Integrated Management of Childhood Illness (IMCI)

WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children

World Health Organization

Departments of Child and Adolescent Health and Development (CAH) and HIV/AIDS

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Abbreviations and definitions

ART	antiretroviral therapy
CDC	Centers for Disease Control and Prevention (USA)
Diarrhoea	the passage of loose or liquid stools more frequently than is normal for the individual
Persistent diarrhoea	diarrhoea for 14 days or more
Chronic diarrhoea	diarrhoea for 28 days or more
Bloody diarrhoea	presence of blood in the stools; also called dysentery
Infant	under 12 months of age
Generalized HIV epidemic	setting in which more than 1% of the population is HIV-positive
GRADE	grading of recommendations assessment, development and evaluation
HIV	human immunodeficiency virus
HIV-exposed	born to a mother who is HIV-infected
HIV-infected	proven to have HIV infection by tests appropriate to age
ORS	oral rehydration solution
PCP	*Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia
Pneumonia	
Danger signs	severe signs, including lethargy or unconsciousness, inability to drink or breastfeed, persistent vomiting, central cyanosis, severe respiratory distress, or convulsions in a child aged 2 months to 5 years
Non-severe	cough or difficult breathing and fast breathing in a child aged 2 months–5 years with no general danger signs
Severe	cough or difficult breathing plus lower chest indrawing with no general danger signs
Very severe	cough or difficult breathing in a child aged 2 months–5 years, chest indrawing and presence of danger signs Note that in the integrated management of childhood illness, both severe and very severe pneumonia are classified as severe pneumonia or very severe disease.
UNAIDS	joint United Nations programme on HIV/AIDS
WHO	World Health Organization

Executive summary

The main causes of death among children under 5 years of age are acute respiratory infection (17%) and diarrhoeal disease (16%), and children infected with human immunodeficiency virus (HIV) have greater morbidity and mortality related to these conditions (WHO, 2008). An estimated 2.1 million children in the world are living with HIV, 90% of whom live in sub-Saharan Africa. The incidence of infection remains high, with 430 000 new HIV infections in children annually. Almost one third of untreated infected infants will die in the first year of life, and up to 50% by 2 years of age.

Although tremendous progress has been made in identifying and treating infants and children with HIV infection, much remains to be done to scale-up and sustain effective prevention, care and treatment, especially of diarrhoea and pneumonia. Currently, only an estimated 15% of exposed infants are tested for HIV in the first 2 months of life, and coverage with paediatric antiretroviral therapy (ART) is 38% (WHO 2009). Coverage of HIV-infected and -exposed infants and children with co-trimoxazole prophylaxis, another highly effective, inexpensive, life-saving intervention, has remained unacceptably low, at about 8%. Interventions that delay morbidity and mortality from diarrhoea and pneumonia can make a significant contribution to the long-term survival of HIV-infected and -exposed infants and children.

The World Health Organization (WHO) departments of Child and Adolescent Health and of HIV/AIDS reviewed the evidence on management of diarrhoea and pneumonia in HIV-infected children, because of the substantial effects of these conditions on morbidity and mortality, potential differences in etiological agents (and thus in recommended empirical regimens) from those for uninfected infants and children, potential changes in the susceptibility of pathogens to co-trimoxazole prophylaxis in these children, and the lack of specific recommendations for this high-risk group. These guidelines are part of a comprehensive set of normative documents being prepared by WHO for the prevention and treatment of common conditions affecting HIV-infected and -exposed infants and children.

A group assessed the evidence on the basis of 'grading of recommendations assessment, development and evaluation' (GRADE), and, during a consultation in October 2009, updated their recommendations for preventing and managing diarrhoea and pneumonia in HIV-infected and -exposed infants and children. The objectives were to summarize WHO recommendations for policy and practice, prepare GRADE 'evidence profiles' and discuss the factors taken into account in deciding on the strength of recommendations. The group also identified gaps in knowledge and set priorities for further research.

Recommendations

The group's recommendations for managing pneumonia and diarrhoea in HIV-infected infants and children are, in most cases, the same as those for management in uninfected children. Most studies providing evidence for recommendations were, however, conducted before widespread use of co-trimoxazole or ART.

The panel found insufficient evidence to justify separate recommendations for infants and children who have been exposed to HIV and for those suspected of or confirmed to have HIV infection. Previous recommendations on co-trimoxazole prophylaxis (WHO, 2006), provider-initiated testing and counselling (WHO, 2007) and safe water and hygiene (WHO, 2008) were incorporated into the guidelines in order to make them comprehensive. In accordance with the existing WHO recommendations on provider-initiated testing and counselling, the panel strongly recommended that all infants and children living in generalized epidemic settings and presenting with pneumonia or diarrhoea should have their HIV status determined.

Diarrhoea

Prevention of diarrhoea

Recommendation 1: Vitamin A supplementation is recommended for all HIV-infected and -exposed infants and children aged 6 months to 5 years, in doses given every 6 months (100 000 IU for those aged 6–12 months and 200 000 IU for those aged > 12 months).

Strong recommendation; low quality of evidence

Treatment of diarrhoea

Recommendation 2: Low-osmolarity oral rehydration solution (ORS) is recommended for the treatment of dehydration, or intravenous electrolyte solution in cases of severe dehydration, in HIV-infected and -exposed infants and children with diarrhoea.

Strong recommendation; high quality of evidence

Recommendation 3: Elemental zinc supplementation for 10–14 days is recommended, with increased fluids and continued feeding, for all HIV-infected and -exposed children with diarrhoea, at 10 mg/day for infants < 6 months of age and 20 mg/day for infants and children > 6 months.

Strong recommendation; high quality of evidence

Recommendation 4: Ciprofloxacin for 3 days at an oral dose of 15 mg/kg is recommended for treating bloody diarrhoea in all HIV-infected and -exposed infants and children.

Strong recommendation; moderate quality of evidence

Recommendation 5: Daily multiple micronutrients for 2 weeks are recommended for all HIV-infected and -exposed infants and children with persistent diarrhoea.

Conditional recommendation; low quality of evidence

Pneumonia

Co-trimoxazole treatment for suspected Pneumocystis jirovecii ***pneumonia***

Recommendation 6: Empiric co-trimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with severe or very severe pneumonia.

Strong recommendation; moderate quality of evidence

Recommendation 7: Empirical co-trimoxazole treatment for PCP is not recommended for HIV-infected and -exposed children over 1 year of age with severe or very severe pneumonia.

Conditional recommendation; moderate quality of evidence

Antibiotic regimens for severe and very severe pneumonia

Recommendation 8:

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as first-line antibiotic treatment for HIV-infected and -exposed infants and children under 5 years of age with severe or very severe pneumonia.

Conditional recommendation; low quality of evidence

Recommendation 9: For HIV-infected and -exposed infants and children with severe or very severe pneumonia who fail treatment while on ampicillin or penicillin plus gentamicin, ceftriaxone alone should be used as second-line treatment.

Conditional recommendation; low quality of evidence

1. Introduction

Diarrhoea and pneumonia are the main causes of morbidity and mortality in infants and children and particularly those infected with HIV. The joint United Nations programme on HIV/AIDS (UNAIDS) has estimated that the number of children < 15 years of age in the world living with HIV increased from 1.6 million in 2001 to 2.1 million in 2008. The deaths of 430 000 children were attributed to AIDS in 2008, and 430 000 children were newly infected with HIV in the same year (UNAIDS/WHO, 2009). Most of the infections (90%) were acquired by vertical transmission from mother to child (UNICEF/WHO, 2009).

Children born to HIV-infected mothers have greater mortality and morbidity than children not exposed to HIV (Marinda et al., 2007; Shapiro et al., 2007; Sutcliffe et al., 2008; Filteau, 2009). Infants who acquire HIV around delivery show rapid progression of disease during the first few months of life and often die. Cohort studies conducted before the introduction of preventive and treatment strategies showed that the survival of HIV-infected infants was poor: nearly 30% died in infancy, and up to 50% died in the first 2 years of life (Taha et al., 1999; Chilongozi et al., 2008; Newell et al., 2004). The peak prevalence of death among HIV-infected African children has been reported to be at 2–3 months of age (Bourne, 2009). Over 200 000 children globally are now on ART, but treatment of infants and young children has been less successful than for older children and even less successful than the estimated 43% coverage of adults (WHO, 2009).

Interventions to delay morbidity and mortality from diarrhoea and pneumonia can make a huge contribution to the long-term survival of HIV-infected and -exposed infants and children. Although the existing interventions (e.g. safe water, ORS and appropriate case management) have been responsible for reducing the rates of mortality of children under 5 worldwide, the coverage of children remains low, particularly in resource-poor settings. Management is often further complicated in HIV-infected and -exposed children by immunodeficiency, malnutrition, other infections, manifestations of primary HIV disease and side-effects of ART.

Given the significant effects of diarrhoea and pneumonia on child morbidity and mortality and the particular susceptibility of those infected with or exposed to HIV, these areas of care management were considered priorities for review. This document summarizes the background, methods, analysis of evidence on diarrhoea and pneumonia management and recommendations of a panel of experts that was convened in October 2009 at WHO headquarters in Geneva, Switzerland. The guidelines are the first in a series planned to address all the main causes of mortality in children under 5. The expert panel will probably consist of many of the same people in order to save costs.

2. Objectives

This document summarizes current knowledge on preventing and treating diarrhoea and managing pneumonia in HIV-infected and -exposed infants and children.

3. Methods

3.1 Target audience

This publication is intended primarily for use by national advisory boards, national HIV/AIDS and child health programme managers and senior policy-makers involved in planning national strategies for child survival and paediatric prevention and care for HIV infection in resource-limited settings. Health-care providers and professional bodies could use these recommendations in advising national programmes and preparing guidelines for treatment and care.

The population of interest is HIV-infected and -exposed infants and children aged 0–18 years, with a particular emphasis on those < 5 years of age. An infant is a child < 12 months old.

3.2 Preparatory work

An internal WHO steering group determined the scope of this document on the basis of the burden of pneumonia and diarrhoeal disease in HIV-infected and -uninfected infants and children, severity, effect on child survival and applicability of the recommendations in first- and second-level health facilities in resource-poor settings. The group first summarized existing WHO recommendations on prevention, diagnosis and treatment of diarrhoea and pneumonia in all children. The summary showed that the available guidelines do not answer all questions about HIV-infected and -exposed children, and the group therefore undertook systematic reviews of studies on the prevention of diarrhoea and the etiological agents and treatment of diarrhoea and pneumonia in these children. Comparisons with uninfected children were made to identify any changes needed to the current recommendations. A guideline development group identified the relevant populations, interventions, comparisons and outcomes and prepared GRADE 'evidence profiles' and risk–benefit tables to guide recommendations. A guideline review group considered new draft recommendations based on the existing WHO guidelines.

Protocols were designed for the systematic reviews. The final protocol included the search strategy, the list of interventions and outcomes, the comparison group and exclusion and inclusion criteria. The HIV/AIDS Cochrane Collaborative Review Group search strategy (http://www.cochrane.org/cochrane-reviews/review-structure) was used for each question on population, intervention, comparison and outcome. The search strategies used in the systematic reviews, meta-analyses and GRADE profiles were those defined in *The Cochrane handbook for systematic reviews of interventions* (version 5.0.2; last updated September 2009; http://www.cochrane-handbook.org/). The search revealed relevant published and unpublished articles, manuscripts, abstracts and presentations. Furthermore, research centres for paediatric HIV and database centres were contacted for publications or the results of ongoing research. Electronic databases and conference proceedings were searched, without limits on language; the proceedings included those of the conferences on retroviruses and opportunistic infections, the international AIDS conferences and the International AIDS Society clinical meetings held every other year, which were searched from their inception dates (1993, 1985 and 2001, respectively). To identify ongoing trials, the ClinicalTrials.gov website (http://www.clinicaltrials.gov/), Current Controlled Trials (www.controlled-trials.com) and the Pan-African Clinical Trials Registry (www.pactr.org) were also searched. The reference lists of published articles were examine for additional pertinent material. As the number of studies was anticipated to be limited, observational studies that met the inclusion criteria were included, in addition to randomized controlled trials. Systematic reviews and meta-analyses of interventions of interest were reviewed in detail. The searches were limited to studies published since 1994.

