

WHO recommendations for management of serious bacterial infections in infants aged 0–59 days

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Cover photo: An elderly woman holds a 2-day-old baby boy after he received double doses of the oral polio vaccine in a nomadic area, about 20 kilometres east of Hargeisa, Somalia, during an immunization campaign on 21 August 2019. © WHO / Ilyas Ahmed

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Page x, table 1, lines 17,18	
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Page 4, table 1.1, column 1, line 4	
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Page 4, table 1.1, column 1, line 15	
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Insert:	[pneumonia]

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Page 56, line 29	
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These corrections have been incorporated into the electronic file.

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The institutional affiliations and geographic locations of all contributors to the guideline are listed in **Annex 1**, while declarations of interests are provided in **Annex 2**.

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Abbreviations

AMR	antimicrobial resistance
AUC	area under the curve
AWaRe	Access, Watch, Reserve (WHO's antibiotic classification)
CHW	community health worker
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
DECIDE	Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence
DOI	declaration of interest
ENAP	Every Newborn Action Plan
EPOC	Effective Practice and Organization of Care
ERG	External Review Group
EST	Evidence Synthesis Team
EtD	Evidence-to-Decision
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIC	high-income country
IMCI	integrated management of childhood illness
IM	intramuscular
IV	intravenous
LMICs	low- and middle-income countries
MCA	Department of Maternal, Newborn, Child and Adolescent Health and Ageing (at WHO)
MIC	minimum inhibitory concentration
OR	odds ratio
PHC	primary health care
PICO	population (P), intervention (I), comparator (C), outcome (O)
PIRD	population (P), index test (I), reference standard (R), diagnosis of interest (D)
POC	point of care
PSBI	possible serious bacterial infection
RCT	randomized controlled trial
RR	relative risk
SBI	serious bacterial infection
spp.	several species
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Background

Among an estimated 3 million young infants who die annually in the first 59 days of life, more than half a million of their deaths are caused by the most important serious bacterial infections (SBIs) – sepsis, meningitis and pneumonia. Furthermore, those infants who survive SBI are at risk of long-term disability. The care of young infants is a global priority and a component of the Every Woman Every Child *Global strategy for women's, children's and adolescents' health* (2016–2030) launched by the United Nations Secretary-General, the United Nations Children's Fund (UNICEF) Every Child Alive campaign, the World Health Organization (WHO) 2025 global nutrition targets, and the joint WHO–UNICEF Every Newborn Action Plan (ENAP), which was endorsed at the World Health Assembly in 2014.

Sepsis is an acute life-threatening condition characterized by organ dysfunction. There is no unified diagnostic approach and many factors complicate the diagnosis of SBIs in young infants. Blood culture is the gold standard for the diagnosis of sepsis in young infants; however, blood cultures miss many causative pathogens. In young infants, the most serious infections are sepsis, meningitis and pneumonia, but there are other important infections, including skin and umbilical infections. Early-onset infections (occurring before the completion of 3 days of life) are associated with vertical bacterial transfer during childbirth, while late-onset infections (from 3 days to under 59 days of life) are more likely due to bacterial exposure during the days after birth.

The evidence base for SBIs in young infants has been limited by the lack of rigorously conducted trials, disparities in diagnostic criteria, heterogenous interventions, and the lack of standardized core outcome sets. The landscape for managing SBIs is also rapidly evolving. There is an urgent need to improve the accuracy of the methods and tools used to identify or diagnose infants who require treatment for sepsis and the methods of identifying which infants should stop antibiotics. Antibiotic resistance is also increasing and recent studies of sepsis in young infants have found that antibiotic resistance patterns vary widely; there is a need for rational use of antibiotics. In response to these concerns, WHO and UNICEF have proposed specific case definitions and clinical algorithms that can be used to identify and treat possible serious bacterial infection (PSBI), fast breathing, sepsis, pneumonia and meningitis (see **Table 1.1** in this guideline).

Integrated management of childhood illness (IMCI) is a joint WHO–UNICEF initiative which was introduced in 1995 with the aim of reducing mortality and morbidity in children aged under 5 years (under-fives) in resource-limited settings. Recognizing the limited resources in primary health care (PHC) facilities, IMCI adopted a syndromic approach, enabling classification of illness severity based only on clinical signs. In 2014, the "WHO 7-sign IMCI algorithm" was developed, and in 2019, WHO designated three separate risk groups for young infants aged 0–59 days: "critical illness" (highest mortality risk), "clinical severe infection" (moderate mortality risk) and "fast breathing in infants aged 7–59 days" (lower mortality risk).

WHO guidelines are first and foremost intended to provide guidance on when to urgently refer infants with suspected sepsis or PSBI to hospital for antibiotic treatment using the 2021 WHO AWaRe classification of antibiotics (Access, Watch, Reserve) and the 2013 *Pocket book of hospital care for children* guidelines. However, it is well known that it may not be possible for many families to access hospitals in low- and middle-income countries (LMICs). These concerns have led WHO, UNICEF and other organizations to develop guidelines for the management of infants with PSBI in hospital and also outside hospital where referral is not possible.

WHO previously developed guidelines for the management of SBI in young infants aged 0–59 days, in 2012 and 2015. However, new evidence has emerged in many areas since the development of those guidelines. In December 2022, an international group of experts defined the scope and priority questions for the development of updated guidance about management of the most serious SBIs – sepsis, meningitis and pneumonia. Although there are many different causes of SBI, the Guideline Development Group (GDG) decided to focus on the following priority questions for this updated guideline:

- Antibiotic treatment effectiveness: For infants aged 0–59 days with suspected sepsis, meningitis, pneumonia, including the IMCI syndromes of possible serious bacterial infection (PSBI), critical illness, clinical severe infection and fast breathing (*population*), are there alternative antibiotic regimens (*intervention*) that are more effective than the standard WHO-recommended antibiotic regimens (*comparator*) for improving the critical outcomes of all-cause or cause-specific mortality, morbidity (treatment failure, treatment success, hospitalizations, adverse events) or neurodevelopmental impairment/disability?
- Diagnostic test accuracy: For infants aged 0–59 days with PSBI (*population*), are clinical sign-based algorithms for suspected sepsis (including the IMCI syndromes of PSBI, critical illness, clinical severe infection and fast breathing) ascertained by any cadre of health worker (*index test*) more accurate for diagnosis than sepsis diagnosis (culture-confirmed or physician judgement) or mortality (*reference standard*)?

Target audience

The recommendations in this guideline are intended to inform the development of national and subnational health policies, clinical protocols and programmatic guides. Therefore, the target audience includes national and subnational public health policy-makers, implementers and managers of maternal, newborn and child health programmes, health facility managers, supervisors/instructors for in-service training, health workers (including midwives, auxiliary nurse-midwives, nurses, paediatricians, neonatologists, general medical practitioners and community health workers), nongovernmental organizations, professional societies involved in the planning and management of maternal, newborn and child health services, staff involved in research and in the pre-service education and training of health workers, and those involved in the education of parents.

Guideline development methods

The guideline was developed using the standard operating procedures described in the *WHO handbook for guideline development*. This involved the convening of an Evidence Synthesis Team (EST) and an international Guideline Development Group (GDG) of experts. The process included: (i) identifying priority questions and outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of the evidence, (iv) formulation of recommendations and write-up of the guideline, and (v) planning for dissemination, implementation, impact evaluation and updating of the recommendations.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to appraise the quality and certainty of the quantitative evidence for each priority question, and for the qualitative evidence, the reviews were appraised using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) tool. The DECIDE approach (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence), an evidence-to-decision tool, was used to guide the evidence search, evidence synthesis and judgements on the different criteria by the EST, and the formulation of recommendations by the GDG. This included assessment of the effects (benefits and harms) of the interventions on infant outcomes, and consideration of the values of families and health workers, acceptability and feasibility of the interventions, the resources required, and equity.

Recommendations were developed using WHO Guidelines Review Committee criteria: “strong” recommendations are generally applicable to all infants with SBI aged 0–59 days, while “conditional” recommendations mean that the intervention is recommended under certain conditions. The GDG members examined and interpreted the evidence, formulated the wording of the final recommendations

and provided related remarks and considerations at virtual meetings held in November 2023.

Recommendations

This guideline presents 11 recommendations which cover antibiotic management of infants with SBI in any health facility or community setting, from birth to 59 days of age unless otherwise indicated (**Table 1**). Of the recommendations, four are new and seven are updated. There are 10 strong recommendations and one conditional recommendation. No recommendation was made for one intervention (B.1). Six recommendations are for non-hospital (i.e. community-based/PHC) settings (section A) and five are for hospital settings (section B).

The GDG also provided remarks related to all the recommendations, as needed, which are presented along with each recommendation in Chapter 3, sections A and B, followed by background information and summaries of the evidence. The GDG also provided remarks about cross-cutting issues that are important for all settings and recommendations, including clinical management, referral, risk groups, antimicrobial resistance (AMR), and antibiotic dosing, which are presented in Chapter 3, section C. All recommended antibiotics are in line with the AWaRe recommendations.

The guideline includes concluding chapters on implementation, applicability issues, research implications, dissemination of the guideline, monitoring and evaluation of the impact of the recommendations, and updating of the guideline. This guideline document also includes four annexes, detailing contributors to the guideline, the summary of declarations of interest from the GDG members and how they were managed, research priorities, and the priority questions and outcomes. The GRADE data tables for each priority question are presented in the **Web Annex: Evidence base**.

Table 1. WHO recommendations for the management of serious bacterial infections in infants aged 0–59 days

No.	Recommendation	Strength of recommendation and certainty of the evidence	Status of recommendation
A. Non-hospital settings			
A.1	**In young infants aged 0–59 days, the WHO 7-sign integrated management of childhood illness (IMCI) algorithm is recommended for the identification of infants with possible serious bacterial infection (PSBI) who require further evaluation or treatment.**	Strong recommendation, moderate-certainty evidence	New recommendation
A.2	**Young infants aged 0–59 days with the IMCI signs of critical illness should be referred to hospital. If referral is not possible, ampicillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended.**	Strong recommendation, very low-certainty evidence	Updated recommendation
A.3a	**Young infants aged 0–59 days with the IMCI signs of clinical severe infection should be referred to hospital. If referral is not possible then oral amoxicillin for at least 7 days plus gentamicin IM/IV for at least 7 days is recommended.**	Strong recommendation, low-certainty evidence	Updated recommendation

No.	Recommendation	Strength of recommendation and certainty of the evidence	Status of recommendation
A.3b	**If 7 days of gentamicin is not feasible, oral amoxicillin for at least 7 days plus gentamicin IM/IV for 2 days may be considered.**	Conditional recommendation, low-certainty evidence	Updated recommendation
A.4	**Young infants aged 0–6 days with fast breathing as the only IMCI sign of illness should be referred to hospital. If referral is not possible, oral amoxicillin for at least 7 days is recommended.**	Strong recommendation, low-certainty evidence	Updated recommendation
A.5	**Young infants aged 7–59 days with fast breathing as the only IMCI sign of illness should be treated with oral amoxicillin for at least 7 days. These infants can be managed outside hospital.**	Strong recommendation, very low-certainty evidence	Updated recommendation
B. Hospital settings			
B.1	**No recommendation was made on diagnostic accuracy of clinical signs of sepsis in young infants aged 0–59 days in hospital settings.**	NA	No previous recommendation
B.2	**In young infants aged 0–59 days who are hospitalized with suspected sepsis, ampicillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended as first-choice antibiotic management.**	Strong recommendation, moderate-certainty evidence	Updated recommendation
B.3	**In young infants aged 0–59 days who are hospitalized with suspected staphylococcal sepsis, cloxacillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended as first-choice antibiotic management.**	Strong recommendation, very low-certainty evidence	Updated recommendation
B.4	**In young infants aged 0–59 days who are hospitalized with suspected meningitis, ampicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV for at least three weeks is recommended as first-choice antibiotic management.**	Strong recommendation, very low-certainty evidence	New recommendation
B.5	**In young infants aged 0–59 days who are hospitalized with suspected pneumonia, ampicillin IM/IV plus gentamicin IM/IV for at least 7 days is recommended as first-choice antibiotic management.**	Strong recommendation, very low-certainty evidence	New recommendation

No.	Recommendation	Strength of recommendation and certainty of the evidence	Status of recommendation
B.6	**In young infants aged 0–59 days who are hospitalized with suspected staphylococcal pneumonia, cloxacillin IM/IV plus gentamicin IM/IV for at least 7 days is recommended as first-choice antibiotic management.**	Strong recommendation, very low-certainty evidence	New recommendation

IM: intramuscular; IMCI: integrated management of childhood illness; IV: intravenous.
Note: Definitions are provided in Table 1.1 in Chapter 1 of the main guideline.

1. Introduction

1.1 Background

Every year, about 3 million young infants die in the first 59 days of life, with 98% of these deaths occurring in low- and middle-income countries (LMICs) *(1, 2)*. The most important serious bacterial infections (SBIs) – sepsis, meningitis and pneumonia – are estimated to cause over 556 000 deaths to infants aged 0–59 days each year *(2, 3)*. Survivors of SBI are at risk of long-term disability *(4)*, and SBI accounts for about 3% of all disability-adjusted life years in estimates of the global burden of disease *(1)*.

The care of young infants is a global priority and a component of the Every Woman Every Child *Global strategy for women's, children's and adolescents' health* (2016–2030) launched by the United Nations Secretary-General *(5)*, the United Nations Children's Fund (UNICEF) *Every Child Alive* campaign *(6)*, the World Health Organization (WHO) 2025 global nutrition targets *(7)*, and the joint WHO–UNICEF Every Newborn Action Plan (ENAP) (*Every newborn: an action plan to end preventable deaths*), which was endorsed at the World Health Assembly in 2014 (Resolution WHA67.10) *(8, 9)*.

Sepsis is an acute life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection and to the direct effect of pathogenic organisms *(10)*. Although there is no unified diagnostic approach, there is general consensus that the diagnosis of sepsis must include signs of systemic involvement such as shock, hypovolemia, hypotension and inflammation *(11-16)*. In young infants, the most serious infections are sepsis, meningitis and pneumonia, but there are other important infections, including skin and umbilical infections. Many factors complicate the diagnosis of sepsis and other SBIs in young infants. For example, it is common for blood cultures and laboratory tests to be negative due to transient bacteraemia or pretreatment with antibiotics. Additionally, venipuncture can be difficult in young infants and blood cultures are commonly not available in many LMICs. Severe viral illness and cardiac failure are known to mimic the signs of bacterial SBIs in young infants. Clinical signs often advance rapidly and recognition of illness by a baby's primary caregiver often only occurs when the baby is already severely ill *(10-12, 17)*. Assessment by health workers is also challenging. The detection of clinical signs of SBIs in young infants is well known to be difficult *(17-20)*. False positives and false negatives are common even when infants are examined by highly trained health personnel *(18, 19)*. Poor specificity of clinical syndromes used in clinical studies is also a problem. Studies that recruit participants based on clinical syndromes often have poor positive predictive value for SBIs, in other words, some participants may not truly have SBIs *(21-23)*.

There is an urgent need to improve the accuracy of the methods and tools used to identify or diagnose infants who require treatment for SBI (e.g. referral to a hospital for admission for treatment) and the methods of identifying which infants should stop antibiotics (e.g. after 24–48 hours of therapy). Antibiotic resistance is increasing and there is a need for rational use of antibiotics *(16, 24, 25)*. However, due to the high mortality from SBI in infants aged 0–59 days, many clinicians consider it important to prioritize clinical signs with higher sensitivity over those with higher specificity.

