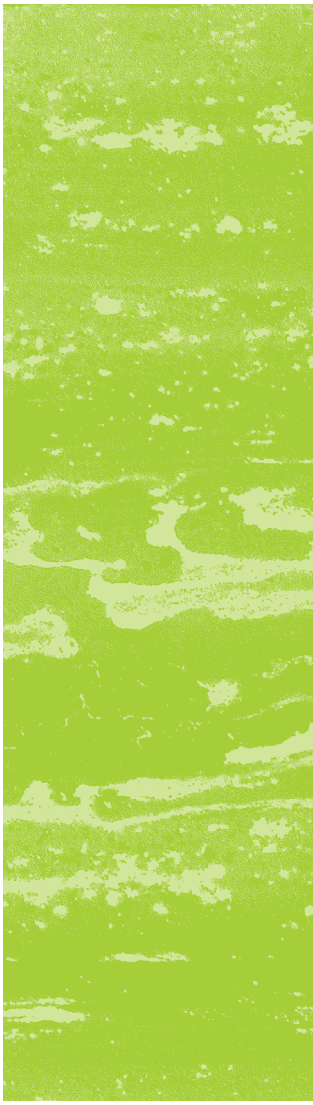
EVIDENCE FOR TECHNICAL UPDATE
OF POCKET BOOK RECOMMENDATIONS

Recommendations for management of common childhood conditions

Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care



World Health Organization

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Abbreviations

ABG	Arterial Blood Gas
AIDS	Acquired Immunodeficiency Syndrome
AIIMS	All India Institute of Medical Sciences
AOM	Acute Otitis Media
BD	Twice Daily
CAH	Child and Adolescent Health and Development
CHERG	Child Health Epidemiology Reference Group
CI	Confidence Interval
CICH	Centre for International Child Health
CSOM	Chronic Suppurative Otitis Media
DSMBs	Data and Safety Monitoring Board
GDG	Guidelines Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
ICHRC	International Child Health Review Collaboration
ICU	Intensive Care Unit
IM	Intramuscular
IMCI	Integrated Management of Childhood Illnesses
IPA	International Paediatric Association
ITT	Intention To Treat
IV	Intravenous
KEMRI	Kenya Medical Research Institute
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
MDI	Metered Dose Inhaler
MDR	Multidrug Resistant/Resistance
NEC	Necrotizing enterocolitis
NICE	National Institute for Clinical Excellence
NICU	Neonatal Intensive Care Unit
NNT	Numbers Needed to Treat
OR	Odds Ratio
PICO	Patient, Intervention, Comparison, and Outcome

PIVKA	Protein Induced Vitamin K Deficiency
QID	Four Times Daily
RCT	Randomized Control Trial
RR	Relative Risk
RSV	Respiratory Syncytial Virus
SAM	Severe Acute Malnutrition
SD	Standard Deviation
SGA	Small for Gestational Age
SSC	Skin-to-Skin Care
TID	Thrice Daily
VKDB	Vitamin K Deficiency Bleeding
VLBW	Very Low Birth Weight
WHO	World Health Organization
WMD	Weighted Mean Difference

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Guidelines development group members

Dr Fizan Abdullah, Johns Hopkins University School of Medicine, USA; Shinjini Bhatnagar All India Institute of Medical Sciences (AIIMS), India; Wills Bridget, Clinical Research Unit, Viet Nam; Harry Campbell, University of Edinburgh Medical School, UK; Leonila Dans, University of Philippines, Philippines; Trevor Duke, Centre for International Child Health, University of Melbourne, Australia; Michael English, University of Nairobi and KEMRI, Kenya; Andy Gray, University of Kwa-Zulu-Natal, South Africa; Sandra Grisi, Sao Paulo University, Brazil; Stuart Macleod, University of British Columbia, Canada; Hilda Mujuru, University of Zimbabwe, Zimbabwe; Susan Niermeyer, University of Colorado, USA; Jesca Nsungwa, Ministry of Health, Uganda; Vinod Paul, AIIMS, India; Haroon Saloojee, Witwatersrand University, South Africa; Mathu Santosham, Johns Hopkins School of Public Health, USA; Giorgio Tamburlini, Institute of Child Health, Italy; and Anita Zaidi, Aga Khan University, Pakistan.

Institutions

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Executive summary

Clinical care at first-referral hospitals in low-income countries is often provided by nurses, paramedical workers, and non-specialist general doctors with very limited resources. There is often inadequate support from the central level, poor access to information, little ongoing professional development or staff training, and most often low staff morale. The WHO *Pocket Book of Hospital Care for Children* was first published in 2005 to provide clinical guidance for the management of common childhood illnesses and to improve quality of care in first-referral hospitals in these settings. Since then, new evidence has emerged and there have been changes to several WHO guidelines requiring update of the Pocket Book.

In line with the current WHO *Handbook for Guideline Development*, key chapters in the *Pocket Book* were reviewed and clinical recommendations that required updating in view of the current evidence were identified. These were prioritized by the Guidelines Steering Committee through a consultative process with regional offices and implementation of the Pocket Book by external experts in an effort to identify gaps, new evidence, or changes to clinical practice that required updating. Several sections were identified as having priority and included management of common causes of fever (acute and chronic otitis media, typhoid fever and meningitis); treatment of acute respiratory infections; treatment of dysentery; use of antibiotics in cases with severe acute malnutrition (SAM); and management of several common neonatal conditions. These priority areas were the basis of the evidence review, and synthesis and development of these revised recommendations.

The development of the recommendations followed the WHO guideline development process and involved identification of review questions, retrieval of up-to-date relevant evidence, assessment and synthesis of the evidence, formulation and external review of the recommendations, and discussion on dissemination, implementation and regular updating of the guidelines.

The scientific evidence for the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. For each preselected priority question, evidence profiles were prepared based on up-to-date systematic reviews. The recommendations were formulated, peer reviewed and agreed on by consensus during the Guidelines Development Group (GDG) meeting held in Geneva, Switzerland, on 14–17 February 2011. The group assessed the available evidence and, by consensus, made a total of 50

recommendations: management of newborn conditions (11); cough and difficult in breathing (9); dysentery (2); fever (11); severe malnutrition (2); hypoglycaemia (1); use of oxygen therapy (11); and choice of fluids (3). In addition, the GDG identified knowledge gaps that needed further primary research and provided guidance on the implementation of the recommendations.

The GDG determined the strength of these recommendations based on the quality of evidence (graded as very low, low, moderate, or high) and additional factors (including values and preferences, the magnitude of effect, the balance of benefits versus risks, resource use, and feasibility of implementation). The recommendations were consequently rated as either strong (confident of desirable effects), weak/conditional (applicable to specific situations) or not recommended (further research required). In addition, the panel made remarks in order to ensure that each recommendation will be understood and used in practice in the context of its intended meaning.

1. Introduction

Every year some 8 million children in developing countries die before they reach their fifth birthday; many during the first year of life. Eight in ten of these deaths are due to neonatal conditions, acute respiratory infections (mostly pneumonia), diarrhoea (including dysentery), malaria, or severe malnutrition – or a combination of these conditions. The *Pocket Book of Hospital Care for Children* was first published in 2005, as a compilation of guidelines for the management of these common childhood illnesses at the first-referral level in low-resource settings with limited equipment and staff capacity. It is part of a series of documents and tools that support the Integrated Management of Childhood Illness (IMCI) guidelines for outpatient management of sick children. The Pocket Book guidelines focus on the inpatient management of the major causes of childhood mortality, such as pneumonia, diarrhoea, malaria, severe acute malnutrition (SAM), HIV/AIDS, and common or life-threatening causes of fever (i.e. meningitis, otitis media, and typhoid fever).

Since the first edition was published in 2005, new evidence has emerged resulting in updates of several WHO guidelines. These include: prevention and antiretroviral treatment in children with HIV; feeding of HIV-exposed children; treatment of tuberculosis (TB), malaria, and convulsions in children; management of chronic pain; and an update of the essential medicine list for children. These updates, and others, have meant that there was a need to update the relevant sections of the *Pocket Book*.

To ensure that most recommendations were up to date, the Pocket Book was reviewed by the Guidelines Steering Committee (GSC), which identified and prioritized chapters requiring updates (**Annex 1**). These constituted the basis of the collation and synthesis of the evidence for the recommendations on the management of common childhood conditions and illnesses. These recommendations specifically focussed on management of newborn conditions, treatment of cough and difficult in breathing, treatment of dysentery, management and treatment of common causes of fever, antibiotics in management of severe malnutrition, sublingual sugar for management of hypoglycaemia, detection of hypoxaemia and use of oxygen therapy, and choice of fluids in the management of shock.

This document provides the background, methods, and analysis of the evidence used in making all the recommendations put forth during the Guidelines Development Group (GDG) meeting convened in February 2011 at WHO headquarters in Geneva,

Switzerland. These recommendations were made based on the best available evidence as of December 2010, and take into consideration their risks and benefits, as well as their acceptability, cost, and feasibility of implementation.

1.1 Target audience

These recommendations are intended primarily for use by policy makers, child health programme managers, health-care providers, and professional bodies or technical partners involved in developing guidelines or advising ministries of health. They can also be used as a resource in medical training institutions in pre-service training.

1.2 Objectives of the recommendations

These recommendations are part of a series that will be used to update several guidelines and tools for clinical management of common childhood illnesses at health facilities at all levels of care. The main objectives are:

- To provide evidence-based recommendations for the clinical management of common childhood illnesses.
- To develop recommendations applicable in low-resource settings that maintain high standards of care.
- To develop evidence based recommendations for the update of the *Pocket Book of Hospital Care for Children* guidelines and IMCI clinical guidelines for management of common illnesses with limited resources.

1.3 Financial support

The main source of funding to support this work, including the systematic review of evidence, evidence compilation, convening the GDG panel meeting, editing, and printing of the recommendations, was provided by Better Medicines for Children Project funded by the Gates Foundation, with additional budget support and staff time from the WHO Department of Maternal, Newborn, Child and Adolescent Health. The WHO Collaborating Centre for International Child Health (CICH) in Melbourne, Australia, provided a full-time consultant to work with department for six months and participated in undertaking some of the systematic reviews.

1.4 Management of conflict of interest

All participants completed and signed a declaration of interest form; decisions taken on verbal declarations by members of the GDG at the meeting were documented and kept as a record. Declaration forms were reviewed and discussed by the WHO GSC before the meeting, and outcomes were approved by the Director of Department of Maternal, Newborn, Child and Adolescent Health. Participants who declared receiving research funding from non-commercial organizations for projects related to the meeting participated in all aspects of the meeting. Those with academic conflicts of interest, i.e. having authored sections of the previous version of the Pocket Book, fully participated in the proceedings, but were not allowed to chair any

of the sessions. Participants who had recent or current research funding or personal payments from commercial entities on topics related to the meeting were excluded from voting on final ratification the recommendations.

The following declarations of interest by members were assessed and found to be insufficient to exclude from full participation:

- Fizan Abdullah declared research grants from NIH for necrotizing enterocolitis;
- Shinjini Bhatnagar declared research funding for projects related to the topic of the meeting;
- Harry Campbell declared making public statements for international action against pneumonia;
- Trevor Duke declared completing systematic reviews related to the subject of the meeting;
- Michael English declared research grants from the Wellcome Trust, the Gates Foundation, the Royal College for Paediatrics and Child Health (RCPCH), and the Hillman Medical Education Fund (HMEF) on topics related to this meeting;
- Andrew Gray declared receiving honorarium and travel support from Aspen pharmaceuticals and Fresenius Kabi South Africa as a guest speaker, in 2009;
- Stuart Macleod declared being a director, which ceased in 2010, of an institution that received research grants with no direct involvement from several commercial and non-commercial entities.

The following members were excluded from final ratification of the recommendations:

- Haroon Saloojee received personal payments from the National Institute of Health (US$ 3000), was an advisory board member on rotavirus project of GlaxoSmith-Kline in 2008, as well as personal payment by Nestle Nutrition (US$ 2500);
- Leonila Dans declared a current research grant not related to the topic of the meeting from Pfizer with personal payments of about US$ 2000/year in 2010.

1.5 Guiding principles

The principles guiding the development of these recommendations were based on providing optimal public health guidance using the best available evidence in the management of common childhood conditions in settings with limited resources. The guiding principles are as follows:

- Prioritize and optimize the best options for treatment of common childhood illnesses to improve quality of care in hospitals in low-resource settings.
- Promote best practices based on a high quality level of evidence supporting strong recommendations in order to deliver the highest standards of care despite limited resources.
- Analyse and balance the benefits, risks, and feasibility of implementation of the recommendations in hospitals with limited resources.
- Build consensus among experts on recommendations in situations where there is very low quality or no supporting evidence.

2. Methodology and process

2.1 Defining the scope

The scope was defined by reviewing the 2005 edition of the *Pocket Book of Hospital Care for Children* and identifying the relevant recommendations that required updating. The department initiated a consultative process in 2009 to map out the status of WHO guidelines and recommendations that contributed to the development of the *Pocket Book*. In 2010, a Guidelines Steering Committee was set up consisting of members from key departments within WHO, including the Department of Maternal, Newborn, Child and Adolescent Health, Global Malaria Program (GMP), Essential Health Technologies (EHT), Mental Health and Substance Abuse (MSD), Essential Medicines and Pharmaceutical Policies (EMP), Stop TB (STB), and Nutrition for Health and Development (NHD). Consultations were undertaken with external experts implementing the *Pocket Book* or and with those who were previously involved in writing and/or editing the first edition in an effort to identify gaps, emerging evidence, or changes to clinical practice. Furthermore, feedback from the two field surveys conducted in 2008 and 2009 on the implementation and use of the *Pocket Book* were drawn upon to identify additional priority areas to be updated.

The process identified two categories of updates for the *Pocket Book*:

- Revisions to align the *Pocket Book* recommendations with recently published Guideline Review Committee (GRC)-approved WHO guidelines.
- Revisions of priority areas that required collation, analysis, and synthesis of the evidence to make recommendations in line with the current level of evidence.

In the first category, recommendations from existing GRC-approved WHO guidelines were identified for direct incorporation into the *Pocket Book*. The second category required systematic reviews to provide evidence to update or make new recommendations. The second category is the basis of this document wherein the group identified specific priority chapters, sections, and subsections of the *Pocket Book* requiring updates. As a result, a total of 34 PICO[1] questions were formulated for evidence collation and synthesis (**Annex 2**).

[1] PICO: Population/Patient Group, Intervention, Comparator, and Outcome. A PICO question is one that is formulated using the PICO framework, wherein the health-care provider asks and answers a series of questions meant to elicit information about their patient and their condition, interventions that have been undertaken or should be taken, any comparisons between the current treatment and possible alternatives, and outcomes to be desired or achieved.

The priority areas that were identified included: management of selected neonatal conditions; management of cough or difficulty breathing; antibiotics for treatment of dysentery; management of conditions with fever; antibiotics for severe acute malnutrition; and supportive care (i.e. oxygen therapy, choice of intravenous fluids, and treatment of hypoglycaemia).

2.2 Evidence retrieval and synthesis process

Throughout 2010, the Department of Maternal, Newborn, Child and Adolescent Health coordinated efforts to review and synthesize the evidence on the various, identified priority questions. This process included targeted, systematic reviews of relevant literature, preparation of GRADE profiles, and analysis of the risk-benefits, feasibility, and costs of implementation.

A literature search of the Cochrane Database and OVID-Medline was conducted in July 2010 to identify high quality, systematic reviews in the last two years that were relevant to the priority PICO questions. Where data were not available or up-to-date from the two sources, systematic reviews were commissioned to various groups to collate the evidence. The systematic reviews, meta-analyses, and GRADE profiles followed the methodology recommended by the GRC and as described in Version 5.1.0 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[1] Where data were lacking, systematic searches were conducted from various electronic databases, including Medline/PubMed, Embase, CENTRAL, NLM Gateway, and WHO regional databases.

For each question, data on critical and secondary outcomes were extracted and appraised by evaluating the quality, consistency, and external validity of the evidence. These were then graded from very low, low, medium, and high in tabular form using the GRADE methodology. Quality was defined as the extent to which one could be confident that an estimate of effect or association is correct and was based on the following criteria:

- study design;
- limitations of the studies, in terms of their conduct and analysis;
- the consistency of the results across the available studies;
- the precision of the results (wide or narrow confidence intervals);
- the directness (or applicability or external validity) of the evidence with respect to the populations of interest, interventions, and low-resource settings where the proposed intervention will be applied.

Additional considerations included the magnitude of the effect, presence or absence of a dose response gradient, and direction of plausible biases.

The quality of evidence was then categorized as: high, moderate, low, or very low as defined in **Table 2.1**.

[1] Higgins J and Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, West Sussex, The Cochrane Collaboration and John Wiley & Sons Ltd, 2008. Available at http://www.cochrane-handbook.org/. Accessed on 29 August 2011.

TABLE 2.1
Assessment of strength of evidence

LEVEL OF EVIDENCE	RATIONALE
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GRADE tables from systematic reviews were cross-checked, and where relevant, risk-benefit analysis was produced by the GSC. Internal discussions were held to evaluate the quality of the evidence presented to the GDG and needed to produce draft recommendations, benefits, harms and risks, costs of implementation, and acceptability. Recommendations were then formulated and drafted in accordance with procedures outlined in the WHO Handbook for Guideline Development,[1] and guided by the quality of evidence using the GRADE methodology.

In drafting the recommendations, the WHO Secretariat used those summaries of evidence for the critical outcomes (i.e. morbidity, mortality, disease progression and sequelae, or adverse events for medicines); quality of evidence; risks and benefits of implementing the recommendations; acceptability; costs; and feasibility. The recommendations were then were then ranked as strong or weak recommendation and research gaps or needs were identified.

2.3 Consensus building and external peer review

Draft recommendations, along with the supportive evidence (including summary of the evidence of the systematic reviews with risk-benefit analysis and GRADE tables) were circulated to selected expert external reviewers and some *Pocket Book* users for feedback (**Annex 4**). This process was managed electronically through a (EZcollab site accessible to external reviewers. Results of the peer review process were used to modify the draft recommendations before presentation to the GDG panel.

To formulate the final recommendations, these evidence summaries, with risk-benefit analysis and GRADE tables, were presented and discussed at an expert panel meeting held at WHO headquarters in Geneva, Switzerland, in February 2011. The panel weighed the quality of evidence, risks, and benefits, including acceptability, and placed emphasis on the values and feasibility of implementation in low-resource settings while ensuring that the recommendations are in line with international standards of care. Although most decisions were based on the evidence from randomized clinical trials (RCTs), or large effect observational cohort data, where the panel determined that there was insufficient evidence, expert consensus was used.

[1] WHO *Handbook for Guideline Development*. Geneva, World Health Organization, March 2010. Available at http://www.who.int/hiv/topics/mtct/grc_handbook_mar2010_1.pdf. Accessed on 29 August 2011.

TABLE 2.2
Assessment criteria for the strengths of recommendations

STRENGTH OF RECOMMENDATION	RATIONALE
Strong	The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional/Weak	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However: the recommendation is only applicable to a specific group, population or setting OR where the new evidence may result in changing the balance of risk to benefit OR where the benefits may not warrant the cost or resource requirements in all settings.
No recommendation	Further research is required before any recommendation can be made.

The grading of the strength of the final recommendations, in addition to the quality of evidence, were influenced by the balance between risks and benefits, acceptability (values and preferences), and cost and feasibility implementation in low-resource settings.

All of the final recommendations were reached by consensus without the need for voting. The panel also provided advise on strategies to support implementation of the recommendations through the *Pocket Book* and other quality-of-care tools.

In deciding on the strength of the recommendations, the panel was guided by the agreed-on assessment criteria described in **Table 2.2**. The decisions were made by consensus or, where necessary, by vote.

The final, graded recommendations and remarks made by the panel were also circulated to external reviewers, including WHO regional and country child health staff, for comments; the results of these comments were posted on the SharePoint for discussion. Where the panel requested more information, the Secretariat provided the information to all panel members for agreement.

2.4 Review and update of the recommendations

These recommendations will be regularly updated as more evidence is collated and analysed on a continuous basis with major reviews and updates at least every 3 to 5 years. However, reviews of evidence will be ongoing and where new data requires update of the recommendations, online interim updates will be produced. These recommendations will also form part of a technical series of the evidence behind several guidelines to be produced by the Department of Maternal, Newborn, Child and Adolescent Health over the coming years. The next major update will be done in 2014.

3. Implementation of the recommendations

3.1 Proposed subsidiary products

Although these recommendations were developed in the context of updating the *Pocket Book of Hospital Care for Children* used at the referral level, they will also be used to update the IMCI guidelines and other subsidiary child health implementation tools. Key tools to assist countries in the revision and update of national paediatric guidelines that are to be updated or developed include, but are not limited to:

- *Pocket Book* training CD-ROM
- *Hospital and self assessment tools*
- *A manual for clinical use of oxygen*
- *Integrated Management of Childhood Illiness clinical algorithms.*

The recommendations will be disseminated through various tools for improving quality of care and capacity building. The *Pocket Book* training CD-ROM used for in-service and pre-service training will be updated and widely distributed. The recommendations and the *Pocket Book* will be made available electronically as part of the quality of care improvement CD-ROM resource package, which will include quality assessment tools, a framework for quality improvement, and self-assessment tools to support managers and clinicians with improving quality of hospital care.

3.2 Implementation of the recommendations

In addition to publishing the recommendations as a stand alone reference document, they will be incorporated into various products mentioned above. They will mainly be circulated through the *Pocket Book of Hospital Care for Children*, which is the standard guideline used at first-referral level. The updated second edition of the *Pocket Book* will be translated into French, Spanish, and Russian in collaboration with regional offices for wider circulation and readership. The *Pocket Book* will be linked to the recommendations and the evidence used.

To increase its accessibility to the evidence used as the basis for the recommendations, it will also be made available for download from all of the WHO websites (headquarters, regional offices, and country offices) and select WHO Collaborating Centres websites in various electronic formats. While wider dissemination will continue through the *Pocket Book* sales in the WHO Bookshop, as well as through

a distribution network to all medical libraries or individuals and through the non-profit Teaching-Aids at Low Cost (TALC) website.[1]

The *Pocket Book* will be introduced in medical and paramedical training institutions through national societies and in collaboration with the International Paediatric Association (IPA). WHO will also continue collaborating with various child health groups that have been instrumental in dissemination, implementation, and evaluation of the *Pocket Book*, including:

- International Child Health Review Collaboration (ICHRC), a database of the evidence-base for the *Pocket Book* recommendations (http://www.ichrc.org).
- Centre for International Child health, a WHO Collaborating Centre in Melbourne, Australia (www.rch.org.au/cich).
- National and regional networks whose missions are to improve the quality of care for children in hospitals, like the Kenya Medical Research Institute (KEMRI) (http://www.idoc-africa.org/).
- Collaboration with various partners like the International Paediatric Association (IPA) who are collaborating with WHO on improving quality of care through their regional and national societies.
- Collaboration with child health specialists at national, regional, and international levels to support national adaptation and implementation of the *Pocket Book* as part of the process of improving quality of care.
- Collaboration with medical students through national, regional, and international societies.

Evaluation of the guidelines will continue to be undertaken through periodic quality of care assessments in hospitals and through country reviews undertaken by the department of Maternal, Newborn, Child and Adolescent Health using the quality of care framework and the hospital assessment tools mentioned above.

3.3 National adaptation and implementation

These recommendations have been developed mainly to provide guidance in the updating and development of standard paediatric treatment guidelines at national level in resource-limited settings. It is expected that each country will adapt these recommendations to suit their context in consideration of the necessary resources required for implementation. This will be facilitated by updating the current *Pocket Book of Hospital Care for Children*, which countries may adapt in developing national standards of care.

Countries may already have various paediatric guidelines in the form of national treatment guidelines or hospital case management protocols. These guidelines would have to be reviewed and compared against the WHO *Pocket Book* for standards of care. It is recognized that implementation of some of the recommendations may be

[1] Teaching-Aids at Low Cost may be obtained at http://www.talcuk.org/books/newborn-and-child-health-b.htm. Accessed on 29 August 2011.

challenging as they require updating national essential medicine lists and building consensus at national level.

Establishing national standards for hospital care for children is critical in improving quality of care and is a major component of the quality improvement process. Countries will be encouraged to set up national technical working groups to support the national adaptation process with the involvement of all stakeholders. The standards will then be adapted and endorsed by stakeholders, locally translated as required, and disseminated to all hospitals in the country. In most cases, it may require orientation of the health workers on the new case management protocols as part of the quality of care improvement process.

4. Recommendations

Recommendations for management of newborn conditions

4.1 Vitamin K prophylaxis in newborns

a) All newborns should be given 1 mg of vitamin K intramuscularly (IM) after birth (i.e. after the first hour by which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated).

(Strong recommendation, moderate quality evidence)

b) Neonates requiring surgical procedures, those with birth trauma, preterm newborns, and those exposed in utero to maternal medication known to interfere with vitamin K are at especially high risk of bleeding and must be given vitamin K (1 mg IM).

(Strong recommendation, moderate quality evidence)

4.2 Prophylactic antibiotics in newborns with risk factors for infection

A neonate with risk factors for infection (i.e. membranes ruptured > 18 hours before delivery, mother had fever > 38 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent) should be treated with the prophylactic antibiotics ampicillin (IM or intravenously, IV) and gentamicin for at least 2 days. After 2 days, the neonate should be reassessed and treatment continued only if there are signs of sepsis (or a positive blood culture).

(Weak recommendation, very low quality evidence)

4.3 Skin-to-skin contact in the first hour of life

Newborns without complications should be kept in skin-to-skin contact with their mothers during the first hour after birth to prevent hypothermia and promote breastfeeding.

(Strong recommendation, low quality evidence)

4.4 Management of neonatal jaundice

a) Term and preterm newbors with hyperbilirubinaemia should be treated with phototherapy or exchange transfusion guided by the following cut-off levels of serum hyperbilirubinaemia:

AGE	PHOTOTHERAPY		EXCHANGE TRANSFUSION	
	HEALTHY NEWBORNS ≥35 WEEKS GESTATION	NEWBORNS <35 WEEKS GESTATION OR ANY RISK FACTORS	HEALTHY NEWBORNS ≥35 WEEKS GESTATION	NEWBORNS <35 WEEKS GESTATION OR ANY RISK FACTORS
Day 1	Any visible jaundice		260 mmol/l (15 mg/dL)	220 mmol/l (10 mg/dL)
Day 2	260 mmol/l (15 mg/dL)	170 mmol/l (10 mg/dL)	425 mmol/l (25 mg/dL)	260 mmol/l (15 mg/dL)
Day ≥3	310 mmol/l (18 mg/dL)	250 mmol/l (15 mg/dL)	425 mmol/l (25 mg/dL)	340 mmol/l (20 mg/dL)

(Weak recommendation, very low quality evidence)

b) Clinicians should ensure that all newborns are routinely monitored for the development of jaundice and that serum bilirubin should be measured in those at risk:
   — in all babies if jaundice appears on day 1
   — in preterm babies (<35 weeks) if jaundice appears on day 2
   — in all babies if palms and soles are yellow at any age

(Strong recommendation, very quality evidence)

c) Phototherapy should be stopped once serum bilirubin is 50 mmol/l (3 mg/dl) or below the phototherapy threshold.

(Weak recommendation, expert opinion)

4.5 Empirical antibiotics for suspected neonatal sepsis

a) Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days.

(Strong recommendation, low quality of evidence)

b) If a neonate with sepsis is at greater risk of staphylococcus infection (e.g. extensive skin pustules, abscess, or omphalitis in addition to signs of sepsis), they should be given cloxacillin and gentamicin instead of penicillin and gentamicin.

(Strong recommendation, expert opinion)

c) Where possible, blood cultures should be obtained before starting antibiotics. If an infant does not improve in 2–3 days, antibiotic treatment should be changed, or the infant should be referred for further management.

(Strong recommendation, expert opinion)

4.6 Head or whole body cooling in management of hypoxic ischaemic encephalopathy

Head or whole body cooling should not be done outside well-resourced, tertiary neonatal intensive care units, because there is potential for harm from this therapy in low-resource settings.

(Strong recommendation, moderate quality evidence)

4.7 Antibiotics for treatment of necrotizing enterocolitis

Young neonates with suspected necrotizing enterocolitis (NEC) should be treated with IV or IM ampicillin (or penicillin) and gentamicin as first line antibiotic treatment for 10 days.

(Strong recommendation, low quality evidence)

4.8 Kangaroo Mother Care

Low birth weight (LBW) neonates weighing < 2000 g who are clinically stable should be provided Kangaroo Mother Care (KMC) early in the first week of life.

(Strong recommendation, moderate quality evidence)

4.9 Prevention of hypothermia immediately after birth in LBW infants

LBW neonates weighing >1200g who do not have complications and are clinically stable should be put in skin-to-skin contact with the mother soon after birth and after drying them thoroughly to prevent neonatal hypothermia.

(Weak recommendation, low quality evidence)

Recommendations for treatment of cough and difficulty in breathing

4.10 Treatment of non-severe pneumonia with wheeze

Antibiotics are not routinely recommended for children aged 2–59 months with non-severe pneumonia (i.e. fast breathing with no chest indrawing or danger sign) with a wheeze but no fever (< temperature 38 °C), as the cause is most likely to be viral.

(Strong recommendation, low quality evidence)

4.11 Antibiotic treatment for non-severe pneumonia with no wheeze

a) Children with non-severe pneumonia (i.e. fast breathing with no chest indrawing or danger sign) should be treated with oral amoxicillin. The exception is in patients with HIV:
   — With low HIV prevalence, give amoxicillin at least 40mg/kg/dose twice daily for 3 days.

— With high HIV prevalance, give amoxicillin of at least 40mg/kg/dose twice daily for 5 days.

(Weak recommendation, moderate quality evidence)

b) Children with non-severe pneumonia who fail on the first line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second line treatment.

(Weak recommendation, expert opinion)

4.12 Antibiotics treatment for severe pneumonia

a) Children aged 2–59 months with severe pneumonia (chest indrawing) should be treated with oral amoxicillin at least 40mg/kg/dose twice daily for 5 days.

(Strong recommendation, moderate quality evidence)

b) In HIV/AIDS infected children, specific guidelines for treatment of severe pneumonia in the context of HIV should be followed.

(Strong recommendation, low quality evidence)

4.13 Antibiotic treatment for very severe pneumonia

a) Children aged 2–59 months with very severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first line treatment.
   — Ampicillin: 50 mg/kg, or Benzyl penicillin: 50,000 units per kg IM/IV every 6 hours for at least 5 days
   — Gentamicin: 7.5 mg/kg IM/IV once a day for at least 5 days

(Strong recommendation, moderate quality evidence)

b) Ceftriaxone should be used as a second line treatment in children with severe pneumonia with failure on the first line treatment.

(Strong recommendation, expert opinion)

4.14 Inhaled salbutamol for treatment of acute wheeze/asthma and bronchoconstriction

a) Children with acute wheeze/asthma and bronchoconstriction should be treated with inhaled salbutamol using a metered dose inhaler (MDI) with spacer devices to relieve bronchoconstriction.

(Strong recommendation, low quality evidence)

b) Oral salbutamol should not be used for treatment of acute or persistent wheeze except where inhaled salbutamol is not available. Oral salbutamol is not useful in testing response to bronchodilators.

(Strong recommendation, low quality evidence)

Recommendations for treatment of dysentery

4.15 Antibiotics for treatment of dysentery

a) Children with diarrhoea and blood in stool (i.e. dysentery) should be treated with ciprofloxacin as a first line treatment. Ceftriaxone should be given as a second line treatment in severely ill children where local antimicrobial sensitivity is not known.
   — Ciprofloxacin: 15 mg/kg/dose twice daily for 3 days
   — Ceftriaxone: 50–80 mg/kg daily for 3 days

(Strong recommendation, low quality evidence)

b) Where local antimicrobial sensitivity is known, local guidelines should be followed.

(Strong recommendation, low quality evidence)

Recommendations for treatment of common causes of fever

4.16 Antibiotics for treatment of acute bacterial meningitis

a) Children with acute bacterial meningitis should be treated empirically with 3rd generation cephalosporins.
   — Ceftriaxone: 50mg/kg per dose IV every 12 hours or 100 mg/kg once daily, or
   — Cefotaxime: 50mg/kg per dose every 6 hours for 10–14 days.

