojofeitimi EO, Elegbe I, Akinola MO

**Pathogenic bacteria isolated from infant feeding teats: contamination of teats used by illiterate and educated nursing mothers in Ile-Ife, Nigeria.**

*American Journal of Diseases of Children*, 1982, 136(8):672-674.

We assessed bacterial contamination of infant feeding teats among nursing mothers and identified pathogenic organisms that might be associated with the incidence of diarrhoea. The incidence of diarrhoea among the infants of illiterate mothers was fivefold that of infants of educated mothers. The vast majority of the illiterate mothers poorly sterilized their infants' feeding utensils. The most prevalent pathogenic organism isolated from the teats was enteropathogenic *Escherichia coli*, followed by *Staphylococcus aureus*. Unhygienic handling of feeds is an important factor in infantile diarrhoea.

Hibbert JM, Golden MH

**What is the weanling's dilemma? Dietary faecal bacterial ingestion of normal children in Jamaica.**

*Journal of Tropical Paediatrics*, 1981, 27(5):255-258.

Childhood gastroenteritis and malnutrition have been associated with a high bacterial contamination of weaning foods and bottle feeds in particular. We have cultured the bottle feeds of 90 well-nourished and 11 undernourished children aged 6-23 months. Four-fifths of the feeds had more than 10,000 viable faecal organisms/ml and two-thirds had more than 100,000. The level of contamination did not differ between milks and porridges or with different methods of sterilization. There was no relationship between the level of contamination and nutritional status of the children. Those who were being breast fed at the time of sampling had experienced fewer episodes of gastroenteritis. The results indicate that well-nourished children can ingest large numbers of viable faecal organisms with relative impunity, particularly if they are breastfed. The factors which dictate a child's response to a load of faecal bacteria should be explored to explain why some children do not succumb.

## **Documents and publications**

Committee on International Nutrition, Institute of Medicine.

***Considerations of the nutrition components of the sick child initiative.***

Washington DC, National Academy Press, 1995, 49p.

This report is the result of the third meeting of the Committee on International Nutrition (CIN) held in January 1995. The purpose was to comment on the nutrition components of the WHO initiative to integrate the management of childhood illness, often called the "Sick Child Initiative" (SCI). Chapter 1 of the report provides background information on the SCI, the charge to the committee, and the scope of the committee's deliberation. Chapter 2 describes the nutrition algorithm in the SCI. In Chapter 3, the committee presents its responses to five questions: (1) practicality of the nutrition component of the (SCI) algorithm; (2) whether the nutrition components of the algorithm should be modified, and how; (3) the additional information on data required to improve the performance of the integrated childhood illness algorithm's nutritional effectiveness; (4) how can nutritional components be monitored during field testing or introduction; and (5) what should the role be for those with experience and expertise in nutrition as field testing or introduction evolves. The committee strongly believes that integration of SCI activities with other local resources for the treatment and prevention of illness and disease, including malnutrition, will be required for SCI to be most effective. Thus the committee ends Chapter 3 with suggestions towards this end. The committee's overall summary and conclusions are presented in Chapter 4.

Michaelsen KF, Weaver L, Branca F, Robertson A

***Feeding and nutrition of infants and young children. Guidelines for the WHO European Region, with emphasis on the former Soviet countries***

WHO Regional Publications, European Series, No. 87,2000, xvi + 288 pages [E]

ISBN 92 890 1354 0

Sw.fr. 82.-/US \$73.80 In developing countries Sw.fr. 57.40

Order No. 1310087

Good feeding practices prevent malnutrition and early growth retardation, which is still common in some parts of the WHO European Region, particularly the former Soviet countries. Yet, despite the importance of infant and young child nutrition and feeding practices, limited attention has been paid to the need for guidelines based on scientific evidence. This publication contains the scientific rationale for the development of national nutrition and feeding recommendations from birth to the age of three years, and provides information that will help national experts to develop or update their current national feeding recommendations. It will also interest ministries of health, paediatricians, dietitians, nutrition scientists and public health and other health professionals concerned with nutrition and the health of young children.

World Health Organization

***Management of severe malnutrition - A manual for physicians and other senior health workers.*** Geneva, World Health Organization 1999, 60p ISBN 9241545119

The manual is intended for health personnel working at central and district level, including physicians, nurses, midwives and auxiliaries. It describes the evaluation of the malnourished child, provides guidelines for initial treatment, rehabilitation and follow-up of severely malnourished children below the 5 years of age in hospitals and health centres. The treatment of severely malnourished adolescents and adults is also considered. An overview of the management of malnutrition in disaster situations and refugee camps is given.

World Health Organization

***Complementary feeding of young children in developing countries: a review of current scientific knowledge.***

Geneva, World Health Organization, 1998, WHO/NUT/98.1ix + 228 pages (English)

Sw.fr. 35.-/US \$31.50; in developing countries: Sw.fr. 24.50

Order no. 1930141

This book provides a state-of-the-art review of what is known about the nutritional needs of young children and the specific feeding practices – from the best time to introduce complementary foods to the preparation of appropriate meals – that contribute to optimal nutritional status and healthy growth and development. Addressed to researchers as well as health professionals, the book responds to several advances in scientific knowledge that either confirm current recommendations for complementary feeding or call for changes. Practical implications for intervention programmes are also considered in detail. Although recommendations and advice have universal relevance, particular attention is given to the needs of children in low-income settings and to feeding practices that can be implemented by caregivers in the developing world. Findings from over 500 recent studies are critically assessed in this thorough, expert review.

The book has nine chapters. The first provides an overview of new findings – and continuing controversies – that influence such important issues as the optimal age for introducing complementary foods, the selection of an appropriate age group for targeted interventions, and the relative importance of various factors known to limit growth. Knowledge about the maturation of physiological processes relevant to child feeding is also briefly reviewed. Chapter two discusses the importance of breast-feeding in child-feeding regimens and addresses key questions concerning the duration of breast-feeding and the appropriate age for introducing complementary foods. Against this background, chapter three provides a broad range of technical information on different aspects of complementary feeding, including the energy required from complementary foods at different ages, appropriate feeding frequency, the energy density of complementary foods, and the importance of their organoleptic characteristics as determinants of intake.

Chapter four provides similarly detailed information concerning the protein and micronutrients required from complementary foods. Since nutritional status is influenced by behaviours surrounding feeding as well as the nutritional content of foods, subsequent chapters review studies of caregiver feeding behaviours in developing countries and discuss food processing procedures – from commercial approaches to simple measures in the home – that help ensure the quality and safety of complementary foods. Chapter seven, which briefly reviews global data on child-feeding practices, is followed by an overview of recent intervention programmes, an evaluation of their impact, and a discussion of factors contributing to success. The final chapter provides a succinct summary of conclusions and recommendations for appropriate child feeding.

World Health Organization

***Persistent diarrhoea and breastfeeding***

Geneva, World Health Organization 1997, 21 p. (unpublished document WHO/CHD/97.8 available on request from the Department of Child and Adolescent Health and Development (CAH)).

(See this chapter, section Breastfeeding counselling)

World Health Organization

***Infant Feeding: The Physiological Basis***

edited by J. Akre 1990, 108 pages [Ar, E, F]

ISBN 92 4 068670 3 Sw.fr. 20.-/US \$18.00; in developing countries: Sw.fr. 14.-

Order no. 0036701

Establishes the scientific basis for addressing the many questions that surround the appropriate feeding of infants during their first year of life. Noting that adequate diet is more critical in early infancy than at any other time in life, the review considers what knowledge about infant physiology can contribute to the understanding of nutritional needs. More than 500 references to the literature are included. The evidence reviewed challenges several widely held assumptions concerning the need for proprietary formulas, the most appropriate time to introduce complementary foods, and the best feeding regimen for low-birth-weight infants.

The book has six chapters. The first examines the physiological mechanisms that operate during pregnancy, affect fetal growth, and govern the newborn's nutritional requirements. Chapter two provides a fascinating account of the physiology of human lactation. Health factors which may interfere with breast-feeding are discussed in the third chapter, which considers the case of infants with congenital and hereditary metabolic disorders, cleft lip and cleft palate, and different maternal illnesses, including infection with HIV. The fourth chapter, on complementary feeding, concludes that breast milk alone satisfies the energy requirements of the average infant for the first six months of life and that complementary feeding before that time can introduce a number of short- and long-term risks. The remaining chapters review the special needs of two particularly vulnerable groups: low-birth-weight infants and infants and young children during periods of acute infection.



## 8. ANAEMIA, INTESTINAL PARASITES

### 8.1. ANAEMIA

#### Articles

#### Assessment

Kalter HD, Burnham G, Kolstad PR, Hossain M, Schillinger JA, Khan NZ, Saha S, de Wit V, Kenya-Mugisha N, Schwartz B, Black RE

**Evaluation of clinical signs to diagnose anaemia in Uganda and Bangladesh, in areas with and without malaria.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):103-112.

The object of this study was to assess the ability of pallor and other clinical signs, including those in the Integrated Management of Childhood Illness (IMCI) guidelines developed by WHO and UNICEF, to identify severe anaemia and some anaemia in developing country settings with and without malaria. A total of 1226 and 668 children aged 2 months to 5 years were prospectively sampled from patients presenting at, respectively, a district hospital in rural Uganda and a children's hospital in Dhaka, Bangladesh. The study physicians obtained a standardized history and carried out a physical examination that included pallor, signs of respiratory distress, and the remaining IMCI referral signs. The haematocrit or haemoglobin level was determined in all children with conjunctival or palmar pallor, and in a sample of the rest. Children with a blood level measurement and assessment of pallor at both sites were included in the anaemia analysis. Using the haematocrit or haemoglobin level as the reference standard, the correctness of assessments using severe and some pallor and other clinical signs in classifying severe and some anaemia was determined. While the full IMCI process would have referred most of the children in Uganda and nearly all the children in Bangladesh with severe anaemia to hospital, few would have received a diagnosis of severe anaemia. Severe palmar and conjunctival pallor, individually and together, had 10-50% sensitivity and 99% specificity for severe anaemia; the addition of grunting increased the sensitivity to 37-80% while maintaining a reasonable positive predictive value. Palmar pallor did not work as well as conjunctival pallor in Bangladesh for the detection for severe or some anaemia. Combining "conjunctival or palmar pallor" detected 71-87% of moderate anaemia and half or more of mild anaemia. About half the children with no anaemia were incorrectly classified as having "moderate or "mild" anaemia. Anaemia was more easily diagnosed in Uganda in children with malaria. Our results show that simple clinical signs can correctly classify the anaemia status of most children. Grunting may serve as a useful adjunct to pallor in the diagnosis of severe anaemia. Conjunctival pallor should be added to the IMCI anaemia box, or the guidelines need to be adapted in regions where palmar pallor may not readily be detected.

Luby SP, Kazembe PN, Redd SC, Ziba C, Nwanyanwu OC, Hightower AW, Franco C, Chitsulo L, Wirima JJ, Olivar MA

**Using clinical signs to diagnose anaemia in African children.**

*Bulletin of the World Health Organization*, 1995, 73(4):477-482.

Anaemia is a serious and common problem among young children in sub-Saharan Africa. As a first step towards developing guidelines for its recognition and treatment, we conducted a study to evaluate the ability of health workers to use clinical findings to identify children with anaemia. Health care workers examined a total of 1104 children under 5 years of age at two hospital-based outpatient clinics in rural Malawi. Blood samples were taken to determine haemoglobin concentrations. Pallor of the conjunctiva, tongue, palm or nail beds was 66% sensitive and 68% specific in distinguishing children with moderate anaemia (haemoglobin concentration, 5-8 g/dl) and 93% sensitive and 57% specific in distinguishing



those with severe anaemia (haemoglobin concentration, < 5 g/dl). Even without laboratory support, which is often unavailable in rural Africa, clinical findings can identify the majority of children with anaemia.

Menendez C, Fleming AF, Alonso PL

**Malaria-related anaemia**

*Parasitology Today* 2000 Nov;16(11):469-76

Malaria infection in humans by Plasmodium species is associated with a reduction in haemoglobin levels, frequently leading to anaemia. Plasmodium falciparum causes the most severe and profound anaemia, with a significant risk of death. This cannot be explained simply by the direct destruction of parasitized red blood cells at the time of release of merozoites, a process shared by all these species. In this review, Clara Menendez, Alan Fleming and Pedro Alonso focus on recent advances in our knowledge of the pathophysiology, epidemiology, management and prevention of anaemia from falciparum malaria.

Simoes EA, Desta T, Tessema T, Gerbresellassie T, Dagnaw M, Gove S

**Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):43-54.

(See chapter Effectiveness of IMCI guidelines).

Stoltzfus RJ, Edward-Raj A, Dreyfuss ML, Albonico M, Montresor A, Dhoj Thapa M, West KP Jr, Chwaya HM, Savioli L, Tielsch J

**Clinical pallor is useful to detect severe anaemia in populations where anaemia is prevalent and severe.**

*Journal of Nutrition*, 1999 Sep;129(9):1675-81

Clinical pallor is recommended as a simple way to detect severe anaemia, but more data are needed on its accuracy and usefulness when assessed by non-physicians in diverse settings. We measured haemoglobin and trained non-physician health workers to assess clinical pallor of the conjunctiva, palm and nail beds in five population samples in Nepal and Zanzibar, where severe anaemia is common. In total, 5,760 individuals were examined, 3,072 of whom were anemic and 192 of whom had severe anaemia (haemoglobin <70 g/L). The prevalence of pallor did not correspond to the prevalence of anaemia or severe anaemia in the groups studied. However, in all studies, pallor at each anatomical site was associated with a significantly lower haemoglobin concentration. The relative performance of different anatomical sites was not consistent among studies, and we recommend that multiple sites be assessed. Pallor at any of the three sites detected severe anaemia with >84% specificity. However, the sensitivity varied from 81% in Nepalese postpartum women to 29% in Zanzibari preschoolers in 1996. Overall estimates for sensitivity and specificity were 50 and 92%, respectively. Although imperfect, use of pallor to screen and treat severe anaemia by primary care providers is feasible and worthwhile where severe anaemia is common. Usually, the majority of persons with severe anaemia will be detected at practically no cost. Many people who are not severely anemic will also receive treatment, but the costs of this error are low compared to the benefits.

Weber MW, Kellingray SD, Palmer A, Jaffar S, Mulholland EK, Greenwood BM

**Pallor as a clinical sign of severe anaemia in children: an investigation in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):113-118.

Anaemia associated with malaria is a major public health problem in African countries. Since most primary health facilities have to rely on physical signs and not laboratory tests to detect anaemic patients who need referral for blood transfusion, we have assessed the reliability of simple clinical signs to predict severe anaemia. A trained field assistant examined 368 children admitted to a tertiary care hospital, assessing the pallor of their eyelids (conjunctiva), palms and nailbeds, counting the respiratory rate, and looking for signs of respiratory distress. After the children's admission, their packed cell volume (PCV) was measured, and the need for transfusion and the outcomes were noted. A second observer examined 173 of these children

so that interobserver variability in the detection of clinical signs could be assessed. A total of 27% of the 368 children had a PCV of < 15%. In a multiple regression analysis, definite pallor of the conjunctiva, definite pallor of the palms, and a "sick" appearance of the child were identified as independent significant predictors of a PCV of < 15%. The best predictor was a combination of definite pallor of the conjunctiva and pallor of the palms, with a sensitivity of 80% and a specificity of 85%. Inclusion of signs of respiratory distress did not improve the prediction. Pallor was a reproducible sign (weighted kappa statistic for the comparison between two observers: kappa = 0.6 for conjunctival pallor). We conclude that pallor can be used as a sign for referring children who may require blood transfusion.

Zucker JR et al. , Perkins BA, Jafari H, Otieno J, Obonyo C, Campbell CC

**Clinical signs for the recognition of children with moderate and severe anaemia in western Kenya.**  
*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):97-102.

Optimal treatment of Plasmodium falciparum-related paediatric anaemia can result in improved haematological recovery and survival. Clinical predictors are needed to identify children with anaemia in settings where laboratory measurements are not available. The use of conjunctival (eyelid), palmar, nailbed, and tongue pallor to detect children with moderate anaemia (haemoglobin, 5.0-7.9 g/dl) or severe anaemia (haemoglobin, < 5.0 g/dl) was evaluated among children seen at an outpatient and inpatient setting in a hospital in western Kenya. Severe nailbed or severe palmar pallor had the highest sensitivity (62% and 60%, resp.), compared with severe conjunctival pallor (sensitivity = 31%), to detect children with severe anaemia in the outpatient setting. Children with moderate anaemia were best identified by the presence of nailbed or palmar pallor (sensitivity = 90% for both signs), compared with conjunctival pallor (sensitivity = 81%). Clinical signs of respiratory distress, in addition to the presence of severe pallor, did not increase the recognition of children requiring hospitalisation for severe anaemia. Among inpatients, the sensitivity of severe nailbed pallor (59%) was highest for detecting children with severe anaemia, although the sensitivity of severe conjunctival pallor and severe palmar pallor was the same (53% for both signs). Presence of conjunctival pallor (sensitivity = 74%) was similar in sensitivity to both nailbed and palmar pallor (70% for both signs) among children with moderate anaemia. The sensitivity of tongue pallor was low among all children evaluated. Low haemoglobin levels were significantly associated with the likelihood of being smear-positive for P. falciparum. This study demonstrates that clinical criteria can be used to identify children with moderate and severe anaemia, thus enabling implementation of treatment algorithms. Children aged < 36 months who live in an area with P. falciparum malaria should receive treatment with an effective antimalarial drug if they have pallor.

## Treatment

Lackritz EM, Campbell CC, Ruebush TK 2d, Hightower AW, Wakube W, Steketee RW, Were JB

**Effect of blood transfusion on survival among children in a Kenyan hospital.**

*Lancet*, 1992, 340(8818):524-528.

