# Guideline on management of pneumonia and diarrhoea in children up to 10 years of age

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ISBN 978-92-4-010341-2 (electronic version)
ISBN 978-92-4-010342-9 (print version)



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# Contents

# Acknowledgements

The World Health Organization (WHO) Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA) gratefully acknowledges the contributions that many individuals and organizations have made to the development of these recommendations.

WHO extends sincere thanks to the chairs of the Guideline Development Group (GDG), Narendra Kumar Arora (The INCLEN Trust International, India) and Jonathon Simon (International consultant for child health, United States of America [USA]), and to all the other GDG members: Ambrose Agweyu (Kenya Medical Research Institute [KEMRI]-Wellcome Trust, Kenya), Lulu Bravo (University of the Philippines, Philippines), Suzanne Farhoud (International consultant for child and adolescent health, Egypt), Olivier Fontaine (International consultant for child health, France), Stephen Howie (University of Auckland, New Zealand), Fyezah Jehan (Aga Khan University, Pakistan), Kristina Keitel (University Hospital Bern, Switzerland), Claudio F Lanata (Instituto de Investigación Nutricional, Peru), You Li (Nanjing Medical University, China), Rakesh Lodha (All-India Institute of Medical Sciences, India), Eric McCollum (Johns Hopkins University, USA [based in South Africa]), Harish Nair (University of Edinburgh, United Kingdom of Great Britain and Northern Ireland), Mark I Neuman (Boston Children's Hospital, USA), Humphreys Nsona (Ministry of Health, Malawi), Kerry-Ann O'Grady (Queensland University of Technology, Australia), Archana Patel (Lata Medical Research Foundation, India), Shamim A Qazi (International consultant for newborn and child health, Switzerland), Zeba Rasmussen (Fogarty International Center, USA), Salim Sadruddin (International consultant for child health, Canada), Mathuram Santosham (Johns Hopkins University, USA), Anthony Scott (KEMRI-Wellcome Trust Research Programme, Kenya), Meseret Tadesse (Ministry of Health, Ethiopia), Robinson Wammanda (Ahmadou Bello University Teaching Hospital, Nigeria) and Heather Zar (University of Cape Town, South Africa). WHO also thanks the members of the External Review Group (ERG): Brekhna Aurangzeb (The Children's Hospital, Pakistan Institute of Medical Sciences, Pakistan), Shally Awasthi (King George's Medical University, India), Sudha Basnet (Tribhuvan University, Institute of Medicine, Nepal), Adegoke Falade (College of Medicine, University of Ibadan, Nigeria), and Chris A Rees (Emory University School of Medicine, USA).

Rebecca Morgan (Case Western Reserve University, USA) was the external guideline methodologist. Ife Babatunde (Case Western Reserve University, USA) provided technical support for analysis, preparation of Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables and guideline content. Special thanks go to the authors of the scoping and systematic reviews. Pneumonia scoping reviews were conducted by the University of Melbourne, Australia (Lead scientists: Kim Mulholland, Hamish R Graham, Trevor Duke, Steve Graham, and Fiona Russell) and diarrhoea scoping reviews were carried out by Boston University, Massachusetts, USA (Lead scientists: Davidson H Hamer, Jennifer Beard, and William B MacLeod). Pneumonia systematic reviews were carried out by the Society for Applied Studies, New Delhi, India (Lead scientists: Uma Chandra Mouli Natchu, Temsunaro Rongsen-Chandola and Bireshwar Sinha), and diarrhoea systematic reviews were conducted by Aga Khan University, Karachi, Pakistan (Lead scientists: Jai K Das, Shabina Ariff and Sajid Soofi).

WHO acknowledges the observers at the GDG meetings representing partner organizations, including the Bill & Melinda Gates Foundation (Keith Klugman, first meeting), the United States Agency for International Development (USAID) (Patricia Jodrey) and Save the Children (Sheetal Lookhar).

WHO also appreciates the contributions of Anne Detjen of UNICEF and Pablo Rojas of UNITAID, who participated as observers in guideline development meetings.

The WHO Steering Group coordinated the guideline development process: Yasir Bin Nisar (responsible technical officer) (Universal Health Coverage [UHC]/Life Course Cluster [UHL], MCA, Newborn and Child Health and Development [NBC] Unit), Annemieke Brands (Universal Health Coverage, Communicable and Noncommunicable Diseases [UCN], Global TB programme [GTB]), Bernadette Daelmans, MCA, Child Health and Development [CHD] Unit), Benedikt Huttner (Antimicrobial Resistance [AMR], Surveillance, Prevention and Control [SPC], Control and Response Strategies [CRS] Surveillance, Infection Control, Lab Capacity [SCC]), Laura Nic Lochlainn (UHL, Immunization, Vaccines and Biologicals, Essential Programme on Immunization), Kirrily De Polnay (Healthier Populations Cluster, Department of Nutrition and Food Safety, Food and Nutrition Actions in Health Systems Unit), Hatim Sati (AMR, Global Coordination and Partnership, Impact Initiatives and Research Coordination & One Health Research Priority Setting and Synergy), Wilson Were (UHL/MCA/NCB) and Nuhu Yaqub (UHL/MCA/NCB). WHO regional advisers who contributed to the guideline include: Teshome Desta Woldehanna (Regional Office for Africa), Khalid Siddeeg (Regional Office for the Eastern Mediterranean), Martin Weber (Regional Office for Europe) and Rajesh Khana (Regional Office for South-East Asia).

USAID provided funding to carry out this work. The views of the funding body have not influenced the content of these recommendations.

# Acronyms

| | |
|---|---|
| CHW | community health worker |
| CI | confidence interval |
| CRES | Chest Radiography in Epidemiological Studies |
| CXR | chest X-ray (radiograph) |
| ERG | External Review Group |
| GDG | Guideline Development Group |
| GRADE | Grading of Recommendations Assessment and Evaluation |
| iCCM | integrated Community Case Management |
| IMCI | Integrated Management of Childhood Illness |
| IV | intravenous |
| LMIC | low- or middle-income country |
| LORS | low osmolarity oral rehydration solution |
| LUS | lung ultrasound |
| MCA | Department of Maternal, Newborn, Child and Adolescent Health and Ageing |
| MD | mean difference |
| ORS | oral rehydration solution |
| PICO | population, intervention, comparator, outcome |
| RR | relative risk (risk ratio) |
| SAE | severe adverse event |
| SG | Steering Group |
| UNICEF | United Nations Children's Fund |
| USAID | United States Agency for International Development |
| WHO | World Health Organization |

# Executive summary

Pneumonia and diarrhoea account for 23% of under-five mortality and were responsible for an estimated 1.17 million deaths in children under five globally. Furthermore, pneumonia and diarrhoea were responsible for 18% of mortality in children 5–9 years of age, resulting in an estimated 86 000 preventable deaths globally in 2021. Existing World Health Organization (WHO) guidance on the clinical management of pneumonia and diarrhoea has mainly focused on children less than 5 years of age. WHO had not developed clinical guidance on the management of these conditions in children 5–9 years of age, which is a gap being addressed in response to calls from national policy- and decision-makers.

Given this situation, as well as the changing epidemiologic and demographic profiles of countries, the enhanced clinical understanding of prevention and management of pneumonia and diarrhoea, and the introduction of new interventions, a state-of-the-art review of existing guidance had been overdue.

The goal of the guideline is to develop, update and consolidate recommendations on the management of pneumonia and diarrhoea in order to inform, revise or update the development of clinical protocols for the management of pneumonia and diarrhoea in children up to 10 years of age.

This guideline aims to help WHO Member States and their partners make evidence-informed decisions on the appropriate actions in their efforts to address common childhood illnesses, including pneumonia and diarrhoea.

The process of updating the existing guidance began in 2020 and was followed by the appointment of a Guideline Development Group (GDG), consultations, development of key questions in Population, Intervention, Comparator and Outcome (PICO) format, and the production of systematic reviews to answer those questions. All steps have followed those laid out in the WHO *Handbook for guideline development*, using the Grading of Recommendations Assessment and Evaluation (GRADE) approach.

Through this process, including extensive discussions continuing into December 2023, the GDG agreed on the recommendations for pneumonia shown in **Table 1**, and for diarrhoea shown in **Table 2**.

The main changes from previous recommendations involve giving greater scope for pneumonia treatment at the community level, using a specific set of signs and symptoms to diagnose hypoxaemia when pulse oximetry is not available, and a new dose for zinc supplementation (see significant changes to recommendations in each section).

Antibiotic resistance issues were taken into account in all relevant discussions, given current global concerns about antibiotic stewardship. Some of the antibiotics considered are on WHO's AWARE watch list.

## Table 1. Key domains and resulting recommendations for the management of pneumonia in children, December 2023

| Key domain | Recommendations |
|---|---|
| **Treatment of children 2–59 months of age with pneumonia** | **1. Treatment of children 2–59 months of age with only fast breathing**<br>In children 2–59 months of age with only fast breathing (no chest indrawing, no general danger signs), WHO **recommends** the use of oral amoxicillin for three or five days (**Strong** recommendation, **Moderate** certainty of evidence). |
| | **2. Treatment of children 2–59 months of age with chest indrawing**<br>**2a.** In children 2–59 months of age with chest indrawing (with or without fast breathing) and no general danger signs WHO **recommends** the use of oral amoxicillin for five days in the outpatient setting rather than injectable antibiotics in the inpatient setting (**Strong** recommendation, **Moderate** certainty of evidence).<br>**2b.** In children 2–59 months of age with chest indrawing (with or without fast breathing) and no general danger signs in settings with functional community health worker programmes, WHO **suggests** the use of community-based care (use of oral amoxicillin for five days with follow-up visits) rather than of standard care (first dose of antibiotic [oral amoxicillin] given by community health worker and referral to a facility for further management) (**Conditional** recommendation, **Low** certainty of evidence). |
| **Diagnosis of children 2–59 months of age with pneumonia** | **Assessment with lung ultrasound**<br>**3.** In children 2–59 months of age presenting with cough and/or difficult breathing, WHO makes **no recommendation** about the use of lung ultrasound to diagnose pneumonia (**Knowledge gap**). |
| | **Assessment with digital auscultation or cough sound algorithms**<br>**4.** In children 2–59 months of age presenting with cough and/or difficult breathing, WHO makes **no recommendation** about the use of digital auscultation or cough sound algorithms as an add-on test to diagnose pneumonia (**Knowledge gap**). |
| **Management of children 2–59 months of age with pneumonia and risk factors for mortality** | **Identification of hypoxaemic children**<br>**5.** *In settings where pulse oximetry is not available*, in children 2–59 months of age diagnosed with pneumonia (fast breathing or chest indrawing without general danger signs), WHO **suggests** evaluation of respiratory distress using a combination of signs and symptoms[a] to detect hypoxaemia (**Conditional** recommendation, **Very low** certainty of evidence). |
| | **Enhanced care for high-mortality risk children**<br>**6.** In children 2–59 months of age with pneumonia (fast breathing and/or chest indrawing without general danger signs) having high risk factors for mortality, WHO makes **no recommendation** on the effectiveness of enhanced care[b] (**Knowledge gap**). |
| **Management of pneumonia in children 5–9 years of age** | **Assessment of children 5–9 years of age for pneumonia**<br>**7.** In children 5–9 years of age presenting at first-level health care facilities, WHO makes **no recommendation** on a standardized clinical assessment of community-acquired pneumonia (**Knowledge gap**). |
| | **Treatment of children 5–9 years of age with pneumonia**<br>**8.** In children 5–9 years of age with suspected pneumonia, WHO makes **no recommendation** about which antibiotic has the highest effectiveness in improving clinical outcomes (**Knowledge gap**). |

[a] Head nodding, or nasal flaring or grunting or severe tachypnoea (respiratory rate ≥20 breaths per minute above the age-specific cut-off).

[b] Such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment.

## Table 2. Key domains and resulting recommendations for the management of diarrhoea in children, December 2023

| Key domain | Recommendations |
|---|---|
| **Treatment of diarrhoea in children up to 10 years of age** | **Treatment of diarrhoea in children up to 10 years of age and use of antibiotics**<br>**1a.** In children up to 10 years of age with acute watery diarrhoea (regardless of etiology), WHO **suggests against** the use of antibiotics (**Conditional** recommendation, **Low** certainty of evidence).<br>**1b.** In children up to 10 years of age with persistent diarrhoea (regardless of etiology), WHO makes **no recommendation** on the use of antibiotics (**Knowledge gap**). |
| | **Treatment of diarrhoea in children up to 10 years of age with blood in stools**<br>**2.** In children up to 10 years of age with diarrhoea and blood in the stools, WHO **recommends** treatment with antibiotics rather than no antibiotics (**Strong** recommendation, **Moderate/Low** certainty of evidence). |
| | **Treatment of children up to 10 years of age with diarrhoea and use of zinc**<br>**3a.** In children up to 10 years of age with acute watery diarrhoea, WHO **recommends** adjunctive treatment with oral zinc (**Strong** recommendation, **Moderate** certainty of evidence).<br>**3b.** In children up to 10 years of age with persistent diarrhoea, WHO **recommends** adjunctive treatment with oral zinc (**Strong** recommendation, **Moderate** certainty of evidence).<br>**3c.** In children up to 10 years of age with acute watery or persistent diarrhoea, WHO **suggests** a 5 mg daily dose of oral zinc for up to 14 days (**Conditional** recommendation, **Low** certainty of evidence). |
| | **Treatment of children up to 10 years of age with diarrhoea and use of probiotics**<br>**4a.** In children up to 10 years of age with acute watery diarrhoea, WHO **suggests against** the use of probiotics (**Conditional** recommendation, **Low** certainty of evidence).<br>**4b.** In children up to 10 years of age with persistent diarrhoea, WHO makes **no recommendation** for the use of probiotics (**Knowledge gap**). |
| | **Treatment of children up to 10 years of age with diarrhoea and dehydration and use of low-osmolarity oral rehydration solution**<br>**5.** In children up to 10 years of age with acute watery diarrhoea and dehydration, WHO **recommends** the use of low-osmolarity oral rehydration solution (**Strong** recommendation, **Moderate** certainty of evidence). |
| **Management of diarrhoea in children up to 10 years of age with risk factors for mortality** | **Enhanced care for high mortality-risk children up to 10 years of age with diarrhoea**<br>**6.** In children up to 10 years of age with acute watery diarrhoea having risk factors for mortality, WHO makes **no recommendation** about enhanced care compared to the usual care (**Knowledge gap**). |

[a] Such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment.

During the discussions on the recommendations, several **knowledge gaps** were identified by the GDG, which in some cases led to an inability to make a recommendation. These gaps and other areas where more research would be beneficial are noted in the section on **Research priorities**.

The new recommendations will be disseminated as widely as possible through WHO's and other stakeholders' channels. The WHO Steering Group will monitor research developments in order to determine when a further update will be needed, but at least in five years.

# Introduction

## Background

Pneumonia and diarrhoea account for 23% of under-five mortality and were responsible for an estimated 1.17 million deaths in children under five in 2021 globally *(1)*. Furthermore, pneumonia and diarrhoea were responsible for 18% of mortality in children 5–9 years of age, resulting in an estimated 86 000 preventable deaths globally in 2021 *(1)*. Existing World Health Organization (WHO) guidance on the clinical management of pneumonia and diarrhoea has mainly focused on children less than 5 years of age. WHO had not developed clinical guidance on the management of these conditions in children 5–9 years of age, which is a gap being addressed in response to calls from national policy- and decision-makers.

The previous guidelines have been incrementally updated since the 1990s as new information has become available from global health research, including WHO-facilitated studies. Given the changing epidemiologic and demographic profiles of countries, the enhanced clinical understanding of prevention and management of both conditions, and the introduction of new interventions, a state-of-the-art review had been overdue. In addition, WHO and UNICEF have been pivoting the global child health agenda towards a life-course approach that promotes health and well-being and covers the critical gap in guidance for children 5–9 years of age *(2)*.

Several research initiatives have been supported by WHO's Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA) and others to examine new interventions and delivery approaches to increase access and quality of care for childhood pneumonia and diarrhoea, for example, appropriate management of pneumonia by community health workers (CHWs), the role of antibiotics in diarrhoea, and the use and dosage of zinc supplementation. The results have provided evidence for reviewing and updating WHO technical guidance.

Several scoping reviews were commissioned in 2020–21 to identify state-of-the-art evidence on the etiology, diagnosis, treatment and follow-up of children with pneumonia and diarrhoea. Subsequently, in October 2021, WHO conducted a three-day *Stakeholder consultative meeting on the prevention and management of childhood pneumonia and diarrhoea (3)* in which the key findings of these scoping reviews were presented and discussed, and the need for the update of guidelines was confirmed (these reviews have been published in an open-access peer-reviewed supplement in the *Journal of Global Health*).[1]

To take forward this process, WHO convened a virtual consultative meeting of the Guideline Development Group (GDG) on pneumonia and diarrhoea from 21–23 March 2023. This was followed by a GDG meeting on pneumonia and diarrhoea management for children up to 10 years of age in Geneva, Switzerland, from 28 November–1 December 2023. Updated systematic reviews on key questions were commissioned earlier in 2023, and presented at the meeting. This document describes the results in terms of evidence-based recommendations and the way forward for implementation.

The objectives of the guideline development meeting were to:

- present and discuss the key findings of systematic reviews on the management of pneumonia and diarrhoea in children up to 10 years of age;
- draft and discuss key recommendations focused on the management of pneumonia and diarrhoea in children up to 10 years of age;

[1] https://jogh.org/category/jogh/jogh-collections/prevention-and-management-of-pneumonia-and-diarrhoea-in-children-evidence-synthesis/.

- identify gaps in knowledge/data and future research directions;
- discuss implications for implementation.

## Objectives and desired impact of the guideline

The goal of the guideline is to develop, update and consolidate recommendations on the management of pneumonia and diarrhoea to inform, revise or update the development of clinical protocols for the management of pneumonia and diarrhoea in children up to 10 years of age.

This guideline aims to help WHO Member States and their partners make evidence-informed decisions on the appropriate actions in their efforts to address common childhood illnesses, including pneumonia and diarrhoea.

## Scope of the guideline

The general scope of the guideline covers the clinical management of pneumonia and diarrhoea in children at all three levels of health care, that is, community, first-level health facilities and hospitals. It addresses the clinical assessment, investigation, diagnosis, treatment and follow-up of children with pneumonia or diarrhoea up to 10 years of age. It does not cover preventive interventions because other WHO departments (immunization, nutrition and environmental health) are leading guidelines development and programmatic implementation on these issues.

The recommendations address new areas of evidence that have emerged since the last publication of guidelines in 2005 and 2012 for the management of diarrhoea and pneumonia in children, respectively.