(Strong recommendation, moderate quality of evidence)

b) Where it is known that there is no significant resistance to chloramphenicol and beta lactam antibiotics among bacteria-causing meningitis follow national guidelines or choose any of the following two regimens:
   — Chloramphenicol: 25 mg/kg IM (or IV) every 6 hours plus ampicillin: 50 mg/kg IM (or IV) every 6 hours

   OR

   — Chloramphenicol: 25 mg/kg IM (or IV) every 6 hours plus benzyl penicillin: 60 mg/kg (100 000 units/kg) every 6 hours IM (or IV).

(Conditional recommendation, moderate quality evidence)

4.17 Antibiotics for treatment of acute otitis media

a) Children with acute otitis media should be treated with oral amoxicillin at 40 mg/kg twice per for 7–10 days.

(Strong recommendation, low quality evidence)

b) Where pathogens causing acute otitis media are known to be sensitive to co-trimoxazole, this antibiotic could be used as an alternative given twice per day for 7–10 days.

(Strong recommendation, low quality evidence)

4.18 Topical antibiotics for treatment of chronic suppurative otitis media (CSOM)

a) Children with chronic suppurative otitis media (CSOM) should, in addition to aural toilet by dry wicking, be treated with instillation of drops containing quinolones (such as ciprofloxacin, norfloxacin, ofloxacin) three times daily for two weeks.

(Strong recommendation, low quality evidence)

b) Children who fail to respond to treatment should be referred for further evaluation for other causes of CSOM, especially tuberculosis.

(Strong recommendation, expert opinion)

4.19 Topical antiseptics for treatment of chronic suppurative otitis media

Topical antiseptics and steroids should not be used for the treatment of CSOM in children.

(Strong recommendation, low quality evidence)

4.20 Topical steroids for treatment of chronic suppurative otitis media

Topical steroids should not be used in treating CSOM.

(Weak recommendation, very low quality evidence)

4.21 Antibiotics for treatment of Typhoid Fever

a) Children with typhoid fever should be treated with a fluoroquinolone (i.e. Ciprofloxacin, Gatifloxacin, Ofloxacin, and Perfloxacin) as a first line treatment for 7–10 days.
   — Ciprofloxacin: orally 15 mg/kg/dose twice daily for 7–10 days.

(Strong recommendation, moderate quality evidence)

b) If the response to treatment is poor, consider drug-resistant typhoid, and treat with a second line antibiotic like 3rd generation cephalosporins or azithromycin.
   — Cetriaxone (IV): 80 mg/kg per day for 5–7 days,
   OR
   — Azithromycin: 20 mg/kg per day for 5–7 days.

(Strong recommendation, moderate quality evidence)

c) Where drug resistance to antibiotics among salmonella isolates is known, follow the national guidelines according to local susceptibility data.

(Strong recommendation, moderate quality evidence)

Recommendation for use of antibiotics in severe acute malnutrition

4.22 Antibiotics in management of severe acute malnutrition (SAM)

a) In children with severe acute malnutrition (SAM) without complications, manage according to the current community case management guidelines.

(Weak Recommendation, expert opnion

b) In children with SAM with complications, give parenteral antibiotics as follows:
   — Benzyl penicillin: 50 000 U/kg IM/IV every 6 hours, or ampicillin: 50 mg/kg IM/IV every 6 hours for 2 days, then oral amoxicillin: 15 mg/kg/dose every 8 hours for 5 days.

   AND

   — Gentamicin: 7.5 mg/kg IM/IV once daily for 7 days.

(Weak recommendation, low quality evidence)

Recommendations on Use and Delivery of Oxygen Therapy

4.23 Pulse oximetry for detection of hypoxaemia

Pulse oximetry is recommended to determine the presence of hypoxaemia and to guide administration of oxygen therapy in infants and children with hypoxaemia.

(Strong recommendation, low quality evidence)

4.24 Clinical signs for detection of hypoxaemia in children

a) Use pulse oximetry wherever possible for the detection of hypoxaemia in children with severe, lower respiratory infections. If oximetry is not available, then the following clinical signs could be used to guide the need for oxygen therapy:
   — central cyanosis
   — nasal flaring
   — inability to drink or feed (where this is due to respiratory distress)
   — grunting with every breath
   — depressed mental state (i.e. drowsy, lethargic)

(Strong recommendation, low quality evidence)

b) In some situations and depending on the overall clinical condition, children with the following less-specific signs may also need oxygen:
   — severe lower chest wall indrawing
   — respiratory rate of 70/min or above
   — head nodding

(Strong recommendation, very low quality evidence)

4.25 Oxygen therapy in treatment of hypoxaemia

a) Children with hypoxaemia should receive appropriate oxygen therapy.

(Strong recommendation, low quality evidence)

b) Effective oxygen delivery systems should be a universal standard of care, and should be made more widely available.

(Strong recommendation, expert opinion)

4.26 Thresholds for administering oxygen therapy

a) Administering oxygen therapy should be guided by pulse oximetry where available and thresholds for giving oxygen may vary depending on the altitude.

(Strong recommendation, very low quality evidence)

b) Children living at ≤ 2500 m above sea level should receive oxygen therapy if their oxygen saturation is ≤ 90%, as measured by pulse oximetry.

(Strong recommendation, very low quality evidence)

c) In children living at high altitude (> 2500m above sea level), the normal oxygen saturation is lower than those living at sea level. At these altitudes, a lower level of saturation, such as SpO_2 ≤ 87%, could be used as a threshold for giving oxygen.

(Recommendation, very low quality evidence)

4.27 Oxygen delivery methods

a) Nasal prongs are the preferred method for delivering oxygen in infants and children under 5 years of age with hypoxaemia who require oxygen therapy.

(Strong recommendation, moderate quality evidence)

b) Where nasal prongs are not available, nasal or nasopharyngeal catheters could be used as alternative delivery methods. Face masks or head-boxes are not recommended.

(Strong recommendation, moderate quality evidence)

4.28 Criteria for starting and stopping oxygen therapy

a) Children with hypoxaemia should be closely monitored using pulse oximetry.

(Strong recommendation, very low quality evidence)

b) Oxygen therapy should be discontinued when oxygen saturation remains stable above recommended levels of 90% (≤ 2500M above sea level) or 87% (> 2500M above sea level) for at least 15 minutes on room air in a clinically stable child.

(Strong recommendation, very low quality evidence)

Recommendations on treatment of hypoglycaemia

4.29 Sublingual administration of sugar in the treatment of hypoglycaemia

Sublingual sugar may be used as an immediate first aid measure in managing hypoglycaemia in children in situations where intravenous administration of glucose may be impossible or delayed.

(Strong recommendation, low quality evidence)

Recommendations on the choice of intravenous fluids

4.30 Choice of intravenous fluids for resuscitation and maintenance in children

a) Resuscitation: Children severely dehydrated or with signs of shock should be resuscitated using isotonic intravenous (IV) solutions such as sodium chloride 0.9% or ringers lactate.

(Strong recommendation, low quality evidence)

b) Intravenous maintenance fluid: For children who require IV fluids for maintenance, options include ringers lactate solution with 5% dextrose, sodium chloride 0.45% with glucose 5%, sodium chloride 0.45% with glucose 2.5%, or 0.9% sodium chloride with glucose 5%.

(Strong recommendation, low quality evidence)

c) Low sodium-containing solutions, such as sodium chloride 0.18% with glucose 4%, or 5% glucose in water, should not be used as there is an increased risk of hyponatraemia leading to cerebral oedema.

(Strong recommendation, low quality evidence)

5. Evidence for recommendations on the newborn conditions

5.1 Vitamin K prophylaxis in newborns

1. All newborns should be given 1 mg of vitamin K intramuscularly (IM) after birth (i.e. after the first hour by which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated).

(Strong recommendation, moderate quality evidence)

2. Neonates requiring surgical procedures, those with birth trauma, preterm babies, and those exposed in utero to maternal medication known to interfere with vitamin K are at especially high risk of bleeding and must be given vitamin K (1 mg IM).

(Strong recommendation, moderate quality evidence)

The panel put large value on the expected benefits of vitamin K prophylaxis which clearly outweigh the harms. It also noted that implementation was feasible, and the cost affordable in most settings.

5.1.1 Evidence and summary of findings

The incidence of classical vitamin K deficiency bleeding in the absence of vitamin K prophylaxis ranges from 10 to 1500 per 100 000 neonates, and that of late Vitamin K Dependant Bleeding (VKDB) ranges from 5 to 80 per 100 000. There is some evidence to indicate that the incidence of VKDB is at the higher end of the ranges given above in less-developed countries. We found moderate quality evidence to show that vitamin K prophylaxis reduces the risk of bleeding in newborns.

Only two RCTs conducted in the 1960s looked at the impact of vitamin K supplementation (0.1 to 5 mg IM) on bleeding in neonates [Vietti 1960, Sutherland 1967]. These studies showed that vitamin K prophylaxis is effective in preventing post-circumcision (39% reduction, NNT 21, 95% CI 13 to 50) and non-circumcision bleeding (43% reduction, NNT 80, 95% CI 42 to 714). One of the above studies showed that vitamin K prophylaxis resulted in an 81% reduction in moderate or severe bleeding (NNT 75, 95% CI 48 to 177) and a 97% reduction in severe bleeding (NNT 140, 95% CI 90 to 500). There was no difference in groups given 0.1 mg or 5 mg of vitamin K. The quality of this evidence was graded as moderate to low (**see GRADE table A7.1**).

Vitamin K prophylaxis has been shown to reduce sub-clinical deficiency in the first week of life (measured as the presence of a protein induced by vitamin K deficiency, or PIVKA). There was no significant difference between oral or IM vitamin K on subclinical deficiency in the first week of life. Studies have also looked as prothrombin time (PT) but none of the studies that included infants had a PT outside the normal range in the intervention and control groups. Two studies, which examined the effect of vitamin K prophylaxis on prothrombin complex deficiency, reported that IM prophylaxis reduced deficiency by 72% and oral prophylaxis by 50%.

Data from two observational studies showed that vitamin K prophylaxis – single dose administered at birth by either IM or oral route – reduces the incidence of late VKDB substantially; prophylaxis by IM route was significantly better (about 97%) than that by the oral route (65–83%) in reducing the incidence of late VKDB. Although late VKDB is rare, about one third of infants with this condition die or have severe handicaps. The NNT estimated from two observational studies (incidence with no vitamin K prophylaxis, 6 per 100 000) is about 18 000. If the incidence were 30 per 100 000, the number needed to treat to prevent a case of late VKDB is about 3000. The quality of this evidence was graded as low or very low.

5.1.2 Benefits and risks

Benefits

Vitamin K prophylaxis significantly reduces the risk of bleeding in neonates. Twenty neonates undergoing circumcision need to be given prophylaxis to prevent one case of bleeding after circumcision. About 80 neonates need to be given prophylaxis to prevent one case of non-circumcision bleeding. Late VKDB can be prevented with vitamin K prophylaxis – one case prevented per about 3000 infants treated.

Risks

The first report of a potential association between vitamin K prophylaxis and childhood cancer appeared in 1990. Subsequent research has not substantiated this concern.

5.1.3 Acceptability and feasibility

Vitamin K intervention is effective but the disease it prevents is relatively rare. Current practice in most developed countries is to give vitamin K prophylaxis to all newborn babies after birth. The cost of the medicine itself is US$ 0.195 per 1 mg injection. Costs of the syringe and needle and the supply of vitamin K, etc. would be additional. The costs for routine vitamin K administration may not be justifiable in low-resource settings.

5.2 Prophylactic antibiotics in newborns at risk of infection

A neonate with risk factors for infection (i.e. membranes ruptured > 18 hours before delivery, mother had fever > 38 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent) should be treated with prophylactic antibiotics

ampicillin (IM or IV) and gentamicin for at least 2 days. After 2 days, the neonate should be reassessed and treatment continued only if there are signs of sepsis (or a positive blood culture).

(Strong recommendation, Very low quality evidence)

The panel made this recommendation based on expert consensus as there was very low quality evidence that the intervention may prevent neonatal sepsis. There was no evidence available to evaluate harms and the risk of increasing antibiotic resistance, injection safety, and keeping a baby in hospital up to or for 5 days.

5.2.1 Evidence and summary of findings

The Cochrane review included only two studies. There were no deaths reported in the intervention or control groups in either of the studies. Similarly, one of the studies found no cases of sepsis in either of the groups. The quality of evidence from these two single studies is very low (**see GRADE table A7.2**).

None of the infants who participated in the trials died in the neonatal period. One of the studies (Wolf, 1976) reported four cases of neonatal sepsis, all of which occurred in the control (selective treatment) group. This difference was statistically non-significant (49 participants, RR = 0.12, 95% CI 0.01 to 2.04).

Data are insufficient to provide evidence of a beneficial effect of immediate prophylactic antibiotic compared to selective use of antibiotics on either neonatal mortality or on incidence of neonatal sepsis. The two trials were small and underpowered to detect any effect on the two outcomes of interest. The overall quality of evidence is very low.

5.2.2 Benefits and risks

Benefits

The intervention is likely to prevent neonatal sepsis.

Risks

No evidence is available to evaluate harms.

5.2.3 Acceptability and feasibility

IM antibiotic administration should be possible in small hospitals. Median price of ampicillin (250 mg) is US$ 0.18/vial and gentamicin (10mg/ml) is US$ 0.07/ml making the cost of implementation affordable in most low-resource settings.

5.3 Skin-to-skin contact in the first hour of life

Newborns without complications should be kept in skin to skin contact (SSC) with their mothers during the first hour after birth to prevent hypothermia and promote breastfeeding.

(Standard recommendation, low quality evidence)

The panel made the recommendation based largely on expert consensus and put large value on the expected benefits of skin-to-skin contact benefits on breastfeeding rates

at 1–4 months age and on exclusive breastfeeding at 4–6 months after birth. It also noted that although there is low quality evidence, the cost of its implementation is low and is most likely to be feasible to implement in low-resource settings.

5.3.1 Evidence and summary of findings

There was very low quality evidence from one Cochrane review published in 2007, although the studied population and intervention evaluated was generally in line with the intervention of interest. The exception was skin-to-skin contact was started after the first hour of birth in some of the studies included in the recommendation. Hence, the results should be interpreted with caution. Notably, there were important variations in the implementation of the intervention of interest. In many studies, the intervention was not initiated immediately after birth and its duration ranged from a few minutes to several hours in different trials. This is a common practice and being implemented currently according to WHO guidelines. Since there was no notable harm in implementing this recommendation, the expected benefits outweighed the risks.

There was very low quality evidence (**see GRADE table A7.3**) in making this recommendation. None of the studies included in the review examined the impact of early SSC on neonatal mortality. Ten studies involving 552 participants have showed significant positive effects of early SSC on breastfeeding at 1–4 months post birth (OR=1.8, 95% CI 1.08 to 3.07). Only one available trial with 92 participants assessed the effect of SSC on exclusive breastfeeding at 4–6 months post birth. Results were positive and statistically significant (OR=5.67, 95% CI 2.27 to 14.16). The pooled effect on mean duration of breastfeeding from seven trials (324 participants) was not statistically significant (weighted mean difference [WMD] = 42.55 days, 95% CI -1.69 to 86.79).

Three studies, with 168 participants, measured the effect of SSC on body temperature in the second hour of life. Two of them measured the temperature after 90 minutes of SSC and the third after 2 hours of SSC. All three studies started the intervention immediately after birth. The first two studies observed a positive, statistically significant effect while the third failed to demonstrate a significant difference in temperature between groups. Meta-analysis of these three studies showed a pooled WMD of 0.25 degrees centigrade, 95% CI -0.15 to 0.65.

Although there were a few studies from developing country settings, the majority were conducted in hospitals from high-income countries. No adverse effects were shown.

5.3.2 Benefits and risks

Benefits

SSC has a positive effect on breastfeeding 1–4 months post birth and on exclusivity of breastfeeding at 4–6 months after birth (low quality evidence for both). As exclusive breastfeeding is associated with improved survival, SSC may be expected to reduce neonatal mortality.

Risks

There is no evidence of harm with this intervention.

5.3.3 Acceptability and feasibility

The intervention has a low cost and should be feasible to implement. However, it requires acceptance by the mother, family, and community in general. Cultural barriers might need to be overcome in order to implement this intervention.

5.4 Management of neonatal jaundice

1. Term and preterm neonates with hyperbilirubinaemia should be treated with phototherapy or exchange transfusion guided by the following cut-off levels of serum hyperbilirubinaemia:

	PHOTOTHERAPY		EXCHANGE TRANSFUSION	
AGE	HEALTHY NEWBORNS ≥35 WEEKS GESTATION	NEWBORNS <35 WEEKS GESTATION OR ANY RISK FACTORS	HEALTHY NEWBORNS ≥35 WEEKS GESTATION	NEWBORNS <35 WEEKS GESTATION OR ANY RISK FACTORS
Day 1	Any visible jaundice		260 mmol/l (15 mg/dL)	220 mmol/l (10 mg/dL)
Day 2	260 mmol/l (15 mg/dL)	170 mmol/l (10 mg/dL)	425 mmol/l (25 mg/dL)	260 mmol/l (15 mg/dL)
Day >3	310 mmol/l (18 mg/dL)	250 mmol/l (15 mg/dL)	425 mmol/l (25 mg/dL)	340 mmol/l (20 mg/dL)

(Standard recommendation, very low quality evidence)

2. Clinicians should ensure that all infants are routinely monitored for the development of jaundice and serum bilirubin should be measured in those at risk:
   — in all babies if jaundice appears on day 1
   — in preterm babies (<35 weeks) if jaundice appears on day 2
   — in all babies if palms and soles are yellow at any age

(Standard recommendation, very quality evidence)

3. Phototherapy should be stopped once serum bilirubin is 50 mmol/l (3 mg/dl) or below the phototherapy threshold.

(Standard recommendation, expert opinion)

These suggested levels represent a consensus by the expert panel members based on very limited evidence, and the levels shown are approximations consistent with other international guidelines. The emphasis should be on preventive actions and risk evaluation where lower cut-offs for exchange transfusion may prevent some additional cases of kernicterus. This recommendation should be accompanied by a brief description on how to give phototherapy in clinical guidelines.

5.4.1 Evidence and summary of findings

Association between serum bilirubin levels and adverse neurodevelopmental outcomes: The systematic review by the National Institute of Health and Clinical Excellence (NICE), UK, and four additional studies were identified. Three observational studies evaluated the association of high serum bilirubin levels (> 340 micro mol/litre) with adverse sequelae: two studies were in term babies and one in babies with birth weight less than 1000 g. One study in term babies found no statistically significant association between hyperbilirubinaemia and IQ, abnormal neurological examination, or sensorineural hearing loss. Another study reported severe jaundice requiring exchange transfusion and early onset of jaundice as statistically significant risk factors for hearing loss. The third study found a weak association between high serum bilirubin levels and neurodevelopmental impairment, hearing impairment, and psychomotor impairment in babies with birth weight less than 1000 g. The NICE Guidelines Development Group (NICE GDG) concluded that term neonates with serum bilirubin > 340 micro mol/litre are at an increased risk of kernicterus.

Age-specific bilirubin cut-offs for instituting phototherapy or exchange transfusion: Two randomized trials relevant for this question were identified. One high quality study addressed this question in extremely low birth weight neonatal population (birth weight < 1000 gm; constituting < 1% of total newborn population) showing no role of aggressive phototherapy. The other trial found that there was little advantage in starting phototherapy early in babies with birth weight greater than 2500g. This evidence indicates that the currently used conventional cut-offs do not need to be further reduced. However, the "conventional" cut-offs are somewhat different than those in the current version of the *Pocket Book*. No direct evidence is available for the cut-off for exchange transfusion. The consensus cut-offs developed by the NICE GDG for exchange transfusions are somewhat lower than those in the current version of the *Pocket Book*.

5.4.2 Benefits and risks

Benefits

Lower cut-offs for phototherapy may avoid the need for exchange transfusion in the majority of infants with jaundice. Lower cut-offs for exchange transfusion may prevent some additional cases of kernicterus; but there is no evidence for the best cut-off which has to be agreed by consensus.

Risks

Aggressive phototherapy may not be beneficial and may be associated with adverse effects in non-specialized settings.

5.4.3 Acceptability and feasibility

Exchange transfusion is only possible in tertiary care settings.

5.5 Empirical antibiotics for suspected neonatal sepsis

a) Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days.

(Strong recommendation, low quality of evidence)

b) If a neonate with sepsis is at greater risk of staphylococcus infection (e.g. extensive skin pustules, abscess, or omphalitis in addition to signs of sepsis), should be given cloxacillin and gentamicin instead of penicillin and gentamicin.

(Strong recommendation, expert opinion)

c) Where possible, blood cultures should be obtained before starting antibiotics. If an infant does not improve in 2–3 days, antibiotic treatment should be changed, or the infant should be referred to a neonatologist for further management.

(Strong recommendation, expert opinion)

In making this recommendation, the panel considered the high antimicrobial sensitivity to third generation cephalosporins, and the lack of enough evidence to choose between beta-lactams plus gentamicin and 3rd generation cephalosporins. In developing countries, streptococci continue to be highly sensitive to beta-lactams, although sensitivity to gentamicin of *staphylococcus aureus* (40–95%) and gram negative enteric bacteria (32–100%) is variable. In order to guide empirical prescribing, it is crucial to monitor changes in the pattern of causative organisms and their antimicrobial susceptibility profiles since the effects may depend on antibiotic susceptibility patterns.

5.5.1 Evidence and summary of findings

The evidence for these recommendations are from two existing Cochrane reviews that have concluded there is not enough evidence to choose between different antibiotic combinations for first line treatment of early or late neonatal sepsis [Mtitima, 2004; Gordon, 2005]. Sepsis in neonates is classified as early (presenting within 72 hours after birth) and late (presenting after 72 hours after birth) because this predicts aetiology. In early sepsis the most common organisms are *Group B streptococcus* and gram negative enteric bacteria (esp. *E. coli*). Late onset community acquired infections are predominantly caused by *Strep. Pneumoniae*, *Staphylococcus aureus*, *E. coli* and other gram negatives.

The evidence is from four RCTs of 3rd generation cephalosporin monotherapy versus penicillin and aminoglycoside combination that were identified. One of these was conducted in South Africa and all others were conducted in Europe. Two trials used cefotaxime and the other two used ceftazidime monotherapy as the intervention. Three trials used ampicillin or benzyl penicillin with gentamicin as the control treatment, while one trial used penicillin with netilmicin as the control treatment. The overall quality of evidence was graded as low (**see GRADE table A7.4**).

Mortality and cure rates were similar between intervention and control groups in three of the four studies. However, there was a significantly higher cure rate in the South African study. Overall, there was no difference in mortality or cure rates

between the intervention and control groups. One study reported that a combination of ceftazidime plus ampicillin had higher cure rates than the ampicillin-gentamicin combination.

5.5.2 Benefits and risks

Benefits

Available evidence indicates no difference in cure rates and mortality between 3rd generation cephalosporin monotherapy and penicillin-aminoglycoside combination therapy. However, effects may vary in different settings depending on antibiotic susceptibility patterns. Other benefits of 3rd generation cephalosporins are good cerebrospinal fluid penetration and convenient once/twice daily administration.

Risks

The risks of ceftriaxone include displacement of bilirubin from albumin leading to higher free bilirubin and risk of kernicterus and promotion of beta-lactamase resistance.

5.5.3 Acceptability and feasibility

Neonates with suspected sepsis will require admission irrespective of the antibiotic chosen. Therefore differences in the convenience of administration are less important. Median price of ampicillin (250 mg) is US$ 0.18/vial, gentamicin (10mg/ml) is US$ 0.07/ml, and ceftriaxone (250 mg) is US$ 0.44/vial. Cefotaxime is more expensive than ceftriaxone.

5.6 Head or whole body cooling in management of hypoxic ischaemic encephalopathy

Head or whole body cooling should not be done outside well-resourced, tertiary neonatal intensive care units, because there is potential for harm from this therapy in low-resource settings.

(Strong recommendation, moderate quality evidence)

The panel made this recommendation on the basis of potential harm from body cooling if applied outside a neonatal intensive care unit where mechanical ventilation, sedation and other supportive care cannot safely be provided. It noted that in low resource settings there was no evidence supporting this therapy and that it was expensive. However, in well resourced tertiary neonatal intensive care units, treatment with whole body cooling as part of high quality intensive care support improves survival and reduces disability for term neonates with asphyxia and hypoxic ischaemic encephalopy.

5.6.1 Evidence and summary of findings

There is moderate quality evidence that induced hypothermia (cooling) of newborn babies who may have suffered from a lack of oxygen at birth reduces death or disability, without increasing disability in survivors. The damage caused by the lack

of oxygen continues for some time afterwards. One way to try and stop this damage is to induce hypothermia by cooling the baby or just the baby's head for hours to reduce the amount of damage to brain cells. The evidence from trials show that induced hypothermia helps to improve survival and development at 18 months for term newborn babies at risk of brain damage. However, all the studies were done in highly resourced, neonatal intensive care units with adequate support with no data from settings in developing countries.

Eight RCTs were included in this review, comprising 638 term infants with moderate or severe encephalopathy and evidence of intrapartum asphyxia [Jacobs, 2007]. Six were performed as pilot studies, three in single centres in New Zealand, Turkey and China; and the others at multiple centres in Australia and North America. All 8 trials included term newborn infants with moderate or severe encephalopathy and evidence of intrapartum hypoxia-ischaemia without obvious congenital abnormalities. Infants in all studies were randomised with initiation of the intervention by six hours of age [mean age at entry range: 1.9 hours to 4.6 hours].

Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neuro-developmental disability to 18 months of age (typical RR 0.76, 95% CI 0.65, 0.89; typical RD -0.15, 95% CI -0.24, -0.07; NNT 7, 95% CI 4,14). Cooling also resulted in statistically significant reductions in mortality (typical RR 0.74, 95% CI 0.58, 0.94; typical RD -0.09, 95% CI -0.16, -0.02; NNT 11, 95% CI 6, 50) and in neurodevelopmental disability in survivors (typical RR 0.68, 95% CI 0.51, 0.92; typical RD -0.13, 95% CI -0.23, -0.03). Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and a significant increase in thrombocytopaenia.

This result is both statistically significant and clinically important, with a relative risk reduction of 24%, absolute risk reduction of 15%, and NNT of 7.

5.6.2 Benefits and risks

Benefits

There clear benefits of cooling on survival and neurodevelopment which outweigh the short-term adverse effects associated with therapeutic hypothermia.

Risks

There is possible increased risk of thrombocytopaenia and hypotension from the therapeutic hypothermia.

5.6.3 Acceptability and feasibility

Parents may be willing to allow their child to undergo this procedure as they would reasonably expect that cooling would decrease their baby's chance of dying and may lessen the occurrence of a major disability, if their child survived.

5.7 Antibiotics for treatment of necrotizing enterocolitis

Young neonates with suspected necrotizing enterocolitis (NEC) should be treated with IV or IM ampicillin (or penicillin) and gentamicin as a first line antibiotic treatment for 10 days.

(Standard recommendation, low quality evidence)

Remarks

The panel noted that it has been common practice to add metronidazole to the treatment of NEC. Although there is no evidence to judge its benefits, metronidazole covers gastrointestinal tract anaerobic bacteria (such as *Bacteroides fragilus*). It also noted that while a combination of vancomycin and ceftriaxone is a suitable alternative, the only evidence is from tertiary western intensive care units. Vancomycin and 3rd generation cephalosporins are expensive, and would not be feasible to use as a first line antibiotic treatment for NEC in low-resource settings.

5.7.1 Evidence and summary of findings

NEC is a serious disease characterized by varying degrees of mucosal necrosis, seen predominantly in premature infants. The underlying pathogenesis remains unclear and pathogenic organisms are not isolated in many cases. Clustering of cases and outbreaks in nurseries suggest an infective component to its aetiology.

Four studies were found directly comparing antibiotic regimens in NEC. One non-concurrent cohort study from Belgium was excluded as the effect of the addition of metronidazole to an existing antibiotic regimen could not be separated from other simultaneous modifications to an existing management protocol (e.g. earlier and different surgical approaches, changes in anaesthesia, and modification of intensive care management routines).

One study included 46 cases of NEC in 1982–3 treated with ampicillin and gentamicin, and 44 cases in 1984–5 treated with vancomycin and ceftriaxone [Scheifele, 1987]. There were no statistical differences in any measured outcomes for infants of birth weight > 2200g and complications were infrequent in both groups. For infants < 2200g, those treated with Vancomycin demonstrated statistically lower rates of death ($p = 0.048$), need for surgery ($p = 0.04$), culture positive peritonitis ($p = 0.01$), and major complications ($p = 0.004$): these included peritonitis, strictures, feed intolerance, and recurrent NEC and thrombocytopenia. The quality of evidence was graded as very low.

One RCT allocated 42 premature infants with radiographically confirmed NEC to receive IV ampicillin and gentamicin or to receive ampicillin, gentamicin, and clindamycin [Faix, 1998]. This study found an increased rate of complicating strictures in the clindamycin group (NNT harm 3, 95% CI 2 to 13) with a consequently longer time needed to restart feeds (8.4 days versus 22.3). There were no significant differences in rates of death or in incidence of gangrene/perforation. The study was terminated early due to significantly higher rates of strictures in the clindamycin group. The quality of evidence was graded as low (**see GRADE table A7.5**).

One RCT allocated 20 infants with NEC to receive ampicillin and gentamicin versus IV ampicillin and gentamicin with oral gentamicin for 4 days [Hansen, 1987]. In this study, enrolled infants were more mature (ampicillin and gentamicin 34.7±1.3 weeks gestation and ampicillin and gentamicin with oral gentamicin 35.6±1.1 weeks) and higher birth weight (ampicillin and gentamicin 2220±295g and ampicillin and gentamicin with oral gentamicin 2180±198g) than many studies reporting NEC. This study found no significant differences in outcomes ($p > 0.05$), including days with peritonitis, days with pneumatosis, major complications including perforation, stricture and ileus, and death. This study was underpowered to detect most differences, with blinding and allocation concealment not well defined. The quality of this evidence was graded as low.

5.7.2 Benefits and risks

Benefits

Vancomycin and ceftriaxone may be better than ampicillin and gentamicin for treatment of NEC but the confidence in this statement is low, because factors other than antibiotics may have resulted in or contributed to the beneficial effect as the study was a non-concurrent study. There is no evidence to judge the benefits of metronidazole.

Risks

Clindamycin was administered in one study to cover gram negative organisms and resulted in a significantly higher rate of stricture formation. There is no evidence to judge the risks of metronidazole.

5.7.3 Acceptability and feasibility

A combination of vancomycin and ceftriaxone may not be feasible and may be expensive to use as a first line antibiotic treatment in infants with NEC.

5.8 Kangaroo Mother Care

Low birth weight (LBW) neonates weighing < 2000 g who are clinically stable should be provided Kangaroo Mother Care (KMC) early in the first week of life.

(Strong recommendation, moderate quality evidence)

The panel noted that although there is no evidence for KMC in babies > 2000 g, KMC may be beneficial in neonates who have temperature instability. However, implementation will require a description on how to provide KMC.

5.8.1 Evidence and summary of recommendations

We identified one recent systematic review [Lawn, 2010] which aimed to assess the effect on neonatal mortality and morbidity from complications of preterm birth of KMC compared to no care at all or compared to conventional care. A preterm death was defined as a neonatal death in a baby with a birth weight < 2000 g. KMC was

defined as the combination of continuous skin-to-skin contact, support for exclusive breastfeeding or other appropriate feeding and early recognition, and response to complications. Studies where KMC was only commenced after the first week of life were excluded. Measured outcomes were neonatal mortality due to complications of preterm birth, or morbidity related to prematurity.

The review included 15 studies: nine randomized controlled trials (RCT), and six observational studies. All studies were from low or middle-income countries. Of the RCTs, six reported mortality data, but only three were included in the analysis. Two studies were excluded because median time of initiation of KMC was greater than 1 week after birth, and the third study – a community trial from Bangladesh – was thought to have important methodological limitations and was not conducted in health facilities. Analysis of the three remaining trials – from India, Colombia and Ethiopia – showed a major mortality reduction with KMC for babies < 2000 g (RR 0.49, 95% CI 0.29 to 0.82; 988 infants (High quality evidence, **see GRADE table A7.6**).