After initial screening of the references, two reviewers independently double-coded and entered information onto standardized data extraction forms. The information included study details (e.g. design and location), participant details (e.g. inclusion and exclusion criteria, population size, attrition rate, HIV diagnosis and disease and any clinical, immunological or virological staging or laboratory information), details of interventions and outcomes (e.g. mortality, clinical disease progression, treatment response, hospitalization and adverse events).

The quality of the evidence for various treatment was assessed by the GRADE method used by WHO, and the end-points included mortality, hospitalization and adverse events. In the GRADE method, the quality of the evidence is evaluated on the basis of established criteria for the design, limitations, consistency and directness of studies; other considerations are precision, reporting bias, effect size, dose–response relations and confounding factors. GRADE tables are prepared with the Profiler software. The evidence is graded as high, moderate, low or very low, as defined in the handbook of the Guidelines Review Committee (Table 1). The review of studies of etiological agents was descriptive and was not assessed with the GRADE system.

Table 1. Grading of recommendations and levels of evidence

Strength of recommendation	GRADE evidence profile
Strong: The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. **Weak or conditional:** The panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects; **however,** it is applicable only to a specific group, population or setting, or new evidence may change the balance of risk to benefit, or the benefits may not warrant the cost or resource requirements. The panel used the terms 'weak' and 'conditional' interchangeably. **Research:** Further research is required before any recommendations can be made.	**High:** Further research is unlikely to change our confidence in the estimate of effect. **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low:** Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low:** Any estimate of effect is uncertain.

3.3 Guideline review panel

The review group comprised members of the expert group that prepared recommendations for integrated management of childhood illness in 2004, health researchers, implementation partners, programme managers, and an independent methodologist, in accordance with the WHO procedures for guideline development. The group assessed the scientific evidence, GRADE and risk–benefit profiles and draft recommendations at a consultation in Geneva in October 2009, and their conclusions provided the basis for the present recommendations. Potential declarations of interest were documented and assessed before the recommendations were drawn up; no conflicts of interest were identified.

All experts contributing to and attending the meeting of the panel of experts also completed declarations of interest. The declarations were reviewed initially by the WHO secretariat, and then experts were requested to declare any conflict of interest publicly during the meeting. None of the members declared any conflict of interest.

The WHO department of Child and Adolescent Health coordinated the revisions to the guidelines with funding from the WHO Core Voluntary Contribution, the United States Agency for International Development and the United States Centers for Disease Control and Prevention (CDC).

3.4 Process

In the GRADE approach, recommendations were made on the basis of considerations of costs, values, preference, feasibility and the balance of desirable and undesirable effects (risk–benefit assessment) and assessment of the quality of the scientific evidence. The criteria used to assess the quality of the evidence and the terms used to rank it are based on definitions in the *WHO handbook for guideline development* (WHO, 2010). When no or minimal evidence was available, the recommendations were based on the group's opinions on what constitutes best practice. The wording and strength of the recommendations were all agreed by consensus; they were further graded as 'strong' or 'conditional'. When recommendations could not be made, the group indicated areas for research.

Subgroups reviewed the evidence profile for each of the recommendations, and the existing and draft recommendations were assessed in plenary. The groups used risk–benefit assessment tables to analyse outcomes (such as mortality, morbidity and serious adverse events), implementation in different settings, acceptability, cost, feasibility, values, preferences, gaps and research needs (see Annex 4). The consultation subsequently reviewed and approved all the recommendations and annexes. The draft guidelines were reviewed between 1 November 2009 and 29 February 2010, and the original group reviewed the suggested modifications and clarifications.

The guidelines are scheduled to be updated in 2012, with reviews ad interim or when new evidence becomes available. The guidelines on vitamin A supplementation for infants and young children are being updated by WHO, including an evaluation of the evidence for this intervention in HIV-positive children. These are expected to be published in the last trimester of 2010.

Recommendations

Prevention of diarrhoea

Vitamin A supplementation (recommendation 1)

Treatment of diarrhoea

- Use of low-osmolarity ORS (recommendation 2)
- Zinc supplementation (recommendation 3)
- Use of ciprofloxacin for treating bloody diarrhoea (recommendation 4)
- Use of daily multiple micronutrients for treating persistent diarrhoea (recommendation 5)

Treatment and management of pneumonia

- Empirical co-trimoxazole treatment for suspected PCP (recommendations 6 and 7)
- First-line treatment for severe or very severe pneumonia (recommendation 8)
- Second-line treatment for severe or very severe pneumonia (recommendation 9)

4.1 Diarrhoea

4.1.1 Burden of disease

Diarrhoea is a major cause of morbidity and mortality among infants and children worldwide. In developing countries, diarrhoeal disease accounts for an estimated 17.5–21% of all deaths in children under the age 5 years, equivalent to 1.5 million deaths per year (Boschi-Pinto et al., 2008). Of all child deaths from diarrhoea, 78% occur in the African and South-East Asian regions, which are also disproportionately burdened with infant and childhood HIV infections (UNAIDS, 2007; Boschi-Pinto et al., 2008). Diarrhoeal disease occurs more commonly in HIV-infected than in uninfected children, and their outcomes are worse (Thea et al., 1993; Amadi et al., 2001; Chokephaibulkit et al., 2001). Administration of ART and restoring immune function are critical for the prevention and treatment of diarrhoea in children with HIV infection.

Research on childhood diarrhoea is a priority of WHO for achieving the United Nations' Millennium Development Goal of reducing childhood mortality by two thirds between 1990 and 2015 (UNICEF/WHO, 2008). While diarrhoeal control strategies developed in the 1980s reduced the number of child deaths from diarrhoea, coverage with these effective interventions is low. Data from 29 countries in 2005 indicated that ORS was being used for only 30–40% of children with diarrhoea (Forsberg et al., 2007; Ram et al., 2008).

Children with HIV infection have higher incidence and mortality rates than uninfected children receiving the same treatment for diarrhoea (Thea et al., 1993; Chhagan, Kauchali, 2006). Persistent diarrhoea in particular is associated with a high risk for death in HIV-infected children. Case management of HIV-infected infants and children is complicated by immunodeficiency, malnutrition, other infections that increase susceptibility, gastrointestinal manifestations of primary HIV disease and gastrointestinal symptoms associated with antiretroviral drugs for those being treated (Ramos-Soriano et al., 1996; Guarino et al., 2004; Thom, Forrest, 2006).

4.1.2 Current guidelines

WHO and UNICEF updated the guidelines for managing diarrhoeal disease in all children in 2004 (WHO/UNICEF, 2004), and WHO updated the guidelines for integrated management of childhood illness in 2005 (WHO, 2005). The current recommendations for assessing and treating diarrhoea involve evaluating dehydration, appropriate fluid replacement, continued feeding or increased breastfeeding, zinc supplementation, antibiotic regimens when indicated and appropriate referral and follow-up (see Annex 1).

The guidelines panel reviewed the evidence on the outcomes of diarrhoea prevention and treatment among HIV-infected and -exposed infants and children in order to update the recommendations and thus improve health outcomes.

4.1.3 Etiological agents

The severity of acute diarrhoeal episodes can range from mild to moderate to severe cases that can lead to hospitalization or death. Severity is influenced by many factors, including the agent (Table 2) and its pathogenicity and host characteristics, such as immunodeficiency and age. Little information is available on the etiology of diarrhoea in HIV-infected or -exposed children, partially because of issues of feasibility and the costs associated with integrating HIV programmes into etiological studies. In general, studies on diarrhoea are limited by a lack of control specimens and testing of a reduced spectrum of enteric pathogens due to cost and lack of the necessary training, advanced laboratory skills, commodities and equipment. As a result, some of the studies of HIV-infected children were conducted in areas with a known high HIV prevalence or among HIV-infected children tested for a limited spectrum of enteric pathogens.

Table 2. Common etiological agents of persistent and bloody diarrhoea

Persistent diarrhoea	Bloody diarrhoea
Enteropathogenic Escherichia coli	Shigella
Enteroaggregative E. coli	Nontyphoidal Salmonella
Nontyphoidal Salmonella	Campylobacter
Cryptosporidium	Enteroaggregative E. coli
Microsporidia	Enteroinvasive E. coli
Giardia lamblia	Shiga toxin-producing E. coli
Ascaris lumbricoides	Entamoeba histolytica
Cytomegalovirus	
Other viruses	

From American Academy of Pediatrics (2009)

In a study in an area of high HIV prevalence in rural Kenya, the rate of campylobacteriosis was highest among children aged < 5 years and decreased with age, whereas the shigellosis rate was lowest in children and increased with age. In this clinic-based study, *Campylobacter* species and diarrhoeagenic *Escherichia coli* were most frequently in stool specimens from children < 5 years with diarrhoea (Brooks et al., 2006). In a cohort study in Kenya among children < 2 years, diarrhoea was commoner among those who were HIV-infected, although bacterial pathogens such as *Campylobacter* and *Shigella* were recovered infrequently from their stool samples, suggesting that other pathogens (such as viruses, parasites and diarrhoeagenic *E. coli*) or other causes (such as malabsorption or metabolic enteritis) are important in this population (van Eijk et al., 2009). In Uganda, *E. coli*, *Salmonella* and *Shigella* species caused most acute diarrhoea in children with high resistance to co-trimoxazole (Musiime et al., 2009).

Non-typhoidal *Salmonella* species are one of the main causes of bacterial bloodstream infections in children in sub-Saharan Africa, and HIV infection is a risk factor (Berkley et al., 2005; Brent et al., 2006; Morpeth, Ramadhani, Crump, 2009). A review of the literature on rotavirus infection in 2009 showed that this virus was as or less frequent in HIV-infected infants with diarrhoea as in uninfected infants; however, the authors noted methodological limitations to their review (Steele et al., 2009). As these studies are subject to limitations, additional data are needed to understand the etiology of acute, bloody and persistent diarrhoea among HIV-infected and -exposed children.

Agents of persistent diarrhoea

Studies of the etiology of persistent diarrhoea provide little evidence of a unique spectrum of diarrhoeagenic agents in HIV-infected children. Common agents were not identified at higher rates in HIV-positive children in some studies (Del Aguila et al., 1997; Amadi et al., 2001), but were in others. A small longitudinal study in Zaire showed a marginally significant association between HIV infection and entero-aggregative *E. coli* infection (Pavia et al., 1992). A study in the United States showed a higher prevalence of *P. carinii* in intestinal tissue from 19 HIV-positive children than in controls (Ramos-Soriano et al., 1996). *Cryptosporidium* and cytomegalovirus were linked to a particularly severe, prolonged form of chronic diarrhoea in HIV-positive children, with some evidence of increased rates of colonization of *Cryptosporidium* in these children (Chintu et al., 1995; Guarino et al., 1997). In addition to Cryptosporidia, Microsporidia and Giardia were also reported at high prevalence in HIV-infected children in Malawi, although only the presence of Microsporidia was related to HIV infection (ten Hove et al. 2008). In this study, *Isospora belli* was not found in HIV-infected children with diarrhoea, although it was found in a concurrent study of HIV-infected adults. Other authors have also not found that *Cryptosporidium* infects HIV-positive children significantly more often than uninfected children (Onyango, Aduma, 2005). Even if HIV-infected children do not have a different spectrum of etiological agents, they are more often colonized with diarrhoeaogenic pathogens than controls (almost twice as many in the study of Al-Tawil et al., 1996) and have more frequent and more severe diarrhoeal illness (van Eijk et al., 2009).