This guideline focuses on what clinical care should be provided for children up to 10 years of age with pneumonia or diarrhoea. The core questions are: 1) what interventions should be provided; and 2) where relevant, optimal dose, intensity and timing of treatment. Data and evidence about related questions, such as the burden of disease and high-risk groups, are already available and have been incorporated into the framework for the guideline.

## Relevant WHO guidelines and tools

Relevant WHO guidelines and derivative documents related to this guideline are shown in **Annex 1**.

## Population of interest

This guideline is concerned with children up to 10 years of age, primarily in low- and middle-income countries (LMICs). Some recommendations are specific to children 2–59 months of age. Recommendations for children less than 2 months of age for pneumonia are covered by guidelines for serious bacterial infection in young infants *(4)*.

## Target audience

The guideline is intended for a wide audience, including practitioners, policy-makers, subject technical expert advisers, and technical and programme staff at organizations involved in assessing, managing, monitoring, and evaluating common childhood illnesses, including pneumonia and diarrhoea.

The end-users for this guideline are thus:

- health workers and clinical practitioners;
- national and local policy-makers;
- implementers and managers of national and local programmes;
- multi-lateral, bilateral and nongovernmental organizations and professional societies;
- health professionals who develop and implement evidence-based policies, regulations and best practices to address the management of pneumonia and diarrhoea in children.

## Conflicts of interest

In compliance with the WHO *Guidelines for the declaration of interests for WHO experts* and in collaboration with the Department of Compliance and Risk Management and Ethics, the WHO Guideline Steering Group (SG) managed potential conflicts of interest. At the meeting, participants declared their interests, and none was deemed to require action (**Annex 2**).

## Guideline development process

This guideline is the result of the process described above, based on systematic reviews of evidence on the management of pneumonia and diarrhoea, following the procedures of the *WHO Handbook for guideline development (5)*. The steps in this process include: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of normative statements, including research priorities; (v) planning for dissemination; (vi) equity, human rights, implementation, regulatory and ethical considerations; and (vii) impact evaluation and updating of the guideline.

The core principles of minimizing bias and maximizing transparency are essential to the guideline development process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is used to ensure these principles translate the best available evidence on effectiveness and other issues into recommendations. GRADE helps to look at the certainty of evidence in terms of effectiveness and other considerations, as well as guiding the determination of the quality of evidence and strength of recommendations. It also reflects a balance of benefits and harms, values and preferences, and resource use. The Evidence-to-decision framework was used during the guideline meeting,[1] in order to structure the discussion of the evidence presented, guided by a methodologist. The full questions used to assess the evidence are listed in **Annex 3**.

The Guideline Review Committee approved the process for the revised guideline on pneumonia and diarrhoea, based on a proposal from MCA.

## WHO SG

The SG identified the External Review Group (ERG), and collected and assessed the disclosures of interest of the Guideline Development Group (GDG). The WHO SG was responsible for defining the scope of the guideline, drafting the questions in Population, Intervention, Comparator, Outcome (PICO) format, identifying and selecting the GDG members, developing the planning proposal and guiding the evidence retrieval, review and grading process. In addition, the SG actively participated and contributed to the meetings with evidence reviewers and the GDG, as well as the finalization of the guideline, and will oversee the dissemination and monitoring of implementation, and respond to user needs and requests.

The SG is comprised of WHO staff from various departments in headquarters and regional offices whose areas of work are relevant to the scope of the guideline. Representatives of two regional offices were unable to participate. (The members of the SG are listed in the **Acknowledgements**.)

## GDG

The GDG is comprised of 26 external experts with various technical skills, diverse perspectives, broad geographic representation and gender balance, and previous participation in WHO expert advisory panels or GDG memberships. (The GDG members are listed in the **Acknowledgements**.)

The GDG members' expertise covers the following perspectives: gender, equity and human rights; resource use considerations; stakeholders, including persons affected by the recommendations; implementation feasibility and acceptability (for example, programme managers); and content expertise.

## Systematic review teams

This guideline is based on a substantial number of reviews that were originally externally commissioned for evidence retrieval and assessment during 2020–21 and published in an open-access, peer-reviewed

[1] Grading of Recommendations Assessment, Development and Evaluation website (https://www.gradeworkinggroup.org/).

supplement of the *Journal of Global Health*. Further reviews and updates were commissioned prior to the GDG meeting in November–December 2023. The contracted evidence reviewers are not members of the GDG. The systematic review teams developed an evidence retrieval plan, evidence assessment plan and a statistical analysis plan aligned to the PICO questions[1] as guided by the methodologists and SG. Based on the analysis plans, the evidence reviewers undertook analyses to assess the quality of evidence for all the PICO questions. The evidence reviewers then presented the final summary of the findings, including analyses, to the GDG.

## Managing group processes and decision-making

The procedures for establishing a decision were decided at the first meeting of the GDG. In fact, all decisions were reached by consensus.

WHO staff, observers and external technical experts who were involved in collecting and grading the evidence did not participate in the decision-making process. Members of the WHO SG were available to help guide the overall meeting process, but did not vote and did not have veto power.

## External peer review

Peer review was provided by the ERG comprised of experts with a similar profile to the GDG members and with technical competence in the subject of the guidelines. (The ERG members are listed in the **Acknowledgements**.) Most are practising clinicians, academics, researchers, policy-makers, and implementing partners. The ERG members were asked to review the draft recommendations to provide peer-review comments, particularly on the clarity of the recommendations, applicability to the intended settings and equity concerns. The ERG comments were taken into consideration, and where the comments on the recommendations were substantial, these were shared with the GDG for them to consider as the recommendations were finalized.

Throughout the guideline development process, input from end-users, patients and lay members of the public was considered where possible. GDG members include representatives of ministries of health, who provided perspectives of health staff, and especially contributed to the discussions on values and feasibility. Many of the researchers present spend much of their time in health facilities interacting with health staff and users, and often provided information they had gathered from their experiences. While this input was indirect, it was helpful and appropriate.

[1] See **Annex 4** for details of PICO questions.

# Evidence and recommendations[1]

## Pneumonia

### Treatment of children 2–59 months of age with pneumonia

#### 1. Treatment of fast-breathing pneumonia

##### Recommendation

In children 2–59 months of age with only fast breathing (no chest indrawing, and no danger sign[2]) WHO recommends using oral amoxicillin for three or five days (**Strong** recommendation, **Moderate** certainty of evidence).

*Remarks*

- The dosage and duration of treatment remain the same as in the previous recommendation: at least 40 mg/kg per dose twice daily (80 mg/kg per day) for five days. In areas with low HIV prevalence,[3] give amoxicillin for three days.

*Significant changes from previous WHO recommendation*

The GDG considered that the most critical outcome was treatment failure (cumulative) by day 14 of the treatment (author-defined including clinical deterioration/failure any time between day 1 and day 14, relapse after first week or mortality). Further, the GDG also examined the outcomes of two recent clinical trials conducted in Africa and Asia since the introduction of vaccination against *Haemophilus influenzae* and *Streptococcus pneumoniae* in many LMICs. These studies were not available when the previous recommendation was made. Their findings are given in the **Summary of evidence** section below. The GRADE table indicates that evidence for the most critical outcome (treatment failure by day 14) was of **Moderate** certainty.

##### PICO question

In children 2–59 months of age with only fast breathing, what is the effectiveness of oral amoxicillin compared to no antibiotic treatment in improving clinical outcomes at all levels of care?

##### Summary of evidence

The previous recommendation for fast breathing pneumonia was based on systematic reviews *(6–8).* Since then, there have been four additional randomized studies comparing a three-day oral amoxicillin treatment versus placebo or no antibiotic. The meta-analysis of these four trials included 7699 children under five from three countries (India, Malawi, Pakistan) *(9–12)*.

The analysis of the four studies included in the review found lower treatment failure rates on day 4 and day 14 in the group receiving oral amoxicillin in comparison to the group not receiving any antibiotics. The relative risk (RR) of treatment failure among children who received amoxicillin was of borderline significance at 26% lower at day 4 (RR 0.74, 95% confidence interval (CI): 0.53–1.02), and 16% lower at day 14 (RR 0.84, 95% CI:

[1] The GRADE tables for all PICO questions are available in **Annex 5**.

[2] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia.

[3] For an explanation of "low prevalence", see WHO, 2013 Guidelines for second generation HIV surveillance: an update: Know your epidemic. (https://iris.who.int/bitstream/handle/10665/85511/9789241505826_eng.pdf?sequence=1)..

0.75–0.94) compared to those who received placebo/no antibiotic. Treatment failure by day 14 was considered the most critical outcome. The sub-analysis of the most recent evidence from Africa and Asia *(11–12)* carried out after the introduction of pneumococcal conjugate and *H. influenzae* vaccines, showing 47% (RR 0.54, 95% CI 0.41–0.72) and 18% (RR 0.82, 95% CI 0.67–0.99), significant reduction in treatment failure at day 4 and day 14, respectively, among the amoxicillin group compared to the no antibiotic group.

The review found no significant difference in the occurrence of adverse events or mortality between the two groups, although the definition of adverse event varied somewhat between studies.

### Evidence-to-decision judgements

The GDG members agreed that this problem is a priority. With changing etiological profiles of pneumonia (such as the relative proportion of bacterial pneumonia and changes in bacteria causing pneumonia with vaccination coverage against *Haemophilus influenzae* and *Streptococcus pneumoniae*), the problem of whether oral amoxicillin should be given to every child aged 2–59 months with only fast breathing, without chest indrawing and/or any danger sign[1] is a pertinent question.

The desirable effects of the intervention are anticipated to be moderate while the undesirable effects were considered trivial, but would be primarily adverse events from antibiotic use and repeated antibiotic exposure during a child's early life. In general, this drug used in children has a good safety profile.

The GDG acknowledges that a subgroup of children with fast breathing pneumonia likely does not benefit from antibiotic treatment. The GDG expressed interest in understanding the differences between subgroups (e.g. geographical context, malnutrition status, vaccination status) to enable the identification of the subgroup of children who truly benefit from antibiotic treatment by new research projects.

Severe adverse events (SAEs) in the studies reviewed were reported by Ginsburg and colleagues *(11)* and Jehan and colleagues *(12)*. Antibiotic stewardship was identified as an important outcome with long-term individual and population effects that should be considered in decision-making.

The GDG noted that there is a trade-off between reduction in treatment failure and antibiotic overuse leading to antibiotic resistance. Overall, the balance of effects was considered to probably favour the intervention. However, there may be variability depending on the context, for example, access to care or HIV prevalence.

The cost of amoxicillin at US$ 0.018 per 250 mg capsule and US$ 0.022 per 250 mg dispersible tablet was considered negligible, looking at the absolute cost and not necessarily the cost for patient cured. The GDG noted amoxicillin is reported as widely available in resource-limited settings *(13)*.

No research evidence was available, but the GDG considered that equity would probably be increased by this intervention, as vulnerable populations (such as children infected with HIV, or those with malnutrition) would benefit.

The intervention is probably acceptable. Home treatment with a three or five-day course of amoxicillin is associated with reductions in referrals, admissions, risk of nosocomial infections and treatment costs.

It is probably feasible to distribute oral amoxicillin in resource-limited settings as it is available in all countries. However, training and education of health workers and appropriate training for CHWs in assessment, classification and treatment of these children are among issues to be considered.

[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia.

## 2a. Management of chest-indrawing pneumonia

### Recommendation

In children 2–59 months of age with chest indrawing (with or without fast breathing) and no danger sign[1] WHO recommends the use of oral amoxicillin for five days in the outpatient setting rather than injectable antibiotics in the inpatient setting (**Strong** recommendation, **Moderate** certainty of evidence).

*Remarks*

- The dosage and duration of treatment remain the same as the previous recommendation: at least 40 mg/kg per dose twice daily (80 mg/kg per day) for five days.
- Based on the most critical outcome, that is, mortality by day 14, the GDG considered the consistency of the evidence as **Moderate**.

*Significant changes from previous WHO recommendation*

The new recommendation essentially reconfirms the previous one.

### PICO question

In children 2–59 months of age with chest indrawing (without any danger sign), what is the effectiveness of oral amoxicillin on an outpatient basis compared to inpatient injectable antibiotics treatment in improving clinical outcomes at all levels of care?

### Summary of evidence

The previous recommendation was based on several clinical trials which compared the efficacy of oral amoxicillin to injectable penicillin *(14)*. Three trials *(15–17)* were included in the present review comparing oral amoxicillin versus injectable antibiotics. The studies used various definitions of clinical deterioration and SAEs, were in different settings in LMICs, and they were open-label trials.

The analysis found that the RR of death on day 14 of enrolment, the most critical outcome, in the group receiving oral amoxicillin in comparison to the group receiving injectable antibiotics was 72% lower (RR 0.28, 95% CI: 0.09–0.86), indicating a statistically significant lower risk of death in the oral amoxicillin group.

The RR for treatment failure in the group receiving oral amoxicillin in comparison to the group receiving injectable antibiotics on day 3 of enrolment was 0.88 (95% CI: 0.62–1.24), on day 6 it was RR 0.96 (95%CI: 0.83–1.11), and on day 14 RR 0.94 (95% CI: 0.79–1.13), indicating no substantial difference between the two types of treatment.

The RR of SAEs on day 14 of enrolment in the group receiving oral amoxicillin in comparison to the group receiving injectable antibiotics was 61% lower (RR 0.39, 95% CI: 0.12–1.26), but not significant.

The findings from these studies are consistent with the findings on which the earlier recommendation was based.

### Evidence-to-decision judgements

To guide the decision on desirable effects of treatment with oral amoxicillin versus injectable antibiotics, the GDG considered any reduction in mortality as important.

A reduced risk of nosocomial infections in the oral amoxicillin arm was noted to be an important desirable effect by the GDG as was a reduction of adverse effects from injectable drug forms, such as injection site pain and infection.

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[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia.

The GDG noted that most caregivers would find oral treatment more acceptable than injectable treatment for their children, as injectable antibiotics would normally require admission to hospital. Although a few might see injectable treatment as more effective or powerful than oral medication, oral antibiotics would be preferred by the majority.

Considering the relative costs of oral treatment versus injectable (the drug plus other associated costs, such as hospitalization), large savings would be possible by adopting oral treatment *(14)*. In decision-making, the GDG assumed that injectable antibiotics would be given to patients admitted to hospital.

It was noted that the cost of a 250 mg capsule of amoxicillin is US$ 0.018 and US$ 0.022 per 250 mg dispersible tablet. The costs of injectable benzylpenicillin 1 million i.u. (600 mg) is US$ 0.354 and of injectable ceftriaxone 1 G is US$ 1.056, which are higher than oral amoxicillin.[1]

Factors considered by the GDG to measure the resources required for hospitalization included direct costs to patients (e.g. costs of the apparatus used to administer the drug, transportation costs to families, lost wages due to absence from work).

The GDG noted that a decrease in hospitalization leads to a reduction of costs to both the health system and patients. There were no studies on cost in the evidence review, but it was pointed out that there was a study reflecting this point *(18)* that had not been identified but was considered because of its relevance. (See also information on cost-effectiveness in pneumonia **PICO 3**).

The acceptability of home treatment with a five-day course of amoxicillin is likely to be greater 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. The perspectives of clinicians and other stakeholders were discussed by the GDG in reaching its judgement.

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

## 2b. Community management versus standard management[2] of chest indrawing pneumonia

### Recommendation

In children 2–59 months of age with chest indrawing (with or without fast breathing) and no danger sign[3] in settings with functional CHW programmes, WHO **suggests** the use of community-based care (oral amoxicillin for five days with follow-up visits) rather than standard care (first dose of antibiotics [oral amoxicillin] given by a CHW and referral to a health facility for further management) (**Conditional** recommendation, **Low** certainty of evidence).

*Remarks*

- A functional CHW programme *(19)* (including trained CHWs equipped with necessary equipment and drugs), with follow-up visits for patients as well as monitoring and evaluation, is necessary to implement this recommendation.
- The dosage and duration of treatment remain the same as the recommendation for health facility treatment (**Recommendation 2a**): at least 40 mg/kg per dose twice daily (80 mg/kg per day) for five days.

*Significant changes from previous recommendation*

In the previous pneumonia management guidelines, due to limited data *(20, 21)* on the effective use of oral amoxicillin by CHWs to treat children 2–59 months of age with chest-indrawing pneumonia, it was decided that more evidence was needed to assess the effectiveness of community case management, which the current systematic review has provided. Integrated Community Case Management (iCCM) considers chest indrawing

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[1] As an example, a child weighing 10 kg needs 10 dispersible tablets in five days (two tablets per day, one in the morning and one in the evening), therefore the cost of a complete course is US$ 0.022*10 = US$ 0.22. To provide injectable antibiotics, additional costs of hospitalization and staff are also required.

[2] Standard care is defined as being given a first dose of antibiotic (oral amoxicillin) given by the CHW and referred to a facility for further management.

[3] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or has stridor or hypoxaemia

as a danger sign and that a child with chest-indrawing pneumonia should be referred to a health facility after receiving the first dose of antibiotic *(19)*.

### PICO question

In children 2–59 months of age with chest indrawing (with or without fast breathing) and no danger sign[1] what is the effectiveness of management done by community-level health workers (using oral amoxicillin) compared to standard management[2] in improving clinical outcomes at all levels of care?

### Summary of evidence

Data were pooled from three trials *(20–22)* on community-based management of chest-indrawing pneumonia with oral antibiotics by CHWs, compared to standard management, that is, a first dose of antibiotic and referral to a health facility. The first two studies were conducted in Pakistan; no pulse oximetry was available to detect hypoxaemia *(20, 21)*. The EMPIC trial was conducted in four countries in Africa and Asia (other than Pakistan), and researchers were able to exclude children with hypoxaemia *(22).* The first two studies were carried out before the 2012 revision of the *Pocket book of hospital care for children (23)*. Additional studies were available on cost-effectiveness.

In these studies, children from 2–59 months of age with chest-indrawing pneumonia (with or without fast breathing) and no danger sign [1] were treated with oral amoxicillin and follow-up visits by CHWs for five days, compared with standard management.[2]

The analysis of three studies included in the review found a 34% lower (RR 0.66, 95% CI: 0.44–0.98) risk of treatment failure by day 6 in the community-based management group compared to the standard management group.[2]

The evidence suggests no substantial difference in the risk of death by day 14 (RR 0.97, 95% CI: 0.35–2.69) in the community-based management group compared to the standard management group.[2]

There appeared to be no difference in SAEs between the two groups when assessed at day 14 (RR 1.20, 95% CI: 0.34–4.26).

### Evidence-to-decision judgements

For this PICO, assumptions by the GDG for discussing the evidence-to-decision framework included:

- setting for recommendation:
  - areas with functional CHW programmes.
- definition of groups:
  - community-based care: oral amoxicillin prescribed by a CHW for five days;
  - standard care: first dose of antibiotics (oral amoxicillin) given and referred to a health facility for further management.