In response to these concerns, WHO and UNICEF have proposed specific case definitions and clinical algorithms that can be used to identify and treat possible serious bacterial infection (PSBI), fast breathing, sepsis, pneumonia and meningitis; these are presented in **Table 1.1**.

Integrated management of childhood illness (IMCI) is a joint WHO–UNICEF initiative which was introduced in 1995 with the aim of reducing mortality and morbidity in children aged under 5 years (under-

fives) in resource-limited settings *(26)*. Recognizing the limited resources in community-level/primary health care (PHC) facilities, IMCI adopted a syndromic approach, enabling classification of illness severity in under-five children based only on clinical signs. Over time, IMCI guidelines have evolved and been adapted to local epidemiological policy, health system and community contexts. In 2014, the "WHO 7-sign IMCI algorithm" was developed *(27)*, which was further refined in 2019 (see row A1 in **Table 1.1**) *(28)*. Also in 2019, WHO designated three separate risk groups for young infants aged 0–59 days: "critical illness" with highest mortality risk, "clinical severe infection" with moderate mortality risk, and "fast breathing in infants aged 7–59 days" with lower mortality risk *(28, 29)*. In addition, the 2013 *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, second edition (12, 13)* described five other signs that can be used for the identification of infants with sepsis, pneumonia and meningitis in hospital (drowsiness or unconsciousness, grunting, central cyanosis, severe jaundice, severe abdominal distention; see rows B1, B3 and B4 in **Table 1.1**).

Table 1.1 Clinical case definitions for serious bacterial infection (SBI)

A. Non-hospital settings

1. Clinical signs of possible serious bacterial infection (PSBI) in young infants aged 0–59 days in non-hospital settings

WHO defines PSBI in an infant aged 0–59 days as the presence of one or more of the following clinical signs:

- not feeding well or not able to feed at all
- movement only when stimulated or no movement at all
- high body temperature (38 °C or above)
- low body temperature (< 35.5 °C)
- severe chest indrawing
- convulsions
- fast breathing (≥ 60 breaths per minute) *in infants aged 0–6 days*

Note: These signs comprise the WHO 7-sign integrated management of childhood illness (IMCI) algorithm.

2. Clinical signs of critical illness in young infants aged 0–59 days in non-hospital settings

WHO defines critical illness in an infant aged 0–59 days as the presence of one or more of the following clinical signs:

- not able to feed at all
- no movement at all
- convulsions

Note: These signs are part of the WHO 7-sign IMCI algorithm specific to critical illness.

3. Clinical signs of clinical severe infection in young infants aged 0–59 days in non-hospital settings

WHO defines clinical severe infection in an infant aged 0–59 days as the presence of one or more of the following clinical signs:

- not feeding well
- movement only when stimulated
- high body temperature (≥ 38 °C)
- low body temperature (< 35.5 °C)
- severe chest indrawing
- fast breathing (≥ 60 breaths per minute) *in infants aged 0–6 days*

Note: These signs are part of the WHO 7-sign IMCI algorithm specific to clinical severe infection.

Table 1.1 continued

4. Fast breathing as the only clinical sign of illness in young infants aged 0–6 days in non-hospital settings

WHO defines fast breathing in an infant aged 0–6 days as:

- ≥ 60 breaths per minute

Note: This sign is part of the WHO 7-sign IMCI algorithm.

5. Fast breathing as the only clinical sign of illness in young infants aged 7–59 days in non-hospital settings

WHO defines fast breathing in an infant aged 7–59 days as:

- ≥ 60 breaths per minute

B. Hospital settings

1. Suspected sepsis in young infants aged 0–59 days in hospital

WHO defines suspected sepsis in a hospitalized infant aged 0–59 days as the presence of one or more of the following clinical signs:

- not feeding well or not able to feed at all
- movement only when stimulated or no movement at all
- high body temperature (≥ 38 °C)
- low body temperature (< 35.5 °C)
- severe chest indrawing
- convulsions
- fast breathing (≥ 60 breaths per minute) *in infants aged 0–6 days*
- drowsiness or unconsciousness
- grunting
- central cyanosis
- severe jaundice
- severe abdominal distention

2. Suspected staphylococcal sepsis in young infants aged 0–59 days in hospital

WHO defines suspected staphylococcal sepsis in a hospitalized infant aged 0–59 days as the presence of one or more of the following clinical signs of sepsis listed above, plus one or more of the following clinical signs of staphylococcal infection:

- skin infection
- pustules
- omphalitis
- abscesses

3. Suspected meningitis in young infants aged 0–59 days in hospital

WHO defines suspected meningitis in a hospitalized infant aged 0–59 days as the presence of one or more of the following clinical signs:

- drowsiness or unconsciousness
- lethargy
- convulsions
- bulging fontanelle
- irritability
- high-pitched cry

Note: Infants commonly have signs of both meningitis and sepsis. Any infant with suspected sepsis may also have meningitis. A stiff neck is rare in a young infant and can be difficult to elicit. Bulging fontanelle can also be difficult to determine in an unwell young infant.

Table 1.1 continued

4. Suspected pneumonia in young infants aged 0–59 days in hospital

WHO defines suspected pneumonia in a hospitalized infant aged 0–59 days as the presence of one or more of the following clinical signs:

- fast breathing (≥ 60 breaths per minute) in infants aged 0–6 days
- fast breathing (≥ 60 breaths per minute) in infants aged 7–59 days
- chest indrawing
- grunting
- central cyanosis
- hypoxaemia

Note: Radiological signs of pneumonia lag behind the clinical presentation, lack both sensitivity and specificity in young infants, and are often unhelpful.

5. Suspected staphylococcal pneumonia in young infants aged 0–59 days in hospital

WHO defines suspected staphylococcal pneumonia in a hospitalized infant aged 0–59 days as the presence of one or more of the following clinical signs of pneumonia listed above, plus one or more of the following clinical signs of staphylococcal infection:

- skin infection
- pustules
- omphalitis
- abscesses

Sources: WHO, 2012, p. xii *(12)*; WHO, 2013, p. 473 *(13)*; WHO, 2014, p. 80 *(27)*; WHO and UNICEF, 2019, p. 29 *(28)*.

With the development of point-of-care (POC) rapid "bedside" laboratory tests (e.g. C-reactive protein [CRP]), there has been much interest in how to integrate laboratory tests with IMCI and other syndromic approaches based on clinical signs. There is also ongoing work to develop more sophisticated predictive algorithms and machine learning tools that may improve the diagnosis of infants with sepsis and other severe illnesses, and assist in the understanding of when to stop antibiotics and the rational use of antibiotics *(11, 28)*.

Early-onset infections (occurring before the completion of 3 days of life) are associated with vertical bacterial transfer during childbirth, while late-onset infections (from 3 days to under 59 days of life) are more likely due to bacterial exposure during the days after birth *(15, 16, 30, 31)*. The pathogens commonly identified from blood cultures of young infants with sepsis are *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp.*, *Acinetobacter spp.*, *Streptococcus agalactiae* and *Streptococcus pneumoniae (15, 16, 30, 31)*. Blood culture is the gold standard for the diagnosis of sepsis in young infants. However, blood cultures miss many causative pathogens, especially fastidious organisms and those that cause rapidly progressive and fulminating disease *(17, 30, 32)*. Multidrug-resistant strains, such as those producing extended-spectrum beta-lactamase (ESBL) and carbapenemases, are becoming more common in both hospital and community-based settings in all countries *(15, 16, 25, 31)*. Recent studies of sepsis in young infants have found that resistance patterns vary widely. In one study of over 36 000 infants from tertiary hospitals in seven LMICs, as many as 60% of bacterial isolates were resistant to both ampicillin and gentamicin *(33)*.

The evidence base for SBIs in young infants has been limited by the lack of rigorously conducted trials, disparities in diagnostic criteria, heterogenous interventions, and the lack of standardized core outcome sets. The landscape for managing SBIs is also rapidly evolving: home births are declining; many more newborns are being exposed to facility-based bacterial pathogens with novel antimicrobial resistance (AMR) patterns; new maternal and newborn immunizations are being scaled up; innovative probiotics and micronutrients are being trialled for mothers and newborns; POC tests and laboratory diagnostics are increasingly available; new methods for developing antibiotics are being developed; and innovative ways to harness artificial intelligence (AI) and measure outcomes are emerging *(34-37)*.

With regard to treatment, to assist with standardization and antibiotic stewardship, WHO has developed the *WHO access, watch, reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use*, *2021* spreadsheet *(38)* and in 2022 published *The WHO AWaRe antibiotic book (16)*. The AWaRe classification gives guidance on first- and second-choice antibiotics for common infections in high-income countries (HICs) and LMICs, and has classified antibiotics into four groups: "Access", "Watch", "Reserve" (AWaRe) and a fourth – "Not Recommended". Access antibiotics are generally considered to have a narrow spectrum of activity, lower cost, a good safety profile and low resistance potential. They are often recommended as empiric first- or second-choice treatment options for common infections. Watch antibiotics are broader-spectrum antibiotics, generally with higher costs and are recommended as first-choice options only for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics. Reserve antibiotics are last-choice antibiotics used to treat multidrug-resistant infections *(16, 38, 39)*.

WHO guidelines are first and foremost intended to provide guidance on when to urgently refer infants with suspected sepsis or PSBI to hospital for antibiotic treatment using the 2021 WHO AWaRe and the 2013 *Pocket book of hospital care for children* guidelines *(13, 38)*. However, it is well known that it may not be possible for many families to access hospitals in LMICs. These concerns have led WHO, UNICEF and other organizations to develop guidance for the management of infants with sepsis in hospital and also those outside hospital where referral is not possible *(11-13, 16, 28)*.

WHO has previously developed guidelines for the management of SBI in young infants aged 0–59 days (*Recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations*, 2012; *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, second edition*, 2013; *Guideline: managing possible serious bacterial infection in young infants when referral is not feasible*, 2015) *(11-13)*. However, new evidence has emerged in many areas since the development of those guidelines.

In December 2022, an international group of experts defined the scope and priority questions for the development of updated guidance about management of important SBIs – sepsis, meningitis and pneumonia (see **Table 1.2**).

Although there are many different causes of SBI, the Guideline Development Group (GDG) decided to focus on the most serious causes (sepsis, meningitis and pneumonia) and the priority questions listed in **Table 1.2** (more detail is in **Annex 3**).

Table 1.2 Overarching questions and framework for the evidence

I. Antibiotic treatment effectiveness	
PICO question	For infants aged 0–59 days with suspected sepsis, meningitis, pneumonia, including the IMCI syndromes of PSBI, critical illness, clinical severe infection and fast breathing *(population)*, are there alternative antibiotic regimens *(intervention)* that are more effective than the standard WHO-recommended antibiotic regimens *(comparator)* for improving the critical outcomes of all-cause or cause-specific mortality, morbidity (treatment failure, treatment success, hospitalizations, adverse events) or neurodevelopmental impairment/disability?
Target population (P)	Infants aged 0–59 days with suspected sepsis, meningitis, pneumonia, including the IMCI syndromes of PSBI, critical illness, clinical severe infection and fast breathing
Intervention (I)	Alternative antibiotic regimens
Intervention period	Birth to 59 days chronological age
Comparator (C)	WHO-recommended antibiotic regimens
Comparator period	Birth to 59 days chronological age
Outcomes (O)	Critical outcomes: all-cause or cause-specific mortality, morbidity (treatment failure,[a] treatment success,[a] hospitalizations, adverse events), neurodevelopmental impairment/disability
Outcome period	Unrestricted, at latest follow-up
II. Diagnostic test accuracy	
PIRD question	For infants aged 0–59 days with PSBI *(population)*, are clinical sign-based algorithms for suspected sepsis (including the IMCI syndromes of PSBI, critical illness, clinical severe infection and fast breathing) ascertained by any cadre of health worker *(index test)* more accurate for diagnosis than sepsis diagnosis (culture-confirmed or physician judgement) or mortality *(reference standard)*?
Target population (P)	All infants aged 0–59 days with PSBIs
Index test (I)	Clinical sign-based algorithms for suspected sepsis, meningitis, pneumonia, including the IMCI syndromes of PSBI, critical illness, clinical severe infection and fast breathing ascertained by any cadre of health worker
Intervention period	Birth to 59 days chronological age
Reference standard (R)	Sepsis diagnosis (culture-confirmed sepsis, physician judgement) or mortality
Reference standard period	Birth to 59 days chronological age
Diagnosis of interest (D)	Serious bacterial infections (SBIs)

Table 1.2 continued

III. Settings and subgroups	
Setting	Health facility or home, in any country or setting
Subgroups	Setting (non-hospital, hospital [health facility level 1,2,3 or equivalent [b]]) Age at presentation (0–6 days, 7–59 days [a]) Single and multiple signs of sepsis, meningitis, pneumonia Phase of illness (at first presentation, after 48–72 hours of treatment [a]) Early onset, late onset (< 3 days, 3 days to < 7 days [a]) Timing of administration of antibiotics after diagnosis (< 2 hours, 2 hours to < 6 hours, 6 hours and more, continuous measure [a]) Prematurity (< 37 weeks' gestation, < 32 weeks' gestation, continuous measure [a]) Birth weight (< 2.5 kg, < 1.5 kg, > 1.0 kg, continuous measure [a]) Prior antibiotic exposure (known exposure, no known exposure) Inborn (birth in a health facility), outborn (birth not in a health facility) Place of acquisition [a] (including community, health facility level 1,2,3 or equivalent [b]) Antibiotic resistance settings [a] Pathogen confirmed/not confirmed [a]

IMCI: integrated management of childhood illness; PICO: population, intervention, comparator, outcomes; PIRD: population, index test, reference standard, diagnosis of interest; PSBI: possible serious bacterial infection.
[a] As defined by the authors of the studies.
[b] As defined by the Every Newborn Action Plan (ENAP) *(40)*.

1.2 Target audience

The recommendations in this guideline are intended to inform the development of national and subnational health policies, clinical protocols and programmatic guides. Therefore, the target audience includes national and subnational public health policy-makers, implementers and managers of maternal, newborn and child health programmes, health facility managers, supervisors/instructors for in-service training, health workers (including midwives, auxiliary nurse-midwives, nurses, paediatricians, neonatologists, general medical practitioners and community health workers), nongovernmental organizations, professional societies involved in the planning and management of maternal, newborn and child health services, staff involved in research and in the pre-service education and training of health workers, and those involved in the education of parents.

1.3 Scope of the guideline

There are 11 recommendations which cover antibiotic management of infants with SBI in any health facility or community setting, from birth to 59 days of age unless otherwise indicated. They are summarized in **Table 1** in the executive summary and presented in detail in **Chapter 3**. Of the recommendations, four are new and seven are updated. There are 10 strong recommendations for all infants and one recommendation that is conditional on particular contexts or conditions. There was one case in which no recommendation was made for the intervention. Six recommendations are for non-hospital (i.e. community-based/PHC) settings (**section A**)and five are for hospital settings (**section B**).

The GDG also provided remarks related to all the recommendations, as needed, and also about

cross-cutting issues that are important for all settings and recommendations, including clinical management, referral, risk groups, antimicrobial resistance, and antibiotic dosing (**section C**).

Other WHO recommendations that are still valid for management of infants with SBI are covered in WHO guidance published in 2012 and 2013 *(12, 13)* and more new and updated recommendations will also be included in a future update. The recommendations presented here are also complementary to existing WHO guidelines for antenatal, intrapartum and postnatal care, and care of the preterm or low-birth-weight infant *(18, 41-44)*. All recommended antibiotics are also in line with the AWaRe recommendations *(16)*.