Agents of bloody diarrhoea

Few studies have linked HIV infection to dysentery in children, and there is little evidence of a different spectrum of etiological agents in bloody diarrhoea in HIV-infected or -exposed children. *Shigella* is the predominant organism in bloody diarrhoea in developing countries, and WHO has estimated that it causes 10% of acute diarrhoea in children < 5 years (Alam, Ashraf, 2003; Brooks et al., 2003; Walker, 2005). *Campylobacter* and non-typhoidal *Salmonella* are also commonly identified agents of dysentery in the developing world (Taylor et al., 1991; Lanata, Mendoza, Black, 2002; Alam, Ashraf, 2003; Pitter, Calles, 2006).

4.1.4 Preventive interventions

A systematic review was conducted of the evidence for an effect of vitamin A supplementation, zinc supplementation and co-trimoxazole prophylaxis on the incidence and severity of diarrhoeal disease in HIV-infected and -exposed children. The steering committee selected these interventions on the basis of current recommendations and their potential effect. As noted above, most of the trials were conducted before widespread use of co-trimoxazole or ART, and their usefulness in preventing and treating diarrhoeal disease in HIV-infected and -exposed children should be elucidated in future studies.

Vitamin A supplementation

A systematic review resulted in identification of four trials of vitamin A supplementation in children with HIV infection or living in countries in Africa (Coutsoudis et al., 1995; Fawzi et al., 2000; Semba et al., 2005; Humphrey et al., 2006). The pooled summary estimate of the relative risk for mortality from all causes (random effects: DerSimonian, Laird, 1986) for HIV-infected children on vitamin A supplementation when compared with those on placebo in three trials was 0.50 (95% confidence interval, 0.31;0.79), with no evidence of heterogeneity. The effects of vitamin A rather than placebo on other outcomes were variable. In one study, vitamin A supplementation was associated with increased growth in a small subset of children with HIV infection (Villamor et al., 2002). Other trials have shown decreased morbidity from diarrhoeal disease in groups receiving vitamin A supplementation (Coutsoudis et al., 1995), a reduced risk for severe watery diarrhoea (Fawzi et al., 2000) and a nonsignificant trend of a reduced frequency of chronic diarrhoea (Semba et al., 2005). The limited findings in HIV-exposed children are less clear: one trial of neonatal supplementation showed an increased risk for mortality with supplementation in comparison with placebo (Humphrey et al., 2006), but another showed no difference (Coutsoudis et al., 1995). WHO does not currently recommend neonatal vitamin A supplementation.

The panel discussed the evidence for use of the interventions in HIV-infected children and decided there should be no change to the recommendations set forth in the booklet on integrated management of childhood illness in high-HIV settings (see below). This recommendation sets a high value on correcting

vitamin A deficiency and reducing mortality due to diarrhoea in HIV-infected children and less value on potential risks or lack of certainty about the effects of supplementation. A risk–benefit assessment and the GRADE profile for this recommendation are shown in Annex 4.

Recommendation 1: Vitamin A supplementation

Vitamin A supplementation is recommended for all HIV-infected and -exposed infants and children aged 6 months to 5 years, in doses given every 6 months (100 000 IU for infants aged 6–12 months and 200 000 IU for children > 12 months).

This recommendation is unchanged and is the same for all children.

Quality of evidence: Low

Strength of recommendation: Strong

Time to review: 2012

Zinc supplementation for prevention

A systematic review of the use of zinc supplementation for primary prevention identified only one randomized controlled trial (Bobat et al., 2005), a study prompted by an early observational report that raised concern about the association between zinc and HIV (Tang et al., 1993). The trial showed no effect of zinc on the primary outcome of plasma HIV-1 viral load in infected South African children aged 6–60 months. The authors reported fewer visits for watery diarrhoea but no significant difference in other morbidity outcomes of infectious disease (Bobat et al., 2005). A trial of combined supplements (vitamin A, vitamin A plus zinc, zinc plus vitamin A plus multiple micronutrients) showed no significant difference in diarrhoeal or respiratory outcomes in HIV-infected, -exposed and -uninfected children (Luabeya et al., 2007). In another analysis, HIV-negative children with stunting who received zinc or a combination of zinc, multiple micronutrients and vitamin A had a lower incidence of diarrhoea than those receiving vitamin A alone; however, there were too few HIV-infected children for a meaningful analysis (Chhagan et al., 2009).

The panel reviewed the evidence for use of zinc as a preventive intervention, even though universal zinc supplementation is not currently a WHO recommendation. The panel did not make a separate recommendation for HIV-infected children but considered the indirect evidence in reviewing the recommendation for zinc supplementation as treatment.

Co-trimoxazole prophylaxis

A trial in Zambia showed that mortality was lower among children on co-trimoxazole than among those given placebo, with a hazard ratio for death of 0.57 (95% confidence interval, 0.43;0.77) for those given co-trimoxazole (Chintu et al., 2004). Follow-up studies confirmed the benefits of co-trimoxazole on both morbidity and mortality, with fewer hospital deaths due to respiratory disease and a trend towards fewer hospital admissions in the treated group (Mulenga et al., 2007). Another study showed reduced morbidity from diarrhoea with co-trimoxazole, although the finding was not significant owing to the small number of children < 5 years (Mermin et al., 2004). Another observational study showed more diarrhoea among children with access to co-trimoxazole, although this finding has no clear clinical significance, given the high baseline rates of diarrhoea and small numbers (Coutsoudis et al., 2005).

The panel considered co-trimoxazole prophylaxis an important intervention for preventing mortality in HIV-infected and -exposed infants and children. This recommendation already appears in separate guidelines (WHO, 2006):

"All HIV-exposed and -infected infants and children should receive daily co-trimoxazole prophylaxis in accordance with existing WHO guidelines. Strong recommendation; high quality of evidence."

Other prevention interventions

The panel discussed other recommendations, including household water treatment methods, proper disposal of faeces and promotion of hand-washing with soap. As systematic reviews of these interventions were conducted previously, the recommendations were not reviewed at this time.

Other recommended preventive measures are given in the guidelines on Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings (WHO, 2008):

Effective methods for treating household water and storage of water in containers that do not allow manual contact are recommended for people with HIV and their households.

Proper disposal of faeces in a toilet or latrine or, at a minimum, by burial in the ground is recommended for people with HIV and their households

Promotion of hand-washing with soap after defaecation and after handling human or animal faeces and before food preparation and eating and the provision of soap are recommended for people with HIV and their households.

4.1.5 Treatment interventions

A systematic review identified evidence for treatment of diarrhoea, including zinc, antibiotics, micronutrients and ORS, in HIV-infected and -exposed children. The studies included only one clinical trial with controlled interventions in children. Several nonrandomized studies of the outcomes of standard care (uncontrolled interventions) in HIV-infected and -uninfected children indicated that diarrhoeal disease occurs more commonly with worse outcomes in HIV-infected children (Thea et al., 1993; Amadi et al., 2001; Chokephaibulkit et al., 2001). The studies of HIV-infected children did not, however, address zinc therapy, antibiotics for bloody diarrhoea or mutivitamins and micronutrients.

Oral rehydration solution

A systematic review identified evidence for use of low-osmolarity ORS from studies in adults, corroborating the existing recommendations on ORS treatment. A systematic review provided high-quality evidence that low-osmolarity ORS in comparison with the standard formula reduces the need for unscheduled intravenous fluids and decreases stool output in children (Hahn, Kim, Garner, 2002).

The panel was not concerned about using indirect evidence in the meta-analysis of low-osmolarity ORS as compared with standard formula. They recognized that the gut mucosa of children infected with HIV might be more fragile, with enteropathy, but considered that these factors would not affect the recommendation. The risk–benefit analysis and GRADE profile for this recommendation are shown in annexes 4 and 5.

Recommendation 2: Management with ORS

Low-osmolarity ORS is preferable to standard ORS for treatment of dehydration (intravenous electrolyte solution in cases of severe dehydration) in HIV-infected and -exposed infants and children with diarrhoea.

This recommendation is the same for all children.

Quality of evidence: High

Strength of recommendations: Strong

Time to review: 2012

Zinc supplementation for treatment

Zinc supplementation has been shown to reduce morbidity with diarrhoea in resource-limited settings (Brown et al., 2009), and WHO recommends its use in treating children with diarrhoea (WHO, 2009). A systematic review of studies in HIV-negative children provided evidence of moderate quality that zinc supplementation reduces the duration of acute or persistent diarrhoea (Lazzerini, Rontani, 2008). A trial of primary prevention showed no evidence of harm and no association between zinc supplementation and an increase in HIV-1 viral load (Bobat et al., 2005).

The panel noted that the studies on zinc treatment for diarrhoea in HIV-infected children are limited. They reviewed the evidence on zinc supplementation for HIV-negative children and a trial on primary prevention in HIV-infected children. The panel was not concerned about the indirectness of the evidence, in view of the biological implausibility that the physiology of zinc supplementation is different in HIV-infected and -uninfected children and in view of the lack of evidence of harm in the trial conducted by Bobat et al. (2005), in which HIV-infected children were given zinc supplementation for 6 months. The risk–benefit analysis and GRADE profiles for this recommendation are shown in annexes 4 and 5.

Recommendation 3: Treatment with zinc

Elemental zinc supplementation is recommended for 10–14 days, with increased fluids and continued feeding, for all HIV-infected and -exposed children with diarrhoea (10 mg per day for infants under 6 months of age, 20 mg per day for infants and children over 6 months).

This recommendation is the same for all children.

Quality of the evidence: High

Strength of the recommendation: Strong

Time to review: 2012

Nitazoxanide for Cryptosporidium diarrhoea

There is currently no WHO recommendation for managing *Cryptosporidium* infection, and treatment of HIV-infected children has proved particularly difficult because of low drug efficacy. The evidence that diarrhoea can be resolved better with nitazoxanide than with supportive care is of very low quality, and no significant improvements in oocyst clearance or mortality were found after 8 days in immunocompromised children and adults (Abubakar et al., 2007). Two randomized controlled trials in Zambia with HIV-infected children found that nitazoxanide did not eradicate cryptosporidial infection, nor did it reduce clinical symptoms, even with a high dose and longer treatment (Amadi et al., 2002, 2009).

After reviewing the evidence, the panel decided not to make a recommendation on nitazoxanide for the treatment of *Cryptosporidium* diarrhoea. The panel considered that HIV-related cryptosporidial diarrhoea might be dramatically reduced when ART is made widely available. Its decision also reflects uncertainty about the therapeutic benefit, the limited evidence on safety and the possibility of drug interactions in HIV-infected children. The panel noted that research is needed on treatment of crytosporidia and other protozoa. A risk–assessment table and GRADE profile are given in annexes 4 and 5.