In Africa, blood transfusions are frequently given to treat severe paediatric anaemia. Because of the risk of HIV transmission, identification of when transfusion will reduce the risk of death for severely anaemic children has become increasingly important. For all children admitted to a Kenyan hospital from October, 1989, to October, 1990, we collected data on clinical presentation, haemoglobin (Hb), receipt of transfusion, and in-hospital survival. Of 2433 admissions, 29% (684) had severe anaemia (Hb less than 5.0 g/dl), and 20% (483) received blood transfusions. Based on laboratory criteria only, children with Hb less than 3.9 g/dl who were transfused had lower mortality than those with Hb less than 3.9 g/dl who were not transfused, but this finding applied only to children transfused on the day of admission (odds ratio [OR] 0.30; 95% CI 0.14, 0.61) or the day after admission (OR 0.37; 95% CI 0.14, 1.00). Based on a combination of laboratory and clinical criteria, children with clinical signs of respiratory distress and Hb less than 4.7 g/dl who were transfused had lower mortality than those who were not (OR 0.19; 95% CI 0.09, 0.41). Among children without respiratory distress, there was no association between receipt of transfusion and mortality, irrespective of admission Hb. The frequency of blood transfusion can be reduced and survival

enhanced by targeting blood to those children with severe anaemia and clinical signs of respiratory distress, and by using transfusion early in the course of hospitalisation.

Comment in: *Lancet* 1992 Oct 10;340(8824):917; *Lancet* 1992 Oct 10;340(8824):917-8

van Hensbroek MB, Morris-Jones S, Meisner S, Jaffar S, Bayo L, Dackour R,  
Phillips C, Greenwood BM

**Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995, 89(6):672-676.

Whether children with malarial anaemia should receive supplementation with iron or folic acid is uncertain. Therefore, the effects of supplementary treatment with iron or folic acid, given together with chloroquine or pyrimethamine-sulfadoxine (Fansidar), has been assessed in 600 Gambian children with uncomplicated falciparum malaria. After one month, haematological recovery was significantly better in the group treated with Fansidar than in the chloroquine-treated group (difference in mean haemoglobin level = 0.54 g/dL,  $P = 0.01$ ). Children who received iron had a significantly better response than those given placebo (differences in mean haemoglobin level after one month and at dry season follow-up = 0.70 g/dL,  $P = 0.006$ , and 0.81 g/dL,  $P = 0.001$ , respectively). Iron supplementation was not associated with increased prevalence of malaria. Supplementation with folic acid did not improve the haematological response but, among children who received Fansidar, the treatment failure rate was significantly higher among those given folic acid than among those given placebo. Thus, supplementation with iron, but not folic acid, improves haematological recovery without increasing susceptibility to malaria.

Publication Types: Clinical trial, Randomised controlled trial

## 8.2. INTESTINAL PARASITES

### Articles

#### Importance

Cook GC

**The clinical significance of gastrointestinal helminths: a review.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1986, 80(5):675-685.

Gastrointestinal helminths (nematodes, trematodes and cestodes) constitute some of the most common and important infective agents of mankind and are responsible for much morbidity and some mortality. Whereas many symptoms and signs are confined to the intestine and less often the associated digestive organs, systemic manifestations are also numerous; this applies especially to indigenous populations of developing 'Third World' countries. Using a clinical classification these organisms can be broadly separated into those involving the small-intestine and those which have a colo-rectal distribution; of the former, a minority has been causally related to intestinal malabsorption. Clearly, however, not all gastrointestinal helminths are associated with disease and it is important to be able to separate these two groups; when present at high concentration and especially in infants and children some of the least pathogenic are not, however, entirely asymptomatic. Maintenance of a high 'index of suspicion' is necessary and this applied especially to 'western' populations in whom rapid and extensive travel to areas of the world with substandard sanitation and contaminated food and water supplies is now common; first evidence of infection in them may result from serious clinical complications. Recent advances have focused on treatment, and especially the introduction of the benzimidazole compounds (especially albendazole) for nematode, and praziquantel for cestode, infections. treatment of strongyloidiasis remains, however, unsatisfactory. Mass elimination of gastrointestinal helminths in developing 'Third World' countries remains a major challenge.

Publication Types: Review

Crompton DW

**Ascariasis and childhood malnutrition.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1992, 86(6):577-579.

The role of *Ascaris lumbricoides* as a determinant of childhood nutritional status proposed by WHO in 1968 was discussed extensively. The results of animal, as well as human studies resulted to a consensus that ascariasis is indeed a factor in the aetiology and persistence of childhood malnutrition. The body of information has helped to define the public health significance of ascariasis and other soil-transmitted diseases. WHO endorsed the recommendation that in areas where the prevalence of mild-moderate underweight in children is greater than 25%, and where parasites are known to be widespread, high priority should be given to deworming programmes for treatment of parasites.

Publication Types: Review, review tutorial

Crompton DW

**Gastrointestinal helminths infections. Nutritional aspects of infection.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1986, 80(5):697-705.

Current knowledge is examined about the means whereby ascariasis, hookworm disease, strongyloidiasis and trichuriasis may contribute to the aetiology of human malnutrition. Results from experiments with related parasites in the laboratory have demonstrated the role of gastrointestinal helminthiases in animal malnutrition. Some evidence shows that in children, infection with the intestinal stages of *Ascaris*

lumbricoides is associated with reduced growth rate, disturbed nitrogen balance, malabsorption of vitamin A, abnormal fat digestion, lactose maldigestion and an increased intestinal transit time. The main impact of hookworm infection is its relationship with iron-deficiency anaemia which may have effects at the community level as regards work and productivity in adults and learning and school performance in children. More research is needed to extend knowledge of the nutritional impact of ascariasis and hookworm disease in order to establish their public health significance. Research is needed also to identify the range of nutritional effects on man that occur as a result of trichuriasis and strongyloidiasis. The significance of less prevalent and more localized gastrointestinal helminthiases should not be ignored.  
Publication Types: Review

Lunn PG, Northrop-Clewes CA.

**The impact of gastrointestinal parasites on protein-energy malnutrition in man.**

*Proceedings of the Nutrition Society*, 1993, 52(1):101-111.

There is no doubt that at high intensity of infection, intestinal parasites can cause severe illness and the death of their hosts. Even with the high prevalence of these infections, however, such severe cases are rare and the norm is for low to moderate numbers of parasites which cause few if any overt symptoms. Nevertheless, it has been argued that by causing subtle reductions in appetite, absorption, digestion and acute-phase status and increasing intestinal nutrient losses, these low-level but long-term infections could be responsible for the persistent, poor nutritional status of so many children in Third World communities. Although geographically, high parasite prevalence occurs in conjunction with high levels of protein-energy malnutrition, attempts to establish a cause and effect relationship have had very limited success with many investigators being unable to demonstrate any detrimental consequence of infection. The unimpressive results might be explained to some extent by the unusual features of helminth infections such as rapid reinfection, the overdispersed distribution pattern and the uncertainty of a host inflammatory response, but they also suggest that *A. lumbricoides* (on which most studies have concentrated) may be of little nutritional importance. It seems likely that the more invasive parasites, e.g. the hookworms, *S. stercoralis*, *T. trichiura* and perhaps *G. lamblia* may have a greater impact and clearly more studies are required here. Safe, cheap and effective anthelmintics are now available and, on the grounds of disease prevention, there is a case for their nationwide use. However, from the available evidence, it would be unwise to expect that such programmes would make a significant impact on the nutritional status of children in Third World communities.

Publication Types: Review, Review, tutorial

Savioli L, Bundy D, Tomkins A

**Intestinal parasitic infections: a soluble public health problem**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1992, 86(4):353-354.

Intestinal parasite helminths and protozoal infections are among the most common infections of humans worldwide. The public health impact has been consistently and considerably underestimated. The mortality rate directly related to *Ascaris lumbricoides* is low, but even so, the absolute number of deaths is fairly high because of high prevalence of infection in developing countries. Iron deficiency anaemia is an inevitable result of hookworm infection. *Trichuris trichiura*, associated with undernutrition, growth stunting and iron deficiency anaemia in intense infections, has more recently been found to have adverse effect on cognitive function even when infections are only moderately intense. Partnership for Child Development, in collaboration with WHO, is now working with endemic country partners to develop an efficient, sustainable and low cost strategy of delivering anthelmintics. Chemotherapy directed against *Ascaris lumbricoides*, hookworms and *Trichuris trichiura* and targeted at school-age children is a feasible and effective approach to worm control. Single dose of mebendazole or albendazole is very effective, safe and inexpensive. The aim of repeated chemotherapy is not to eradicate or prevent infection but to ensure that levels of infection are below those associated with morbidity. The programmes to control intestinal protozoal infections are at earlier stage of development. *Entamoeba histolytica*, *Giardia duodenalis* and *Cryptosporidium parvum* are found both in industrialized and developing countries. However the epidemiology of these infections differs in these settings as do the resources available for treatment and control.

**CONCLUSIONS:** There is now overwhelming evidence that the disease caused by the intestinal helminth and protozoan infections is a pervasive public health problem. There is also good evidence from pilot studies, for helminthiasis at last, that the problem is amendable to solution. Current efforts are needed to improve sanitation and water supplies, but are not sufficient. The challenge is to develop affordable and sustainable solutions, which are appropriate to the scale of the problem.

Publication Types: Editorial

Stephenson LS

**Helminth parasites, a major factor in malnutrition.**

*World Health Forum*, 1994, 15(2):169-172.

The author discusses the significance of helminth and schistosome infections in exacerbating nutritional problems in many countries, and advocates population-wide treatment where there is clear evidence that this would yield substantial gains in the quality of life.

Stoltzfus RJ, Albonico M, Chwaya HM, Tielsch JM, Schulze KJ, Savioli L

**Effects of the Zanzibar school-based deworming program on iron status of children.**

*The American Journal of Clinical Nutrition*, 1998,68:179-86.

We evaluated the effects of the Zanzibar school-based deworming program on the iron status of primary school children. Parasitologic and nutritional assessments were carried out at baseline, 6 mo, and 12 mo in 4 nonprogram schools (n = 1002), 4 schools in which students received twice-yearly deworming (n = 952), and 4 schools in which students received thrice-yearly deworming (n = 970) with 500 mg generic mebendazole. Schools were randomly selected for evaluation and allocated to program groups. Relative to no treatment, thrice-yearly deworming caused significant decreases in protoporphyrin concentrations and both deworming regimens caused marginally significant increases in serum ferritin concentrations. The average annual changes in protoporphyrin concentrations were -5.9 and -23.5 micromol/mol heme in the control and thrice-yearly deworming groups, respectively (P < 0.001). The average changes in ferritin concentration were 2.8 and 4.5 microg/L, respectively (P = 0.07). Deworming had no effect on annual haemoglobin change or prevalence of anaemia. However, the relative risk of severe anaemia (haemoglobin < 70 g/L) was 0.77 (95% confidence limits: 0.39, 1.51) in the twice-yearly deworming group and 0.45 (0.19, 1.08) in the thrice-yearly deworming group. The effects on prevalence of high protoporphyrin values and incidence of moderate-to-severe anaemia (haemoglobin < 90 g/L) were significantly greater in children with > 2000 hookworm eggs/g feces at baseline. We estimate that this deworming program prevented 1260 cases of moderate-to-severe anaemia and 276 cases of severe anaemia in a population of 30,000 schoolchildren in 1 y. Where hookworm is heavily endemic, deworming programs can improve iron status and prevent moderate and severe anaemia, but deworming may be needed at least twice yearly.

## Treatment

Albonico M, Smith PG, Hall A, Chwaya HM, Alawi KS, Savioli L

**A randomised controlled trial comparing mebendazole and albendazole against *Ascaris*, *Trichuris* and hookworm infections.**

*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, 88(5):585-589.

The efficacies and side effects of single dose treatments with 500 mg mebendazole (Janssen Pharmaceutica) and 400 mg albendazole (SmithKline Beecham) against intestinal nematodes were compared in a single-blind, randomised controlled trial among 2294 children aged 6 to 12 years on Pemba Island, Zanzibar, among whom infections with *Ascaris*, hookworms and *Trichuris* were highly prevalent. Both drugs were highly effective against *Ascaris*, with cure rates of over 97%. The cure rates for *Trichuris* were low, but mebendazole was significantly better than albendazole and produced a greater reduction in the geometric mean egg count. Mebendazole was inferior to albendazole in curing hookworm infections

and in reducing the geometric mean egg count. There was no difference in the frequency of side effects reported by heavily infected children treated with either drug. In a trial on 402 children, 500 mg mebendazole (Janssen) was compared with a generic version of the drug, 500 mg mebendazole (Pharmamed). No difference was apparent in the efficacies of the 2 treatments against any of the 3 parasites studied.

Publication Types: Clinical trial, Randomised controlled trial

de Silva NR, Sirisena JL, Gunasekera DP, Ismail MM, de Silva HJ

**Effect of mebendazole therapy during pregnancy on birth outcome.**

Lancet 1999 Apr 3;353(9159):1145-9

**BACKGROUND:** In areas endemic for hookworm, routine antenatal mebendazole therapy could greatly reduce the prevalence of anaemia in pregnancy. At present, however, this is not a widely accepted control strategy because of a lack of data on the safety of the drug. We assessed the effect of mebendazole therapy during pregnancy on birth outcome. **METHODS:** A cross-sectional study was done in Sri Lanka, where prescription of mebendazole to women in the second trimester of pregnancy is recommended. Two hospitals were chosen for the study, and women who gave birth there between May, 1996, and March, 1997, were recruited. We compared the rates of major congenital defects, stillbirth, perinatal death, and low birthweight (< or = 1500 g) among babies of mothers who had taken mebendazole during pregnancy with those whose mothers had not taken an anthelmintic (controls). **FINDINGS:** The rate of major congenital defects was not significantly higher in the mebendazole group than in the control group (97 [1.8%] of 5275 vs 26 [1.5%] of 1737; odds ratio 1.24 [95% CI 0.8-1.91], p=0.39). Among 407 women who had taken mebendazole in the first trimester (contrary to medical advice), 10 (2.5%) had major congenital defects (odds ratio vs controls 1.66 [0.81-3.56], p=0.23). The proportions of stillbirths and perinatal deaths were significantly lower in the mebendazole group (1.9 vs 3.3%, 0.55 [95% CI 0.4-0.77]), as was the proportion of low-birthweight babies (1.1 vs 2.3%, 0.47 [95% CI 0.32-0.71]). **INTERPRETATION:** Mebendazole therapy during pregnancy is not associated with a significant increase in major congenital defects, but our results indicate that it should be avoided during the first trimester. This therapy could offer beneficial effects to pregnant women in developing countries, where intestinal helminthiasis are endemic.

Atukorala TM, de Silva LD, Dechering WH, Dassenaieike TS, Perera RS

**Evaluation of effectiveness of iron-folate supplementation and anthelmintic therapy against anaemia in pregnancy. A study in the plantation sector of Sri Lanka.**

*American Journal of Clinical Nutrition*, 1994, 60(2):286-292.

Intervention measures against anaemia available to plantation workers during pregnancy include fortified food supplements (thriposha) and iron-folate supplements containing 60 mg elemental Fe. The effectiveness of these intervention measures was studied in 195 subjects whose iron and nutritional status were assessed at < 24 and > 32 wk of gestation. Taking thriposha conferred no significant benefit on maternal nutritional status, probably because sufficient amounts were not consumed. An increase in the duration of iron-folate supplementation to > 17 wk caused a significant positive change (P < 0.01) in haemoglobin, whereas an increase in the dose frequency had no significant benefit. Anthelmintic therapy in addition to iron-folate supplements caused a significant positive change in haemoglobin (P < 0.001) and serum ferritin (P < 0.005) compared with no supplementation. Thus, anthelmintic therapy significantly increased the beneficial effects of iron supplementation on haemoglobin concentration and iron status.

Comment in: *Am J Clin Nutr* 1995 Nov;62(5):1023-4

Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Brigham H

**Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuristrichiura*, and *ascaris lumbricoides* infections.**

*American Journal of Tropical Medicine and Hygiene*, 1989, 41(1):78-87.

We studied the growth of primary schoolchildren with hookworm (87%), *T. trichiura* (97%), and *A. lumbricoides* (49%) who received a single 400 mg dose of albendazole or an identical placebo. Children were allocated at random to placebo (PL, n = 72) or albendazole (A, n = 78) groups, treated, and re-examined 6 months later. The A group gained significantly more than the PL group in weight (1.3 kg), percent weight for age (4.5% age points), percent height for age (0.5% age points), percent weight for height (4.3% age points), percent arm circumference (2.9% age points), and in triceps and subscapular skinfold thicknesses (1.2 mm). The PL group showed significant decreases between exams in percent weight for age, percent height for age, percent weight for height, percent arm circumference for age, and skinfold thicknesses for age. The A group had highly significant increases (P less than 0.0002) in all of these parameters except height for age. From Exam 1 to 2, the A group exhibited decreases (P less than 0.0002) in geometric means eggs per gram of feces (epg): for hookworm, means = 1,183 epg at Exam 1 vs. 136 epg at Exam 2 (67% egg reduction); for *T. trichiura*, means = 2,857 epg at Exam 1 vs. 1,061 epg at Exam 2 (28% egg reduction); and for *A. lumbricoides*, means = 86 epg at Exam 1 vs. 2 epg at Exam 2 (91% egg reduction). The PL group had a borderline increase in geometric means hookworm egg count, no significant change in *T. trichiura* egg count, and a small but significant decrease in *A. lumbricoides* egg count. Decreases in intensities of all infections were significant predictors of growth improvement. Hookworm egg count entered the equations for all 6 measurements, and *A. lumbricoides* and *T. trichiura* entered 4/6 equations. Single dose treatment with albendazole, despite continual exposure to infection, can permit improved growth rates in areas where intestinal helminths and protein-energy malnutrition are highly prevalent.