The WHO Guidelines Review Committee (GRC) approved the scope of this guideline in December 2022, and no subsequent changes were made.

2. Methods

This document was developed using the standard operating procedures described in the *WHO handbook for guideline development, second edition (45)*. The process included: (i) identifying priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations and write-up of the guideline; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

2.1 Contributors to the guideline

The groups involved in the development of the guideline are described below. The members of these groups are listed in **Annex 1**.

2.1.1 WHO Steering Group

The guideline development process was supervised by the WHO Steering Group, comprising staff members from three WHO departments: Maternal, Newborn, Child and Adolescent Health and Ageing; Prevention and Control of Antimicrobial Resistance; and Global Coordination and Partnership for Antimicrobial Resistance. The Steering Group drafted the initial scope of the guideline; identified priority questions in the "PIRD" format for diagnostic accuracy (encompassing population, index test, reference standard and diagnosis of interest) and "PICO" format for effectiveness evidence (encompassing population, intervention, comparator[s] and outcome[s]); prepared the guideline planning proposal; identified and invited systematic review teams, a guideline methodologist and members of the Guideline Development Group (GDG) and the External Review Group (ERG); supervised evidence retrieval, assessment and synthesis; organized the GDG meetings; prepared draft recommendations for consideration of the GDG; compiled the final guideline document; and managed the guideline publication and dissemination.

2.1.2 Guideline Development Group (GDG)

The WHO Steering Group identified 20 external experts and stakeholders from the six WHO regions to form the GDG. Criteria included geographic representation, gender balance and no conflicts of interest. The final GDG was a diverse group of individuals with expertise in research, clinical practice, policy and programmes, guideline development methods and service delivery approaches, including patient and consumer representatives.

The GDG participated in two virtual scoping meetings with the Steering Group in January and June 2022 and provided input on the PIRD and PICO questions and related details that had been drafted to guide the evidence reviews. The GDG members examined and interpreted the evidence, formulated the wording of the final recommendations and provided related remarks and considerations at the virtual GDG meeting in November 2023. The GDG also reviewed and approved the final guideline document.

2.1.3 External Review Group (ERG)

The ERG comprised three technical experts with expertise and experience in the management of severe infections in young infants. The ERG peer-reviewed the draft guideline document after the GDG had approved it. They assessed and provided feedback on: factual errors; clarity of language; guideline decision-making processes; values and preferences of persons affected by the recommendations (including families, health workers, managers and policy-makers); and the implications for implementation. It was not within the remit of this group to change recommendations that were formulated by the GDG.

2.1.4 Evidence Synthesis Team (EST)

The EST included a guideline methodologist, two analysts and a member of the WHO Steering Group, who began the work with an overview of existing

systematic reviews and appraisal of their quality *(46)*. A study of what matters to mothers about the care of their infant in the postpartum period was also reviewed *(47)*. The EST then commissioned systematic review teams to conduct new systematic reviews, structured searches and meta-analyses, and to assess the risk of bias and rate the certainty of the evidence. The EST reviewed this work, prepared the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence-to-Decision (EtD) frameworks for each priority question and attended all GDG meetings.

2.1.5 External partners and observers

Representatives of the United Nations Children's Fund (UNICEF), Save the Children, the Bill & Melinda Gates Foundation, the International Pediatric Association (IPA) and the United States Agency for International Development (USAID) were invited to the GDG meetings as observers. These organizations are potential partners in the implementation of the guideline, as they have a history of collaboration with WHO in guideline dissemination and implementation. Observers were allowed to make comments during technical discussions at selected times during the GDG meetings. Observers did not participate in discussions on the final recommendations.

2.2 Declaration of interests by external contributors

In accordance with WHO procedures for declaration of interests (DOIs) *(48)*, all GDG, EST and ERG members and other external collaborators were asked to declare in writing any competing interests (whether academic, financial or other), using the standard WHO DOI form, before engaging in the guideline development process. All experts were instructed to notify the responsible technical officer of any change in relevant interests, in order to update and review potential conflicts of interest accordingly. In addition, the GDG members were requested to submit an electronic copy of their curriculum vitae.

The names and short curriculum vitae of the GDG members were published on the WHO website for public review and comment two weeks prior to the first GDG meeting.

The WHO Steering Group reviewed all DOI forms and curriculum vitae to determine whether a conflict of interest existed. All findings from the DOI forms were managed in accordance with the WHO DOI guidelines on a case-by-case basis. To ensure consistency, the Steering Group applied the criteria for assessing the severity of a conflict of interest from the *WHO handbook for guideline development (45)*.

For this guideline, none of the declared interests were considered serious enough to pose any risk to the guideline development process or to reduce its credibility. However, all experts were still required to declare any interests at the first GDG meeting. At each subsequent GDG meeting, GDG and EST members and observers were required to share any new potential conflicts of interest with the group. There were no important conflicts of interest among the ERG members.

A summary of the GDG DOIs and how conflicts of interest were managed is provided in **Annex 2**.

2.3. Identifying priority questions and outcomes

At the scoping meeting, the GDG decided on the priority questions in the PIRD and PICO formats based on the following criteria:

- values and preferences of families as outlined in the systematic review, "What matters to women in the postnatal period" *(47)*;
- public health importance;
- availability of new evidence; and
- questions not addressed by existing WHO guidelines or those identified for update.

The final scope of the guideline is presented in **Table 1.2**. The PIRD and PICO questions can be found in **Annex 4**.

2.4 Evidence search, retrieval and review

The DECIDE approach (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence) *(49)* was used to guide the evidence search, evidence synthesis and judgements by the EST, and the formulation of recommendations by the GDG. The DECIDE framework has nine core domains: benefits, harms, balance of effects, certainty, values, acceptability, resources, feasibility and equity (**Table 2.1**).

Table 2.1 Evidence-to-Decision (EtD) framework workstreams and methods

Domain	Questions to be answered	Methods	Range of ratings
I. Antibiotic treatment effectiveness			
Benefits	What are the benefits of the intervention?	Quantitative systematic reviews of effectiveness studies	Don't know, varies, large reduction, moderate reduction, small reduction, trivial or no difference, small increase, moderate increase, large increase
Harms	Are there important adverse events reported by the study from the intervention?	Quantitative systematic reviews of effectiveness studies	Don't know, varies, large reduction, moderate reduction, small reduction, trivial or no difference, small increase, moderate increase, large increase
Balance of effects	Does the balance between benefits and harms favour the intervention?	DECIDE approach *(49)*	Don't know, varies, favours control, probably favours control, does not favour intervention or control, probably favours intervention, favours intervention
Certainty	What is the certainty of the effectiveness evidence?	GRADE *(50)* or GRADE-CERQual *(51)* assessment of the certainty of the body of evidence	No included studies, very low, low, moderate, high
Values	Is there important variability in values/preferences regarding outcomes, that would impact judgements about the balance of accuracy?	GDG expert opinion	Don't know, varies, no, probably no, probably yes, yes
Acceptability	Is the index test acceptable?	GDG expert opinion	Don't know, varies, no, probably no, probably yes, yes
Resources	What resources are required and what are their costs	GDG expert opinion	Don't know, varies, large costs, moderate costs, low costs, negligible costs
Feasibility	What is the feasibility of the index test? Can it be implemented easily and conveniently?	GDG expert opinion	Don't know, varies, very limited feasibility, limited feasibility, feasible, very feasible

Table 2.1 continued

Domain	Questions to be answered	Methods	Range of ratings
Equity	Will the intervention be equitable and improve critical outcomes in low-resource settings? Will the populations that most need the intervention receive it quickly and at low cost?	GDG expert opinion	Don't know, varies, not equitable, probably not equitable, probably equitable, equitable
Antimicrobial resistance (AMR)	What effect will the intervention have on AMR?	GDG expert opinion	Don't know, varies, trivial or no concerns, small concerns, moderate concerns, large concerns
II. Diagnostic test accuracy			
Sensitivity[a] accuracy	What is the accuracy of the index test for sensitivity?	Quantitative systematic reviews of diagnostic accuracy studies	Don't know, varies, very poor, poor, fair, good, very good
Sensitivity certainty	What is the certainty of the sensitivity evidence?	GRADE assessment of the certainty of the body of evidence *(52)*	No included studies, very low, low, moderate, high
Specificity[b] accuracy	What is the accuracy of the index test for specificity?	Quantitative systematic reviews of diagnostic accuracy studies	Don't know, varies, very poor, poor, fair, good, very good
Specificity certainty	What is the certainty of the specificity evidence?	GRADE assessment of the certainty of the body of evidence *(52)*	No included studies, very low, low, moderate, high
Values	Is there important variability in values/preferences regarding outcomes that would impact judgements about the balance of accuracy?	GDG expert opinion	Don't know, varies, no, probably no, probably yes, yes
Acceptability	Is the index test acceptable?	GDG expert opinion	Don't know, varies, no, probably no, probably yes, yes
Resources	What resources are required and what are their costs?	GDG expert opinion	Don't know, varies, large costs, moderate costs, low costs, negligible costs
Feasibility	What is the feasibility of the index test? Can it be implemented easily and conveniently?	GDG expert opinion	Don't know, varies, very limited feasibility, limited feasibility, feasible, very feasible

Table 2.1 continued

Domain	Questions to be answered	Methods	Range of ratings
Equity	Will the intervention be equitable and improve critical outcomes in low-resource settings? Will the populations that most need the intervention receive it quickly and at low cost?	GDG expert opinion	Don't know, varies, not equitable, probably not equitable, probably equitable, equitable

AMR: antimicrobial resistance; CERQual: Confidence in the Evidence from Reviews of Qualitative Research; DECIDE: Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence; GDG: Guideline Development Group; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

[a] Sensitivity is the probability of correctly diagnosing a person with a condition (true positive). For possible serious bacterial infection (PSBI), if an algorithm has low sensitivity this means that infants with life-threatening sepsis may be missed.

[b] Specificity is the probability of correctly diagnosing a person without a condition (true negative). For PSBI, if an algorithm has poor specificity this would mean that infants may receive antibiotics unnecessarily.

Range of ratings for sensitivity and specificity: don't know; varies; < 60%: very poor accuracy; 60–69%: poor accuracy; 70–79%: fair accuracy; 80–89%: good accuracy; ≥ 90%: very good accuracy.

For effects (benefits and harms), evidence was derived from systematic reviews of randomized controlled trials (RCTs) where possible. If reviews of RCTs were not available, then systematic reviews of non-randomized studies of interventions were used. An overview of systematic reviews was compiled to identify all eligible systematic reviews that had been conducted in the last three years *(46)*. If systematic reviews were not available, they were commissioned from expert systematic review groups. Each commissioned systematic review followed standard methods, including: a standard protocol published in advance; a clear PICO question; criteria for identification of studies, including search strategies for different bibliographic databases; methods for assessing risk of bias; and a data analysis plan. The protocols were reviewed and approved by members of the Steering Group. The language used to describe the evidence on effects was consistent with the Cochrane Effective Practice and Organization of Care (EPOC) approach *(53)*. The GDG carefully considered the benefits and harms, the balance of effects, and the certainty of the evidence of effectiveness for each PICO question. The GDG also considered the available evidence in the strata and subgroups listed in **Table 1.2** in Chapter 1.

For diagnostic test accuracy, evidence was derived from systematic reviews of studies that compared clinical sign algorithms for PSBI in infants aged 0–59 days with a defined reference standard (sepsis diagnosis [culture-confirmed sepsis, physician judgement] or mortality). An overview of systematic reviews was compiled to identify all eligible systematic reviews that had been conducted in the last three years *(46)*. If systematic reviews were not available, they were commissioned from expert systematic review groups. All commissioned systematic reviews followed standard methods, including: a standard protocol published in advance; a clear PIRD question; criteria for identification of studies, including search strategies for different bibliographic databases; methods for assessing risk of bias; and a data analysis plan. The protocols were reviewed and approved by members of the Steering Group. The language used to describe the evidence on effects was consistent with the Cochrane EPOC approach *(53)*. The GDG carefully considered the diagnostic test accuracy, and the certainty of the evidence of accuracy for each PIRD. The GDG also considered the available evidence in the strata and subgroups listed in **Table 1.2** in Chapter 1.

For values and acceptability, a recent WHO systematic review on what matters to women in the postnatal period was used *(47)*. This systematic review also followed standard methods for qualitative reviews, including: a standard protocol published in advance; a clear research question; criteria for identification of studies, including search strategies for different bibliographic databases; methods for assessing quality; and a data analysis plan.

The protocol was also reviewed and approved by members of the WHO Steering Group.

For resources, feasibility and equity, structured searches were done using search terms from effectiveness reviews and guidance published in the last five years. The following databases were searched: Excerpta Medica database (Embase), MEDLINE, UNICEF supply catalogue, International Medical Products Price Guide, and the *WHO compendium of innovative health technologies for low-resource settings (54-58)*.

This evidence was then compiled into a DECIDE EtD framework for each priority question (see **section 2.8**).

2.5 Grading of the quality and certainty of the evidence

The GRADE approach was used to appraise the quality and certainty of the quantitative evidence for each priority question. GRADE is a standard systematic approach for developing and presenting summaries of evidence for clinical practice recommendations *(50)*. It uses standard tools, which are published online, including GRADE protocols and risk-of-bias tools for assessing randomized and non-randomized studies.

For the effectiveness data, a GRADE EtD framework is prepared for each quantitative outcome and the certainty of evidence is rated as "high", "moderate", "low" or "very low" (see **Table 2.1** above). Standard criteria for baseline GRADE ratings are that RCTs provide "high-certainty" evidence while non-randomized trials and observational studies provide "low-certainty" evidence. This baseline certainty rating is then downgraded based on characteristics of the study design: risk of bias, inconsistency, imprecision, indirectness and publication bias. Magnitude of effect and dose response allow upgrading of certainty for observational studies. Further details of the standard GRADE approach can be found online *(50)*.

For the diagnostic accuracy data, the GRADE approach was also used for diagnostic tests and strategies to evaluate the certainty of evidence *(52)*. Criteria used to assess and grade the risk of bias, indirectness, inconsistency and imprecision are shown in **Table 2.1**.

For this guideline, both the systematic review teams and the external guideline methodologist (members of the EST) independently performed grading of the quantitative evidence for each priority question and outcome. Consensus was reached through discussion among the methodologist and all other members of the EST.

For the qualitative evidence, the review was appraised using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) tool *(51)*. This tool uses an approach that is similar conceptually to other GRADE tools and provides a transparent method for assessing and assigning the level of confidence that can be applied to qualitative evidence. The three domains are values, acceptability and feasibility, and each of them has four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question.

2.6 Review of evidence, decision-making and recommendations

The WHO Steering Group provided the EtD frameworks to the GDG members as soon as the documents had been drafted, and in advance of the virtual GDG meetings. The GDG was asked to review and provide comments on the documents electronically before the GDG meetings where possible. At the virtual meetings, under the leadership of the GDG chair, GDG members collectively reviewed the EtD frameworks, the draft recommendations and any comments received through preliminary feedback.

The meetings included: presentation of the evidence and EtD frameworks by the EST; consideration of each EtD domain; presentation of draft recommendations by the WHO Steering Group; deliberations on each recommendation; and discussion about justification, caveats or difficulties, implementation considerations and research gaps.

The purpose of the GDG meetings was to reach consensus on each recommendation, including its direction, strength and conditions, based on explicit consideration of all the domains within the EtD frameworks.

Recommendations were developed using WHO Guidelines Review Committee (GRC) criteria, as outlined in **Box 2.1** *(45)*.