Ciprofloxacin for bloody diarrhoea

The systematic review of treatment interventions did not identify any studies of antibiotic regimens for bloody diarrhoea in children with HIV infection or exposure. There is moderate indirect evidence that ciprofloxacin is more active than naladixic acid and is less prone to resistance, as reviewed in the technical update on integrated management of childhood illness in 2005 (WHO/UNICEF, 2005).

The panel discussed regional differences in resistance to specific organisms, including *Salmonella* spp, and areas of insufficient evidence and uncertainty (e.g. if longer treatment is necessary for HIV-infected children). The panel decided to retain the recommendation on ciprofloxacin in the technical update on integrated management of childhood illness (WHO/UNICEF, 2005). The risk–benefit assessment is given in Annex 4; there is no GRADE profile for this recommendation.

Recommendation 4: Ciprofloxacin

Ciprofloxacin is recommended for 3 days at an oral dose of 15 mg/kg for treating bloody diarrhoea.

This recommendation is the same for all children.

Quality of the evidence: Moderate

Strength of the recommendation: Strong

Time to review: 2012

Micronutrients for persistent diarrhoea

No direct evidence was found for the use of micronutrients to treat persistent diarrhoea in HIV-infected or -exposed children. Indirect, low-quality evidence from one trial of adults with HIV wasting syndrome did not show a difference in morbidity or mortality among those given albendazole, with or without micronutrients and multivitamins (Kelly et al., 2008) No studies were identified in a systematic review of studies of micronutrient supplementation in HIV-infected children other than vitamin A (Irlam et al., 2005).

In reviewing the evidence for the recommendation on multiple micronutrient supplementation for the treatment of persistent diarrhoea, the panel placed strong value on correcting nutritional deficiencies in children with HIV and diarrhoea and less emphasis on potential risks or lack of certainty about the effect of multiple micronutrient supplementation. Further, the panel recognized that it is important to distinguish components of multiple micronutrients; vitamin A and zinc, for instance, were considered separately. The optimal formulation of micronutrients is specified in materials on the integrated management of childhood illness (WHO/UNICEF, 2005). A risk-assessment table and GRADE profile are given in annexes 4 and 5.

Recommendation 5 : Multiple micronutrients for persistent diarrhoea

Daily micronutrients are recommended for 2 weeks for all HIV-infected and -exposed infants and children with persistent diarrhoea.

This recommendation is the same for all children.

Quality of the evidence: Low

Strength of the recommendation: Conditional

Time to review: 2012

Other treatments for managing persistent diarrhoea

- The panel reviewed the existing recommendations on persistent diarrhoea in children. While the following were not systematically reviewed, the panel included them, as they remain important guidelines:
- Give a lactose-free or low-lactose diet to children with persistent diarrhoea who are over 6 months old and unable to breastfeed.
- Assess every child with persistent diarrhoea for nonintestinal infections (e.g. pneumonia, sepsis, urinary tract infection, oral thrush, otitis media), and treat them appropriately.
- Use antibiotics only when appropriate (i.e. bloody diarrhoea), and abstain from administering antidiarrhoeal drugs.
- Provide HIV testing and counselling for infants and children living in generalized epidemic settings and for children in all epidemic settings who present with persistent diarrhoea or other signs and symptoms that could indicate HIV infection (including tuberculosis), children born to HIV-positive women, and children with suboptimal growth or malnutrition who are not responding to appropriate nutritional therapy.

4.1.6 Outstanding issues for research

The panel identified significant gaps in the available information on the prevention and treatment of diarrhoea in HIV-infected and -exposed children. Appropriately large prevention and intervention trials are needed, particularly in the context of the scaling-up of paediatric ART and co-trimoxazole prophylaxis. Additional studies are required to determine:

- the etiology of acute, bloody, persistent (14–28 days) and chronic (> 28 days) diarrhoea among HIV-infected and -exposed children;
- patterns of resistance of etiological agents;
- the prevalence of pathogens such as cryptosporidia;
- the effect of vitamin A supplementation for infants under 6 months of age;
- the efficacy of different treatment regimens for diarrhoea;
- the effect of co-trimoxazole prophylaxis and ART on morbidity and mortality from diarrhoea in HIV-infected children; and
- the importance of lactose-free and low-lactose diets in the management of diarrhoea in HIV-infected children.

4.2 Pneumonia

4.2.1 Burden of disease

Pneumonia is the single biggest killer of children worldwide, accounting for nearly one in five deaths among young children, with an estimated 1.8 million deaths annually (Thea, Qazi, 2008). Most of the deaths occur in resource-constrained countries, with 50% in sub-Saharan Africa and 20% in South-East Asia, where an estimated 151 million cases of childhood pneumonia occur each year, 11–20 million of which may require hospitalization (Rudan et al., 2008).

As high as the estimates of the global pneumonia burden are, they may not accurately reflect the full impact of HIV infection on these rates over the past decade (Thea, Qazi, 2008). The most recent figures are essentially incidence rate estimates drawn from studies conducted between 1969 and 1999, which were applied to the current populations of children at risk (Rudan et al., 2008). In high-burden countries, however, HIV infection has changed the picture, dramatically increasing the incidence, severity and mortality associated with pneumonia.

4.2.2 Current guidelines (2004 and 2005)

WHO recommendations for the management of severe and very severe pneumonia are described in the 'pocket book' on integrated management of childhood illness (WHO, 2005), and WHO recommendations for the treatment of pneumonia in HIV-infected or -exposed children were formulated during a consultation in Zimbabwe in 2003 (WHO, 2004).

Clinical diagnosis at primary care level follows the WHO guidelines for integrated management of childhood illness, which is a simplified guide based on the detection of fast breathing or lower chest wall indrawing; the guidelines do not include other aspects of chest examination, like auscultatory findings (e.g. wheeze, crackles, bronchial breath sounds, percussion findings, general features like clubbing). Cyanosis may be a less sensitive and specific sign, and may not be useful for diagnostic purposes at community level. Fast breathing, as defined by WHO, can be used to detect pneumonia in about 80% of children who need antibiotic treatment, and lower chest wall indrawing was found to be 89% sensitive and specific for a paediatrician's decision to admit a child for an acute lower respiratory infection. Care at referral level (e.g. a district hospital) may include a chest radiograph; this cannot be used in first-line diagnosis because of its low sensitivity, but it is an excellent adjunct because of its high specificity (WHO/UNICEF, 1998). Current evidence shows that the etiological agents of pneumonia still cannot be differentiated clearly clinically or radiologically.

4.2.3 Etiological agents

Many organisms cause pneumonia. While respiratory viruses are the most commonly identified pathogens in HIV-uninfected children with pneumonia, there is a high prevalence of bacterial infection or co-infection in many of these and other severe cases of pneumonia (Michelow et al., 2000; Madhi et al., 2002a,b). In the absence or minimal use of ART and co-trimoxazole prophylaxis, *P. jirovecii* and cytomegalovirus are frequent causes of pneumonia in HIV-infected children, especially very young infants. The clinical presentation of pneumonia is similar in HIV-infected and -uninfected children (Madhi et al., 2002a,b); however, the case fatality rates are higher in infected children.

Up to two thirds of all cases of pneumonia have a mixed bacterial and viral etiology, and various tests might be needed, sometimes concurrently, to detect the etiological agent. Agents can vary by age: children under 2 months of age are more often infected with Gram-negative organisms, anaerobes and PCP, while children aged between 2 months and 5 years are frequently affected by the common organisms *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*. Children over 5 years more often have *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*.

Most HIV-infected children have recurrent pneumonia, irrespective of the etiology. The association of lymphocytic interstitial *pneumonia* and tuberculosis contributes to frequent episodes of pneumonia, leading to chronic lung disease and bronchiectasis. In addition to the increased burden of pneumonia, HIV-infected and -exposed children are more susceptible to a broad spectrum of pneumonia-associated pathogens, including opportunistic agents such as PCP, *Mycobacterium tuberculosis* and cytomegalovirus (Ruffini, Madhi, 2002; McNally et al., 2007).

WHO conducted a systematic review of studies on etiological agents for pneumonia, which comprised nine descriptive studies, including two post-mortem studies, and 15 analytical studies, of which five were post-mortem studies. Most of the studies reviewed were conducted in Africa prior to 2004, before the widespread availability and use of ART. The methods used varied widely; however, extractable data were available for a meta-analysis to obtain summary estimates of the prevalence of *P. jirovecii*, cytomegalovirus, adenovirus, *M. tuberculosis, S. pneumoniae, H. influenzae, S. aureus* and *Salmonella* spp. as associated causative agents of morbidity or mortality. *P. jirovecii* was the most commonly identified etiological agent, with a summary odds ratio of 10.14 (95% confidence interval, 1.66;62.07) in ante-mortem studies and 9.08 (95% confidence interval, 2.49;33.09) in post-mortem studies (Table 3).

P. jiroveci *pneumonia in infants and children in highly HIV endemic settings*

From the early stages of the HIV epidemic, PCP was recognized as an important indicator of HIV/AIDS. It presented in HIV-infected adults and children, but early data from Europe, Thailand and the USA showed that the peak prevalence of PCP in children was in infants under 12 months and usually under 6 months of age (Simonds et al., 1993; European Collaborative Study, 1994; Chokephaibulkit et al., 1999). A recent report from Ireland and the United Kingdom showed that, before 1998, 27% of HIV-infected infants had PCP or cytomegalovirus as a first indicator, and 91% were young infants (Williams et al., 2001).

PCP was first reported in HIV-endemic regions of Africa, in autopsy studies in Côte d'Ivoire, South Africa and Zimbabwe (Jeena, Coovadia, Chrystal, 1996; Lucas et al., 1996; Ikeogu, Wolf, Mathe, 1997). All 46 cases of PCP were reported in infants of a mean age of 3–4 months. The findings of these and subsequent autopsy and clinical studies in the region are listed in Tables 4 and 5. The heterogeneity of PCP diagnoses and of the reporting of age in the clinical studies might have skewed some data, resulting in miscalculation of the proportion of infant cases. Nevertheless, autopsy and clinical data provide consistent evidence that most cases of PCP occur in young infants, as in the United Kingdom. Of 130 autopsy cases reported, only 5% were in children over 12 months of age.

Table 5 summarizes data on the ages of African infants and children with severe pneumonia and a diagnosis of PCP in clinical studies; the majority are infants. While data on fatal cases of PCP are not shown, the proportion of deaths among infants is even greater.

Incidence of P. jiroveci *pneumonia*

Few community-based cohort studies are available of HIV-infected children before the use of co-trimoxazole to allow calculation of PCP incidence rates. In two studies of children hospitalized with severe pneumonia (Chintu et al., 2004; Mulenga et al., 2007), pneumonia was the commonest morbid condition, but PCP was not reported in the placebo arm of a randomized-controlled trial of co-trimoxazole for HIV-infected children. Children in the placebo group were followed-up for a median of 17 months, and no confirmed case of PCP was found. Similarly, the incidence of severe pneumonia was high in a cohort study of HIV-infected Malawian children, mostly over 2 years of age, and no cases of PCP were diagnosed (Laufer et al., 2006). These studies, however, included only children who were older than those in whom PCP was identified in cross-sectional, hospital-based etiological studies.