The GDG considered the desirable effects of the intervention to be moderate, and noted treatment failure by day 6 as the factor driving its decision. It was assumed that the intervention would be for up to five days.

It was noted that there were similar rates of SAEs and loss to follow-up in the different studies.

There is probably no important uncertainty or variability in this question. The GDG noted that caregivers will likely value the lower transportation, hospital and other costs.

The balance of effects probably favours the intervention with desirable effects being moderate and undesirable ones being trivial, although the certainty of evidence was low.

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[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia

[2] Standard care is defined as being given a first dose of antibiotic (oral amoxicillin) given by the CHW and referred to a facility for further management

The GDG considered that community-based care would probably bring large savings, including taking into account the direct costs to patients and caregivers. Sadruddin and colleagues *(24)* concluded that expanding the treatment of chest indrawing pneumonia to community level could significantly reduce household costs, improve access to treatment and ultimately prevent many deaths.

Data on cost-effectiveness probably favour the intervention, with various studies *(25–29)* providing evidence on this point.

The GDG considered that equity would be increased with community-based care, as there would be more access for patients in marginalized societies, as well as an increase in gender equity.

Community-based care is probably acceptable overall. Caregivers would appreciate issues such as lower transportation costs, but the intervention may be less acceptable to clinicians due to community administration of antibiotics (antimicrobial stewardship reasons) and professional associations (with political and governmental influence) might also not deem this as acceptable. It was suggested that the health care system may find it acceptable due to lower system costs.

The GDG noted that the intervention is probably feasible to implement, but that the decision might vary due to capacity and other contextual factors in different settings (i.e. presence of functional iCCM programmes, training of CHWs *(19)*, availability of necessary equipment [such as respiratory timers and pulse oximeters], health education for caregivers, etc.).

## Diagnosis of children 2–59 months of age with pneumonia

### 3. Assessment with lung ultrasound (LUS)

#### Recommendation

In children 2–59 months of age presenting with cough and/or difficult breathing, WHO makes **no recommendation** about the use of lung ultrasound (LUS) to diagnose pneumonia (**Knowledge gap**).

*Significant changes from previous WHO recommendation*

No previous recommendation existed on the use of lung ultrasonography in the diagnosis of pneumonia in children 2–59 months of age presenting with cough and/or difficult breathing at the hospital level.

#### PICO question

In children 2–59 months of age, what is the diagnostic accuracy of LUS compared to the chest radiograph (CXR) or paediatric adjudication panel to identify pneumonia cases at the hospital level?

#### Summary of evidence

Six studies which used the WHO Chest Radiography in Epidemiological Studies (CRES) methodology for the diagnosis of radiographic pneumonia contributed data to the systematic review *(30–35)*. All the studies were fairly small, and some had issues with blinding, as the ultrasonologists had knowledge of clinical findings or indications of the CXR. Other studies *(36–39)* where the methodology used for CXR diagnosis was not specified or did not use CRES methodology for the diagnosis of radiographic pneumonia, were not included in the primary analysis.

Data from the six studies that used CRES methodology *(30–35)* showed that LUS provided a sensitivity of 0.88 (95% CI: 0.69–0.96) and specificity of 0.82 (95% CI: 0.42–0.96) compared to CXR. The sensitivity in the six studies varied from 47% to 99%, and specificity from 59% to 100%. (The panel noted that CXR is not an ideal reference standard as it is an imperfect proxy for bacterial pneumonia).

When all studies (N=10) *(30–39)*, including the ones that did not use CRES methodology, were included in the analysis, the LUS provided a sensitivity of 0.90 (95% CI: 0.76-0.96) and specificity of 0.82 (95% CI: 0.55–0.94). Thus, adding the four studies made only a small difference in the estimates of both sensitivity and specificity.

No data were available for pneumonia outcomes (including from studies with paediatric adjudication panels), such as requiring treatment with antibiotics, or clinical deterioration/treatment failure and mortality.

The review concluded that there is a low certainty of evidence to use LUS in place of CXR to make a diagnosis of pneumonia in children aged 2–59 months presenting with cough and/or difficult breathing, and no evidence to use LUS in place of CXR to decide on the use of antibiotics (or etiology) or predict outcomes such as clinical deterioration or mortality. There is currently no recommendation to use CXR in the context of integrated management of childhood illness (IMCI) to make decisions on antibiotic treatment or to predict outcomes given insufficient evidence on the utility of CXR to diagnose pneumonia in these settings.

### Evidence-to-decision judgements

Before proceeding with completing the evidence-to-decision framework, the GDG considered whether the PICO question should be revised, for example to, "In children aged 2–59 months with WHO clinical pneumonia (i.e. fast breathing and/or chest indrawing), should LUS be used rather than CXR at the hospital level?". After discussion, it was decided to continue the assessment as per the original PICO question.

In making its decisions, the GDG recognized that in this context, LUS would be used as an add-on test and not a replacement or triage test. It would be added to the initial clinical assessment (using a clinical algorithm) of the patient for fast breathing and/or chest indrawing.

The most appropriate integration of LUS into clinical guidance and workflow should be determined before implementation.

LUS for diagnosing pneumonia in children 2–59 months of age was considered accurate, with reasonable sensitivity and specificity, as noted in the systematic review. There were concerns about the positive predictive value of LUS for the diagnosis of pneumonia due to its comparison with CXR, which is less sensitive. Therefore, the GDG considered this as a **knowledge gap** and emphasized the need to improve the use of a referral/gold standard for LUS pneumonia diagnostic studies.

Undesirable effects were judged as moderate, taking into account the consequences of an incorrect diagnosis.

The certainty of evidence of the accuracy of LUS was deemed to be very low, and concern was expressed around the burden of false positives. However, the GDG noted that the test gives confidence in initiating treatment, and might also be useful in determining when to stop treatment; there were no included studies to give evidence on this point.

The resources required for LUS in different settings are not known, although the GDG noted that the cost of equipment might be significant. The cost of establishing LUS in a facility would probably be lower than establishing a chest radiology unit; however, no data were presented on the cost, as it was not available in the studies reviewed and would vary greatly between settings.

Equity would probably be increased by implementing LUS, with various factors considered by the GDG to influence it:

- some hospitals might not have facilities for CXR;
- LUS may increase equity because of increasing access to a test;
- there is potential for machine learning to decrease the need for specialized personnel.

## 4. Assessment with digital auscultation or cough sound algorithms

### Recommendation

In children 2–59 months of age presenting with cough and/or difficult breathing, WHO makes **no recommendation** about the use of digital auscultation or cough sound algorithms as an add-on test to diagnose pneumonia (**Knowledge gap**).

*Significant changes to previous recommendation*

There was no existing recommendation on the use of digital auscultation or cough sound algorithms for diagnosis of pneumonia in children 2–59 months of age presenting with cough and/or difficult breathing.

### PICO question

In children 2–59 months of age, should digital auscultation or cough sound algorithms be used as an add-on test to improve the assessment of pneumonia at the hospital level, compared to a CXR or paediatric adjudication panel?[1]

### Evidence summary

Five studies provided data for the systematic review, two for digital auscultation and three for cough sound algorithms.

Meta-analysis was not possible for digital auscultation as the two studies identified had designs that were too different to combine.

A meta-analysis was conducted on the three studies on cough sound algorithms *(40–42)*, which were carried out in various settings, using different reference standards. The analysis found the pooled sensitivity for the cough sound algorithm to be 0.82 (95% CI: 0.61–0.93), and the pooled specificity for the three studies together was 0.77 (95% CI: 0.60–0.88).

The systematic review team and the GDG noted issues such as methodological inconsistencies, broad age at inclusion (1 month to 15 years), lack of uniformity in reference diagnostics, and wide CIs. They concluded that there was very low evidence to use algorithms in place of a clinical diagnosis because of small numbers, bias, and lack of standard methods of diagnosis.

Very low evidence was found to use algorithms in addition to a clinical diagnosis (only one study looked at this).

There is insufficient evidence to make a determination about the use of digital auscultation or cough sound algorithms. However, it was noted that there may be greater benefits to these interventions at a lower level of the health system.

### Evidence-to-decision judgements

Before commencing the discussion of the findings in the evidence-to-decision framework, the GDG decided that there was a large knowledge gap for this issue. As a result, the framework was not completed.

## Management of children 2–59 months of age with pneumonia and risk factors for mortality

### 5. Identification of hypoxaemic children

### Recommendation

*In settings where pulse oximetry is not available*, in children 2–59 months of age diagnosed with pneumonia (fast breathing or chest indrawing, without danger sign[2]), WHO **suggests** evaluation of respiratory distress using a combination of signs and symptoms[3] to detect hypoxaemia (**Conditional** recommendation, **Very low** certainty of evidence).

*Remarks*

- The GDG emphasized that the signs and symptoms considered are only appropriate for use by trained health workers at the facility level and not for community-level health workers. Before implementing this recommendation, facility-level health workers should be trained in using these signs and symptoms when a pulse oximeter is not available.
- Various issues were raised by the GDG about the variation in risk depending on age and nutritional status, and the need to connect this recommendation to other related WHO recommendations.

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[1] Note that this PICO was revised at the beginning of the discussion.

[2] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor.

[3] Head nodding or nasal flaring or grunting or severe tachypnoea (respiratory rate ≥20 breaths per minute above the age-specific cut-off).

- The GDG stated strongly that pulse oximetry should be available at the primary health care level to detect hypoxaemia in children.

*Significant changes to previous recommendation*

There was no previous WHO recommendation related to the signs and symptoms to be used to diagnose hypoxaemia in children 2–59 months of age.

## PICO question

In children 2–59 months of age, what is the diagnostic accuracy of additional signs of respiratory distress (grunting, nasal flaring, head nodding, very fast breathing), alone or in combination with fast breathing and/or chest indrawing, compared to pulse oximetry measurements to identify hypoxaemic pneumonia cases at all levels of care?

## Evidence summary

The identification of hypoxaemia is important as it relates to the need for referral or a change in management of pneumonia. The current evidence on this topic is usually embedded in studies undertaken at the hospital level.

The systematic review team identified 15 relevant studies, but only 11 were included in the meta-analysis because they used the same oxygen saturation ($SpO_2$) cut-off (less than 90%) to identify hypoxaemia. Two of the studies were of a case-control design.

Analysis was done on four signs: head nodding; grunting; nasal flaring; and severe tachypnoea.

For head nodding, six studies *(43–48)* provided data giving a sensitivity of 0.19 (95% CI: 0.09-0.36) and specificity of 0.97 (95% CI: 0.93-0.99).

Nasal flaring was analysed in seven studies *(43–46, 48–50)*, giving a sensitivity of 0.67 (95% CI: 0.54–0.77) and specificity of 0.67 (95% CI: 0.50–0.81).

Information on grunting was available in nine studies (*43*, *44*, *46–52*), resulting in a sensitivity of 0.38 (95% CI: 0.20–0.60) and specificity of 0.89 (95% CI: 0.73–0.96). Grunting is traditionally considered a sign of severe disease; there was a very high prevalence of non-hypoxaemic children with grunting in two studies (*48*, *52*).

There was variability in the studies contributing to the analysis, probably from differences in disease severity and recording of clinical signs.

A very serious risk of bias was found in some studies in patient selection, the index test, reference test and time.

The systematic review team and the GDG concluded that there was a large inconsistency in the results due to two studies (*48*, *52*). The reporting of symptoms and signs may not be standardized in studies where data were collected from records or when reporting was not standardized as part of care. Nasal flaring appeared to perform better as a diagnostic test than the other signs studied.

During the discussion after the presentation by the systematic review team, participants identified two more studies that the GDG considered relevant to the PICO question that had not been found in the search for evidence because one was published after the review was completed and the other had not yet been published *(53–54)*. The studies were deemed to be relevant to the discussion, and the review team presented the findings before the evidence-to-decision judgements were made. The review team also repeated the systematic search and did not find any other relevant publications.

The two additional studies were carried out in LMIC settings, at different altitudes, with high numbers of subjects. These studies used the least absolute shrinkage and selection operator (LASSO) regression method to assess the role of these clinical signs (nasal flaring, grunting, head nodding and severe tachypnoea) using different models. In the independent LASSO analysis, various signs of respiratory distress and other factors were given scores based on the log odds ratio. While interesting, it was not clear how this sort of scoring system could be made useful for a field-level health worker. The GDG decided to include severe tachypnoea

(respiratory rate ≥20 breaths per minute above the age-specific cut-off) along with other signs[1] as a sign of respiratory distress.

### Evidence-to-decision judgements

The GDG noted that the goal of the question is to clarify if the additional signs of respiratory distress[2] are useful in detecting hypoxaemia when compared to pulse oximetry (the reference standard).

These signs are intended as replacement tests (in the absence of pulse oximetry) in settings such as primary health care, emergencies, etc., where there is low health worker capacity. As such, the signs are considered to be accurate in comparison with not using them.

The desirable effects of the intervention were considered to be large, with the GDG identifying direct consequences of the test as referring children who would need referrals and possible mortality reduction.

The GDG judged that the intervention could have large undesirable effects, as it could lead to an incorrect diagnosis. If the prevalence of pneumonia and the specificity of a sign is low, many children could be referred unnecessarily, overwhelming the health system.

The certainty of evidence of test accuracy was very low because of concerns with risk of bias in studies, inconsistency and imprecision when considered against pulse oximetry.

The GDG noted that caregivers might prefer pulse oximetry to have more certainty about the child's status, and they might also not want to be sent to a hospital unnecessarily. Therefore, possibly important uncertainty or variability exists for this measure.

The GDG noted that referrals would need to be arranged which might influence resources required, and there may also be training needs. The cost of the intervention was considered to be moderate, but there were no specific data on the costs of such training, as it would vary greatly between settings, and also depend on whether it could be easily integrated into other training, such as for IMCI.

The GDG considered that equity would probably be increased by having a protocol for referral based on clinical signs since more children would have the opportunity to be diagnosed correctly at lower levels of the health system.

The intervention would probably be acceptable to the various stakeholders, but there would need to be a decision-support system to ensure this.

The GDG noted that additional training of health care workers at primary level health facilities would be needed, and referrals would need to be arranged, which might influence cost, but that the intervention was probably feasible.

## 6. Enhanced care for high-mortality risk children

### Recommendation

In children 2–59 months of age with pneumonia (fast breathing and/or chest indrawing without danger sign[1] ) having high-mortality risk factors, WHO makes **no recommendation** on the effectiveness of enhanced care[2] (**Knowledge gap**).

*Significant changes from previous recommendation*

There was no previous specific recommendation for providing alternate/enhanced care to children with fast breathing and/or chest-indrawing pneumonia (without any general danger sign[1]), who also have risk factors for mortality.

### PICO question

In children 2–59 months of age with fast breathing and/or chest indrawing, what are the risk factors for mortality (such as nutritional status, HIV status, pallor, pulse oximetry measurements), and what is the

[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor.

[2] Such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment.

effectiveness of enhanced care (such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment) compared to the usual care in improving clinical outcomes at all levels of care?

### Summary of evidence

Three studies *(17, 22, 55)* carried out in settings in Africa, Asia and South America provided data for the review. Four other studies were excluded as there was no information on the outcomes of the subgroups of interest. These subgroups were age less than 12 months, moderate malnutrition, HIV and hypoxaemia, associated with high mortality as identified by a previous review *(56)*.

Before 2012, for children 2–59 months of age with chest indrawing (with or without fast breathing) and no danger sign[1] the standard of care was hospitalization for parenteral antibiotics and other supportive care if needed. The various studies provided somewhat different interventions for enhanced care, for example, in some cases there was educational counselling, follow-up and close monitoring.

Definitions of treatment failure varied slightly between the studies. The EMPIC study *(22)*, which used the current management of chest-indrawing pneumonia (CHWs identified children 2–59 months of age with chest indrawing, provided the first dose of antibiotic and referred them to a health facility for further management) compared to the intervention (children were treated with oral amoxicillin for five days, same management as currently offered at health facility level). In this study, children were screened by pulse oximetry to exclude those with hypoxaemia. Further analysis for this review showed that the RR for treatment failure by day 14 was 1.1 (95% CI: 0.8–1.6) for infants less than 12 months of age compared to children 12–59 months of age, and the RR was 1.8 (95% CI: 0.9–3.6) for moderately malnourished children compared to children with normal nutritional status, both findings non-significant. Moreover, the RR for mortality by day 14 was 0.9 (95% CI: 0.3–3.3) for infants less than 12 months of age compared to children 12–59 months of age and 3.2 (95% CI: 0.3–3.2) for moderately malnourished children compared to children with normal nutritional status, also both non-significant. However, the review could not identify studies that reported enhanced management for children with pneumonia and mortality risk factors.

### Evidence-to-decision judgements

The GDG did not complete the evidence-to-decision framework, as it noted that the included studies might be too indirect to answer the original PICO question, that is, enhanced care for children 2–59 months old with pneumonia and mortality risk factors. Furthermore, based on the above information regarding the evidence on enhanced care, the GDG suggested not to produce a GRADE table. There is a **knowledge gap**.

## Management of pneumonia in children 5–9 years of age

### 7. Assessment of children 5–9 years of age to diagnose pneumonia

### Recommendation

In children 5–9 years of age presenting at first-level health care facilities, WHO makes **no recommendation** on a standardized clinical assessment of community-acquired pneumonia (**Knowledge gap**).

*Remarks*

- Given the importance of providing clinical guidance for this population, WHO will coordinate with experts and investigators to develop evidence-based algorithms to address this important knowledge gap.

*Significant changes from previous WHO recommendation*

No previous WHO guidelines existed for a field-level clinical definition of pneumonia in children 5–9 years of age. Guidance is needed for this age group, in contrast to children under 5, because of factors which could complicate the assessment, such as physiological changes with age, the absence of bronchiolitis, an increase in the prevalence of asthma, and a change in the etiology and causative microorganisms among these children.

[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia.

### PICO question

In children 5–9 years of age, what are the best clinical signs to identify community-acquired pneumonia cases?

### Summary of evidence

No literature was found assessing the sensitivity and specificity of clinical signs in making a diagnosis of pneumonia in children 5–9 years of age at the community level or those seen on an outpatient basis at primary health care facilities. It was thus not possible to provide evidence that would lead to a clinical diagnosis of pneumonia for health workers in these settings. Therefore, the review expanded in scope to hospital-based studies that evaluated clinical signs for making a diagnosis of pneumonia.

Out of an initial 6784 studies identified in the preliminary search, eight studies were identified, but three were excluded from the analysis as data for the diagnostic accuracy of each sign were not available. This left five studies *(57–61)* included in the review. These studies were mostly carried out in high-income countries, and had varying age groups (from 1 month up to less than 18 years), different or varying reference standards or criteria for diagnosis.

The different studies included in the meta-analysis provided data on the sensitivity and specificity of eight symptoms and signs of pneumonia: cough, tachypnoea, decreased breath sounds, retractions (subcostal/intercostal), hypoxaemia, grunting, crackles and wheeze on lung auscultation (see **Table 3**). In general, sensitivity was much lower than specificity for these signs (except for cough). In some cases, for example decreased breath sounds, there were wide differences between studies.