These mortality results are supported by results from three observational studies (8257 infants) which also showed a mortality reduction (RR 0.68, 95% CI 0.58–0.79), though this was heavily influenced by a large South African study that contributed 96% to the weight of the pooled estimate.

Five RCTs reported data on serious morbidity, defined as severe pneumonia, sepsis, jaundice, and other severe illness. There were variations in study definitions and heterogeneity in the results (I^2 = 70%, P < 0.01). However, KMC was associated with a reduction in serious neonatal morbidity (RR 0.34; 95% CI 0.17 to 0.65; 1520 babies. (Moderate quality evidence, **see GRADE table A7.6**).

5.8.2 Benefits and risks

Benefits

There is high quality evidence that KMC leads to a significant reduction in neonatal mortality, and moderate quality evidence that it reduces serious morbidity, when compared to conventional care for babies < 2000 grams in low- to middle-income countries. Other benefits were seen with breastfeeding and bonding.

Risks

Possible risks include apnoea and bradycardia in some babies. It should be noted that KMC should be started once the LBW infants are clinically stable.

5.8.3 Acceptability and feasibility

The benefits would be highly valued by families, health providers and programme managers/policy makers. Additional costs for training health workers and counseling mothers and families in KMC would be offset by the cost for conventional care (i.e. use of incubators).

5.9 Prevention of hypothermia immediately after birth in low birth weight infants

Low birth weight (LBW) neonates weighing > 1200 g who do not have complications and are clinically stable should be put in skin-to-skin contact with the mother soon after birth and after drying them thoroughly to prevent neonatal hypothermia.

(Strong recommendation, low quality evidence)

In making the recommendation, the panel noted that although the plastic wraps for LBW infants are beneficial in reducing hypothermia, the possible risks of using plastic wraps in settings in developing country were not known. There is very little experience with this intervention in developing countries and further research into the type of plastic to be used, as well as the practicality and appropriateness of using the plastic-wrap technique in low-resource settings, is required.

5.9.1 Evidence and summary of findings

We identified one recent systematic review through Cochrane [McCall 2010] that sought to assess the effect on interventions to prevent hypothermia in preterm and/or LBW infants. The review included three interventions of interest: (1) plastic wraps; (2) plastic caps; and (3) skin-to-skin contact. Studies were included that evaluated these interventions started within 10 minutes of birth. Hypothermia was defined as core body temperature < 36.5 °C on admission to neonatal intensive care unit (NICU) or up to 2 hours after birth. There was low to moderate quality evidence that caps or plasticwraps reduced hypothermia, and moderate quality evidence that skin to skin contact significantly reduced hypothermia in LBW newborns (**GRADE table A7.7**)

Plastic wraps or bags were effective in reducing heat loss in infants < 28 weeks' gestation (four studies; n = 223; WMD 0.68 °C; 95% CI 0.45, 0.91), but not in infants between 28 to 31 weeks gestation (1 study, n = 41). Two of the studies in infants of gestational age < 29 weeks showed that plastic wrap significantly reduces the risk of hypothermia on admission to the NICU (two studies, n = 152; RR 0.66, 95% CI 0.51, 0.84; RD -0.27; 95% CI -0.41, -0.13). Four infants would need to be wrapped in plastic in order to prevent one infant from becoming hypothermic (NNT 4, 95% CI 2 to 8).

Plastic caps were effective in reducing heat losses in infants < 29 weeks' gestation (one study; n = 64; MD 0.80°C; 95% CI 0.41, 1.19). This study also reported that plastic caps significantly reduce the risk of hypothermia on admission to the NICU (RR 0.48, 95% CI 0.32, 0.73; RD -0.47; 95% CI -0.67, -0.27). Two infants would need to wear a plastic cap in order to prevent one infant from becoming hypothermic (NNT 2, 95% CI 2 to 4).

For infants with a birth weight between 1200 and 2199g, evidence suggests that skin-to-skin contact significantly reduces the risk of hypothermia (as defined by the study) within 6 hours of birth when compared to conventional incubator care (one study; n = 31; RR 0.09, 95% CI 0.01, 0.64; RD -0.56, 95% CI -0.84, -0.27). Two infants would need to receive skin-to-skin contact in order to prevent one infant from becoming hypothermic (NNT 2, 95% CI 1 to 4).

5.9.2 Benefits and risks

Benefits

Plastic wrap or plastic cap used immediately after birth prevents hypothermia in infants of gestation < 29 weeks. For LBW infants above 1200 g, skin-to-skin contact immediately after birth effectively prevents hypothermia.

Risks

No evidence of reported harms was available.

5.9.3 Acceptability and feasibility

Plastic wraps are relatively of low cost, may be easy to use and acceptable to parents of LBW newborns.

6. Evidence for recommendations for treatment of pneumonia

6.1 Antibiotic treatment for non-severe pneumonia with wheeze

Antibiotics are not routinely recommended for children with non-severe pneumonia (i.e. fast breathing with no chest indrawing or danger sign) with a wheeze but with no fever (< temperature 38 °C), as the cause is most likely to be viral.

(Strong recommendation, low quality evidence)

This recommendation is applicable only in situations where the health workers are able to assess "wheeze". The panel observed that there is evidence that WHO criteria for diagnosing pneumonia performs poorly in children with wheeze; that the addition of fever to WHO criteria improves diagnostic accuracy in this group of children; and that children with wheeze and no fever are very unlikely to have bacterial pneumonia.

6.1.1 Evidence and summary of findings

No systematic reviews addressing the effectiveness of antibiotics in children with non-severe pneumonia were identified. However, two recent RCTs provide direct evidence. The evidence for the effectiveness of antibiotics is mixed, in part due to the significant (but as yet undetermined) proportion of children fulfilling the criteria for non-severe pneumonia, who have either a viral illness or non-infectious aetiology. In Asia, up to 60% of children with non-severe pneumonia are reported to also have an audible wheeze by auscultation.

Observational data provides evidence that: the addition of fever to the WHO criteria for pneumonia improves its specificity for children with wheeze, and children with non-severe pneumonia and wheeze, with no fever or history of fever, have a low risk of bacterial pneumonia and most recover without antibiotics. There is also new evidence from one trial in Pakistan showing that antibiotics are no better than placebo for children with WHO-defined non-severe pneumonia (**see GRADE table A7.8**).

Antibiotics in all children presenting with non-severe pneumonia in Pakistan

Hazir et al (2010) conducted a double-blinded, randomized, placebo-controlled trial of oral amoxicillin versus placebo for non-severe pneumonia in four centres in Pakistan. Children were enrolled if they fulfilled WHO criteria for non-severe pneumonia: cough or difficulty breathing and fast breathing (using age-dependant WHO cut-offs). The study recruited 900 children, and randomized 450 children

to each group. At baseline, 73–80% of children had a history of fever, and 30–50% recorded a temperature >37.8 °C. While 50–60% of children had wheeze on examination, only 5–6% reported history of wheeze.

Using intention-to-treat (ITT) analysis, by day 3, 50 children in the amoxicillin group (11.1%) and 45 children in the placebo group (10%) failed treatment. The difference was not statistically significant: odds ratio (95% CI) 1.13 (0.72 to 1.76). Cumulative treatment failure by day 5 was also similar between the two groups (OR 0.87, 95% CI 0.61 to 1.24). Per-protocol, 7.2% (31/431) of children in the amoxicillin group and 8.3% (37/442) in the placebo group failed treatment on day 3 (OR 0.85, 95% CI 0.50 to 1.43). There was no difference in relapse by day 14 (OR 0.58, 95% 0.11 to 2.81).

There were no differences between groups in the number of children requiring change (or initiation) of antibiotics, the number of children who developed danger signs, or the number of children requiring hospitalization. There were no deaths.

On logistic regression analysis, treatment failure was associated with a history of difficulty breathing (OR 2.86, 95% CI 1.13 to 7.23), and temperature > 37.8 °C (OR 1.99, 95% CI 1.37 to 2.90) at enrolment.

Antibiotics in children presenting with non-severe pneumonia and wheeze in India

Awasthi et al (2008) was a double-blinded, randomized controlled multi-centre trial in India using amoxicillin (31–54 mg/kg/day) versus placebo for children 2–59 months with WHO non-severe pneumonia and wheeze (audible or auscultatory). The study was powered to detect non-inferiority of placebo. Children were enrolled if they presented with WHO-defined non-severe pneumonia, did not respond to up to three doses of inhaled salbutamol, and had a normal chest X-ray. Recruited children were treated as outpatients with oral salbutamol and either amoxicillin or placebo. Outcomes were treatment failure at day 4, defined as development of WHO-defined severe or very severe pneumonia, hypoxaemia (SpO2<90%), or persistence of non-severe pneumonia, wheeze or fever. Clinical relapse was defined as cases which were clinically cured by day 4, but showed signs of WHO-defined pneumonia by day 11–14.

The study recruited 1671: 836 in the placebo group and 835 in the amoxicillin group. Loss to follow-up was <5% by day 14. Baseline characteristics of both groups were similar: adherence to placebo and amoxicillin was higher than 95%, and there were no differences between groups in adherence to oral salbutamol. Respiratory syncytial virus (RSV) was detected in nasopharyngeal aspirates of 48 of 778 children in the placebo group (6.2%) and 40 of 780 children in the amoxicillin group (5.1%). About 15% of children had audible wheeze; for the rest, wheeze was only heard on auscultation.

On ITT analysis, placebo was inferior to amoxicillin: 24% of children in the placebo and 19.9% in the amoxicillin groups failed treatment (difference 4.2%, 95% CI 0.2 to 8.2). There was no difference in the rates of relapse. Clinical failure due to the development of severe or very severe pneumonia or hypoxaemia was similar between groups.

Evidence from observational studies and indirect evidence

Hazir et al (2004) showed that 62% of 1004 children presenting with non-severe pneumonia and wheeze responded to bronchodilators. Among responders, only 15% showed clinical deterioration at follow-up. Predictors of deterioration were: fever > 38 °C (OR 6.61, 95% CI 2.73 to 16.11); history of fever (OR 2.11, 95% CI 1.44 to 3.03); or age 1-11 months (OR 1.83, 95% CI 1.26 to 2.66).

A prospective observational study of children presenting with fast breathing or lower chest indrawing and wheeze [Lochindarat, 2008] followed-up with children fulfilling the WHO criteria for non-severe pneumonia and wheeze responsive to bronchodilator. Of 263 children with non-severe pneumonia and wheeze, 85% responded to bronchodilators and were discharged on oral salbutamol but no antibiotics. On follow-up, symptoms had resolved in 96% of children by day 3, and in 97% by days 5–7. The only independent predictor of clinical deterioration was age 1–11 months. On a separate analysis, the following factors predicted non-response to bronchodilators in children presenting with WHO-defined non-severe or severe pneumonia and wheeze: age 12–59 months; history of fever; no family history of wheeze; fever > 38.0 °C; and presence of lower chest indrawing.

Kabir et al (2009) conducted a non-blinded, randomized multi-centre trial of antibiotics for bronchiolitis in Bangladesh. Children aged <24 months with runny nose, cough, breathing difficulty, chest indrawing, and rhonchi on auscultation were enrolled and allocated to one of three groups: ampicillin (7 days); oral erythromycin (7 days); or no antibiotics. All children received nebulized salbutamol, oxygen (if SpO_2 < 90%), IV fluids, nasogastric feeding, and oropharyngeal suction. The study recruited 327 children; 10% dropped out. Baseline characteristics were similar across groups. There were no significant differences in clinical improvement between groups. Children in the no-antibiotic group had a significantly shorter duration of hospital stay than the antibiotic groups ($p<0.001$). For all children, most breathing or chest symptoms (i.e. cough, breathing difficulty, wheeze, chest indrawing, tachypnoea, tachycardia, rhonchi, and crepitations) gradually improved after day 4.

Cardoso et al (2010) studied the ability of WHO criteria to identify pneumonia among children presenting with wheeze. Children 2–59 months presenting to the paediatric emergency department of five hospitals in Brazil with acute lower respiratory tract infections (LRTI) were prospectively recruited. Diagnoses were further subclassified as pneumonia, acute bronchitis, acute bronchiolitis, wheezing, and recurrent wheezing. All diagnoses where made by three physicians, blinded to each others' diagnoses: the admitting paediatrician; a chest physician; and a radiologist. Chest X-rays were taken for all cases of suspected pneumonia and bronchiolitis. Where a chest X-ray was done, the final diagnosis required the agreement of at least two of the three physicians.

Data for 390 children were analyzed. Chest X-rays were performed for 153 of these children. Diagnoses were acute bronchitis in 28 (7%) children, acute bronchiolitis in 7 (2%), wheezing in 117 (30%), recurrent wheezing in 168 (43%) and pneumonia

in 70 (18%; 15 of whom also had recurrent wheezing). Agreement between the paediatricians' and the paediatric chest physicians' diagnoses was high (κ=0.86, 95% CI 0.82 to 0.90).

Overall, WHO criteria had a sensitivity of 84% and a specificity of 19% in predicting pneumonia. Adding fever to the WHO criteria slightly reduced the sensitivity to 81%, but improved specificity to 46%. In children with wheeze, WHO criteria had a sensitivity of 90% and a specificity of 12% for predicting pneumonia. The addition of fever reduced the sensitivity to 85%, but improved specificity to 42%. The ability of WHO criteria to predict pneumonia was much better in children without wheeze (sensitivity 76% and specificity 62%). The addition of fever to the criteria had no effect on the sensitivity and improved the specificity to 70%.

[Mathews et al 2009] conducted a prospective cohort study in a paediatric emergency department in the USA to determine the clinical predictors of pneumonia among children with wheeze. Children (<18 years) with wheeze on examination, and who underwent a chest X-ray for evaluation of pneumonia were enrolled. Pneumonia was defined radiographically, and required the consensus of two blinded radiologists.

The study included 526 patients; 75% were less than 5 years old. A total of 26 patients had pneumonia. Eighty-one percent of patients with pneumonia had a history of fever at home, compared with 58% of patients with no pneumonia (positive LR: 1.39, 95% CI: 1.13–1.70); $p < 0.02$). Fifty percent of patients with pneumonia had a triage temperature of < 38.0 °C, compared with only 25% of patients without pneumonia (positive LR: 2.03, 95% CI: 1.34–3.07; $p < 0.01$). Seventy-three percent of patients with pneumonia had a temperature of < 38.0°C in the emergency department, compared with 38% of patients who did not have pneumonia (positive LR: 1.92, 95% CI: 1.48–2.49; $p < 0.001$). Among afebrile children (temperature of < 38 °C) with wheezing, pneumonia was very uncommon (2.2%, 95% CI: 1.0–4.7).

6.1.2 Benefits and risks

Benefits

Rationalizing antibiotic therapy avoids the risk of side effects for the patient, and reduces the risk of antimicrobial resistance.

Risks

Withholding antibiotics from children with bacterial pneumonia.

6.1.3 Acceptability and feasibility

Withholding antibiotics may be less acceptable to caregivers. Implementation of this recommendation will require training health workers to educate and council caregivers, and the need for close follow-up. Health workers will require training in auscultation.

6.2 Antibiotic treatment for non-severe pneumonia with no wheeze

a) Children with non-severe pneumonia (i.e. fast breathing with no chest indrawing or danger sign) should be treated with oral amoxicillin. The exception is in patients with HIV.
   — With low HIV prevalence, give amoxicillin of at least 40mg/kg/dose twice daily for 3 days.
   — With high HIV prevalence, give amoxicillin of at least 40mg/kg/dose twice daily for 5 days.

(Weak recommendation, moderate quality evidence)

b) Children with non-severe pneumonia who fail on the first line treatment with amoxicillin should have the option of referral where there is no appropriate second line treatment.

(Weak recommendation, expert opinion)

This recommendation was made based on mostly RCTs that were conducted in Asia, and more likely in low HIV prevalence settings. Amoxicillin was recommended based on values and preferences since dispersible amoxicillin is becoming more available and the cost is decreasing. The panel also clarified that the moderate quality evidence relates to comparisons of the duration of the two antibiotic regimens of amoxicillin for 3 versus 5 days which showed that they were no different in terms of cure and clinical failure rates.

6.2.1 Evidence and summary of findings

Randomized trials have not shown significant differences in the effectiveness of different oral antibiotics for the treatment of non-severe pneumonia in children (**see GRADE table A7.9**). Amoxicillin and co-trimoxazole are the most widely available antibiotics. Amoxicillin has been shown to be more effective than co-trimoxazole for treating severe pneumonia in one trial. There is no significant difference between short duration (3 day) and long duration (5 day) antibiotic therapy for non-severe pneumonia in low HIV prevalence settings.

A systematic review [Sajwani, 2010] identified trials comparing different oral antibiotics and short-course (3 days) versus long-course (5 days) oral antibiotics.

Choice of antibiotic

Three studies compared oral co-trimoxazole with oral amoxicillin. The studies involved 3952 children (2067 in the co-trimoxazole group and 1885 in the amoxicillin group) between 2 months and 59 months of age with WHO-defined non-severe pneumonia. One study [Strauss, 1998] also included a subset of children with severe pneumonia. Two studies were double blinded RCTs, with adequate allocation concealment. The third study was an open-label and cluster-randomized. Primary outcomes were clinical cure and failure. Comparing amoxicillin to co-trimoxazole, pooled analysis shows no difference in clinical failure (RR 1.09, 95% CI 0.93 to 1.27; 3 studies) nor cure rate (RR 0.99, 95% CI 0.96 to 1.01; 2 studies).

One open-label RCT compared oral levofloxacin with oral co-amoxiclavulanic acid. The study involved 708 children (including 270 children < 5 years), with infiltrates on chest X-ray and at least two clinical indicators of pneumonia. There was no difference in cure rate at 10–17 days after completing treatment for children < 5 years between the two groups (RR 1.02, 95% CI 0.93 to 1.11).

Two RCTs involving 393 children compared azithromycin with co-amoxiclavulanic acid in children with chest X-ray and clinical findings of pneumonia. Treatment failure at 2 weeks was not significantly different between groups (RR 1.20, 95% CI 0.45 to 3.21).

One study from Chile of 47 children between 1 month and 14 years with X-ray and clinical signs suggestive of classical bacterial pneumonia compared oral azithromycin and oral amoxicillin. Children receiving azithromycin normalised their chest X-ray on day 7 significantly more often than those treated with amoxicillin ($p<0.009$). However, clinical response on days 3, 7, and 14 were not significantly different.

One open-label RCT involving 100 children aged 2 months to 12 years with non-severe pneumonia in Nigeria compared amoxicillin with co-amoxyclavulanic acid. Cure rates were better with co-amoxiclavulanic acid (OR 10.44, 95% CI 2.85 to 38.21); however, allocation concealment was inadequate.

An open randomized multi-centre study involving 68 children aged 2–16 years with radiologically proven pneumonia compared oral azithromycin with oral erythromycin. There was no significant difference in clinical success or adverse outcomes.

Aetiology and antibiotic susceptibility [Grant et al, 2009]

Aetiological data comes from studies of inpatients with severe pneumonia. The common bacterial pathogens are *Streptococcus pneumoniae* (17–37%), *Haemophilus influenzae* (0–31%) and *Staphylococcus aureus* (1–33%). Approximately 25% of community acquired pneumonia has a positive viral diagnostic test.

Given that there are limited data on the aetiology of non-severe pneumonia, antibiotics have been targeted at the pathogens known to cause severe pneumonia. There are limited data on the effect of antibiotic resistance in pneumonia. There are data showing in-vitro resistance to co-trimoxazole correlating with poor clinical outcome in acute otitis media. Although the trial by Strauss et al showed higher failure rate for children with severe pneumonia receiving co-trimoxazole as compared to amoxicillin, it is not clear whether this was due to resistance.

Treatment duration

Four studies involving 6513 participants were identified that compared the same antibiotic for different durations (3 days versus 5 days). Two studies compared amoxicillin three times daily (30–50 mg/kg/day), and two studies compared co-trimoxazole. All were randomized, double-blinded, placebo-controlled trials. Pooled analysis found no difference in cure rates (RR 0.99, 95% CI 0.98 to 1.01, n=5892), failure rates (RR 1.07, 95% CI 0.92 to 1.25, n=5892), and relapse rate (RR 1.06, 95% CI 0.82 to 1.37, n=2753) between long- versus short-duration treatment.

6.2.2 Benefits and risks

Amoxicillin and co-trimoxazole are the most widely available oral antibiotics for non-severe pneumonia. The study by Strauss et al suggests higher treatment failure in severe pneumonia with co-trimoxazole as compared to amoxicillin.

Studies of the duration of amoxicillin therapy are briefly summarized here, and have been assessed and summarized in a WHO 2003 consultative meeting report [WHO, 2003]. Trials in low-HIV prevalence settings have shown equal effectiveness between short- (3 days) and long- (5 day) duration therapy. The benefits of short-term therapy are increased compliance, lower cost, and lower exposure to potential antibiotic side effects. However, shortened courses have not been as well-studied in areas of high-HIV prevalence, where a substantially greater burden of severe bacterial pneumonia exists among persons infected with HIV. Prudence indicates that shortening treatment to a 3-day course should be studied before being implemented in such settings.

6.2.3 Acceptability and feasibility

Amoxicillin and co-trimoxazole are widely available. Oral amoxicillin was preferred as first line treatment over co-trimoxazole, because it is effective against both non-severe and severe pneumonia in low HIV settings. In high HIV settings, amoxicillin is also preferred because oral co-trimoxazole is recommended for PCP prophylaxis. Oral amoxicillin will also be recommended as first line treatment for children with severe pneumonia tolerating feeds, and this should simplify uptake.

Amoxicillin is slightly more expensive than co-trimoxazole. Cost of amoxicillin 250 mg is US $0.018 per capsule and US$ 0.022 per dispensable tablet. Cost of standard combination co-trimoxazole is US$ 0.013 [UNICEF, 2010].

6.3 Antibiotics treatment for severe pneumonia

a) Children aged 2–59 months with severe pneumonia (chest indrawing) should be treated with oral amoxicillin of at least 40mg/kg/dose twice a day for 5 days.

(Strong recommendation, moderate quality evidence)

Although this recommendation may be applicable to case management at the community or outpatient level, its implementation should be guided by the clinical context and setting. It is not applicable in children infected with HIV/AIDS for whom clinicians should follow the current HIV specific guidelines.

b) In children infected with HIV/AIDS, specific guidelines for treatment of severe pneumonia in the context of HIV should be followed.

(Strong recommendation, low quality evidence)

6.3.1 Evidence and summary of findings

A recent systematic review included five studies that compared oral with injectable antibiotics for WHO-defined severe pneumonia [Jabeen et al 2010]. Overall, there is moderate quality evidence that oral therapy with amoxicillin is an effective and safe

alternative to parenteral antibiotics in low HIV settings (**see GRADE tables A7.10 & A7.11**). Oral amoxicillin is an effective and safe alternative to parenteral antibiotics in low HIV settings in children with severe pneumonia (chest indrawing) who do not have any other serious signs or symptoms.

Campbell et al (1988) compared oral co-trimoxazole versus IM procaine penicillin followed by oral ampicillin in 134 children with non-severe or severe pneumonia. At day 7 of follow up, treatment failure occurred in 6 out of 66 patients (9.1%) in the oral co-trimoxazole group and 7 out of 68 patients (10.2%) in the combined-treatment group. The risk difference was not significant: -0.01% (95% CI -0.11 to 0.09). The study reported one death during the follow-up period in the injectable therapy group.

Straus et al (1998) included 302 children with severe pneumonia and compared oral cotrimoxazole (n=203) with oral amoxicillin (n=99). Treatment failure rates were higher in the cotrimoxazole group (33%) compared to oral amoxicillin (18%) (RR 1.79; 95% CI 1.13 to 2.84). There was no significant association between antimicrobial minimum inhibitory concentration and outcome among bacteraemic children treated with co-trimoxazole and amoxicillin.

Addo-yobo et al (2004) evaluated 1702 children with severe pneumonia, comparing oral amoxicillin (n = 857) versus IV penicillin (n = 845) for two days followed by oral amoxicillin. After 48 hours, treatment failure occurred in 161 out of 845 patients (19%) in the amoxicillin group and 167 out of 857 patients (19%) in the parenteral penicillin group. The risk difference was not significant: -0.4% (95% CI -4.2 to 3.3). At the end of follow up (14 days), the cumulative proportion of deaths in each group was 0.2% in oral versus 1% in parenteral, but this did not reach statistical significance (RD -0.6%, 95% CI -0.1 to 1.3). The authors reported similar recovery in both groups at 5 and 14 days.

Atkinson et al (2007) conducted a study in eight paediatric centres in England (general district and tertiary hospitals) and enrolled all but the most severe cases of pneumonia. Children were randomly assigned to a 7-day treatment of either oral amoxicillin (n = 100) or IV benzyl penicillin (n = 103). The primary outcome examined was time for temperature to be < 38 °C for 24 continuous hours. The study found equivalence between the two treatments, with a median time of 1.3 days for the primary outcome to be achieved in both groups.

Hazir et al 2008 compared hospitalization and parenteral ampicillin four times a day for 2 days followed by 3 days oral amoxicillin with ambulatory home-treatment (n = 1025) versus oral amoxicillin twice daily for 5 days (n = 1012). The primary outcome was treatment failure measured by clinical deterioration. There were 87 (8.6%) treatment failures in the hospitalization group and 77 (7.5%) treatment failures in the ambulatory group by day 6: a non-statistically significant risk difference of 1.1%, 95% CI - 1.3 to 3.5. Five (0.2%) children died within 14 days of enrolment, one in the ambulatory group and four in the hospitalized group. In each case, treatment failure was declared before death and the antibiotic had been changed. None of the deaths were considered to be associated with treatment allocation.

Another RCT that compared day care versus hospital care management of pneumonia [Ashraf, 2010], but did not compare an oral antibiotic arm with injectable

antibiotics. Children 2 to 59 months of age with severe pneumonia received either day care, with injectable ceftriaxone once daily for 5 days, feeding, and supportive care (n = 180) or hospital care (n = 180) with similar 24-hour treatment. The mean ± SD durations of day care and hospital care were 7.1 ± 2.3 and 6.5 ±2.8 days, respectively. Primary outcome was treatment success based on SpO_2 > 95% in-room air. In the day care group, 24 (13.3%) children failed therapy, while in the hospital care group 7 (3.9%) children failed therapy (RR 3.4, 95% CI 1.5 to 7.8) with the difference in failure rate being predominantly due to hypoxaemia defined as SpO_2 ≤ 95%. During the follow-up period, 22 (14.1%) children in the day care group and 11 (6.4%) children in the hospital care group required readmission to hospitals (RR 2.0, 95% CI 0.99 to 4.0). Two children died in the hospital group during the 3-month follow-up period. The estimated cost per child treated successfully at the clinic and the hospital were US$ 114 and US$ 178, respectively.

6.3.2 Benefits and risks

Benefits

Oral antibiotic therapy will be favorable to the health system as it will be less expensive and will lead to reduced burden on the health system. Despite concerns about reported in vitro (laboratory) resistance of pneumococcus to penicillin, there are no reports of clinical failure. Oral amoxicillin is more effective than oral co-trimoxazole for the treatment of severe pneumonia (chest indrawing).

Risks

Amoxicillin is a very safe drug. Mild adverse events like skin rash and diarrhoea may occur in a small number of children. In rare cases, penicillin-related anaphylactic reaction may.

6.3.3 Acceptability and feasibility

Home treatment with a 5-day course of amoxicillin is preferable, because of the associated reduction in referral, admission, risk of nosocomial infections, and treatment costs as well as the reduced invasiveness of oral treatment when compared with parenteral treatment. Day care treatment with injectable ceftriaxone would be much more expensive than oral antibiotic treatment at home. Cost of amoxicillin 250 mg is US$ 0.018 per capsule and US$ 0.022 per dispersible tablet. Cost of injectable benzyl penicillin 1 million i.u (600 mg) is US$ 0.354 and of injectable ceftriaxone 1G is US$ 1.056, which is higher than oral amoxicillin.

It is feasible to distribute oral amoxicillin in resource-limited settings as it is available in all countries.

6.4 Antibiotics treatment for very severe pneumonia

1. Children aged 2–59 months with very severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first line treatment.
   — Ampicillin: 50 mg/kg, or Benzyl penicillin: 50,000 units per kg IM/IV every 6 hours for at least 5 days

— Gentamicin: 7.5 mg/kg IM/IV once a day for at least 5 days

(Strong recommendation, moderate quality evidence)

2. Ceftriaxone should be used as second line treatment in children with severe pneumonia with failure of the first line treatment.

(Strong recommendation, expert opinion)

In making this recommendation, the panel noted that there is good evidence for the superiority of ampicillin and gentamicin over chloramphenicol, as well as major concerns about future supplies. However, there is poor evidence in favour of ampicillin and gentamicin as compared to other antibiotics. Although there was no data on the use of ceftriaxone, the panel recognized the need to include ceftriaxone as a second line treatment for children with very severe pneumonia, especially for hospital care.

6.4.1 Evidence and summary of findings

Evidence from one systematic review that included two large, RCTs comparing beta-lactam and gentamicin versus chloramphenicol for very severe pneumonia shows high quality evidence that ampicillin/penicillin and gentamicin reduce clinical failure rates compared to chloramphenicol. There is moderate quality evidence for a trend towards reduced death rates for treatment with ampicillin/penicillin and gentamicin compared to chloramphenicol (**see GRADE table A7.12**).

The first RCT [Duke, 2002] conducted in the highlands of Papua New Guinea (1600-1800 m above sea level) included 1116 children aged 1–59 months with WHO-defined very severe pneumonia (modified to include heart failure as a danger sign). Enrolled children had a median oxygen saturation of 71%. Five hundred and fifty-nine (559) children were treated with 100 mg/kg/day chloramphenicol; 557 children were treated with penicillin (200 mg/kg/day) plus gentamicin (7.5 mg/kg/day). Duration of treatment was 14 days. Measured outcomes were: death, treatment failure by day 5, and readmission. More children in the penicillin/gentamicin group required a change of antibiotic (60 versus 49), while 147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes ($p = 0.11$, not significant). Thirty-six children treated with chloramphenicol and 29 treated with penicillin and gentamicin died (difference not significant). More children treated with chloramphenicol than penicillin and gentamicin represented with severe pneumonia within 1 month of hospital discharge ($p = 0.03$).

The second RCT [Asghar, 2008] was a multi-country study, with 80% of children residing at sea level. Children aged 2–59 months were enrolled: 479 randomized to receive chloramphenicol (75 mg/kg/day), and 479 randomized to receive amoxicillin (200 mg/kg/day) and gentamicin (7.5 mg/kg/day). Median oxygen saturation on admission was higher than for the PNG study (88%). Duration of treatment was 10 days. More children in the chloramphenicol group required a change in antibiotic (45 versus 26). Measured outcomes were death or treatment failure by days 5, 10, and 21. More children failed treatment with chloramphenicol at day 5 (16% versus 11%; relative risk 1.43, 95% CI 1.03 to 1.97) and also by days 10 and 21. There was a trend

towards reduced death rates in children treated with amoxicillin plus gentamicin, but this was not significant.

6.4.2 Benefits and risks

Benefits

Combination beta-lactam plus gentamicin reduces failure rates and may reduce pneumonia mortality.

Risks

Side effects/toxicity of recommended antibiotics as outlined in **section 6.2** in the WHO *Model Formulary for Children* [WHO 2010].

6.4.3 Acceptability and feasibility

Value was placed on reduction in failure rates and likely reduction in mortality with beta-lactam and gentamicin combination. All drugs are in the Essential Medicines for Children List. Ampicillin, gentamicin and chloramphenicol are the currently recommended options for management of very severe pneumonia.

Ampicillin and gentamicin are more expensive per dose than chloramphenicol. Median price [Management Science for Health/WHO 2010]:

- Ampicillin 250 mg: US$ 0.1786/vial
- Gentamicin 10mg/ml: US$ 0.0665/ml
- Chloramphenicol 1 g: US$ 0.3600/vial

6.5 Salbutamol for treatment of acute wheeze/asthma and bronchoconstriction

a) Children with acute wheeze/asthma and bronchoconstriction should be treated with inhaled salbutamol using a metered dose inhaler (MDI) with spacer devices to relieve bronchoconstriction.