The final adoption of each recommendation was made by consensus, defined as the agreement by three quarters or more of the GDG. Consensus was reached for all recommendations in this guideline and there were no strong disagreements.

The GDG also identified important research gaps and implications. Where the certainty of available evidence was rated as "low" or "very low", the GDG considered whether further research should be prioritized, based on whether the research would: contribute to improvements in care of the infant with PSBI; fill a knowledge gap that would inform new recommendations or change an existing recommendation; be likely to promote equity; or be feasible to implement. The research implications are summarized in **Chapter 6** and full details can be found in **Annex 3**.

2.7 Document preparation and peer review

Following the final GDG meeting, the WHO responsible technical officer prepared a draft of the full guideline document to accurately reflect the deliberations and decisions of the GDG. Other members of the WHO Steering Group provided comments on the draft document before it was sent electronically to the GDG members for review and further comment. Subsequently, the revised document was also sent to the ERG members for peer review. The Steering Group carefully evaluated the input of the GDG members and the ERG peer reviewers for inclusion in the guideline document and made revisions to the draft document as needed. Further modifications to the guideline were limited to corrections of factual errors and improvements in language to address any lack of clarity and to conform to WHO style.

2.8 Presentation of the recommendations and evidence

The recommendations are presented in the summary table in the executive summary of this guideline (**Table 1**). In **Chapter 3**, the recommendations and associated GDG remarks are presented at the start of the sections about each intervention, followed by background information and definitions, and a summary of the evidence for each recommendation. The evidence summaries present the evidence on diagnostic test accuracy or effectiveness (benefits and harms) of the interventions (sources and characteristics of the evidence, critical outcomes, other outcomes and subgroup analysis) followed by a summary of other evidence (values and acceptability, resources, feasibility and equity). Finally for each intervention, a summary of findings is presented in a table at the end of the section.

Box 2.1 Approach for developing recommendations

The recommendation is:

A "**strong recommendation**" if the intervention is applicable to all infants with possible serious bacterial infection (PSBI)

- Strong recommendations should be phrased as "is recommended", "is not recommended", "should receive", "should not receive".

A "**conditional recommendation**" if the intervention is recommended under certain conditions, which could be shared decision-making, or in certain populations or settings

- Conditional recommendations should be phrased as "may be considered".

The recommendations should be accompanied by a description of the certainty of the body of evidence: "high", "moderate", "low" or "very low".

Source: WHO, 2014 *(45)*.

The GRADE data tables for each priority question are presented in the **Web Annex**. The GRADE tables contain the grading of: bias, inconsistency, indirectness, imprecision, number of participants, diagnostic test accuracy, relative and absolute effect, risk difference and 95% confidence intervals. Further detail on methods can be found in the *WHO handbook for guideline development* and other documents *(45, 50)*.

This guideline document also includes four annexes:

Annex 1. Contributors to the guideline
Annex 2. Summary of declarations of interest from the Guideline Development Group (GDG) members and how they were managed
Annex 3. Research priorities
Annex 4. Summary of key details for each priority question and recommendation

3. Recommendations and evidence

This guideline includes 11 recommendations for antibiotic management of infants with serious bacterial infection (SBI), from birth to 59 days of age unless otherwise indicated. They are summarized in **Table 1** in the executive summary and presented in detail in this chapter. Of the recommendations, four are new and seven are updated. There are 10 strong recommendations for all infants and one recommendation that is conditional on particular contexts or conditions. No recommendation was made for one intervention (**section B.1**). Six recommendations are for non-hospital (i.e. community-based/outpatient/primary health care [PHC]) settings (presented in **section A** of this chapter) and five are for hospital settings (**section B**).

The Guideline Development Group (GDG) provided remarks related to all the recommendations, where needed. Users of the guideline should refer to these remarks, which are presented prominently along with the recommendations in sections A and B of this chapter.

The GDG also made remarks about cross-cutting issues that are important for all settings and recommendations, including clinical management, referral, risk groups, antimicrobial resistance (AMR), and antibiotic dosing (**section C**)

The recommendations and GDG remarks have been divided into the following categories, as presented in this chapter:

A. Non-hospital
(six recommendations, plus remarks)

B. Hospital
(five recommendations, plus remarks)

C. Cross-cutting issues
(remarks only)

A. Non-hospital settings

A.1 Diagnostic accuracy of clinical signs of sepsis in young infants aged 0–59 days in non-hospital settings

Recommendation and remarks

Recommendation A.1 (NEW)

In young infants aged 0–59 days, the WHO 7-sign integrated management of childhood illness (IMCI) algorithm is recommended for the identification of infants with possible serious bacterial infection (PSBI) who require further evaluation or treatment. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The recommendation was based on two studies that recruited a total of 9284 infants aged 0–59 days from primary health care (PHC) clinics and other outpatient settings in Bangladesh, Bolivia (Plurinational State of), Ghana, India, Pakistan and South Africa. Both studies used physician judgement of possible sepsis as the reference standard. One included laboratory testing. Both studies assessed the 7-sign IMCI algorithm. Both studies assessed diagnoses by community health workers (CHWs) and health workers.
- Overall, the GDG considered that both the sensitivity and specificity of the WHO 7-sign IMCI algorithm were sufficient for the diagnosis of sepsis in young infants:
  - aged 0–59 days: sensitivity 0.79 (95% CI: 0.77 to 0.82) and specificity 0.77 (95% CI: 0.76 to 0.78);
  - aged 0–6 days: sensitivity 0.84 (95% CI: 0.81 to 0.87) and specificity 0.78 (95% CI: 0.76 to 0.79); and
  - aged 7–59 days: sensitivity 0.74 (95% CI: 0.68 to 0.81) and specificity 0.79 (95% CI: 0.73 to 0.84).

Background and definitions

Possible serious bacterial infection (PSBI) is defined by WHO as an illness with one or more of the following seven clinical signs: not feeding well or not able to feed at all, movement only when stimulated or no movement at all, high body temperature (≥ 38 °C), low body temperature (< 35.5 °C), severe chest indrawing, convulsions in infants aged 0–59 days or fast breathing (≥ 60 breaths per minute) in infants aged 0–6 days (**see Table 1.1**).

In 2014, the IMCI programme was updated to include a "7-sign IMCI algorithm" with the signs listed in **Table 1.1** to define the target population in need of treatment. This was done using a WHO guideline development process by a GDG, including a systematic review of six randomized controlled trials (RCTs) which compared home visits by a community health worker (CHW) to identify young infants with serious illness to no home visits (i.e. the control group) in children 0–59 days old, and found a significant improvement in care seeking in the intervention arm compared with the control arm (relative risk [RR]: 1.35; 95% confidence interval [CI]: 1.15–1.58). However, diagnostic accuracy of the clinical signs was not specifically assessed in 2014 and there have been new studies published since that time.

Summary of the evidence: diagnostic accuracy

Overview
Question: Among young infants aged 0–59 days with PSBI, in non-hospital settings, what is the diagnostic accuracy (sensitivity and specificity) of clinical sign-based algorithms of PSBI[a] compared with a reference standard (culture-confirmed sepsis, physician judgement of sepsis, or mortality) in identifying infants who require treatment for PSBI?
Population, index test, reference standard and diagnosis of interest (PIRD) details
Population: Young infants aged 0–59 days with PSBI
Index test: Clinical sign-based algorithms of PSBI ascertained by any cadre of health worker
Reference standard: Sepsis diagnosis (culture-confirmed or physician judgement) or mortality
Diagnosis of interest: Serious bacterial infections (SBIs)
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Non-hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in Table 1.2

[a] Definitions are provided in Table 1.1.

Sources and characteristics of studies

The diagnostic accuracy evidence was derived from a systematic review that identified 6701 studies in infants aged 0–59 days, of which 19 met inclusion criteria *(59)*. All studies examined diagnostic accuracy at first presentation of suspected sepsis and assessed the potential need to initiate antibiotic therapy. None of the studies examined diagnostic accuracy after treatment to identify when antibiotics should be stopped. Twelve studies were identified that examined IMCI algorithms. Two of these studies specifically examined the 7-sign IMCI algorithm, including a total of 9284 infants who attended PHC clinics and other outpatient settings in Bangladesh, Bolivia (Plurinational State of), Ghana, India, Pakistan and South Africa *(17, 60)*. Both studies used physician judgement of possible sepsis and the need for antibiotics as the reference standard. One study included laboratory testing *(17)*. Both studies assessed diagnoses by CHWs and health workers as the index test; the diagnoses were made using the 7-sign IMCI algorithm *(17, 60)*.

Comparison

Index test: WHO 7-sign IMCI algorithm
versus
Reference standard: culture-confirmed sepsis, physician judgement of sepsis, or mortality

Critical outcomes

For this comparison, which assesses the accuracy of the 7-sign IMCI algorithm (by any cadre of health worker) to diagnose sepsis in infants aged 0–59 days, one study with 8889 participants assessed sensitivity and specificity *(17)*. (Full details are provided in GRADE Table A.1.1 in the **Web Annex**).

- Physician judgement of sepsis as the reference standard: Moderate-certainty evidence suggests fair diagnostic accuracy for sensitivity 0.79 (1 study, 8889 participants, 95% CI: 0.77 to 0.82) and fair diagnostic accuracy for specificity 0.77 (1 study, 8889 participants, 95% CI: 0.76 to 0.78).
- Culture-confirmed sepsis as the reference standard: No studies
- Mortality as the reference standard: No studies

For the same comparison in the subset of infants aged 0–6 days, two studies assessed sensitivity and specificity *(17, 60)*. (Full details are provided in GRADE Table A.1.2 in the **Web Annex**).

- Physician judgement of sepsis as the reference standard: Low-certainty evidence suggests good diagnostic accuracy for sensitivity 0.84 (2 studies, 3572 participants, 95% CI: 0.81 to 0.87) and fair diagnostic accuracy for specificity 0.78 (2 studies, 3572 participants, 95% CI: 0.76 to 0.79).
- Culture-confirmed sepsis as the reference standard: No studies
- Mortality as the reference standard: No studies

For the same comparison in the subset of infants aged 7–59 days, one study assessed sensitivity and specificity *(17)*. (Full details are provided in GRADE Table A.1.3 in the **Web Annex**).

- Physician judgement of sepsis as the reference standard: Low-certainty evidence suggests fair diagnostic accuracy both for sensitivity 0.74 (1 study, 5712 participants, 95% CI: 0.68 to 0.81) and specificity 0.79 (1 study, 5712 participants, 95% CI: 0.73 to 0.84).
- Culture-confirmed sepsis as the reference standard: No studies
- Mortality as the reference standard: No studies

Subgroup analyses

No studies

Other studies

One systematic review by Lee et al. (2014) examined the accuracy of the assessment of PSBI in infants aged 0–59 days by CHWs based at PHC acilities in low- and middle-income countries (LMICs) *(61)*. This review reported that frontline health workers diagnosed very severe disease (including PSBI) with a sensitivity of 82% (95% CI: 76%–88%) and specificity of 69% (95% CI: 54%–83%) compared with trained physicians (reference standard) in eight studies of 11 857 infants *(61)*.

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

The GDG also assessed other non-IMCI sign checklists and more complex IMCI algorithms with additional clinical signs, but no other algorithms were identified that were more accurate than the WHO 7-sign IMCI algorithm *(59)*. The GDG also considered that the other algorithms were not feasible for implementation in PHC settings in many LMICs.

Summary of findings

Comparison	**Index test:** 7-sign IMCI algorithm vs reference standard: culture-confirmed sepsis, physician judgement of sepsis, or mortality
Summary of diagnostic accuracy evidence	**0–59 days and 7–59 days:** Fair sensitivity and fair specificity [a] of the 7-sign IMCI algorithm compared with physician judgement of sepsis as the reference standard; there was no evidence for either culture-confirmed sepsis or mortality as the reference standard. **0–6 days:** Good sensitivity and fair specificity [a] of the 7-sign IMCI algorithm compared with physician judgement of sepsis as the reference standard; there was no evidence for either culture-confirmed sepsis or mortality as the reference standard.
Evidence-to-Decision summary[a]	
Sensitivity accuracy	Fair[a]
Sensitivity certainty	Moderate
Specificity accuracy	Fair[a]
Specificity certainty	Moderate
Values	Probably no variability
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Feasible
Equity	Probably equitable

[a] Definitions are provided in **Table 2.1**.

A.2 Critical illness in young infants aged 0–59 days in non-hospital settings

Recommendations and remarks

Recommendation A.2 (UPDATED)

Young infants aged 0–59 days with the IMCI signs of critical illness should be referred to hospital. If referral is not possible, ampicillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended. *(Strong recommendation, very low-certainty evidence)*

Remarks

- There were no included trials.
- The GDG recognized that there were limited data on the appropriate dose of antibiotics. Based on current clinical practice, the GDG considered that the following antibiotic doses should be used: ampicillin intramuscular or intravenous (IM/IV) 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 10 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 10 days.
- The GDG made a strong recommendation despite the lack of trials in non-hospital settings as they felt strongly about the importance of providing clear guidance for the management of critically ill infants when referral to hospital is not possible. The GDG were able to use their knowledge and experience in best practice clinical management of sepsis in young infants to make this recommendation by consensus.

Background and definitions

Critical illness is defined as one or more of the following clinical signs: not able to feed at all, no movement on stimulation, convulsions in an infant aged 0–59 days *(27, 28)*. There are pre-existing WHO recommendations (i) to provide ampicillin plus gentamicin via the intramuscular or intravenous (IM or IV) routes for at least 10 days to hospitalized infants with critical illness *(13)* and (ii) that infants who have any sign of critical illness identified in the community should be hospitalized after a single dose of pre-referral treatment with ampicillin or benzyl penicillin and gentamicin IM/IV *(11)*. These recommendations were made in 2013 and 2015 on the basis of GDG expert opinion *(27, 28)*. However, there has been no WHO guidance on "follow-up" doses of antibiotics after initial treatment of infants in the community where referral to hospital is not possible. There have also been changes to antimicrobial resistance (AMR) and new technologies for improving access to health facilities through telehealth and online platforms and community ambulances, especially in humanitarian settings *(62, 63)*.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with critical illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, index test, reference standard and diagnosis of interest (PIRD) details
Population: Young infants aged 0–59 days with critical illness
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes): All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Non-hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in Table 1.2

[a] Definitions are provided in Table 1.1.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2390 trials in infants aged 0–59 days, of which 41 RCTs met the inclusion criteria *(64)*. Among these, 35 trials examined hospital-based regimens for when hospital referral was possible. Six trials examined WHO non-hospital-based regimens, however none of these six trials examined regimens in infants with critical illness.

Comparison

Intervention: alternative antibiotic regimens
versus
Comparator: antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV

Critical outcomes

No trials were located that examined regimens in infants with critical illness.

Other outcomes

No trials.

Subgroup analyses

No trials.

Other studies

There were no other included studies.

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** alternative antibiotic regimens **vs** **Comparator:** antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV
Summary of effectiveness evidence	Not estimable
Evidence-to-Decision summary[a]	
Benefits	Don't know
Harms	Don't know
Antimicrobial resistance	Don't know
Balance of effects	Don't know
Certainty	Very low
Values	Don't know
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Feasible
Equity	Probably equitable

[a] Definitions are provided in Table 2.1.