No information was available for more than one sign in the same individual. The systematic review team noted that this analysis could be carried out if this individual data could be obtained from researchers. They also noted that gold standards for diagnosis of pneumonia also present an issue – CXRs underdiagnose pneumonia while clinicians may over-diagnose it.

**Table 3. Sensitivity and specificity of clinical signs for the diagnosis of pneumonia**

| Sign | Sample size | Pooled sensitivity (95% CI) | Pooled specificity (95% CI) |
|---|---|---|---|
| Cough *(57–59, 61)* | 1535 | 0.88 [0.79–0.93] | 0.11 [0.05–0.24] |
| Tachypnoea *(57–59, 61)* | 1535 | 0.47 [0.27–0.69] | 0.64 [0.36–0.85] |
| Decreased breath sounds *(57–61)* | 2105 | 0.14 [0.22–0.63] | 0.93 [0.65–0.99] |
| Hypoxaemia *(57, 59, 61)* | 1278 | 0.19 [0.14–0.27] | 0.93 [0.89–0.95] |
| Retractions (subcostal/intercostal) *(57, 58, 60)* | 1352 | 0.11 [0.03–0.31] | 0.98 [0.91–0.99] |
| Grunting *(58, 60, 61)* | 1186 | 0.04 [0.01–0.13] | 1.00 [1.00–1.00] |
| Crackles on lung auscultation *(57–61)* | 2105 | 0.30 [0.27–0.39] | 0.79 [0.63–0.89] |
| Wheeze on lung auscultation *(57–59, 61)* | 1535 | 0.04 [0.01–0.13] | 0.78 [0.68–0.86] |

The systematic review team and GDG concluded from the meta-analysis that there was no evidence to evaluate the diagnostic accuracy of clinical signs in making a diagnosis of pneumonia in children 5–9 years of age at community and primary health care levels.

The GDG also concluded that it was not possible to make an evidence-based statement on simple signs-based diagnosis of pneumonia in children 5–9 years of age by workers at the community level or at primary health care facilities. None of the clinical signs in hospitalized children with respiratory distress are sensitive enough to be used for this purpose. Cough (sensitivity 88%, 95% CI 0.79–0.93) may be useful at the hospital level but would pick up many upper respiratory infections in other settings. Specific signs have very low sensitivity to be of any use; for example, tachypnoea has a sensitivity of 47% (95% CI 0.27–0.69), which is insufficient for field-level diagnosis.

The team noted the need for individual-level data, to look at the use of a combination of signs for diagnosis.

### Evidence-to-decision judgements

Before completing the framework, the GDG discussed the complexity of the issue, considering the evidence presented. Efforts at clarification were made, with WHO expressing how useful a recommendation on the question would be, and the participants advocating for the development of an algorithm.

The consensus of the GDG regarding accuracy was "Don't know", looking at the totality of the signs and tests considered, as there is a gap in the evidence in understanding how accurate the signs are for the diagnosis of pneumonia in children 5–9 years of age. It was also noted that the evidence presented was indirect, as it applies to a population attending hospitals, mostly in higher-income settings, and not to the population of interest to the GDG.

After the discussion about concerns with low sensitivity for all signs, meaning cases testing false negative are missed, but also considering that thresholds for some tests could be adjusted to find more cases, the GDG could not determine the undesirable effects because of a lack of data. This rating may vary depending on the signs eventually included in any algorithm.

The GDG considered that stakeholders would consider this question as having possibly important uncertainty or variability. The highest priority would be on a true diagnosis.

The GDG acknowledged the benefits of having a structured approach using signs and symptoms to identify pneumonia cases and initiating appropriate management strategies (at any level of care). However, there is currently a lack of evidence supporting this approach, so the GDG could not judge the balance of effects.

Depending on what emerges in terms of equipment, supplies and training needed to implement the diagnosis of pneumonia based on a set of signs, the intervention would probably be feasible.

## 8. Treatment of children 5–9 years of age with pneumonia

### Recommendation

In children 5–9 years of age with suspected pneumonia, WHO makes **no recommendation** about which antibiotic has the highest effectiveness in improving clinical outcomes (**Knowledge gap**).

*Remarks*

- There was concern about making a recommendation for the use of a specific antibiotic in the light of insufficient evidence, which perhaps would encourage antibiotic use, in the context of current antibiotic stewardship recommendations *(62)*.

*Significant changes from previous WHO recommendation*

There were no established recommendations regarding the optimal antibiotic for enhancing clinical outcomes in children 5–9 years of age who are diagnosed with community-acquired pneumonia.

### PICO question

In children 5–9 years of age with suspected community-acquired pneumonia, which antibiotic has the highest effectiveness in improving clinical outcomes?

### Evidence summary

After screening the literature, the systematic review team identified five articles for inclusion *(63–67)*. The team was not able to find any study that included only children from 5–9 years of age. The studies included subgroup analysis from 5 years and above (up to 18) and were conducted in various settings, mostly high-income ones, both outpatient and inpatient.

The team concluded that in outpatient settings, a combination (macrolide and B-lactam) of antibiotics has possibly lower treatment failure compared to B-lactam monotherapy, and macrolide monotherapy probably has lower treatment failure compared to B-lactam monotherapy. In inpatient settings, a combination

(macrolide and B-lactam) of antibiotics possibly shows no difference in treatment failure rates compared to B-lactam monotherapy. However, the GRADE table showed no substantial differences in the outcomes between groups receiving one antibiotic versus a combination. There was a risk of bias, as well as indirectness, in the studies.

Cost data from one study *(66)* showed that among children 5–17 years of age, there was no significant difference in cost for those receiving combination compared to monotherapy[1] (cost ratio: 1.01, 95% CI 0.98–1.04).

### Evidence-to-decision judgements

Although this question is a priority, the GDG recognized that the data presented by the systematic review team included several concerns over the risk of bias and indirectness, which would not adequately lead to a concrete recommendation. The GDG decided to recognize this as a knowledge gap and not complete the evidence-to-decision framework.

[1] Monotherapies used were B-Lactam monotherapy (penicillins, 2nd and 3rd generation; Aminopenicillin, or 2nd or 3rd generation cephalosporins; IV Ceftriaxone; or Fluoro-quinolones (Levofloxacin). Combination therapies were B-Lactam and Macrolides. (erythromycin, clarithromycin, azithromycin; or IV Ceftriaxone and macrolide [oral or IV]) or ceftriaxone with clarithromycin or erythromycin lactobinate).

# Diarrhoea[1]

## Treatment of diarrhoea in children up to 10 years of age

### 1. Treatment of children up to 10 years of age with diarrhoea and use of antibiotics

#### Recommendation

1a. In children up to 10 years of age with acute watery diarrhoea (regardless of etiology), WHO **suggests** against the use of antibiotics (**Conditional** recommendation, **Low** certainty of evidence).

1b. In children up to 10 years of age with persistent diarrhoea (regardless of etiology), WHO makes **no recommendation** on the use of antibiotics (**Knowledge gap**).

*Remarks*

- The GDG's decision places higher value on the larger uncertain undesirable effects of overtreatment (including antibiotic resistance) and a lower value on the uncertain trivial benefit of antibiotic treatment.
- Some of the evidence was indirect.

*Significant changes from previous WHO recommendation*

WHO has not recommended antibiotics for acute watery or persistent diarrhoea in children under 10 years of age.

#### PICO question

In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of any antibiotic compared to no antibiotic treatment in improving clinical outcomes?

#### Evidence summary

The systematic review team identified five relevant studies *(68–72)* on acute watery diarrhoea to include in the meta-analysis, but no relevant studies on persistent diarrhoea. The five studies involved 13 114 participants, including some above 5 years of age. They were conducted in LMICs (Egypt, India) *(68–70)*, with one multi-country study *(72)*. The antibiotics used were nitazoxanide and azithromycin.

The result of the meta-analysis for clinical cure by day 7 using nitazoxanide was RR of 2.28 (95% CI 1.52–3.41); parasitological cure with nitazoxanide was RR of 2.86 (95% CI 1.72–4.74); all-cause mortality (one trial using azithromycin) showed a non-significant RR of 0.71 (95% CI 0.40–1.27); for mean duration of diarrhoea (hours) using nitazoxanide, the mean duration (MD) was -24.90 (95% CI -34.09–-15.71) hours; and for the need for intravenous (IV) fluid therapy in the intervention group (one study), the non-significant RR was 0.50 (95% CI 0.05–5.17).

It was concluded that there was low-quality evidence indicating a substantial increase in clinical cure, decrease in duration of diarrhoea and no substantial difference in all-cause mortality in the antibiotic group; and very low-quality evidence for parasitological cure and no substantial difference in the frequency of IV fluid therapy between the two groups.

*Note.* The GDG discussed at length whether the underlying evidence as presented could be considered for this PICO. The GDG found the data from the studies to be indirect due to the potential that these addressed parasitological diarrhoea. Nitazoxanide was identified as an anti-parasitological agent which also has some anaerobic bacterial activity.

The GDG also discussed a recently published clinical trial *(72)* included in the systematic review that investigated the effects of adding azithromycin to the standard WHO case management for acute watery diarrhoea in children aged 2–23 months. This study aimed to determine if adding azithromycin could reduce mortality and improve growth in low-resource settings. The results showed no significant difference in 180-day mortality rates between the groups that received azithromycin and those that received a placebo. Additionally, there was a small, non-significant improvement in linear growth in the group that received azithromycin, and no

[1] Cholera was not considered within these recommendations, as per a decision by the GDG at a scoping meeting in March 2023.

differences in antibiotic resistance were found between the two groups. The study concluded that the use of azithromycin did not lead to a significant improvement in survival among young children with acute diarrhoea.

### Evidence-to-decision judgements

The GDG was unable to quantify any mortality benefit from giving antibiotics. Because of the side effects of antibiotics, and more importantly, concern for antibiotic resistance at the population level, a large number would need to be treated to show benefit for any patients. The GDG recognized that various stakeholders may view the benefits differently.

Large costs would be anticipated for providing antibiotics, and the number needed to treat to see an overall benefit was the driver of the GDG's decision on the size of the resources required.

Equity would probably be reduced by providing antibiotics. Factors noted by the GDG that might impact equity included that there may be out-of-pocket costs for certain patients; and programmes/systems might bear some cost with policy changes.

The acceptability of the intervention varies by the perspectives of different stakeholders:

- for patients/caregivers it would be acceptable because of the potential of a cure for a child;
- for clinicians it would probably not be acceptable because of concerns with antimicrobial resistance increasing, for example with azithromycin which is the established treatment for typhoid;
- from a public health viewpoint it might not be acceptable, because there would be a highly uncertain benefit for the additional cost.

## 2. Treatment of children up to 10 years of age with diarrhoea and blood in stools

### Recommendation

In children up to 10 years of age with diarrhoea and blood in the stool, WHO **recommends** treatment with antibiotics rather than no antibiotics (**Strong** recommendation, **Moderate/Low** certainty of evidence).

*Remarks*

- This recommendation was informed by a previous Cochrane Review *(73)* on antibiotics in *Shigella* dysentery.
- The dosage and duration of the first- and second-line antibiotics are according to the existing recommendation (first line: Ciprofloxacin: 15 mg/kg per dose twice daily for three days; second line: Ceftriaxone: 50–80 mg/kg daily for three days) *(13)*.
- The GDG was advised by the methodologists on the discordant recommendation which was made on this subject in the previous guideline. The panel was asked to justify the discordant recommendation taking into account the low certainty of evidence. In response, the GDG maintained a discordant recommendation because it noted that there is a potential for catastrophic harm if children are not treated immediately when they present with dysentery. An example was given of an observational study (unpublished, so not included in the review) carried out during the conflict in Rwanda in 1994 where children in one group who had *Shigella* dysentery were not given antibiotics immediately. The outcomes in this group were considerably worse than in the group which received antibiotics.
- The GDG again noted, as in the previous recommendation, that health workers should refer to local sensitivity patterns of antibiotics, and the attention of policy-makers is drawn to WHO's AWARE watch list for other issues about antibiotic stewardship *(62)*.

*Significant changes to previous WHO recommendation*

WHO previously specifically recommended that children with diarrhoea and blood in stools (i.e. dysentery) should be treated with Ciprofloxin as a first-line treatment, and Ceftriaxone should be given as a second-line treatment in severely ill children where local antimicrobial sensitivity is not known.

### PICO question

In children up to 10 years of age with diarrhoea and blood in stools, what is the effectiveness of any antibiotic compared to no antibiotic treatment in improving clinical outcomes?

### Evidence summary

The systematic review team was not able to identify any new trials since the existing recommendation on this subject was made that compared the use of antibiotics with no antibiotic treatment. The Cochrane Review published in 2010 *(73)* included just two trials which were conducted in 1986 and 1989. The team assumed this absence of new evidence was probably because it would be considered unethical to conduct trials as antibiotics are already recommended for bloody diarrhoea. Hence, it was irrelevant for the team to prepare a GRADE table, as suggested by the GDG.

### Evidence-to-decision judgements

As there was no new evidence, the GDG did not complete the evidence-to-decision framework. The detailed rationale is given above under "Remarks".

## 3. Treatment of children up to 10 years of age with diarrhoea and use of zinc

### Recommendations

3a. In children up to 10 years of age with acute watery diarrhoea, WHO **recommends** adjunctive treatment with oral zinc (**Strong** recommendation, **Moderate** certainty of evidence).

3b. In children up to 10 years of age with persistent diarrhoea, WHO recommends adjunctive treatment with oral zinc (**Strong** recommendation, **Moderate** certainty of evidence).

3c. In children up to 10 years of age with acute watery or persistent diarrhoea, WHO **suggests** a 5 mg dose of oral zinc (**Conditional** recommendation, **Low** certainty of evidence).

*Remarks*

- Zinc gluconate formulation has shown a better vomiting profile than other forms of zinc.
- For the duration of treatment, refer to existing recommendations (10–14 days).
- The justification for the recommendation for dose of zinc was driven by a reduction in vomiting and the lack of inferiority for diarrhoea outcomes.

*Significant changes from previous WHO recommendation*

WHO previously recommended zinc supplementation, but at a higher dose, and did not differentiate the recommendation between children with acute watery or persistent diarrhoea. The recommendation is extended for children up to 10 years of age.

### PICO question

In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of oral zinc compared to no oral zinc treatment in improving clinical outcomes? If effective, what is the optimum dose, duration and formulation?

### Evidence summary

Many studies have been carried out since the last guideline on diarrhoea was produced. The systematic review team identified 43 papers from 38 primary trials for inclusion in a meta-analysis *(74)*: 35 on acute and three on persistent diarrhoea; 37 trials on zinc compared to no zinc; and one trial on low zinc compared to high zinc doses. Eleven trials were conducted in high-income countries, 27 in LMICs and one in multiple countries. Only four studies enrolled children with an age group inclusive of 5 up to 10 years of age.

Eighteen studies reported recovery from diarrhoea at the last follow-up comparing groups receiving zinc versus not receiving zinc; analysis showed RR 1.07 (95% CI 1.03–1.10) favouring zinc. Subgroup analyses were

carried out by definition of diarrhoea; dose of zinc administered; duration of zinc supplementation; and zinc formulation.

For the duration of diarrhoea, there was a statistically significant reduction of 13.27 (95% CI 17.66–8.89) hours in the group receiving zinc compared to the no zinc treatment group. In the subgroup that used the WHO definition of diarrhoea, there was a decrease of 11.26 (95% CI 17.51–5.00) hours in the duration of diarrhoea in the zinc groups, while studies using other definitions reported a slightly higher reduction of 16.69 (95% CI 27.78–5.60) hours of duration of diarrhoea in the zinc groups compared to no zinc treatment. After taking zinc, patients had a 46% higher risk of vomiting (RR 1.46, 95% CI 1.22–1.76), compared to those not taking zinc.

Four studies were included in the analysis for mortality, showing no significant reduction (RR 0.71, 95% CI 0.10–4.88) among those who received zinc.

Vomiting was found to be 29% (RR 0.71, 95% CI 0.59-0.86) lower in the 5 mg group compared to the 20 mg group.

For persistent diarrhoea, recovery at the last follow-up after starting zinc supplementation (according to varying definitions) showed RR of 1.75 (95% CI 1.34–2.30), indicating a 75% higher recovery in the zinc group. Duration of diarrhoea was 26.29 (95% CI 47.35–5.23) hours lower in the zinc group, and mortality was comparable in both groups.

The systematic review team concluded:

#### Acute watery diarrhoea

- moderate quality evidence indicates 7% (RR 1.07, 95% CI 1.03–1.10) higher recovery at the last follow-up and a decrease of 13.27 (95% CI 17.66–8.89) hours in the duration of acute diarrhoea in the zinc group compared to the control group;
- low quality evidence indicates a 46% (RR 1.46, 95% CI 1.22–1.76) increase in the number of participants who experienced vomiting in the zinc group compared to the control; and
- moderate quality evidence suggests no substantial difference in mortality between the zinc group and the controls.

#### Persistent diarrhoea

- low quality evidence indicates 75% (RR 1.75, 95% CI 1.34–2.30) higher recovery at the last follow-up in the zinc group compared to the control group;
- very-low quality evidence indicates a decrease of 26.29 (95% CI 47.35–5.23) hours in the duration of diarrhoea in the zinc group compared to the control group;
- moderate quality evidence suggests no substantial difference in mortality from diarrhoea between the two groups.

### Evidence-to-decision judgements

*Acute watery diarrhoea*

The GDG decision that desirable effects were moderate was driven by the large difference in the RR of recovery between the zinc and no zinc groups, although the difference in other outcomes was more moderate.

The GDG noted that there is some evidence that higher doses of zinc provide a residual effect on the prevention of diarrhoea and pneumonia. Compliance and adherence were monitored very carefully in the studies providing this information.

The evidence also shows that the 5 mg dosing has comparable effects with higher doses and fewer complaints of vomiting and better adherence. The dose of 20 mg has been hard to implement, and the resources put in by governments have not yielded the desired benefits in coverage or acceptance.

The GDG considered the undesirable effects of zinc to be moderate, noting more vomiting in subgroups receiving 20 mg (RR 2.20, 95% CI 1.75–2.75) of zinc compared to subgroups receiving 5 mg or 10 mg or weight-based dosing, with little additional benefit from the higher dose.

Vomiting was discussed as an important values and compliance/adherence factor. There was concern that vomiting as a result of high zinc intake could affect oral rehydration solution (ORS), breastfeeding or food intake as well as compliance, and cause repeat visits to a health provider. Improved formulations may overcome some of the issues of side effects.

Zinc is noted by the GDG to be very cheap to patients and caregivers, widely available in various settings, and an established intervention. Thus, there would be negligible costs and savings to continue the practice, and the GDG noted that a decrease in the use of antibiotics, which could result from the intervention, would be important.