(Strong recommendation, low quality evidence)

b) Oral salbutamol should not be used for treatment of acute or persistent wheeze except where inhaled salbutamol is not available but has no utility in testing response to a bronchodilator.

(Strong recommendation, low quality evidence)

6.5.1 Evidence and summary of findings

The panel identified a review undertaken for the Expert Committee on the Selection and Use of Essential Medicines 2008, focusing on whether oral salbutamol should remain on the WHO Paediatric Model List [Sani, 2008]. The review identified five studies comparing lung function tests of asthmatics treated with oral, inhaled, or combination oral and inhaled salbutamol. Most studies showed that inhaled salbutamol was superior in improving lung function, was effective at lower doses, and therefore caused fewer side effects than oral salbutamol. However, oral salbutamol

was still an effective bronchodilator and, in one study, the bronchodilatory effect of oral salbutamol lasted longer than inhaled salbutamol.

One study randomized 780 children with WHO-defined non-severe or severe pneumonia and wheeze to standard dosages of either oral (390 children) or inhaled (390 children) salbutamol. Children were sent home on antibiotics and a bronchodilator. Sixty-six children in the oral group and 62 children in the inhaled group failed treatment by day 5, but this difference did not reach statistical significance (RR 0.94, 95% CI 0.68 to 1.29) (**see GRADE table A7.13**).

6.5.2 Benefits and risks

Benefits

Oral salbutamol is inexpensive (taking into account the cost of metered-dose inhalers for inhaled salbutamol), easy to store, easy to deliver, and therefore more likely to promote compliance.

Risks

With delayed onset of action, a higher dose is required, and there is a greater likelihood of side effects. Oral salbutamol cannot be used as a 'trial of bronchodilator' (for which inhaled salbutamol should be used) as recommended by IMCI for children with wheeze and fast-breathing.

6.5.3 Acceptability and feasibility

Oral salbutamol is inexpensive, much easier to prescribe and deliver than inhaled salbutamol, and is likely to be more acceptable to parents and children. However, it is an inferior mode of delivery. The emphasis should therefore be on making inhaled salbutamol and metered-dose inhalers more available globally.

7. Evidence for recommendations for treatment of dysentery

7.1 Antibiotics for treatment of dysentery

a) Children with diarrhoea and blood in stool (i.e. dysentery) should be treated with ciprofloxacin as a first line treatment. Ceftriaxone should be given as a second line treatment in severely ill children where local antimicrobial sensitivity is not known.
   — Ciprofloxacin: 15 mg/kg/dose twice daily for 3 days
   — Ceftriaxone: 50–80 mg/kg daily for 3 days

(Strong recommendation, low quality evidence)

b) Where local antimicrobial sensitivity is known, local guidelines should be followed.

(Strong recommendation, low quality evidence)

The panel noted that the evidence of impact of antibiotics comes from epidemics in the 1970s where different antibiotics were used with widely varying case fatality rates, and only one randomized control trail. It was also noted that although the evidence from RCTs is specifically for management of Shigella dysentery, the guidelines refer to bloody diarrhoea as in most cases there will be no prior testing before treatment.

The increasingly widespread antibiotic resistance to ampicillin, co-trimoxazole, chloramphenicol, nalidixic acid, tetracycline, gentamicin, and 1st and 2nd generation cephalosporin make them less effective for treatment. There is also reported resistance to ciprofloxacin, and hence the need for continued drug resistance surveillance.

7.1.1 Evidence and summary of findings

There was low quality evidence from two systematic reviews, a recently updated Cochrane review (**see GRADE table A7.14**) and a WHO Children Health Epidemiology Reference Group (CHERG) review that most of the antibiotics used were effective depending on antimicrobial sensitivity patterns [Christopher, 2010; Traa, 2010]. The reviews confirm the current WHO recommendations and current practice as it is not possible to recommend a specific antibiotic or antibiotic group that would be universally effective due to wide variation in antimicrobial sensitivity.

The Cochrane review included all RCTs comparing the efficacy of one antibiotic to placebo, or comparing the efficacy of various antibiotics, in children as well as in adults. Many of the RCTs included in this systematic review were conducted

prior to the 1990s and involved antibiotics that are no longer used because of highly resistant Shigella (i.e., cotrimoxazole, ampicillin, nalidixic acid). The review focused on outcome variables of limited interest: duration of diarrhoea and continuation of dysentery. It also includes studies conducted in developing as well as developed countries, without taking into account the type of Shigella strains responsible for the dysentery, therefore limiting the generalizability of the findings.

The CHERG review only included studies published after 1990, evaluating the efficacy of antibiotics presently recommended by WHO (i.e. ciprofloxacin, ceftriaxone, pivmecillinam, and azithromycin) and to which resistance is so far not a problem in children aged < 16 years, and conducted in middle- and low-income countries. The review was, therefore, more generalizable to the paediatric population and low-resource settings. The review also focused on three outcome variables that have a direct impact on survival:

- Clinical failure: Absence of marked improvement in, or worsening of, illness with the presence of bloody mucoid stools, more than a trace of blood in stool, abdominal pain, tenesmus and/or fever;
- Cacteriological failure: Failure to clear an enteropathogen isolated from an individual on admission to the study, by the end of the treatment period; and
- Bacteriological relapse: Reappearance of an enteropathogen in stool after the enteropathogen was cleared by treatment.

The Cochrane systematic review identified two RCTs comparing antibiotics and placebo or no drug, and 14 RCTs comparing the effectiveness of different antibiotics regimens for treatment of Shigella dysentery [Christopher, 2010]. The trials included a total of 1748 participants and were randomized based on clinical symptoms of dysentery, prior to bacteriological confirmation. The GRADE tables show low- to moderate quality evidence that antibiotic therapy significantly reduces the number of children with dysentery on follow-up compared to no antibiotic [Kabir 1986; Rodriguez 1989].

The review had two primary efficacy outcomes. The first primary outcome, diarrhoea on follow-up, was reported by all but three trials [Kabir 1986; Gotuzzo 1989; Islam 1994]; the duration of follow-up was five days in 10 out of 13 trials. The second primary outcome, relapse, was reported by four trials [Haltalin 1973; Salam, 2010; Shanks 1999; Leibovitz 2000); the duration of follow-up for this outcome ranged from 10 to 20 days.

Limited data from one three-armed trial of people with moderately severe illness suggest that antibiotics reduce the episodes of diarrhoea at follow-up (furazolidone versus no drug RR 0.21, 95% CI 0.09 to 0.48, 73 participants; cotrimoxazole versus no drug RR 0.30, 95% CI 0.15 to 0.59, 76 participants)[Rodriguez 1989].

The review did not find robust evidence to suggest that antibiotics of a particular class were better than those belonging to a different class. However, there were limited data from a subgroup of studies to suggest that fluoroquinolone (ciprofloxacin) was more effective than beta-lactam (ampicillin) in reducing diarrhoea among adults and

that beta-lactams were more effective than fluoroquinolones in reducing diarrhoea among children with proven Shigella dysentery [pivmecillinam and nalidixic acid, Alam 1994; ciprofloxacin and ampicillin, Bennish 1990; nalidixic acid and ampicillin, Haltalin 1973; ciprofloxacin and ceftriaxone, Leibovitz 2000; nalidixic acid and ampicillin, Salam 1988; ciprofloxacin and pivmecillinam, Salam 1998].

Drug resistance patterns from several trails show that at various periods of time different antibiotics have been effective against Shigella dysentery isolates in different parts of the world (**Table A6.1**). The antibiotics used included ampicillin, co-trimoxazole, nalidixic acid, and fluoroquinolones like ciprofloxacin, pivmecillinam, ceftriaxone, and azithromycin. Oral gentamicin was relatively ineffective, due to poor absorption when given orally, compared to nalidixic acid and therefore is not recommended. However, there is evidence of high rates of resistance of Shigella dysentery in some parts of the world to ampicillin, co-trimoxazole, chloramphenicol, and nalidixic acid.

The CHERG systematic review identifies eight studies, with some studies contributing data for multiple antibiotics or more than one outcome measure. Eight studies reported on clinical failure (12 unique data points), most of them 3 days after treatment was initiated (range 3–6 days). Four studies reported on bacteriological failure (6 unique data points) and five reported on bacteriological relapse (seven unique data points).

Results of the CHERG systematic review were as follows:

- Clinical failure: Antibiotics (ciprofloxacin, pivmecillinam, ceftriaxone, and azithromycin) reduce clinical signs of dysentery in 99.9% (95% CI 99.5–100) of cases.
- Bacteriological failure: Antibiotics successfully clear dysentery pathogens from 100% (95% CI 99.9–100) of cases.
- Bacteriological relapse: Antibiotics successfully prevent bacteriological relapse in 100% (95% CI 99–100) of cases.

7.1.2 Benefits and risks:

Benefits

Reductions in clinical and bacteriological failure, likely reduction in time to cessation of diarrhoea or bloody stools.

Risks

None of the antibiotics studied in the trials were associated with major adverse events that were drug related.

7.1.3 Acceptability and feasibility:

Shigellosis can lead to life-threatening complications, including sepsis, intestinal perforation, toxic megacolon, and, in predisposed individuals, haemolytic uraemic syndrome and Reiter's syndrome. As a result, value was placed on recommending an effective antibiotic treatment. The benefits of effective antibiotic therapy outweigh

the risk of side effects, and short duration of treatment (3 to 5 days) poses minimal burden to patients.

Oral ciprofloxacin and ceftriaxone are the currently recommended treatment for dysentery and already on the Essential Medicines List for Children [WHO, 2005; WHO 2010]. It is therefore feasible to implement as it will not require policy change in most countries.

8. Evidence for recommendations on treatment of fever conditions

8.1 Antibiotics for treatment of acute bacterial meningitis

a) Children with acute bacterial meningitis should be treated empirically with 3rd generation cephalosporins.
   — Ceftriaxone: 50mg/kg per dose IV every 12 hours, or 100 mg/kg once daily, or
   — Cefotaxime: 50mg/kg per dose 6 hourly for 10–14 days.

(Strong recommendation, moderate quality of evidence)

b) Where it is known that there is no significant resistance to chloramphenicol and beta lactam antibiotics among bacteria-causing meningitis, follow national guidelines or choose any of the following two regimens:
   — Chloramphenicol: 25 mg/kg IM (or IV) every 6 hours plus ampicillin: 50 mg/kg IM (or IV) every 6 hours.

   OR

   — Chloramphenicol: 25 mg/kg IM (or IV) every 6 hours plus benzyl penicillin: 60 mg/kg (100 000 units/kg) every 6 hours IM (or IV).

(Conditional recommendation, moderate quality evidence)

The panel noted that, based on data from developed countries, most international guidelines recommended treatment for at least 10 days for bacterial meningitis patients with no adverse or poor prognostic factors. However, data from recent multicentre study conducted in five developing countries showed that in children beyond the neonatal age with purulent meningitis caused by *Staphylococcus pneumoniae*, *Haemophilus influenzae*, Type b, or *Nesiria meningitidis* who are stable by day 5 of ceftriaxone treatment, could safely discontinue antibiotics. However, the panel choose to adopt the more conservative approach pending further evidence of the safety of shortened duration treatment.

The panel also raised concern about the possibility of overuse of ceftriaxone if there is a loose definition of "suspected meningitis", hence the need for promoting use of a lumbar puncture in suspected meningitis before commencing treatment.

It was also noted that the use of steroids is not effective in developing countries most likely due to late presentation.

8.1.1 Evidence and summary of findings

The panel identified one Cochrane review comparing 3rd generation cephalosporin with standard chloramphenicol-based regimes for bacterial meningitis in children [Prasad, 2007]. The review involved 19 RCTs with 1496 patients comparing 3rd generation cephalosporins (ceftriaxone or cefotaxime) with conventional antibiotics (penicillin/ampicillin-chloramphenicol combination, or chloramphenicol alone) as empirical therapy for treating acute bacterial meningitis. The primary outcomes evaluated were death, severe sensorineural deafness, and other disabling sequelae.

The evidence used for making this recommendation was of moderate quality showing no differences in efficacy and safety between conventional antibiotics and cephalosporins in the initial treatment of acute bacterial meningitis (**see GRADE table A7.15**). However, there was increasing evidence from several sensitivity studies that bacteria which cause meningitis are more likely to be resistant to conventional antibiotics leading to increased mortality and morbidity. Early appropriate treatment with 3rd generation cephalosporins may improve patient outcomes since the choice of antibiotic is often made without knowledge of drug resistance.

The systematic review of 3rd generation cephalosporins versus chloramphenicol-based regimens show that there is moderate quality evidence of no difference between chloramphenicol-based regimens and 3rd generation cephalosporins in terms of mortality or rates of treatment failure. There is low quality evidence of a decreased risk of culture positivity for treatment with ceftriaxone compared to chloramphenicol-based regimens.

Overall, there were no statistically significant differences in the risk of death 52 (6.9%) of 750 in the cephalosporin group versus 50 (6.7%) of 746 in the conventional group (RD -0%; 95% CI -3% to +2%), risk of sensorineural deafness 21 (8.5%] of 247 in the cephalosporin group versus 30 (11.8%) of 254 in the conventional group (RD -4%; 95% CI -9% to +1%), and risk of treatment failure 63 (8.4%) of 750 in the cephalosporin group versus 65 (8.7%) of 746 in the conventional group (RD -1%; 95% CI -4% to +2%). There was a statistically significant difference in cerebrospinal fluid culture positivity 10-48 hours after the start of treatment favouring cephalosporins – 14 (6.1%) of 228 in the cephalosporin group versus 25 (11.7%) of 214 in the conventional group (RD -6%; 95% CI, -11% to -0%). (See GRADE table 15).

Subgroup analysis of 10 of the 19 trials included from developing country settings showed no statistical difference in the primary outcomes: risk of death 37 (9.0%) of 409 in the cephalosporin group versus 36 (9.4%) of 382 in the conventional group (RD -1%; 95% CI -5% to +3%), risk of sensorineural deafness two (3.6%) of 55 in the cephalosporin group versus three (4.5%) of 66 in the conventional group (RD -1%; 95% CI -9% to +8%), and risk of treatment failure 39 (9.5%) of 409 in the cephalosporin group versus 39 (10.2%) of 382 in the conventional group (RD -1%; 95% CI -5% to +3%).

Treatment duration

A review of five RCTs involved children (3 weeks to 16 years) of short- (4–7 days) versus long-course (7–14) duration of ceftriaxone for meningitis [Karageorgopoulos, 2009). No difference was demonstrated between short-course and long-course treatment with intravenous ceftriaxone with regard to end-of-therapy clinical success (five RCTs, 383 patients, fixed effect model [FEM], OR 1.24, 95% CI 0.73 to 2.11); long-term neurological complications (five RCTs, 367 patients, FEM, OR 0.60, 95% CI 0.29 to 1.27); long-term hearing impairment (four RCTs, 241 patients, FEM, OR 0.59, 95% CI 0.28 to 1.23); total adverse events (two RCTs, 122 patients, FEM, OR 1.29, 95% CI 0.57 to 2.91); or secondary nosocomial infections (two RCTs, 139 patients, random effects model, OR 0.45, 95% CI 0.05 to 3.71). In two RCTs where hospital stay was not determined by protocol, the duration of hospitalisation was significantly shorter in the short-course treatment arms, (137 patients, FEM, WMD 22.17 days, 95% CI 23.85 to 20.50).

There is low quality evidence that for patients with no adverse prognostic factors (i.e. delayed presentation, severe illness, persistent CSF culture), short course (4–7 days) is equivalent to long course (7–14 days) ceftriaxone for rates of clinical success and neurological sequelae, and reduces duration of hospital stay (**see GRADE table A7.16**).

Antimicrobial resistance

There is a reported, increasing trend in the proportion of *H. influenzae*, *S. pneumoniae* and *N. meningitidis* showing resistance to penicillin and chloramphenicol [Akpede, 1994; Muhe, 1999; Emele, 2000; Hoban, 2001; Molyneux, 2002; Duke, 2003;Wasfy 2005]. Thus, use of conventional antibiotics may be associated with higher mortality and morbidity. Penicillin-resistant pneumococcal meningitis has been shown to have poor response to treatment with chloramphenicol [Friedland, 1993]. The list below shows reported chloramphenicol resistance:

- Pneumococcal resistance to chloramphenicol [Hoban, 2001]:
  - 6.4% USA
  - 4.8% Latin America
  - 10% Europe
  - 15.8% Asia Pacific
- Chloramphenicol resistance in children with meningitis:
  - 11–14% in Nigeria [Akpede, 1994; Emele, 2000]
  - 13% in Ethiopia [Muhe, 1999]
  - 17% in Malawi [Molyneux, 2002]
  - 5.6% of all meningitis, and 20% of haemophilus meningitis in PNG [Duke, 2003]

8.1.2 Benefits and risks

Benefits

Although there is no difference between cephalosporins and conventional antibiotics in the clinical outcomes, cephalosporins provide an advantage because of the

reduced culture positivity after 10 to 48 hours, currently low levels of resistance, and only once daily required dosing. Single daily dosing of ceftriaxone is a significant advantage over the 6-hourly injections of the standard chloramphenicol/beta-lactam combination. Use of cephalosporins as initial therapy would be of benefit in situations where antimicrobial resistance is not known in the context of increasing resistance to avoid high mortality.

There is substantial evidence to suggest that an increasing proportion of *H. influenzae* and *S. pneumoniae* isolated from meningitis cases are resistant to ampicillin and chloramphenicol. Since these are the common causes of acute bacterial meningitis, their use as an empirical treatment may lead to poor clinical outcomes.

Risks

Cephalosporins were associated with short-term diarrhoea.

8.1.3 Acceptability and feasibility

Single daily dosing of ceftriaxone has significant advantage over the multiple, daily injections that require more staff time and inconvenience children and caregivers. Single daily dosing recommendation is much simpler than the current recommendation and may be preferred by clinicians and nurses.

The reduced frequency of administration of ceftriaxone, along with the reduced time burden on staff, offsets its cost. The cost of cephalosporins will decrease with the increasing availability of generics. Median prices [MSH/WHO 2010]:

- Chloramphenicol 1 g: US$ 0.4372/vial
- Ampicillin 250 mg: US$ 0.1786/vial
- Benzyl penicillin 600 mg: US$ 0.0864/vial
- Ceftriaxone 250 mg: US$ 0.4395/vial

8.2 Antibiotic treatment for Acute Otitis Media (AOM)

a) Children with acute otitis media (AOM) should be treated with oral amoxicillin 40 mg/kg twice per day for 7–10 days.

OR

b) Where pathogens causing acute otitis media are known to be sensitive to co-trimoxazole, this antibiotic could be used as an alternative given twice per day for 7–10 days.

(Strong recommendation, low quality evidence)

The panel noted that there was a lack of RCTs addressing the treatment of AOM from developing countries as most studies had been conducted in developed countries. In addition, it was noted that poor performance of diagnostic criteria makes interpretation of AOM studies difficult as has been reported in a recent systematic review [Coker, 2010].

The choice of amoxicillin was not entirely based on the evidence from the data reviewed in the RCTs, but also on the consideration of aetiological causes of AOM and data on antibiotic resistance. It was also found much more feasible and easy to

implement by keeping the same first line antibiotic recommendation for treatment of AOM and non-severe pneumonia.

8.2.1 Evidence and summary of findings

There were no placebo-controlled trials from developing countries.

A Cochrane review (updated 2010) assessed 10 placebo controlled trials of oral antibiotics conducted in developed countries with a total of 2928 children ranging in age from infancy to 15 years [Sanders S, 2004]. Enrolment in the trials was based on clinical diagnosis, and primary outcomes included reported pain and health professional-determined clinical cure. The antibiotics used were mostly beta-lactams, although macrolides and sulphonamides were also studied (**see GRADE table A7.17**). There is low-moderate quality evidence from the review for the equivalence of a range of antibiotics, although the studies that were included were small, and the outcome-used, clinical response is likely to overestimate the effect of ineffective antibiotics because of a high rate of spontaneous recovery (**see GRADE table A7.18**).

Combined results of the trials showed that pain was not reduced at 24 hours from the start of treatment but it was reduced at 2 to 7 days, (RR 0.72; 95% CI 0.62 to 0.83). Compared with delayed treatment, immediate antibiotic treatment was associated with decreased ear pain at day four (RR 0.77; 95% CI 0.50 to 1.17). In the four trials that measured tympanometry, there was no clinically or statistically significant difference in tympanometry results at 1 or 3 months after the acute episode, suggesting no effects on hearing. The review also found that antibiotics appeared to reduce the development of contralateral otitis, although the difference was not statistically significant. Individual patient data meta-analysis of a subset of the included trials found antibiotics to be most beneficial in children aged less than 2 years or those with bilateral AOM and otorrhoea.

There are too few complications to be able to compare these across groups (eg. one child out of 2928 children had mastoiditis). In applying these results to developing countries with a higher frequent risk of more serious complications like mastoiditis, antibiotic treatment would be strongly advised.

A meta-analysis of 1643 children from six trials aged 6 months to 12 years looked at the effect of antibiotics on an extended episode of AOM lasting 3–7 days [Rovers, 2006]. Randomized placebo-controlled trials were included. Three of the six trials were included in the Cochrane review [Sanders S, 2004]. The relative risk of an extended course of AOM at 3–7 days with antibiotics was 0.83 (95% CI 0.78–0.89), for fever was 0.95 (95% CI 0.92–98), and for pain was 0.86 (95% CI 0.81–0.91). A significant reduction in pain, fever, or both was noted in the treatment arm for those less than 2 years of age with bilateral disease (55% versus 30%; RD -25; 95% CI -36,-15) with a NNT of 4 and those with otorrhoea (60% versus 24%; RD -36; 95% CI -53,-19; NNT 3).

In another systematic review, short-term clinical success was higher for immediate use of ampicillin or amoxicillin versus placebo respectively (73% versus 60%; pooled rate difference, 12%; 95% CI 5%–18%; pooled rate difference, 12%; 95% CI 5%–18%]; NNT, 9, 95% CI, 6-20) [Coker, 2010].

Resistance profiles of pathogens causing AOM are variable across studies, but show a high level of co-trimoxazole resistance (28–45%), although data are only from two countries (Israel and Costa Rica) (**see table A6.2**). Resistance to penicillins is lower (2–29%) [Gelbart B, 2010; WHO unpublished review]. Amoxicillin is preferred over co-trimoxazole because of its lower rates of in-vitro resistance, and because it is the first line outpatient antibiotic for non-severe pneumonia, and may therefore be more accessible.

Short versus long course treatment

Thirty-five trials primarily conducted in developed countries (11 in Europe, 10 each in North America and Asia, and four were multi-centre from different continents) were evaluated. The duration of antibiotic use in the long course arm was 10 days in 33 analytic components, 7–14 days in two analytic components, seven days in two analytic components, and five days in one analytic component. Of the 35 trials, three used short-acting oral antibiotics, 21 used azithromycin, and 11 used parenteral ceftriaxone in the short course arm.

There was no evidence of an increased risk of treatment failure with a shorter course of antibiotics (≤ 3 days). The overall relative risk for treatment failure with a short course of antibiotics in comparison to a longer course was 1.06 (95% CI 0.95 to 1.17, P=0.298; test for heterogeneity: Cochran Q=37.02, I2=0.1%, P=0.468). Use of a short acting oral antibiotic in the short course arm was associated with a significantly increased risk of treatment failure (2.27, 95% CI 1.04 to 4.99). The slightly increased risk of treatment failure with parenteral ceftriaxone (1.13, 95% CI 0.99 to 1.30) was not statistically significant; however, the lower limit of confidence interval was close to 1. There is very low quality evidence for the equivalence of short-course (≤ 3 days) versus-long course (> 3 days) antibiotics [Gulani, WHO 2009] (**see Grade table A7.19**).

Limited data did not suggest that a short course of antibiotics resulted in an increased risk of: (i) treatment failure in culture positive cases or in high-risk groups (children below two years of age, perforated eardrum, recurrent otitis media, and specific bacterial pathogens), (ii) bacteriologic failure, (iii) relapse, (iv) recurrence, or (v) persistent middle ear effusion.

8.2.2 Benefits and risks

Benefits

There is no evidence for the safety of not giving antibiotics for AOM in settings where the prevalence of AOM and its complications are high. The benefits of antibiotic treatment for AOM are:

- reduced pain in acute ear infection;
- reduced risk of acute, serious complications;
- possible reduced risk of long-term sequelae, including chronic suppurative otitis media (CSOM) and mastoiditis.

In developing countries where there could be a high rate of serious acute complications, such as mastoiditis, and where short-term and long-term complications of untreated AOM can lead to death or severe disability, antibiotic use is beneficial.

Risks

In a Cochrane review, use of antibiotics resulted in a 37% (95% CI 0.05 to 0.67) relative increase in risk of adverse events: 16% (110 out of 690) of children treated with antibiotics versus 11% (83 out of 711) of children treated with placebo experienced vomiting, diarrhoea, or rash. Others have reported antibiotics to cause adverse effects in 4% to 10% of children [Coker, 2010].

8.2.3 Acceptability and feasibility

Until there is more direct evidence specifically addressing the effectiveness of antibiotics in children with AOM in developing countries, and the safety of withholding them, it would not be safe to withhold antibiotics. There is a high incidence of possible complications; the 'watch and wait' approach of not giving antibiotics and observation is limited in developing countries by poor systems for follow-up, poor access to health facilities, and resource limitations.

Implementation of this recommendation exists based on the fact that it is feasible to distribute oral amoxicillin in resource-limited settings as it is available in tablet and suspension form in all countries. Oral amoxicillin is the recommended treatment for non-severe pneumonia, and should therefore be widely accessible.

8.3 Antibiotic treatment for Chronic Suppurative Otitis Media (CSOM)

a) Children with chronic suppurative otitis media (CSOM) should, in addition to aural toilet by dry wicking, be treated with instillation of drops containing quinolones (such as ciprofloxacin, norfloxacin, ofloxacin) three times daily for two weeks.

(Strong recommendation, low quality evidence)

b) Children who fail to respond to treatment should be referred for further evaluation for other causes of CSOM, especially tuberculosis.

(Strong recommendation, expert opinion)

Remarks

The duration of treatment was not clear from studies and depended on clinical circumstances, therefore the panel could not make a definitive recommendation on the duration of treatment. It was noted that the price of ciprofloxacin varies widely across different countries, and in some settings it may not be the cheapest fluoroquinolone and therefore necessitates the recommendation of any of the other available alternative fluoroquinolones.

8.3.1 Evidence and summary of findings

Two systematic reviews of antibiotic therapy for CSOM in children were identified: one compared topical versus systemic antibiotics and the other compared the effec-

tiveness of various topical antibiotics. There is low-moderate quality evidence that topical quinolones are better than topical non-quinolones at reducing discharge at 2–3 weeks, but there was no significant difference in discharge at 1 week (**see GRADE A7.20**).

There was moderate quality evidence that improvement in hearing thresholds is better with topical quinolone when compared to topical antiseptics or no treatment. The review of topical antibiotics included 14 trials (1724 ears). Study quality was low-moderate and definitions of CSOM varied, with some studies including children with otitis externa and mastoid cavity infections. There is moderate quality evidence that topical quinolone antibiotics were better than no treatment in preventing the persistence of discharge at 1 week (RR 0.83, 95% CI 0.76 to 0.89) (**see GRADE table A7.21**). One study in Malawi [Macfadyn, 2005] compared hearing thresholds for children treated with ciprofloxacin versus boric acid and showed a difference in mean 59 improvement of 2.17db (95% CI 0.09 to 4.24) at 2 weeks, and 3.43 (95% CI 1.34 to 5.52) at 4 weeks in favour of ciprofloxacin.

The review of systemic versus topical antibiotics included 8 trials (474 participants). The definition of CSOM varied between studies. Study quality ranged from very low to moderate, with most studies having inadequate allocation concealment and no blinding. There was moderate quality evidence for higher rates of treatment failure with systemic antibiotics compared to topical quinolone antibiotics. There was no significant difference in treatment failure between systemic non-quinolone and topical non-quinolones antibiotics (very low quality evidence), or systemic antibiotics and topical antiseptics (moderate quality evidence) (**see GRADE table 22**).

8.3.2 Benefits and risks

Benefits

Topical quinolone antibiotics reduce persistent discharge, hearing thresholds improve.

Risks

Local discomfort, opportunistic fungal infection. [WHO 2010].

8.3.3 Acceptability and feasibility

Ear drops are easy to apply by health workers and caregivers, requiring minimal training. Topical ciprofloxacin is in the WHO *Model Formulary for Children* [WHO 2010]. Cost is US$ 1.00 for a 10 ml bottle. [MSH/WHO 2010].

8.4 Topical antiseptics for treatment of Chronic Suppurative Otitis Media (CSOM)

Topical antiseptics and steroids should not be used for the treatment of chronic suppurative otitis media (CSOM) in children.

(Strong recommendation, low quality evidence)

Remarks

There was no evidence to support the use of topical antiseptics and steroids in the treatment of CSOM in children.

8.4.1 Evidence and summary of findings

One systematic review identified two RCTs that included arms which compared the effectiveness of topical antiseptics versus no treatment or placebo [Acuin, 2007]. There was low quality evidence that there is no statistically significant difference in the rates of treatment failure between topical antiseptic and placebo or no treatment (**see GRADE table A7.23**). However, both studies were underpowered and had some methodological flaws.

In the first RCT, 60 children with otorrhoea in a hospital clinic in South Africa compared aluminium acetate solutions of varying concentrations (13.00%, 3.25%, and 1.30%) [Thorp, 2000]. The most dilute solution was considered to be inactive. The RCT found no significant difference in dry ears after 2 weeks (21 out of 26 patients (81% of ears) with 13.00% aluminium acetate versus 15 out of 20 patients (75%) with 3.25% aluminium acetate versus 5 out of 10 patients (50%) with 1.30% aluminium acetate; p = 0.18). However, this study may have lacked power to detect a clinically significant difference.

The second RCT included 134 children (180 ears) and compared five interventions: ear cleansing alone, ear cleansing plus topical antiseptic, ear cleansing plus topical antiseptic plus topical antibiotics plus corticosteroid, ear cleansing plus topical antiseptic plus topical antibiotics plus corticosteroid plus oral antibiotic (clindamycin), and no treatment [Eason, 1986]. It found no significant difference between ear cleansing plus topical antiseptic (boric acid 2%) 4 times daily and ear cleansing alone in the proportion of children with no change in otoscopic appearance after 6 weeks (43 children, 58 ears: 12 out of 32 [38%] with topical antiseptic versus 13 out of 26 [50%] with ear cleansing alone; OR 0.61, 95% CI 0.22 to 1.71).

8.4.2 Benefits and risks

Benefits

The studies show that there is no added value in using topical antiseptics as they do not reduce ear discharge compared to placebo. Therefore, they do not have a benefit in treating CSOM.

Risks

The two RCTs gave no information on adverse effects where topical antiseptics were used compared to placebo. However, in one systematic review of topical antiseptics versus topical antibiotics, there was increased adverse events (e.g. ear pain, irritation, and bleeding on ear mopping combined; 30 out of 206 [14.6%] with boric acid versus 17 out of 210 [8.1%] with ciprofloxacin; Absolute Risk 6.5%, 95% CI 0.3% to 12.7%) [Macfadyen, 2005]. One study also reported cochlear and vestibular ototoxity at high doses [Perez, 2000].

There is also a risk of delaying effective treatment, especially in children infected with HIV, who may have tuberculosis as the cause of CSOM.

8.4.3 Acceptability and feasibility

Although this has been previously recommended, the use of topical antiseptics has not been widespread due to limited availability. The current evidence does not justify the cost or the potential discomfort associated with the use of topical antiseptics; as a result, they will be less accepted by clinicians. Antibiotics would be much preferred to the use of topical antiseptics.

Topical antiseptics are not currently part of the WHO Essential Medicines List for Children (WHO, 2010).

8.5 Topical steroids for treatment of Chronic Suppurative Otitis Media (CSOM)

Topical steroids should not be used in treating chronic suppurative otitis media (CSOM).