Table 3. Odds ratios for identifying specific pathogens in HIV-infected and -uninfected children with pneumonia

Pathogen	Study setting	No. of studies	Odds ratio (95% confidence interval)		Q test (*p* value)
			Fixed effects	Random effects	
P. jiroveci	Clinical	3	8.17 (3.59;18.79)	10.14 (1.66;62.07)	0.033
	Post-mortem	5	7.45 (4.12;13.49)	9.08 (2.49;33.09)	0.029
Cytomegalovirus	Clinical	1	1.43 (0.61;3.58)	N/A	N/A
	Post-mortem	5	14.35 (6.69;30.75)	14.35 (6.69;30.75)	0.60
M. tuberculosis	Clinical	2	1.08(0.69;1.67)	1.08(0.69;1.67)	0.667
	Post-mortem	5	0.73 (0.43;1.25)	0.73 (0.43;1.25)	0.69
S. pneumoniae	Clinical	4	2.32 (1.47;3.66)	1.52 (0.47;4.93)	0.012
	Post-mortem	1	1.29 (0.39;4.31)	1.29 (0.39;4.31)	1.0
H. influenzae	Clinical	4	1.24 (0.74;2.11)	1.22 (0.65;2.27)	0.323
	Post-mortem	1	0.33 (0.05;2.02)	0.33 (0.05;2.02)	1.0
S. aureus	Clinical	3	2.38 (1.27;4.49)	2.29 (1.02;5.11)	0.206
	Post-mortem	1	1.02 (0.29;3.52)	1.02 (0.29;3.52)	1.0
Salmonella spp.	Clinical	3	0.76 (0.27;2.11)	0.75 (0.26;2.13)	0.649
	Post-mortem	0	N/A	N/A	N/A
E. coli	Clinical	2	3.82 (0.86;17.09)	3.00 (0.37;24.54)	0.188
	Post-mortem	0	N/A	N/A	N/A
Adenovirus	Clinical	1	0.289 (0.11;0.75)	0.289 (0.11;0.75)	1.0
	Post-mortem	3	0.72 (0.22;2.34)	0.73 (0.20;2.61)	0.58
All-cause* invasive bacteria	Clinical	3	1.76 (1.31;2.38)	1.46 (0.77;2.79)	0.024
	Post-mortem	4	1.32 (0.95;1.84)	1.48 (0.77;2.89)	0.012

N/A refers to Not Applicable.

* Concomitant positive blood culture in clinical studies and either positive bacterial culture (from lung aspirate or blood obtained within 3 h of death) or histopathological finding of pyogenic pneumonia in post-mortem studies

From Jeena, Coovadia, Chrystal, 1996; Lucas et al., 1996; Ikeogu, Wolf, Mathe, 1997; Mofenson et al., 1998; Chokephaibulkit et al., 1999; Graham et al., 2000; Madhi et al., 2000a,b; Zar et al., 2000; Kattan et al., 2001; Nathoo et al., 2001; Zar et al., 2001; Chintu et al., 2002; Madhi et al., 2002b; Rennert et al., 2002; Ruffini and Madhi, 2002; Ansari et al., 2003; Bakeera-Kitaka et al., 2004; Bii et al., 2006; Surve and Rathod, 2006; Toro et al., 2006; Madhi et al., 2006; Madhi et al., 2007; McNally et al., 2007

Table 4. Autopsy studies in which PCP was reported in HIV-infected African children

Study site (reference)	Reported age range of all patients	No. of PCP cases	Reported age of PCP patients
Cote d'Ivoire (Lucas et al., 1996)	1 month–12 years	11	100% infants
Zimbabwe (Ikeogu, Wolf, Mathe, 1997)	0–5 years	19	Mean age, 3 months Range, 1–7 months
South Africa (Jeena, Coovadia, Chrystal, 1996)	1–18 months	16	Mean age, 4 months
Zimbabwe (Nathoo et al., 2001)	Not specified	16	100% infants
Zambia (Chintu et al., 2002)	0–16 years	58	88% infants
Botswana (Ansari et al., 2003)	1 month–13 years	10	100% infants

Table 5. Ages of HIV-infected infants and children with PCP in clinical studies in Africa

Study site (reference)	Reported age range of all patients	No. of PCP cases	Reported age of PCP patients
Malawi (Kamiya et al., 1997)	2–24 months	5	80% aged 3–6 months
Malawi (Graham et al., 2000)	2 months–5 years	16	100% aged 2–6 months
South Africa (Zar et al., 2000)	Median, 9 months; interquartile range, 3–23 months	15	Median, 3 months; interquartile range, 3–4 months
South Africa (Ruffini, Madhi, 2002)	2–24 months	51	Median, 4 months; range, 1–19 months
South Africa (Madhi et al., 2002b)	1–40 months	101	Median, 4 months; range, 1–28 months
Uganda (Bakeera-Kitaka et al., 2004)	2–60 months	20	70% were infants
South Africa (McNally et al., 2007)	1 month–5 years	29	100% were infants
South Africa (Morrow et al., 2010)	Median, 3 months; interquartile range, 2–5 months	43	Median, 3.5 months; interquartile range, 3–5 months
Malawi (Graham et al., 2010)	2 months–13 years	16	94% median age, 3 months

Effect of HIV infection on mortality and P. jiroveci *pneumonia*

A recent review was conducted of all studies in the HIV-endemic region of Africa in which cases of severe or very severe pneumonia were diagnosed and managed according to the WHO strategy, including empiric PCP therapy in some studies (Enarson et al., 2010). HIV infection increased the risk for death significantly, by sixfold overall. The effect of HIV infection on case fatality was largely confined to infants aged 2–12 months, and PCP contributed strongly to this effect; however, heterogeneity in the methods and reporting obviated a quantitative meta-analysis of the data. Nevertheless, PCP affected the HIV-related pneumonia case fatality rate, mainly among infants.

4.2.3 Preventive interventions

Co-trimoxazole (see also recommendations for prevention of diarrhoea)

Co-trimoxazole prophylaxis has been the recommended standard of care for preventing PCP among HIV-infected and -exposed infants and children since the 1990s. The results of randomized clinical trials and observational studies also demonstrate the effectiveness of co-trimoxazole in reducing morbidity and mortality from pneumonia (presumed bacterial) among infants and children living with HIV in resource-limited settings. The WHO guidelines for co-trimoxazole prophylaxis (WHO, 2006) should be followed, in view of the importance of this intervention in preventing pneumonia.

Other interventions

The Global Action Plan for the Prevention and Control of Pneumonia (WHO/UNICEF, 2009) represents a comprehensive summary of WHO recommendations for other preventive interventions, such as vaccination against *S. pneumoniae* and *H. influenzae* type b and the promotion of breastfeeding. The panel did not review the Plan for these guidelines.

4.2.4 Treatment interventions

WHO conducted a systematic review to identify effective antimicrobial or adjunctive systemic therapy for community-acquired pneumonia in HIV-infected and -exposed infants and children.

Empirical co-trimoxazole treatment

A systematic review of etiological pathogens strongly suggested an etiological role of PCP in young infants, particularly those with new HIV infection in the absence of treatment with co-trimoxazole and ART. The panel recognized the importance of covering clinically suspected PCP and endorsed previous recommendations for empirical treatment with co-trimoxazole. The panel also agreed that PCP is important only in children under 1 year of age (Zar et al., 2000). Risk–benefit assessments are given in Annex 4.

Recommendation 6: Empirical co-trimoxazole treatment

Empirical co-trimoxazole treatment for suspected PCP is recommended as an addition for HIV-infected and -exposed infants from 2 months to 1 year old with severe or very severe pneumonia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Time to review: 2012

Recommendation 7: Empirical co-trimoxazole treatment

Empirical co-trimoxazole treatment for PCP is not recommended for HIV-infected and -exposed children over 1 year of age with severe or very severe pneumonia.

Quality of evidence: Low

Strength of recommendation: Conditional

Time to review: 2012

Antibiotic regimens for non-severe pneumonia

The current treatment recommendation for non-severe pneumonia is co-trimoxazole or amoxicillin (WHO, 2007). No randomized controlled trial designed on the basis of an a-priori hypothesis has been conducted to examine the efficacy of different regimens of antibiotics or case management for identified pneumonia, nor have any observational studies been reported on non-severe pneumonia in HIV-infected or -exposed children. The panel has therefore made no new recommendations.

Antibiotic regimens for severe and very severe pneumonia

While there has been no randomized controlled trial designed on the basis of an a-priori hypothesis to examine the efficiency of antibiotic regimens or case management, a subgroup analysis was conducted in one randomized controlled trial in which oral amoxicillin was compared with parenteral penicillin for severe pneumonia in children. The response rates with the two regimens were comparable, but the treatment failure rate was significantly higher for HIV-infected infants at day 14 (40.7% versus 24.3%; odds ratio, 2.8; 95% confidence interval 1.35; 3.5). The response rates were similar for children over 12 months of age, irrespective of HIV status.

The panel based new recommendations on these findings. The review was undertaken to quantify the relative contributions of potential pathogens associated with community-acquired pneumonia in HIV-infected children (Table 3). The wide variations in method among studies hampered the review and made it difficult to compare the results of studies. The variation was exacerbated by discrepancies in results obtained with fixed- and random-effects models. The extent to which this variation affected the estimates was difficult to ascertain.

The systematic review also showed that the frequency with which Gram-negative bacilli were identified did not differ significantly between HIV-infected and -uninfected children, although the lack of significance might have been due to selection bias or lack of power. A significant association found between *S. aureus* infection and HIV status in studies in South Africa indicates the importance of considering empirical antibiotic regimens with coverage against *S. aureus* and treating *S. aureus* infection in the absence of response to first-line antibiotic treatment.

On the basis of the review of etiological agents, the panel discussed the use of oral amoxicillin for treating children over 1 year of age with severe pneumonia and discouraged its use for HIV-infected children. The panel also considered the use of co-amoxiclav and gentamicin for treating very severe pneumonia in HIV-infected children. In view of the poor quality of the evidence, the cost of amoxicillin–clavulanate and the lack of availability of an injectable form, the panel discouraged its use. On similar grounds, the panel did not recommend cephalosporin (first or second generation) for treatment of severe pneumonia, owing to the poor quality of the evidence and the higher cost in comparison with ampicillin plus gentamicin.

The panel did, however, recommend use of ceftriaxone as an alternative first-line antibiotic for treating very severe pneumonia or as a second-line option for children who do not respond to ampicillin plus gentamicin. The rationale for recommending ceftriaxone as alternative first- or second-line treatment is that it provides better coverage than second-generation cephalosporins, such as cefuroxime, or the combination of ampicillin plus aminoglycoside, against penicillin-resistant *S. pneumoniae* and many Gram-negative infections. Furthermore, ceftriaxone is susceptible in vitro to methicillin-sensitive *S. aureus*. In areas of high prevalence of methicillin-resistant *S. aureus*, use of cloxacillin or vancomycin is recommended when there is strong clinical suspicion or microbiological evidence of *S. aureus* pneumonia.

Recommendation 8

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and children under 5 years of age with severe or very severe pneumonia.

Quality of evidence: Low

Strength of recommendation: Conditional

Time to review: 2012

Recommendation 9

For HIV-infected and -exposed infants and children with severe or very severe pneumonia who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

Quality of evidence: Low

Strength of recommendation: Conditional

Time to review: 2012

*Adjunctive corticosteroid treatment for suspected **P. jiroveci** pneumonia*

Trials of PCP treatment have focused on adjunctive systemic corticosteroids or alternative antimicrobial regimens. A single randomized controlled trial showed a nonsignificant effect against mortality in HIV-exposed children with a clinical suspicion of PCP, and an observational study indicated a significant reduction in PCP case fatality rates. Both studies were subject to methodological limitations and are qualified as providing low-quality evidence. The panel could not make new recommendations on the basis of these two studies and instead recommended further research. Risk–benefit assessments and GRADE profiles are shown in annexes 4 and 5.