A.3 Clinical severe infection in young infants aged 0–59 days in non-hospital settings

Recommendations and remarks

Recommendation A.3a (UPDATED)

Young infants aged 0–59 days with the IMCI signs of clinical severe infection should be referred to hospital. If referral is not possible then oral amoxicillin for at least 7 days plus gentamicin IM/IV for at least 7 days is recommended. *(Strong recommendation, low-certainty evidence)*

Recommendation A.3b (UPDATED)

If 7 days of gentamicin IM is not feasible, oral amoxicillin for at least 7 days plus gentamicin IM/IV for 2 days may be considered. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation was based on four trials of 9823 infants aged 0–59 days in rural and semi-urban PHC facilities in five countries: Bangladesh, Democratic Republic of the Congo, Kenya, Nigeria and Pakistan. The trials all compared simplified regimens that included oral antibiotics (oral amoxicillin or cotrimoxazole) versus the comparator – WHO-recommended treatment of penicillin IM for 7 days plus gentamicin IM for 7 days. Four regimens were tested.
  - Regimen 1: oral cotrimoxazole for 7 days plus gentamicin IM/IV for 7 days
  - Regimen 2: procaine penicillin IM/IV plus gentamicin IM/IV for 2 days followed by oral amoxicillin for 5 days
  - Regimen 3: oral amoxicillin for 7 days plus gentamicin IM/IV for 2 days
  - Regimen 4: oral amoxicillin for 7 days plus gentamicin IM/IV for 7 days.
- The GDG considered that regimen 1 may cause harm (increased mortality, treatment failure, adverse events) so did not recommend it.
- The GDG considered that regimen 2 had no benefit over the comparator (penicillin plus gentamicin IM for 7 days) so did not recommend it.
- The GDG considered that regimens 3 and 4 may improve critical outcomes when compared with penicillin plus gentamicin IM for 7 days (the comparator). The GDG noted that the evidence for both regimen 3 and 4 was low certainty: evidence for regimen 3 was available only from a single trial in Africa (Democratic Republic of the Congo, Kenya and Nigeria) while for regimen 4 data were available from three trials from both Asia and Africa (Bangladesh, Democratic Republic of the Congo, Kenya, Nigeria and Pakistan).
- Thus, the GDG made a strong recommendation for regimen 4 and a conditional recommendation for regimen 3, meaning that if regimen 4 was not possible (i.e. if 7 days of gentamicin was not feasible), then regimen 3 may be considered (i.e. gentamicin for only 2 days).
- The evidence for regimen 4 was judged to be of moderate certainty in the previous guideline and low certainty in this guideline. The evidence was considered to be low certainty as there was serious imprecision for treatment failure (RR 0.86, 95% CI: 0.72 to 1.02) and a serious risk of bias (substantial number of missing participants relative to outcome events in both arms of the study, and poor adherence by the parent to parental administration in the oral amoxicillin arm).
- The GDG also emphasized that it was important to continue parenteral antibiotics for such a serious condition as septicaemia for at least 7 days where feasible.
- The GDG made these recommendations recognizing that regimen 4 would have additional costs (e.g. the cost of the longer duration of antibiotics and additional staff time).
- The GDG recognized that there were limited data on the dose of antibiotics. Based on the trials included in the evidence review, the GDG considered that the following antibiotic doses should be used: oral amoxicillin 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 7 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 7 days (regimen 4) or for 2 days if 7 days is not possible (regimen 3).

- The GDG made a strong recommendation despite the limited evidence in non-hospital settings as they felt strongly about the importance of providing clear guidance for the management of unwell infants when referral to hospital is not possible. The GDG were able to use their knowledge and experience in best practice clinical management of sepsis in young infants to make this recommendation by consensus.

Background and definitions

Clinical severe infection is defined by WHO as one or more of the following clinical signs in infants aged 0–59 days: not feeding well, movement only when stimulated, high body temperature (≥ 38 °C), low body temperature (< 35.5 °C), and/or severe chest indrawing. An additional sign of clinical severe infection in infants aged 0–6 days is fast breathing (≥ 60 breaths per minute) *(27, 28)*.

In 2014, WHO developed guidelines to provide simplified antibiotic regimens (gentamicin IM for either 2 or 7 days plus oral amoxicillin for 7 days) to infants aged 0–59 days with clinical severe illness whose families do not accept or cannot access referral care at a hospital *(27, 28)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with clinical severe infection,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with clinical severe infection
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing oral amoxicillin, penicillin IM/IV or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Non-hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definitions are provided in **Table 1.1**.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2390 studies in infants aged 0–59 days, of which 41 RCTs met the inclusion criteria *(64)*. Among these, 35 trials examined hospital-based regimens for when hospital referral was possible and six trials examined WHO non-hospital-based regimens. Four trials of 9823 infants aged 0–59 days with clinical severe infection in rural and semi-urban PHC facilities in five countries (Bangladesh, Democratic Republic of the Congo, Kenya, Nigeria and Pakistan) compared simplified regimens that included oral antibiotics (oral amoxicillin or cotrimoxazole) versus penicillin IM plus gentamicin IM for 7 days *(65-68)*.

Comparison 1

Intervention: oral cotrimoxazole plus gentamicin IM for 7 days
versus
Comparator: penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison (using regimen 1, as labelled above), one study with 288 participants assessed the following outcomes with the following findings *(68).*

- Mortality: Moderate-certainty evidence suggests increased all-cause mortality after two weeks (1 RCT, 288 participants, RR 5.58, 95% CI: 1.26 to 24.72).
- Treatment failure: Moderate-certainty evidence suggests increased treatment failure after 7 days (1 RCT, 288 participants, RR 2.03, 95% CI: 1.09 to 3.79).
- Treatment success: Moderate-certainty evidence suggests a decrease in treatment success after 7 days (1 RCT, 288 participants, RR 0.90, 95% CI: 0.82 to 0.99).
- Adverse events: Not possible to estimate due to very low-certainty evidence (1 RCT, 288 participants, RR 5.07, 95% CI: 0.25 to 104.67).

No studies assessed hospitalizations or neurodevelopment for this comparison. (Full details are provided in GRADE Table A.3.1 in the **Web Annex**).

Comparison 2

Intervention: procaine penicillin IM plus gentamicin IM for 2 days followed by oral amoxicillin for 5 days
versus
Comparator: penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison (using regimen 2, as labelled above), one, two or three trials assessed the following outcomes with the following findings.

- Mortality: Very low-certainty evidence suggests little or no difference in all-cause mortality after two weeks (3 RCTs, 5066 participants, RR 1.16, 95% CI: 0.77 to 1.75) *(65-67)*.
- Treatment failure: Moderate-certainty evidence suggests little or no difference in treatment failure after one week (3 RCTs, 5066 participants, RR 0.98, 95% CI: 0.81 to 1.19) *(65-67)*.
- Relapse: Very low-certainty evidence from two trials of 3329 participants suggests a decrease in relapse after two weeks (2 RCTs, 3329 participants, RR 0.55, 95% CI: 0.16 to 1.97) *(65, 66)*.
- Treatment success: Low-certainty evidence from one trial of 1639 participants suggests little or no difference in treatment success after 11–15 days (1 RCT, 1639 participants, RR 1.01, 95% CI: 0.98 to 1.05) *(65)*.
- Hospitalizations: Low-certainty evidence from two trials of 3276 participants suggests little or no difference in hospitalizations after two weeks (2 RCTs, 3276 participants, RR 0.91, 95% CI: 0.69 to 1.22) *(66, 67)*.
- Adverse events: Low-certainty evidence suggests little or no difference in serious adverse events after two weeks (3 RCTs, 5066 participants, RR 0.89, 95% CI: 0.22 to 3.57) *(65-67)*.

No studies assessed neurodevelopment for this comparison. (Full details are provided in GRADE Table A.3.2 in the **Web Annex**).

Comparison 3

Intervention: oral amoxicillin for 7 days plus gentamicin IM for 2 days
versus
Comparator: penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison (using regimen 3, as labelled above), one trial assessed the following outcomes with the following findings *(65)*.

- Mortality: Very low-certainty evidence suggests little or no difference in all-cause mortality after 7 days (1 RCT, 1784 participants, RR 0.91, 95% CI: 0.39 to 2.14) and after two weeks (1 RCT, 1784 participants, RR 0.92, 95% CI: 0.41 to 2.08).
- Treatment failure: Moderate-certainty evidence suggests a decrease in treatment failure after one week (1 RCT, 1784 participants, RR 0.67, 95% CI: 0.47 to 0.95).
- Relapse: Very low-certainty evidence suggests little or no difference in relapse after two weeks (1 RCT, 1676 participants, RR 0.85, 95% CI: 0.31 to 2.35).
- Adverse events: Not possible to estimate due to very low-certainty evidence (1 RCT, 1784 participants, RR 0.33, 95% CI: 0.01 to 8.22).

No studies assessed treatment success, hospitalizations or neurodevelopment for this comparison. (Full details are provided in GRADE Table A.3.3 in the **Web Annex**).

Comparison 4

Intervention: oral amoxicillin for 7 days plus gentamicin IM for 7 days
versus
Comparator: penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison (using regimen 4, as labelled above), one, two and three studies assessed the following outcomes with the following findings.

- Mortality: Low-certainty evidence suggests little or no difference in all-cause mortality after two weeks (3 RCTs, 5054 participants, RR 0.86, 95% CI: 0.55 to 1.34) *(65-67)*.
- Treatment failure: Low-certainty evidence suggests little or no difference in treatment failure after one week (3 RCTs, 5054 participants, RR 0.86, 95% CI: 0.72 to 1.02) *(65-67)*.
- Relapse: Low-certainty evidence suggests little or no difference in relapse after two weeks (2 RCTs, 3294 participants, RR 1.05, 95% CI: 0.57 to 1.93) *(65, 66)*.
- Treatment success: Low-certainty evidence suggests little or no difference in treatment success after 11–15 days (1 RCT, 1640 participants, RR 0.99, 95% CI: 0.97 to 1.03) *(65)*.
- Hospitalizations: Low-certainty evidence suggests a decrease in hospitalization after two weeks (2 trials, 3276 participants, RR 0.78, 95% CI: 0.58 to 1.05) *(66, 67)*.
- Adverse events: Low-certainty evidence suggests little or no difference in serious adverse events (3 RCTs, 5054 participants, RR 1.00, 95% CI: 0.27 to 3.69) *(65-67)*.

No studies assessed neurodevelopment for this comparison. (Full details are provided in GRADE Table A.3.4 in the **Web Annex**).

Other outcomes
No studies

Subgroup analyses
No studies

Other studies
A systematic review by Duby et al. (2019) *(69)* of community-based antibiotic delivery for PSBI in neonates in LMICs located five additional trials with a total of 145 899 participants that compared hospital referral to community-based packages which combined antibiotics with other co-interventions. The meta-analysis from Duby et al. concluded that community-based antibiotic packages reduced neonatal mortality when compared with standard hospital referral for neonatal PSBI in resource-limited settings, though the use of co-interventions prevented disentanglement of their contribution from that of the community-based antibiotic packages *(69)*. Duby et al. also concluded that simplified, community-based treatment of PSBI using regimens that rely on the combination of oral and injectable antibiotics does not result in increased neonatal mortality when compared with the standard treatment of using only injectable antibiotics (i.e. the control for this comparison) *(69)*.

A meta-analysis by Longombe et al. (2022) *(70)* of pooled individual patient-level data from three trials in Africa and Asia *(65-67)* (including 5075 intention-to-treat [ITT] participants and 4729 per protocol [PP] participants analysed for the primary outcome) reported a reduced risk of the primary outcome (poor clinical outcome defined as death by day 15, treatment failure by day 7 or non-fatal relapse between days 8 and 15) in infants who received oral amoxicillin for 7 days and gentamicin IM for 7 days (= intervention group) compared with the infants who received the standard of care (procaine penicillin and gentamicin IM for 7 days) (= control group) (ITT analysis RR 0.84, 95% CI: 0.72 to 0.99; PP analysis RR 0.81, 95% CI: 0.69 to 0.96). Longombe et al. concluded that oral amoxicillin plus gentamicin IM regimens may be superior to the procaine penicillin plus gentamicin IM regimens for treatment of young infants with PSBI when referral to hospital is not feasible *(70)*.

Acceptability, feasibility and equity evidence
No additional evidence.

Resources, costs and implementation evidence
No additional evidence.

Additional considerations
See section C for further details and cross-cutting issues.

Summary of findings

Comparisons	**Intervention 1:** oral cotrimoxazole for 7 days plus gentamicin IM for 7 days **vs** **Comparator:** penicillin IM plus gentamicin IM for 7 days	**Intervention 2:** procaine penicillin IM for 2 days plus gentamicin IM for 2 days followed by oral amoxicillin for 5 days **vs** **Comparator:** penicillin IM plus gentamicin IM for 7 days	**Intervention 3:** oral amoxicillin for 7 days plus gentamicin IM for 2 days **vs** **Comparator:** penicillin IM plus gentamicin IM for 7 days	**Intervention 4:** oral amoxicillin for 7 days plus gentamicin IM for 7 days **vs** **Comparator:** penicillin IM plus gentamicin IM for 7 days
Summary of effectiveness evidence	■ Increased all-cause mortality and treatment failure ■ Decreased treatment success ■ No evidence for treatment success, hospitalizations, adverse events and neuro-developmental impairment/ disability	■ Little or no difference in all-cause mortality, treatment failure, treatment success, relapse and hospitalizations ■ No evidence for adverse events and neuro-developmental impairment/ disability	■ Decreased treatment failure ■ Little or no difference in all-cause mortality and relapse ■ No evidence for treatment success, hospitalizations, and adverse events and neuro-developmental impairment/ disability	■ Decreased treatment failure ■ Little or no difference in all-cause mortality, relapse and adverse events ■ No evidence for treatment success, hospitalizations and neuro-developmental impairment/ disability
Evidence-to-Decision summary [a]				
Benefits	Moderate decrease	Trivial or no difference	Small increase	Small increase
Harms	Don't know	Trivial or no difference	Don't know	Trivial or no difference
Antimicrobial resistance	Small concerns	Small concerns	Small concerns	Small concerns
Balance of effects	Favours control	Does not favour intervention or control	Probably favours intervention	Probably favours intervention
Certainty	Moderate	Low to moderate	Low	Low
Values	Probably no variability	Probably no variability	Probably no variability	Probably no variability
Acceptability	Probably acceptable	Probably acceptable	Probably acceptable	Probably acceptable
Resources	Low costs	Low costs	Low costs	Low costs
Feasibility	Feasible	Feasible	Feasible	Feasible
Equity	Probably equitable	Probably equitable	Probably equitable	Probably equitable

[a] See Table 2.1.

A.4 Isolated fast breathing in young infants aged 0–6 days in non-hospital settings

Recommendation and remarks

Recommendation A.4 (UPDATED)

Young infants aged 0–6 days with fast breathing as the only IMCI sign of illness should be referred to hospital. If referral is not possible, oral amoxicillin for at least 7 days is recommended. *(Strong recommendation, low-certainty evidence)*

Remarks

- The recommendation was based on two RCTs of 1308 infants aged 0–6 days with fast breathing (≥ 60 breaths per minute) as their only clinical sign in rural and semi-urban PHC facilities in four countries: the Democratic Republic of the Congo, Kenya, Nigeria and Pakistan.
- For the trial examining oral amoxicillin versus placebo, the GDG considered that there was a small improvement in critical outcomes in the oral amoxicillin arm, based on low-certainty evidence.
- For the trial examining oral amoxicillin versus penicillin IM plus gentamicin IM, the GDG considered that there were similar effects on critical outcomes in both arms; however, the evidence was very low certainty as there was serious imprecision (for treatment failure, RR 0.99, 95% CI: 0.77 to 1.27), a serious risk of bias (protocol deviations unbalanced between arms) and only a single study reporting outcomes.
- The GDG recognized the possible adverse effects of oral antibiotics on the microbiome and AMR in young infants aged 0–6 days but considered that the benefits of oral antibiotics outweighed the potential risks.
- The GDG also recognized that there were limited data on dose and duration of oral amoxicillin antibiotic therapy. Based on the trials included in the evidence review, the GDG considered that the following antibiotic dose should be used: oral amoxicillin 50 mg/kg every 12 hours for at least 7 days.
- The GDG made a strong recommendation despite the limited evidence in non-hospital settings as they felt strongly about the importance of providing clear guidance for the management of unwell infants when referral to hospital is not possible. The GDG were able to use their knowledge and experience in best practice clinical management of fast breathing in young infants to make this recommendation by consensus.