The GDG also noted that this drug is familiar in resource-limited settings, and is very acceptable to stakeholders.

No supply chain or other feasibility issues were raised by the GDG.

## 4. Treatment of children up to 10 years of age with diarrhoea and use of probiotics

### Recommendations

4a. In children up to 10 years of age with *acute watery* diarrhoea, WHO **suggests** against the use of probiotics (**Conditional** recommendation, **Low** certainty of evidence).

4b. In children up to 10 years of age with *persistent* diarrhoea, WHO makes **no recommendation** for the use of probiotics (**Knowledge gap**).

*Remarks*

- As noted in the discussion, there are many issues, such as high cost; regulatory issues; and poor shelf life (storage), to be confronted regarding probiotics for acute watery or persistent diarrhoea before their use can be recommended.
- While their use in treating persistent diarrhoea may be promising, there is a considerable **knowledge gap** on the issue of probiotics.

*Significant changes from previous WHO recommendation*

WHO has not previously made a recommendation on the use of probiotics in acute watery or persistent diarrhoea in children.

### PICO question

In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of probiotics treatment compared to no probiotics treatment in improving clinical outcomes? If effective, what is the optimum dose, duration and formulation?

### Evidence summary

The systematic review team identified 99 relevant studies *(75)*, mostly randomized controlled trials, in a variety of settings, on children up to 10 years of age with acute watery or persistent diarrhoea. Probiotic preparations used contained single or multiple organism strains.

*Acute watery diarrhoea*

For clinical cure (using the WHO definition), assessed variously on days 3, 5, 7 and 14, the meta-analysis of five studies reported on day 7 favoured probiotics (RR 1.23, 95% CI 1.01–1.49).

All-cause mortality was reported in four studies, with the results of borderline significance in favour of probiotics (RR 0.17, 95% CI 0.03–0.98). However, there was no evidence for diarrhoea-related mortality.

Duration of diarrhoea in hours was reported in 11 studies. The duration varied significantly, with a lower duration of 7.2 hours in those who received probiotics (MD -7.20, 95% CI -13.36–1.03).

Six studies gave information on clinical deterioration, and found no significant difference (RR 1.16, 95% CI 0.83–1.60).

SAEs were reported by 6 studies, showing no significant difference (RR 0.81, 95% CI 0.23–2.81).

*Persistent diarrhoea*

Two studies were found with data on persistent diarrhoea. The decrease in the duration of diarrhoea (hours) was significant in favour of probiotics (MD -96.45, 95% CI -110.53–-82.37).

The systematic review team summarized their findings:

Acute watery diarrhoea

- low certainty evidence indicates an apparent role of probiotics in clinical cure;
- low certainty evidence suggests a protective role of probiotics against all-cause mortality;
- low certainty evidence indicates a shorter duration of diarrhoea and an inconclusive role of probiotics in clinical deterioration;
- low certainty evidence suggests no role of probiotics in relation to adverse events and SAEs.

Persistent diarrhoea

- very-low certainty evidence suggests a substantial difference in the duration of diarrhoea among children receiving probiotics compared to controls.

### Evidence-to-decision judgements

The GDG considered the desirable effects of probiotics to be small. The decision was based on thresholds:

- meaningful clinical reduction of diarrhoea duration, at least one day (24 hours);
- meaningful number of patients achieving clinical cure, 10% (100 patients out of 1000). The estimate from the review just crosses the threshold.

The GDG noted inconsistent directionality of the outcomes driving the desirable effects (seven hours in reduction of duration and 189 more patients achieving clinical cure). Different decisions were made for acute watery (small desirable effects) and persistent diarrhoea (with a need for confirmation of results).

The GDG determined that the duration of diarrhoea recorded by the trials was important in their decision-making. However, different studies recorded the duration of diarrhoea very inconsistently (i.e. diarrhoea duration from onset versus diarrhoea duration from randomization).

The GDG noted that vomiting was an undesirable adverse effect for probiotics depending on the strain, but judged undesirable effects for acute watery diarrhoea as trivial. For persistent, it was unknown.

The GDG panel was split between whether the balance of effects probably favours the intervention or does not favour either the intervention or the comparison for acute watery diarrhoea due to a lack of clarity in results. This decision was driven by inconsistent directionality of the outcomes contributing to the desirable effects, as above.

The GDG noted that providing probiotics might have large costs (for both acute watery and persistent diarrhoea) to individual patients and to the health system. There might also be supply chain issues which could involve additional expenses.

No studies related to cost-effectiveness were included in the review, but attention was drawn to one study *(76)* that investigated the cost-benefit of using probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) in the treatment of children hospitalized with acute diarrhoea using a double-blind, randomized, placebo-controlled trial. A greater cost-benefit with the probiotic treatment was found to be probable, but not statistically significant in this small study.

The GDG noted that the cost of probiotics would probably reduce equity in relation to both acute watery and persistent diarrhoea, not only because of possible patient out-of-pocket expenses, but because the health system funds spent on this intervention would not be spent on something else that has a more proven impact.

Probiotics would probably not be acceptable to most stakeholders. The GDG discussed different perspectives. For caregivers, there may be high costs; for clinicians, the clinical benefits are trivial and costly.

The GDG noted several concerns with the feasibility of probiotics, which led to a decision that the intervention is probably not feasible: high cost; regulatory issues; and poor shelf life (storage) of probiotics. Keeping probiotic strains alive can be difficult, and there is a lack of studies discussing temperature control.

## 5. Treatment of children up to 10 years of age with diarrhoea and dehydration and use of Low Osmolarity Oral Rehydration Salt Solution

### Recommendation

In children up to 10 years of age with acute watery diarrhoea and dehydration, WHO **recommends** Low Osmolarity Oral Rehydration Salt Solution (LORS) (**Strong** recommendation, **Moderate** certainty of evidence).

*Remarks*

- Despite the absence of published clinical trials for the use of LORS, the GDG recommended extending this life-saving recommendation to children 5–10 years of age. The recommendation was based on an analysis of the biological plausibility of LORS being efficacious in this age group, the lack of any evidence of safety concerns, and the experience of medical professionals of the effectiveness and safety of LORS in this population. This benefit-risk assessment was sufficient for the GDG to recommend extending the age range of the current recommendation.

*Significant changes from previous WHO recommendation*

WHO previously recommended LORS for all children with diarrhoea and dehydration.

### PICO question

In children up to 10 years of age with acute watery diarrhoea and dehydration, what is the effectiveness of LORS compared to standard ORS in improving clinical outcomes?

### Evidence summary

The systematic review team identified nine relevant randomized controlled trials *(77)*, including a collective participant pool of 1942. Seven of these studies were conducted on acute watery diarrhoea, while two focused on persistent diarrhoea. The sample sizes of children ranged from 61 to 676, and the included age ranges were 0–2 months (1 study), 1–24 months (3 studies), 3–24 months (2 studies), 4–24 months (1 study), 6–48 months (1 study) and 3–59 months (1 study). Studies were conducted in LMICs, including Bangladesh (n=3), India (n= 3), and Egypt (n= 2); one study was a multi-country study and included Brazil, India, Mexico and Peru. All studies were conducted in a tertiary care setting and used LORS with osmolarity ranging from 210 mmol/L to 245 mmol/L.

For the comparison of LORS to standard ORS in acute watery diarrhoea, there was a comparable effect on the number of patients cured within five days (RR 0.95, 95% CI 0.61–1.49), and frequency of unscheduled IV therapy (RR 0.77, 95% CI 0.72–1.02), and a borderline significant effect on treatment failure (RR 0.13, 95% CI 0.02–1.00). However, there was a significant decrease in the mean log approximated duration of diarrhoea (hours) (MD -0.29, 95% CI -0.42–-0.16), mean log approximated stool output (g/kg) (MD -0.24, 95% CI -0.37–0.10), and ORS intake (ml/kg) (MD -0.18, 95% CI -0.28–0.07) in patients taking LORS.

### Evidence-to-decision judgements

The desirable effects of LORS were judged to be large by the GDG, noting that the previous recommendation was driven by the reduction in unscheduled IV fluids.

The certainty of evidence is high, with this review confirming previous findings from other reviews.

Any additional resources needed for implementation would be negligible, as LORS costs 70% less than standard ORS.

No change was expected in equity considerations, although evidence suggests that children from families in the poorest wealth quintile are less likely to receive high impact interventions for diarrhoea than those in the richest quintile.

LORS is widely acceptable and has been shown to be feasible.

## Management of diarrhoea in children up to 10 years of age with risk factors for mortality

### 6. Enhanced care for high-mortality risk children up to 10 years of age with diarrhoea

#### Recommendation

In children up to 10 years of age with acute watery diarrhoea having risk factors, WHO makes **no recommendation** about enhanced care compared to the usual care (**Knowledge gap**).

*Remarks*

- limited evidence was available to make any recommendation on enhanced care for children with diarrhoea having risk factors. The GDG emphasised the importance of conducting further research in this area.

*Significant changes from previous WHO recommendation*

WHO has not previously had a recommendation related specifically to enhanced care.

#### PICO question

In children up to 10 years of age with acute watery diarrhoea having risk factors (age, nutritional status, HIV status), what is the effectiveness of enhanced care (such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment) compared to the usual care in improving clinical outcomes?

#### Evidence summary

Three studies *(78–80)* provided evidence for the systematic review, but the subject numbers were small (61, 126 and 208, respectively). The care provided was considered "alternate" by the systematic review team rather than "enhanced" and differed between studies, so no meta-analysis was carried out. The studies took place in Bangladesh and Kenya and were hospital based.

The review team summarized the evidence:

- alternate care (isotonic fluids – Ringer's lactate) compared to standard care (defined slightly differently in each study) showed a non-significant reduction in mortality (43% versus 68%) in the study by Akech and colleagues *(78)* ($P = 0.11$).
- treatment failure reported by Alam and colleagues *(80)* was lower with alternate care (modified WHO ORS plus partially hydrolized guar gum) (53.9%) compared to standard care (modified WHO ORS) (69.8%) (RR 0.66, 95% CI 0.41–1.4, $P = 0.06$), but the difference was not significant.
- a non-significant higher rate of treatment failure was observed in one study *(79)* with rapid rehydration with cholera saline solution (2.8%) compared to slow rehydration (1.9%) (RR 1.5, 95% CI 0.2–9.0).
- SAEs, reported in two studies, were comparable across the alternate and standard care groups.

#### Evidence-to-decision judgements

The GDG decided that the systematic review evidence was too indirect to answer the original PICO question, that is, enhanced care for children with diarrhoea and mortality risk factors, to proceed with the evidence-to-decision exercise. Furthermore, based on the above information regarding the lack of evidence on enhanced care, the GDG suggested not to produce a GRADE table. It also noted that one study that may have been relevant *(72)* was not included in the original analysis by the reviewers because it was primarily a drug trial, with the care consisting of follow-up visits, mainly aimed at determining mortality. While advice on referral could be given during the visits, it was not recorded how much actually took place. There is a **knowledge gap**.

# Research priorities

During the discussions on the evidence presented and in formulating the recommendations, the GDG identified some questions and issues with a knowledge gap. In other cases, further research would be helpful to enable more specific recommendations. WHO will encourage research in these areas and, where appropriate, endeavour to assist in identifying funding.

## Pneumonia

### Fast-breathing pneumonia

- Understanding the granularity around the data subgroups (e.g. geographical context [including altitude], nutrition status, vaccination status) to identify which children would truly benefit from antibiotics.
- Better understanding of diagnostic measures, which would help in screening and diagnosing patients and reduce the use of antibiotics.
- Improving diagnostic tools to distinguish between viral and bacterial pneumonia.
- Impact of respiratory syncytial virus (RSV) vaccination (including passive immunization) on pneumonia case management.
- Trials to determine for which children antibiotics can be safely delayed/withheld.
- Strengthening of WHO research networks for robust collaborative studies.

### Chest-indrawing pneumonia

- Implementation research on treatment for high-risk children to see the impact of the recommendation.
- Implementation research to develop and test district-level optimal delivery models to improve childhood pneumonia treatment coverage.

### Community versus standard management of chest-indrawing pneumonia

- Implementation research to understand how recommendations are performing.
- Risk stratification studies in children to understand: a) when antibiotics can be safely withheld; and b) how they improve outcomes, especially mortality.
- Quantitative and qualitative studies to assess health worker skills in identifying chest indrawing and other danger signs in community settings, and development of strategies and methods to improve skills.
- Monitoring and evaluation of implementation.

### LUS

- Use of a paediatric adjudication panel.
- Potential for machine learning.
- Feasibility of LUS in different settings.
- Identifying other diagnostic tests to compare with LUS and to model the effect on downstream management decisions.

### Digital auscultation and cough sound algorithms

- Identification of better diagnostic tests and evaluation criteria for comparison with digital auscultation, and to model effects on downstream management decisions.
- Comparison of these tests with other investigative techniques.
- Development of devices which can be used in LMICs and remote settings.

### Identification of hypoxaemic children through signs of respiratory distress and use of pulse oximetry

- Implementation research on how this intervention would impact the assessment of pneumonia at various levels of care, especially for CHWs and front-line health workers.
- Skills assessment in CHWs and first-line health workers on identifying the clinical signs of respiratory distress[1] and strategies to improve skills.
- Effect of various levels of $SpO_2$, particularly between 90% and 92%, or 90% and 93%, on mortality outcomes in a range of geographical settings.
- Implementation research to evaluate feasibility and challenges for the use of pulse oximetry among children less than 5 years of age at various levels of care and settings.
- Implementation research on including pulse oximetry within the IMCI consultation.
- Empowerment of health workers at all levels to use pulse oximetry.

### Enhanced care for high-risk children

- Community-level studies comparing children with pneumonia and high risk factors for mortality who receive alternate/enhanced care compared to those who do not.
- Strategies for identifying children with risk factors, enhanced management strategies, and follow-up (risk stratification and differential care).
- Studies to evaluate the history of prematurity and low birth weight on the poor outcomes of children with pneumonia receiving standard care, especially in the first 2 years of life, and evaluating alternate management of pneumonia among these children.

### Assessment of children 5–9 years of age

- Identification and analysis of combinations of signs (including the development of an algorithm) which can diagnose pneumonia, and validation studies of these signs.
- Use of fever as a sign for the diagnosis of pneumonia in this age group.
- Studies at community and primary care levels, which would look at signs such as difficult breathing (patients might have difficult breathing, but not tachypnoea).
- More studies in this age group from LMIC settings.
- Appropriate thresholds for clinical signs at which antibiotics would be administered.
- Effectiveness of management strategies in improving outcomes in children older than 5 years of age, especially serious outcomes such as mortality.
- How to distinguish signs and symptoms related to pneumonia in children with tuberculosis, and understanding the role of tuberculosis presenting as acute pneumonia.

### Treatment of children 5–9 years of age

- Clinical trials to evaluate the effectiveness of various antibiotics for the treatment of suspected pneumonia in children 5–9 years of age in hospitals and the community in LMICs.

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[1] Head nodding or nasal flaring or grunting or severe tachypnoea (respiratory rate ≥20 breaths per minute above the age-specific cut).

- Comparison of costs of macrolides compared to amoxicillin.
- Epidemiological studies on antibiotics in infections, especially pneumonia.
- Risk stratification studies in situations where antibiotics can be safely and effectively withheld.

## Diarrhoea

### Antibiotics

- The use of antibiotics for malnourished children with diarrhoea and dehydration.
- Understanding the etiology of acute watery and persistent diarrhoea for better management.
- Clinical trials including patients with acute watery (or persistent) diarrhoea to evaluate the effectiveness of antibiotics.
- Risk stratification and the value of antibiotics or other therapeutic agents.
- Identification of different pathogens in malnourished children in order to better target therapy for both pneumonia and diarrhoea.
- Studies on agents which are purely antibacterial.
- Duration of treatment with antibiotics.
- Studies in children from 5–9 years of age.
- Correlation between sensitivity patterns and treatment failure.
- Disease-specific patterns.
- Microbiological versus treatment failure.
- Perspectives on antimicrobial resistance.

### Zinc

- Improving the taste and quality of the zinc formulations provided by the pharmaceutical industry.
- Implementation research to improve the supply of and demand for zinc supplementation together with ORS for diarrhoea management.
- Phase IV trials to monitor adverse effects of zinc.
- Research on zinc gluconate and other salts.

### Probiotics

- Probiotics for treating persistent diarrhoea to confirm potential benefits.
- Implementation research on the viability and storage conditions for probiotics.
- Effectiveness of strains and dosages of probiotics in different settings.
- Gut microbiome make-up of people in different settings.
- Re-colonization of the gut flora by the probiotics.

### Enhanced care for high-mortality risk children

- Community-level studies comparing children who receive enhanced care to those who do not.
- Whether prematurity and low birth weight should be considered as risk factors, especially in the first 2 years of life.
- Management of diarrhoea in premature or low-birth-weight infants.
- Effectiveness of enhanced clinical care in improving diarrhoea outcomes (i.e. treatment success and mortality).
- Strategies for identifying children with risk factors, enhanced management strategies, and follow-up (risk stratification and differential care).

# Implementation of the guideline

### Implementation considerations

Specific implementation considerations, such as the need for training or equipment, relevant to subject areas around the recommendations were identified by the GDG. These include:

### Pneumonia

- Risk stratification (i.e. oxygen saturation, prematurity) and implementing better diagnostic measures (e.g. pulse oximetry) to assist in understanding which patients would most benefit from antibiotic treatment.
- Functional iCCM and IMCI incorporated into competent health systems in order to implement recommendations at the primary health care level.
- Education of caregivers on antibiotic use, adherence and monitoring.
- Training for health workers on antibiotic use and recognizing signs of respiratory distress.
- Increasing functionality and competency as well as capacity of the health care system (i.e. increasing the number of health workers).
- Government buy-in (including operational research to re-assure stakeholders and increase acceptability).
- Capacity-building for CHWs.
- A decision-support system to implement recommendations at different levels of care.
- A monitoring and evaluation plan.

### Diarrhoea

- Increasing the low uptake of LORS and zinc.
- A need for education of health workers and caregivers on LORS and zinc.

Since this is a global guideline, Member States may adapt the recommendations according to their setting and feasibility. WHO regional and country offices will assist with these processes. Engaging with multiple stakeholders and partners will be critical in strengthening implementation and sustaining progress. Working in collaboration with other sectors involved, where relevant, can help ensure a comprehensive, cross-sectoral and more sustainable approach.

Implementation of the new recommendations should be facilitated by their inclusion in other relevant WHO guidelines, training materials and other publications, such as the *Pocket book of hospital care for children*, as they are updated.