Publication Types: Clinical trial, Randomised controlled trial

## **Documents and publications**

Stephenson L

***The impact of helminth infections on human nutrition: schistosomes and soil-transmitted helminths.***

London; New York: Taylor and Francis, 1987, 127 p

Helminth infection, and malnutrition are among the most important, most common and most persistent health problems in developing countries today. This chapter discusses the prevalence and functional significance of the helminth infections and the types of malnutrition of greatest public health importance for man, presents an overview of mechanisms by which helminth infection could affect nutritional status and outlines methodological approaches for the planning and evaluation of useful nutrition-parasite studies. Discussion concentrates on five helminthiases: those caused by the four major soil-transmitted helminths (*Ascaris lumbricoides*, hookworms, *Trichuris trichiura*, and *Strongyloides stercoralis*) and schistosomiasis, because these infections are highly prevalent in developing countries and their potential relationship to malnutrition is too often overlooked. The focus is on the effect on parasites on the nutrition of the human host to determine the effects which parasites have on their host.



World Health Organization

***Report of the WHO Informal Consultation on hookworm infection and anaemia in girls and women.*** Geneva, 5-7 December 1994. Geneva, World Health Organization, 1994 (document WHO/CTD/SIP/96.1; available on request from the Schistosomiasis and Intestinal Parasites Unit, Division of Control of Tropical Diseases, formerly the Programme of Intestinal Parasitic Infections Division of Communicable Diseases). [http://whqlibdoc.who.int/hq/1996/WHO\\_CTD\\_SIP\\_96.1.pdf](http://whqlibdoc.who.int/hq/1996/WHO_CTD_SIP_96.1.pdf)

An informal consultation was held in Geneva in December 1994 in order to address the issue of hookworm infection and anaemia in girls and women. The report provides an overview of the global magnitude of the problem. It describes in detail the life cycles, epidemiology and population biology of hookworms, biology of hookworm infections in female hosts, neonates and infants. An analysis applied to the population of Sub-Saharan Africa offers the estimates of the number of women, who are both pregnant and infected with hookworm burdens of a magnitude, which is likely to be associated with disease. Multifactorial aetiology of iron-deficiency anaemia in adolescent girls and women of reproductive age is described and the assessment of anaemia and restoration of iron status is discussed. The part on anthelmintic treatment deals with the pharmacokinetics in humans, therapeutic efficacy, adverse effects and safety aspects of albendazole, mebendazole, levamisole and pyrantel. The report is concluded by a list of research topics and recommendations.

## 9. IMMUNIZATION

### Articles

Clements CJ, von Reyn CF, Mann JM

**HIV infections and routine childhood immunisation: A review.**

*Bulletin of the World Health Organization*, 1987, 65(6):905-11.

This review summarizes current experience with immunisation of children infected with human immunodeficiency virus (HIV, relevant data on immunisation of HIV-infected adults, and in vitro studies with vaccine antigens and HIV-infected cells. theoretical concerns about the possible effects of repeated antigenic stimulation on the course of HIV infection are also summarized. Finally, available information on the course of vaccine preventable diseases in HIV-infected children is reviewed. Together these studies provide a current database for decisions about immunisation of HIV-infected children.

Galazka AM, Lauer BA, Henderson RH, Keja J

**Indications and contraindications for vaccines used in the Expanded Programme on Immunisation: A review.**

*Bulletin of the World Health Organization*, 1984, 62(3):357-366.

The aim of the Expanded Programme on Immunisation is to reduce morbidity and mortality from six diseases that can be prevented by immunisation. In many countries the immunisation coverage is still less than optimal; one of the reasons for this is the fact that frequently health workers are faced with long lists of contraindications to immunisation.

The present review discusses the risks of adverse reactions after immunisation and compares these risks with the complication rates following natural disease. It is concluded that the decision to withhold the benefits of immunisation from an eligible child should not be taken lightly, particularly in areas where access to immunisation services is limited and the incidence of the vaccine-preventable diseases is still high.

Malnutrition should be a prime indication for immunisation. Low-grade fever, mild respiratory infection, or diarrhoea should not be considered a contraindication to immunisation. Measles immunisation of children who have to be admitted to hospital has been shown to reduce the overall mortality rates in paediatric wards. It is recommended that all countries should formulate their own national policy, carefully considering the risks of disease as well as the benefits and potential risks of immunisation.

Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, Weber M, Palmer A, Schneider G, Jobe K, Lahai G, Jaffar S, Secka O, Lin K, Ethevenaux C, Greenwood B

**Randomised trial of *Haemophilus influenzae* type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants.**

*Lancet*, 1997 April, 349(9060):1191-1197.

**BACKGROUND:** In developing countries, pneumonia and meningitis due to *Haemophilus influenzae* type b (Hib) are common in children under age 12 months and the mortality from meningitis is high. Protein-polysaccharide conjugate vaccines have brought Hib disease under control in industrialised countries. We did a double-blind randomised trial in The Gambia to assess the efficacy of a Hib conjugate vaccine for the prevention of meningitis, pneumonia, and other invasive diseases due to Hib. **METHODS:** Between March, 1993, and October, 1995, 42,848 infants were randomly allocated the conjugate vaccine Hib polysaccharide tetanus protein (PRP-T) mixed with diphtheria-tetanus-pertussis vaccine (DTP), or DTP alone at age 2 months, 3 months, and 4 months. Children who presented with signs of invasive Hib were investigated by blood culture and, where appropriate, by lumbar puncture, chest radiograph, or percutaneous lung aspirate. Children were followed up for between 5 and 36 months. **FINDINGS:** The median ages at which children received the study vaccine were 11 weeks, 18 weeks, and 24 weeks. 83% of children enrolled received all three doses of vaccine. 17 cases of culture-positive Hib pneumonia, 28

of Hib meningitis, and five of other forms of invasive Hib disease were detected amongst the study children. The efficacy of the vaccine for the prevention of all invasive disease after three doses was 95% (PRP-T vaccinees 1, controls 19 [95% CI 67-100]), for the prevention of Hib pneumonia after two or three doses, 100% (vaccinees 0, controls 10 [55-100]), and for the prevention of radiologically defined pneumonia at any time after enrolment, 21.1% (PRP-T vaccinees 198, controls 251 [4.6-34.9]).

INTERPRETATION: PRP-T conjugate Hib vaccine prevented most cases of meningitis and pneumonia due to Hib in Gambian infants. The reduction in the overall incidence of radiologically defined pneumonia in PRP-T vaccinees suggests that about 20% of episodes of pneumonia in young Gambian children are due to Hib. The introduction of Hib vaccines into developing countries should substantially reduce childhood mortality due to pneumonia and meningitis.

Published erratum appears in Lancet 1997 Aug 16;350(9076):524 Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants.

Publication Types: Clinical trial, Controlled clinical trial, Randomised controlled trial

Comment in: Lancet 1997 Apr 26;349(9060):1186-7

World Health Organization

**Global Programme for Vaccines and Immunisation (GPV): The WHO Position Paper on Haemophilus influenzae type b conjugate vaccines.**

*Weekly Epidemiological Record*, 1998 March, 73(10):64-68.

Wherever thorough studies have been performed, Haemophilus influenzae type b, (Hib) has been shown to be an important cause of childhood meningitis and a major cause of bacterial pneumonia in children. Although little population-based incidence data are available from most of Asia and the Newly Independent States, Hib is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths annually, worldwide. The most important manifestations of Hib disease, namely pneumonia and meningitis, are seen mainly in children under 5 years of age, particularly infants. Currently, several different Hib vaccines, all conjugate vaccines, are on the market. These vaccines have shown protective efficacy in early infancy. Hib vaccines are now used as part of routine childhood vaccination programmes in more than 20 countries including Canada, the United States of America, Australia and New Zealand, and many countries of western Europe, and have proven to be highly efficacious and virtually free from serious side-effects. Also, excellent results of trials or national introduction in Chile, Uruguay, and the Gambia show that Hib conjugate vaccines are effective in developing country settings. Because these vaccines significantly reduce nasopharyngeal carriage, a herd effect is achieved through Hib vaccination. In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and authorities, in routine infant immunisation programmes. In geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of this problem.

## **Documents and publications**

Global Programme for Vaccines and Immunisation, Expanded Programme on Immunisation

***Integration of vitamin A supplementation with immunisation: policy and programme implications.***

Report of a meeting, 12-13 January 1998, UNICEF, New York. World Health Organization, Geneva 1998  
20 p. (Unpublished document WHO/EPI/GE/98.07)

(See chapter Fever – Measles and vitamin A supplementation)

World Health Organization

***Consultation on human immunodeficiency virus (HIV) and routine childhood immunisation.***

WHO Special Programme on AIDS and Expanded Programme on Immunisation Joint Statement. Geneva, World Health Organization, 1987, 20 p. (unpublished document SPA/INF/87.11; available on request from the WHO Expanded Programme on Immunisation (EPI)).

[http://whqlibdoc.who.int/hq/1987/WHO\\_SPA\\_INF\\_87.11.pdf](http://whqlibdoc.who.int/hq/1987/WHO_SPA_INF_87.11.pdf)

Having reviewed the available information, the WHO informal consultation on HIV and routine immunisation lists EPI antigens endorsed for the use in asymptomatic HIV infection and in clinical AIDS, and provides detailed recommendations concerning the use of live vaccines. It emphasizes the EPI recommendation to immunize children as early in life as possible and endorses the simultaneous administration of multiple antigens when indicated. The consultation provides areas in which further investigation is strongly encouraged.

World Health Organization

***Immunisation policy.***

Geneva, World Health Organization, 1995 (unpublished document WHO/EPI/GEN/95.3; available on request from the WHO Global Programme on Vaccines and Immunisation (GPV/EPI)).

[http://whqlibdoc.who.int/hq/1995/WHO\\_EPI\\_GEN\\_95.03\\_Rev.1.pdf](http://whqlibdoc.who.int/hq/1995/WHO_EPI_GEN_95.03_Rev.1.pdf)

Corrigendum

[http://whqlibdoc.who.int/hq/1995/WHO\\_EPI\\_GEN\\_95.03\\_Corr.2.pdf](http://whqlibdoc.who.int/hq/1995/WHO_EPI_GEN_95.03_Corr.2.pdf)

The document provides a review of present immunisation policies recommended by WHO/EPI. Special emphasis has been devoted to principles and topics which are new, have changed since 1986, or are considered controversial.

World Health Organization

***WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunisation sessions.***

WHO, Geneva 2000 (unpublished document WHO/V&B/00.09; available on request from the WHO Department of Vaccines and Biologicals)



This document revises and replaces the previous policy statement with the same title issued in 1995 as WHO EPI/LHIS/95.01.

Sufficient data have been collected on the safety and potency of vaccines recommended to use in immunisation services to warrant a change in the WHO policy on the use of multi-dose vials of vaccine. The revised policy has the potential to reduce vaccine wastage rates by up to 30%, resulting in annual savings worldwide of USD 40 million in vaccine costs.

[http://whqlibdoc.who.int/hq/2000/WHO\\_V&B\\_00.09.pdf](http://whqlibdoc.who.int/hq/2000/WHO_V&B_00.09.pdf)



## 10. YOUNG INFANT, PREVENTION AND TREATMENT OF HYPOGLYCAEMIA AND HYPOTHERMIA

See also chapter **Nutritional status, nutrition and breast-feeding counselling**

### 10. 1. YOUNG INFANT

#### Articles

##### **Importance**

Gatchalian SR, Quiambao BP, Morelos AM, Abraham L, Geapanayao CP, Sombrero LT, Paladin JF, Soriano VC, Obach M, Sunico ES

##### **Bacterial and viral aetiology of serious infections in very young Filipino infants.**

*The Pediatric Infectious Disease Journal* 1999 Oct;18(10 Suppl):S50-5

**OBJECTIVE:** Pneumonia, meningitis and other serious infections are leading causes of death in developing countries. As part of a multicenter study we aimed to determine the aetiology of pneumonia, meningitis and other serious infections in a cohort of Filipino infants ages 90 days or younger. **METHOD:** During a 2-year period, 2053 infants age 90 days or younger presenting to 1 of 3 Manila community hospitals were screened; 873 had signs or symptoms suggestive of an infectious illness, and 608 were judged to have clinical features suggestive of severe infection and had laboratory workup including blood for culture and white blood cell count, nasopharyngeal aspirate for virology, cerebrospinal fluid culture when indicated and chest radiograph. Chest radiographs were read independently by 3 radiologists without knowledge of clinical findings. **RESULTS:** Of the 873 enrolled infants, 81 died (91%). After exclusion of presumed contaminants, positive bacterial culture from blood and/or cerebrospinal fluid was obtained in 35 infants (5.8%; 95% confidence interval 4%, 8%), 9 of whom died. The organisms responsible for meningitis were *Acinetobacter* spp. (4), *Streptococcus pneumoniae* (2), *Escherichia coli* (2), *Enterobacter* spp. (1), *Pseudomonas aeruginosa* (1), *Haemophilus influenzae* (1) and *Staphylococcus aureus* (1); those responsible for the other clinical diagnoses were *Salmonella* spp. (6), *Enterobacter* spp. (3), *Streptococcus pyogenes* (3), other Gram-negative organisms (8), *S. pneumoniae* (1) and *Staphylococcus aureus* (2). In 685 infants examined for viral causes of their illness, 223 viruses were isolated from 219 infants (32%; 95% confidence interval 28%, 36%). Enteroviruses were the most common potential pathogens identified (22% of infants studied), followed by respiratory syncytial virus (17%), rhinovirus (10%) and adenovirus (4%).

Concomitant virus identification occurred in 10 of those with positive bacterial culture (29%; 95% confidence interval, 15%, 46%), with enterovirus being found in 7 of these cases.

**CONCLUSIONS:** Many young Filipino infants with life-threatening illness were evaluated in this study. Thirty-five had infections attributable to bacteria, with *Salmonella* spp. being the most common, followed by Gram-negative organisms. *Pneumococcus* was an unusual cause.

Publication Types: Multicenter study

Gupta R, Sachdev HP, Shah D

**Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of one week to two months.**

*Indian Pediatrics* 2000 Apr;37(4):383-90

(See chapter Effectiveness of IMCI guidelines)

Lehmann D, Michael A, Omena M, Clegg A, Lupiwa T, Sanders RC, Marjen B, Wai'in P, Rongap A, Saleu G, Namuigi P, Kakazo M, Lupiwa S, Lewis DJ, Alpers MP

**Bacterial and viral aetiology of severe infection in children less than three months old in the highlands of Papua New Guinea.**

*The Pediatric Infectious Diseases Journal* 1999 Oct;18(10 Suppl):S42-9

**OBJECTIVE:** Determine the bacterial and viral aetiology of severe infection in young Papua New Guinean infants as part of a multicenter study in four developing countries aimed at improving case management guidelines. **METHODS:** Between March, 1991, and April, 1993, children aged <3 months were recruited at the outpatient department of Goroka Base Hospital, Papua New Guinea (PNG). Children with pre-defined inclusion criteria were enrolled, a history was taken and clinical examination was performed. Blood and urine were collected from children with signs suggestive of severe disease together with eye, umbilical and pernasal swabs as appropriate. Nasopharyngeal aspirates (NPAs) were collected from children with and without signs of severe disease for identification of viruses and *Chlamydia trachomatis* by direct fluorescent antibody staining. **RESULTS:** 3280 infants were triaged and 2168 enrolled, among whom 968 had signs suggestive of severe disease. Group A *Streptococcus* (*Streptococcus pyogenes*) and *Staphylococcus aureus* were the most important bacterial pathogens isolated from children < 1 month old with severe infections, and *Streptococcus pneumoniae*, *S. pyogenes* and *Staphylococcus aureus* were most important in older children. Of 292 eye swabs 19 (7%) grew *Neisseria gonorrhoeae*. Of 116 umbilical swabs 51 (44%) grew *S. pyogenes* and 45 (39%) grew *Staphylococcus aureus*. Respiratory syncytial virus was the most important viral cause of acute lower respiratory infection.

**CONCLUSIONS:** *S. pyogenes*, *S. pneumoniae* and *Staphylococcus aureus* are important causes of severe infection in young children in the PNG highlands. It is necessary to improve access to clean water, promote hand-washing in the hospital and at home and investigate further the use of maternal immunisation for the prevention of severe disease in young infants.

Publication Types: Multicenter study

Muhe L, Tilahun M, Lulseged S, Kebede S, Enaro D, Ringertz S, Kronvall G, Gove S, Mulholland EK

**Aetiology of pneumonia, sepsis and meningitis in infants younger than three months of age in Ethiopia.**

*The Pediatric Infectious Disease Journal* 1999 Oct;18(10 Suppl):S56-61

**METHODS:** Within a multicenter study coordinated by WHO, an investigation of the etiologic agents of pneumonia, sepsis and meningitis was performed among infants younger than 3 months of age seen at the Ethio-Swedish Children's Hospital in Addis Ababa for a period of 2 years. Of the 816 infants enrolled 405 had clinical indications for investigation.

**RESULTS:** There were a total of 41 isolates from blood cultures from 40 infants. The study showed that the traditionally known acute respiratory infection pathogen *Streptococcus pneumoniae* was most common in this extended neonatal age group, found in 10 of 41 blood isolates. *Streptococcus pyogenes* was a common pathogen in this setting (9 of 41 blood isolates), whereas *Salmonella* group B was found in 5 of 41 isolates. *Streptococcus agalactiae*, which is a common pathogen in developed countries, was absent. A study of the susceptibility pattern of these organisms suggests that a combination of ampicillin with an aminoglycoside is adequate for initial treatment of these serious bacterial infections, but the combination is not optimal for the treatment of *Salmonella* infections. Among 202 infants on whom immunofluorescent antibody studies for viruses were performed based on nasopharyngeal aspirates, respiratory syncytial virus was found in 57 (28%) infants, and *Chlamydia trachomatis* was isolated in 32 (15.8%) of 203 infants.