The panel was uncertain whether adjunctive corticosteroid treatment for severe PCP affects latent cytomegalovirus infection. Although a pooled analysis indicated a strong association between cytomegalovirus infection and fatal HIV-associated pneumonia, the clinical significance remains unclear. In the presence of a high prevalence of different pathogens, it is difficult to disentangle the effects of one pathogen. Earlier clinical studies showed that concomitant pulmonary cytomegalovirus infection did not affect survival. The panel was concerned that progression of latent cytomegalovirus infection could contribute to treatment failure of severe PCP among children receiving adjunctive corticosteroid.

4.2.6 Outstanding issues for research

The panel noted significant gaps in the evidence for management of pneumonia in HIV-infected and -exposed infants and children, including:

- the efficacy of first- and second-line antibiotics for treatment of non-severe, severe and very severe pneumonia;
- the optimal duration of antibiotic treatment;
- the causes of treatment failure;
- the effectiveness of cortisteroids in HIV-infected children with pneumonia;
- compliance to primary and secondary PCP prophylaxis;
- the effect of prevention of mother-to-child transmission and co-trimoxazole prophylaxis on the incidence, associated mortality and etiology of pneumonia;
- the effect of ART on the incidence, associated mortality and etiology of pneumonia;
- the etiology of pneumonia in children infected with and suspected of infection with HIV; and
- appropriate data for annual monitoring.

5. Dissemination and implementation of guidelines

A summary of the revised recommendations will be available on the WHO website, and the guidelines, training materials, and other operational manuals for integrated management of childhood illness will be updated to reflect the revised recommendations.

The WHO departments of Child and Adolescent Health and HIV at Headquarters will inform WHO regional and country representatives, implementing partners, other stakeholders and professional groups involved in child health and paediatric HIV about the revised recommendations.

WHO, in collaboration with various partners, will provide or facilitate technical support to countries that require it, to adopt and adapt the revised guidelines.

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Annex 1. Existing WHO guidelines for preventing and treating diarrhoea in children

Prevention	Give vitamin A to all children > 6 months of age every 6 months (100 000 IU for 6–12 months and 200 000 IU for ≥ 12 months) up to 5 years of age.
Treatment and management	Treat dehydration with ORS solution (or an intravenous electrolyte solution in cases of severe dehydration).
	With increased fluids and continued feeding, all children with diarrhoea should be given zinc supplementation at 20 mg for 10–14 days; infants < 6 months should receive 10 mg.
	Use antibiotics only when appropriate (i.e. bloody diarrhoea), and abstain from administering anti-diarrhoeal drugs. Ciprofloxacin is the most appropriate drug for treatment of bloody diarrhoea, rather than nalidixic acid, which leads to rapid development of resistance. Ciprofloxacin should be used at an oral dose of 15 mg/kg twice daily for 3 days.
	Advise mothers to increase fluids and continue feeding during future episodes.
	Give multivitamins and micronutrients daily for 2 weeks to all children with persistent diarrhoea (folate 50 µg, zinc 10 mg, vitamin A 400 µg, iron 10 mg, copper 1 mg, magnesium 80 mg).
	Give lactose-free (or low-lactose) diet to children > 6 months with persistent diarrhoea and who are unable to breastfeed.
	Assess every child with persistent diarrhoea for nonintestinal infections (pneumonia, sepsis, urinary tract infection, oral thrush, otitis media), and treat appropriately.
Other related recommendations	Test children of unknown HIV status, who are living in areas of where HIV prevalence is 1% or more and who present to a health facility.
	Household water treatment methods that are effective in reducing diarrhoea and storage of water in containers that do not allow manual contact are recommended for people with HIV and their households.
	Proper disposal of faeces in a toilet or latrine or at a minimum, by burial in the ground is recommended for people with HIV and their households.
	Promotion of hand-washing with soap after defaecation, handling of human or animal faeces and before food preparation and eating, with the provision of soap, are recommended for people with HIV and their households.
	Refer HIV-exposed infants and children for co-trimoxazole prophylaxis and HIV-infected children for ART.

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Annex 2. Existing WHO recommendations for managing pneumonia in children

Diagnosis	Guidelines
Clinical diagnosis	1. A child aged under 5 years presenting with cough or difficult breathing and fast breathing or chest indrawing is classified as having non-severe 'pneumonia'.
	2. A child aged under 5 years presenting with cough or difficult breathing and any one of the general danger signs (history of convulsions or convulsing now, lethargic or unconscious, vomiting everything or not able to drink or breastfeed) or stridor or cyanosis, clubbing or grunting is classified as having very severe pneumonia or severe disease.
	3. *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia should be considered in all HIV-exposed and -infected infants aged under 1 year presenting with pneumonia or severe pneumonia.
Radiological pneumonia	Chest radiographs do not allow identification of bacterial pneumonia in all cases.
Bacteriological pneumonia	An etiological diagnosis of bacterial pneumonia can be made from blood culture in 10–15% of cases.
Treatment	Recommendation
Antibiotics	*Non-severe* Amoxycillin is effective for the treatment of non-severe pneumonia in children aged 2 months–5 years. Amoxycillin given for 5 days is effective for treatment of non-severe pneumonia.
	Severe Parenteral ampicillin (or penicillin if ampicillin is not available) and gentamicin for 10 days is effective for treatment of severe pneumonia. ● If not improved by 48–72 h, change to ceftriaxone (if not available, use cloxacillin plus gentamicin). ● Add high-dose cotrimoxazole (8 mg of trimethoprim per kg) for 3 weeks for children aged < 12 months. ● For children aged > 12 months, give cotrimoxazole only when clinically indicated. *Very severe* Same treatment as severe, but always add co-trimoxazole.
Supportive therapy, including oxygen	Oxygen therapy should be considered if hypoxaemia is present or suspected.
Antifungal agents	No guideline
Steroids	No guideline

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Annex 3. Review questions for preventing and treating diarrhoea and managing pneumonia in HIV-infected and -exposed infants and children

Table A3.1. Review questions for diarrhoea

1A. Is the pattern of etiological agents of bloody diarrhoea different in HIV-infected or -exposed infants and children?
1B. Is the pattern of etiological agents of persistent diarrhoea different in HIV-infected or -exposed infants and children?
(These two questions are addressed as a literature review with no GRADE tables.)
2A. Does vitamin A supplementation prevent diarrhoea in children with HIV infection?
2B. Is reduced-osmolarity ORS more effective than standard ORS in preventing death or continuation of the diarrhoea in HIV-infected or -exposed infants and children?
2C. Is zinc supplementation effective in reducing the severity of episodes of acute, persistent and bloody diarrhoea and preventing further clinical or recurrent episodes in the subsequent 2–3 months in HIV-infected or -exposed infants and children?
2D. Is the recommended antibiotic regimen for bloody diarrhoea or persistent diarrhoea effective in preventing death or limiting complications in HIV-infected or -exposed infants and children? Is the recommended antibiotic regimen for diarrhoea due to *Cryptosporidium, Campylobacter, Microspora* and *Isospora* effective in preventing death or limiting complications in HIV-infected or -exposed infants and children?
2E. Are multiple micronutrients effective in preventing persistent diarrhoea in HIV-infected or -exposed infants and children?

Table A3.2. Review questions for pneumonia

1. Is the pattern of etiological agents of pneumonia different among HIV-infected infants and children?
(This question is addressed in a literature review with no GRADE tables.)
2A. Should the management of pneumonia (non-severe and severe) in HIV-infected infants and children be different from that for uninfected children, and how?
2B. Should the management of pneumonia (non-severe and severe) in infants and children of unknown HIV status living in areas of generalized HIV epidemic be different from that for children in areas of low HIV prevalence, and how?

Annex 4. Risk–benefit assessments

Vitamin A supplementation

Should vitamin A versus placebo be used for the prevention of diarrhoea in children with HIV infection?

Population: HIV-infected and -exposed infants and children with diarrhoea in resource-limited settings

Intervention: Vitamin A supplementation by mouth every 6 months for children aged > 6 months–5 years (100 000 IU for children aged 6–12 months and 200 000 IU for those aged > 12 months)

Factor	Findings	Decision
Quality of evidence	Low (see GRADE profile 1). Four trials were identified in which vitamin A supplementation was compared with placebo, which included children with HIV infection or exposure and in which mortality or morbidity from diarrhoea were evaluated. In one of the four, vitamin A supplementation in the neonatal period was studied. A pooled summary estimate for three studies showed a reduction in mortality associated with vitamin A supplementation, although the quality of the body of evidence is limited by the low overall number of events and children and losses to follow-up in some studies.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Reduced mortality was seen in three studies (pooled summary estimate, relative risk = 0.55). In general, the individual studies were not sufficiently powerful to evaluate mortality. The benefits with regard to diarrhoeal morbidity were less consistent, and the methods of reporting varied widely among studies (no summary estimate). One study showed a benefit from visits for watery diarrhoea for children given vitamin A rather than placebo (Semba et al., 2005).	Uncertainty about the balance of benefits versus harms and burdens? ☐ Yes X No
Risks or undesired effects	One study of HIV-exposed neonates given vitamin A supplementation showed an association with increased mortality (Humphrey et al., 2006). Th panel considered that this potential risk was not of concern to the current recommendation, as vitamin A supplementation is recommended after 6 months of age.	
Values and preferences	This recommendation places a high value on correcting vitamin A deficiency and on the reduced mortality associated with vitamin A supplementation and a lower value on potential risks or lack of certainty about the effect of supplementation.	Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs	This recommendation is consistent with current recommendations, and therefore no new costs are incurred.	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Feasibility was not raised as a barrier to implementation of this recommendation.	
Key questions arising		

Final strength and direction of recommendation	X	Strong recommendation
	☐	Weak or conditional recommendation
	X	For the intervention
	☐	Against the intervention

Humphrey JH et al. (2006). Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. Journal of Infectious Diseases, 193:860–71.

Semba RD et al. (2005). Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. Nutrition, 21:25–31.

Use of low-osmolarity oral rehydration solution

Should reduced-osmolarity ORS be used for acute diarrhoea in children rather than standard ORS?

Population: HIV-infected and -exposed infants and children with diarrhoea in resource-limited settings

Intervention: Low-osmolarity ORS

Factor	Findings	Decision
Quality of evidence	High (See GRADE profile 2). The systematic review of studies in children (not specifically HIV-infected) provides indirect evidence of high quality for a benefit of administering low-osmolarity ORS rather than standard ORS, with reduced need for unscheduled intravenous fluids and reduced stool output. The panel was not concerned about the indirectness of the evidence. It discussed the greater fragility of the gut mucosa in children with HIV infection and the presence of enteropathy but considered that these factors would not alter the benefit of low-osmolarity ORS. The review used for the GRADE profile 2 was from 2002, as no more recent evidence was available.	Lower quality evidence? ☐ Yes X No
Benefits or desired effects	The panel recognized the benefits (noted above). An added benefit is that low-osmolarity ORS is already in pharmacopoeias, and the formulation for its manufacture is available to countries.	Uncertainty about the balance of benefits versus harms and burdens? ☐ Yes X No
Risks or undesired effects	No risks or undesired effects were identified, and it was considered that the benefits of low-osmolarity ORS outweighed any harm.	
Values and preferences	This recommendation places high value on the evidence for use of low-osmolarity ORS rather than standard formula and is in line with current recommendations.	Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs	Low-osmolarity ORS costs 70% less than standard ORS	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Low-osmolarity ORS is currently recommended by WHO as treatment for dehydration. Studies on the uptake and use of ORS have, however, been discouraging (Ram et al., 2008).	
Key questions		
Final strength and direction of recommendation	X Strong recommendation ☐ Weak or conditional recommendation X For the intervention ☐ Against the intervention	

Ram PK et al. (2008). Declines in case management of diarrhoea among children less than five years old. Bulletin of the World Health Organization, 86:161–240.