### Monitoring and evaluation of the quality and implementation of the guideline

Monitoring and evaluation should be built into implementation processes, in order to document important lessons for uptake, provide evidence for refining recommendations, and for broader implementation. WHO will aim to collaborate with national authorities to include questions about the new recommendations, and how health workers have experienced implementing these, into relevant routine national training assessments and supervision. Evaluations of the programmes that are expected to incorporate these recommendations, such as IMCI, will also be carried out.

## Supporting local adaptation

Local adaptation of the guideline will be supported through WHO country offices and ministries of health. Relevant national guidelines, such as for IMCI, that are likely to be affected by the recommendations should be specifically reviewed in order to ensure updated approaches can be adopted. National training courses and pre- and in-service training on pneumonia and diarrhoea should be reviewed for opportunities to update materials in a locally relevant way.

WHO, in collaboration with other partners, will support national and subnational working groups to adopt, adapt and implement the guideline.

## Dissemination

The recommendations will be disseminated through WHO regional and country offices, ministries of health, professional associations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. The recommendations will be available on the WHO website and also as a printed publication. Online versions will be available via the websites of the relevant WHO departments.

Technical meetings for IMCI and related programmes will be used by WHO and stakeholders to share the recommendations and derivative products.

Where appropriate, the executive summary and recommendations from this publication will be translated into relevant languages for dissemination through the WHO regional and country offices, and web versions of any translations will be available via the websites of the WHO departments, as above. In addition, a number of articles presenting the evidence, recommendations and key implementation considerations will be published, in compliance with WHO's open access and copyright policies. Relevant WHO departments will also be part of the dissemination process. This will include the development or revision of existing national policies, guidelines or protocols in line with the WHO recommendations, and tools to support the adaptation and implementation processes as well as technical support for local guideline implementers in the development of training materials and quality indicators.

## Updating the guideline

The WHO SG will continue to follow research developments in pneumonia and diarrhoea, particularly for questions in which the quality of evidence was found to be low or very low. If the guideline merits an update, or if there are concerns that one or more recommendations in the guideline may no longer be valid, WHO will coordinate a guideline update, following the formal procedures of the WHO *Handbook for guideline development (5)*.

As the guideline nears a five-year review period, WHO, along with partners, will be responsible for conducting a search for new evidence. WHO will welcome suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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# Annex 1.

## WHO guidelines and tools on management of pneumonia and diarrhoea in children

| WHO Guideline | Year | WHO department responsible |
|---|---|---|
| Diarrhoea treatment guidelines including new recommendations for the use of ORS and zinc supplementation for clinic-based healthcare workers | 2004 | MCA |
| Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae type 1 | 2004 | MCA |
| WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children | 2010 | MCA |
| Recommendations for the management of common childhood conditions: evidence for the technical update of pocketbook recommendations | 2012 | MCA |
| **Derivative documents** | **Year** | **WHO department** |
| The treatment of diarrhoea: a manual for physicians and other senior health workers | 2005 | MCA |
| Caring for newborns and children in the community: caring for the sick child | 2011 | MCA |
| Pocket book of hospital care for children: Second edition. Guidelines for the management of common childhood illnesses | 2013 | MCA |
| Ending preventable child deaths from pneumonia and diarrhoea by 2025: the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) | 2013 | MCA |
| Integrated management of childhood illness (IMCI) chart booklet | 2014 | MCA |
| Revised WHO classification and treatment of childhood pneumonia at health facilities – Evidence summaries | 2014 | MCA |

# Annex 2.

## Summary of declarations of conflicts of interest

| Name | Declared interest(s) | Management of conflict(s) of interest |
|---|---|---|
| **Ambrose Agweyu** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Narendra Arora** | None declared | Not applicable |
| **Lulu Bravo** | None declared | Not applicable |
| **Suzanne Farhoud** | None declared | Not applicable |
| **Olivier Fontaine** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Stephen Howie** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Fyezah Jehan** | None declared | Not applicable |
| **Kristina Keitel** | None declared | Not applicable |
| **Claudio Lanata** | None declared | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **You Li** | None declared | Not applicable |
| **Rakesh Lodha** | None declared | Not applicable |
| **Eric McCollum** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Harish Nair** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Mark Neuman** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Humphreys Nsona** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Kerry-Ann O'Grady** | None declared | Not applicable |
| **Archana Patel** | None declared | Not applicable |
| **Shamim Qazi** | None declared | Not applicable |
| **Zeba Rasmussen** | None declared | Not applicable |

| Name | Declared interest(s) | Management of conflict(s) of interest |
|---|---|---|
| **Salim Sadruddin** | None declared | Not applicable |
| **Mathuram Santosham** | None declared | Not applicable |
| **Anthony Scott** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Jonathon Simon** | Yes | The declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility |
| **Meseret Zelalem Tadesse** | None declared | Not applicable |
| **Robinson Wammanda** | None declared | Not applicable |
| **Heather Zar** | None declared | Not applicable |

# Annex 3.

## Evidence-to-decision framework questions

| Domain | Questions to be answered |
|---|---|
| **Priority** | Is the problem a priority? |
| **Test accuracy (for diagnostic tests)** | How accurate is the test? |
| **Desirable effects** | How substantial are the desirable anticipated effects? |
| **Undesirable effects** | How substantial are the undesirable anticipated effects? |
| **Certainty of the evidence of test accuracy (for diagnostic tests)** | What is the overall certainty of the evidence of test accuracy? |
| **Certainty of the evidence of test's effects (for diagnostic tests)** | What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test? |
| **Certainty of the evidence of management's effects (for diagnostic tests)** | What is the overall certainty of the evidence of effects of the management that is guided by the test results? |
| **Certainty of the evidence of test result/ management (for diagnostic tests)** | How certain is the link between test results and management decisions? |
| **Certainty of effects** | What is the overall certainty of the evidence of effects? |
| **Values** | Is there important uncertainty about or variability in how much people value the main outcomes? |
| **Balance of effects** | Does the balance between desirable and undesirable effects favour the intervention or the comparison? |
| **Resources required** | How large are the resource requirements (costs)? |
| **Certainty of evidence of required resources** | What is the certainty of the evidence of resource requirements (costs)? |
| **Cost-effectiveness** | Does the cost-effectiveness of the intervention favour the intervention or the comparison? |
| **Equity** | What would be the impact on health equity? |
| **Acceptability** | Is the intervention acceptable to key stakeholders? |
| **Feasibility** | Is the intervention feasible to implement? |

# Annex 4.
## PICO questions

### Pneumonia PICO 1

*Population* children aged 2–59 months of age with only fast breathing (no chest indrawing or no general danger sign[1])

*Intervention* oral amoxicillin

*Comparator* no antibiotics/placebo

*Outcomes*

- primary: clinical deterioration/treatment failure[2] (at day 4 and day 14)
- secondary: mortality, SAE, cost-effectiveness
- adverse events: nausea and mild vomiting, diarrhoea, rash, itching, tremors, mouth ulcer, severe diarrhoea for which IV hydration warranted, anaphylaxis, organ failure

### Pneumonia PICO 2a

*Population* children 2–59 months of age with chest-indrawing pneumonia (without any danger sign)

*Intervention* oral amoxicillin

*Comparator* injectable antibiotics

*Outcomes*

- primary: treatment failure/clinical deterioration at day 3, day 6, or day 14 (as defined by the study) or no resolution of chest indrawing; mortality; SAEs (death, rash, diarrhoea, allergy to study drug, discontinuation or change of study drug);
- cost-effectiveness.

### Pneumonia PICO 2b

*Population* children 2–59 months of age with chest-indrawing pneumonia (with or without fast breathing) and no general danger sign

*Intervention* community-based care (treatment with oral amoxicillin)

*Comparator* standard care

*Outcomes*

- primary: treatment failure/clinical deterioration at day 6 (as defined by the study); mortality at day 14; no resolution of chest-indrawing pneumonia as per WHO definition; need to add another antibiotic or change antibiotic;
- adverse events: SAEs (serious anaphylactic reaction, severe diarrhoea, generalized severe rash, events that required a change of therapy or discontinuation of therapy).

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[1] Child is not able to drink or breastfeed, or vomits everything, or has had convulsions, or is lethargic or unconscious, or stridor or hypoxaemia.

[2] Authors' definitions.

### Pneumonia PICO 3

*Population* children 2–59 months of age presenting with cough and/or difficult breathing at hospital level

*Intervention* LUS

*Purpose of the test* add-on test in pneumonia diagnostics

*Role of the test* diagnosis of pneumonia

*Linked treatments* antibiotic therapy

*Comparator* CXR or paediatric/physician adjudication panel

*Outcomes* pneumonia diagnosed at hospitals; pneumonia requiring treatment with antibiotics; clinical deterioration/treatment failure and mortality; mortality reduction, adverse effects reduction; initiation of antibiotic therapy

### Pneumonia PICO 4

*Population* children 2–59 months of age presenting with cough and/or difficult breathing at hospital level

*Intervention* digital auscultation or cough sound algorithms

*Purpose of the test* diagnosis of pneumonia

*Role of the test* add-in test of new technology

*Linked treatment* antibiotic therapy

*Comparator* not doing additional digital auscultation or cough sound analysis

*Outcomes* mortality reduction, cure, adverse event reduction

### Pneumonia PICO 5

*Population* children 2–59 months of age diagnosed with pneumonia (fast breathing and/or chest indrawing, without danger sign)

*Intervention* clinical signs and symptoms

*Purpose of the test* detection of hypoxaemia

*Role of the test* diagnosis

*Linked treatment* antibiotic therapy

*Outcomes* patient referral, mortality reduction

### Pneumonia PICO 6

*Population* children 2–59 months of age with fast breathing and/or chest-indrawing pneumonia (without general danger sign) with risk factors for mortality

*Intervention* outpatient-based care

*Comparator* standard or routine care

*Outcomes* treatment failure at day 14; mortality at day 14

### Pneumonia PICO 7

*Population* children 5–9 years of age presenting at a primary or community health facility

*Purpose of the test* diagnosis of pneumonia

*Role of the test* diagnosis

*Linked treatments* bronchodilators, antibiotics, additional assessment

*Intervention* clinical signs

*Comparator* CXR, LUS, paediatric adjudication panel

*Outcomes* diagnosis of pneumonia, pneumonia requiring treatment with antibiotics, clinical deterioration/ treatment failure/mortality reduction

### Pneumonia PICO 8

*Population* children 5–9 years of age with community-acquired pneumonia

*Intervention* any antibiotic (any route)

*Comparator* any antibiotic (any route)

*Outcomes* clinical cure at 10–17 days; treatment failure by day 14; average length of stay in hospital; re-admission rates; inpatient mortality; adverse reactions; adverse events; clinical deterioration, mortality, SAEs, cost-effectiveness

### Diarrhoea PICO 1

*Population* children up to 10 years of age with acute or persistent diarrhoea

*Intervention* antibiotic

*Comparator* no antibiotic (placebo)

*Outcomes* clinical cure/treatment failure, parasitological cure, mortality, duration of diarrhoea, IV fluid therapy, mortality

### Diarrhoea PICO 2

*Population* children up to 10 years of age with diarrhoea and blood in stool

*Intervention* antibiotics

*Comparator* no antibiotics

*Outcomes* clinical cure; treatment failure; mortality; duration of diarrhoea

### Diarrhoea PICO 3

*Population* children up to 10 years of age with acute watery or persistent diarrhoea

*Intervention* zinc treatment in any form (ORS/syrup/dispersible tablets, etc.)

*Comparator* no zinc treatment

*Outcomes* recovery; clinical deterioration/treatment failure; duration of diarrhoea (hours); mortality

### Diarrhoea PICO 4

*Population* children up to 10 years of age with acute watery or persistent diarrhoea

*Intervention* probiotics

*Comparator* no probiotics or placebo

*Outcomes* clinical cure; duration of diarrhoea; clinical deterioration; SAEs and adverse events; mortality

### Diarrhoea PICO 5

*Population* children up to 10 years of age with acute watery or persistent diarrhoea and dehydration

*Intervention* LORS (≤ 245 mmol/L)

*Comparator* standard ORS

*Outcomes* clinical cure/treatment failure, stool output, duration of diarrhoea, unscheduled IV fluid infusion; rehydration; ORS consumed (L)

### Diarrhoea PICO 6

*Population* children up to 10 years of age with acute watery or persistent diarrhoea and dehydration

*Intervention* any alternate care other than standard care or usual care

*Comparator* standard care or usual care

*Outcomes* clinical deterioration/treatment failure, mortality (up to 30 days), reinfection (up to 30 days), SAEs, cost-effectiveness

# Annex 5.

## GRADE tables

**Pneumonia PICO 1.** In children 2–59 months of age with only fast breathing, what is the effectiveness of oral amoxicillin compared to no antibiotic treatment in improving clinical outcomes at all levels of care?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral amoxicillin | No antibiotics | Relative (95% CI) | Absolute (95% CI) | | |
| **Treatment failure at day 4** | | | | | | | | | | | | |
| 4[1] | randomized trials | serious[a] | not serious | not serious | serious[b] | none | 288/3840 (7.5%) | 379/3840 (9.9%) | **RR 0.74** (0.53 to 1.02) | **26 fewer per 1000** (from 46 fewer to 2 more) | ⨁⨁◯◯ Low[a,b] | IMPORTANT |
| **Treatment failure at day 14** | | | | | | | | | | | | |
| 4[1] | randomized trials | serious[a] | not serious | not serious | not serious | none | 451/3840 (11.7%) | 536/3828 (14.0%) | **RR 0.84** (0.75 to 0.94) | **22 fewer per 1000** (from 35 fewer to 8 fewer) | ⨁⨁⨁◯ Moderate[a] | CRITICAL |
| **Adverse events** | | | | | | | | | | | | |
| 2[2] | randomized trials | serious[a] | not serious | not serious | serious[b] | none | 149/2567 (5.8%) | 160/2561 (6.2%) | **RR 0.93** (0.75 to 1.15) | **4 fewer per 1000** (from 16 fewer to 9 more) | ⨁⨁◯◯ Low[a,b] | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| 4[1] | randomized trials | serious[a] | not serious | not serious | serious[b] | none | 1/3840 (0.0%) | 1/3828 (0.0%) | **RR 1.00** (0.17 to 5.75) | **0 fewer per 1000** (from 0 fewer to 1 more) | ⨁⨁◯◯ Low[a,b] | CRITICAL |

[a] Downgraded one level as one study had high risk of bias.
[b] Downgraded one level due to a wide CI.
[1] Awasthi et al., PlosOne, 2008 ; Hazir et al., Clin Infect Dis, 2011; Ginsburg et al., JAMA Pediatrics, 2019; Jehan et al., NEJM, 2020.
[2] Ginsburg et al., JAMA Pediatrics, 2019; Jehan et al., NEJM, 2020.

**Pneumonia PICO 2a.** In children 2–59 months of age with chest indrawing (without any danger sign), what is the effectiveness of oral amoxicillin on an outpatient basis compared to inpatient injectable antibiotics treatment in improving clinical outcomes at all levels of care?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral amoxicillin | Injectable Antibiotics | Relative (95% CI) | Absolute (95% CI) | | |
| **Treatment failure at day 3** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious[b] | not serious | serious[c] | none | 234/2172 (10.8%) | 248/2157 (11.5%) | **RR 0.88** (0.62 to 1.24) | **14 fewer per 1000** (from 44 fewer to 28 more) | ⨁⨁◯◯ Low[a,b,c] | IMPORTANT |
| **Treatment failure at day 6** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | serious[c] | none | 304/2172 (14.0%) | 314/2156 (14.6%) | **RR 0.96** (0.83 to 1.11) | **6 fewer per 1000** (from 25 fewer to 16 more) | ⨁⨁◯◯ Low[a,c] | IMPORTANT |
| **Treatment failure at day 14** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | serious[c] | none | 376/2153 (17.5%) | 389/2143 (18.2%) | **RR 0.94** (0.79 to 1.13) | **11 fewer per 1000** (from 38 fewer to 24 more) | ⨁⨁◯◯ Low[a,c] | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | not serious | none | 4/2173 (0.2%) | 14/2156 (0.6%) | **RR 0.28** (0.09 to 0.86) | **5 fewer per 1000** (from 6 fewer to 1 fewer) | ⨁⨁⨁◯ Moderate[a] | CRITICAL |
| **SAEs** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | serious[c] | none | 3/2173 (0.1%) | 12/2156 (0.6%) | **RR 0.39** (0.12 to 1.26) | **3 fewer per 1000** (from 5 fewer to 1 more) | ⨁⨁◯◯ Low[a,c] | IMPORTANT |

a. Downgraded one level as three studies had some concerns in risk of bias assessment.
b. I-square value 59.45%; however, CIs overlap and interpretation is similar.
c. Downgraded one level due to a wide CI.
1 Addo Yobo et al., Lancet, 2004; Hazir et al., Lancet, 2008; Agweyu et al., Clin Infect Dis, 2014.

**Pneumonia PICO 2b.** In children 2–59 months of age with chest indrawing (with or without fast breathing) and no general danger sign, what is the effectiveness of management done by community-level health workers (using oral amoxicillin) compared to standard management in improving clinical outcomes at all levels of care?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Community-based care | Standard care | Relative (95% CI) | Absolute (95% CI) | | |
| **Treatment failure at day 14** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | serious[b] | not serious | not serious | none | 434/6279 (6.9%) | 587/5239 (11.2%) | **RR 0.66** (0.44 to 0.98) | **38 fewer per 1000** (from 63 fewer to 2 fewer) | ⨁⨁◯◯ Low[a,b] | IMPORTANT |
| **Mortality at day 14** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | serious[c] | none | 8/6279 (0.1%) | 8/5239 (0.2%) | **RR 0.85** (0.31 to 2.30) | **0 fewer per 1000** (from 1 fewer to 2 more) | ⨁⨁◯◯ Low[a,c] | CRITICAL |
| **SAEs** | | | | | | | | | | | | |
| 3[1] | randomized trials | serious[a] | not serious | not serious | serious[c] | none | 5/6279 (0.1%) | 3/5332 (0.1%) | **RR 1.20** (0.34 to 4.26) | **0 fewer per 1000** (from 0 fewer to 2 more) | ⨁⨁◯◯ Low[a,c] | IMPORTANT |

[a.] Downgraded two levels as three studies had some concerns in risk of bias assessment.
[b.] Downgraded one level as I square value 90.13% and p=<0.0001.
[c.] Downgraded one level due to a wide CI.
[1] Bari et al., Lancet, 2011; Soofi et al., Lancet, 2012; EMPIC, BMJ Global Health, 2021.