Publication Types: Multicenter study

Mulholland EK, Ogunlesi OO, Adegbola RA, Weber M, Sam BE, Palmer A, Manary MJ, Secka O, Aidoo M, Hazlett D, Whittle H, Greenwood BM

### **Aetiology of serious infections in young Gambian infants.**

*Paediatric Infectious Diseases Journal* 1999 Oct;18(10 Suppl):S35-41

**BACKGROUND:** Despite improvements in infant mortality rates in many developing countries including The Gambia, neonatal mortality remains high and many neonatal deaths are caused by infection. The study described in this paper was conducted to determine the bacterial and viral aetiology of serious infections in Gambian infants younger than 91 days old. **METHODS:** At a first level health facility 497 infants with symptoms that could indicate serious infection were enrolled, of whom 239 with 1 or more signs of serious infection and 55 with no signs were investigated, yielding 17 cases with positive bacterial cultures of blood and/or cerebrospinal fluid. At a nearby paediatric referral hospital 198 infants were seen and 182 were investigated, yielding 35 positive bacterial cultures. **RESULTS:** There were 15 culture positive cases of meningitis caused by *Streptococcus pneumoniae* (7), *Streptococcus pyogenes* (2), *Enterobacter cloacae* (2), *Escherichia coli* (1), *Haemophilus influenzae* type b (1), *Streptococcus agalactiae* (1) and *Salmonella* spp. (1). Six of these children died. Thirty-three infants without meningitis had positive blood cultures for *Staphylococcus aureus* (17), *S. pneumoniae* (3), *Salmonella* spp. (5), *E. coli* (3), other enterobacteria (4) and *S. agalactiae* (1), of whom 14 died. Nasopharyngeal aspirates from 438 children were investigated for common respiratory viruses. Respiratory syncytial virus was found in 51, influenza A in 46, influenza B in 22, parainfluenza in 26 and adenovirus in 16. Respiratory syncytial virus and influenza A isolates were found most frequently toward the end of the wet season. Nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae* was studied in 320 infants recruited during the first year. Of these 184 (58%) were positive for *S. pneumoniae* and 141 (44%) were positive for *H. influenzae*, 18 of which were type b. Infants with a bacterial isolate from blood or cerebrospinal fluid were more likely than the rest to die, whereas those with a viral isolate were less likely to die.

**CONCLUSIONS:** The most important causes of serious infections in young Gambian infants are *Staphylococcus aureus*, *S. pneumoniae* and *Salmonella* spp.

Publication Types: Multicenter study

## **Assessment**

Gupta R, Sachdev HP, Shah D

### **Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of one week to two months.**

*Indian Pediatrics* 2000 Apr;37(4):383-90

(See section Effectiveness of IMCI guidelines)

The World Health Organization Young Infants Study Group

### **Clinical prediction of serious bacterial infections in young infants in developing countries.**

*The Pediatric Infectious Disease Journal* 1999 Oct;18(10 Suppl):S23-31

Publication Types: Multicenter study

**OBJECTIVE:** The purpose of this multicenter study coordinated by WHO was to develop a clinical prediction instrument that would identify infants at risk of serious bacterial illness on the basis of clinical examination findings. **METHODS:** Four sites, Ethiopia, the Gambia, Papua New Guinea and The Philippines, represented a range of developing country settings with high neonatal mortality rates. A total of 8418 infants younger than 91 days who presented ill to one of the study institutions were triaged, of whom 4552 satisfied the enrollment criteria. All infants underwent a standardized history and physical examination. Of these, 2398 infants with prespecified symptoms associated with possible bacterial infection underwent a laboratory evaluation that included blood culture, white blood cell count, chest radiograph and pulse oximetry. Specific criteria were also used to identify infants for lumbar puncture. **RESULTS:** The result of a structured analysis was a relatively simple model involving weight, age, temperature, respiratory rate and five clinical signs (auscultation, respiratory effort, evidence of neurological infection, inability to feed, and lethargy) These were able to predict the presence of serious disease with a high degree of accuracy. The described algorithm would result in the referral of 80% of infants with any hypoxemia, radiographic abnormality or positive culture, 88% of those with positive culture or severe hypoxaemia and 94% of those who would die of current illness, at the cost of 49 referrals



of infants without positive culture, positive chest radiograph or hypoxaemia for every 100 referrals. The algorithm can be adjusted to produce 95% sensitivity for any hypoxaemia, radiographic abnormality or positive culture at the cost of 60 referrals of infants without positive culture, positive chest radiograph or hypoxaemia for every 100 referrals.

The World Health Organization Young Infants Study Group

**Conclusions from the WHO multicenter study of serious infections in young infants.**

*Paediatric Infectious Diseases Journal* 1999 Oct;18(10 Suppl):S32-4.

The paper summarizes the important findings of the multicenter study coordinated by WHO conducted in Ethiopia, The Gambia, Papua New Guinea and The Philippines, discusses the implications for the management of infections in young infants in developing countries and discusses the future work that could facilitate progress in this difficult area (see other references in this section). As a result of this study we now have a clear view of the etiologic spectrum of agents causing serious infections in very young infants in developing countries. This information, combined with recent data on regional trends in antimicrobial resistance patterns, should help guide health planners and clinicians to the most appropriate antibiotic therapy for this group of infants. However, recognition and referral of sick infants remain a major challenge. The model proposed based on the analysis of this study may be usable in some settings as a part of strategy to train traditional birth attendants or other health workers in contact with neonates. It may need further simplification for use as part of a more general strategy for acute paediatric care such as the Integrated Management of Childhood Illness currently being promoted by WHO.

## Treatment

The World Health Organization Young Infants Study Group

**Bacterial aetiology of serious infections in young infants in developing countries: results of a multicenter study.**

*The Pediatric Infectious Disease Journal* 1999 Oct;18(10 Suppl):S17-22

**OBJECTIVE:** The purpose of this multicenter study coordinated by WHO was to determine the bacterial causes of serious infections in young infants in developing countries.

**METHODS:** Four sites, Ethiopia, The Gambia, Papua New Guinea and The Philippines, represented a range of developing country settings with high neonatal mortality rates. A total of 8418 infants younger than 91 days who presented ill to one of the study institutions were triaged, of whom 4552 satisfied the enrollment criteria. All infants underwent a standardized history and physical examination. Of these, 2398 infants with prespecified symptoms associated with possible bacterial infection underwent a laboratory evaluation that included blood culture, urine culture, haematologic examination, blood film for malaria, nasopharyngeal aspirate and lumbar puncture (where indicated). **RESULTS:** The main causes of serious infection in the four sites of this study were the Gram-positive primary pathogens *S. aureus*, *S. pneumoniae* and *S. pyogenes*. *E. coli* was the most important Gram-negative organism, followed by a wide range of enteric pathogens. Although this study supports the use of ampicillin and gentamicin currently recommended by WHO for the initial therapy of suspected neonatal sepsis, where meningitis is present, or where infection with penicillin resistant *S. pneumoniae* or *Salmonella* is suspected, a third generation cephalosporin should be used. Where skin sepsis or another marker of staphylococcal infection is present, an antistaphylococcal agent should be added.

**CONCLUSIONS:** The studies described in this paper represent the largest prospective study of early infant infections in developing countries. Better treatment of seriously ill young infants in developing countries is urgently needed. In most cases this can still be achieved with relatively inexpensive antibiotics. However, this study has shown that, even with adequate treatment, there is a high mortality. Prevention must be the central to efforts to control this problem.

Publication Types: Multicenter study

The World Health Organization Young Infants Study Group

**Conclusions from the WHO multicenter study of serious infections in young infants.**

*Paediatric Infectious Diseases Journal* 1999 Oct;18(10 Suppl):S32-4.

(see part Assessment in this chapter)



## 10.2. PREVENTION AND TREATMENT OF HYPOGLYCAEMIA

Williams AF

### **Hypoglycaemia of the newborn: a review.**

*Bulletin of the World Health Organization* 1997;75(3):261-90

It is almost a century since hypoglycaemia (a reduction in the glucose concentration of circulating blood) was first described in children, and over 50 years since the condition was first recognized in infants. Nevertheless, controversy still surrounds the definition, significance, and management of neonatal hypoglycaemia. Technological developments such as bedside glucose monitoring have, paradoxically, exacerbated rather than eased the situation. This article reviews the literature on hypoglycaemia of the newborn, and covers the following: historical aspects; glucose homeostasis and metabolic adaptation at birth; the effect of low blood glucose levels on the central nervous system; the definition of hypoglycaemia; screening; prevention; treatment; research needs; and concludes with recommendations for prevention and management.

Publication Types: Review, Review, tutorial

Also available as unpublished document WHO/CHD/97.1, Geneva, World Health Organization 1996.

[http://whqlibdoc.who.int/hq/1997/WHO\\_CHD\\_97.1.pdf](http://whqlibdoc.who.int/hq/1997/WHO_CHD_97.1.pdf)

**See documents and publications in this chapter**



### **10.3. PREVENTION AND TREATMENT OF HYPOTHERMIA**

**See documents and publications in this chapter**

## **Documents and publications**

Maternal Health and Safe Motherhood Programme

***Mother-Baby Package: Implementing safe motherhood in countries.***

WHO/FHE/MSM/94.11, 1996, 89 p. [E, F]

<http://www.who.int/rht/documents/MSM94-11/9411.htm>

Sw.fr. 15.-/US \$13.50; in developing countries: Sw.fr. 10.50 Order no. 1930070

The material explains how the new WHO Mother-Baby Package can be used as a powerful tool for improving the health of mothers and infants - immediately and dramatically. Designed for use in national programmes in the developing world, the package consists of 18 simple interventions that have proven their capacity to reduce maternal and infant mortality in resource-poor settings. Recommended interventions were selected on the basis of considerable scientific knowledge about the causes of complications during pregnancy and childbirth and the best ways to prevent them. Pragmatic as well as scientifically valid, the package can be implemented within the existing health care system and without the need for sophisticated equipment, expensive drugs, or additional resources and facilities.

The document, which is addressed to national decision-makers and health planners, provides both an explanation of general strategies crucial to the success of the Package and a detailed guide to the actions required to implement each of the 18 core interventions. Concerning strategic issues, the book advocates an integrated approach to service delivery aimed at reducing the number of high-risk and unwanted pregnancies, reducing the number of complications, and reducing case fatality rates when complications occur. Essential service-related components of the package are identified as family planning, quality antenatal care, clean and safe delivery, and access to essential obstetric care for high-risk pregnancies and complications.

Against this background, the most extensive part of the document provides a detailed guide to the “what” and “how” of specific actions required to implement the Mother-Baby Package. The final chapter offers advice on general strategies for implementation.

World Health Organization, Family and Reproductive Health, Maternal and Newborn Health/ Safe Motherhood

***Management of the sick newborn. Report of a Technical Working Group Ankara, 5-8 June 1995.***

Geneva, World Health Organization 1996. WHO/FRH/MSM/96.12(1996), 20 p.

[http://whqlibdoc.who.int/hq/1996/WHO\\_FRH\\_MSM\\_96.12.pdf](http://whqlibdoc.who.int/hq/1996/WHO_FRH_MSM_96.12.pdf)

This report summarizes the discussions of the Technical Working Group on the care of the sick newborn at health centre and referral hospital. It outlines danger signs for early detection at home and health centre as well as management at health centre and referral hospital. This report does not provide complete guidelines on detection and management at the three levels of care but the Technical Working Group gave guidance to the secretariat for further development of materials on these topics.

World Health Organization, Division of Diarrhoeal and Acute Respiratory Infections

***Breastfeeding counselling: A training course.***

Geneva, World Health Organization, 1993 (unpublished document WHO/CDR/93.4; available on request from the Department of Child and Adolescent Health and Development (CAH), formerly the Division of Diarrhoeal and Acute Respiratory Disease Control (CDR)).

The training course materials consist of five volumes: Director’s Guide, Trainer’s guide, Participants manual, Overhead figures, and Answer sheets.

World Health Organization

***Care in normal birth: a practical guide. Report of a Technical Working Group***

Geneva, WHO 1997, WHO/FRH/MSM/96.24, iv + 54 pages [E]

WHO/FRH/MSM/96.24

Sw.fr. 10.-/US \$9.00; in developing countries: Sw.fr. 7.-

Order no. 1930104

Establishes universal guidelines for the routine care of women during uncomplicated labour and childbirth. Reflecting the consensus reached by an international group of experts, the report responds to the recent proliferation of practices designed to start, augment, accelerate, regulate or monitor the physiological process of labour in industrialized and developing countries alike. Recommendations for routine care are based on a critical review of what considerable research has to say about the effectiveness and safety of 59 common procedures and practices.

The report has six sections. The first establishes a definition of normal birth, and then considers the reasons why, in the interest of improving care, so many maternity services have uncritically introduced interventions that have been shown, in well-designed studies, to be useless, inappropriate, excessively costly, and frequently dangerous for mothers and babies. The differences between normal birth in hospitals and in homes, in industrialized and in developing countries are also considered together with the personnel, training, and skills needed to attend a normal delivery.

The four sections which constitute the core of the report systematically review the available evidence for and against the use of specific procedures in general labour care and during each of the three stages of labour. Details of this evaluation range from the advisability of withholding food and drink during labour, through a review of evidence demonstrating that routine use of episiotomy is harmful, to a description of several non-invasive, non-pharmacological methods of proven efficacy in pain relief.

In a key achievement, the final section classifies each of the 59 practices considered into one of four categories: clearly useful, clearly harmful or ineffective, inadequately supported by research findings and thus to be used with caution, and frequently used inappropriately.

<http://www.who.int/rht/documents/MSM96-24/msm9624.htm> publication

World Health Organization

***Thermal protection of the newborn: a practical guide***

Geneva, WHO 1996. WHO/RHT/MSM/97.2

1997, iii + 64 pages [E]

WHO/RHT/MSM/97.2

Sw.fr. 10.-/US \$9.00; in developing countries: Sw.fr. 7.-

Order no. 1931047

An illustrated guide to a series of simple measures, taken at birth and during the first days of life, that can help ensure that newborn babies do not become either too cold or too hot. Though emphasis is placed on the severe risks posed by hypothermia, the guide also includes information about the causes of hyperthermia and measures for prevention. Since hypothermia occurs mainly because of lack of knowledge rather than lack of equipment, the guide aims to give health workers all the information and advice needed to take appropriate action, whether to prevent hypothermia in the first place or to save an endangered life.

Now in its second edition, the guide has been revised in line with experiences gained during field testing of the first edition in eight developing countries. Revisions also reflect new evidence about the effectiveness of skin-to-skin contact and the overall importance of thermal protection. Also new is the concept of the "warm chain": a set of ten interlinked procedures, carried out at birth and during the following hours and days, which has been shown to minimize the likelihood of hypothermia in all newborns.

The guide opens with a description of the principles and procedures of thermal protection, giving special attention to the needs of preterm, low birth weight, and sick babies. Subsequent chapters describe the management of hypothermia and hyperthermia, and explain the harmful effects of certain cultural and institutional practices. Information ranges from the question of whether hypothermic babies should be warmed quickly or slowly, to the simple reminder that a "thermally comfortable" room for health staff can be dangerously cold for a newborn. For keeping high-risk babies warm, measures described include the



use of kangaroo-mother care, warm rooms, heated water-filled mattresses, radiant heaters, and incubators.

New in this edition is a 21-page summary explaining and illustrating the principles of thermal protection. Simply written and abundantly illustrated, the summary is intended for use in training and designed for easy translation and adaptation.

World Health Organization

***Basic newborn resuscitation: A practical guide.***

Geneva, WHO 1998. WHO/RHT/MSM/98.1, 32 p. [E]

Sw.fr. 10.-/US \$9.00; in developing countries: Sw.fr. 7.-

Order no. 1930124

Presents and explains a simple method of newborn resuscitation capable, when carried out quickly and correctly, of reviving more than three-quarters of infants who do not breathe at birth. Noting that some 900,000 newborns in the developing world die each year as the result of asphyxia, the document aims to give decision-makers - whether responsible for national programmes or in charge of local facilities - all the information needed to introduce the method and understand what it will require in terms of policies, training, equipment and supplies.

The document opens with a discussion of the problems surrounding birth asphyxia in developing countries, where most cases are inadequately managed and the risk of permanent brain damage in surviving infants is of major concern. The first main section, which can be used for training purposes, provides a step-by-step illustrated guide to the method and the simple equipment it requires: a heat source, a mucus extractor, a self-inflating bag, two masks, and a clock. Section two gives a fully referenced account of the technical basis for the method. Also included are alerts to many practices, both modern and traditional, that have no proven benefit, waste time, and may cause more harm than good. Other sections offer advice on how to select the best equipment and suggest a model form for recording data on resuscitation and its outcome.

Several difficult ethical questions are considered in the next section, which addresses the widespread concern that simple resuscitation merely delays death or results in a severely disabled infant that burdens the family and society. Arguing that decisions about when to start and stop resuscitation should be guided by institutional policy and not left to the birth attendant, the section offers policy guidelines for situations involving the apparently stillborn fetus, malformations, extremely low gestational age, and failed resuscitation. The remaining sections describe special situations where the recommended method may need to be modified, and outline a series of suggested activities, at national and local level, that will help health care institutions introduce or improve resuscitation practices.

World Health Organization

***Management of severe malnutrition - A manual for physicians and other senior health workers.*** Geneva, World Health Organization 1999, 60p ISBN 9241545119

(See chapter Nutritional status, nutrition and breastfeeding counselling)

## 11. HIV/AIDS

See also section **HIV and breastfeeding in chapter Nutritional status, nutrition and breastfeeding counselling**

### Articles

#### **Importance**

Adjorlolo-Johnson G, De Cock KM, Ekpini E, Vetter KM, Sibailly T, Brattegaard K, Yavo D, Doorly R, Whitaker JP, Kestens L, et al

#### **Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast.**

Projet RETRO-CI, Abidjan, Ivory Coast. *JAMA*, 1994, 272(6):462-466.