Background and definitions

In infants aged 0–6 days, WHO defines fast breathing as 60 breaths per minute or more *(27, 28)*. In 2014, WHO recommended simplified antibiotic regimens (oral amoxicillin for 7 days) for infants aged 0–6 days with fast breathing whose families do not accept or cannot access referral care *(27, 28)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–6 days with fast breathing as the only clinical sign of illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–6 days with fast breathing as the only clinical sign of illness
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing only oral amoxicillin or a combination of penicillin or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes): All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 6 days chronological age
Setting: Non-hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definitions are provided in **Table 1.1**.
[b] As defined by authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2390 studies in infants aged 0–59 days, of which 41 RCTs met the inclusion criteria *(64)*. Among these, 35 trials examined hospital-based regimens for when hospital referral was possible and six trials examined WHO non-hospital-based regimens.

Two trials of 1308 infants from four countries (Democratic Republic of the Congo, Kenya, Nigeria and Pakistan) examined isolated fast breathing in infants aged 0–6 days. One trial of 426 infants aged 0–6 days *(71)* compared oral amoxicillin for 7 days with placebo for 7 days, while the other trial of 882 infants aged 0–6 days *(72)* compared oral amoxicillin for 7 days with penicillin IM plus gentamicin IM for 7 days.

Comparison 1

Intervention: oral amoxicillin for 7 days
versus
Comparator: placebo for 7 days

Critical outcomes

For this comparison, one study of 426 participants assessed the following outcomes with the following findings *(72)*.

- Mortality: Very low-certainty evidence (1 RCT, 426 participants) and RR and CI not estimable for all-cause mortality after two weeks.
- Treatment failure: Low-certainty evidence suggests a decrease in treatment failure after one week (1 RCT, 426 participants, RR 0.45, 95% CI: 0.17 to 1.16).
- Relapse: Very low-certainty evidence suggests a decrease in relapse after one week (1 RCT, 426 participants, RR 0.68, 95% CI: 0.26 to 1.75).
- Hospitalizations: Very low-certainty evidence suggests a decrease in hospitalization after one week (1 RCT, 426 participants, RR 0.49, 95% CI: 0.09 to 2.63).

No studies assessed treatment success, neurodevelopment or adverse events for this comparison. (Full details are provided in GRADE Table A.4.1 in the **Web Annex**).

Comparison 2

Intervention: oral amoxicillin for 7 days
versus
Comparator: penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison, one study of 882 participants assessed the following outcomes with the following findings *(71)*.

- Mortality: Very low-certainty evidence suggests increase in all-cause mortality after two weeks (1 RCT, 882 participants, RR 1.50, 95% CI: 0.25 to 8.93).
- Treatment failure: Very low-certainty evidence suggests little or no difference in treatment failure after one week (1 RCT, 882 participants, RR 0.99, 95% CI: 0.77 to 1.27).
- Relapse: Very low-certainty evidence suggests little or no difference in relapse after 1–2 weeks (1 RCT, 882 participants, RR 1.08, 95% CI: 0.50 to 2.35).

Adverse events: Not possible to estimate due to very low-certainty evidence from the trial with 882 participants (RR and CI not estimable).

No studies assessed treatment success, hospitalizations or neurodevelopment for this comparison. (Full details are provided in GRADE Table A.4.2 in the **Web Annex**).

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

None

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparisons	**Intervention 1:** oral amoxicillin for 7 days **vs** **Comparator 1:** oral placebo for 7 days	**Intervention 2:** oral amoxicillin for 7 days **vs** **Comparator 2:** penicillin IM plus gentamicin IM for 7 days
Summary of effectiveness evidence	■ Little or no difference in all-cause mortality ■ Decrease in treatment failure and relapse ■ No evidence for treatment success, hospitalizations, adverse events and neurodevelopmental impairment/ disability	■ Little or no difference in all-cause mortality, treatment failure and relapse ■ No evidence for treatment success, hospitalizations, adverse events and neurodevelopmental impairment/ disability
Evidence-to-Decision summary [a]		
Benefits	Small increase	Don't know
Harms	Don't know	Don't know
Antimicrobial resistance	Small concerns	Small concerns
Balance of effects	Probably favours intervention	Don't know
Certainty	Low	Very low
Values	Probably no variability	Don't know
Acceptability	Probably acceptable	Probably acceptable
Resources	Low costs	Low costs
Feasibility	Feasible	Feasible
Equity	Probably equitable	Probably equitable

[a] See **Table 2.1**.

A.5 Isolated fast breathing in young infants aged 7–59 days in non-hospital settings

Recommendation and remarks

Recommendation A.5 (UPDATED)

Young infants aged 7–59 days with fast breathing as the only IMCI sign of illness should be treated with oral amoxicillin for at least 7 days. These infants can be managed outside hospital. *(Strong recommendation, very low-certainty evidence)*

Remarks

- The recommendation was based on three trials of 4307 infants aged 7–59 days from PHC clinics in Bangladesh, the Democratic Republic of the Congo, Ethiopia, India, Kenya, Malawi, Nigeria and Pakistan.
- For the trial that compared oral amoxicillin for 7 days with procaine penicillin IM plus gentamicin IM for 7 days (1451 infants in the Democratic Republic of the Congo, Kenya and Nigeria), the evidence was judged as low certainty in the previous WHO guideline (2014) and very low certainty in this guideline. This was due to the serious imprecision for treatment failure (RR 0.86, 95% CI: 0.70 to 1.07) and the serious risk of bias (comparator arm had more protocol deviations, and different people administered antibiotics – parents in the intervention arm and study personnel in the comparator arm).
- The GDG also considered evidence from one trial of 544 infants aged 7–59 days in Pakistan that compared oral amoxicillin versus placebo and from another trial of 2312 infants in Bangladesh, Ethiopia, India and Malawi that compared oral amoxicillin plus enhanced CHW community case management versus standard community case management. Both trials found little or no difference in the effect of oral amoxicillin based on low- or very low-certainty evidence.
- The GDG recognized that there were limited data available on dose and duration of antibiotic therapy. Based on the trials included in the evidence review, the GDG considered that the following antibiotic dose should be used: oral amoxicillin 50 mg/kg every 12 hours for at least 7 days.
- The GDG made a strong recommendation despite the limited evidence in non-hospital settings as they felt strongly about the importance of providing clear guidance for the management of infants with fast breathing. The GDG were able to use their knowledge and experience in best practice clinical management of fast breathing in young infants to make this recommendation by consensus.

Background and definitions

In infants aged 7–59 days, WHO defines fast breathing as 60 breaths per minute or more *(28)*. In 2014, WHO recommended simplified antibiotic regimens (oral amoxicillin for 7 days) for infants aged 7–59 days with fast breathing whose families do not accept or cannot access referral care *(28)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 7–59 days with fast breathing as the only sign of illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 7–59 days with with fast breathing as the only sign of illness
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing only oral amoxicillin, or a combination of penicillin or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: 7–59 days chronological age
Setting: Non-hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definitions are provided in **Table 1.1**.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2601 studies in infants aged 0–59 days, of which 10 RCTs met the inclusion criteria *(73)*.

Among these, seven of the studies examined hospital-based regimens and three trials of 4307 infants aged 7–59 days examined fast breathing as an isolated clinical sign in eight countries, and these are the three trials that the recommendation is based on. One was a trial in Pakistan of 544 infants with isolated fast breathing where referral was not possible and it compared oral amoxicillin for 7 days with placebo *(72)*. Another of these three trials was a larger multi-country trial of 2312 infants with isolated fast breathing in Bangladesh, Ethiopia, India and Malawi that compared oral amoxicillin for 7 days plus enhanced CHW community case management (assess hypoxaemia with a pulse oximeter and refer hypoxaemic infants to a referral facility/hospital) with standard community case management (assess fast breathing and danger signs and refer) *(74)*. The third trial included 1451 infants with isolated fast breathing in the Democratic Republic of the Congo, Kenya and Nigeria, and it compared oral amoxicillin for 7 days with procaine penicillin IM plus gentamicin IM for 7 days *(71)*.

Comparison 1

Intervention: oral amoxicillin for 7 days
versus
Comparator: oral placebo for 7 days

Critical outcomes

For this comparison, one study of 544 participants assessed the following outcomes with the following findings *(72)*.

- Mortality: Very low-certainty evidence (1 RCT, 544 participants), and RR and CI are not estimable for all-cause mortality after two weeks.
- Treatment failure: Very low-certainty evidence suggests a decrease in treatment failure after 1–2 weeks (1 RCT, 544 participants, RR 0.51, 95% CI: 0.20 to 1.35).
- Relapse: Very low-certainty evidence suggests little or no difference in relapse after 1–2 weeks (1 RCT, 544 participants, RR 1.18, 95% CI: 0.43 to 3.20).
- Hospitalizations: Very low-certainty evidence suggests a decrease in hospitalization after one week (1 RCT, 544 participants, RR 0.77, 95% CI: 0.17 to 3.42).

No studies assessed treatment success, neurodevelopment or adverse events for this comparison. (Full details are provided in GRADE Table A.5.1 in the **Web Annex**).

Comparison 2

Intervention: oral amoxicillin for 7 days plus enhanced community case management for 7 days
versus
Comparator: standard community case management for 7 days

Critical outcomes

For this comparison, one study of 2312 participants assessed the following outcomes with the following findings *(74)*.

- Mortality: Low-certainty evidence suggests little or no difference in all-cause mortality after two weeks (1 RCT, 2312 participants, adjusted RR [aRR] 0.99, 95% CI: 0.14 to 6.97).
- Treatment failure: Low-certainty evidence suggests little or no difference in treatment failure after one week (1 RCT, 2312 participants, aRR 0.86, 95% CI: 0.58 to 1.26).
- Hospitalizations: Very low-certainty evidence suggests decrease in hospitalization after one week (1 RCT, 2312 participants, aRR 0.63, 95% CI: 0.29 to 1.33).
- Adverse events: Not possible to estimate due to very low-certainty evidence from the trial of 2312 participants (RR and CI not estimable).

No studies assessed treatment success or neurodevelopment for this comparison. (Full details are provided in GRADE Table A.5.2 in the **Web Annex**).

Comparison 3

Intervention: oral amoxicillin for 7 days
versus
Comparator: procaine penicillin IM plus gentamicin IM for 7 days

Critical outcomes

For this comparison one study assessed the following outcomes with the following findings *(71)*.

- Mortality: Very low-certainty evidence suggests a decrease in all-cause mortality after two weeks (1 RCT, 1451 participants, RR 0.50, 95% CI: 0.05 to 5.56).
- Treatment failure: Very low-certainty evidence suggests little or no difference in treatment failure after one week (1 RCT, 1451 participants, RR 0.86, 95% CI: 0.70 to 1.07).
- Relapse: Very low-certainty evidence suggests little or no difference in relapse after one week (1 RCT, 1180 participants, RR 0.98, 95% CI: 0.41 to 2.33).
- Adverse events: Very low-certainty evidence (1 RCT, 1451 participants) suggests little or no difference in serious adverse events (not estimable).

No studies assessed treatment success, hospitalizations or neurodevelopment for this comparison. (Full details are provided in GRADE Table A.5.3 in the **Web Annex**).

Other outcomes
No studies

Subgroup analyses
No studies

Other studies
None

Acceptability, feasibility and equity evidence
No additional evidence.

Resources, costs and implementation evidence
No additional evidence.

Additional considerations
See section C for further details and cross-cutting issues.

Summary of findings

Comparisons	Intervention 1: oral amoxicillin **vs** Comparator 1: placebo for 7 days	Intervention 2: oral amoxicillin plus enhanced community case management by CHW **vs** Comparator 2: standard case management by CHW without oral amoxicillin for 7 days	Intervention 3: oral amoxicillin **vs** Comparator 3: penicillin plus gentamicin IM for 7 days
Summary of effectiveness evidence	■ Decrease in treatment failure and hospitalization ■ Little or no difference in all-cause mortality and relapse ■ No evidence for treatment success, adverse events and neurodevelopmental impairment/disability	■ Decrease in hospitalization ■ Little or no difference in all-cause mortality, treatment failure ■ No evidence for treatment success, hospitalizations, adverse events and neurodevelopmental impairment/disability	■ Decrease in all-cause mortality ■ Little or no difference in treatment failure, relapse, serious adverse events ■ No evidence for treatment success, hospitalizations and neurodevelopmental impairment/disability
Evidence-to-Decision summary [a]			
Benefits	Don't know	Trivial or no difference	Don't know
Harms	Don't know	Don't know	Don't know
Antimicrobial resistance	Small concerns	Small concerns	Small concerns
Balance of effects	Don't know	Does not favour either	Don't know
Certainty	Very low	Low	Very low
Values	Don't know	Probably no variability	Don't know
Acceptability	Probably acceptable	Probably acceptable	Probably acceptable
Resources	Low	Low	Low
Feasibility	Feasible	Feasible	Feasible
Equity	Probably equitable	Probably equitable	Probably equitable

[a] See **Table 2.1**.

B. Hospital settings

B.1 Diagnostic accuracy of clinical signs of sepsis in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.1
No recommendation
Remarks

- The GDG reviewed 28 studies that recruited 138 575 infants aged 0–59 days in 20 countries – 17 LMICs: Bangladesh, Bolivia (Plurinational State of), Brazil, China, Ethiopia, Gambia, Ghana, India, Kenya, Pakistan, Papua New Guinea, the Philippines, South Africa, Thailand, Uganda, Viet Nam and Zimbabwe; and three high-income countries (HICs): Canada, Greece and Italy.
- All 28 studies compared assessment of clinical signs of sepsis with physician judgement of sepsis or mortality as the reference standard. The studies used a range of prediction models, weighted scores and checklists.
- The GDG decided not to make a recommendation on use of hospital-based algorithms for diagnosing sepsis as all studies used algorithms with laboratory tests that are not currently feasible in low-resource settings.
- The GDG recognized that some of these algorithms were routinely being used for risk stratification in HICs. However, they considered that evidence about these algorithms was limited to single studies with small sample sizes and did not have external validation. The GDG considered that further research is needed before recommendations on their use can be developed.
- The GDG proposed further research using harmonized and standardized assessment tools.

Background and definitions

For hospitalized infants, the WHO *Pocket book of hospital care for children* defined suspected sepsis in 2013 as one or more of the following clinical signs: not feeding well, movement only when stimulated, high body temperature (≥ 38 °C), low body temperature (< 35.5 °C), severe chest indrawing, not able to feed at all, no movement on stimulation, convulsions, drowsiness or unconsciousness, grunting, central cyanosis, severe jaundice and severe abdominal distention in infants aged 0–59 days, or fast breathing (≥ 60 breaths per minute) in infants aged under 0–6 days *(12, 13)*. In 2013, this definition did not include laboratory tests due to the lack of availability of simple tests in district hospitals, such as full blood count and C-reactive protein (CRP). However, these tests have become more widely available and POC rapid "bedside" laboratory tests are becoming much more common *(10, 75)*. There has also been much interest in how to integrate laboratory tests with IMCI and other clinical algorithms, and ongoing work to develop more sophisticated predictive algorithms and machine-learning tools to improve sepsis diagnosis, assist clinicians in determining when to stop antibiotics and rationalizing antibiotic therapy *(75)*.