Zinc supplementation

Should zinc be used to treat persistent or acute diarrhoea?

Population: HIV-infected and -exposed infants and children with diarrhoea in resource-limited settings

Intervention: Zinc (10 mg per day by mouth for infants < 6 months of age and 20 mg per day by mouth for infants and children > 6 months of age) for 10–14 days

Factor	Findings	Decision
Quality of evidence	Moderate (See GRADE profiles 3a and 3b). Indirect evidence of moderate quality is available. (studies conducted on children who were not specifically HIV-infected or -exposed) for a benefit of zinc supplementation for acute and persistent diarrhoea in terms of the duration of diarrhoea. The panel was not concerned about the indirectness of the evidence because it considered that it was not biologically plausible that the physiological effects of zinc would be different in HIV-infected and -uninfected children, and as there was no evidence of harm in the trial of Bobat et al. (2005), in which HIV-infected children received zinc for 6 months (as primary prevention).	Lower quality evidence? ☐ Yes X No
Benefits or desired effects	The benefits of zinc supplementation include a shorter duration of diarrhoea and prevention of recurrence. In addition, zinc supplementation might correct any deficiency.	Uncertainty about the balance of benefits versus harms and burdens? ☐ Yes X No
Risks or undesired effects	The undesired effects include increased vomiting with some formulations of zinc. In addition, children with HIV infection who are on multiple medications may experience drug–drug interactions and side-effects. A brief review indicated no interactions between zinc formulations and ART. There are limited data in HIV-infected children.	
Values and preferences	This recommendation places a higher value on the benefit of zinc supplementation in reducing the duration of diarrhoea and correction of any zinc deficiency and a lower value on potential undesired effects or lack of certainty about other risks or drug interactions.	Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs	Costs are significantly lower	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	The panel discussed the challenges of drug supply and distribution.	

Factor	Findings	Decision
Key questions arising		
Final strength and direction of recommendation		

Bobat R et al. (2005). Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. *Lancet*, 366:1862–7.

Ciprofloxacin for bloody diarrhoea

Should ciprofloxacin (as opposed to nalidixic acid) be used to treat bloody diarrhoea in children with HIV infection or exposure?

Population: HIV-infected and -exposed infants and children with diarrhoea in resource-limited settings

Intervention: Ciprofloxacin (15 mg/kg by mouth twice daily for 3 days)

Factor	Findings	Decision
Quality of evidence	No direct evidence was identified. The panel reviewed indirect evidence of moderate quality that ciprofloxacin has more activity than nalidixic acid and is less prone to resistance (WHO, 2005).	Lower quality evidence? ☐ Yes X No
Benefits or desired effects	Ciprofloxacin has a better resistance profile than nalidixic acid.	Uncertainty about the balance of benefits versus harms and burdens? ☐ Yes X No
Risks or undesired effects	The panel was concerned about the safety (arthropathy) of quinolones (both nalidixic acid and ciprofloxacin). More recent safety review and guidelines showed no known interaction with antiretroviral drugs.	
Values and preferences	Value was placed on the current ciprofloxacin recommendation (WHO, 2005).	Uncertainty of differences in patient values and preferences? ☐ Yes X No
Costs	Ciprofloxacin is cheaper than nalidixic acid.	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Implementation is feasible as other antibiotics are distributed in resource-limited settings, and ciprofloxacin is now available in those settings.	
Key questions arising	Would longer treatment be more effective in HIV-infected children? Are there regional differences in the etiological agents that cause bloody diarrhoea and in resistance patterns?	
Final strength and direction of recommendation	X Strong recommendation ☐ Weak or conditional recommendation X For the intervention ☐ Against the intervention	

WHO. *The treatment of diarrhoea: a manual for physicians and other senior health workers*. Geneva, World Health Organization, 2005. Available online at: http://www.who.int/child_adolescent_health/documents/9241593180/en/index.html.

Micronutrients for diarrhoea

Should multiple micronutrients be used to treat HIV-infected and -exposed children with persistent diarrhoea?

Population: HIV-infected and -exposed infants and children with persistent diarrhoea in resource-limited settings

Intervention: Multivitamins and micronutrients

Factor	Findings	Decision
Quality of evidence	Very low (See GRADE profile 4). A systematic review of studies on administration of micronutrients to HIV-infected patients (Irlam et al., 2005) provided no conclusive evidence that micronutrient supplementation reduces morbidity or mortality among HIV-infected adults. Only one of the studies (Kelly et al., 1999) was relevant to the review question, as it was specific to diarrhoea. This study showed no difference in morbidity or mortality from diarrhoea among HIV-infected adults with AIDS diarrhoea-wasting syndrome who were given multiple micronutrients or placebo.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Supplements would help correct any deficiency.	Uncertainty about the balance of benefits versus harms and burdens? X Yes ☐ No
Risks or undesired effects	The panel discussed the possible harm or side-effects of supplements, including potential drug–drug interactions, cumulative side-effects, increased pill burden and potential distraction from other interventions (such as ART).	
Values and preferences	High value was placed on correcting nutritional deficiencies in children with HIV and diarrhoea and a lower value on the potential risks or lack of certainty about the effects of supplementation.	Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs		Uncertainty about whether the net benefits are worth the costs? X Yes ☐ No
Feasibility	The panel discussed difficulties in supply and distribution in some settings. In addition, it was concerned about specific formulations and potential confusion about the contents of multi-component micronutrients or multivitamin supplements.	

Factor	Findings		Decision
Key questions arising			
Final strength and direction of recommendation	☐	Strong recommendation	
	X	Weak or conditional recommendation	
	X	For the intervention	
	☐	Against the intervention	

Irlam JH et al. (2005). Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database of Systematic Reviews* 19:CD003650.

Kelly P et al. (1999). Micronutrient supplementation in the AIDS diarrhoea-wasting syndrome in Zambia: a randomized controlled trial. *AIDS*, 13:495–500.

Empirical co-trimoxazole for children aged < 1 year

Should empirical co-trimoxazole treatment be used for HIV-infected or -exposed infants under 1 year of age with severe or very severe pneumonia?

Population: HIV-infected or -exposed infants under 1 year of age with severe or very severe pneumonia

Intervention: Co-trimoxazole (20 mg/kg per day trimethoprim for 21 days)

Factor	Findings	Decision
Quality of evidence	The evidence was considered to be of moderate quality, as it was imputed from data on adults. No randomized controlled trial for comparison with an alternative in children was available. The systematic review of etiological pathogens strongly suggested a causative role of PCP in this age group.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Emprircal use of co-trimoxazole would brroaden coverage to include treatment of PCP.	Uncertainty about the balance of benefits versus harms and burdens? ☐ Yes X No
Risks or undesired effects	The panel found that severe adverse events are infrequent. Emprircal use of co-trimoxazole is, however, associated with emergence of antimicrobial resistance.	
Values and preferences		Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs		Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Emprircal use of co-trimoxazole would be feasible in most settings.	
Key questions arising	More information is needed on the optimal duration of treatment.	
Final strength and direction of recommendation	X Strong recommendation ☐ Weak or conditional recommendation X For the intervention ☐ Against the intervention	

Empirical co-trimoxazole for children aged > 1 year

Should co-trimoxazole be given empirically to HIV-infected or -exposed children over 1 year of age with severe or very severe pneumonia?

Population: HIV-infected or -exposed children over 1 year of age with severe or very severe pneumonia

Intervention: Co-trimoxazole (20 mg/kg per day trimethoprim for 21 days)

Factor	Findings	Decision
Quality of evidence	The evidence was considered to be of moderate quality, as it was imputed from data on adults. No randomized controlled trial for comparison with an alternative in children was available. The panel considered that there was limited evidence that PCP contributes to morbidity and mortality in older children.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Emprical use of co-trimoxazole would broaden coverage to include treatment of PCP.	Uncertainty about the balance of benefits versus harms and burdens? X Yes ☐ No
Risks or undesired effects	Although severe adverse events are infrequent, empirical ise of co-trimoxazole is associated with the emergence of antimicrobial resistance.	
Values and preferences		Uncertainty or differences in patient values and preferences? ☐ Yes X No
Costs		Uncertainty about whether the net benefits are worth the costs? X Yes ☐ No
Feasibility	Empircal use of co-trimoxazole would be feasible in most settings.	
Key questions arising	A randomized controlled trial of empirical use in this age group is needed.	
Final strength and direction of recommendation	☐ Strong recommendation X Weak or conditional recommendation ☐ For the intervention X Against the intervention	

Ceftriaxone as first-line treatment for very severe pneumonia

Could ceftriaxone be used in children with very severe pneumonia as a first-line regimen in place of ampicillin or penicillin plus gentamicin when the child is known or suspected to be HIV-infected?

Population: HIV-infected or -exposed infants and children aged 2 months–5 years with very severe pneumonia

Intervention: Ceftriaxone instead of ampicillin or penicillin plus gentamicin

Factor	Findings	Decision
Quality of evidence	The evidence was considered to be of very low quality. No randomized controlled trial has been conducted to compare this regimen with ampicillin or penicillin and gentamicin.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Use of ceftriaxone w ould broaden coverage to include treatment of selected Gram–negative bacteria, including methicillin-sensitive S. aureus. The panel considered that ceftriaxone provides better coverage than ampicillin plus gentamicin against penicillin-resistant S. pneumoniae and Gram-negative bacteria. Furthermore, it is given as a daily dose, and it is associated with lower risks for oto- and nephrotoxicity.	Uncertainty about the balance of benefits versus harms and burdens? X Yes ☐ No
Risks or undesired effects	Inappropriate use of ceftriaxone has been associated with an increase in the frequency of extended-spectrum ⊡lactamase in Gram-negative bacteria. In general, caution must be exercised in using calcium-containing intravenous solutions.	
Values and preferences		Uncertainty or differences in patient values and preferences? ☐ Yes ☐ No
Costs	The direct cost of the ampicillin plus gentamicin combination is lower than that of ceftriaxone; however, this cost does not include that of intravenous lines.	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Giving a daily dose of ceftriaxone is feasible in many settings.	
Key questions arising	Use could be affected by a high prevalence of methicillin-resistant S. aureus, in which case vancomycin would be appropriate; however, it is not affordable in many settings.	
Final strength and direction of recommendation	☐ Strong recommendation X Weak or conditional recommendation X For the intervention ☐ Against the intervention	

Ceftriaxone as second-line treatment for severe or very severe pneumonia

Could ceftriaxone be used as second-line treatment in children with severe or very severe pneumonia in the event of treatment failure* with ampicillin or penicillin plus gentamicin?