**OBJECTIVE**—To compare mother-to-child transmission of human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2, respectively) and to assess the impact of maternal HIV-1 and HIV-2 infections on child survival. **DESIGN**—Prospective cohort study. **SETTING**—Maternal and child health center in a lower socioeconomic class district of Abidjan, Ivory Coast. **PARTICIPANTS**—A total of 18,099 women delivering between 1990 and 1992 were tested for HIV-1 and HIV-2 antibodies. A cohort of 613 pregnant women and their infants was followed prospectively (138 women reactive to HIV-1, 132 reactive to HIV-2, 69 reactive to both viruses, and 274 HIV-seronegative). **MAIN OUTCOME MEASURES**—Rates of perinatal transmission for HIV-1, HIV-2, and both viruses, determined from results of serological and polymerase chain reaction tests on children; survival of infants born to HIV-1-positive, HIV-2-positive, dually reactive, and HIV-seronegative women. **RESULTS**—Of the 18,099 women tested, 9.4% were reactive to HIV-1 alone, 1.6% to HIV-2 alone, and 1.0% to both viruses. The rate of perinatal transmission of HIV-1 was 24.7% (95% confidence interval [CI], 15.8% to 33.7%), compared with 1.2% (95% CI, 0.0% to 3.5%) for HIV-2 (relative risk, 21.3; 95% CI, 2.9 to 154.3). Overall, 19.0% (95% CI, 9.0% to 29.0%) of infants of dually reactive women became infected; of the 11 children concerned, 10 were infected with HIV-1 and one with HIV-1 and HIV-2. Infants of HIV-seropositive mothers had a reduced survival; mortality rates were 15.1, 13.0, 6.5, and 3.4 deaths per 100 child-years, respectively, for children of HIV-1-positive, dually reactive, HIV-2-positive, and HIV-seronegative women.

**CONCLUSIONS**—The rate of perinatal transmission of HIV-2 (1.2%) was much lower than the rate of perinatal transmission of HIV-1 (24.7%), and this was associated with more favorable survival for infants of HIV-2-infected mothers. Dually reactive women could transmit both viruses, although transmission usually involved HIV-1 only. Public health guidelines should incorporate advice that perinatal transmission of HIV-2 is rare.

Comment in: *JAMA* 1994 Aug 10;272(6):487-8

Published erratum appears in *JAMA* 1994 Nov 16;272(19):1482

Barnett ED, Klein JO, Pelton SI, Luginbuhl LM

#### **Otitis media in children born to human immunodeficiency virus-infected mothers.**

*The Pediatric Infectious Disease Journal*, 1992, 11(5):360-364.

Acute otitis media (AOM) is thought to occur frequently in children infected with human immunodeficiency virus (HIV). We compared experience with AOM of 28 HIV-infected children with that of 33 children who seroreverted to HIV antibody negative status by age 18 months. The mean number of episodes/year of AOM for children who seroreverted decreased from 1.33 in the first year of life to 0.13 in the third year, whereas the mean number of episodes/year in HIV-infected children increased from 1.89 to 2.40. By age 3 years, all HIV-infected children had experienced 1 or more episodes of AOM, and 80% had experienced 6 or more, whereas 75% of children who seroreverted had experienced 1 or more episodes,

and none had had 6 or more. HIV-infected children with normal T4 lymphocyte counts had a mean of 1.18 episodes of AOM in the first year of life compared with 2.35 episodes in HIV-infected children with decreased counts ( $P = 0.023$ ). HIV-infected children with low counts had a nearly 3-fold increased risk of recurrent AOM (47% vs. 18%).

Bernstein LJ, Krieger BZ, Novick B, Sicklick MJ, Rubinstein A

**Bacterial infection in the acquired immunodeficiency syndrome of children.**

*The Pediatric Infectious Disease Journal*, 1985, 4(5):472-475.

We have followed 46 children with acquired immunodeficiency syndrome and acquired immunodeficiency syndrome-related complex. Twenty-six patients had at least one episode of serious bacterial infection. Twenty-seven episodes of sepsis were documented in 21 patients. Soft tissue infection was common in both the presence and the absence of documented bacteremia. Urinary tract infection commonly presented as worsening diarrhoea in the absence of sepsis. Organisms commonly isolated included *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Salmonella* sp. Staphylococcal infection accompanied episodes of cellulitis/abscess. *Escherichia coli* commonly caused urinary tract infection in the absence of sepsis. Enteric and nosocomial sepsis was limited to hospitalised, instrumented patients or to individuals who had received prior antibiotic therapy as outpatients.

**CONCLUSIONS:** Bacterial infection causes serious morbidity in acquired immunodeficiency syndrome and acquired immunodeficiency syndrome-related complex and may be further evidence for altered humoral immunity in the disorder.

Blanche S, Rouzioux C, Moscato ML, Veber F, Mayaux MJ, Jacomet C, Tricoire J, Deville A, Vial M, Firtion G, et al

**A prospective study of infants born to women seropositive for human immunodeficiency virus type 1.**

HIV Infection in Newborns French Collaborative Study Group. *New England Journal of Medicine*, 1989, 320(25):1643-1648

Assessment of the risks of transmission of infection with human immunodeficiency virus type 1 (HIV-1) from mother to newborn is difficult, partly because of the persistence for up to a year of maternal antibodies transmitted passively to the infant. To determine the frequency of perinatal transmission of HIV infection, we studied from birth 308 infants born to seropositive women, 62 percent of whom were intravenous drug abusers. Of 117 infants evaluated 18 months after birth, 32 (27 percent) were seropositive for HIV or had died of the acquired immunodeficiency syndrome (AIDS) ( $n = 6$ ); of the 32, only 2 remained asymptomatic. Another 76 infants (65 percent) were seronegative and free of symptoms, whereas 9 (8 percent) were seronegative but had symptoms suggestive of HIV-1 infection. The infants infected with HIV-1 did not differ from the others at birth with respect to weight, height, head circumference, or rate of malformations, but as compared with newborns who were seronegative at 18 months, their serum IgM levels were higher (78 +/- 81 mg per deciliter vs. 38 +/- 39 mg per deciliter;  $P$  less than 0.03) and their CD4 lymphocyte counts were lower (2054 +/- 1221 per cubic millimeter vs. 2901 +/- 1195 per cubic millimeter;  $P$  less than 0.006). Neither maternal risk factors nor the route of delivery was a predictor of seropositivity at 18 months; however, 5 of the 6 infants who were breast-fed became seropositive, as compared with 25 of 99 who were not ( $P$  less than 0.01).

**CONCLUSIONS:** Approximately one third of the infants born to seropositive mothers will have evidence of HIV-1 infection or of AIDS by the age of 18 months, and that about one fifth of this group will have died.

Publication Types: Clinical trial, Multicenter study

Domachowske JB

**Paediatric human immunodeficiency virus infection.**

*Clinical Microbiology Reviews*, 1996, 9(4):448-468.

In the past decade, an increase in paediatric human immunodeficiency virus (HIV) infection has had a substantial impact on childhood morbidity and mortality worldwide. The vertical transmission of HIV from mother to infant accounts for the vast majority of these cases. Identification of HIV-infected pregnant women needs to be improved so that appropriate therapy can be initiated for both mothers and infants. While recent data demonstrate a dramatic decrease in HIV transmission from a subset of women treated with zidovudine during pregnancy, further efforts at reducing transmission are desperately needed. This review focuses on vertically transmitted HIV infection in children, its epidemiology, diagnostic criteria, natural history, and clinical manifestations including infectious and noninfectious complications. An overview of the complex medical management of these children ensues, including the use of antiretroviral therapy. Opportunistic infection prophylaxis is reviewed, along with the important role of other supportive therapies.

Publication Types: Review, Review, academic

Hutto C, Parks WP, Lai SH, Mastrucci MT, Mitchell C, Munoz J, Trapido E, Master IM, Scott GB

**A hospital-based prospective study of perinatal infection with human immunodeficiency virus type 1.**

*The Journal of Pediatrics*, 1991, 118(3):347-53.

Most infants with paediatric acquired immunodeficiency syndrome and infections with human immunodeficiency virus type 1 (HIV-1) are infected perinatally by their mothers. To determine the proportion of exposed infants who are infected, we conducted a hospital-based prospective study in HIV-1-infected women whose infants were delivered at a single metropolitan hospital in Miami, Fla. A population of uninfected women and their infants was also enrolled and followed longitudinally for 2 years to assess laboratory and clinical measurements. The median follow-up is now 18 months for 82 infants born to HIV-1-infected mothers. The proportion of infected infants in this group is 0.30 (25/82). None of the infants born to 110 HIV-1-seronegative mothers were seropositive. Infected infants were easily distinguished from noninfected infants by virus isolation. No single immunologic or haematologic measure was predictive of infection for all infants at risk for HIV-1 infection who were 6 months of age or younger. As a group, however, infected infants could be distinguished from uninfected index infants by a number of immunologic measures by 6 months of age; the absolute number of CD4+ lymphocytes and the CD4+/CD8+ lymphocyte ratio were the variables most predictive of infection. As in retrospective studies, clinical disease developed in 80% of infected infants within the first 24 months of life. This study provides documentation of HIV-1 perinatal transmission risk and early correlates of infection in young infants from a single hospital.

Kotloff KL, Johnson JP, Nair P, Hickman D, Lippincott P, Wilson PD, Clemens JD

**Diarrhoeal morbidity during the first 2 years of life among HIV-infected infants.**

*JAMA*, 1994, 271(6):448-452.

**OBJECTIVE**—To determine the incidence, cause, and patterns of diarrhoea during the first 2 years of life among infants infected perinatally with the human immunodeficiency virus (HIV). **DESIGN**—A cohort study in which infants were enrolled shortly after birth and followed up longitudinally using biweekly surveillance for the occurrence of diarrhoea. Stool specimens collected at the onset of diarrhoea were evaluated for enteropathogens. Infants who were infected with HIV were compared with uninfected infants. **SUBJECTS**—Infants born to HIV-infected women at the University of Maryland Hospital, Baltimore, were recruited at 0 to 3 months of age. This analysis included 58 infants enrolled in the cohort and followed up at least 15 months (unless death intervened) whose HIV status was established (18 HIV-infected infants and 40 HIV-uninfected infants). **MEASUREMENTS AND RESULTS**—The overall incidence of diarrhoea in HIV-infected infants was 3.2 episodes per 12 child-months compared with 1.5 episodes per 12 child-months among HIV-uninfected infants (incidence density ratio, 2.2;  $P < .05$ ). An enteropathogen was identified in stool specimens collected during 20% of diarrhoeal episodes occurring in HIV-infected infants and during 25% of diarrhoeal episodes occurring in HIV-uninfected infants.

Episodes that persisted for 14 days or longer were significantly more common among HIV-infected infants. The peak incidence of diarrhoea occurred at 0 to 5 months of age for HIV-infected infants compared with 6 to 11 months for HIV-uninfected infants. Early onset of diarrhoea (< 6 months old) in HIV-infected infants was associated with the later development of persistent episodes of diarrhoea, and those with persistent episodes had more severe HIV infection, characterised by a significantly higher frequency of opportunistic infections and lower CD4+ T-lymphocyte counts by 1 year of age. **CONCLUSIONS:** Both acute and persistent episodes of diarrhoea are major sources of morbidity in HIV-infected infants. Moreover, persistent diarrhoea is a marker for rapid progression of HIV disease.

Krasinski K, Borkowsky W, Bonk S, Lawrence R, Chandwani S

**Bacterial infections in human immunodeficiency virus-infected children.**

*The Pediatric Infectious Disease Journal*, 1988, 7(5):323-328.

A retrospective review of 71 children infected with human immunodeficiency virus cared for over a 3.5-year period revealed that 44 of 71 (63%) required a bacterial culture and 27 of 71 (37%) had bacteriologically documented infection. There were 125 episodes in 27 patients. Pneumonia (24 of 125 (19%)), upper respiratory tract syndromes (23 of 125 (19%)), urinary tract infection (24 of 125 (19%)) and wound infection (12 of 125 (10%)) were the most common syndromes identified. Bacteraemic infections occurred in 35 of 125 (28%), and in 17 of 125 (14%) no other primary source could be identified. Pneumococci (11 of 35 (31%)) and Salmonella (4 of 35 (11%)) were the most common blood isolates; however, a wide spectrum of Gram-positive and Gram-negative pathogens were recovered. Bacterial pneumonia directly contributed to the death of 4 patients, in whom pneumonia caused by *Pneumocystis carinii* (2), cytomegalovirus (1) or varicella-zoster virus (1) also coexisted, respectively. Absolute T4 counts less than 400 and depressed lymphocyte-proliferative responses to diphtheria and tetanus toxoids, *Candida* antigen and pokeweed mitogen correlated with the occurrence of bacterial infection in human immunodeficiency virus-infected children. Although bacterial infections are a frequent cause of morbidity in human immunodeficiency virus-infected children, they are usually treatable.

Marchisio P, Principi N, Sorella S, Sala E, Tornaghi R

**Aetiology of acute otitis media in human immunodeficiency virus-infected children.**

*The Pediatric Infectious Disease Journal*, 1996, 15(1):58-61.

**BACKGROUND:** Acute otitis media (AOM) is one of the most common infections that are implicated as significant contributors to morbidity in HIV-infected children. To establish the optimal antibiotic therapy tympanocentesis is indicated as the first line diagnostic procedure, because unusual pathogens may play a role in advanced stages of deficient humoral or cellular immunity. **METHODS:** The microbiology of 60 episodes of AOM diagnosed in 21 symptomatic HIV-infected children (ages 9 months to 12 years) was compared with that of 121 episodes of AOM occurring in 113 immunocompetent HIV-negative children (ages 6 months to 12 years) in the last 5 years. **RESULTS:** The prevalence of the three most common pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and group A beta-haemolytic *Streptococcus*) was similar in HIV-infected and in normal children (56.5% vs. 54.9% of the ears). *Staphylococcus aureus* was significantly more frequent in AOM diagnosed in severely immunosuppressed stages. A significantly lower proportion of middle ear effusions obtained in HIV-infected children yielded no bacteria compared with normal children. Beta-lactamase production among isolates of *H. influenzae* was a rare phenomenon, both in HIV-infected and in normal children. No penicillin-resistant *S. pneumoniae* was found.

**CONCLUSIONS:** In HIV-infected children with absent or moderate immunosuppression empiric antibiotic therapy should be based on the recommendations given for immunocompetent children of the same geographic area. In severe immunosuppressed stages, given the possible role of *Staph. aureus*, extended spectrum antibiotics should be considered.

Publication Types: Clinical trial

Nathoo KJ, Chigonde S, Nhembe M, Ali MH, Mason PR

**Community-acquired bacteremia in human immunodeficiency virus-infected children in Harare, Zimbabwe.**

*The Pediatric Infectious Disease Journal*, 1996, 15(12):1092-1097.

**BACKGROUND:** HIV infection is common in mothers and their children in Zimbabwe, and HIV-infected children are particularly susceptible to bacterial infections. There is little information on the aetiology and outcome of HIV-related bacteremia in African children. **METHODS:** Blood cultures from 309 hospitalised children in Zimbabwe, of whom 168 were diagnosed as having HIV, were examined for pathogens. The association among significant bacteremia, HIV infection and mortality was assessed in these children. **RESULTS:** The most common isolates were coagulase-negative staphylococci (31 children, 25 clinically significant), *Staphylococcus aureus* (22 children) and *Streptococcus pneumoniae* (20 children). Nontyphoidal *Salmonella* (10 children), *Escherichia coli* (4 children) and *Klebsiella* sp. (4 children) were the most frequent Gram-negative bacteria. Two children had *Rhodococcus equi* pneumonia. HIV-infected children showed increased risk of bacteremia (odds ratio (OR) = 2.68), especially if younger than 18 months of age (OR = 2.94), and high risk of enterobacteremia (OR = 15.76). There was no significant association of bacteremia with nutritional status. Mortality was 17% overall but was higher in HIV-infected children up to 6 months of age (OR = 2.81) and in bacteraemic children of any age (OR = 2.03). **CONCLUSIONS:** Prompt recognition of pathogens and early administration of appropriate antimicrobials is important in reducing the morbidity and mortality associated with bacteremia in HIV-infected children in Africa.

Comments: *Pediatr Infect Dis J* 1997 May;16(5):537-8

Oshitani H, Kasolo FC, Mpabalwani M, Luo NP, Matsubayashi N, Bhat GH, Suzuki H, Numazaki Y, Zumla A, DuPont HL

**Association of rotavirus and human immunodeficiency virus infection in children hospitalised with acute diarrhoea, Lusaka, Zambia.**

*Journal of Infectious Diseases*, 1994, 169(4):897-900.

In Lusaka, Zambia, rotavirus (RV) and human immunodeficiency virus (HIV) infection commonly coexist; 132 (25%) of 537 consecutively studied infants < 5 years old hospitalised with diarrhoea were positive for both viral infections. Infants with RV infection were younger than those who were RV-negative ( $P > .05$ ), and infants with both viruses more frequently experienced dehydration ( $P < .05$ ). HIV-infected children more often exhibited respiratory symptoms on admission to the study ( $P < .0001$ ) and were more frequently underweight ( $P < .0001$ ) than were HIV-negative children, independent of RV infection. The mortality rate was highest in HIV-positive infants ( $P < .05$ ), and coinfection with RV did not increase the risk of fatality. This study demonstrates that while RV and HIV infections commonly coexist in one region of Africa, RV infection is no more common nor is the illness more severe in HIV-positive infants.