**Pneumonia PICO 3.** In children 2–59 months of age, what is the diagnostic accuracy of LUS compared to CXR or paediatric adjudication panel to identify pneumonia cases at the hospital level?

| Sensitivity | 0.88 (95% CI: 0.69 to 0.96) | | | | | | Effect per | 1000 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specificity | 0.82 (95% CI: 0.42 to 0.96) | | | | | | Prevalence | 10% | 20% | 30% | | |
| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1000 patients tested | | | Test accuracy CoE | Importance |
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pre-test probability of 10% | Pre-test probability of 20% | Pre-test probability of 30% | | |
| True positives (patients with pneumonia) | 6 studies 521 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[c] | serious[d] | None | 88 (69 to 96) | 176 (138 to 192) | 264 (207 to 288) | ⨁◯◯◯ Very low | CRITICAL |
| False negatives (patients incorrectly classified as not having pneumonia) | | | | | | | | 12 (4 to 31) | 24 (8 to 62) | 36 (12 to 93) | | CRITICAL |
| True negatives (patients without pneumonia) | 6 studies 802 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[e] | very serious[f] | None | 738 (378 to 864) | 656 (336 to 768) | 574 (294 to 672) | ⨁◯◯◯ Very low | CRITICAL |
| False positives (patients incorrectly classified as having pneumonia) | | | | | | | | 162 (36 to 522) | 144 (32 to 464) | 126 (28 to 406) | | CRITICAL |

[a] Ellington et al., Respir Med, 2017; Yadav et al., Indian J Pediatr, 2017; Ginsburg et al., Pediatr Pulmonol, 2021; Amatya et al., Int J Emerg Med, 2023; Buz Yaşar et al., Ultrasound Q, 2023; Venkatakrishna et al., Pediatr Radiol, 2024.

[b] Downgraded because of risk of bias due to patient selection and other issues.

[c] Sensitivity estimates across studies vary from 47% to 99%. I-square value is 90% which indicates a high level of heterogeneity among studies.

[d] Wide CI for pooled sensitivity ranges between 69% to 96%.

[e] Specificity estimates across studies range from 59% to 100%. I-square value is 91% which indicates high level of heterogeneity among studies.

[f] Wide CI for pooled specificity ranges between 42%-96%.

**Pneumonia PICO 4.** In children 2–59 months of age, should digital auscultation or cough sound algorithms be used as an add-on test to improve the assessment of pneumonia at the hospital level, compared to a CXR or paediatric adjudication panel?

A. Digital auscultation (meta-analysis was not performed)

B. Cough sound algorithm

| Sensitivity | 0.82 (95% CI: 0.61 to 0.93) | | | | | | Effect per | 1000 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specificity | 0.77 (95% CI: 0.60 to 0.88) | | | | | | Prevalence | 10% | 20% | 30% | | |
| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1000 patients tested | | | Test accuracy CoE | Importance |
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pre-test probability of 10% | Pre-test probability of 20% | Pre-test probability of 30% | | |
| True positives (patients with pneumonia) | 3 studies 177 patients[a] | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious[b,c] | very serious[d] | None | 82 (61 to 93) | 164 (122 to 186) | 246 (183 to 279) | ⨁◯◯◯ Very low | CRITICAL |
| False negatives (patients incorrectly classified as not having pneumonia) | | | | | | | | 18 (7 to 39) | 36 (14 to 78) | 54 (21 to 117) | | CRITICAL |
| True negatives (patients without pneumonia) | 3 studies 1667 patients[e] | cross-sectional (cohort type accuracy study) | not serious | not serious | very serious[b,c] | serious[d] | None | 693 (540 to 792) | 616 (480 to 704) | 539 (420 to 616) | ⨁◯◯◯ Very low | CRITICAL |
| False positives (patients incorrectly classified as having pneumonia) | | | | | | | | 207 (108 to 360) | 184 (96 to 320) | 161 (84 to 280) | | CRITICAL |

[a] Kosasih et al., IEEE Trans Biomed Eng, 2015; Porter et al., Respir Res, 2019 ; Moschovis et al., Contemp Clin Trials, 2021.

[b] Inconsistency: the largest study (Moschovis et al., n=1250) had a lower sensitivity (63%) and specificity (62%) than the other two studies (Porter et al., 2019, n= 569, sensitivity = 86.7%, specificity= 85.1%; Kosasih et al., 2015, n= 25, sensitivity = 94.1%, specificity = 87.5%).

[c] Method heterogeneity reference diagnostics – not uniform across studies. Index test – different cough sound algorithms used in each study. Cough sound extraction method was manual (Kosasih et al., 2015) and two different automated methods (Moschovis et al., 2021; Porter et al., 2019)

[d] Imprecision: CIs range from 61.4% to 92.9% for sensitivity and from 60.3% to 88.4% for specificity. This is likely due to the study by Kosasih et al., 2015, where the CI is very wide (sensitivity 71.3%–99.9% and specificity 44.3%–99.7%). The sample size for this study was 25.

[e] Porter et al., Respir Res, 2019; Kosasih et al., IEEE Trans Biomed Eng, 2015; Moschovis et al., Contemp Clin Trials, 2021.

**Pneumonia PICO 5.** In children 2–59 months of age, what is the diagnostic accuracy of additional signs of respiratory distress (grunting, nasal flaring, head nodding, decreased breath sounds), alone or in combination with fast breathing and/or chest indrawing, compared to pulse oximetry measurements to identify hypoxaemic pneumonia cases at all levels of care?

A. Nasal flaring as a predictor of hypoxemia

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sensitivity** | **0.67 (95% CI: 0.54 to 0.77)** | | | | | | **Effect per** | **1000** | | | | |
| **Specificity** | **0.67 (95% CI: 0.50 to 0.81)** | | | | | | **Prevalence** | **3%** | **5%** | **10%** | | |
| **Outcome** | **№ of studies (№ of patients)** | **Study design** | **Factors that may decrease certainty of evidence** | | | | | **Effect per 1000 patients tested** | | | **Test accuracy CoE** | **Importance** |
| | | | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Publication bias** | **Pre-test probability of 3%** | **Pre-test probability of 5%** | **Pre-test probability of 10%** | | |
| True positives (patients with pneumonia) | 7 studies 588 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[c] | very serious[d] | none | 20 (16 to 23) | 33 (27 to 39) | 67 (54 to 77) | ⨁◯◯◯ Very low | CRITICAL |
| False negatives (patients incorrectly classified as not having pneumonia) | | | | | | | | 10 (7 to 14) | 17 (11 to 23) | 33 (23 to 46) | | CRITICAL |
| True negatives (patients without pneumonia) | 7 studies 1175 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[c] | very serious[e] | none | 654 (481 to 789) | 640 (471 to 772) | 607 (446 to 732) | ⨁◯◯◯ Very low | CRITICAL |
| False positives (patients incorrectly classified as having pneumonia) | | | | | | | | 316 (181 to 489) | 310 (178 to 479) | 293 (168 to 454) | | CRITICAL |

[a] Lamen et al., Ann Trop Paediatr, 2005; Basnet et al., Indian J Pediatr, 2006 ; Supartha et al., Paediatrica Indonesiana, 2010; Bassat et al., Trop Med Int Health, 2016; Alwadhi et al., Indian Pediatr, 2017; Kushwah et al., Int J Contemp Pediatr, 2018; Odeyemi et al., Res J Health Sci, 2020.

[b] Risk of bias very serious because of issues around patient selection, index and references tests, and time and flow.

[c] I-square is more than 80% for sensitivity as well as specificity which suggests serious heterogeneity/inconsistency across studies. More importantly, studies vary in design issues.

[d] CI for pooled sensitivity estimates ranges from 54.3% to 77.4%.

[e] CI for pooled specificity estimates ranges from 49% to 81%.

B. Head nodding as a predictor of hypoxaemia

| Sensitivity | 0.19 (95% CI: 0.09 to 0.36) | | | | | | Effect per | 1000 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specificity | 0.97 (95% CI: 0.93 to 0.98) | | | | | | Prevalence | 10% | 20% | 30% | | |
| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1000 patients tested | | | Test accuracy CoE | Importance |
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pre-test probability of 10% | Pre-test probability of 20% | Pre-test probability of 30% | | |
| True positives (patients with pneumonia) | 6 studies 381 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[c] | very serious[d] | none | 6 (3 to 11) | 9 (4 to 18) | 19 (9 to 36) | ⨁◯◯◯ Very low | CRITICAL |
| False negatives (patients incorrectly classified as not having pneumonia) | | | | | | | | 24 (19 to 27) | 41 (32 to 46) | 81 (64 to 91) | | CRITICAL |
| True negatives (patients without pneumonia) | 6 studies 827 patients[a] | cross-sectional (cohort type accuracy study) | very serious[b] | not serious | very serious[c] | not serious | none | 938 (898 to 955) | 919 (880 to 936) | 870 (833 to 887) | ⨁◯◯◯ Very low | CRITICAL |
| False positives (patients incorrectly classified as having pneumonia) | | | | | | | | 32 (15 to 72) | 31 (14 to 70) | 30 (13 to 67) | | CRITICAL |

[a] Lamen et al., Ann Trop Paediatr, 2005; Supartha et al., Paediatrica Indonesiana, 2010; Kuti et al., S Afr J Child Health, 2014; Alwadhi et al., Indian Pediatr, 2017; Kushwah et al., Int J Contemp Pediatr, 2018; Odeyemi et al., Res J Health Sci, 2020.

[b] Spectrum bias, blinding was absent in most of the studies.

[c] I-square is more than 80% for sensitivity as well as specificity which suggests serious heterogeneity/inconsistency across studies. More importantly, studies vary in design issues.

[d] CI for pooled sensitivity estimates ranges from 8.7% to 36%.

**Pneumonia PICO 6.** In children 2–59 months of age with fast breathing and/or chest indrawing, what are the risk factors for mortality (such as nutritional status, HIV status, pallor, pulse oximetry measurements), and what is the effectiveness of enhanced care (such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment) compared to the usual care in improving clinical outcomes at all levels of care?

No GRADE tables prepared.

**Pneumonia PICO 7.** In children 5–9 years of age, what are the best clinical signs to identify community-acquired pneumonia cases?

Cough as best clinical sign to identify pneumonia

| Sensitivity | 0.88 (95% CI: 0.79 to 0.93) | | | | | | Effect per | 1000 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specificity | 0.11 (95% CI: 0.05 to 0.24) | | | | | | Prevalence | 10% | 20% | 30% | | |
| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1000 patients tested | | | Test accuracy CoE | Importance |
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pre-test probability of 10% | Pre-test probability of 20% | Pre-test probability of 30% | | |
| True positives (patients with pneumonia) | 4 studies 571 patients[a] | cross-sectional (cohort type accuracy study) | serious[b] | not serious | very serious[c] | not serious | none | 88 (79 to 93) | 175 (157 to 187) | 263 (236 to 280) | ⨁◯◯◯ Very low | CRITICAL |
| False negatives (patients incorrectly classified as not having pneumonia) | | | | | | | | 12 (7 to 21) | 25 (13 to 43) | 37 (20 to 64) | | CRITICAL |
| True negatives (patients without pneumonia) | 4 studies 784 patients[a] | cross-sectional (cohort type accuracy study) | serious[b] | not serious | very serious[c] | not serious | none | 100 (43 to 212) | 89 (38 to 189) | 78 (34 to 165) | ⨁◯◯◯ Very low | IMPORTANT |
| False positives (patients incorrectly classified as having pneumonia) | | | | | | | | 800 (688 to 857) | 711 (611 to 762) | 622 (535 to 666) | | IMPORTANT |

[a] Bilkis et al., Pediatr Emerg Care, 2010; Neuman et al., Pediatrics, 2011; Ayalon et al., Pediatr Emerg Care, 2013; Berg et al., Eur J Pediatr, 2017.

[b] Risk of bias – studies represent a broad age from 0-18 years and disaggregated data were not available (Ayalon et al., 2013; Berg et al., 2017). Results are highly contaminated with under-5 population. Reference diagnostic test is not uniform across studies.

[c] Inconsistency – serious as reference diagnostic test is not uniform across studies. I- square is 80% for sensitivity and 95% for specificity estimates.

**Pneumonia PICO 8.** In children 5–9 years of age with suspected community-acquired pneumonia, which antibiotic has the highest effectiveness in improving clinical outcomes?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Any antibiotics (any route) | Any antibiotics (any route) | Relative (95% CI) | Absolute (95% CI) | | |
| **Clinical cure at 10–17 days** | | | | | | | | | | | | |
| 1[1] | randomized trials | not serious | not serious | very serious[a] | serious[a] | none | Clinical cure rates (sample size 353 [265/88]): 96.5% in the levofloxacin group vs 97.1% in the comparator group* | | | | ⨁◯◯◯ Very low[a] | CRITICAL |
| **Treatment failure by day 14** | | | | | | | | | | | | |
| 2[2] | non-randomized studies | serious[b] | not serious | very serious[a] | not serious | none | Study 1 – macrolide monotherapy vs. beta-lactam monotherapy: OR: 0.48 (95% CI 0.22, 1.01)<br>Study 2 – combination vs. monotherapy: AOR: 0.51; (95%CI: 0.28, 0.95). | | | | ⨁◯◯◯ Very low[a,b] | CRITICAL |
| **Readmission rates** | | | | | | | | | | | | |
| 1[3] | non-randomized studies | serious[b] | very serious[c] | not serious | serious[c] | none | Monotherapy: 12/2584 (0.5%) and combination: 11/2419 (0.6%); (**RR**: 1.02; [95% CI 0.45, 2.31];<br>**Absolute values**: 0 fewer per 1000, from 3 fewer to 6 more) | | | | ⨁◯◯◯ Very low[b,c] | CRITICAL |
| **Inpatient mortality** | | | | | | | | | | | | |
| 1[4] | non-randomized studies | serious[b] | very serious[c] | very serious[a] | serious[c] | none | Monotherapy: 0/2584 and combination: 1/2419 (0.04%), (**RR**: 0.31; [95% CI 0.01, 7.66];<br>**Absolute values**: 0 fewer per 1000, from 0 fewer to 3 more) | | | | ⨁◯◯◯ Very low[a,b,c] | CRITICAL |
| **Adverse reactions** | | | | | | | | | | | | |
| 1[5] | randomized trials | not serious | not serious | very serious[a] | serious[a] | none | 2/30 patients (40%) in the ceftaroline fosamil group and 8/10 (80%) in the comparator group (Ceftriaxone IV) | | | | ⨁◯◯◯ Very low[a] | IMPORTANT |

a. Study population has wide age range and sample size does not meet optimal information size.
b. Study design, observational.
c. Wide CI crossing the null.
1 Bradley et al., Pediatr Infect Dis J, 2007.
2 Ambroggio et al., Pediatr Infect Dis J, 2015; Ambroggio et al., J Pediatr, 2016.
3 Ambroggio et al., J Pediatr, 2012.
4 Leyenaar_et al., Pediatr Infect Dis J, 2014.
5 Blumer et al., Pediatr Infect Dis J, 2016.

**Diarrhoea PICO 1.** In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of any antibiotic compared to no antibiotic treatment in improving clinical outcomes?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | antibiotic | no antibiotic | Relative (95% CI) | Absolute (95% CI) | | |
| **Clinical cure by day 7** | | | | | | | | | | | | |
| 2[1] | randomized trials | not serious | not serious | not serious[a] | very serious[b] | none | 37/41 (90.2%) | 15/38 (39.5%) | **RR 2.28** (1.52 to 3.41) | **505 more per 1000** (from 205 more to 951 more) | ⨁⨁◯◯ Low[a,b] | CRITICAL |
| **Duration of diarrhoea (In hours)** | | | | | | | | | | | | |
| 2[2] | randomized trials | not serious | not serious | serious[a] | serious[b] | none | 43 | 45 | – | MD **24.9 hours lower** (34.09 lower to 15.71 lower) | ⨁⨁◯◯ Low[c,d] | CRITICAL |
| **Mortality (all cause)** | | | | | | | | | | | | |
| 1[3] | randomized trials | not serious | not serious | serious[c] | serious[b] | none | 20/4133 (0.5%) | 28/4135 (0.7%) | **RR 0.71** (0.40 to 1.27) | **2 fewer per 1000** (from 4 fewer to 2 more) | ⨁⨁◯◯ Low[c,d] | CRITICAL |
| **IV fluid therapy** | | | | | | | | | | | | |
| 1[4] | randomized trials | not serious | not serious | serious[a] | very serious[b] | none | 1/25 (4.0%) | 2/25 (8.0%) | **RR 0.50** (0.05 to 5.17) | **40 fewer per 1000** (from 76 fewer to 334 more) | ⨁◯◯◯ Very low[a,b] | IMPORTANT |
| **Parasitological cure** | | | | | | | | | | | | |
| 2[1] | randomized trials | not serious | not serious | serious[a] | very serious[b] | none | 34/41 (82.9%) | 11/39 (28.2%) | **RR 2.86** (1.72 to 4.74) | **525 more per 1000** (from 203 more to 1000 more) | ⨁◯◯◯ Very low[a,d] | IMPORTANT |

[a] Trials conducted in populations with confirmed parasitic disease and overestimates the baseline risk.
[b] Small sample size, wide CI.
[c] Trial has underlying population of children with watery stool with either dehydration or malnutrition and thought to overestimate a mortality benefit.
[d] CI crosses null value.
[1] Rossignol et al., J Infect Dis, 2001; Rossignol et al., Trans R Soc Trop Med Hyg, 2007.
[2] Mahapatro et al., J Trop Med, 2017; Rossignol et al., Lancet, 2006.
[3] Ahmed et al., JAMA Netw Open, 2021.
[4] Mahapatro et al., J Trop Med, 2017.

**Diarrhoea PICO 2.** In children up to 10 years of age with diarrhoea and blood in stools, what is the effectiveness of any antibiotic compared to no antibiotic treatment in improving clinical outcomes?

No GRADE tables as not relevant.

**Diarrhoea PICO 3.** In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of oral zinc compared to no oral zinc treatment in improving clinical outcomes? If effective, what is the optimum dose, duration and formulation?

3a. Effectiveness of oral zinc compared to no oral zinc treatment for acute watery diarrhoea

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | zinc | no zinc | Relative (95% CI) | Absolute (95% CI) | | |
| **Recovery at last followup** | | | | | | | | | | | | |
| 18[1] | randomized trials | not serious[a] | serious[b] | not serious | not serious | none[c] | 3001/3542 (84.7%) | 2885/3578 (80.6%) | **RR 1.07** (1.03 to 1.10) | **56 more per 1000** (from 24 more to 81 more) | ⨁⨁⨁◯ Moderate[a,b,c] | CRITICAL |
| **Duration of diarrhoea (hours)** | | | | | | | | | | | | |
| 20[2] | randomized trials | not serious[d] | serious[e] | not serious | not serious | none | 3381 | 2868 | – | MD **13.27 hrs lower** (17.66 lower to 8.89 lower) | ⨁⨁⨁◯ Moderate[d,e] | IMPORTANT |
| **Vomiting** | | | | | | | | | | | | |
| 11[3] | randomized trials | not serious[f] | serious[g] | not serious | not serious | none | 783/3500 (22.4%) | 546/3543 (15.4%) | **RR 1.46** (1.22 to 1.76) | **71 more per 1000** (from 34 more to 117 more) | ⨁⨁⨁◯ Moderate[f,g] | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 4[4] | randomized trials | not serious[h] | not serious | not serious | serious[i] | none | 2/1139 (0.2%) | 2/970 (0.2%) | **RR 0.71** (0.10 to 4.88) | **1 fewer per 1000** (from 2 fewer to 8 more) | ⨁⨁⨁◯ Moderate[h,i] | CRITICAL |

[a] High risk of bias in some domains for four studies; however, all reported estimates including the null/no meaningful difference.
[b] p value <0.0001 and I-square 66%.
[c] Some asymmetrical funnel plot; however, larger studies and studies with lower risk of bias concerns still report benefit.
[d] Six studies at high risk of bias, all others with some concerns except two at low risk of bias; however, sensitivity analysis of risk of bias removing studies with serious concerns does not change the effect estimate substantially.
[e] p<0.00001, I-square 89%.
[f] Despite high risk risk of bias assessment in three studies and some concerns in five others; sensitivity analysis excluding studies at high risk of bias are robust.