(Weak recommendation, very low quality evidence)

8.5.1 Evidence and summary of findings

A PubMed search was conducted using the terms 'chronic suppurative otitis media' and 'steroids'. Forty-five results were retrieved; there was only one relevant study from Malaysia [Indudharan 2005]. The most recent review the panel could find was from 2006 [Verhoeff, 2006], and this concluded that there had been no formal evaluations of the role of topical steroids up to that point. The 2004 WHO report on Chronic Suppurative Otitis Media [WHO, 2004] was also consulted to cross-check results and identify indirect evidence.

Overall, the only study identified that directly evaluated the role of steroids in CSOM shows no difference in outcomes between two groups treated with antibiotics with steroids and antibiotics without steroids. Indirect evidence suggests that steroids may have a role in improving the efficacy of topical quinolones and reducing the toxicity of amingoglycosides. However, there is currently insufficient evidence to support their use in the treatment of children with CSOM.

Indudharan (2005) conducted a non-blinded, quasi-randomized trial in Malaysia to assess the role of topical steroids in the management of CSOM with perforation. Subjects with specialist-diagnosed CSOM with perforation (no diagnostic criteria provided), but no complications, were enrolled. The external ear of these patients were cleaned with antiseptic and dried. The middle ear was then cleaned by suction.

Consecutive subjects were alternately divided into two groups to receive either 0.3% gentamicin or 0.3% gentamicin with 0.1% betamethasone combination drops. Treatment was continued for 3 weeks, with follow-up at the end of week 4. Middle ear swabs and pure-tone audiogram were performed pre- and post-treatment. Outcomes were clinical and bacteriological improvement. Clinical improvement was defined as

a dry ear on follow-up. Bacteriological improvement was defined as failure to isolate organisms on post-treatment middle-ear swab.

A total of 135 patients (152 ears) aged 2–84 years were enrolled: 77 ears were treated with gentamicin and 75 with gentamicin-betamethasone. Only 70% of patients in both groups were followed-up, but attrition was similar in both groups. Bacteria were isolated from 83% of pre-treatment middle-ear swabs. The most common organisms were *Pseudomonas aeruginosa* (34%) and *Staphylococcal aureus* (17%).

Comparing the gentamicin and the gentamicin-betamethasone groups, there was no statistical difference in clinical improvement (87.7% versus 86.5%, $p > 0.05$) nor bacteriological improvement (82.5% versus 75%, $p > 0.05$). Bone and air conduction were not statistically different between groups, and no complications attributable to the treatment regimens.

Effect of topical steroid in acute otitis media with otorrhoea through a tympanostomy tube

Roland (2003) was a multicentre trial that compared the effectiveness of ciprofloxacin 0.3%/dexamethasone 0.1% with ciprofloxacin 0.3% in resolving acute tympanostomy tube otorrhoea. Children aged 6 months to 2 years with acute otitis media (AOM) with tympanostomy tubes (AOMT) of less than or equal to 3 weeks' duration and visible otorrhoea were randomized to either group. Clinical signs and symptoms of AOMT were evaluated on days 1 (baseline), 3, 8 (end-of-therapy), and 14 (test-of-cure), and twice-daily assessments of otorrhoea were recorded in patient diaries.

One hundred and sixty-seven (167) children had a positive culture. For these children, the mean time to cessation of otorrhoea were significantly shorter (4.22 versus 5.31 days; $p = .004$). The clinical responses on days 3 and 8 were significantly better ($p < .0001$ and $p = .0499$, respectively) with topical ciprofloxacin/dexamethasone than with ciprofloxacin alone. There were no significant differences between the two treatment groups in either the clinical response or the microbial eradication rate by day 14.

Indirect evidence

A number of in-vitro studies have suggested a protective role of topical steroids on reducing the toxicity of topical antibiotics. Park (2004) demonstrated in-vitro that the toxicity of gentamicin to rodent-isolated outer cochlear cells was reduced with the addition of dexamethasone. Himeno (2002) showed that intra-cochlear administration of dexamethasone attenuated aminoglycoside toxicity in the guinea pig.

8.5.2 Benefits and risks

No data on benefits or risks of using topical steroids are available. The addition of steroids to other topical medications did not seem to provide any additional benefit. There is a possible risk of exaggerating fungal overgrowth that is reported when using topical antibiotics.

8.5.3 Acceptability and feasibility

This has no additional value and use will increase the cost of treatment.

8.6 Antibiotic treatment for Typhoid Fever

a) Children with typhoid fever should be treated with a fluoroquinolone (i.e. ciprofloxacin, gatifloxacin, ofloxacin, and perfloxacin) as a first line treatment for 7–10 days.
   — Ciprofloxacin: orally 15 mg/kg per dose twice daily for 7–10 days.

(Strong recommendation; moderate quality evidence)

b) If the response to treatment is poor, consider drug-resistant typhoid and treat with a second line antibiotic like 3rd generation cephalosporins or azithromycin.
   — Cetriaxone IV: 80 mg/kg per day for 5–7 days
   OR
   — Azithromycin: 20 mg/kg per day for 5–7 days

(Strong recommendation, moderate quality evidence)

c) Where drug resistance to antibiotics among salmonella isolates is known, follow the national guidelines according to local susceptibility data.

(Strong recommendation, moderate quality evidence)

The panel noted that patterns of antimicrobial resistance to salmonella isolates are constantly changing, making continuous surveillance of resistance levels critical for clinicians to keep abreast of treatment options. Currently, nalidixic acid resistance is very common and widespread across many countries and there is increasing resistance to ciprofloxacin. This trend in antibiotic resistance to fluoroquinolones may have implications on the effectiveness of ciprofloxacin in some countries, which may require use of alternative fluoroquinolone determined by local susceptibility data.

It was also noted that the duration of treatment varied from 7 to15 days in the RCTs studies that were reviewed making it difficult to draw a conclusive decision about duration. However, it was clear that treatment required at least ≥ 7 days of first line antibiotics.

8.6.1 Evidence and summary of findings

First line antibiotics, including beta-lactams and chloramphenicol, have gradually become less useful with increasing drug resistance. Studies of antibiotic resistance since 1989 in the Indian subcontinent and China have shown that 50–80% of all Salmonella typhi isolates were multidrug resistant (MDR) [Lee 2000]. The choice of antibiotics for enteric fever has been based on studies of the prevalence of MDR *Salmonella typhi* and *paratyphi*.

A Cochrane review evaluated fluoroquinolone antibiotics for treating enteric fever in children and adults compared with other antibiotics, different fluoroquinolones, and different durations of fluoroquinolone treatment [Thaver, 2008]. The review included 38 trials; 22 had unclear allocation concealment and 34 did not use blinding. Only four trials exclusively included children, seven had both adults and children, and three studied outpatients. There are no conclusive data to make firm recommendations regarding the superiority of fluoroquinolones over first line

antibiotics (i.e. chloramphenicol, ampicillin, amoxicillin) or cephalosporins (i.e. cefixime, ceftriaxone) in children. However, there is a general trend in favour of using fluoroquinolones as first line treatment, and either 3rd generation cephalosporins or azithromycin as second line antibiotics for enteric fever due to the rising level of resistance in many parts of the world.

In children, there was a high proportion of nalidixic acid-resistant strains; older fluoroquinolones increased clinical failures compared with azithromycin (OR 2.67, 95% CI 1.16 to 6.11; 125 participants, one trial), with no differences using newer fluoroquinolones (285 participants, one trial). Fluoroquinolones and cefixime were not statistically significantly different (82 participants, one trial).Trials comparing different durations of fluoroquinolone treatment also were not statistically significantly different (889 participants, nine trials). Norfloxacin had more clinical failures than other fluoroquinolones (417 participants, five trials).

Indirect evidence from the adults showed that there is:

- Moderate quality evidence that fluoroquinolones are superior to chloramphenicol in reducing relapse and duration of hospital stay (**see GRADE table A7.24**).
- Low quality evidence that fluoroquinolones are superior to amoxicillin or ampicillin in reducing clinical or microbiological failure (**see GRADE table A7.25**).
- Low quality evidence that fluoroquinolones are superior to ceftriaxone in reducing clinical failure in settings of low nalidixic acid resistance (**see GRADE table A7.25**).
- Moderate quality evidence that azithromycin is superior to fluoroquinolones in reducing clinical failures in settings of high nalidixic acid resistance (**see GRADE table A7.26**).

There was a wide range of different durations of therapy compared in several trials, and the trials for each comparison were small – mostly with small sample sizes and lacking considerably in statistical power. The review found only two trials that compared a short-course regimen (7 days or less) with a long-course regimen (more than 7 days). Clinical failure, microbiological failure, and relapse rates were low in both arms, but the data were not sufficient to make any conclusion.

8.6.2 Benefits and risks

Benefits

Although there was no difference in the clinical failure in patients without MDR when fluoroquinolones are compared with first line antibiotics, there was a clear benefit in favour of fluoroquinolones in fever clearance, microbiological failure, and relapse. There is also a clear benefit of using fluoroquinolones over chloramphenicol; reduced relapse rate and convalescent faecal carriage (298 patients in three studies with RR 0.17, 95% CI 0.04 to 0.70); and reduced risk of treatment failure given increasing frequency of participants with MDR.

Risks

There is now growing concern about increasing frequency of MDR strains of *S. Typhi* and *S. Paratyphi* with reduced susceptibility to first line antibiotics and old fluoroquinolones. Resistance to nalidixic acid has been used to identify these strains. There is, therefore, a risk of treatment failure, if the current first line antibiotics are used for treatment.

The review identified only three instances of adverse events: severe leucopenia in the chloramphenicol group; anaphylaxis in the ceftriaxone group, and a rash in the ciprofloxacin group. Side effects/toxicity of recommended antibiotics as outlined in section 6.2, WHO Model Formulary for Children [WHO 2010].

8.6.3 Acceptability and feasibility:

Value was placed on the benefits of recommended antibiotics in hastening recovery, improving symptoms, and preventing complications of poorly treated disease. Although the current first line antibiotics may be cheap, the cost of a shorter course of ciprofloxacin may be comparable to a 14-day chloramphenicol regimen [Phongmany 2005]. In addition, the increasing numbers of clinical failures with the current first line treatment suggest there is a cost advantage of using more efficacious medicines in the rising levels of resistance.

Although fluoroquinolones are effective and safe, there are still unfounded concerns of ciprofloxacin safety in children that may still affect its uptake by physicians.

9. Evidence for recommendation on use of antibiotics in SAM

9.1 Antibiotics use in the management of severe acute malnutrition

a) In children with severe acute malnutrition (SAM) without complications, manage according to the current community case management guidelines.

(Weak Recommendation, expert opinion)

b) In children with severe acute malnutrition with complications, give parenteral antibiotics as follows:

— Benzyl penicillin: 50 000 U/kg IM/IV every 6 hours, or ampicillin 50 mg/kg IM/IV every 6 hours for 2 days, then oral amoxicillin: 15 mg/kg/dose every 8 hours for 5 days)

AND

— Gentamicin: 7.5 mg/kg IM/IV once daily for 7 days.

(Weak recommendation, low quality evidence)

The recommendation was based on the current WHO definition of complicated Severe Acute Malnutrition (SAM). The panel emphasized that where a child with SAM has complications of very severe pneumonia or meningitis, treatment should be based on the specific guidelines for these conditions.

The panel had concern that the recommendation to give antibiotic to all children with SAM, even those with no complications, would apply to a substantial number of children in the Indian subcontinent. It was observed that there should be a distinction between the acute form of SAM, which is common in Africa and chronic SAM, which is common in Asia. The panel made a decision not to make a recommendation to give antibiotics in SAM with no complications, but to follow community case management recommendations for consistency.

9.1.1 Evidence and summary of findings

A systematic review [Lazzerini, 2010] identified three studies of antibiotic effectiveness in treating children with SAM. The use of broad-spectrum antibiotics in children hospitalized with SAM is supported by strong epidemiological data and low quality clinical studies. However, there is insufficient data from RCTs to determine the most effective antibiotic regimen. The role of antibiotics in home treatment of 'uncomplicated' malnutrition is not clear, and there is very low quality evidence that antibiotics may not be of benefit in this group (**see GRADE table A7.27**).

Wilkinson et al. (1996), used a pre-post design to compare mortality rates of 300 children admitted with SAM in South Africa over two time periods: a 6-month period before introduction of a specific antibiotic protocol compared with the following 6-month period, when standardized guidelines for antibiotics and management of hypoglycemia were introduced. The recommended antibiotics were ampicillin (7 days) and gentamicin (5 days). In the pre-protocol period, there were 32 deaths in 162 admissions (case rate fatality [CFR] 20%). In the post-protocol period, there were 8 deaths in 138 admissions (CFR 6%). This translates to a risk ratio of 0.25 (95% CI 0.14 to 0.62), or a 75% (95% CI 38-86%) reduction in the risk of mortality.

In a cohort of children with uncomplicated SAM treated at home, Amthor et al (2009) retrospectively analyzed the recovery at 12 weeks (Weight for Height > 2 Standared Deviation and no oedema) between a group treated with oral amoxicillin for 7 days (n = 514) with a group not receiving antibiotics (n = 1850). The chance of recovery was 29% (95% CI 7–46%) higher in the group not receiving antibiotics. However, the two studied populations differed, in that children in the antibiotic group were more likely to be wasted and less likely to have oedema.

In an open, randomized, controlled trial in a therapeutic feeding centre in Sudan, Dubray et al (2008) compared ceftriaxone (75 mg/kg/day once daily for 2 days) with oral amoxicillin (80 mg/kg/day, twice daily for 5 days) for uncomplicated malnutrition. Two hundred and thirty (230) children were randomized to the amoxillin group, and 228 to the ceftriaxone group. Randomization was adequate, with intention-to-treat analysis. There was no significant difference between the two groups in weight gain (RR 0.96, 95% CI 0.81 to 1.31), recovery rate (RR 0.94, 95% CI 0.84 to 1.05), mortality (RR 1.27, 95% CI 0.48 to 3.36) or antibiotic-related adverse events (RR 3.9, 95% CI 0.85 to 18.5). The cost of treatment with amoxicillin was significantly lower than ceftriaxone (US$ 1.60 versus US$ 0.20 for a 10 kg child).

Indirect evidence

Uncomplicated SAM

There are no data on the prevalence or aetiology of bacteraemia in children with 'uncomplicated malnutrition', and the role of antibiotics for 'treatment' of an occult infection is therefore not clear. SAM in children is a cause of immunosuppression [Beisel 1996; Chandra 1991; Chandra 1999]. Cotrimoxazole prophylaxis reduces mortality and morbidity in children with HIV/AIDS and is currently recommended [WHO 2006]. Cotrimoxazole prophylaxis may have similar benefits in children with malnutrition given the associated immunosuppression.

Complicated SAM

There is a high incidence of bacterial infections in children with SAM, with bacteraemia reported in 9–29% of children (seven studies), UTI in 17–31% (three studies) and pneumonia in 28%. In 162 severely malnourished children in Tanzania, 92% had at least one bacterial infection, and 49% acquired an infection during hospitalization [Isaack, 1992].

Frequently isolated pathogens include *pneumococcus*, *staph. aureus*, *Klebsiella*,

Salmonella typhi/enteritidis, *E.coli* and other enteric bacilli (**see table A6.3**). Recent studies of antibiotic resistance/sensitivity patterns show high levels of resistance to co-trimoxazole (75% and 93%, two studies) and some resistance to ampicillin and sensitivity to ciprofloxacin and ceftriaxone.

Pharmacokinetic studies do not provide evidence for the need for dose or frequency adjustment for beta lactams antibiotics, gentamicin or ceftriaxone in severe malnutrition. The majority of studies of chloramphenicol suggest greater drug accumulation, and erratic oral absorption in malnourished children.

9.1.2 Benefits and risks

Benefits

There is significant reduction in mortality for children with complicated malnutrition. Antibiotics may be of benefit in uncomplicated malnutrition in preventing opportunistic infections or treating occult infections.

Risks

Side effects/toxicity of recommended antibiotics as outlined in **section 6.2**, *WHO Model Formulary for Children* [WHO 2010].

9.1.3 Acceptability and feasibility

Value was placed on the significant reduction in mortality with antibiotic therapy for children with complicated malnutrition. Given the increased risk of mortality associated with malnutrition, value was also placed on the likely benefits of antibiotics in uncomplicated malnutrition. All drugs are in the Essential Medicines List for Children.

10. Evidence for recommendations on the oxygen use and delivery

10.1 Pulse oximetry for detection of hypoxaemia

1. Pulse oximetry is recommended to determine the presence of hypoxaemia and to guide administration of oxygen therapy in all infants and children with hypoxaemia.

(Strong recommendation, low quality evidence)

The panel noted that although there are no studies comparing arterial blood gases versus pulse oximetry in children, the meta-analysis in adults shows a very high correlation. Pulse oximetry is non-invasive, feasible to implement, and does not require any special skills. It is, therefore, more suitable for use more widely.

10.1.1 Evidence and summary of findings

A systematic review of the accuracy of pulse oximetry in children was not found. A meta-analysis of 74 studies of adult subjects, published between 1976-1994, reported the correlation between pulse oximetry measurements and arterial blood gas (ABG) analysis, and investigated how a number of factors affected this relationship [Jensen, 1998] (**see GRADE table A7.28**). The available low quality evidence shows that pulse oximetry is the best non-invasive method of detecting hypoxaemia, and should be made globally available.

Subjects included in the studies were healthy adult volunteers (25.7%), respiratory patients (20.3%), cardiac and thoracic surgical patients (18.9%), critically ill patients (16.2%), and athletes (5.4%). Of 39 studies that reported sufficient data on the number of subjects and data points to calculate the correlation coefficient (r) between pulse oximetry and ABG, the weighted mean r was 0.895 (+/- 0.014). This estimate did not significantly change when only higher quality studies were considered (r = 0.883). The highest correlation was in healthy volunteers (r = 0.957), and the lowest in critically ill patients (r = 0.760).

The accuracy of oximeters differed depending on the oximeter make, particularly at saturations below 70%. Finger probes were found to have a significantly higher correlation with SaO_2 than ear probes ($p < 0.0001$). The correlation coefficient in five studies of hypoxic subjects (SaO_2 67.6 -87.8%) was high (r = 0.938). Factors that reduced accuracy included dyshemoglobinemia, hypothermia, and skin pigmentation.

10.1.2 Benefits and risks

Benefits

As compared to clinical signs, pulse oximetry is:

- much more accurate at detecting hypoxaemia
- requires less training than detection of clinical signs

As compared to blood gas analysis, pulse oximetry is:

- non-invasive
- faster
- less expensive
- requires minimal infrastructure and no laboratory facilities
- less prone to erroneous measurements
- allows continuous monitoring

Risks

Unlike blood gas analysis, pulse oximetry does not give an indication of ventilation (pCO_2) or pH.

10.1.3 Acceptability and feasibility

Given the large global burden of hypoxaemia, the mortality benefit in detecting and treating with oxygen, and the inaccuracy and unreliability of the detection and interpretation of clinical signs, the cost of pulse oximetry is justified. Blood gas analysis is expensive for most low-resource settings, given the high level of laboratory infrastructure required, as well as the cost and difficulty in obtaining and analysing an arterial sample in a timely manner.

Oximeters are becoming more affordable. Depending on the type and make, prices can range from US$ 35–400 (digit oximeters), US$ 60–1200 (hand-held oximeters) to US$ 800–4500 (oximeters with monitor displays, which can also be used in ICU and theatre).

Several studies have shown the feasibility of implementing and sustaining oxygen systems, including pulse oximetry, in low-resource district and provincial hospitals in developing countries, including Malawi and Papua New Guinea [Duke, 2008; Enarson, 2009].

10.2 Clinical signs in detection of hypoxaemia in children

a) Use pulse oximetry wherever possible is recommended for the detection of hypoxaemia in children with severe lower respiratory infections. If oximetry is not available then the following clinical signs could be used to guide the need for oxygen therapy:
   — central cyanosis
   — nasal flaring
   — inability to drink or feed (where this is due to respiratory distress)
   — grunting with every breath

— depressed mental state (drowsy, lethargic)

(Strong recommendation, low quality evidence)

b) In some situations and depending on the overall clinical condition, children with the following less-specific signs may also need oxygen:
   — severe lower chest wall indrawing
   — respiratory rate of 70/min or above
   — head nodding

(Strong recommendation, very low quality evidence)

In view of the unreliability of the clinical signs in detecting hypoxaemia, the panel strongly recommended that clinical signs should not be relied upon to detect hypoxaemia. Pulse oximetry is a non-invasive procedure and relatively inexpensive. It should be made globally available to ensure that it is part of the assessment of hypoxaemia in seriously ill children.

10.2.1 Evidence and summary of findings

A systematic review of the clinical signs of hypoxaemia in children aged 2–59 months with pneumonia [Rigau, 2010] identified 11 diagnostic studies (**see table A6.5**). Included studies differed in inclusion criteria (radiological pneumonia, WHO-defined pneumonia, or physician diagnosis), altitude (six studies at altitude > 1500 m above sea level), and the definition of hypoxaemia (ranging from < 93% at sea level to < 85% at high altitudes). Three studies included neonates, while five did not stratify results by age. Most studies clearly described the clinical signs investigated, and all used pulse oximetry as the gold standard. The clinical signs investigated were, in order of those most studied: tachypnoea, cyanosis, grunting, crepitations, chest indrawing, difficulty feeding, nasal flaring, and altered mental status.

Overall, all clinical signs tested had poor accuracy for predicting hypoxaemia. Most of the respiratory signs and symptoms have better specificity than sensitivity. However, signs with high specificity (i.e. cyanosis, grunting, difficulty feeding, altered mental status), also had poor sensitivity, and vice versa. Cyanosis, nasal flaring, grunting, mental status, or difficulty in feeding are moderately specific signs. Nasal flaring, chest indrawing, and crepitations were most sensitive.

10.2.2 Benefits and risks

There were no data to assess benefits and risks.

10.2.3 Acceptability and feasibility

More data on how accurately health workers can detect these signs in daily clinical practice are needed. Pulse oximetry is a much more accurate method of detecting hypoxaemia.

10.3 Oxygen therapy in treatment of hypoxaemia

a) Children with hypoxaemia should receive appropriate oxygen therapy.

(Strong recommendation, low quality evidence)

b) Effective oxygen delivery systems should be a universal standard of care, and should be made more widely available.

(Strong recommendation, expert opinion)

The panel noted that although there are no RCTs on the effectiveness of oxygen use, new studies cannot be conducted as it will be unethical. The recommendation was made based on historical and ecological data of very low quality, and pre-post observational data of low quality but with large sample size.

10.3.1 Evidence and summary of findings

A systematic review [Steer, 2010] found no trials comparing outcomes of children receiving oxygen versus those not receiving it. A WHO review of oxygen therapy, published in 1993, compared mortality rates for pneumonia in the pre-antibiotic era for patients who were treated prior to oxygen being standard treatment, and therefore did not receive it, and patients who did receive oxygen. Overall, there was a trend towards mortality reduction with oxygen (RR 0.79, 95% CI 0.53 to 1.18). When only patients with saturation < 80% at admission are considered, there is a significant reduction in mortality (RR 0.50, 95% CI 0.38 to 0.66).

There is low quality evidence from two pre-post observational studies in PNG comparing pneumonia mortality rates before and after the introduction of pulse oximetry and improved oxygen supplies (**table A6.4**). These showed a 38% reduction in pneumonia mortality (RR 0.72, 95% CI 0.60 to 0.86) (**see GRADE table A7.29**).

10.3.2 Benefits and risks

Benefits

Significant reduction in mortality for hypoxaemic patients.

Risks

No significant risk in the post-neonatal period.

10.3.3 Acceptability and feasibility:

Oxygen is currently available in most hospitals, though supplies are unreliable. In hospitals with no or poor access to oxygen, studies from Malawi, the Gambia, and PNG have shown the feasibility of implementing systems for addressing this. Oxygen concentrators, machines that distil room air to produce > 95% oxygen, are becoming less expensive and cost US$ 800–1500; these can supply 2–4 patients at one time.

10.4 Thresholds for administering oxygen therapy

a) Administering oxygen therapy should be guided by pulse oximetry where available and thresholds for giving oxygen vary depending on the altitude.

(Strong recommendation, very low quality evidence)

b) Children living at ≤ 2500 m above sea level should receive oxygen therapy if their oxygen saturation is ≤ 90%, as measured by pulse oximetry.

(Strong recommendation, very low quality evidence)

c) In children living at high altitude (> 2500 m above sea level), the normal oxygen saturation is lower than those living at sea level. At these altitudes, a lower level of saturation, such as SpO_2 ≤ 87%, could be used as a threshold for giving oxygen.

(Recommendation, very low quality evidence)

The panel strongly recommended that children with oxygen saturation < 90% should be administered oxygen therapy. At high altitudes, a lower level of SpO_2 was recommended because of resource implications by consensus. However, this recommendation excludes oxygen therapy in preterm neonates, where care needs to be taken to avoid hyperoxia-related complications.

10.4.1 Evidence and summary of findings

A systematic review [Subhi, 2010] could not identify any studies that have compared outcomes of children receiving oxygen at different thresholds. The evidence base for the cut-off of SpO_2 indicating the need for oxygen is weak. The normal saturation drops with increasing altitude. A threshold of 90–94% at sea level and 85–87% at high altitudes has been used in clinical studies, and is reported to be safe.

One observational study at high altitude shows increasing risk of death with lower saturations at admission, and mortality benefit using SpO_2 < 85% as threshold for giving oxygen [Duke, 2001]. At sea level, there is a physiological argument to maintain oxygen saturation above 90%, because the sigmoidal shape of the oxygen dissociation curve means that for saturations below this a small drop in SaO_2 corresponds to a large drop of PaO_2. Studies of normal saturation in healthy children at sea level show that normal SpO_2 ranges from 97–100% in this population. However, using any SpO_2 below this range to indicate the need for oxygen would result in over-treatment of healthy children. Anecdotally, thresholds between 90–94% have been used in clinical practice and studies for decades.

Normal oxygen saturation drops with altitude. Figure 1 shows at an altitude of 2500 m above sea level, SpO_2 of 90% is within the normal range. Therefore, at high altitude, a lower level of SpO_2 defines hypoxaemia than at sea level, and using a universal threshold would therefore result in over-treatment of children residing in these settings. The potential drawbacks of over-treating non-hypoxaemic children with oxygen are increased rates of hospitalization, increase lengths of stay in hospital, and parental anxiety. Previous studies at high altitude have used definitions ranging from SpO_2 85–87% to account for the effect of altitude, and have not reported any adverse outcomes as a result of this.

The definition has resource implications. One observational study from PNG reports on the prevalence of hypoxaemia when it is defined at varying levels of SpO_2. Thirteen percent of children were hypoxaemic using a definition of $SpO_2 < 85\%$; 26% using $SpO_2 < 90\%$ and 44% using $SpO_2 < 93\%$ [Laman, 2005].

10.4.2 Benefits and risks

Benefits

Oxygen reduces pneumonia mortality in children with hypoxaemia. Pulse oximetry is the most reliable method of detecting hypoxaemia. Having clear and simple guidelines that health workers can follow is necessary for the timely detection and treatment of hypoxaemia.

Recommending a cut-off SpO_2 of 90% and a lower level (85–87%) at high altitudes to indicate the need for oxygen:

- prevents over-hospitalization
- conserves oxygen in settings where it is a limited resource

Risks

Oxygen being combustible, fire hazard and tank explosion is always there. Catheters and masks used to administer oxygen may cause injury to the nose and mouth while dry and non-humidified gas can cause dryness and crusting. Hypoventilation can lead to hypercapnia and CO_2 narcosis although the risk is small with low flow oxygen therapy.

10.4.3 Acceptability and feasibility

Value was placed on having clear and simple guidelines for oxygen therapy to address the large global burden of hypoxaemia. Pulse oximetry is the best method of detecting the presence or absence of hypoxaemia. The technology is affordable (oximeters range from US$ 35 for handheld devices to US$ 4500 for more sophisticated models). Studies from Malawi [Enarson, 2009] and PNG [Duke, 2008] have shown that it is feasible to train health workers in criteria for initiating oxygen therapy using recommended cut-offs of SpO_2.

10.5 Oxygen therapy delivery methods

a) Nasal prongs are the preferred method for delivering oxygen in infants and children under five years of age with hypoxaemia who require oxygen therapy.

(Strong recommendation, moderate quality evidence)

b) Where nasal prongs are not available, nasal or nasopharyngeal catheters could be used as alternative delivery methods. Face masks or head-boxes are not recommended.

(Strong recommendation, moderate quality evidence)

The panel noted that the use of face masks or head-boxes is not recommended as the preferred method because it requires higher flow rates leading to oxygen wastage.

Patients using a nasopharyngeal catheter should be closely monitored, as they are likely to develop serious complications (e.g. catheter entering the oesophagus).

10.5.1 Evidence and summary of findings

A systematic review [Rigau, 2010] identified four relevant studies. Overall, there is moderate quality evidence that nasal prongs and catheters are equivalent in terms of treatment failure and flow rates. There is high quality evidence for a lower risk of nasal obstruction/severe mucous production with nasal prongs compared to catheters (relative risk 0.18, 95% CI 0.08 to 0.43) (**see GRADE table A7.30**). There is very low quality evidence that the use of a head-box or face mask is associated with lower rates of treatment failure (RR 0.4, 95% CI 0.34 to 0.5) (**see GRADE table A7.31**). However, these methods required four times higher flow rate (4 l/min) than catheters or nasal prongs.

Treatment failure was measured as the number of hypoxaemic episodes during therapy, or the time or flow required to achieve adequate SpO_2. Complications assessed were mucous production, nasal ulceration, intolerance, nasal obstruction, and abdominal distension (secondary to dislodgement).

Three studies (399 children) compared nasal prongs with nasal or nasopharyngeal catheters. There was no difference in treatment failure (RR 0.96, 95% CI 0.51 to 1.78) or mean flow rates required (standard mean difference 0.08, 95% CI -0.14 to 0.29). In one study [Muhe 1998], treatment failure for nasal catheters was not significantly different to that of nasal prongs ($p = 0.64$). There was a significantly lower risk of nasal obstruction when prongs were used (RR 0.18, 95% CI 0.08 to 0.43), but no significant difference in nasal ulceration or discomfort.

Only one study assessed face-masks and head-box. These methods required a much higher flow (4 l/min, compared to 1 l/min for prongs and catheters). The risk of treatment failure ($PaO_2 \leq 60$) was significantly lower with either a head box or a face-mask as compared to catheters or nasal prongs. However, this study had important limitations. It was a cross-over design, where 80 children were treated with different delivery methods sequentially, but no information was provided as to how or when children were allocated to each group.

10.5.2 Benefits and risks

Benefits

As compared to a face-mask or head-box, prongs and catheters are less expensive, easier to use, more available, require lower flow rates, and conserve oxygen supplies.

As compared to catheters, nasal prongs have a lower risk of nasal obstruction or excessive mucous production, are easier to apply, and do not require humidified oxygen.

Risks

Oesophageal placement of nasopharyngeal catheters, nasal ulceration, and obstruction.

10.5.3 Acceptability and feasibility

Value was placed on nasal prongs being easier to apply than catheters. Both prongs and catheters are less expensive and require lower flow rates of oxygen than face-masks and head-boxes. They are, therefore, more appropriate in low-resource settings. Nasal prongs are more expensive than catheters, but can be washed and reused.

10.6 Criteria for starting and stopping oxygen therapy

a) Children with hypoxaemia should be closely monitored using pulse oximetry.

(Strong recommendation, very low quality evidence)

b) Oxygen therapy should be discontinued when oxygen saturation remains stable above recommended levels of 90% (≤2500M above sea level) or 87% (> 2500M above sea level) for at least 15 minutes on room air in a clinically stable child.

(Strong recommendation, very low quality evidence)

10.6.1 Evidence and summary of findings

A systematic review [Tickell, 2010] could not identify any studies comparing outcomes for different criteria of starting and stopping oxygen therapy. There is expert opinion that where pulse oximetry is available, a safe way to ensure that a child is no longer hypoxaemic is a trial off oxygen once they are stable. Maintaining saturations above 90% on room air for 15 minutes has been used in clinical trials that employed hypoxaemia as an outcome. Studies that have implemented these criteria, combined with improvements in the detection and treatment of hypoxaemia, have demonstrated a 35–50% reduction in pneumonia mortality (Duke, 2008; Enarson 2009).