Semba RD, Miotti PG, Chipangwi JD, Saah AJ, Canner JK, Dallabetta GA, Hoover DR

**Maternal vitamin A deficiency and mother to child transmission of HIV-1.**

*Lancet*, 1994, 343(8913):1593-1597.

Studies show that around 10-40% HIV-positive women will give birth to children who are also infected. However, the risk factors for transmission from mother to child are not well understood and the effects of maternal nutritional status are unknown. We conducted a study of vitamin A status in pregnant women as a risk factor for mother-to-child transmission of HIV in Malawi. Serum vitamin A, height, weight, CD4 T-cell counts, and duration of breastfeeding were measured in 338 HIV-positive mothers whose infant's HIV serostatus was known. Mother-to-child transmission of HIV was 21.9% among mothers whose infants survived to 12 months of age. Mean vitamin A concentration in 74 mothers who transmitted HIV to their infants was lower than that in 264 mothers who did not transmit HIV to their infants (0.86 [0.03] vs 1.07 [0.02],  $p < 0.0001$ ). We divided HIV positive mothers to 4 groups, those with vitamin A concentrations of less than 0.70, between 0.70 and 1.05, between 1.05 and 1.40, and greater than or equal to 1.40  $\mu\text{mol/L}$ . The mother-to-child transmission rates for each group were 32.4%, 26.2%, 16.0%, and 7.2%, respectively ( $p < 0.0001$ ). Maternal CD4 cell counts, CD4%, and CD4/CD8 ratio were also associated with increased mother-to-child transmission of HIV. Maternal age, body-mass index, and

breastfeeding practices were not significantly associated with higher mother-to-child transmission. Our study suggests that maternal vitamin A deficiency contributes to mother-to-child transmission of HIV. Comment in: *Lancet* 1994 Jun 25;343(8913):1585-6

Simonon A, Lepage P, Karita E, Hitimana DG, Dabis F, Msellati P, Van Goethem C, Nsengumuremyi F, Bazubagira A, Van de Perre P

**An assessment of the timing of mother-to-child transmission of human immunodeficiency virus type 1 by means of polymerase chain reaction.**

*Journal of Acquired Immune Deficiency Syndromes*, 1994, 7(9):952-957.

To approximate the contributions of in utero, intrapartum, and postnatal transmission of human immunodeficiency virus type-1 (HIV-1) and to evaluate polymerase chain reaction (PCR) as a diagnostic tool for paediatric HIV infection, blood was collected at birth (cord blood), and at 3, 6-12, and 13-24 months in 218 children born to HIV-1-seropositive mothers in Kigali, Rwanda. Proviral DNA was detected by a double PCR using two sets of three primers (gag, pol, and env). Paediatric HIV-1 infection was defined according to serological and clinical criteria. The probability of having a positive PCR at a given time was calculated by a nonparametric method. Among children with unequivocal evidence of infection (n = 47), it was 30.5% on cord blood and 80.6% at 3 months. Thus, in children born to HIV-1-infected mothers, the estimated rate of transmission in the late postnatal period is 4.9%, and the rate of transmission in the intrapartum plus postnatal periods is 17.6%. Among 117 HIV-1-uninfected children born to HIV-1-infected mothers, six (5%) had a false-positive PCR on cord blood. These results should be taken into account in designing intervention trials aimed at reducing mother-to-child transmission of HIV-1.

Spira R, Lepage P, Msellati P, Van De Perre P, Leroy V, Simonon A, Karita E, Dabis F

**Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda.**

Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics* 1999 Nov;104(5):e56

**OBJECTIVE:** To compare morbidity and mortality of human immunodeficiency virus type 1 (HIV-1)-infected and HIV-1-uninfected children and to identify predictors of acquired immunodeficiency syndrome (AIDS) and death among HIV-1-infected children in the context of a developing country. **DESIGN:** Prospective cohort study. **SETTING:** Maternal and child health clinic of the Centre Hospitalier de Kigali, Rwanda. **PARTICIPANTS:** Two hundred eighteen children born to HIV-1-seropositive mothers and 218 born to seronegative mothers of the same age and parity were enrolled at birth. **OUTCOME MEASURES:** Deaths, clinical AIDS, nonspecific HIV-related manifestations, and use of health care services. **RESULTS:** Fifty-four infected and 347 uninfected children were followed up for a median of 27 and 51 months, respectively. With the exception of chronic cough, the risk of occurrence of nonspecific HIV-related conditions was 3 to 13 times higher in infected than in uninfected children. The recurrence rate and severity of these findings were increased systematically in infected infants. Estimated cumulative risk of developing AIDS was 28% and 35% at 2 and 5 years of age, respectively. Estimated risk of death among infected children at 2 and 5 years of age was 45% and 62%, respectively, a rate 21 times higher than in uninfected children. Median survival time after estimated infection was 12.4 months. Early infection, early onset of HIV-related conditions, failure to thrive, and generalised lymphadenopathy were associated with subsequent risk of death and/or AIDS, whereas lymphoid interstitial pneumonitis was predictive of a milder disease.

**CONCLUSIONS:** In Africa, HIV-1-infected children develop disease manifestations early in life. Specific clinical findings are predictive of HIV-1 disease, AIDS stage, and death. Bimodal expression of HIV-1 paediatric disease is encountered in Africa, as in industrialized countries, but prognosis is poorer. human immunodeficiency virus infection, children, vertical transmission, natural history, Africa.

Thea DM, St Louis ME, Atido U, Kanjinga K, Kembo B, Matondo M, Tshiamala T, Kamenga C, Davachi F, Brown C, et al

**A prospective study of diarrhoea and HIV-1 infection among 429 Zairian infants.**

*New England Journal of Medicine*, 1993, 329(23):1696-1702.

**BACKGROUND.** Persistent diarrhoea is a prominent feature of the acquired immunodeficiency syndrome in adults, but its cause and its effect on children with human immunodeficiency virus (HIV) infection are largely unknown, particularly in Africa. **METHODS.** We studied a birth cohort of 429 infants born to HIV-positive or HIV-negative mothers in Zaire to determine the incidence of acute, recurrent (> or = 2 episodes), and persistent (> or = 14 days) diarrhoea; outcome; and risk factors. **RESULTS.** Of the 238 infants whose mothers were HIV-positive, 53 were infected, 139 were uninfected, and the HIV status of 46 could not be determined. As compared with uninfected infants, infected infants had higher incidence rates for acute diarrhoea (170 vs. 100 episodes per 100 child-years,  $P = 0.003$ ), recurrent diarrhoea (21 vs. 11,  $P = 0.12$ ), and persistent diarrhoea (19 vs. 4,  $P < 0.003$ ). Persistent diarrhoea developed in 11 HIV-infected infants; all but 1 died. It also developed in 19 uninfected infants; all but 1 survived. The prevalence of stool pathogens was similar in the two groups. In a multivariate model, persistent diarrhoea in an infant was independently associated with symptomatic HIV type 1 infection in the mother (relative hazard, 1.5;  $P = 0.08$ ). The incidence of persistent diarrhoea in the uninfected infants of seropositive mothers was nearly double that in the uninfected infants of seronegative mothers (4.9 vs. 2.7 episodes per 100 child-years), and the risk increased if the mother died (relative hazard, 10.4). Significant growth impairment and severe immunosuppression occurred in the six to eight weeks before the onset of persistent diarrhoea.

**CONCLUSIONS.** In Zaire, infants with HIV infection have an 11-fold increased risk of death from diarrhoea, largely persistent diarrhoea, which is often preceded by recurrent episodes of acute diarrhoea, malnutrition, or immunosuppression. Illness and death of the mother increase that risk, even among her uninfected infants.

Vetter KM, Djomand G, Zadi F, Diaby L, Brattegaard K, Timite M, Andoh J, Adou JA, De Cock KM  
**Clinical spectrum of human immunodeficiency virus disease in children in a west African city.**  
Projet RETRO-CI, Abidjan, Cote d'Ivoire.  
*The Pediatric Infectious Disease Journal*, 1996, 15(5):438-442.

**OBJECTIVES.** To determine the prevalence of HIV infection in children and to compare diagnostic syndromes and outcomes in HIV-positive and HIV-negative children. **METHODS.** Consecutive children hospitalised in Abidjan's three university hospitals were examined, tested for HIV infection and followed to discharge. Admission or discharge diagnoses and outcome (survived or died) were compared in HIV-positive and HIV-negative children. **RESULTS.** The prevalence of HIV infection in the 4480 children hospitalised for the first time was 8.2%; the highest age-specific rate (11.2%) was in children ages 15 to 23 months. Six clinical syndromes accounted for more than 80% of admissions in HIV-positive and -negative children (all ages combined): respiratory infection; malnutrition; malaria; anaemia; diarrhoea; and meningitis. The dominant syndromic diagnoses in HIV-positive children were respiratory infection (26.1%) and malnutrition (25.8%); in HIV-negative children they were malaria (30.4%) and respiratory infection (19.1%). The overall mortality rate in HIV-positive children was 20.8%, compared with 8.7% in HIV-negative children (relative risk, 2.4; 95% confidence interval, 1.9 to 3.1); the highest death rate (28.1%) was in children younger than 15 months.

**CONCLUSIONS.** Clinical syndromes associated with HIV infection in African children are difficult to recognize without access to HIV serology. Respiratory infection and malnutrition were the dominant clinical syndromes in HIV-positive children in Abidjan. Greater overlap exists between the clinical presentations of HIV-associated disease and other common health problems in African children than in adults.



## Assessment

Dabis F, Msellati P, Dunn D, Lepage P, Newell ML, Peckham C, Van de Perre P  
**Estimating the rate of mother-to-child transmission of HIV: report of a workshop on methodological issues Ghent (Belgium), 17-20 February 1992.**  
*AIDS*, 1993, 7(8):1139-1148.

**PURPOSE:** In the last 8 years, numerous cohort studies have been conducted to estimate the rate of mother-to-child transmission (MTCT) of HIV. Many of these have faced problems in data collection and analysis, making it difficult to compare transmission rates between studies. This workshop on methodological aspects of the study of MTCT of HIV-1 was held in Ghent (Belgium) in February 1992. **STUDY SELECTION AND DATA EXTRACTION:** Fourteen teams of investigators participated, representing studies from Central (five) and Eastern Africa (three), Europe (two), Haiti (one) and the United States (three). A critical evaluation of the projects was carried out, under four headings: (1) enrolment and follow-up procedures, (2) diagnostic criteria and case definitions, (3) measurement and comparison of MTCT rates and (4) determinants of transmission. **RESULTS:** Reported transmission rates ranged from 13 to 32% in industrialized countries and from 25 to 48% in developing countries. However, no direct comparisons could be made because methods of calculation differed from study to study. Based on this review, a common methodology was developed. Agreement was reached on definitions of HIV-related signs/symptoms, paediatric AIDS and HIV-related deaths. A classification system of children born to HIV-1-infected mothers according to their probable HIV infection status during the first 15 months of life, allowed the elaboration of a direct method of computation of the transmission rate and of an indirect method for studies with a comparison group of children born to HIV-seronegative mothers. This standardized approach was subsequently applied to selected data sets.

**CONCLUSIONS:** The described methodology can now be applied to all studies with sufficient follow-up and comparisons made between transmission rates. This step is essential for assessing determinants of transmission and for the development of a common approach for the evaluation of interventions aimed at reducing or interrupting MTCT of HIV.

Graham SM, Mtitimila EI, Kamanga HS, Walsh AL, Hart CA, Molyneux ME  
**Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children.**  
*Lancet* 2000 Jan 29;355(9201):369-73  
Published erratum appears in *Lancet* 2000 Mar 4;355(9206):850

**BACKGROUND:** Necropsy studies from Africa have shown that *Pneumocystis carinii* pneumonia (PCP) is common in infants with HIV infection. We aimed to describe the rate, clinical presentation, and outcome of PCP in young Malawian children with acute severe pneumonia. **METHODS:** Children aged between 2 months and 5 years who were in hospital with a diagnosis of severe pneumonia were admitted to a study ward for clinical monitoring. We carried out blood culture, immunofluorescence on nasopharyngeal aspirate samples to test for PCP, polymerase chain reaction to detect HIV, and chest radiography. **FINDINGS:** 16 cases of PCP were identified among 150 children with radiologically confirmed severe pneumonia. All were HIV-positive and younger than 6 months. 21 children had bacterial pneumonia (including one who was also PCP positive) and 114 were not confirmed. The most common bacterial pathogens among children without PCP were *Streptococcus pneumoniae* (eight) and non-typhoidal salmonellae (seven). On admission, children with confirmed PCP had a lower mean age, body temperature, and oxygen saturation than children with bacterial pneumonia and were less likely to have a focal abnormality on auscultation. Oxygen requirements were much greater in children with PCP than those with bacterial pneumonias (96 of 105 hospital days vs 15 of 94,  $p < 0.0001$ ). Ten of 16 children with PCP and six of 21 with bacterial pneumonia died (relative risk 2.19 [95% CI 1.0-4.7]). The overall case-fatality rate of severe pneumonia was 22%. In addition to a strong association with PCP, a fatal outcome was significantly and independently associated with HIV infection (2.98 [1.1-7.9]) and with age under 6 months (2.76 [1.0-5.2]).

**INTERPRETATION:** PCP is common and contributes to the high mortality from pneumonia in Malawian infants. Clinical features are helpful in diagnosis. The study highlights the impact of HIV infection and difficult issues of management in countries with few resources.

Comments in: *Lancet* 2000 Jun 10;355(9220):2074-5

Miller RF, Mitchell DM

**AIDS and the lung: update 1995. 1. *Pneumocystis carinii* pneumonia.**

*Thorax*, 1995, 50(2):191-200.

Molecular biological techniques have clearly demonstrated that *P. carinii* is a fungus and that there is genetic diversity with different strains infecting different animals.

An improved understanding of the epidemiology of the natural history of *P. carinii* suggests that clinical disease arises by re-infection and not reactivation. Frequent re-infection results in colonisation in some healthy individuals and colonisation, with subsequent disease, in the immunodeficient.

An empirical approach to diagnosis for patients with typical presentations remains an appropriate management strategy, but other diagnoses may be missed. For those with atypical presentation or lack of response to treatment bronchoscopy, bronchoalveolar lavage, transbronchial biopsy, or open lung biopsy may be necessary to secure a diagnosis.

Indirect diagnostic tests are of little diagnostic use except to confirm the presence of organic disease (in contrast to a common cold) in symptomatic HIV positive patient. With further calibration DNA amplification on saliva/mouthwash samples may become a highly sensitive and specific non-diagnostic tool for diagnosis of *P. carinii*.

There has been a little change in recommendations for treatment over the last two years: cotrimoxazole remains the agent of choice, and is so effective that it will be difficult to displace it as first line therapy. Nebulised pentamidine should not be used to treat pneumocystis pneumonia. The overall death rate from pneumocystis pneumonia in the UK is now about 5%, somewhat less than that of hospitalised patients with community acquired pneumonia.

Anti-pneumocystis prophylaxis is effective, the drug of first choice being oral cotrimoxazole. Clearly, significant numbers of HIV positive patients with low CD4 lymphocyte counts are not taking prophylaxis as many continue present with pneumocystis pneumonia.

Publication Types: Review, Review, tutorial

Scarlatti G

**Paediatric HIV infection.**

*Lancet*, 1996, 348(9031):863-868.

For diagnosis of HIV- 1 infection in children, it is no longer necessary to wait for clinical signs of AIDS to appear or for the child to reach 18 months of age, when conventional serological tests can be used. With appropriate techniques, early diagnosis is now possible by 3 months of age. Multivariate analysis of virological and immunological variables soon after birth should provide a reliable picture of markers of disease progression. The evidence of abundant virus replication at an early age has important implications for clinical management, and for initiation of medical therapies. The discovery of a class of HIV co-receptors gives a new insight into virus-host interactions; control of viral load and cell tropism via different use of co-receptors has become important to the understanding of disease progression and transmission.

## Treatment, prevention

Centres for Disease Control and Prevention

**1995 revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus.**

*Morbidity and Mortality Weekly Report*, 1995, 44(RR-4):1-10.

*Pneumocystis carinii* pneumonia (PCP) is the most common opportunistic infection in children who have acquired immunodeficiency syndrome (AIDS). Despite the publication of guidelines for prophylaxis against PCP for children infected with human immunodeficiency virus (HIV) in 1991, ongoing AIDS surveillance has detected no substantial decrease in PCP incidence among HIV- infected infants. Studies indicate that this continued incidence is associated with failure to identify HIV-infected children before PCP occurs and with limitations in the ability of CD4+ measurements to identify children at risk for PCP. In March 1994, the National Paediatric & Family HIV Resource Centre, in collaboration with CDC,

convened a working group to review additional data about the occurrence of PCP among HIV-infected children and to re-evaluate the 1991 PCP prophylaxis guidelines for children. This report summarizes these new data and presents revised PCP prevention guidelines that recommend a) promptly identifying children born to HIV-infected women and initiating regular diagnostic and immunologic monitoring of such children; b) beginning PCP prophylaxis at 4-6 weeks of age for all children who have been perinatally exposed to HIV; c) continuing prophylaxis through 12 months of age for H/V-infected children; and d) making decisions regarding prophylaxis for HIV-infected children 12 months of age or older based on CD4+ measurements and whether PCP previously has occurred.

Hughes WT

**Trimethoprim-Sulfamethoxazole therapy for *Pneumocystis carinii* pneumonitis in children.**

*Reviews of Infectious Diseases*, 1982, 4(2):602-607.

Trimethoprim-sulfamethoxazole (TMP-SMZ) is effective in both the treatment and the prevention of *Pneumocystis carinii* pneumonitis. After initial evaluation in an animal model, TMP-SMZ was shown to be as clinically effective as pentamidine isethionate for the treatment of pneumonitis in children with cancer and to have minimal adverse effects. Treatment with TMP-SMZ (20 mg of TMP and 100 mg of SMZ per kg of body weight per day) was successful in three-fourths of patients tested. Administered prophylactically, TMP-SMZ (5.0 mg of TMP and 25 mg of SMZ per kg of body weight per day) prevented *P. carinii* infection in high-risk immunocompromised patients. Studies of the unstructured delivery of prophylactic TMP-SMZ have demonstrated the regimen to be feasible and effective, with a favorable benefit-risk ratio for a large number of children with cancer.