Summary of the evidence: diagnostic accuracy

Overview
Question: Among young infants aged 0–59 days, in hospital settings, what is the diagnostic accuracy (sensitivity and specificity) of clinical sign-based algorithms of suspected sepsis[a] compared with a reference standard (physician judgement of sepsis or mortality) in identifying infants who require treatment for suspected sepsis?
Population, index test, reference standard and diagnosis of interest (PIRD) details
Population: Young infants aged 0–59 days with suspected sepsis
Index test: Clinical sign-based algorithms of suspected sepsis ascertained by any cadre of health worker
Reference standard: Physician judgement of sepsis or mortality
Diagnosis of interest: Sepsis
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in Table 1.2

[a] Definitions are provided in Table 1.1.

Sources and characteristics of studies

The diagnostic accuracy evidence was derived from two systematic reviews *(59, 76)*. In one systematic review, 11 studies met the inclusion criteria *(76)*, and included 115 040 infants from 17 countries: Bangladesh, Brazil, Canada, China, Ethiopia, Gambia, Greece, India, Italy, Kenya, Papua New Guinea, the Philippines, South Africa, Thailand, Uganda, Viet Nam and Zimbabwe. The 11 studies reported on 26 different algorithms: 13 were IMCI-based checklists *(60, 77, 78)* and the other 13 were regression-based prediction models *(15, 78-85)*. In the other systematic review, 19 studies met the inclusion criteria *(59)*, and included 24 046 infants from 13 countries: Bangladesh, Bolivia, Brazil, Ethiopia, Gambia, Ghana, India, Kenya, Pakistan, Papua New Guinea, the Philippines, South Africa and Zimbabwe. The 19 studies reported on 20 different algorithms: 12 were IMCI-based checklists and the remainder were non-IMCI checklists (4), weighted scores (2) and regression-based prediction models (2) *(59)*.

Comparison

Index test: clinical sign-based algorithms of suspected sepsis ascertained by any cadre of health worker
versus
Reference standard: physician judgement of sepsis or mortality in hospitals

Critical outcomes

Twenty-five studies reported sensitivity and specificity, and 11 reported the area under the curve (AUC). However, all studies used different algorithms with different combinations of clinical signs and laboratory tests, thus evidence could not be pooled. The evidence from the studies was also judged by the GDG to be very low certainty.

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

Two systematic reviews have examined the diagnostic accuracy of algorithms that include clinical signs, laboratory tests, decision support tools and predictive modelling for diagnosis of neonatal sepsis *(86, 87)*. These reviews identified seven different algorithms used for this purpose. However, the algorithms all included different clinical signs and laboratory tests and thus their results could not be pooled.

Two additional systematic reviews examined the diagnostic accuracy of laboratory biomarkers to diagnose culture-confirmed sepsis *(88)* or clinical or culture-confirmed sepsis *(89)* in infants aged 0–59 days at the time of presentation to health facilities. Brown et al. (2019) identified 20 studies of 1615 infants reporting upon diagnostic accuracy of CRP in neonates and reported that at median specificity (0.74), sensitivity was 0.62 (95% CI: 0.50 to 0.73) *(88)*. Rees et al. (2023) examined CRP, procalcitonin (PCT), erythrocyte sedimentation rate (ESR) and white cell count (WCC) in 134 studies, and concluded that CRP and PCT demonstrated good discriminatory ability to diagnose sepsis with blood culture as the reference (CRP of ≥ 60 mg/L, AUC: 0.87, 95% CI: 0.76 to 0.91, n=1339 neonates; and PCT of ≥ 0.5 ng/ml, AUC: 0.87, 95% CI: 0.70 to 0.92, n=617 neonates), while ESR and WCC had poor discriminatory ability *(89)*.

One further systematic review of seven studies and a total of 505 infants examined the use of CRP in decision-making for stopping antibiotic treatment in newborns diagnosed with sepsis *(90)*. Petel et al. (2018) reported that CRP-based algorithms shortened antibiotic treatment duration by 1.45 days (95% CI: −2.61 to −0.28) in two RCTs, and by 1.15 days (95% CI: −2.06 to −0.24) in two cohort studies, with no differences in mortality or infection relapse in neonates *(90)*.

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

None

Summary of findings

Comparison	**Index test:** clinical sign-based algorithms of suspected sepsis ascertained by any cadre of health worker **vs** **Reference standard:** physician judgement of sepsis or mortality
Summary of diagnostic accuracy evidence	Not estimable
Evidence-to-Decision summary[a]	
Sensitivity accuracy	Don't know
Sensitivity certainty	Don't know
Specificity accuracy	Don't know
Specificity certainty	Don't know
Values	Probably no variability
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Feasible
Equity	Probably equitable

[a] See **Table 2.1**.

B.2 Suspected sepsis in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.2 (UPDATED)

In young infants aged 0–59 days who are hospitalized with suspected sepsis, ampicillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended as first-choice antibiotic management. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The recommendation was based on six trials of 1083 infants aged 0–59 days from Europe, Malawi, Pakistan and Türkiye, which compared third-generation cephalosporins (ceftriaxone or cefotaxime) IM/IV versus ampicillin IM/IV or penicillin IM/IV plus gentamicin IM/IV.
- The GDG considered that third-generation cephalosporins had no clear benefits over the WHO-recommended hospital regimen of ampicillin IM/IV plus gentamicin IM/IV, that they may increase antimicrobial resistance and also had significant costs.
- The GDG noted the increase in neurologic sequelae in the intervention (cephalosporin) group but considered the evidence to be of very low certainty.
- The evidence was judged as low in the previous guideline and moderate in this guideline, as additional evidence was located from a large trial from Pakistan *(68)* which increased the precision of point estimates.
- The GDG made this recommendation recognizing that all trials were based in tertiary hospitals except for the Pakistan trial, which was based at PHC facilities.
- The GDG also recognized that there were limited data on antibiotic dosing. Based on the trials included in the evidence review, the GDG considered that the following antibiotic doses should be used: ampicillin IM/IV 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 10 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 10 days.
- The GDG emphasized the importance of adjusting empiric antibiotic therapy doses during the course of the illness, as is routinely done in many hospitals. This includes targeting individual antibiotic therapy regimens based on microbiological test results, and stopping antibiotic therapy based on validated clinical and laboratory risk stratification algorithms.

Background and definitions

For hospitalized infants, the 2013 WHO *Pocket book of hospital care for children* defined suspected sepsis as one or more of the following clinical signs: not feeding well, movement only when stimulated, high body temperature (≥ 38 °C), low body temperature (< 35.5 °C), severe chest indrawing, not able to feed at all, no movement on stimulation, convulsions, drowsiness or unconsciousness, grunting, central cyanosis, severe jaundice and severe abdominal distention in infants aged 0–59 days, or fast breathing (≥ 60 breaths per minute) in infants aged 0–6 days *(13)*.

The WHO *Pocket book of hospital care for children* also recommended providing ampicillin or penicillin plus gentamicin IM/IV for at least 10 days to infants aged 0–59 days with suspected sepsis *(13)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with suspected sepsis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with suspected sepsis
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definitions are provided in **Table 1.1**.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2390 studies in infants aged 0–59 days, of which 41 RCTs met the inclusion criteria *(64)*. Among these, 35 trials examined hospital-based regimens for when hospital referral was possible and six trials examined WHO non-hospital-based regimens.

One hospital-based trial examined cephalothin combined with tobramycin *(91)*. The five remaining hospital-based trials compared alternative antibiotic regimens with WHO-recommended antibiotic regimens among a total of 2248 infants *(68, 92-95)*. All five of these trials compared third-generation cephalosporins with ampicillin or penicillin IM/IV plus gentamicin IM/IV. The five trials were based in 13 countries: Belgium, Denmark, France, Germany, Greece, Israel, Italy, Malawi, Pakistan, Portugal, Sweden, Türkiye and the United Kingdom of Great Britain and Northern Ireland. All five trials were based in tertiary hospitals except the Pakistan trial, which was based at PHC facilities *(68)*. The duration of antibiotic therapy in the trials varied as follows: 7 days *(68)*, 2–10 days *(92, 95)*, 5–15 days *(94)*, and 10–17 days *(93)*.

Comparison

Intervention: third-generation cephalosporins for 2–17 days
versus
Comparator: ampicillin or penicillin IM/IV plus gentamicin IM/IV for 2–17 days

Critical outcomes

For this comparison, one, two, three and four studies assessed the following outcomes with the following findings.

- Mortality: Very low-certainty evidence suggests a decrease in all-cause mortality from birth to hospital discharge (3 RCTs, 711 participants, RR 0.64, 95% CI: 0.25 to 1.65) *(68, 93, 94)*.
- Treatment failure: Very low-certainty evidence suggests little or no difference in treatment failure after seven days of enrolment (2 RCTs, 955 participants, RR 1.02, 95% CI: 0.38 to 2.71) *(68, 92)*.
- Treatment success: Moderate-certainty evidence suggests little or no difference in treatment success after 48 hours to treatment completion (4 RCTs, 1983 participants, RR 1.03, 95% CI: 0.93 to 1.13) *(68, 92, 93, 95)*.
- Neurodevelopment: Very low-certainty evidence suggests an increase in neurologic sequelae after six months (1 RCT, 140 participants, RR 1.39, 95% CI: 0.69 to 2.78) *(94)*.
- Adverse events: Moderate-certainty evidence suggests a decrease in adverse events after 5–14 days (3 RCTs, 628 participants, RR 0.35, 95% CI: 0.15 to 0.82) *(68, 93, 94)*.

No studies assessed hospitalizations. (Full details are provided in GRADE Table B.2.1 in the **Web Annex**).

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

Two systematic reviews both by Korang et al. and both published in 2021 examined (i) antibiotic management for early-onset sepsis, in infants aged 0 to < 3 days (5 RCTs, 865 participants) *(96)* and (ii) late-onset sepsis, in infants aged 3–28 days (5 RCTs, 580 participants) *(97)*. These reviews excluded all trials that recruited infants outside these specific age ranges and the evidence was considered to be inconclusive and of very low certainty.

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** third-generation cephalosporins for a total of 2–17 days **vs** **Comparator:** penicillin or ampicillin IM/IV plus gentamicin IM/IV for a total of 2–17 days
Summary of effectiveness evidence	■ Decrease in all-cause mortality and adverse events ■ Increase in neurologic sequelae ■ Little or no difference in treatment failure and treatment success ■ No evidence for hospitalizations
Evidence-to-Decision summary[a]	
Benefits	Trivial or no difference
Harms	Moderate decrease
Antimicrobial resistance	Moderate concerns
Balance of effects	Does not favour intervention or control
Certainty	Moderate certainty for treatment success and adverse events, very low certainty for other outcomes
Values	Probably no variability
Acceptability	Probably acceptable
Resources	Moderate costs
Feasibility	Feasible
Equity	Varies

[a] See Table 2.1.

B.3 Suspected staphylococcal sepsis in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.3 (UPDATED)

In young infants aged 0–59 days who are hospitalized with suspected staphylococcal sepsis, cloxacillin IM/IV plus gentamicin IM/IV for at least 10 days is recommended as first-choice antibiotic management. *(Strong recommendation, very low-certainty evidence)*

Remarks

- There were no included trials.
- The GDG recognized that there were limited data on antibiotic dosing. Based on clinical practice, the GDG considered that the following antibiotic doses should be used: cloxacillin IM/IV 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 10 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 10 days.
- The GDG made a strong recommendation despite the lack of trials as they felt strongly about the importance of providing clear guidance for the management of infants with sepsis. The GDG were able to use their knowledge and experience in best practice clinical management in young infants to make this recommendation by consensus.

Background and definitions

For hospitalized infants, the 2013 WHO *Pocket book of hospital care for children* defines suspected staphylococcal sepsis as one or more of the following clinical signs: not feeding well, movement only when stimulated, high body temperature (≥ 38 °C), low body temperature (< 35.5 °C), severe chest indrawing, not able to feed at all, no movement on stimulation, convulsions, drowsiness or unconsciousness, grunting, central cyanosis, severe jaundice and severe abdominal distention in infants aged 0–59 days, or fast breathing (≥ 60 breaths per minute) in infants aged 0–6 days; plus one or more of the clinical signs of staphylococcal infection: skin infection, pustules, omphalitis or abscesses *(13)*.

The WHO *Pocket book of hospital care for children* recommended providing cloxacillin plus gentamicin IV for at least 10 days to infants aged 0–59 days with suspected staphylococcal sepsis *(13)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with suspected staphylococcal sepsis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with suspected staphylococcal sepsis
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing cloxacillin plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in Table 1.2

[a] Definitions are provided in Table 1.1.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2390 studies in infants aged 0–59 days, of which 41 RCTs met the inclusion criteria *(64)*. Among these, 35 trials examined hospital-based regimens but none of them compared alternative antibiotic regimens to WHO-recommended antibiotic regimens for suspected staphylococcal sepsis.

Comparison

Intervention: alternative antibiotic regimens
versus
Comparator: antibiotic regimens containing cloxacillin plus gentamicin IM/IV

Critical outcomes

No studies were located for this comparison.

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

No studies

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** alternative antibiotic regimen **vs** **Comparator:** antibiotic regimens containing cloxacillin plus gentamicin IM/IV
Summary of effectiveness evidence	Not estimable
Evidence-to-Decision summary[a]	
Benefits	Don't know
Harms	Don't know
Antimicrobial resistance	Small concerns
Balance of effects	Don't know
Certainty	Very low
Values	Don't know
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Limited feasibility
Equity	Varies

[a] See **Table 2.1.**

B.4 Suspected meningitis in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.4 (NEW)

In young infants aged 0–59 days who are hospitalized with suspected meningitis, ampicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV for at least three weeks is recommended as first-choice antibiotic management. *(Strong recommendation, very low-certainty evidence)*

Remarks

- There were no included trials.
- The GDG emphasized that this recommendation is for therapy with ampicillin, cefotaxime or ceftriaxone combined with gentamicin. However, the GDG emphasized that ampicillin should be given in addition to third-generation cephalosporins and gentamicin (i.e. triple therapy) if *Listeria monocytogenes* is suspected.
- The GDG made these recommendations for empiric first-choice treatment of suspected meningitis in infants where the causative organism is unknown.
- The GDG recommended that cerebrospinal fluid (CSF) cultures and antimicrobial sensitivity testing should be used to inform therapy for infants with suspected meningitis wherever possible. However, the GDG recognized that CSF specimens may not be available and that microscopy and culture-testing facilities may be limited in LMICs.
- The GDG recognized that ceftriaxone has been associated with bilirubin binding and jaundice in young infants but considered that data were limited.
- The GDG recognized that regimens without gentamicin are used in some settings, such as third-generation cephalosporin monotherapy or third-generation cephalosporins plus ampicillin. They also recognized that there are toxicities associated with short- and long-term gentamicin use, there are difficulties in measuring gentamicin levels, and that observational studies report that gentamicin may have poor penetration into CSF. However, the GDG also considered that gentamicin penetration may be enhanced by inflamed meninges and that gentamicin is widely used for treatment of suspected meningitis in both HIC and LMIC settings. The GDG also emphasized that gentamicin levels should be measured wherever possible.
- The GDG emphasized that the antibiotics must be given by the parenteral (IM or IV) route for suspected meningitis.
- The GDG emphasized that care with antibiotic dosing is needed. The GDG recognized that there were limited data on antibiotic dosing. The GDG suggested that the following doses of antibiotics should be used: ampicillin IM/IV 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for at total of at least three weeks, or cefotaxime IM/IV 50 mg/kg every 12 hours in the first week of life and every 6 hours after the first week of life for a total of at least three weeks, or ceftriaxone IM/IV 100 mg/kg once a day (whether starting in the first week of life or later) for a total of at least three weeks, plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least three weeks (see also **Table 3.1** later in this chapter).
- The GDG considered that antibiotic duration should be for at least three weeks, and continued for longer if the infant is not improving. The GDG emphasized the importance of adjusting empiric antibiotic therapy during the course of the illness, as is routinely done in many hospitals. This includes targeting individual antibiotic therapy regimens based on microbiological test results and stopping antibiotic therapy based on validated, clinical and laboratory risk stratification algorithms.
- The GDG made a strong recommendation despite the lack of trials as they felt strongly about the importance of providing clear guidance for the management of infants with meningitis. The GDG were able to use their knowledge and experience in best practice clinical management in managing meningitis in young infants to make this recommendation by consensus.