Where pulse oximetry is not available, then the only indication of recovery from hypoxaemia is the absence of clinical signs of hypoxaemia.

10.6.2 Benefits and risks

Benefits

Clear guidelines for when to start and stop oxygen therapy are important for improving the detection and treatment of hypoxaemia.

10.6.3 Acceptability and feasibility

Pulse oximetry is a non-invasive method and the best method of detecting the presence or absence of hypoxaemia which is easily acceptable by patients. The technology is affordable (oximetres range from US$ 35 for handheld devices to US$ 4500 for more sophisticated models), and numerous studies have shown it to be adaptable and sustainable in low-resource settings.

11. Evidence for Recommendations for Treatment of Hypoglycaemia

11.1 Sublingual administration of sugar in treatment of hypoglycaemia

Sublingual sugar may be used as an immediate first aid measure in managing hypoglycaemia in children in situations where intravenous administration of glucose may be impossible or delayed.

(Strong recommendation, low quality evidence)

This recommendation places value on ease of use, low cost, and high availability in the absence of any serious risk, although the evidence is of low quality.

11.1.1 Evidence and summary of findings

The panel identified two randomized controlled trials (RCTs) from Burkina Faso and Mali, cited in a recent review of the management of hypoglycaemia [Achoki, 2010].

Barennes et al (2005) conducted an open-label, quazi-randomized trial of intravenous glucose, sublingual sugar, and oral sugar in Burkina Faso. Children aged 6 months to 15 years presenting to the outpatient department were eligible if: 1) they had symptoms and signs of either acute respiratory infection (excluding pneumonia) or malaria; 2) the caregiver agreed to attend an appointment the next morning; and 3) they had a blood glucose level between 3.3 to 5 mmol/l.

The study screened 156 children; 87 were excluded, including 19 children initially assigned to the sublingual group, who swallowed the sugar within the first 10 minutes. Sixty-nine were randomized to one of five groups: 1) half a tablespoon of water (n = 11); 2) IV glucose (8 mL of 30% dextrose administered in a single bolus); 3) oral glucose (2.5 g sugar); 4) single dose sublingual group (2.5 g of wet sugar under the tongue); or 5) double dose sublingual group. The main outcome was treatment failure: the proportion of children who did not reach blood glucose >5.6 during the study period.

Baseline characteristics were similar across groups. There were no treatment failures in the sublingual or intravenous groups, compared with 8 (53%) and 9 (81.8%) in the oral and water groups respectively ($p < 0.05$). The approximate bioavailability was 84% for sublingual administration. The mean (SD) time to reach a blood glucose > 5.6 was 28.5 (10.6) minutes and 25.7 (9.5) for the sublingual and intravenous groups, respectively.

Graz et al (2008) was an open-RCT of intravenous versus sublingual sugar in children with severe malaria and hypoglycaemia in Mali. Children were eligible if

they had: 1) WHO-defined severe malaria; 2) seizures, or an altered/impaired state of consciousness; and 3) hypoglycaemia (blood gluocose < 3.3 mmol/L).

Twenty-six children were randomly allocated to receive sublingual sugar (a teaspoon [2.5–3.5 g] of moistened sugar; n = 14) or intravenous sugar (5 ml/kg 10% glucose; n = 12). Sublingual administration was repeated every 20 minutes for 2 hours. Primary outcome was treatment response rate: reaching a blood glucose > 3.3 mmol/L during the first 40 minutes. Secondary outcomes included relapse rate and treatment delay.

The only difference in baseline characteristics was a trend towards more children with coma in the intravenous group (p = 0.06). There was no significant difference in the treatment response rate (71% in sublingual and 67% in intravenous, p = 0.81). However, there was a trend towards more relapses in the sublingual group (30% versus 17%, p=0.55). Treatment delay was longer for the intravenous group (18.9 minutes versus 5 minutes), and due to this, the increase in blood glucose from time of diagnosis of hypoglycaemia was faster in the sublingual group.

Complications: two children in the sublingual group swallowed the sugar, and failed to reach normo-glycaemia by 40 minutes. According to study protocol, they were switched to intravenous delivery. In the intravenous group, the infusion was blocked in one child.

11.1.2 Benefits and risks

Benefits

Sublingual sugar appears to be well-tolerated, safe, and efficacious. It is easy to administer, rapidly increases blood glucose levels, and is better than no treatment in situations where IV glucose infusion may be delayed or not available. It can be administered by unskilled health-care workers or parents as a first-aid measure in many rural health centres.

Risks

Possibility of treatment failures because of clenched teeth and swallowing of the sugar. It has 30% hypoglycaemia relapse and could give false confidence in situations where blood glucose levels may not be monitored.

11.1.3 Acceptability and feasibility

Sublingual sugar is child-friendly, easy to administer, and does not require skilled health workers. Children will not be distressed due to inserting an IV line and would be a more acceptable treatment than IV infusions. Active participation by parents in the care of their children may also increase. As sugar is readily available in most places, it may be immediately administered in most circumstances and does not require a prescription or other additional materials for use. It is easy to implement widely in all settings, including peripheral health centres and in the communities where intravenous glucose is not available.

12. Evidence for recommendations on the choice of intravenous fluids

12.1 Choice of intravenous fluids for resuscitation and maintenance in children

a) Resuscitation: Children severely dehydrated or with signs of shock should be resuscitated using isotonic intravenous (IV) solutions such as sodium chloride 0.9% or ringers lactate.

(Strong recommendation, low quality evidence)

b) Intravenous maintenance fluid: For children who require intravenous (IV) fluids for maintenance, options include ringers lactate solution with 5% dextrose, sodium chloride 0.45% with glucose 5%, sodium chloride 0.45% with glucose 2.5%, or 0.9% sodium chloride with glucose 5%.

(Strong recommendation, low quality evidence)

c) Low sodium-containing IV solutions such as sodium chloride 0.18% with glucose 4%, or 5% glucose in water, should not be used as there is an increased risk of hyponatraemia.

(Strong recommendation, low quality evidence)

There is evidence that there is a greater level of risk of hyponatraemia associated with the use of very low sodium-containing solutions in paediatric patients in comparison to fluids where the sodium content is 75–150mmol/L.

The panel also emphasized that IV maintenance fluids should contain glucose to avoid hypoglycaemia and starvation ketosis. Enteral feeding should be used in sick children, as it provides nutrition and avoids complications associated with IV fluids. If oral nutrition is not tolerated, nasogastric tube feeding should be considered.

12.1.1 Evidence and summary of findings

There is evidence of a greater level of risk of hyponatraemia associated with the use of hypotonic solutions: the odds of developing hyponatraemia following hypotonic solutions are 17.2 times greater than with isotonic fluids. Within the range of hypotonic solutions available, the use of sodium chloride 0.18% with glucose 4% presents an even greater risk.

The panel identified a systematic review published in 2006 that sought to compare outcomes for children receiving hypotonic versus isotonic fluid therapy [Choong, 2006]. The review included six studies: two controlled trials of children (1-12 years,

n = 60) and adolescent females (12–18 years, n = 12) undergoing elective procedures; one trial of children with gastroenteritis and dehydration (6 months–14 years, n = 104); one case-control study of children treated for iatrogenic hyponatraemia (mean age 7 years, n = 148); one cohort study of children undergoing scoliosis repair (6–16 years, n = 24); and one retrospective chart review of children undergoing craniofacial surgery (2 months–15 years, n = 56). Hypotonic solutions used in the studies ranged from 0.16–0.45% sodium chloride.

Only three studies reported on morbidity and mortality. Wilkinson et al [1992], reported seizures in 2 out of 26 patients receiving hypotonic fluids (OR 6.22; 95% CI 0.29 to 135.8). Hoorn et al [2004] reported nausea and vomiting more commonly in patients with hospital acquired hyponatraemia (p = 0.008) but numbers were too small to evaluate these outcomes with sufficient power.

Meta-analysis of the effect on serum sodium showed that hypotonic maintenance solutions significantly increased the risk of developing hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2). Mean plasma sodium in patients following hypotonic solutions was significantly lower (OR -3.39 mmol/l; 95% CI -5.35 to -1.43), than those who received isotonic solutions. In children receiving hypotonic solutions, the mean plasma sodium decreased significantly more after fluid administration (OR -5.37 mmol/l; 95% CI -8.79 to -1.94). Three studies reported a decrease in plasma sodium despite the infusion of isotonic or near-isotonic maintenance fluids, but none reported on the risk of hypernatraemia with these fluids.

12.1.2 Benefits and risks

In two institutions in the UK where there were incidents of hyponatraemia due to use of hypotonic fluids, no further cases of iatrogenic hyponatraemia have been reported since the solution was removed from the ward stock. There is growing awareness of the dangers associated with use of hypotonic solutions and there have been various statements and changes in the national guidelines discouraging their use in children. In 2003, the Royal College of Anaesthetists issued a statement advising against the use of hypotonic fluids. In 2007, the UK National Patient Safety Agency (NPSA) issued an alert advice to health-care organizations of how to minimize the risks associated with administering intravenous infusions to children.

Risks

All sick children are potentially at risk of hyponatraemia, especially those with pulmonary and central nervous system infections, and post operative surgical cases. The use of hypotonic fluids may be harmful and cause water overload with possible severe hyponatraemia and other complications. Among children who develop symptomatic hyponatraemia, the incidence of permanent brain damage in adulthood is significantly increased [Chung 1986].

13. Outline of the research gaps

13.1 Vitamin K prophylaxis in newborns

1. Research to understand why vitamin K usage is low in developing countries
2. Need for more information on incidence of Vitamin K Dependent Bleeding in developing countries
3. Evaluation of intervention delivery issues and into How to best deliver the intervention in remote settings
4. Testing the possibility of combining with the birth dose of Hepatitis B vaccine
5. Research to improve injection safety

13.2 *Prophylactic antibiotics to neonates with risk factors for infection*

1. RCT for determining efficacy of prophylactic antibiotics to the neonate when the mother has risk factors for neonatal infection
2. What should be the duration of treatment?
3. What is the efficacy of a combination of oral antibiotic (e.g. amoxicillin) and IM gentamicin
4. Bacteriology data on neonatal sepsis

13.3 Skin-to-skin contact in the first hour of life

1. New studies to have high quality evidence of efficacy of this intervention. Also, to ascertain:
   — effect on preterm and SGA infants?
   — effect and feasibility after caesarean section?
2. The studies should be designed for the outcomes to include breastfeeding, hypothermia, engorgement, and bonding. Control group should receive immediate drying and wrapping, and counselling for early breastfeeding.
3. Health care providers and mothers views on acceptability of early skin-to-skin contact of neonates with mothers after birth

13.4 Management of neonatal jaundice

1. Non-invasive serum bilirubin measurement at point of care
2. RCTs evaluating different cut-offs for phototherapy in babies with hyperbilirubinaemia
3. Perceptions, care seeking and causes of prolonged jaundice

13.5 Kangaroo Mother Care

1. Implementation, scaling up issues
2. Ongoing KMC at home post-discharge, feasibility, how long to continue
3. Effectiveness, feasibility of early community initiation of KMC

13.6 Prevention of hypothermia immediately after birth in VLBW infants

1. The group recommended an RCT of plastic wraps for VLBW babies in district and provincial hospitals in developing country settings

13.7 Management of children with non-severe pneumonia and wheeze

1. Studies on withholding antibiotics in young children with wheeze, no fever and non-severe pneumonia need to be replicated in other settings, including health workers ability to identify these children at very low risk of bacterial infection, and the acceptability of withholding antibiotics
2. Studies testing accuracy of different diagnostic algorithms for pneumonia and definitions of treatment failure

13.8 Antibiotics for severe pneumonia

1. More data is needed to assess appropriate antibiotic therapy of severe pneumonia in high HIV settings
2. More research is needed on ambulatory care for severe pneumonia/requisites for safely treating such children at home or in day clinic settings
3. Research in moderately malnourished children with pneumonia
4. Repeat the clinical trials for treatment outcomes in countries with high Hib and pneumococcal vaccine coverage.

13.9 Antibiotics for very severe pneumonia

1. Data on shifts in bacterial patterns due to coverage of *H. influenzae* type b and *S. pneumococcus* vaccines and implications for treatment of pneumonia and antimicrobial resistance
2. Comparison of the recommended treatment (injectable ampicillin (or penicillin) and gentamicin) versus injectable ceftriaxone
3. What should be second line therapy for children failing on first line therapy?
4. Impact of improved comprehensive care packages on outcomes for children with very severe pneumonia.

13.10 Treatment of non-severe pneumonia

1. Studies to determine the duration of therapy in settings other than Asia
2. Repeat the clinical trials for treatment outcomes in countries with high Hib and pneumococcal vaccine coverage
3. Research on treatment failure definition, and choice of second line treatment
4. Research on increasing specificity of pneumonia diagnosis and aetiology of pneumonia

13.11 Antibiotics for Meningitis

1. There is need for comparative studies on dose and frequency of ceftriaxone,
2. Improved surveillance for antibiotic resistance among pathogens causing meningitis
3. The role and accuracy of rapid point of care diagnostic tests, that can be used in district hospitals that do not have culture facilities
4. Studies of the aetiology on meningoencephalitis in settings with high coverage of SP/Hib vaccine coverage

13.12 Antibiotics for Acute Otitis Media

1. RCTs in developing countries with pragmatic definition of otitis
2. Follow up studies in developing countries to quantify complication rates, especially in high prevalence HIV settings
3. Systematic review of treatment of otorrhoea (as may merit separate guidelines)
4. RCT of different durations of antibiotic treatment (including BD versus TID)

13.13 Antibiotics for Typhoid Fever

1. Develop point of care diagnostic tests with higher specificity than current tests
2. Define local resistance patterns
3. Studies of basic epidemiology of typhoid in Africa
4. Continuing need for effective vaccine

13.14 Antibiotics for severe acute malnutrition

1. The role of metronidazole in controlling intestinal bacterial overgrowth in children with Severe Acute Malnutrition? There is currently one ongoing trial in Senegal
2. The effectiveness of different antibiotic regimens in the treatment of complicated SAM.
3. A randomised controlled trial on the role of antibiotics in uncomplicated SAM.

13.15 Oxygen systems and delivery methods

1. Large-scale effectiveness trials of improved oxygen systems on outcomes from pneumonia
2. Studies of alternative power supplies to run oxygen concentrators and pulse oximeters in remote settings where power supplies are unreliable
3. The role of inexpensive forms of CPAP in the management of severe pneumonia
4. Are there safe methods for cleaning and reuse of oxygen delivery equipment in high HIV prevalence settings?

13.16 Pulse oximetry

1. Studies of different types of pulse oximetry – such as hand-held devices – in field settings

13.17 Thresholds for giving oxygen

1. Studies with adequate power to better define thresholds at high altitude (e.g. randomised cohorts using different thresholds with follow-up)
   Clinical studies comparing outcomes when oxygen is given at different thresholds

Annexes

ANNEX 1

Overview of the *Pocket Book* chapter update

CHAPTER/SECTION	NO CHANGE REQUIRED	ALIGN WITH RECENT WHO GUIDELINES	NEW RECOMMENDATIONS
1. Triage and emergency conditions			
1.1 Summary of steps	✔		
1.2 Notes for the assessment of emergency and priority signs	✔		
1.3 Notes for giving emergency treatment to the child with severe malnutrition			✔
1.4 Diagnostic considerations of children presenting with emergency conditions	✔		
1.5 Common poisoning	✔		
1.6 Snake bite	✔		
1.7 Scorpion sting	✔		
1.8 Other sources of envenoming	✔		
2. Diagnostic approach to the sick child			
All sub-chapters	✔		
3. Problems of the neonate and young infant			
3.1 Routine care of the newborn at delivery			✔
3.2 Neonatal resuscitation		✔	
3.3 Routine care for all newborn babies after delivery			✔
3.4 Prevention of neonatal infections			✔
3.5 Management of the child with perinatal asphyxia			✔
3.6 Danger signs in newborns and young infants			✔
3.7 Serious bacterial infections			✔
3.8 Meningitis			✔
3.9 Supportive care for the sick neonate	✔		
3.10 Babies with low birth weight			✔
3.11 Necrotising enterocolitis			✔

CHAPTER/SECTION	NO CHANGE REQUIRED	ALIGN WITH RECENT WHO GUIDELINES	NEW RECOMMENDATIONS
3.12 Other common neonatal problems			✔
3.13 Babies of mothers with infections			✔
Drug doses of common drugs for neonates and LBW babies		✔	
4. Cough or difficulty breathing			
4.1 Child presenting with cough	✔		
4.2 Pneumonia		✔	✔
4.3 Cough or cold	✔		
4.4 Conditions presenting with wheeze			✔
4.5 Conditions presenting with stridor	✔		
4.6 Conditions presenting with chronic cough	✔		
4.7 Pertussis	✔		
4.8 Tuberculosis		✔	
4.9 Foreign body inhalation	✔		
4.10 Heart failure	✔		
5. Diarrhoea			
5.1 Child presenting with diarrhoea	✔		
5.2 Acute diarrhoea			
5.3 Persistent diarrhoea	✔		
5.4 Dysentery	✔		✔
6. Fever			
6.1 Child presenting with fever	✔		
6.2 Malaria		✔	
6.3 Meningitis			✔
6.4 Measles	✔		
6.5 Septicaemia			✔
6.6 Typhoid fever			✔
6.7 Ear infections			✔
6.8 Urinary tract infections	✔		
6.9 Septic arthritis or osteomyelitis	✔		
6.10 Dengue	✔		
7. Severe malnutrition			
7.1 Diagnosis		✔	
7.2 Initial assessment of the severely malnourished child	✔		

CHAPTER/SECTION	NO CHANGE REQUIRED	ALIGN WITH RECENT WHO GUIDELINES	NEW RECOMMENDATIONS
7.3 Organization of care	✔		
7.4 General treatment		✔	
7.5 Treatment of associated conditions		✔	
7.6 Discharge and follow-up		✔	
7.7 Monitoring the quality of care		✔	
8. Children with HIV/AIDS			
All sub-chapters		✔	
9. Common surgical conditions			
All sub-chapters	✔		
10. Supportive care			
10.1 Nutritional management	✔		
10.2 Fluid management	✔		
10.3 Management of fever	✔		
10.4 Pain control		✔	
10.5 Management of anaemia	✔		
10.6 Blood transfusion	✔		
10.7 Oxygen therapy			✔
10.8 Toys and play therapy	✔		
11. Monitoring the child's progress			
All sub-chapters	✔		
12. Counselling and discharge from hospital			
All sub-chapters	✔		
Appendices			
1. Practical procedures	✔		
2. Drug dosages/regimens		✔	
3. Equipment size for children	✔		
4. Intravenous fluids	✔		
5. Assessing nutritional status	✔		
6. Job aids and charts	✔		

Represents sections where no or editorial changes are expected to be made in the pocket book.

Represents sections where changes will be made to align with new recommendations/ guidelines already approved through GRC

Represents sections where evidence was reviewed and recommendations made by the expert panel meeting in February 2011 are provided in this publication.

ANNEX 2
List of PICO questions

CHAPTER	SUB-CHAPTER	QUESTION
3. Problems of the neonate and young infant	3.1 Routine care of the newborn at delivery	Among healthy newborn infants in low- and middle-income countries (P), does early skin-to-skin contact of the baby with the mother in the first hour of life (I) compared with drying and wrapping (C) have an impact on neonatal mortality, hypothermia or initiation/ exclusivity/ duration of breastfeeding (O)?
	3.3 Routine care for all newborn babies after delivery	For all neonates (P), should vitamin K prophylaxis (I) be given for the prevention of vitamin K deficiency bleeding (O)?
	3.5 Management of the child with perinatal asphyxia	For neonates requiring prolonged resuscitation and at risk of HIE (P), should head or body cooling (I) be initiated to prevent death and sequelae (O)?
	3.7 Serious bacterial infections	For young infants (0-2 months) with suspected sepsis managed in health facilities (P), should third generation cephalosporin monotherapy (I) replace currently recommended ampicillin-gentamicin combination (C) as first line empiric treatment for preventing death and sequelae (O)?
	3.10 Babies with low birth weight	In low-birth-weight/pre-term neonates in health facilities (P), are plastic wraps or caps used immediately after birth (I) more effective than conventional care (C) in preventing hypothermia (O)?
		In low-birth-weight/pre-term neonates in health facilities (P), is skin to skin contact immediately after birth (I) more effective than conventional care (C) in preventing hypothermia (O)?
		In low-birth-weight/pre-term neonates in health facilities (P), is Kangaroo Mother Care (I) more effective than conventional care (C) in reducing mortality and/or morbidity (O)?
	3.11 Necrotising enterocolitis	For young infants with suspected NEC (P), what is the effectiveness of different parenteral antibiotics (I, C) in preventing progression and sequelae (O)?

CHAPTER	SUB-CHAPTER	QUESTION
	3.12 Other common neonatal problems	For term, preterm and SGA neonates with hyperbilirubinemia (P), when should the options of exchange transfusion be performed or phototherapy be instituted (I, C), depending on day of life (T), in preventing morbidity and sequalae (O)?
	3.13 Babies of mothers with infections	Among term/near term newborn infants born to mothers with risk factors for neonatal infection (P), does the use of immediate prophylactic antibiotic (I), compared to selective use of antibiotics (C) have an impact on neonatal mortality and/or on neonatal sepsis (O)?
4. Cough or difficulty breathing	4.2 Pneumonia	In children aged 2–59 months (P), what is the most effective antibiotic therapy (I, C) for very severe pneumonia (O)?
		In children aged 2–59 months (P), what is the most effective antibiotic therapy (I,C) for severe pneumonia (O)?
		In children aged 2–59 months (P), what is the most effective antibiotic regimen (I, C) for treatment of non-severe pneumonia (O)?
		For children aged 2–59 months (P), should antibiotics be given (I,C) for non-severe pneumonia and wheeze (O)?
	4.4 Conditions presenting with wheeze	In children 2–59 months of age (P), should oral salbutamol be used as a bronchodilator (I,C) to relieve acute wheeze and bronchoconstriction (O)?
5. Diarrhoea	5.4 Dysentery	For children less than 5 years of age with bloody diarrhoea (P), what is the effectiveness of the recommended antibiotic regimen (I) in preventing death or limiting complications (O)?
6. Fever	6.3 Meningitis	In children aged 2–59 months in developing countries (P), which parenteral antibiotic or combination of antibiotics (I), at what dose and duration, is effective for the treatment of suspected bacterial meningitis in hospital in reducing mortality and sequelae (O)?
	6.6 Typhoid fever	In children with typhoid fever, (P), what are the most effective antibiotics (I, C), in preventing severe morbidity or preventing complications and death (O)?
	6.7 Ear infections	In children with acute otitis media, (P), are antibiotics more effective than placebo (I, C), in reducing duration of illness and clinical course (O)?
		In children aged 2–59 months (P), what should be the first line antibiotic treatment (I) for chronic otitis media?
		In children aged 2–59 months (P), what is the effectiveness of local topical antiseptics (I) in the treatment of chronic suppurative otitis media?

CHAPTER	SUB-CHAPTER	QUESTION
		In children aged 2–59 months (P), what is the effectiveness of topical steroids (I) in the treatment of chronic otitis suppurative media?
7. Severe malnutrition	7.5 Treatment of associated conditions	In children with acute severe malnutrition (P), are antibiotics (I) effective in preventing death and sequelae (O)?
10. Supportive care	10.7 Oxygen therapy	In children aged 2–59 months with acute lower respiratory tract infection (P), which clinical signs (D) best indicate hypoxaemia (O)?
		In infants and children in low-resource settings (P), what is the most appropriate method (D) of detecting hypoxaemia in hospitals (O)?
		In infants and children with lower respiratory tract infections with hypoxaemia (P), what is the effectiveness of administering oxygen (I)?
		Among, children with lower respiratory tract infection (P), what are the best cut off oxygen saturation levels (D), at different altitudes that will determine hypoxaemia requiring oxygen therapy (O)?
		In children aged 2–59 months (P), what is the safest and most effective way of delivering oxygen (I,C) to improve oxygenation and prevent complications (O)?
		What are the most effective criteria for starting and stopping oxygen therapy?
	Treatment of hypoglycaemia	In fully conscious children with hypoglycaemia (P) what is the effectiveness of administering sublingual sugar (I)?
Appendix 4		In children with shock (P), what is the most appropriate choice of intravenous fluid therapy (I) to prevent death and sequelae (O)?

ANNEX 3

Members of expert panel, expertise and affiliations

LAST NAME	FIRST NAME	GENDER	COUNTRY	TITLE	AFFILIATION	CONTRIBUTION
CONTENT EXPERTS						
ABDULLAH	Dr FIZAN	Male	USA	Professor of Pediatric Surgery, Assistant Program Director, General Surgery	Johns Hopkins University School of Medicine	Paediatric surgery
BHATNAGAR	Dr. SHINJINI	Female	India	Senior clinical research scientist, Paediatrician/Nutritionist	All-India Institute (AIIMS), New Delhi	Diarrhoeal diseases
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DUKE	Dr. TREVOR	Male	Australia	Professor of International Child Health, Paediatric Intensive Care physician	Centre for International Child Health, University of Melbourne	Child health and pediatrics in developing countries; Paediatric critical care
ENGLISH	Dr. MICHAEL	Male	UK	Professor of Clinical paediatrics	University of Nairobi and KEMRI, Oxford	Paediatrics and child health; quality of care
MACLEOD[a]	Dr. STUART	Male	Canada	Professor of pediatrics	University of British Columbia	Pediatric clinical pharmacology & drug evaluation; knowledge translation for implementation
GRISI	Dr. SANDRA	Female	Brazil	Professor of paediatrics	Sao Paulo University	Respiratory infectious diseases; infantile diarrhea
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LAST NAME	FIRST NAME	GENDER	COUNTRY	TITLE	AFFILIATION	CONTRIBUTION
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SALOOJEE	Dr. HAROON	Male	South Africa	Professor	Witwatersrand University	Neonatology
SANTOSHAM[b]	Dr. MATHU	Male	USA	Professor	Johns Hopkins School of Public Health	Diarrhoeal diseases, vaccines
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Programme Managers						
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RATHMONY[b]	Dr. HONG	Male	Cambodia	Vice Director, MOH, Community Disease Control	MOH, Cambodia	Communicable disease; health administration
BRIDGET	Dr. WILLS	Female	Viet Nam	Senior scientist and fellow	Oxford University Clinical Research Unit in Viet Nam	Paediatric infectious diseases
Methodologists						
DANS	Dr. LEONILA	Female	Philippines	Associate professor	University of Philippines	Paediatric clinical epidemiologist and guidelines methodologist
GRAY	Dr. ANDY	Male	South Africa	Senior consultant	University of KwaZulu-Natal; Nelson Mandela Medical School	Pediatric pharmacologist and guidelines methodologist

[a] Chair of the Guidelines Expert Panel
[b] Unable to attend

ANNEX 4
List of external reviewers

LAST NAME	FIRST NAME	COUNTRY	AFFILIATION
1. Stephen	Dr Bickler	USA	Associate Clinical Professor of Surgery and Pediatrics, University of California
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3. Sabrina	Dr Bakeera-Kitaka	Uganda	Lecturer, Makerere University Medical School, Uganda
4. Molyneux	Dr Elizabeth	Malawi	Queen Elizabeth Hospital
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7. Adonis-Koffy	Dr Lawrence	Côte d'Ivoire	Service de pédiatrie du CHU de Yopougon
8. Carolyn	Dr MacLennan	Australia	Consultant Paediatrician, Flinders University, Australia
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10. Bodhankar	Dr Uday	India	Bodhankar Children's Hospital
11. Bhutta	Dr Zulfiqar	Pakistan	Professor of paediatrics and head of the division of maternal and child health at the Aga Khan, University

ANNEX 5

Members of the WHO Guideline Steering Group

Members comprise of departmental focal persons for area of work:

NAME	DEPARTMENT
1. Rajiv BAHL	CAH/NCH
2. Meena CHERIAN	EHT/CPR
3. Tarun DUA	MSD/MER
4. Olivier FONTAINE	CAH/NCH
5. Sandra GOVE	HIV/CBH
6. Malgorzata GRZEMSKA	STB/TBC
6. Suzanne HILL	EMP/MAR
7. Lulu MUHE	CAH/NCH
8. Peter OLUMESE	GMP/CMR
10. Zita WEISE PRINZO	NHD/NLU
11. Shamim QAZI	CAH/NCH
12. Wilson WERE	CAH/CIS

ANNEX 6
Tables

TABLE A6.1
Antibiotic sensitivity studies of Shigella dysentery in children: % resistant (number tested)

COUNTRY	YEAR	AMPICILLIN/ AMOXICILLIN	GENTAMICIN	CO-TRIMOXA-ZOLE	CIPRO-FLOX-ACIN	NORFLOXACIN	CHLORAM-PHENICOL	NALIDIXIC ACID	MECILLINAM	CEFOTAXIME	CEFTRIAXONE
Bangladesh	2000–1	51 (227)	–	74 (227)	0 (227)	–	–	30 (227)	0 (227)	–	–
Central African Republic	2004–5	76 (155)	2 (155)	86 (155)	0 (155)	–	71 (110)	71 (155)	–	2 (155)	–
China	1991–2000	53 (409)	13 (232)	62 (407)	20 (209)	4.9 (234)	18 (405)	–	–	–	–
Ethiopia[a]	2000–2	73 (74)	82 (74)	73 (74)	0 (74)	–	86 (74)	91 (74)	–	–	–
India	2004	50 (193)	–	36 (193)	25 (193)	35 (193)	–	38 (193)	–	–	–
India	2002–7	55.2 (134)	–		21 (134)		43 (134)	62 (134)			0 (134)
Senegal	2004–6	31 (165)	0 (165)	88 (145)	0 (0)	–	27 (165)	1 (165)	–	0 (165)	–

[a] Antibiotic sensitivity only reported for *S. dysenteriae* type 1 and *S. flexneri* (74 of the 84 isolates of *Shigella*)

TABLE A6.2

Antibiotics for acute otitis media

Antibiotic resistance for important pathogens in AOM
Setting: Mixed developed and developing countries
Outcome: Treatment failure

ORGANISM	STUDY	POPULATION	YEAR	PENICILLIN NON SUSCEPTIBLE (%)	PENICILLIN RESISTANT (%)	COTRIMOXAZOLE NON SUSCEPTIBLE (%)	COTRIMOXAZOLE RESISTANT (%)	CEPHALOSPORIN RESISTANT (%)	MACROLIDE RESISTANT (%)	BETA LACTAMASE (%)	7PCV
Streptococcus pneumoniae	Leach [2007]	Aboriginal Australians	1996–2001	27–37 (MIC >0.1)					16–20		pre
				34–40[b]	2–4						
	Arguedas [2006]	CR, Arg, US, Isr[a]	2002–2003	29	29						not stated
	Arguedas [1998]	Costa Rica	1995–1997	17.4	2.2				9–11		pre
	Tanon-Anoh [2006]	Cote d'Ivoire	2002–2003	11.8							not stated
	Pichichero [1995]	US	1989–1992	9	9						pre
	Lieberman	Israel	1998–1999	33	21	21	42				
	Arguedas [2006]	Costa Rica	2002–2003			2	45				
	Soley	Cost Rica	2004–2005			56					

ORGANISM	STUDY	POPULATION	YEAR	PENICILLIN NON SUSCEPTIBLE (%)	PENICILLIN RESISTANT (%)	COTRIMOXAZOLE NON SUSCEPTIBLE (%)	COTRIMOXAZOLE RESISTANT (%)	CEPHALOSPORIN RESISTANT (%)	MACROLIDE RESISTANT (%)	BETA LACTAMASE (%)	7PCV
Haemophilus influenzae	Leach[2007]	Aboriginal Australians	1996–2001							2–6	pre
										5–10[c]	
	Pichichero [1995]	US	1989–1992							83	pre
	Arguedas [1998]	Costa Rica	1995–1997							3.7	pre
	Arguedas [2006]	Costa Rica	2002–2003			5	28				
	Soley	Cost Rica	2004–2005			50					
Moraxella cattharalis	Pichichero	US	1989–1992							100	pre
	Arguedas	Costa Rica	1995–1997							100	pre
Pseudomonas aureginosa	Tanon-Anoh [2006]	Cote d'Ivoire	2002–2003					35.5[d]			not stated