Publication Types: Clinical trial, Randomised controlled trial

Lepage P, Spira R, Kalibala S, Pillay K, Giaquinto C, Castetbon K, Osborne C, Courpotin C, Dabis F

**Care of human immunodeficiency virus-infected children in developing countries.**

International Working Group on Mother-to-Child Transmission of HIV.

*The Pediatric Infectious Disease Journal* 1998 Jul;17(7):581-6

CONTEXT: There is urgent need to strengthen the area of paediatric HIV/AIDS care in developing countries. Clinical research in this area is also scarce. METHODOLOGY: A literature review and a postal survey were used to obtain updated information on mortality, morbidity and current standards of care of children born to HIV-infected mothers in developing countries. A 2-day workshop was organised to review the available data and to identify the key areas where clinical research should be conducted. MAIN FINDINGS: Rates of mortality and morbidity were very different from one study to another but generally higher than in industrialized countries. Prognostic studies for HIV-1-infected children in developing countries were not available. Based on the report of 14 teams from 11 countries, specific protocols for HIV-infected children with persistent diarrhoea or severe malnutrition were documented in fewer than one-half of the cases. Secondary antimicrobial prophylaxis after interstitial pneumonia or recurrent infections was still infrequent, as primary prophylaxis of opportunistic infections. The following list of clinical research priorities was identified by the workshop participants: primary prophylaxis of opportunistic and bacterial infections; case management of persistent diarrhoea; reassessment of the performance of p24 antigen for diagnostic and prognosis use; studies on the aetiology of pulmonary infections; long term observational paediatric cohorts; current weaning practices and duration of breast-feeding; counselling and HIV testing of children and families; prevention of HIV sexual transmission in children and adolescents.

Miller RF, Mitchell DM

**AIDS and the lung: update 1995. 1. *Pneumocystis carinii* pneumonia.**

*Thorax*, 1995, 50(2):191-200.

(See this chapter, Assessment)

Simonds RJ, Lindegren ML, Thomas P, Hanson D, Caldwell B, Scott G, Rogers M

**Prophylaxis against *Pneumocystis carinii* pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States.**

*New England Journal of Medicine*, 1995, 332(12):786-790.

**BACKGROUND.** *Pneumocystis carinii* pneumonia (PCP) remains a common and often fatal opportunistic infection among children infected with the human immunodeficiency virus (HIV). HIV-infected infants between three and six months of age are particularly vulnerable. Current guidelines recommend prophylaxis in children from birth to 11 months old who have CD4+ counts below 1500 cells per cubic millimeter. **METHODS.** We used national surveillance data to estimate the annual incidence of PCP among children less than one year old. We reviewed the medical records of 300 children given a diagnosis of PCP between January 1991 and June 1993 to determine why treatment according to the 1991 guidelines for prophylaxis against PCP either was not given or failed to prevent the disease. **RESULTS.** In our study the incidence of PCP in the first year of life among infants born to HIV-infected mothers changed little between 1989 and 1992. Among 7080 children born to HIV-infected mothers in 1992, PCP developed in 2.4 percent. Of 300 children with PCP diagnosed from January 1991 through June 1993, 199 (66 percent) had never received prophylaxis, and for 118 of those children (59 percent) exposure to HIV was first identified 30 days or less before the diagnosis of PCP. Among 129 children less than one year old, the CD4+ count declined by an estimated 967 cells per cubic millimeter (95 percent confidence interval, 724 to 1210 cells per cubic millimeter) during the three months before the diagnosis of PCP. Among infants in whom CD4+ counts were determined within one month of the diagnosis of PCP, 18 percent (20 of 113) had at least 1500 cells per cubic millimeter, a level higher than the currently recommended threshold for prophylaxis.

**CONCLUSIONS.** In the United States the incidence of PCP among HIV-infected infants has not declined. If this infection is to be prevented, infants exposed to HIV must be identified earlier, and prophylaxis must be offered to more children than the guidelines currently recommend.

Comment in: *N Engl J Med* 1995 Aug 3;333(5):320-1

## **Documents and publications**

AHRTAG briefing paper

***Caring with confidence: Practical information for health workers who prevent and treat HIV infection in children*** AHRTAG 1997, 60 p.

This briefing paper has been produced as a contribution to the 1997 World AIDS Campaign with the theme "Children living in a World with AIDS". The purpose of the publication is to increase awareness of the issues being faced by children and families affected by the HIV epidemic.

The publication describes how HIV and AIDS affect young children, how to prevent HIV infection in young children, diagnosis and management of infected children. It gives an overview of issues for health workers including increased pressure and stress, the need to follow safety precautions in health facilities and the ways of counseling parents and children.

Harries AD, Maher D, with contributions from M.C. Raviglione, P. Chaulet, P.P. Nunn and E. van Praag

***TB/HIV: A Clinical Manual***

World Health Organization, Geneva, 1996, 135 pages, WHO/TB/96.200;

Sw.fr. 12.-/US \$ 10.80; in developing countries: Sw.fr. 8.40

Order no 1930088,

This manual provides a pocket-sized guide to the clinical management of tuberculosis, particularly in patients suffering from co-infection with HIV. Designed for use by busy clinicians, the manual aims to promote the best possible diagnosis and treatment in low-income countries where the prevalence of TB and HIV infection is high, case loads are heavy, and laboratory support may be limited. With these needs in mind, the manual combines the latest scientific knowledge about these diseases with authoritative advice based on extensive field experience in several of the hardest hit countries.

Throughout the manual, tables, flow charts, lists of do's and don'ts, and numerous practical tips are used to facilitate quick reference and correct decisions. Information ranges from advice on how to distinguish TB from other HIV-related pulmonary diseases, through a coloured score chart to aid the diagnosis of TB in children, to the simple reminder that in sub-Saharan Africa, anyone with TB is in a high risk group for HIV. Though primarily addressed to clinicians working at district hospitals in sub-Saharan Africa, the manual is also suitable for use in areas of Asia and South America where the problem of TB and HIV co-infection poses a growing clinical challenge.

The manual has twelve concise chapters presented in a convenient spiral-bound format. Background information is provided in the first chapters, which summarize basic facts about TB, HIV, and HIV-related TB, and outline a framework for effective TB control. Diagnosis is covered in four chapters, which set out detailed principles and procedures for the diagnosis of TB in adults and in children, and for the diagnosis of HIV infection in adults and in children with TB. Chapter seven presents standardized TB case definitions, by site of disease, result of sputum smear, and by previous treatment, and explains how these case definitions allow categorisation of patients for treatment purposes.

Extensive treatment guidelines are presented in chapters devoted to the treatment of TB patients, management of the side effects of specific anti-TB drugs, and the management of other HIV-related diseases in TB patients. The manual concludes with a discussion of the importance of coordinated care in different settings, followed by advice on the prevention of TB in HIV-infected individuals.

Preble EA, Piwoz EG

**HIV and Infant Feeding: A Chronology of Research and Policy Advances and their Implications for Programmes.**

*The LINKAGES Project The Support for Analysis and Research in Africa (SARA) Project.* September 1998, 27 p.

The paper has five major goals with respect to this important issue. These goals are to: 1) review the major advances in the study of HIV and infant feeding and the policy responses to these findings; 2) describe several design and interpretation issues to take into consideration when reading and comparing research studies on this issue; 3) report the findings of several studies and mathematical models which have been developed to guide program and policy recommendations on HIV and infant feeding; 4) summarize what existing studies do and do not reveal about this issue; and 5) recommend areas requiring further research to facilitate adaptation and application of the UNAIDS/UNICEF/WHO guidelines on HIV and infant feeding. The paper is intended to inform program managers and others who are interested in learning more about HIV and infant feeding but who are not necessarily familiar with all of the technical issues in either of these fields.

World Health Organization

***Guidelines for the Clinical Management of HIV Infection in Children***

1993, x + 88 pages [E, F]

WHO/GPA/IDS/HCS/93.3

Sw.fr. 13.-/US \$11.70; in developing countries: Sw.fr. 9.10

Order no. 1930046

[http://whqlibdoc.who.int/hq/1993/WHO\\_GPA\\_IDS\\_HCS\\_93.3.pdf](http://whqlibdoc.who.int/hq/1993/WHO_GPA_IDS_HCS_93.3.pdf)

A practical step-by-step guide to the clinical management of infections and other symptoms commonly seen in children with HIV infection. Responding to the need for a clear and consistent clinical approach, the manual sets out the information needed to facilitate a provisional or definitive diagnosis, appropriate treatment, and suitable resource planning. Focused on common symptoms and diseases, the manual makes abundant use of “decision maps” or flow-chart algorithms that guide readers from the recognition of a clinical state, through a decision, to the appropriate therapeutic or diagnostic action at three different levels of care, moving from facilities with no laboratory or X-ray service, through small hospitals, to fully-equipped major hospitals. Throughout, emphasis is placed on measures that can decrease suffering and prolong life. Information ranges from precise guidelines on appropriate drugs and therapeutic regimens, through advice on what to do when no improvement is observed, to the simple reminder that the possibility of tuberculosis should always be considered in an HIV-infected child.

The manual has eleven chapters. The first two provide basic information on the recognition of symptomatic HIV infection in children and describe the various tests available or under investigation for obtaining laboratory evidence of infection. Subsequent chapters set out guidelines for the diagnosis and management of seven common clinical conditions: persistent diarrhoea, oral thrush, respiratory conditions, including *pneumocystis carinii* pneumonia and tuberculosis, neurological abnormalities, persistent or recurrent fever, failure to thrive, and HIV-associated skin diseases. The manual concludes with chapters on the counselling of infected children and their families and the follow-up of infected or seropositive children, including recommended physical and laboratory examinations, drug therapies, and immunisations.

World Health Organization Global Programme on AIDS.

***Management of sexually transmitted diseases.***

Document WHO/GPA/TEM/94.1 (1994).

[http://whqlibdoc.who.int/hq/1997/WHO\\_GPA\\_TEM\\_94.1\\_Rev.1.pdf](http://whqlibdoc.who.int/hq/1997/WHO_GPA_TEM_94.1_Rev.1.pdf)

In 1991, WHO published recommendations for the comprehensive management of patients with sexually transmitted diseases (STD) within the broader context of control, prevention and care programmes for STD and HIV infection. WHO convened an Advisory Group Meeting on Sexually Transmitted Diseases Treatment in 1993 to review and update treatment recommendations in the light of recent development. This document presents the revised recommendations, both for a syndromic approach to the management of patients with STD symptoms and for the treatment of specific STD infections. It also provides information on the notification and management of sexual partners, and on STD in children. The document opens with a description of the background, rationale for standardized treatment recommendations, case management, syndromic management and selection of drugs. Subsequent chapters describe the treatment of STD associated syndromes, treatment of specific infections, key considerations underlying treatments and practical considerations in case management. A special chapter is devoted to children and STD.



## 12. WHERE REFERRAL IS DIFFICULT OR IMPOSSIBLE

### Articles

Kalter HD, Schillinger JA, Hossain M, Burnham G, Saha S, de Wit V, Khan NZ, Schwartz B, Black RE

#### **Identifying sick children requiring referral to hospital in Bangladesh.**

*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):65-76.

The object of this study was to evaluate and improve the guidelines for the Integrated Management of Childhood Illness (IMCI) with respect to identifying young infants and children requiring referral to hospital in an area of low malaria prevalence. A total of 234 young infants (aged 1 week to 2 months) and 668 children (aged 2 months to 5 years) were prospectively sampled from patients presenting at a children's hospital in Dhaka, Bangladesh. The study paediatricians obtained a standardized history and carried out a physical examination, including items in the IMCI guidelines developed by WHO and UNICEF. The paediatricians made a provisional diagnosis and judged whether each patient needed hospital admission. Using the paediatrician's assessment of a need for admission as the standard, the sensitivity and specificity of the current and modified IMCI guidelines for correctly referring patients to hospital were examined. The IMCI's sensitivity for a paediatrician's assessment in favour of hospital admission was 84% (95% confidence interval (CI): 75-90) for young infants and 86% (95% CI: 81-90) for children, and the specificity was, respectively, 54% (95% CI: 45-63) and 64% (95% CI: 59-69). One fourth or more in each group had a provisional diagnosis of pneumonia, and the IMCI's specificity was increased without lowering sensitivity by modifying the respiratory signs calling for referral. These results show that the IMCI has good sensitivity for correctly referring young infants and children requiring hospital admission in a developing country setting with a low prevalence of malaria. The guidelines' moderate specificity will result in considerable over-referral of patients not needing admission, thereby decreasing opportunities for successful treatment of patients at first-level health facilities. The impact of the IMCI guidelines on children's health and the health care system must be judged in the light of current treatment practices, health outcomes and referral patterns.

Nolan T, Angos P, Cunha AJ, Muhe L, Qazi S, Simoes EA, Tamburlini G, Weber M, Pierce NF

#### **Quality of hospital care for seriously ill children in less-developed countries.**

*Lancet* 2001 Jan 13;357(9250):106-10

**BACKGROUND:** Improving the quality of care for sick children referred to hospitals in less-developed countries may lead to better outcomes, including reduced mortality. Data are lacking, however, on the quality of priority screening (triage), emergency care, diagnosis, and inpatient treatment in these hospitals, and on aspects of these potential targets that would benefit most from interventions leading to improved health outcomes. **METHODS:** We did a qualitative study in 13 district hospitals and eight teaching hospitals in seven less-developed countries. Experienced paediatricians used a structured survey instrument to assess initial triage, emergency and inpatient care, staff knowledge and practices, and hospital support services. **FINDINGS:** Overall quality of care differed between countries and among hospitals and was generally better in teaching hospitals. 14 of 21 hospitals lacked an adequate system for triage. Initial patient assessment was often inadequate and treatment delayed. Most emergency treatment areas were poorly organised and lacked essential supplies; families were routinely required to buy emergency drugs before they could be given. Adverse factors in case management, including inadequate assessment, inappropriate treatment, and inadequate monitoring occurred in 76% of inpatient children. Most doctors in district hospitals, and nurses and medical assistants in teaching and district hospitals, had inadequate knowledge and reported practice for managing important childhood illnesses. **INTERPRETATION:** Strengthening care for sick children referred to hospital should focus on achievable objectives with the greatest potential benefit for health outcome. Possible targets for improvement include initial triage, emergency care, assessment, inpatient treatment, and monitoring. Priority targets for individual hospitals may be determined by assessing each hospital.

Comment in: *Lancet*. 2001 Jan 13;357(9250):86-7



## **Documents and publications**

### ***Management of the Child with a Serious Infection or Severe Malnutrition Guidelines for Care at the First-referral Level in Developing Countries***

Geneva, World Health Organization 2000, xiii + 162 pages

(available in English; Arabic, French, Portuguese, Russian, and Spanish in preparation)

ISBN 92 4 154531 3

Sw.fr. 15.–/US \$13.50; in developing countries: Sw.fr. 10.50 Order no. 1150481

This manual gives small hospitals in developing countries expert advice on the management of young children suffering from serious infections or severe malnutrition. Addressed to doctors and senior nurses, the manual aims to provide all the practical and technical guidance needed to facilitate quick decisions and life-saving interventions. Although advice on outpatient care is included, the manual concentrates on the inpatient management of diseases known to be the major killers of children in the developing world. Conditions covered range from pneumonia, diarrhoea, and severe malnutrition to malaria, meningitis, and measles.

The manual follows a logical, sequential approach to management that relies on a limited number of drugs, laboratory investigations, and practical procedures. Recommended lines of action combine the latest clinical knowledge with extensive practical experience concerning what works best when resources, drugs, and equipment are limited. Throughout, charts, tables, model forms, alerts to common errors, and step-by-step instructions enhance the manual's value as a practical tool.

The manual opens with a chapter on triage, which explains a rapid process for detecting emergency cases and starting treatment immediately. Exact instructions for treatment are set out in a series of ten charts. All treatments rely on a limited number of drugs and procedures which can be given safely by nurses and medical assistants after brief training. Chapter two, on assessment and diagnosis, presents the key symptoms and signs to look for in children with specific problems, giving particular attention to the importance of differential diagnosis. Tables list the differential diagnoses for common problems and give details of the symptoms, examination findings, and laboratory results which can be used to determine the main diagnosis and any secondary diagnoses.

Against this background, the core of the manual provides detailed treatment instructions for individual clinical conditions, specifying the standard course and duration of treatment. Separate chapters cover the management of over twenty diseases in children presenting with cough or difficult breathing, diarrhoea, and fever. Additional chapters cover the management of common problems in young infants, of children suffering from severe malnutrition, and of children with HIV/AIDS. The remaining chapters provide detailed guidelines for supportive care, propose a system for the regular monitoring of patients, and offer advice on when and how to discharge the child from hospital.

Further practical assistance is provided in five appendices, which offer an illustrated guide to the performance of practical procedures, list recommended dosages and regimens for some 57 drugs, give formulas and recipes for treating severely malnourished children, and provide tables and charts for assessing nutritional status and recovery. Advice on play therapy and the construction of simple toys is also included. The manual is part of a series of documents and tools that support the WHO Integrated Management of Childhood Illness initiative.