Population: HIV-infected or -exposed infants and children aged 2 months–5 years with very severe pneumonia

Intervention: Ceftriaxone instead of ampicillin or penicillin plus gentamicin

Factor	Findings	Decision
Quality of evidence	The evidence was considered to be of very low quality, with no randomized controlled trial to compare this regimen with ampicillin or penicillin plus gentamicin.	Lower quality evidence? X Yes ☐ No
Benefits or desired effects	Use of ceftriaxone would broaden coverage to include treatment of selected Gram–negative bacteria, including methicillin-sensitive S. aureus. Ceftriaxone provides better coverage than ampicillin plus gentamicin against penicillin-resistant S. pneumoniae and Gram-negative bacteria. Furthermore, it is given as a daily dose, and it is associated with lower risks for oto- and nephrotoxicity.	Uncertainty about the balance of benefits versus harms and burdens? X Yes ☐ No
Risks or undesired effects	Inappropriate use of ceftriaxone has been associated with an increase in the frequency of extended-spectrum β-lactamase in Gram-negative bacteria. In general, caution must be exercised in using calcium-containing intravenous solutions.	
Values and preferences		Uncertainty or differences in patient values and preferences? ☐ Yes ☐ No
Costs	The direct cost of the ampicillin plus gentamicin combination is lower than that of ceftriaxone; however, this cost does not include that of intravenous lines.	Uncertainty about whether the net benefits are worth the costs? ☐ Yes X No
Feasibility	Giving a daily dose of ceftriaxone is feasible in many settings.	
Key questions arising	Use could be affected by a high prevalence of methicillin-resistant S. aureus, in which case vancomycin would be appropriate; however, it not affordable in many settings.	
Final strength and direction of recommendation	☐ Strong recommendation X Weak or conditional recommendation X For the intervention ☐ Against the intervention	

* Failure to improve clinically or no resolution of fever after 48 h of first-line antibiotic treatment

Annex 5 GRADE profiles

Vitamin A supplementation: GRADE profile 1

Question: Should vitamin A versus placebo be used for the prevention of diarrhoea in children with HIV infection?[a]

Settings: Resource limited settings

References: Coutsoudis et al., 1995; Fawzi et al., 1999; Fawzi et al., 2000; Villamor et al., 2002; Semba et al., 2005

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin A	Placebo	Relative (95% CI)	Absolute		
Mortality, all-cause (median follow-up, 17–28 months)												
3	Randomized trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	27/131 (20.6%)	51/136 (37.5%)	RR 0.5 (0.31–0.79)	188 fewer per 1000 (79–259 fewer)	Low	Critical
Mortality, diarrhoea-specific (median follow-up, 17–28 months)												
2	Randomized trials	Serious[b]	Serious[d]	No serious indirectness[e]	Serious[c]	None	9/413 (2.2%)	27/416 (6.5%)	RR 0.26 (0.03–2.26)	48 fewer per 1000 (63 fewer to 82 more)	Very low	Critical
Hospitalizations for diarrhoea (follow-up, 97 child–months; number of episodes per number of follow-up months)												
1	Randomized trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	2/97 (2.1%)	8/97 (8.2%)	RR 0.25 (0.05–1.15)	62 fewer per 1000 (78 fewer to 12 more)	Low	Important
Incidence of acute diarrhoea (median follow-up, 17–28 months; history)												
3	Randomized trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	131	136	Not pooled	Not pooled[f]	Low	Critical
Incidence of persistent diarrhoea												
2	Randomized trials	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	None	100	109	Not pooled	Not pooled[g]	Low	Critical

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin A	Placebo	Relative (95% CI)	Absolute		
Severity of diarrhoea (median follow-up, 17–28 months; history or physical examination)												
2	Randomized trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	118	121	Not pooled	Not pooled[h]	Low	Important
Respiratory infections (follow-up, 17–28 months and 97 child–months in one study; history or physical examination)												
3	Randomized trials	Serious	No serious inconsistency	No serious indirectness	Serious[c]	None	131	136	Not pooled	Not pooled[i]	Low	Important
Anthropometric outcomes (median follow-up, 12 months; measured as height in centimeters; better indicated by higher values)												
1	Randomized trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	13	15	Not applicable	Sample mean, 2.8 higher (1–4.6 higher)	Low	Important

[a] Vitamin A given at similar doses: 200 000 IU for children aged > 1 year and 100 000 IU for those aged < 1 year at different intervals. Semba et al. (2005) gave 60 mg retinol equivalent every 3 months starting at age 15 months. Coutsoudis et al. (1995) gave vitamin A at 1, 3, 6, 9, 12 and 15 months of age. Fawzi et al. (1999) gave vitamin A on days 1 and 2 and 4 and 8 months later.

[b] Large losses to follow-up

[c] Few events

[d] I-square statistic = 75%

[e] Deaths reported here from Fawzi et al. (1999) include all children (HIV-stratified, count data not reported); not down-graded for indirect population

[f] Variable methods and reporting from three studies. Coutsoudis et al. (1995) reported adjusted OR for diarrhoea in HIV-infected children in vitamin A arm compared to placebo arm = 0.51 (95% CI, 0.27–0.99). Semba et al. (2005) reported OR for diarrhoea within last 7 days in vitamin A arm compared to placebo arm = 1.13 (95% CI, 0.88–1.46). Fawzi et al. (2000) reported RR for acute diarrhoea in HIV-infected children in vitamin A arm compared to placebo arm = 1.55 (95% CI, 0.75–3.17).

[g] Variable measures and definitions. Semba et al. (2005) reported OR for diarrhoea lasting > 30 days = 0.48 (95% CI, 0.19–1.18). Coutsoudis et al. (1995) reported OR for diarrhoea lasting > 7 days in HIV-infected children = 0.44 (95% CI, 0.17–1.18). Fawzi et al. (2000), numbers not stratified by HIV status.

[h] Variable measures. Semba et al. (2005) reported OR for blood in stools in vitamin A compared to placebo group = 0.65 (95% CI, 0.20–2.04). Fawzi et al. (2000) reported an adjusted OR for vitamin A compared to placebo for severe watery diarrhoea = 0.57 (95% CI, 0.34–0.97) and for severe dysentery = 1.16 (95% CI, 0.82–1.64) in a multivariate analysis that included HIV status.

[i] Variable measures. Coutsoudis et al. (1995) reported an OR for hospitalization for lower respiratory tract infection in HIV-infected children in vitamin A arm compared to placebo arm = 0.59 (95% CI, 0.13–2.65). Semba et al. (2005) reported an OR for persistent cough lasting > 30 days in vitamin A compared to placebo = 0.47 (95% CI, 0.23–0.96). Fawzi et al. (2000) reported an RR for cough and rapid respiratory rate in HIV-infected children in vitamin A group compared to placebo = 0.54 (95% CI, 0.24–1.20).

Use of low-osmolarity oral rehydration solution: GRADE profile 2

Question: Should reduced-osmolarity rehydration solution instead of standard ORS be used for acute diarrhoea in children?

Settings: Resource-limited settings

Reference: Hahn, Kim, Garner (2002).

Quality assessment						Summary of findings					
						No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Reduced-osmolarity ORS	Standard ORS	Relative (95% CI)	Absolute		
Mortality											
0	–	–	–	–	–	–	–	–	–		Critical
Need for unscheduled intravenous fluids											
8	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	No serious imprecision[b]	92/1004 (9.2%)	142/992 (14.2%)	OR 0.59 (0.45–0.79)	17 fewer per 1000 (9–23 fewer)	High	Critical
Stool output (measured as standardized mean difference in volume of stool output; better indicated by lower values)											
11	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	No serious imprecision	889	887	–	Sample mean, 0.23 lower (0.33–0.14 lower)	High	Critical
Asymptomatic hyponatraemia											
6	Randomized trials	No serious limitations	No serious inconsistency	Serious indirectness[a,d]	Serious[c]	51/562 (9.1%)	36/558 (6.5%)	OR 1.44 (0.93–2.24)	26 more per 1000 (4 fewer to 69 more)	Low	Important

[a] Population is HIV-uninfected children, but not downgraded for indirectness as it was assumed that the populations would not be different in terms of the intervention

[b] < 300 events, but not down-graded because of large total population

[c] < 300 events and CI indicates potential benefit and harm

[d] Asymptomatic hyponatraemia is an indirect measure of treatment outcome.

Zinc supplementation for persistent diarrhoea: GRADE profile 3a

Question: Should zinc be used for persistent diarrhoea?

Settings: Resource-limited settings

Reference: Lazzerini, Ronfani (2008)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	Control	Relative (95% CI)	Absolute		
Mortality												
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	Serious[b]	None	1/226 (0.4%)	5/225 (2.2%)	RR 0.2 (0.02–1.69)	18 fewer per 1000 (22 fewer to 15 more)	Moderate	Critical
Duration of diarrhoea (measured as hours with diarrhoea as defined in study; better indicated by lower values)												
5	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	No serious imprecision	None	267	262	–	Sample mean, 15.84 lower (25.43–6.24 lower)	High	Critical
Adverse events: vomiting												
4	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	Serious[b]	None	4/256 (1.6%)	2/249 (0.8%)	RR 1.97 (0.37–10.59)	8 more per 1000 (5 fewer to 77 more)	Moderate	Important

[a] Population is children without known HIV status (presumed uninfected), but not downgraded for indirectness as it was assumed that it is not biologically plausible that the populations differed in terms of the intervention.

[b] Few events

Zinc supplementation for acute diarrhoea: GRADE profile 3b

Question: Should zinc be used for acute diarrhoea?

Settings: Resource limited settings

Reference: Lazzerini, Ronfani (2008)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	Control	Relative (95% CI)	Absolute		
Mortality												
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[a]	Serious[b]	None	1/655 (0.2%)	1/735 (0.1%)	RR 1.12 (0.07–17.90)	0 more per 1000 (1 fewer to 23 more)	Moderate	Critical
Duration of diarrhoea (better indicated by lower values)												
9	Randomized trials	No serious limitations	Serious[c]	No serious indirectness[a]	No serious imprecision	None	1417	1324	–	Sample mean, 12.27 lower (23.02–1.52 lower)	Moderate	Critical
Adverse events: vomiting												
8	Randomized trials	No serious limitations	Serious[d]	No serious indirectness[a]	No serious imprecision	None	466/2390 (19.5%)	275/2337 (11.8%)	RR 1.71 (1.27–2.30)	84 more per 1000 (32–153 more)	Moderate	Important

a Population is uninfected children, but not downgraded for indirectness as it was assumed that it is not biologically plausible that the populations differed in terms of the intervention.

b Few events

c Heterogeneity present; I-square 84%; subgroup analyses of infants < 6 months and > 6 months of age without heterogeneity: sample mean, 5.23 (95% CI, –4 – 14.45) for < 6 months of age and 16.67 (95% CI, –31.03 – – 2.31) for > 6 months of age

d Heterogeneity present; I-square 69%; subgroup analyses of infants < 6 months and > 6 months of age without heterogeneity: RR 1.54 (95% CI, 1.02–2.24) for < 6 months of age and 1.72 (95% CI, 1.36–2.17) for > 6 months of age

Micronutrients for diarrhoea: GRADE profile 4

Question: Should multiple micronutrients be used in HIV-infected and -exposed children with persistent diarrhoea?

Settings: Resource-limited settings

Reference: Irlam et al. (2005)*

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-nutrients	Control	Relative (95% CI)	Absolute		
Morbidity (measured as proportion of self-reported weeks with diarrhoea per total weeks of follow-up; mean follow-up, 12 weeks)												
1	Randomized trial	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	66	69	RR 1.28 (0.81–2.02)	Not estimable[d]	Very low	Critical
Mortality (follow-up mean 12 weeks)												
1	Randomized trial	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	66 (0%)	69	RR 1.06	Not estimable[d]	Very low	Critical

* Includes the data published by Kelly et al. (1999), which were also used in the GRADE table as they are the only data specific to the effect of multiple micronutrients on persistent diarrhoea in the papers included in the review.

[a] No description of sequence generation or allocation concealment and large loss to follow-up other than deaths

[b] Study of adults with diarrhoea wasting syndrome; same data in both papers

[c] Few events, and (for diarrhoea morbidity) 95% CI indicates benefit and harm

[d] Raw numbers not provided; both RRs reported to be not significant between arms

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