[a] Study period
[b] At end of therapy; no statistical difference with pre-therapy rate
[c] At end of therapy; no statistical difference with pre-therapy rate
[d] Anti-pseudomonal cephalosporin

TABLE A6.3

Studies reporting the prevalence of bacterial infections in malnourished children

YEAR	SITE	N° PTS (% HIV+)	TYPE OF SPECIMEN	INCIDENCE OF INFECTIONS (ISOLATED ORGANISMS)	SENSITIVITY PATTERN	RESISTANCE PATTERN
2006	Uganda	450 (36%)	Blood	Bacteraemia: 17% (*S. typhimurium* 27%, *S. enteritidis* 11%, *S. aureus* 26%, *S. pneumoniae*)	cipro: 80%	cotrimoxazole: 75%, ampicillin: 50%, gentamicin, ceftriaxone, CAF
2006	Uganda	134 (44%)	Blood	Bacteraemia: 22% (Salmonella, *E. coli* 67%)	ceftriaxone: 100% cipro: 97%	cotrimoxazole 93%, amp 76%, genta 66%, CAF 60%
2005	Kenya	91 (43%)	Blood Multiple cultures	Bacteraemia: 29% (Coagulase negative staphylococci)	G+ & G-: cipro 80%. G-: third generation cephalosporins and ceftazidime.	staphylococci: erythro, amp, cotrimoxazole, CAF, oxacillin
2001	Congo	Unclear	Blood	Bacteraemia: 13.2% (Enterobacteraciae)		ampicillin and genta 52% CAF
2001	Jamaica	150	Blood	Bacteraemia: 10% (Coagulase negative staphylococci 40%)	amoxi-clavulanic 70% genta 77%, methicillin 85%	penicillin
2000	Malawi	75	Blood	Bacteremia: 9 % (*S. pneumoniae*, Klebsiella, *E. coli*) UTI: 17% (*E. coli*, Klebsiella)		
2000	Turkey	103	Urine	UTI: 31% (*E. coli* 54%)	*E. coli*: gentamicin 100% cotrimoxazole	*E. coli*: cotrimoxazole 82%, ceftriaxone 17%, cefotaxime 17%, cipro 17%
1996	South Africa	323	Blood	Bacteremia: 9.6% (Gram-negative enteric bacilli 48%)	ampicillin and gentamicin: 95%	
1995	South Africa	134	Urine	UTI: 26% (Gram-negative enteric bacilli)	gentamicin, ampicillin	

YEAR	SITE	N° PTS (% HIV+)	TYPE OF SPECIMEN	INCIDENCE OF INFECTIONS (ISOLATED ORGANISMS)	SENSITIVITY PATTERN	RESISTANCE PATTERN
1995	Gambia	111[a]	Nasopharyngeal and lung aspirate	(*S. pneumoniae*, Haemophilus, Salmonella, *E. coli*, *S. aureus* and other staphylococci)	*S. pneumoniae: cotrimoxazole 100%, CAF 90%.*	
1994	Gambia	378[a]	Blood, lung spirate, pleural fluid	Pneumonia: 28% (*S. pneumoniae*, Haemophilus, viral)		
1993	Nigeria	99[a]	Blood Lung puncture aspirates	Klebsiella 39%, *S. aureus* 20%, *E. coli* 8 %	gentamicin, cloxacillin	
1992	Tanzania	164	Blood Urine Multiple site cultures	Infections on admission: 92% Bacteremia (*S. Aureus*), UTI (E. coli, Klebsiella) Hospital infections: 49% (*S. aureus*, *Strep faecalis*, Klebsiella, *E. coli*)	*S. aureus*: erythro, genta, clox. G-: gentamicin *Strep. faecalis*: amp, erythro, penicillin.	
1992	South Africa19	134	Urine	UTI=26%		

[a] children with pneumonia

cipro = ciprofloxacin; genta = gentamicin; amp = ampicillin; clox= cloxacillin; erythro= erythromycin; CAF= chloramphenicol; G– & G+ = gram negative and positive bacteria; UTI= urinary tract infection

TABLE A6.4
Clinical signs of hypoxaemia

STUDY'S FIRST AUTHOR, PUBLICATION DATE, SETTING	SETTING (ALTITUDE ABOVE SEA LEVEL)	STUDY OBJECTIVES	DESIGN	AGE	SAMPLE SIZE (NUMBER WITH HYPOXAEMIA)	INCLUSION CRITERIA	EXCLUSION CRITERIA	DEFINITION OF HYPOXIA	METHODOLOGY FOR DETECTING CLINICAL SIGNS CLEARLY DESCRIBED?	METHODOLOGY FOR GOLD STANDARD MEASUREMENTS CLEARLY DESCRIBED?	NOTES
Reuland, 1991 Peru	Hospital and clinic (1750 m)	1) Define normal respiratory rate, pulse rate, oxygen sarturation, Hb concentration and SaO2 in health children at high altitude.									
		2) Investigate clinical predictors of hypoxaemia in children with ALRI at high altitude	Prospective observational	2–60 mths	423 (132)	Rhinorrhea, cough or difficulty breathing less than 14 days duration	Chronic illness including asthma, congenital heart disease or murmurs.	<82% for age 2–11 months <85% for age ≥12 months	Yes	Yes	Results not stratified by age
Onynango 1993 Kenya	Paediatric ED, Tertiary hospital, (1670m)	Determine prevalence, clinical predictors and outcomes of hypoxaemia in children with respiratory illness.	Prospective observational	7 days–36 mths	256 (151)	Cough and other symptoms of ARI.	Dehydration or evidence of cardiac, renal, or CNS, metabolic disease, or severe anaemia.	<90%	Yes	Yes	

STUDY'S FIRST AUTHOR, PUBLICATION DATE, SETTING	SETTING (ALTITUDE ABOVE SEA LEVEL)	STUDY OBJECTIVES	DESIGN	AGE	SAMPLE SIZE (NUMBER WITH HYPOXAEMIA)	INCLUSION CRITERIA	EXCLUSION CRITERIA	DEFINITION OF HYPOXIA	METHODOLOGY FOR DETECTING CLINICAL SIGNS CLEARLY DESCRIBED?	METHODOLOGY FOR GOLD STANDARD MEASUREMENTS CLEARLY DESCRIBED?	NOTES
Lozano 1994 Colombia	ED or OPD of Tertiary hospital (2640m)	Determine the usefulness of clinical signs in predicting hypoxaemia and radiological pneumonia	Prospective observational	7 days–36 mths	200 (125)	Cough lasting up to 7 days and had a chest X-ray ordered.	Cardiovascular, pulmonary, neurological congenital defects, pre-term, chronic disease, immuno-compromise, wheezing	<88%	Yes	Yes	Results not stratified by age
Dyke 1995 PNG	District hospital (1800m)	Determine the usefulness of clinical signs in predicting hypoxaemia, and use these to develop a model of composite signs.	Prospective observational	3 mths–3 years	91 (47)	Children diagnosed with pneumonia by nurses. No details given about inclusion criteria.	Not mentioned	<85%	No	No	A refresher course for nurses on clinical signs and use of oximetry
Weber 1997 The Gambia	Paediatric ward, tertiary hospital (SL)	Determine the usefulness of clinical signs and symptoms in predicting hypoxaemia	Case-control	2 mths–5 years	69 hypoxaemic 67 control (pneumonia but no hypoxaemia)	Referral with ALRI. No details given.	Signs of congenital heart disease or meningitis	<90%	Yes	No	

STUDY'S FIRST AUTHOR, PUBLICATION DATE, SETTING	SETTING (ALTITUDE ABOVE SEA LEVEL)	STUDY OBJECTIVES	DESIGN	AGE	SAMPLE SIZE (NUMBER WITH HYPOXAEMIA)	INCLUSION CRITERIA	EXCLUSION CRITERIA	DEFINITION OF HYPOXIA	METHODOLOGY FOR DETECTING CLINICAL SIGNS CLEARLY DESCRIBED?	METHODOLOGY FOR GOLD STANDARD MEASUREMENTS CLEARLY DESCRIBED?	NOTES
Smyth 1998 Zambia	Children's ward, Tertiary hospital (1150m)	Determine the usefulness of clinical signs and symptoms in predicting hypoxaemia	Prospective observational	1 mths–4 yrs	167 (55)	WHO-defined severe or very severe pneumonia, or pneumonia with complications	Widespread wheeze	<92%	Yes	Yes	
Usen 1999 The Gambia	Paediatric ward, tertiary hospital (SL)	Determine clinical predictors and outcomes of hypoxaemia in children with ALRI	Prospective cohort	2–33 mths	1072 (63)	Admitted with pneumonia or other ALRI. No details given.	Structural heart disease, Down's syndrome	<90%	Yes	Yes	Results not stratified by age
Duke 2002 PNG	Children's ward, Provincial hospital (1600m)	Determine in sick neonates and children: 1) incidence and severity of hypoxaemia 2) hypoxaemia in non-ALRI illnesses 3) power of clinical signs to predict hypoxaemia	Prospective observational	1 mths–5 years	491 (257)	Children admitted over 12 month period by 2 investigators. Representatives of all admissions.	Nil.	86% for neonates 88% for older children	Yes	Yes	

STUDY'S FIRST AUTHOR, PUBLICATION DATE, SETTING	SETTING (ALTITUDE ABOVE SEA LEVEL)	STUDY OBJECTIVES	DESIGN	AGE	SAMPLE SIZE (NUMBER WITH HYPOXAEMIA)	INCLUSION CRITERIA	EXCLUSION CRITERIA	DEFINITION OF HYPOXIA	METHODOLOGY FOR DETECTING CLINICAL SIGNS CLEARLY DESCRIBED?	METHODOLOGY FOR GOLD STANDARD MEASUREMENTS CLEARLY DESCRIBED?	NOTES
Lodha 2004 India	ED, tertiary hospital (239 m)	Determine clinical predictors of hypoxaemia in children with ALRI	Prospective observational	<5 years	109 (28)	WHO defined pneumonia	Asthma, congenital heart disease, severe anaemia, severe dehydration, peripheral shut down, ventilation	<90%	Yes	Yes	
Laman 2005 PNG	Paediatric ward, tertiary hospital (SL)	Determine clinical predictors of hypoxaemia in ALRI using different definitions of hypoxaemia.	Prospective observational	1–60 mths	77 <93% (34) <90% (20) <85% (10)	WHO-defined severe or very severe pneumonia	Heart disease, asthma, HIV, severe malnutrition	<93% <90% <85%	No	Yes	Results not stratified by age
Basnet 2006 Nepal	ED or OP of childrens hospital (1336m)	Determine prevalence of hypoxaemia and its clinical predictors in children with ARI	Prospective observational	2 mths–5 years	250 (58)	Cough and difficulty breathing	Murmur on auscultation, non-ARI	<90%	No	Yes	

TABLE A6.5

Mortality caused by pneumonia, stratified by saturation (1919–1929, adapted from WHO 1993)

	WITH OXYGEN			WITHOUT OXYGEN			RELATIVE RISK		
	DEATHS	TOTAL	%	DEATHS	TOTAL	%	RR	95% CI	P-VALUE
Saturation <80%	34	73	47	14	15	93	0.50	0.38–0.66	0.0009
Saturation >=80%	5	20	38	4	19	50	1.19	0.37–3.80	0.77
Total	39	93	42	18	34	53	0.79	0.53–1.18	0.27

RR – relative risk; CI – confidence interval

ANNEX 7
GRADE Evidence tables

TABLE A7.1

Vitamin K prophylaxis

Question: Should vitamin K prophylaxis be given to newborns for prevention of vitamin K deficiency bleeding?
Population: Neonates in low and middle income countries
Intervention: Vitamin K prophylaxis
Control: No prophylaxis
References: Puckett RM, Offringa M [Cochrane review 2000], Paul VK, Jeevasankar M, Aggarwal R [WHO. Unpublished 2010)

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE					PRECISION BASED ON 95% CI OF THE POOLED EFFECT SIZE	CONSISTENCY	GENERALIZ-ABILITY/ DIRECTNESS	OVERALL QUALITY OF EVIDENCE BASED ON THE TOTAL OF COLUMNS ON THE LEFT	POOLED EFFECT SIZE
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEAL-MENT (LOW RISK OF SELECTION BIAS)	BLINDING WHERE POSSIBLE (LOW RISK OF MEASURE-MENT BIAS)	ANALYSIS INTENTION TO TREAT (ADJUSTED)	LOSS TO FOLLOW-UP					
Post-circumcision bleeding	2 Vietti 1960 Sutherland 1967	Most evidence from RCT 0	Adequate 0	Yes 0	Yes 0	No 0	OK 0	Only two studies -0.5	Developed country setting -0.5	Final score = -1.0 MODERATE	RR 0.61 (0.46 to 0.81) NNT 21 (13 to 50) (Incidence in placebo group 12.5%)
Non-circumcision bleeding	1 Sutherland 1967	RCT 0	Adequate 0	Yes 0	Yes 0	No 0	Some imprecision -0.5	Single study -1.0	Developed country setting -0.5	Final score = -2.0 LOW	RR 0.57 (0.36 to 0.91) NNT 80 (42 to 714) (Incidence in placebo group 2.9%)
ANY moderate to severe bleeding	1 Sutherland 1967	RCT 0	Adequate 0	Yes 0	Yes 0	No 0	OK 0	Single study -1.0	Developed country setting -0.5	Final score = -1.5 MODERATE	RR 0.19 (0.08 to 0.46) NNT 75 (48 to 177) (Incidence in placebo group 2.9%)

TABLE A7.2

Prophylactic antibiotics for newborn born of mother with risk factors for neonatal infection

Question: Does the use of immediate prophylactic antibiotics have an impact on neonatal mortality and/or on neonatal sepsis?
Population: Term newborn infants of mothers with risk factors for neonatal infection
Intervention: Prophylactic antibiotics
Settings: Belgium and South Africa
References: Gerard [1979]; Wolf [1976]

STUDY'S FIRST AUTHOR, PUBLICATION DATE AND SETTING	LEVEL (REFERRAL, FIRST LEVEL HEALTH FACILITY, COMMUNITY)	STUDY DESIGN	ALLOCATION CONCEALMENT	BLINDING	COMPLETENESS OF FOLLOW-UP	ANALYSIS (INTENT TO TREAT)	NO. OF EVENTS/ TOTAL IN INTER-VENTION GROUP	NO. OF EVENTS/ TOTAL IN CONTROL GROUP	EFFECT SIZE RR (95% CI)
Neonatal mortality									
Gerard 1979 (Charleroi, Belgium)[a]	Hospital	Quasi- RCT	No (Quasi-RCT)	Unclear	100%	Unknown	0/29	0/38	–
Wolf 1976 (Johannes-burg, South Africa)[b]	Hospital	RCT	Unclear	Unclear	100%	Unknown	0/24	0/25	–
Neonatal sepsis									
Gerard 1979 (Charleroi, Belgium)[c]	Hospital	Quasi- RCT	No (Quasi-RCT)	Unclear	100%	Unknown	0/29	0/38	–
Wolf 1976 (Johannes-burg, South Africa)[d]	Hospital	RCT	Unclear	Unclear	100%	Unknown	0/24	4/25	RR=0.12 (0.01; 2.04)

[a] Risk factor was maternal group B streptococcus colonization. It is unknown whether women who were found to carry Group B streptococcus received antepartum or intrapartum antibiotics or not.
[b] Risk factors were maternal fever in labor, prolonged rupture of membrane. Both term and preterm babies included. Average gestational age 37.4 (treatment group) and 37.7 (control group). It was assumed that >90% were near-term. 24 of the total 49 mothers had received antibiotics before delivery.
[c] Risk factors were maternal group B streptococcus colonization. It is unknown whether women who were found to carry Group B streptococcus received antepartum or intrapartum antibiotics or not.
[d] Risk factors were maternal fever in labor, prolonged rupture of membrane. Both term and preterm babies included. Average gestational age 37.4 (treatment group) and 37.7 (control group). It was assumed that >90% were near-term. 24 of the total 49 mothers had received antibiotics before delivery.

TABLE A7.3

Skin-to-skin contact between the mother and her baby in the first hour of life

Question: Does early skin-to-skin contact of the baby with the mother in the first hour of life have an impact on neonatal mortality, hypothermia or initiation/ exclusivity/ duration of breastfeeding?
Population: newborns
Intervention: Early skin-to-skin contact of the baby with the mother
Settings: Canada, Guatemala, Sweden, Taiwan, and United Kingdom
References: Moore E, Anderson GC, Bergman N. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD003519. DOI: 10.1002/14651858.CD003519.pub2. Issue 4, 2009 (Status in this issue: Unchanged)

OUTCOME	NO. OF STUDIES/ DESIGN	LIMITATIONS OF STUDIES	PRECISION	CONSISTENCY	GENERALIZABILITY/DI-RECTNESS	OVERALL QUALITY OF EVIDENCE	POOLED/SINGLE STUDY EFFECT SIZE (95% CI)
Breastfeeding 1–4 months post birth	10 All RCTs (0)	Limitations in allocation concealment, loss to follow up and analysis (-1.5)	95% CI does not include the null; wide CI (-0.5)	83.3% of the total weight of evidence in the same direction of the pooled effect size (0)	About 55% of the total weight of evidence from high-income settings (-0.5)	LOW (Total score = -2.5)	OR=1.82 (1.08; 3.07)
Exclusive breastfeeding at 4–6 months post birth	1 RCT (0)	Unknown if allocation concealment, follow up and analysis was adequate (-1.5)	95% CI does not include the null; narrow CI (0)	Only one study (-1)	Study in middle-income setting (0)	LOW (Total score = -2.5)	OR= 5.67 (2.27; 14.16)
Duration of breastfeeding	7 All RCTs (0)	Limitations in allocation concealment, loss to follow up and analysis (-1.5)	95% CI includes the null, wide CI (-1)	About 86% of the total weight of evidence in the same direction of the pooled effect size (0)	About 60% of the total weight of evidence from middle- or low-income settings (0)	LOW (Total score = -2.5)	Mean difference 42.55 (-1.69; 86.79)
Axillary temperature 90–120 minutes post birth	3 All RCTs (0)	Limitations in allocation concealment and analysis (-1.0)	95% CI includes the null, wide CI (-1)	About 64% of the total weight of evidence in the same direction of the pooled effect size (-1)	About 64% of the total weight of evidence from high-income settings (-0.5)	VERY LOW (Total score = -3.5)	Mean difference (-0.15; 0.65)

TABLE A7.4

Antibiotics for suspected neonatal sepsis

Question: Should third generation cephalosporin monotherapy replace currently recommended ampicillin-gentamicin combination as first line empiric treatment for neonatal sepsis?

Population: Neonates with suspected neonatal sepsis

Intervention: Third generation cephalosporin monotherapy versus ampicillin-gentamicin combination

Settings: Europe, South Africa

References: Mtitimila EI, Cooke RWI [2004]; Gordon A, Jeffery HE [2005]; Downie L, Armiento R [WHO, unpublished, 2010]; Mueni E, Opanga S, English M [unpublished 2010]; De Louvois et al [1992];

			LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE								
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	POLLED EFFECT SIZE (CI-95%)	OVERALL QUALITY
Mortality	4	RCT (0)	Adequate (0)	No, but objective outcome (0)	No (0)	Old studies, with very low levels of resistance to tested antibiot-ics. (-1)	CI includes null and is wide (-1)	No inconsist-ency (0)	Mostly from high-income countries. (-0.5)	0.88 (0.39 to 1.98)	LOW (Final score = -2.5)
Cure rate	4	RCT (0)	Adequate (0)	No (-0.5)	No (0)	Old studies, with very low levels of resistance to tested antibiot-ics. (-1)	CI includes null but is quite narrow (0)	No inconsist-ency (0)	Mostly from high-income countries. (-0.5)	1.01 (0.94 to 1.08)	LOW (Final score = -2)

TABLE A7.5

Mortality from NEC with different antibiotic regimens[a]

Question: Should children with necrotizing enterocolitis be given antibiotics? If yes, what antibiotic regimen?
Population: Neonates with necrotizing enterocolitis
Intervention: Comparison of antibiotic regimens in necrotizing enterocolitis
Settings: Developed countries.
References: David Tickell, Trevor Duke [WHO, unpublished, 2011]; Hansen [1980]; Faix [1998]; Scheifele [1987]

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
							NO. OF NEC INFANTS				
NUMBER OF STUDIES	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	EXPOSED WHO DIED/ TOTAL EXPOSED	NON-EXPOSED WHO DIED/TOTAL NON-EXPOSED	OR [95% CI] (P VALUE)	QUALITY	IMPORTANCE
IV cefotaxime & vancomycin (intervention) versus ampicillin & gentamicin (control)											
1: Scheifele [1987] (90 infants)	Prospective observational (non-concurrent cohort)	Major risk of selection bias[b]	Single study	No serious indirectness	Some imprecision[e]	None	0/30 (only <2200g included)	5/38 (only <2200g included)	0.00 [0.0-0.895] (p=0.048)	Very low ⨁000	HIGH
IV ampicillin, gentamicin and Clindamycin (intervention) versus IV ampicillin & gentamicin (control)											
1: Faix [1998] (42 infants)	RCT	Minor limitations[c]	Single study	No serious indirectness	CI includes null, wide CI[e]	None	4/20	4/22	1.125 [0.26-4.86] (p>0.05)	Low ⨁⨁00	
IV ampicillin and gentamicin with ORAL gentamicin (intervention) versus IV ampicillin & gentamicin (control)											
1: Hansen [1980] (20 infants)	RCT	Serious limitations[d]	Single study	No serious indirectness	Wide CI, includes null[e]	Compares addition of oral drug, not IV	1/10	2/10	0.44 [0.05-4.25] (p>0.05)	Very low ⨁000	

[a] given the large differences in antibiotic regimens used as comparisons, studies cannot be analysed as a group
[b] non-concurrent controls, assessment based on the Newcastle-Ottowa Quality Assessment Scale for Cohort Studies (Selection 4*/4*, Comparability 1*/2*, Outcome 3*/3*): minimal controlling for confounders reduces comparability
[c] blinding not well detailed; 2 control patients treated in Clindamycin group after 24 hours when deteriorating (results still analysed with intention to treat); study ceased early due to rate of strictures in Clindamycin group
[d] blinding & allocation concealment not detailed adequately – quality downgraded
[e] small numbers limits precision – quality downgraded

TABLE A7.6

Kangaroo Mother Care

Question: Is Kangaroo Mother Care more effective than conventional care in reducing mortality and/or morbidity?
Population: Preterm or low birth weight neonates
Intervention: KMC versus conventional care.
Setting: India, Colombia, Ethiopia
References: Lawn, [2010]

LIMITATIONS IN METHODS							PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	NO EVENTS/ TOTAL		RELATIVE RISK (95% CI)
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEAL-MENT	BLINDING	LOSS TO FOLLOW-UP	OTHER					KMC	CONTROL	
Mortality	3 (988)	RCT (0)	Adequate (0)	Not possible (0)	No (0)	No (0)	No impre-cision (0)	No incon-sistency (0)	(-0.5)[a]	HIGH	17/517	33/ 471	0.49 (0.29 to 0.82)
	3 (8257)	Observa-tional (-1)	High risk of selection bias (-0.5)	Objective outcome (0)	OK (0)	Inadequate adjustment for con-founding (-0.5)	No impre-cision (0)	(0)[b]	As above (-0.5)	LOW	281/4585	329/3672	0.68 (0.58 to 0.79)
Severe morbidity	5 (1520)	RCT (0)	Adequate (0)	Risk of measure-ment bias (-0.5)	No (0)	No (0)	No impre-cision (0)	(-0.5)[c]	As above (-0.5)	MODER-ATE	54/782	131/738	0.34 (0.17 to 0.65)

[a] All low-middle income countries, but comparison group is good incubator care apart from Ethiopian study
[b] Consistent direction of effect but some heterogeneity
[c] Some heterogeneity, probably due to differences in outcome definition

TABLE A7.7

Prevention of hypothermia immediately after birth in LBW infants

Question: Are plastic wraps or caps used immediately after birth more effective than conventional care in preventing hypothermia?
Population: LBW infants, most <29 weeks gestation
Intervention: comparison of plastic wrap/bag, Plastic cap and skin-to-skin contact immediately after birth
Control: Conventional care (ambient temperature, drying, removing wet cloth, wrapping
Settings: Developed countries
References: [McCall 2010, Cochrane review]

OUTCOME	NO. OF STUDIES/DESIGN	LIMITATIONS OF STUDIES	PRECISION	CONSISTENCY	GENERALIZABILITY/ DIRECTNESS	OVERALL QUALITY OF EVIDENCE	POOLED/SINGLE STUDY EFFECT SIZE (95% CI)
Plastic wrap/bag immediately after birth for LBW infants <29 weeks gestation							
Core body temperature (4 in infants <29 wk)	5 All RCTs (4 in infants <29 wk) (0)	Limitations in comparability of groups (-0.5)	OK (0)	All studies in the same direction (0)	Developed country settings. Outcome not direct (-1)	MODERATE (Total score = -1.5)	RR 0.57 [0.37, 0.77]
Hypothermia on admission to NICU	2 RCTs (both in infants <29 wk) (0)	Limitations in comparability of groups (-0.5)	OK (0)	Two studies - in the same direction (-0.5)	Developed country settings (-0.5)	MODERATE (Total score = -1.5)	RR 0.66 (0.51, 0.84)
Plastic cap immediately after birth for LBW infants <29 weeks gestation							
Hypothermia on admission to NICU	1 RCT (in infants <29 wk) (0)	Limitations in comparability of groups (-0.5)	OK (0)	Single study (-1.0)	Developed country settings (-0.5)	LOW (Total score = -2)	0.48 (0.32, 0.73]
Skin-to-skin contact immediately after birth for LBW infants 1200–2199 g							
Hypothermia	1 RCT (1200–2200 g) (0)	Allocation concealment unclear (-0.5)	OK (0)	Single study (-1.0)	Developing country setting (0)	MODERATE (Total score = -1.5)	0.48 [0.32, 0.73] (Study terminated early due to benefits in interim analysis)

TABLE A7.8

Antibiotics for non-severe pneumonia with or without wheeze

Question: Should antibiotics be given for non-severe pneumonia with or without wheeze?
Population: Children with non-severe pneumonia.
Intervention: Antibiotics versus placebo for non-severe pneumonia
Setting: India and Pakistan
References: Hazir, et al [2010], Awasthi, et al [2008]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICI-PANTS)	DESIGN	ALLOCATION CONCEAL-MENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	ODDS RATIO (95% CI)	IMPORTANCE
Antibiotics versus placebo for non-severe pneumonia												
Clinical failure by day 3	1 (900)	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	One study -1	Only Pakistan -0.5	LOW	1.13 (0.72–1.76)	Important
Cumulative failure by day 5	1 (900)	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	One study -1	Only Pakistan -0.5	LOW	0.87 (0.61–1.24)	Important
Antibiotics versus placebo for non-severe pneumonia plus wheeze												
Clinical failure by day 4	1 (1671)	RCT 0	Adequate 0	Yes 0	No 0	Wheeze was a criteria for treatment failure -0.5	No imprecision 0	NoIncon-sistency 0	Only India -0.5	MODERATE	4.2% (0.2–8.2)	Important
Relapse by day 14	1 (1671)	RCT 0	Adequate 0	Yes 0	No 0	As above -0.5	No imprecision 0	No incon-sistency 0	Only India -0.5	MODERATE	0.8 (-1.9–3.5)	Important

TABLE A7.9

Antibiotic for treatment of non-severe pneumonia

Question: which oral antibiotic is most appropriate for treatment of non-severe pneumonia?
Population: Children with non-severe pneumonia.
Intervention: Comparison of different antibiotics for treatment of non-severe pneumonia
Setting: Multi-centre, Americas
References: [Sajwani, 2010] [WHO, 2003] [Grant et al, 2009]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Amoxicillin versus co-trimoxazole for non-severe pneumonia												
Cure rate	2 (3468)	RCT 0	Inadequate -0.5	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	Both in Asia -0.5	MODERATE	0.99 (0.96 to 1.01)	Important
Clinical failure	3 (3759)	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	All in Asia -0.5	MODERATE	1.09 (0.93 to 1.27)	Important
Levofloxacin versus co-amoxyclavulanic acid for non-severe pneumonia												
Cure rate	1 (270)	RCT 0	Inadequate -0.5	No -0.5	No 0	No 0	Some imprecision -0.5	No inconsistency 0	Only in Americas -0.5	LOW	1.02 (0.93 to 1.11)	Important
Azithromycin versus co-amoxyclavulanic acid for non-severe pneumonia												
Treatment failure at 2 weeks	2 (276)	RCT 0	Inadequate -0.5	Yes 0	No 0	No 0	Some imprecision -0.5	Serious inconsistency -1	Only USA -0.5	LOW	1.20 (0.45 to 3.21)	Important
Short (3 days) versus long (5 days) duration of antibiotics for non-severe pneumonia												
Treatment failure	3 (5763)	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	All from Asia -0.5	MODERATE	0.86 (0.74 to 1.01)	Important
Relapse rate	4 (5469)	RCT 0	Inadequate -0.5	No 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	All from Asia -0.5	LOW	1.06 (0.82 to 1.37)	Important

TABLE A7.10

Antibiotics for severe pneumonia

Question: Is oral amoxicillin equivalent to parenteral antibiotics for treatment of pneumonia?
Intervention: Oral versus injectable antibiotics for children hospitalized with pneumonia
Population: Children with WHO-defined severe pneumonia or equivalent
Settings: Low-income countries and UK
References: [Addo Yobo, 2004], [Hazir, 2008], [Atkinson, 2006]

QUALITY ASSESSMENT							SUMMARY OF FINDINGS			
NUMBER OF STUDIES	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	PARENTERAL ANTIBIOTICS	ORAL AMOXICILLIN	QUALITY	IMPORTANCE
							EFFECT SIZE (-5 TO 5 %) (95% CI)			
Treatment failure at day 2										
1	RCT	No blinding -0.5	Only one study -0.5	Some indirectness -0.5	No serious imprecision	None	-0.4% (-4.2 to 3.3)		MODERATE	Important
Treatment failure by day 5–6										
2	RCT	No blinding -0.5	No serious inconsistency	Some indirectness -0.5	No serious imprecision	None	-2.4% (-3.4 to 4.5)		MODERATE	Important
Treatment failure at day 6–14										
2	RCT	No blinding -0.5	No serious inconsistency	Some indirectness -0.5	No serious imprecision	None	-0.05% (-5 to 3.4)		MODERATE	Important
Time for response										
1	RCT	No blinding -0.5	Only one study -0.5	Some indirectness -0.5	No serious imprecision	High income setting[a] -1	0.3 hours (0.21 to 0.4) P<0.03		LOW	Important

QUALITY ASSESSMENT							SUMMARY OF FINDINGS			
NUMBER OF STUDIES	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	PARENTERAL ANTIBIOTICS	ORAL AMOXICILLIN	QUALITY	IMPORTANCE
							EFFECT SIZE (-5 TO 5 %) (95% CI)			
Time in hospital										
1	RCT	No blinding -0.5	Only one study -0.5	Some indirectness -0.5	No serious imprecision	As above	Median (IQR) days 1.77 (1 to 2.2.0)	Median (IQR) days 2.1 (1.8 to 2.9)	Mean diff. (95% CI) 0.60 (0.15 to 1.13) days	LOW
Complications (empyema)										
1	RCT	No blinding -0.5	Only one study -0.5	Some indirectness -0.5	No serious imprecision	As above	0	3/103	-	LOW

[a] Children (both groups) failing treatment at 48 hours received additional antibiotics as standard treatment.