## 13. EFFECTIVENESS OF IMCI GUIDELINES

### Articles

Gupta R, Sachdev HP, Shah D

**Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of one week to two months.**

*Indian Pediatrics* 2000 Apr;37(4):383-90

**OBJECTIVE:** To evaluate the utility of the WHO/UNICEF algorithm for integrated management of childhood illness (IMCI) between the ages of 1 week to 2 months. **DESIGN:** Prospective observational. **SETTING:** The Outpatient Department and Emergency Room of a medical college hospital. **METHODS:** 129 infants presenting to Outpatient Department (n=70) or Emergency Room (n=59) were assessed and classified as per 'IMCI' algorithm and treatment required was identified. A detailed evaluation with all relevant investigations was also done for these subjects. The final diagnoses made and therapies instituted on this basis served as 'gold standard'. The diagnostic and therapeutic agreement between 'gold standard' and the 'IMCI' was computed. **RESULTS:** More than one illness was present in 97(75.2%) of subjects as per 'gold standard' (mean 2.1). Subjects having any referral criteria as per 'IMCI' algorithm had a greater ( $p=0.002$ ) co-existence of illnesses (mean 2.3 vs. 1.8 illnesses per child, respectively). IMCI algorithm covered majority (81-84%) of the recorded diagnoses either partly (40-41%) or fully (40-44%). The referral criteria proved quite sensitive (86-87%) in predicting hospitalisation but had a lower specificity (53-58%). A total agreement with IMCI was found in 60-66% cases. The mismatch (34-40%) was more commonly of overdiagnosis (21-23%) rather than underdiagnosis (15-21%). The sensitivity of the algorithm to identify serious bacterial infection was high (96.1-96.5%) while the specificity was relatively low (51.8-59.7%). Upper respiratory infection (URI) emerged as an important cause resulting in unnecessary referrals (13 out of 21 cases). Of the 43 cases identified as diarrhoea by the algorithm, 6 had breast fed stools, which do not require any therapy. The 'IMCI' algorithm had a provision for preventive services of immunisation and breastfeeding counselling (18% possibility of availing missed opportunities in both). **CONCLUSION:** There is a sound scientific basis for adopting IMCI approach even in young infants as there is a need to improve the specificity of referral criteria. Two important conditions identified for possible refinement are URI and breast fed stools

Lambrechts T, Bryce J, Orinda V

**Integrated management of childhood illness: a summary of first experiences.**

*Bulletin of the World Health Organization* 1999;77(7):582-94

The strategy of Integrated Management of Childhood Illness (IMCI) aims to reduce child mortality and morbidity in developing countries by combining improved management of common childhood illnesses with proper nutrition and immunisation. The strategy includes interventions to improve the skills of health workers, the health system, and family and community practices. This article describes the experience of the first countries to adopt and implement the IMCI interventions, the clinical guidelines dealing with the major causes of morbidity and mortality in children, and the training package on these guidelines for health workers in first-level health facilities. The most relevant lessons learned and how these lessons have served as a basis for developing a broader IMCI strategy are described

Kolstad PR, Burnham G, Kalter HD, Kenya-Mugisha N, Black RE

**Potential implications of the integrated management of childhood illness (IMCI) for hospital referral and pharmaceutical usage in western Uganda.**

*Tropical Medicine and International Health* 1998 Sep;3(9):691-9

The integrated management of childhood illness approach (IMCI) is currently being implemented by a number of countries worldwide. This is the second report from a study in western Uganda comparing the assessment and classification of disease by medical assistants using the IMCI algorithm with that of

hospital-based general medical officers, who used their clinical judgement to assess and provide treatment. Treatment prescribed by the hospital medical officers was compared to that indicated by IMCI disease classifications. The study population comprised 1226 children aged 2-59 months. Medical assistants had some difficulty in completing the IMCI assessment, leading to incorrect classification of findings in 138 of 1086 completed forms (13%). If their classifications had been used to decide on hospital referral, 37 children who met IMCI criteria for referral would have been sent home. Consultations took on average 7.2 min, longer than usual for several African countries. Use of the IMCI guidelines would have referred 16.2% of children to hospital, compared with 22% referred by the medical officers. Use of IMCI could have reduced the cost of medication to US\$0.17 per child compared to the treatment cost of US\$0.82 as prescribed by medical officers. Medical officers prescribed both a greater number and a greater variety of drugs than indicated by the IMCI algorithm. Compared to the present management of sick children by medical officers at Kabarole district hospital, using the IMCI algorithm would bring major changes in pharmaceutical use and referral practices. However, there is concern about the difficulty medical assistants had in using it, and the potential for longer consultation times.

No authors listed

**Health worker performance after training in integrated management of childhood illness—Western Province, Kenya, 1996-1997.**

*Morbidity and Mortality Weekly Report* 1998 Nov 27;47(46):998-1001

Each year, approximately 12 million children die in developing countries before age 5 years; 70% of these deaths are caused by respiratory infections, diarrhoea, malaria, measles, and malnutrition, alone or in combination. In 1994, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) developed the Integrated Management of Childhood Illness (IMCI) guidelines, which call for non-physician health workers (HWs) to evaluate every sick child presenting to a first-level health facility (HF) for each of these conditions, regardless of the child's presenting complaint(s). Even though IMCI is being incorporated into the national health-care programs of many developing countries, little is known about HW performance after IMCI training. To measure the level of performance achieved and maintained by IMCI-trained HWs, during 1996-1997 CDC, the Kenya-Finland Primary Health Care Program, and the Ministry of Health of Kenya prospectively evaluated the level of performance achieved by IMCI-trained HWs at the end of training (EOT) and the level of performance maintained during the first 3 months post-training (1-3MPT) with monthly or bimonthly clinical supervision. This report summarizes the results of this evaluation, which indicate that HWs achieved reasonably high performance levels managing ill children with mild and moderate disease classifications but performed at a much lower level when managing severely ill children at EOT.

Oluwole D

**Management of childhood illness in Africa.**

*British Medical Journal*, 2000, 320(4):594-5

The editorial gives an overview of the integrated management of childhood illness (IMCI) strategy and discusses its benefits, future needs and problems in the African context. IMCI has now been introduced into 28 countries in Africa. It has been operating for about 3 years, and most evaluations show positive results. The benefits appear to include more rational drug use, increased attendance at health clinics, improved health care providers morale, and improved perception of quality of care by mothers. A positive effect of the training of health workers on outcomes such as child mortality is more difficult to demonstrate. Up to 80% of childhood deaths in Africa occur at home. Tackling this problem needs development of the community component of IMCI strategy – promotion of preventive activities and prompt seeking of help by caretakers. IMCI should not be seen as a magic solution for unacceptable burden of childhood illness in Africa, but proper implementation should contribute to a steady reduction in childhood mortality.

Publication type: Editorial

Perkins BA, Zucker JR, Otieno J, Jafari HS, Paxton L, Redd SC, Nahlen BL, Schwartz B, Oloo AJ, Olango C, Gove S, Campbell CC

**Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):33-42.

In 1993, the World Health Organization completed the development of a draft algorithm for the integrated management of childhood illness (IMCI), which deals with acute respiratory infections, diarrhoea, malaria, measles, ear infections, malnutrition, and immunisation status. The present study compares the performance of a minimally trained health worker to make a correct diagnosis using the draft IMCI algorithm with that of a fully trained paediatrician who had laboratory and radiological support. During the 14-month study period, 1795 children aged between 2 months and 5 years were enrolled from the outpatient paediatric clinic of Siaya District Hospital in western Kenya; 48% were female and the median age was 13 months. Fever, cough and diarrhoea were the most common chief complaints presented by 907 (51%), 395 (22%), and 199 (11%) of the children, respectively; 86% of the chief complaints were directly addressed by the IMCI algorithm. A total of 1210 children (67%) had *Plasmodium falciparum* infection and 1432 (80%) met the WHO definition for anaemia (haemoglobin < 11 g/dl). The sensitivities and specificities for classification of illness by the health worker using the IMCI algorithm compared to diagnosis by the physician were: pneumonia (97% sensitivity, 49% specificity); dehydration in children with diarrhoea (51%, 98%); malaria (100%, 0%); ear problem (98%, 2%); nutritional status (96%, 66%); and need for referral (42%, 94%). Detection of fever by laying a hand on the forehead was both sensitive and specific (91%, 77%). There was substantial clinical overlap between pneumonia and malaria (n = 895), and between malaria and malnutrition (n = 811). Based on the initial analysis of these data, some changes were made in the IMCI algorithm. This study provides important technical validation of the IMCI algorithm, but the performance of health workers should be monitored during the early part of their IMCI training.

Shah D, Sachdev HP

**Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the age of two months to five years.**

*Indian Pediatrics* 1999 Aug;36(8):767-77

**OBJECTIVE:** To evaluate the utility of the “WHO/UNICEF algorithm for integrated management of childhood illness (IMCI) between the age of 2 months to 5 years. **DESIGN:** Prospective observational. **SETTING:** The Outpatient Department and Emergency Room of a medical college hospital. **METHODS:** 203 children presenting to Outpatient Department (n=101) or Emergency Room (n=102) were assessed and classified as per ‘IMCI’ algorithm and treatment required was identified. A detailed evaluation with all relevant investigations was also done for these subjects. The final diagnoses made and therapies instituted on this basis served as ‘gold standard’. The diagnostic and therapeutic agreements between the ‘gold standard’ and the IMCI and vertical (on the basis of primary presenting complaint) algorithms were computed. **RESULTS:** More than one illness was present in 135 (66.5%) of subjects as per ‘gold standard’. The mean (SD) numbers of morbidities as per the gold standard and IMCI- low and high malaria risks were 2.1 (1.1), 1.8 (1.0) and 2.2 (1.1), respectively. Subjects having any referral criteria as per IMCI module had a greater co-existence of illnesses (mean 2.6 vs. 1.6 illnesses per child, respectively). The referral criteria proved useful in predicting hospitalisation and a combination of hospitalisation and observation; their sensitivity and specificity were 81% and 69% and 74% and 85%, respectively. IMCI algorithms covered majority (92%) of the recorded illnesses. A total agreement with IMCI (malaria low risk) was found in 129 (64%) cases while in 43 (22%) cases, there was partial agreement. Corresponding figures for vertical (split IMCI) program were 93 (46%; p<0.001) and 41 (25%). The difference was primarily due to underdiagnoses (30%). Diagnostic discordance of IMCI algorithm and gold standard was evident for the cough category due to underdiagnosis of bronchial asthma and bronchiolitis and an overdiagnosis of pneumonia whereas the discordance for fever was due to an overdiagnosis of malaria. Identical results were found for broad treatment categories. The IMCI algorithm had a provision for preventive services of immunisation (16.3% possibility of availing missed opportunities) and feeding advice.

**CONCLUSIONS:** There is a sound scientific basis for adopting the IMCI approach since: (i) co-existence of morbidities is frequent; (ii) severe illness is assessed with good sensitivity and specificity; and (iii) the

IMCI algorithm is diagnostically and therapeutically superior to the vertical disease specific algorithms. The generic IMCI algorithm needs adaptation to reflect the regional morbidity profile. Comment in: *Indian Pediatr* 1999 Aug;36(8):759-62; *Indian Pediatr* 1999 Nov;36(11):1177-8; discussion 1179-80; *Indian Pediatr* 1999 Nov;36(11):1178-80

Simoes EA, Desta T, Tessema T, Gerbresellassie T, Dagnaw M, Gove S

**Performance of health workers after training in integrated management of childhood illness in Gondar, Ethiopia.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):43-53.

The performance of six primary health workers was evaluated after following a 9-day training course on integrated management of childhood illness (IMCI). The participants were selected from three primary health centres in the Gondar District, Ethiopia, and the course was focused on assessment, classification, and treatment of sick children (aged 2 months to 5 years) and on counselling of their mothers. Immediately following this training, a 3-week study was conducted in the primary health centres to determine how well these workers performed in assessing, classifying and treating the children and in counselling the mothers. A total of 449 sick children who presented at the three primary health centres during the study period were evaluated. Most of the complaints (87%) volunteered by the mothers (fever, cough, diarrhoea, and ear problems) were covered by the IMCI charts. The assessment of commonly seen signs (tachypnoea or ear pain) or easily identifiable signs (slow return after skin pinch, wasting, or pedal oedema) was good, with sensitivities of 67-91%, whereas the assessment of uncommonly seen signs (dry mouth, corneal clouding) or less easily quantifiable signs (eyelid pallor, absence of tears) had a fair or poor sensitivity of 20-45%. The classification of pneumonia, diarrhoea with signs of dehydration, and malnutrition showed sensitivities of 88%, 76%, and 85% and specificities of 87%, 98%, and 96%, respectively. However, the classification of febrile illnesses had a sensitivity of only 39% due to problems in using the draft algorithm in areas with a mixture of high, low, and no malaria risk, and due to confusion between axillary and rectal temperature thresholds. Of 39 children classified as having severe disease, 9 were misclassified, mostly by one nurse. Treatment of patients improved over the three weeks of observation, their completeness increasing from 69% to 88%. Health workers usually communicated appropriate advice to the mother. They learned to use checking questions but failed to adequately solve problems in the majority of cases. The mother's counselling card, which summarized recommendations on feeding and home fluids, and advice on when to return, was widely used to aid communication. The time taken to perform the complete management of children did not change significantly (20 to 19 minutes) during the study. Lessons from our findings have been incorporated into an improved version of the IMCI charts.

Publication Types: Multicenter study

Weber MW, Mulholland EK, Jaffar S, Troedsson H, Gove S, Greenwood BM

**Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia.**

*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):25-32.

Most of the 12.4 million deaths occurring every year among under-5-year-olds in developing countries could be prevented by the application of simple treatment strategies. So that health professionals who have had limited training can identify and classify the common childhood diseases, WHO developed a treatment algorithm (the Integrated Management of Childhood Illness (IMCI) or Sick Child algorithm), a prototype of which was tested in 440 Gambian children aged between 2 months and 5 years. The children were first assessed by a trained field worker using the algorithm, and then by a paediatrician whose clinical diagnosis was supported by laboratory investigations and, when indicated, a chest X-ray. Compared with the paediatrician's diagnosis, the sensitivity and specificity of the draft IMCI algorithm were, respectively, 81% and 89% for the detection of pneumonia, 67% and 96% for dehydration, 87% and 8% for malaria parasitaemia (any level), 100% and 9% for malaria parasitaemia (above 5000 parasites/microliter), 100% and 99% for measles, 31% and 97% for otitis media, and 89% and 90% for malnutrition. Among the children admitted by the physician, 45% had been recommended for admission by the algorithm. Intermittent fever, chills and sweats did not help in discriminating between malaria and non-malarious fevers; shivering or shaking of the body had a sensitivity of only 35%. While the algorithm dealt with the majority of presenting complaints, the most common problems not addressed by the chart were skin rashes

(21%), mouth problems (8%), and eye problems (6%). The draft IMCI algorithm proved to be effective in the diagnosis of pneumonia, gastroenteritis, measles and malnutrition, but not malaria where its use without microscopy would result in considerable over-treatment, especially in a low transmission area or during a low transmission season in countries with seasonal malaria. The current algorithm would benefit from expansion to cover management of localized infections as well as skin, mouth and eye problems.

World Health Organization, Department of Child and Adolescent Health and Development  
***Multi-country evaluation of IMCI – Effectiveness, Cost and Impact. Report of the Meeting of Principal Investigators and Technical Advisers.*** Cuzco, Peru, 4-8 December 2000.  
Geneva, World Health Organization, 2001, 65 p. (unpublished document WHO/FCH/CAH01.07 available on request from the Division of Child and Adolescent Health and Development)

The multi-country evaluation of IMCI effectiveness, cost and impact (MCE) is a set of studies, using complementary designs, that will assess the behavioural, nutritional and mortality impact of IMCI. The objectives are both, to document the effect of IMCI interventions on health worker performance, health systems and family behaviours, and to measure the impact of the IMCI strategy as a whole on health outcomes. In addition, the evaluation describes the costs of IMCI implementation.

World Health Organization Division of Child Health and Development , WHO Regional Office for Africa  
**Integrated management of childhood illness: field test of the WHO/UNICEF training course in Arusha, United Republic of Tanzania.**  
*Bulletin of the World Health Organization*, 1997, 75 (Supplement 1):55-64.

The 11-day training course on Integrated management of childhood illness was field tested with three types of first-level facility health workers: medical assistants, rural medical aides, and MCH (maternal and child health) aides. The objective of the field test was to determine whether the materials were effective in preparing participants to manage correctly sick children and to suggest improvements in the course materials and teaching procedures. The course combined classroom work and daily inpatient and outpatient clinical sessions. Each participant individually examined 9-10 inpatients and managed more than 30 sick children as outpatients. Individual feedback from facilitators during clinical practice and module work, combined with data collection documenting the adequacy of the assessment, classification, treatment and counselling carried out by the participants, allowed an assessment of the participants' mastery of key clinical skills. Although some participants had difficulty in reading the modules in English, all three groups overall were able to assess, classify, and treat most sick children by the end of the course, and most of them were able to provide adequate counselling. Specific improvements were suggested and subsequently incorporated into the guidelines and training materials.

World Health Organization Division of Child Health and Development  
**Integrated management of childhood illness: conclusions.**  
*Bulletin of the World Health Organization*, 1997, 75(Supplement 1):119-128.

The 11-day training course on Integrated management of childhood illness was field tested with three types of first-level facility health workers: medical assistants, rural medical aides, and MCH (maternal and child health) aides. The objective of the field test was to determine whether the materials were effective in preparing participants, to manage correctly sick children and to suggest improvements in the course materials and teaching procedures. The course combined classroom work and daily inpatient and outpatient clinical sessions. Each participant individually examined 9-10 inpatients and managed more than 30 sick children as outpatients. Individual feedback from facilitators during clinical practice and module work, combined with data collection documenting the adequacy of the assessment, classification, treatment and counselling carried out by the participants, allowed an assessment of the participants' mastery of key clinical skills. Although some participants had difficulty in reading the modules in English, all three groups overall were able to assess, classify, and treat most sick children by the end of the course, and most of them were able to provide adequate counselling. Specific improvements were suggested and subsequently incorporated into the guidelines and training materials.







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