[g] I-square value is 69%. Subgroup analyses of dose (increased dose leading to increased vomiting) and definition of diarrhoea contribute statistical heterogeneity.
[h] Two high risk studies and two with some concerns; however, only one study contributes to the analysis and is consistent with the study without risk of bias concerns.
[i] CI crossing null value.
[1] Awasthi et al., J Pediatr Gastroenterol Nutr, 2008; Bahl et al., J Pediatr, 2002; Bhatnagar et al., J Pediatr Gastroenterol Nutr, 2002; Crisinel et al., Eur J Pediatr, 2015; Dutta et al., J Trop Peds, 2000; Dutta et al., J Pediatr, 2011; Fischer Walker et al., J Pediatr Gastroenterol Nutr, 2006; Gregorio et al., J Clin Epidemiol, 2007; Kakar et al., Pakistan J Med Health Sci, 2022; Patel et al., BMC Med, 2009; Patel et al., Drugs & Therapy Pers, 2015; Patro et al., J Peds, 2010; Polat et al., Pediatr Int, 2003; Rerksuppaphol et al., Paediatr Int Child Health, 2020; Shah et al., Pakistan J Med Health Sci, 2021; Shimelis et al., Ethiopian J Health Sci, 2008; Strand et al., Pediatrics, 2002; Yazar et al., Turk J Gastroenterol, 2016.
[2] Al Sonboli et al., Ann Trop Paediatr, 2003; Bahl et al., J Pediatr, 2002; Bhatnagar et al., J Pediatr Gastroenterol Nutr, 2004; Boran et al., Arch Dis Child, 2005; Brooks et al., Am J Clin Nutr, 2005; Crisinel et al., Eur J Pediatr, 2015; Dalgic et al., Pediatr Int, 2011; Dutta et al., J Trop Peds, 2000; Dutta et al., J Pediatr, 2011; Fischer Walker et al., J Pediatr Gastroenterol Nutr, 2006; Fischer Walker et al., J Health Popul Nutr, 2008; Gregorio et al., J Clin Epidemiol, 2007; Kakar et al., Pakistan J Med Health Sci, 2022; Patel et al., BMC Med, 2009; Patro et al., J Peds, 2010; Polat et al., Pediatr Int, 2003; Rerksuppaphol et al., Paediatr Int Child Health, 2020; Roy et al., BMJ, 2008; Yalcin et al., J Pak Med Assoc, 2022; Yazar et al., Turk J Gastroenterol, 2016.
[3] Awasthi et al., J Pediatr Gastroenterol Nutr, 2006; Bahl et al., J Pediatr, 2002; Bhatnagar et al., J Pediatr Gastroenterol Nutr, 2004; Brooks et al., Am J Clin Nutr, 2005; Crisinel et al., Eur J Pediatr, 2015; Fischer Walker et al., J Pediatr Gastroenterol Nutr, 2006; Larson et al., J Health Popul Nutr, 2005; Polat et al., Pediatr Int, 2003; Shimelis et al., Ethiopian J Health Sci, 2008; Strand et al., Pediatrics, 2002; Wadhwa et al., J Pediatr Gastroenterol Nutr, 2011.
[4] Brooks et al., Am J Clin Nutr, 2005; Fischer Walker et al., J Pediatr Gastroenterol Nutr, 2006; Patel et al., BMC Med, 2009; Shimelis et al., Ethiopian J Health Sci, 2008.

3b. Effectiveness of oral zinc compared to no oral zinc treatment for persistent diarrhoea

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | zinc | no zinc | Relative (95% CI) | Absolute (95% CI) | | |
| **Recovery at last follow-up (range: 5–7 days)** | | | | | | | | | | | | |
| 2[1] | randomized trials | serious[a] | not serious | not serious | serious[b] | none | 49/55 (89.1%) | 29/57 (50.9%) | **RR 1.75** (1.34 to 2.30) | **382 more per 1000** (from 173 more to 661 more) | ⨁⨁◯◯ Low[a,b] | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| 2[2] | randomized trials | not serious[c] | not serious | not serious | serious[b] | none | 6/102 (5.9%) | 7/100 (7.0%) | **RR 0.84** (0.29 to 2.37) | **11 fewer per 1000** (from 50 fewer to 96 more) | ⨁⨁⨁◯ Moderate[b,c] | CRITICAL |
| **Duration of diarrhea (hours)** | | | | | | | | | | | | |
| 2[2] | randomized trials | serious[c] | serious[d] | not serious | serious[b] | none | 122 | 120 | – | MD **26.29 hours lower** (47.35 lower to 5.23 lower) | ⨁◯◯◯ Very low[b,c,d] | IMPORTANT |

[a] One study had high risk of bias.
[b] Small sample size.
[c] studies included had some concerns.
[d] Heterogeneity p value = 0.004 and I-square 88%.
[1] Khatun et al., Acta Pediatrica, 2001; Wang et al., J Clin Bio Nutr, 2016.
[2] Khatun et al., Acta Pediatrica, 2001; Roy et al., J Health Popul Nutr, 2007.

3c. Optimum dose of zinc for acute watery/persistent diarrhoea

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5 mg zinc | 20 mg zinc | Relative (95% CI) | Absolute (95% CI) | | |
| **Diarrhoea after 5 days** | | | | | | | | | | | | |
| 1[1] | randomized trials | not serious | not serious | not serious | very serious[a] | none | 106/1480 (7.2%) | 96/1479 (6.5%) | **RR 1.10** (0.85 to 1.44) | **7 more per 1000** (from 11 fewer to 25 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Vomiting** | | | | | | | | | | | | |
| 1[1] | randomized trials | not serious | not serious | not serious | serious[b] | none | 206/1504 (13.7%) | 289/1498 (19.3%) | **RR 0.71** (0.59 to 0.86) | **56 fewer per 1000** (from 82 fewer to 30 fewer) | ⨁⨁⨁◯ Moderate | CRITICAL |

[a] Data from only one study included, and estimate is statistically non-significant.
[b] Data from only one study included.
[1] Dhingra et al., New Engl J Med, 2020.

**Diarrhoea PICO 4.** In children up to 10 years of age with acute watery or persistent diarrhoea, what is the effectiveness of probiotics treatment compared to no probiotics treatment in improving clinical outcomes? If effective, what is the optimum dose, duration and formulation?

4a. Effectiveness of probiotics treatment compared to no probiotics treatment for acute watery diarrhoea

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Probiotics | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Clinical cure (<3 stools in 24 hours) – acute watery diarrhoea** | | | | | | | | | | | | |
| 5[1] | randomized trials | not serious | serious[a] | not serious | serious[b] | none | 555/604 (91.9%) | 495/603 (82.1%) | **RR 1.23** (1.01 to 1.49) | **189 more per 1000** (from 8 more to 402 more) | ⨁⨁◯◯ Low[a,b] | CRITICAL |
| **Mortality – acute watery diarrhoea** | | | | | | | | | | | | |
| 4[2] | randomized trials | not serious | not serious | not serious | very serious[b] | none | 1/781 (0.1%) | 7/594 (1.2%) | **RR 0.17** (0.03 to 0.98) | **10 fewer per 1000** (from 11 fewer to 0 fewer) | ⨁⨁◯◯ Low[b] | CRITICAL |
| **Duration of diarrhoea (hours) – acute watery diarrhoea** | | | | | | | | | | | | |
| 11[3] | randomized trials | not serious | serious[c] | not serious | serious[d] | none | 1827 | 1833 | – | MD **7.2 hours lower** (13.36 lower to 1.03 lower) | ⨁⨁◯◯ Low[c,d] | CRITICAL |
| **Clinical deterioration (including IV fluid use, hospitalizations, worsening of symptoms) – acute watery diarrhoea** | | | | | | | | | | | | |
| 6[4] | randomized trials | not serious | not serious | not serious | very serious[b] | none | 72/1309 (5.5%) | 63/1317 (4.8%) | **RR 1.16** (0.83 to 1.60) | **8 more per 1000** (from 8 fewer to 29 more) | ⨁⨁◯◯ Low[b] | IMPORTANT |
| **SAEs – acute watery diarrhoea** | | | | | | | | | | | | |
| 6[5] | randomized trials | not serious | not serious | not serious | very serious[e] | none | 12/1266 (0.9%) | 16/1274 (1.3%) | **RR 0.81** (0.23 to 2.81) | **2 fewer per 1000** (from 10 fewer to 23 more) | ⨁⨁◯◯ Low[e] | CRITICAL |

[a] I-square = 96%.
[b] CIs include the null effect.
[c] I-square = 81%.
[d] If 12 hours is considered clinically important, the 95% CI crosses a decision-making threshold.
[e] CI includes the null value.
[1] Correa et al., J Pediatr Gastroenterol Nutr, 2011; Henker et al., Eur J Pediatr, 2007; Henker et al., Pediatr Infect Dis J, 2008; Hong et al., Pediatr Infect Dis J, 2018; Lahiri et al., Trop Dis Travel Med Vaccines, 2022.
[2] Basu et al., J Clin Gastroenterol, 2009; Lahiri et al., Trop Dis Travel Med Vaccines,2022; Pernica et al., PLoS One, 2017; Pernica et al., BMJ Glob Health, 2022.

[3] Basu et al., J Paediatr Child Health, 2007b; Chen et al., Pediatr Infect Dis J, 2010; Dhongade et al., Ped Infect Dis, 2022; Freedman et al., Clin Pediatr (Phila), 2015; Freedman et al., N Engl J Med, 2018; Hong et al., Pediatr Infect Dis J, 2018; Maugo et al., East African Medical Journal, 2021; Misra et al., J Pediatr, 2009; Salazar-Lindo et al., J Pediatr Gastroenterol Nutr, 2007; Schnadower et al., N Engl J Med, 2018; Sudha et al., Benef Microbes, 2019.

[4] Freedman et al., Clin Pediatr (Phila), 2015; Freedman et al., N Engl J Med, 2018; Lahiri et al., Trop Dis Travel Med Vaccines, 2022; Mourey et al., Pediatr Infect Dis J, 2020; Salazar-Lindo et al., J Pediatr Gastroenterol Nutr, 2004; Schnadower et al., N Engl J Med, 2018.

[5] Freedman et al., Clin Pediatr (Phila), 2015; Freedman et al., N Engl J Med, 2018; Lahiri et al., Trop Dis Travel Med Vaccines, 2022; Pernica et al., PLoS One, 2017; Schnadower et al., N Engl J Med, 2018; Sindhu et al., Clin Infect Dis, 2014.

## 4b. Effectiveness of probiotics treatment compared to no probiotics treatment for persistent diarrhoea

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Probiotics | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Duration of diarrhoea (hours) – persistent diarrhoea** | | | | | | | | | | | | |
| 2[1] | randomized trials | serious | not serious | serious[a] | serious[b] | none | 177 | 147 | – | MD **96.45 hours lower** (110.53 lower to 82.37 lower) | ⨁◯◯◯ Very low[a,b] | CRITICAL |

[a] Different definitions of the outcome are used.

[b] Small sample size not meeting optimal information size.

[1] Basu et al., J Clin Gastroenterol, 2007a; Gaon et al., Medicina (B Aires), 2003.

**Diarrhoea PICO 5.** In children up to 10 years of age with acute watery diarrhoea and dehydration, what is the effectiveness of LORS compared to standard ORS in improving clinical outcomes?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | LORS | standard ORS | Relative (95% CI) | Absolute (95% CI) | | |
| **Patients cured (number of patients cured/had resolution of diarrhoea at day 5)** | | | | | | | | | | | | |
| 2[1] | randomized trials | not serious | not serious[a] | not serious | very serious[b] | none | 71/105 (67.6%) | 76/103 (73.8%) | **RR 0.95** (0.61 to 1.49) | **37 fewer per 1000** (from 288 fewer to 362 more) | ⨁⨁◯◯ Low[a,b] | IMPORTANT |
| **Treatment failure (persistence of clinical signs of dehydration for more than 12 hours after rehydration had been initiated)** | | | | | | | | | | | | |
| 1[2] | randomized trials | not serious | not serious | not serious | very serious[c] | none | 1/94 (1.1%) | 8/96 (8.3%) | **RR 0.13** (0.02 to 1.00) | **73 fewer per 1000** (from 82 fewer to 0 fewer) | ⨁⨁◯◯ Low[c] | CRITICAL |
| **Duration of diarrhoea (hours)** | | | | | | | | | | | | |
| 6[3] | randomized trials | not serious[d] | serious[a] | not serious | not serious | none | 784 | 765 | – | MD **0.29 hours lower** (0.42 lower to 0.16 lower) | ⨁⨁⨁◯ Moderate[a,d] | CRITICAL |
| **Stool output at last follow-up (g/kg)** | | | | | | | | | | | | |
| 4[4] | randomized trials | not serious | not serious | not serious | serious[e] | none | 667 | 655 | – | MD **0.24 g/kg lower** (0.37 lower to 0.1 lower) | ⨁⨁⨁◯ Moderate[e] | CRITICAL |
| **Stool output (g/kg)** | | | | | | | | | | | | |
| 6[5] | randomized trials | serious[f] | very serious[a] | not serious | not serious | none | 773 | 759 | – | MD **0.25 g/kg lower** (0.35 lower to 0.16 lower) | ⨁◯◯◯ Very low[a,f] | IMPORTANT |
| **Stool output at rehydration phase (g/kg)** | | | | | | | | | | | | |
| 1[6] | randomized trials | not serious | not serious | not serious | serious[g] | none | 94 | 96 | – | MD **0.31 g/kg lower** (0.35 lower to 0.27 lower) | ⨁⨁⨁◯ Moderate[g] | CRITICAL |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | LORS | standard ORS | Relative (95% CI) | Absolute (95% CI) | | |
| **Stool output at 24 hours (g/kg)** | | | | | | | | | | | | |
| 6[3] | randomized trials | serious[f] | serious[h] | not serious | serious[e] | none | 773 | 759 | – | MD **0.23 g/kg lower** (0.3 lower to 0.16 lower) | ⨁◯◯◯ Very low[e,f,h] | IMPORTANT |
| **Stool output at 72 hours (g/kg)** | | | | | | | | | | | | |
| 1[7] | randomized trials | not serious | not serious | not serious | very serious[g] | none | 32 | 32 | – | MD **1.33 g/kg lower** (1.63 lower to 1.03 lower) | ⨁⨁◯◯ Low[g] | IMPORTANT |
| **Frequency of unscheduled IV therapy** | | | | | | | | | | | | |
| 3[8] | randomized trials | serious[i] | not serious | not serious | serious[b] | none | 75/635 (11.8%) | 96/623 (15.4%) | **RR 0.77** (0.58 to 1.02) | **35 fewer per 1000** (from 65 fewer to 3 more) | ⨁⨁◯◯ Low[b,i] | IMPORTANT |
| **ORS intake (ml/kg)** | | | | | | | | | | | | |
| 6[9] | randomized trials | serious[j] | not serious[a] | not serious | not serious | none | 769 | 754 | - | MD **0.18 lower** (0.28 lower to 0.07 lower) | ⨁⨁⨁◯ Moderate[a,j] | CRITICAL |

[a] High heterogeneity, unchanged on sub-group analysis. CIs are overlapping.
[b] CIs are crossing null value.
[c] Small sample size. CI approaching null.
[d] One study shows an overall high risk of bias, and three studies show some concerns.
[e] Small sample size.
[f] One study shows an overall high risk of bias, and two studies show some concerns.
[g] Small sample size. Only one study.
[h] I-square = 92%.
[i] Two studies show some concerns.
[j] One study has an overall high risk of bias while three studies shows some concerns
[1] Dutta et al., Arch Dis Child, 2001; Khan et al., J Health Pop Nutr, 2005.
[2] Santosham et al., J Pediatr, 1996.
[3] Alam et al., Indian Pediatr, 2000; Choice Study Group, Paediatrics, 2001; Dutta et al., Arch Dis Child, 2001; El-Mougi et al., J Pediatr Gastroenterol Nutr, 1994; Santosham et al., J Pediatr, 1996; International Study Group, Lancet, 1995.
[4] Choice Study Group, Paediatrics, 2001; Dutta et al. Arch Dis Child, 2001, Khan et al., J Health Pop Nutr, 2005; International Study Group, Lancet, 1995.

[5] Choice Study Group, Paediatrics, 2001; Dutta et al., Arch Dis Child, 2001, El-Mougi et al., J Pediatr Gastroenterol Nutr, 1994; Khan et al., J Health Pop Nutr, 2005; Santosham et al., J Pediatr, 1996; International Study Group, Lancet, 1995.
[6] Alam et al., Indian Pediatr, 2000.
[7] Dutta et al., Arch Dis Child, 2001.
[8] Alam et al., Indian Pediatr, 2000; Choice Study Group, Paediatrics, 2001; Khan et al., J Health Pop Nutr, 2005.
[9] Choice Study Group, Paediatrics. 2001; Dutta et al., Arch Dis Child, 2001; El-Mougi et al., J Pediatr Gastroenterol Nutr, 1994; Khan et al., J Health Pop Nutr, 2005; Santosham et al., J Pediatr, 1996; International Study Group, Lancet, 1995.

**Diarrhoea PICO 6.** In children up to 10 years of age with acute diarrhoea having risk factors (age, nutritional status, HIV status), what is the effectiveness of enhanced care (such as hospitalization, close clinical monitoring and/or longer follow-up after completion of treatment) compared to the usual care in improving clinical outcomes?

No GRADE tables prepared as evidence too indirect.

**For more information, please contact:**

**World Health Organization**
**Avenue Appia 20, CH 12-11 Geneva 27**
**Switzerland**

**Department of Maternal, Newborn, Child and Adolescent Health and Ageing**

**Email: mncah@who.int**

**Website: https://www.who.int/teams/maternal-new-born-child-adolescent-health-and-ageing**