TABLE A7.11

Ambulatory care of severe pneumonia

Question: Can children with severe pneumonia be managed as outpatients?
Intervention: Oral versus injectable antibiotics for children hospitalized with pneumonia
Population: Children with WHO-defined severe pneumonia
Settings: Pakistan, Bangladesh, The Gambia
References: [Ashraf, 2010; Hazir, 2008]

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
NUMBER OF STUDIES	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	OUTPATIENT TREATMENT	INPATIENT TREATMENT	RELATIVE EFFECT (95% CI)	QUALITY	IMPORTANCE
Treatment failure											
2	RCT	No blinding -0.5	Different outcome measures. One study is of day-care treatment, another of home-treatment -0.5	No serious indirectness	No serious imprecision	None	Results could not be pooled due to heterogeneity of How outcomes are reported. Hazir et al showed equivalence: risk diff. 1·1% (-1·3 to 3·5) Ashraf et al showed higher treatment failure in the intervention group: relative risk 3.4 (1.5 to 7.8)			MODERATE	Important
Death											
1	RCT	No blinding -0.5	Only one study -0.5	No serious indirectness	Only 2 deaths -1	None	0	2/180	-	LOW	Important
Readmission											
1	RCT	No blinding -0.5	Only one study -0.5	No serious indirectness	No serious imprecision	None	22/180	11/180	2.0 (0.99 to 4.0)	MODERATE	Important

Note: Campbell et al (1988), in comparing oral and injectable antibiotics, enrolled an hospitalized and ambulatory group of children with severe pneumonia. However, outcome definitions were not consistent with the Ashraf and Hazir studies, and assessments were partially completed by field workers.

TABLE A7.12

Antibiotics for very severe pneumonia

Question: What is the most effective antibiotic therapy treatment of very severe pneumonia?
Population: Children with severe very severe pneumonia
Intervention: Amoxicillin/Penicillin and gentamicin versus chloramphenicol
Setting: Developing countries
References: Jabeen M, Lassi Z, Bhutta Z, [WHO, Unpublished, 2010]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Death	2 (2074)	RCT 0	Adequate 0	No But outcome objective 0	No 0	No 0	Serious imprecision -1	No inconsistency 0	Generalizable 0	MODERATE	0.71 (0.51–1.00)	Important
Clinical failure	2 (2074)	RCT 0	Adequate 0	No -0.5	No 0	No 0	No impreci-sion 0	No inconsistency 0	Generalizable 0	HIGH	0.79 (0.66 to 0.94)	Important

TABLE A7.13

Inhaled salbutamol for management of bronchoconstriction

Question: Should oral salbutamol be used as a bronchodilator to relieve acute wheeze and bronchoconstriction?
Intervention: Oral salbutamol versus inhaled salbutamol
Population: Children with wheeze
Settings: Pakistan
References: Azeem MS, Lassi ZS, Bhutta ZA. Systematic review of the management of bronchoconstriction with rapid acting bronchodilator therapy [unpublished, WHO, 2010]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Treatment failure on day 5 (continuing to wheeze)	1 (780)	RCT 0	Adequate 0	No -0.5	No 0	No 0	Some imprecision -0.5	One study -0.5	Only Pakistan -0.5	LOW	0.94 (0.68 to 1.29)	Important

TABLE A7.14

Antibiotic treatment for dysentery

Question: Which antibiotic is effective for treatment of dysentery?
Intervention:
Population: Children with Shigella dysentery
Settings: Bangladesh and Kenya Mexico Bangladesh (4 trials), Israel (1 trial), USA (1 trial)
References:

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE									
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI)
Antibiotic versus no drug or placebo											
Diarrhoea on F/UP at 6 days	1	RCT 0	Adequate 0	Not blinded -0.5	No 0	No 0	No imprecision 0	1 study -1	Developing country in children 0	MODERATE (Total -1.5)	RR 0.21 (0.09 to 0.48)
Fluoroquinolones versus macrolides											
Diarrhoea on F/UP	2	RCT 0	Adequate 0	Yes 0	No 0	Not intention to treat -0.5	Some imprecision -0.5	Outcome from only 1 study. -1	Conducted in a developing country 0	LOW (Total -2)	RR 0.6 (0.24 to 1.49)
Other adverse events	1	RCT 0	Adequate 0	Yes 0	No 0	Not intention to treat -0.5	Some imprecision -0.5	1 study -1	Conducted in a developing country 0	LOW (Total -2)	RR 1.33 (0.32 to 5.56)

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE									
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI)
Fluoroquinolones versus beta-lactams											
Diarrhoea on follow-up at 6 days	5	RCT 0	Adequate 0	Yes 0	No 0	No 0	Imprecision -1	Some inconsist-ency -0.5	Most studies LIC and in children 0	MODERATE (Total -1.5)	RR 1.03 (0.45 to 2.37)
Relapse	3	RCT 0	Adequate 0	Yes 0	Yes 0	Loss to follow-up <20% 0	CI includes 1 and wide -1	Study estimates in opposite directions -1	Most studies LIC and in children 0	LOW (Total -2)	RR 0.91 (0.11 to 7.55)
Other adverse events	4	RCT 0	Adequate 0	Yes 0	No -0.5	Loss to follow-up <20% 0	CI includes 1 -0.5	Most in direc-tion of pooled estimate 0	Most studies LIC and in children 0	MODERATE (Total -1)	RR 10.9 (0.61 to 4.82)

TABLE A7.15

Antibiotics for treatment of meningitis:

Question: Which parenteral antibiotic or combination of antibiotics, at what dose and duration, is effective for the treatment of suspected bacterial meningitis in hospital?
Population: Children with acute bacterial meningitis.
Intervention: 3rd generation cephalosporins versus chloramphenicol-based regimens for meningitis
Setting: Low and middle income countries (10 studies) and high income countries (9 studies)
References: Prasad K, Kumar A, Gupta PK, Singhal T (2007)[a]

	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI) RISK DIFFER-ENCE
Death	19 (1496)	RCT 0	Inadequate -0.5	No -0.5	No 0	No intention to treat analysis -0.5	Some imprecision -0.5	No inconsistency 0	Old studies, 9 from high income countries -0.5	LOW (Total -2.5)	0.00 (-0.03 to 0.02)
Treatment failure	19 (1496)	RCT 0	Inadequate -0.5	No -0.5	No 0	As above -0.5	Some imprecision -0.5	No inconsistency 0	As above -0.5	LOW (Total -2)	-0.01 (-0.04 to 0.02)
Culture positivity	12 (442)	RCT 0	Inadequate -0.5	No -0.5	No 0	As above -0.5	No imprecision 0	No inconsistency 0	As above -0.5	LOW (Total	-0.06 (-0.11 to 0.00)

[a] Includes update by Kiang K, Antibiotics for children aged 2–59 months with suspected bacterial meningitis. Unpublished. 2010.

TABLE A7.16

Short course antibiotics for meningitis

Population: Children with acute bacterial meningitis
Intervention: Short course (4–7 days) versus long course (7–14 days) ceftriaxone for bacterial meningitis
Setting: USA, Greece, Switzerland, Chile and India
References: Karageorgopoulos et al (2009)

	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE										
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI)
Clinical success	5 (383)	RCT 0	Adequate 0	No -0.5	No 0	No intention to treat analysis. Heterogeneity in duration of treatment -1	Some imprecision -0.5	No inconsistency 0	Old studies, most from high income countries -0.5	LOW (Total -2.5)	RR 1.04 (0.94 to 1.10)
Neurological sequelae	5 (367)	RCT 0	Adequate 0	No -0.5	No 0	As above -1	Some imprecision -0.5	No inconsistency 0	As above -0.5	LOW (Total -2.5)	RR 0.61 (0.30 to 1.25)
Length of hospital stay	2 (137)	RCT 0	Adequate 0	No -0.5	No 0	As above -0.5	No imprecision 0	No inconsistency 0	As above -0.5	LOW (Total -2.5)	Weighted mean difference -2.17 days (-3.85 to -0.50)

TABLE A7.17

Antibiotics for acute otitis media

Question: Do all children aged 2–59 months, in developing countries with signs of acute otitis media need oral antibiotics
Population: Children with Acute Otitis Media
Intervention: Antibiotics versus no antibiotics
Setting: Developed countries
References: 2008 updated Cochrane review, [Sanders S, 2004][a]

	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE										
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI) RR[b]
Pain (24 hours)	5	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	Studies mainly conducted in developing countries with very low rate of baseline burden of ear disease -1	MODERATE (Total -1.5)	RR 0.90 (0.78 to 1.04)
Pain (2 to 7 days)	10	RCT 0	Adequate 0	Yes 0	No 0	No 0	No imprecision 0	No inconsistency 0	As above -1	MODERATE (Total -1)	RR 0.72 (0.62 to 0.83)
Abnormal tympanometry at 1 month	4	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	As above -1	MODERATE (Total -1.5)	RR 0.89 (0.75 to 1.07)
Vomiting, diarrhoea, or rash	5	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	No inconsistency 0	Yes 0	HIGH (Total -0.5)	RR 1.38 (1.09 to 1.76)

[a] includes update by Gelbart B, in children aged 2–59 months, which oral antibiotic is effective for the treatment of acute otitis media? Unpublished review WHO, 2010.
[b] Assumed risk is the median control group risk across studies (consistent with Cochrane summary of findings tables). The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **CI:** Confidence interval

TABLE A7.18

Choice of antibiotics for acute otitis media

Population: Children with acute otitis media
Intervention: Comparison of different oral antibiotics
Setting: Developed countries
Outcome: Clinical response[a]
References: 2008 updated Cochrane review, [Sanders S, 2004] [b]

	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE										
COMPARISON	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE 95% CI
Ampicillin Vs penicillin	3	RCT 0	Adequate 0	Yes 0	Not mentioned -0.5	No 0	Some imprecision -0.5	No inconsistency 0	Old studies may not reflect current resistance patterns; conducted in low burden settings -1	LOW (Total -2)	Risk difference -0.68 (-15.2 to 1.5)
Amoxicillin Vs ceflacor	4	RCT 0	Adequate 0	Yes 0	No 0	No 0	No imprecision -0.5	No inconsistency 0	As above -1	MODER-ATE (Total -1.5)	Risk difference 6.4 (-10.2 to 22.9)
Amoxicillin Vs cefixime	3	RCT 0	Adequate 0	Not mentioned -0.5	Not mentioned -0.5	No 0	Some imprecision -0.5	No inconsistency 0	As above -1	LOW (Total -1.5)	Risk difference -3.9 (-10.4 to 2.6)

[b] Includes update by Gelbart B, In children aged 2–59 months, which oral antibiotic is effective for the treatment of acute otitis media? Unpublished review WHO, 2010.

TABLE A7.19

Short course antibiotics for acute otitis media

Population: Children with acute otitis media
Intervention: Short-course (≤3 days) versus long course (>3 days) antibiotics for acute otitis media in children
Setting: Mainly developed countries
Outcome: Treatment failure
References: Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K. [2010]

LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE							PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER					
Treatment failure until 1 month	35 (38 analytical components)	RCT 0	Inadequate -0.5	No -0.5	No 0	Most comparisons of antibiotic duration used 2 different antibiotics -1	Some imprecision -0.5	Some inconsistency -0.5	Most children studied from low burden countries -0.5	VERY LOW Total -3.5	OR 1.06 (0.95 to 1.17) *p*-value = 0.298

TABLE A7.20

Topical quinolone versus non quinolone for chronic suppurative otitis media (CSOM)

Question: What should be the first line treatment for chronic otitis media?
Intervention: Topical quinolone versus topical non-quinolone
Setting: Turkey, Spain, Malawi
References: Macfadyen CA, Acuin JM, Gamble CL. [2005]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)[a]	IMPORTANCE
Discharge at 1 week	3 (402)	RCT 0	Inadequate -0.5	No -0.5	No -0.5	>20% -0.5	Some imprecision -0.5	No inconsistency 0	Generalizable 0	LOW	0.95 (0.78 to 1.11)	Important
Discharge at 2 weeks	5 (276)	RCT 0	Inadequate -0.5	No -0.5	No -0.5	No 0	No imprecision 0	No inconsistency 0	Generalizable 0	MODERATE	0.76 (0.60 to 0.95)	Important
Discharge at 2–3 weeks	6 (313)	RCT 0	Inadequate -0.5	No -0.5	No -0.5	No 0	Some imprecision -0.5	No inconsistency 0	Generalizable 0	LOW	0.98 (0.65 to 1.35)	Important

[a] Odds ratios reported in review converted to relative risks
[b] Assumed risk is the median control group risk across studies (consistent with Cochrane summary of findings tables). The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval

TABLE A7.21

Topical quinolone antibiotics for chronic suppurative otitis media (CSOM)

Question: What should be the first line treatment for chronic otitis media?
Intervention: Topical quinolone antibiotic versus no treatment or topical antiseptic
Setting: India, Israel, Kenya, Malawi and Thailand
References: Macfadyen CA, Acuin JM, Gamble CL. [2005],

	LIMITATIONS IN METHODS											
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Topical quinolone antibiotic versus no treatment												
Persistent discharge at 1 week	2 (197)	RCT 0	Inadequate -0.5	Yes 0	>20% -0.5	Baseline characteristics of studied populations not reported -0.5	No imprecision 0	No inconsistency 0	Generalizable 0	MODERATE	0.83 (0.76 to 0.89)	Important
Topical quinolone antibiotic versus topical antiseptic												
Discharge at 1 week	3 (263)	RCT 0	Inadequate -0.5	Yes 0	>20% -0.5	No 0	No imprecision 0	No inconsistency 0	Generalizable 0	MODERATE	0.88 (0.82 to 0.93)	Important
Discharge at 2–4 weeks	4 (519)	RCT 0	Adequate 0	Yes 0	No 0	No 0	No imprecision 0	No inconsistency 0	Generalizable 0	MODERATE	0.80 (0.72 to 0.88)	Important
Healing of the tympanic membrane	1 (399)	RCT 0	Adequate 0	Yes 0	No 0	No 0	Some imprecision -0.5	Only 1 study -1	Generalizable 0	MODERATE	1.46 (0.91 to 2.25)	Important

TABLE A7.22

Systemic antibiotics for chronic suppurative otitis media (CSOM)

Question: What should be the first line treatment for chronic otitis media?
Intervention: Systemic antibiotic versus topical antiseptic
Setting: Gran Canaria, Hong Kong, Italy, Spain, United Kingdom.
References: Macfadyen CA, Acuin JM, Gamble CL. [2005], Macfadyen, et al. [2005]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERAL-IZABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Systemic antibiotic versus topical antiseptic												
Treatment failure (persistent discharge) at 2–4 weeks	2 (152)	RCT 0	Inadequate -0.5	No -0.5	No 0	No 0	Some imprecision -0.5	No inconsistency 0	General-izable 0	MODERATE	0.92 (0.80 to 1.03)	Important
Systemic non-quinolone versus topical non-quinolone												
Treatment failure (persistent discharge)	1 (31)	RCT	Unclear -0.5	Yes 0	>20% -0.5	Not intention to treat -0.5	Some imprecision -0.5	Only 1 study -1	General-izable 0	VERY LOW	0.95 (0.84 to 1.03)	Important
Systemic non-quinolone versus topical quinolone												
Treatment failure (persistent discharge)	2 (116)	RCT 0	Adequate 0	Unclear -0.5	No 0	Not intention to treat -0.5	CI does not cross 1 0	Both study estimates in same direction as pooled RR 0	General-izable 0	MODERATE	2.21 (1.59 to 2.87)	Important
Systemic quinolone versus topical quinolone												
Treatment failure (persistent discharge)	3 (175)	All RCTs 0	Unclear -0.5	Unclear -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	General-izable 0	MODERATE	2.30 (1.21 to 3.73)	Important

TABLE A7.23

Topical antiseptics for treatment of CSOM

Population: Children with CSOM
Intervention: Topical antiseptic versus placebo or no treatment
Setting: South Africa, Solomon Islands
References: Eason et al [1986], Thorp MA, Gardiner IB, Prescott CA [2000]

			LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE								
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT (LOW RISK OF SELECTION BIAS)	BLINDING WHERE POSSIBLE (LOW RISK OF MEASUREMENT BIAS)	ANALYSIS INTENTION TO TREAT (ADJUSTED)	LOSS TO FOLLOW-UP	PRECISION BASED ON 95% CI OF THE POOLED EFFECT SIZE	CONSISTENCY	GENERALIZABILITY/ DIRECTNESS	OVERALL QUALITY OF EVIDENCE BASED ON THE TOTAL OF COLUMNS ON THE LEFT	POOLED EFFECT SIZE
Reduction in ear discharge	2 (94)	RCT 0	Inadequate -0.5	No -0.5	No -0.5	No 0	Some imprecision -0.5	No serious inconsistency 0	Conducted in developing country 0	LOW (Total -2.0)	RR 0.62 (0.37 to -1.05)

TABLE A7.24

Fluoroquinolones versus chloramphenicol for typhoid fever[a]

Question: What are the most effective antibiotics for treating typhoid fever in children?
Population: Children with typhoid fever
Intervention: Fluoroquinolone versus chloramphenicol for enteric fever
Location: Philippines, Italy, Indonesia, Mexico, and Pakistan
References: Thaver, et al. [2008].

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE									
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	POOLED EFFECT SIZE (95% CI)[b]
Clinical failure	9	RCT 0	Inadequate -0.5	No -0.5	No 0	Outcome not adequately defined for 4 studies -0.5	Some imprecision -0.5	No inconsistency 0	Adults Low reported rates of MDR isolates -0.5	LOW (Total -2)	RR 0.66 (0.26 to 1.68)
Micro-biological failure	6	RCT 0	Inadequate -0.5	No -0.5	No 0	Wide range of time at which outcome is measured (day 3 to day 23) -0.5	Some imprecision -0.5	No inconsistency 0	As above -0.5	LOW (Total -2)	RR 0.45 (0.20 to 1.03)
Relapse	6	RCT 0	Inadequate -0.5	No -0.5	No 0	Outcome not defined for 3 studies, variable in others. -0.5	No imprecision Large effect +0.5	No inconsistency 0	As above -0.5	MODERATE (Total - 1.5)	RR 0.15 (0.04 to 0.52)
Length of hospital stay	2	RCT 0	Adequate 0	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	As above -0.5	MODERATE (Total - 1.5)	Mean differ-ence in days (95% CI): -2.57 (-3.53 to -1.62)

[a] None of the studies were analyzed as 'intention to treat', as culture negative subjects were excluded. However, this applied to both intervention and comparison, and it is unlikely that this would have biased the results in a given direction. Therefore no points were deducted.

[b] OR (Odds Ratio) reported in the review converted to RR (Relative Risk).

TABLE A7.25

Fluoroquinolones versus beta lactam antibiotics for typhoid fever[a]

Population: Children with typhoid fever
Intervention: Fluoroquinolone versus amoxicillin/ampicillin or ceftraixone
Location: Bahrain, Mexico, Pakistan and Vietnam
References: Thaver, et al. [2008].

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE									
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	POOLED EFFECT SIZE[b]
Fluoroquinolone versus amoxicillin/ampicillin											
Clinical failure	2	RCT 0	Inadequate -0.5	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	Adults, resistance levels not reported -1	LOW (Total -2)	RR 0.11 (0.01 to 0.54)
Micro-biological failure	2	RCT 0	Inadequate -0.5	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	Adults Resistance levels not reported -1	LOW (Total -2)	RR 0.12 (0.03 to 0.64)
Fluoroquinolone versus ceftriaxone for enteric fever											
Clinical failure	3	RCT 0	Adequate 0	No -0.5	>20% -0.5	No 0	No imprecision 0	No inconsistency 0	Adults, very low rates of nalidixic acid resistance -1	LOW (Total -2)	RR 0.11 (0.01 to 0.53)
Micro-biological failure	3	RCT 0	Adequate 0	No -0.5	>20% -0.5	Outcome definition variable across studies -0.5	Serious imprecision -0.5	No inconsistency 0	As above -1	VERY LOW (Total -3)	RR 0.33 (0.03 to 2.9)
Relapse	3	RCT 0	Adequate 0	No -0.5	>20% -0.5	No 0	Serious imprecision -0.5	No inconsistency 0	Adults -0.5	LOW (Total -2)	RR 0.35 (0.03 to 3.1)

[a] None of the studies were analyzed as 'intention to treat', as culture negative subjects were excluded. However, this applied to both intervention and comparison, and it is unlikely that this would have biased the results in a given direction. Therefore no points were deducted.
[b] OR (Odds Ratio) reported in the review converted to RR (Relative Risk).

TABLE A7.26

Azithromycin for typhoid fever

Population: Children with typhoid fever
Intervention: Azithromycin versus fluoroquinolone for enteric fever
Setting: Vietnam and Egypt
References:

		LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE									
OUTCOME	NO. OF STUDIES	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI) †OR REPORTED IN REVIEW CONVERTED TO RR
Clinical failure	4	RCT 0	Adequate 0	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	Mostly adults, high areas with high NaR -0.5	MODERATE (Total -1)	RR 0.50 (0.28 to 0.90)
Microbiological failure	4	RCT 0	Adequate 0	No -0.5	No 0	No 0	Serious imprecision -1	No inconsistency 0	As above -0.5	LOW (Total -2)	RR 1.01 (0.33 to 3.04)
Relapse	4	RCT 0	Adequate 0	No -0.5	No 0	No 0	Imprecision. Low event rate -0.5	No inconsistency 0	As above -0.5	MODERATE (Total -1.5)	RR 0.13 (0.01 to 1.08)
Duration of hospital stay	2	RCT 0	Adequate 0	No -0.5	No 0	No 0	No imprecision 0	No inconsistency 0	1 country, high levels of nalidixic acid resistance -1	MODERATE (Total -1.5)	Mean difference -1.04 days (-1.73 to 0.34)

OUTCOME	NO. OF STUDIES	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE: DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	EFFECT SIZE (95% CI) †OR REPORTED IN REVIEW CONVERTED TO RR
Azithromycin versus ceftriaxone for enteric fever											
Clinical failure	2	RCT 0	Adequate 0	No -0.5	No 0	No 0	Serious imprecision -1	No inconsistency 0	1 study, low levels of MDR and no data on nalidixic acid resistance -1	LOW (Total -2.5)	RR 2.46 (0.49 to 9.95)
Microbiological failure	2	RCT 0	Adequate 0	No -0.5	No 0	Outcome not defined for 1 study -0.5	Serious imprecision -1	No inconsistency 0	As above -1	VERY LOW (Total -3)	RR 0.59 (0.07 to 4.2)

[a] None of the studies were analyzed as 'intention to treat', as culture negative subjects were excluded. However, this applied to both intervention and comparison, and it is unlikely that this would have biased the results in a given direction. Therefore no points were deducted.

TABLE A7.27

Antibiotics in the management of severe acute malnutrition

Question: What is the effectiveness of different parenteral antibiotic regimens in children with severe malnutrition?
Population: Children with severe acute malnutrition
Intervention: No antibiotic versus amoxicillin (comparison) for uncomplicated malnutrition
Setting: Malawi, South Africa and Sudan
References: Lazzerini, [2010] Unpublished.

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSIST-ENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
No antibiotic versus amoxicillin for uncomplicated malnutrition												
Recovery at 12 weeks	2364 (1)	Observa-tional -1	Inadequate. -0.5	No -0.5	Retrospec-tive 0	Antibiotics for more severe disease -1	No imprecision 0	1 study -1	Uncompli-cated treated at home -0.5	VERY LOW	0.71 (0.54- 0.93) Favouring no antibiotic	Important
Amoxicillin and gentamicin versus no antibiotic for all malnutrition												
Case fatality rate	300 (1)	Observa-tional -1	Inadequate. -0.5	No -0.5	Retrospec-tive 0	Not adjusted for confounding -0.5	No imprecision 0	1 study -1	Generalizable 0	VERY LOW	0.25 (0.14–0.62) Favouring antibiotics	Critical
Amoxicillin versus ceftriaxone for severe acute malnutrition												
Weight gain >10g/kg/d > 14 days	458 (1)	RCT 0	Adequate 0	No -0.5	No 0	Intention to treat analysis 0	CI cross 1 and wide -0.5	1 study -1	Generalizable 0	LOW	0.96 (0.81–1.13)	Important
Recovery rate (Wt for Ht >85%)	458 (1)	RCT 0	Adequate 0	No -0.5	No 0	Intention to treat analysis 0	CI cross 1 and wide -0.5	1 study -1	Generalizable 0	LOW	0.94 (0.84–1.05)	Important

		LIMITATIONS IN METHODS									
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSIST-ENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Case fatality rate	458 (1)	RCT 0	Adequate 0	No -0.5	No 0	Intention to treat analysis 0	CI cross 1 and wide -0.5	1 study -1	Generalizable 0	LOW	1.27 (0.48–3.36)	Important
	458 (1)	RCT 0	Adequate 0	No -0.5	No 0	Intention to treat analysis 0	CI cross 1 and wide -0.5	1 study -1	Generalizable 0	LOW	3.9 (0.85–18.5)	Important

TABLE A7.28

Detection of hypoxia using pulse oximetry

Question: What is the most appropriate method of detecting hypoxaemia in hospitals?
Population: Children with hypoxaemia
Intervention: correlation of pulse oximetry readings (SpO2) with arterial oxygen saturation
References: Jensen, [1998]; Rigau D, Rojas MX, Alonso P,[2010]; Enarson et al [2009]; Duke et al [2008]

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
									EFFECT		
NO. OF STUDIES (N OF TRIALS[a])	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	NO. OF PATIENTS/ SAMPLE POINTS		CORRELATION COEFFICIENT (R)[b]	QUALITY	IMPORTANCE
Global											
39 (62)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	UNK	UNK	0.895 (± 0.014)	VERY LOW	
Hypoxic conditions											
5 (15)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	UNK	UNK	0.938 (± 0.008)	VERY LOW	
Dyshemoglobinemia											
5 (6)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	UNK	515	0.717 (± 0.035)	VERY LOW	
Temperature											
3 (3)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	UNK	UNK	0.665 (± 0.024)	VERY LOW	

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
NO. OF STUDIES (N OF TRIALS[a])	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	NO. OF PATIENTS/ SAMPLE POINTS		EFFECT CORRELATION COEFFICIENT (R)[b]	QUALITY	IMPORTANCE
Skin pigmentation											
1 (2)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	Some limitations[f] (-1)	No	15	43	0.800 (± 0.0002)	VERY LOW	
Hyperbilirubinemia											
1 (1)	Case series or cross sectional studies	Some limitations[c] (-1)	No5	Some limitations[e] (-1)	Some limitations[g] (-1)	No	11	UNK	0.850	VERY LOW	
Healthy volunteers											
13 (32)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	318	3683	0.957 (± NR)	VERY LOW	
Anesthetized patients											
1 (1)	Case series or cross sectional studies	Some limitations[c] (-1)	No[g]	Some limitations[e] (-1)	Some limitations[f] (-1)	No	34	94	0.950 (± NR)	VERY LOW	
Athletes											
2 (2)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	Some limitations[f] (-1)	No	21	313	0.948 (± NR)	VERY LOW	
Thoracic surgical patients											
2 (2)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	Some limitations[f] (-1)	No	72	125	0.930 (± NR)	VERY LOW	

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
NO. OF STUDIES (N OF TRIALS[a])	DESIGN	LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	NO. OF PATIENTS/ SAMPLE POINTS		EFFECT CORRELATION COEFFICIENT (R)[b]	QUALITY	IMPORTANCE
Cardiac surgical patients											
2 (2)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	Some limitations[f] (-1)	No	72	287	0.904 (± NR)	VERY LOW	
Respiratory patients											
8 (11)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No		558	1590	0.880 (± NR)	VERY LOW	
Critically ill/intensive care unit patients											
8 (8)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	No	329	1012	0.760 (± NR)	VERY LOW	
Ear probe location											
3 (3)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	Direct comparisons	UNK	UNK	0.938 (± 0.002)	VERY LOW	
Finger probe location											
3 (3)	Case series or cross sectional studies	Some limitations[c] (-1)	Some limitations[d] (-1)	Some limitations[e] (-1)	No	Direct comparisons	UNK	UNK	0.963 (± 0.001)	VERY LOW	

[a] Some studies assessed different pulse oximetres or co-oximetre models (trials)

[b] Aggregated results are expressed as weighted mean except for those coming from a single study – single trial.

[c] Most of the studies failed to report confounding factors or method reliability (inter and intra rater reliability). Studies assessing more than one model used a different number of patients and sample points

[d] There is unexplained variability (underestimation or overestimation of the test versus gold standard). In addition to methodological sources of variability such as study quality, year of publication or oximetre models, the systematic review explores different subgroups. The association of more than one of these factors could have better explained the variability.
[e] Evidence from adults in different clinical situations, some of them healthy volunteers with no hypoxemia.
Very low number of events leading to wide confidence intervals
[f] Very low number of patients included in the analysis
[g] Data from a single study
UNK: Unknown
NR: not reported

TABLE A7.29
Effectiveness of oxygen therapy

Question: What is the effectiveness of administering oxygen to children with hypoxaemia?
Population: Children with hypoxaemia
Intervention: oxygen therapy for hypoxaemia.
Setting: PNG
References: [Steer, 2010 WHO unpublished]

		LIMITATIONS IN METHODS										
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE RISK (95% CI)	IMPORTANCE
Pneumonia case fatality rate	2 (12252)	Pre-post -1	Not adjusted for confound-ing -0.5	No 0	No 0	No 0	No imprecision 0	No inconsistency 0	Only 1 country -0.5	Low	0.72 (0.6 to 0.86)	Critical

TABLE A7.30

Oxygen delivery methods

Question: What is the safest and most effective method of delivering oxygen to children with hypoxia?
Intervention: Nasal prongs versus nasopharyngeal catheters for delivering oxygen to children
Population: Children up to 15 years
Settings: Ethiopia and The Gambia
References: Rojas MX, Granados Rugeles C, Charry-Anzola LP. [2009], [Rigau, 2010]

	LIMITATIONS IN METHODS											
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZ-ABILITY	OVERALL QUALITY	RELATIVE EFFECT (95% CI)[c]	IMPORTANCE
Treatment failure[a]	3 (399)	2 RCTs 1 cohort -0.5	Adequate 0	No (not possible) 0	No 0	Intention to treat analysis unclear -0.5	Some imprecision -0.5	No inconsistency 0	Generalizable 0	MODERATE	RR 0.96 (0.51 to 1.78)	Important
Mean flow rates required with each method	3 (338)	RCTs 0	Adequate 0	No (not possible) 0	No 0	As above -0.5	Some imprecision -0.5	No inconsistency 0	Generalizable 0	MODERATE	0.08[b] (-0.14 to 0.29)	Important
Adverse events[f]	3 (338)	RCTs 0	Adequate 0	No (not possible) 0	No 0	As above -0.5	Some imprecision -0.5	No inconsistency 0	Generalizable 0	MODERATE	RR 0.39 (0.16 to 1.04)	Important
Adverse events[e]	3 (338)	RCTs 0	Adequate 0	No (not possible) 0	No 0	As above -0.5	No imprecision 0	No inconsistency 0	Generalizable 0	HIGH	RR 0.18 (0.08 to 0.43)	Important
Adverse events[f]	2 (239)	RCTs 0	Adequate 0	No (not possible) 0	No 0	As above -0.5	Some imprecision -0.5	No inconsistency 0	Generalizable 0	MODERATE	RR 0.73 (0.35 to 1.40)	Important

[a] Failure to achieve adequate oxygenation
[b] Standard mean difference of mean episodes of hypoxaemia
[c] Odds ratios reported in studies have been converted to relative risks
[d] Nose ulceration or bleeding
[e] Nasal obstruction/severe mucous production
[f] Fighting/ Discomfort in the first 24 hours

TABLE A7.31

Oxygen delivery methods

Question: What is the safest and most effective method of delivering oxygen to children with hypoxia?
Intervention: Head box or mask versus nasal prongs or catheter
Population: Children up to 15 years
Settings: India
References: Rojas MX, Granados Rugeles C, Charry-Anzola LP. [2009], [Rigau, WHO unpublished, 2010]

	LIMITATIONS IN METHODS BASED ON METHODS OF STUDIES WITH ≥50% OF THE TOTAL WEIGHT OF EVIDENCE											
OUTCOME	NO. OF STUDIES (PARTICIPANTS)	DESIGN	ALLOCATION CONCEALMENT	BLINDING	LOSS TO FOLLOW-UP	OTHER	PRECISION	CONSISTENCY	GENERALIZABILITY	OVERALL QUALITY	RELATIVE RISK[a] (95% CI)	IMPORTANCE
Treatment failure	1 (264)	Cohort -1	Unclear -0.5	No (not possible) 0	No 0	Intention to treat analysis unclear -0.5	No imprecision 0	1 study -1	Generalizable 0	VERY LOW	0.4 (0.34 to 0.5)	Important

[a] Odds ratios reported in studies have been converted to relative risk

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