Background and definitions

For hospitalized infants, the 2013 *WHO Pocket book of hospital care for children* defines suspected meningitis as one or more of the following clinical signs: drowsiness, lethargy, unconsciousness, convulsions, bulging fontanelle, irritability and high-pitched cry in an infant aged 0–59 days *(13)*. Infants commonly have signs of both meningitis and sepsis, meaning that an infant with suspected sepsis may also have meningitis. It is also well known that these clinical signs are often absent or difficult to determine in a young infant, e.g. a stiff neck is rare in a young infant and can be difficult to elicit. Bulging fontanelle can also be difficult to determine in an unwell young infant *(13)*.

The *WHO AWaRe antibiotic book* and the *WHO Pocket book of hospital care for children* recommended providing ampicillin, penicillin, ceftriaxone or cefotaxime plus gentamicin IM/IV for at least three weeks to infants aged 0–59 days with suspected meningitis *(13, 16)*. These recommendations were made in 2013 and 2015 on the basis of expert opinion *(13, 16)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with suspected meningitis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with suspected meningitis
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing penicillin, ampicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definition provided in **Table 1.1**.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 1088 studies in infants aged 0–59 days, of which two RCTs met the inclusion criteria *(64)*. Both trials were hospital-based, but one trial compared different antibiotic durations *(98)* and the other trial compared intrathecal gentamicin for three days plus ampicillin IV plus gentamicin IM for three weeks with ampicillin IV plus gentamicin IM for three weeks *(99)*. No trials compared alternative antibiotic regimens to the WHO regimens of ampicillin, penicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV.

Comparison

Intervention: alternative antibiotic regimens
versus
Comparator: antibiotic regimens containing penicillin, ampicillin, cefotaxime or ceftriaxone plus gentamicin IM/IV

Critical outcomes

No studies were located for this comparison.

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

A systematic review of RCTs and observational studies of the effect of the duration of antibiotic therapy by Van Hentenryck et al. (2022) *(100)* included one RCT *(98)* and one cohort study *(101)* that examined the relationship between duration of parenteral therapy and clinical outcomes. However, none of the patients in the included studies who received antibiotic courses shorter than the recommended duration had CSF culture-positive meningitis. The review concluded that rigorous, prospective clinical trial data are lacking to determine the optimal parenteral antibiotic duration in bacterial meningitis in young infants.

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** alternate antibiotic regimens **vs** **Comparator:** antibiotic regimens containing penicillin, ampicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV for at least three weeks
Summary of effectiveness evidence	Not estimable
Evidence-to-Decision summary[a]	
Benefits	Don't know
Harms	Don't know
Antimicrobial resistance	Don't know
Balance of effects	Don't know
Certainty	Very low
Values	Don't know
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Feasible
Equity	Varies

[a] See **Table 2.1**.

B.5 Suspected pneumonia in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.5 (NEW)

In young infants aged 0–59 days who are hospitalized with suspected pneumonia, ampicillin IM/IV plus gentamicin IM/IV for at least 7 days is recommended as first-choice antibiotic management. *(Strong recommendation, very low-certainty evidence)*

Remarks

- There were no included trials.
- The GDG recognized that there were also limited data on antibiotic dosing. Based on clinical practice, the GDG considered that the following antibiotic doses should be used: ampicillin IM/IV 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 7 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 7 days.
- The GDG emphasized the importance of adjusting empiric antibiotic therapy during the course of the illness, as is routinely done in many hospitals. This includes targeting individual antibiotic therapy regimens based on microbiological test results, and stopping antibiotic therapy based on validated, clinical and laboratory risk stratification algorithms.
- The GDG made a strong recommendation despite the lack of trials as they felt strongly about the importance of providing clear guidance for the management of infants with pneumonia. The GDG were able to use their knowledge and experience in best practice clinical management of pneumonia in young infants to make this recommendation by consensus.

Background and definitions

For hospitalized infants, the 2013 WHO *Pocket book of hospital care for children* defines suspected pneumonia as one or more of the following: fast breathing of 60 breaths per minute or more in infants aged 0–6 days or fast breathing of 60 breaths per minute or more in infants aged 7–59 days, chest indrawing, grunting, cyanosis and hypoxaemia *(13)*. Radiological signs are not often used in the diagnosis of pneumonia as they can lag behind the clinical presentation, and lack both sensitivity and specificity in young infants *(13)*.

The WHO *Pocket book of hospital care for children* also recommended providing ampicillin or penicillin plus gentamicin IM/IV for at least 7 days to infants aged 0–59 days with suspected pneumonia *(13)*. This guidance was developed in 2013 on the basis of expert opinion *(13)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence

Overview
Question: Among young infants aged 0–59 days with suspected pneumonia,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with suspected pneumonia
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in **Table 1.2**

[a] Definition provided in **Table 1.1**.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2601 studies in infants aged 0–59 days, of which 10 RCTs met the inclusion criteria *(73)*. Seven of the 10 trials examined hospital regimens *(102-108)*. Of these seven trials, one compared penicillin with cephalosporin but did not specify if the cephalosporin was first, second or third generation *(105)*, three examined antibiotic duration *(102, 103, 106)* and three examined non-WHO antibiotic regimens: meropenem and imipenem *(107)*, cefoperazone and meropenem *(104)* and amoxicillin plus clavulanic acid *(108)*.

Comparison

Intervention: alternative antibiotic regimens
versus
Comparator: antibiotic regimens containing penicillin or ampicillin plus gentamicin IM/IV

Critical outcomes

No studies were located for this comparison.

Other outcomes

No studies

Subgroup analyses
No studies

Other studies
A systematic review by Korang et al. (2018) assessed the effectiveness of antibiotics in treating hospital-acquired pneumonia in neonates and children under the age of 5 years (a total of 84 participants) *(109)*. All four of the reviewed trials were assessed as having high risk of bias and the authors did not conduct any meta-analyses.

Another systematic review by Lassi et al. (2021) assessed the effectiveness of antibiotics for the treatment of non-severe pneumonia in young infants and children aged 2–59 months (three trials, 3256 participants) *(110)*. The authors concluded that there was insufficient evidence to support or challenge the continued use of antibiotics for the treatment of non-severe pneumonia.

Acceptability, feasibility and equity evidence
No additional evidence.

Resources, costs and implementation evidence
No additional evidence.

Additional considerations
See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** alternative antibiotic regimens **vs** **Comparator:** antibiotic regimens containing penicillin or ampicillin plus gentamicin IM/IV
Summary of effectiveness evidence	Not estimable
Evidence-to-Decision summary [a]	
Benefits	Don’t know
Harms	Don’t know
Antimicrobial resistance	Small concerns
Balance of effects	Don’t know
Certainty	Very low
Values	Don’t know
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Feasible
Equity	Varies

[a] See **Table 2.1.**

B.6 Suspected staphylococcal pneumonia in young infants aged 0–59 days in hospital settings

Recommendation and remarks

Recommendation B.6 (NEW)

In young infants aged 0–59 days who are hospitalized with suspected staphylococcal pneumonia, cloxacillin IM/IV plus gentamicin IM/IV for at least 7 days is recommended as first choice antibiotic management. *(Strong recommendation, very low-certainty evidence)*

Remarks

- There were no included trials.
- The GDG recognized that there were also limited data on antibiotic dosing. Based on clinical practice, the GDG considered that the following antibiotic doses should be used: cloxacillin IM/IV 50 mg/kg every 12 hours in the first week of life and every 8 hours after the first week of life for a total of at least 7 days plus gentamicin IM/IV 5 mg/kg once a day in the first week of life and 7.5 mg/kg once a day after the first week of life for a total of at least 7 days.
- The GDG emphasized the importance of adjusting empiric antibiotic therapy during the course of the illness, as is routinely done in many hospitals. This includes targeting individual antibiotic therapy regimens based on microbiological test results, and stopping antibiotic therapy based on validated, clinical and laboratory risk stratification algorithms.
- The GDG made a strong recommendation despite the lack of trials as they felt strongly about the importance of providing clear guidance for the management of infants with pneumonia. The GDG were able to use their knowledge and experience in best practice clinical management of pneumonia in young infants to make this recommendation by consensus.

Background and definitions

For hospitalized infants, the 2013 WHO *Pocket book of hospital care for children* defined suspected staphylococcal pneumonia as one or more of the following: fast breathing of 60 breaths per minute or more in infants aged 0–6 days, fast breathing of 60 breaths per minute or more in infants aged 7–59 days, chest indrawing, grunting, cyanosis and hypoxaemia, plus one or more of the clinical signs of staphylococcal infection: skin infection, pustules, omphalitis or abscesses *(13)*.

The WHO *Pocket book of hospital care for children* also recommended providing cloxacillin plus gentamicin IV for at least 7 days to infants aged 0–59 days with suspected staphylococcal pneumonia *(13)*. This guidance was developed in 2013 on the basis of expert opinion *(13)*. However, there have been changes to AMR in hospital and community settings since that time.

Summary of the evidence: effectiveness

Overview
Question: Among young infants aged 0–59 days with suspected staphylococcal pneumonia,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?
Population, intervention, comparator and outcomes (PICO) details
Population: Young infants aged 0–59 days with suspected staphylococcal pneumonia
Intervention: Alternative antibiotic regimens
Comparator: WHO-recommended antibiotic regimens containing cloxacillin IM/IV plus gentamicin IM/IV
Outcomes (critical outcomes)**:** All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
Timing, setting and subgroups
Timing of the intervention: Birth to 59 days chronological age
Setting: Hospital settings in any high-, middle- or low-income country
Strata and subgroups: As defined in Table 1.2

[a] Definition provided in Table 1.1.
[b] As defined by the authors of the studies.

Sources and characteristics of studies

The effectiveness evidence was derived from a systematic review that identified 2601 studies in infants aged 0–59 days, of which 10 RCTs met the inclusion criteria *(73)*. Seven of the 10 trials examined hospital regimens *(102-108)*. Of the seven trials, one compared penicillin with cephalosporin but did not specify if the cephalosporin was first, second or third generation *(105)*, three examined antibiotic duration *(102, 103, 106)* and three examined non-WHO antibiotic regimens: meropenem and imipenem *(107)*, cefoperazone and meropenem *(104)* and amoxicillin plus clavulanic acid *(108)*.

Comparison

Intervention: alternative antibiotic regimens
versus
Comparator: antibiotic regimens containing cloxacillin plus gentamicin IM/IV

Critical outcomes

No studies were located for this comparison.

Other outcomes

No studies

Subgroup analyses

No studies

Other studies

No studies

Acceptability, feasibility and equity evidence

No additional evidence.

Resources, costs and implementation evidence

No additional evidence.

Additional considerations

See section C for further details and cross-cutting issues.

Summary of findings

Comparison	**Intervention:** alternative antibiotic regimens **vs** **Comparator:** antibiotic regimens containing cloxacillin plus gentamicin IM/IV
Summary of effectiveness evidence	Not estimable
Evidence-to-Decision summary[a]	
Benefits	Don't know
Harms	Don't know
Antimicrobial resistance	Don't know
Balance of effects	Don't know
Certainty	Very low
Values	Don't know
Acceptability	Probably acceptable
Resources	Low costs
Feasibility	Limited feasibility
Equity	Varies

[a] See Table 2.1.

C. Cross-cutting issues

The GDG also made remarks about cross-cutting issues that are important for all settings and recommendations. These remarks are summarized below.

Clinical management

- The GDG emphasized that clinical signs can be difficult to ascertain in young infants and that clinical management of unwell infants aged 0–59 days requires careful clinical judgement.
- The GDG emphasized the importance of carefully managing coinfections and comorbidities in the young infant, including malnutrition, according to WHO guidelines and guidance *(12, 13, 27, 28)*.
- The GDG emphasized the importance of counselling families about the standard WHO newborn care practices for small and sick newborns *(111)*, including keeping the infant warm and supporting the mother to provide exclusive breastfeeding.
- The GDG emphasized that health workers who care for unwell young infants must receive ongoing in-service training and supportive supervision specific to the care of infants aged 0–59 days.
- Links to key WHO resources are provided below.
  - *Recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations*
  - *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, second edition* (WHO, 2013)
  - *Integrated management of childhood illness: chart booklet* (WHO, 2014)
  - *Integrated management of childhood illness: management of the sick young infant aged up to 2 months: IMCI chart booklet* (WHO and UNICEF, 2019)
  - *Standards for improving quality of maternal and newborn care in health facilities* (WHO, 2016)



Referral to hospital and what to do when referral is not possible

- The GDG emphasized the importance of referring all infants aged 0–59 days with signs of PSBI to hospital and noted that the recommendations for non-hospital settings are only for situations where referral is not possible. If referral to hospital is not possible, the GDG emphasized that the health worker must:
  - seek the highest possible level of medical advice, consultation and care for the infant;
  - explain to the caregiver that the infant is very sick and reinforce the importance of hospital care;
  - manage the infant in the clinic wherever possible;
  - monitor the infant continuously on cardiac, respiratory and pulse oximetry monitors wherever possible until the infant is considered stable and no longer critical (if continuous monitoring is not possible then frequent vital signs and observations must be taken, ideally every hour);
  - review the infant's condition in the clinic if possible (if this is not possible then the clinic team should perform home visits wherever feasible);
  - review all infants on the day after stopping treatment; and
  - ensure that all infants have careful long-term follow-up care to assess and manage complications and sequelae.

Risk groups

- The GDG was unable to make specific recommendations for infants in any of the pre-specified high-risk subgroups, including preterm infants, due to insufficient evidence.
- The GDG was also unable to recommend further risk stratification (e.g. by gestational age, birthweight or maternal risk factors) due to lack of evidence, and emphasized the need for further research.

Settings with different antimicrobial resistance (AMR) patterns

- The GDG was unable to make recommendations for settings with different AMR patterns due to insufficient evidence.
- The GDG recognized the problems with emerging AMR in community and hospital settings and encouraged governments and all stakeholders to set up community and hospital-based AMR surveillance to guide future regional-level decisions about antibiotic use.
- The GDG strongly recommended investment in clinical and laboratory training, equipment and AMR surveillance in community and hospital settings.
- The GDG emphasized the importance of antimicrobial stewardship programmes in hospitals, including the use of the WHO AWaRe antibiotic classification system.

Antibiotic doses

The GDG recognized that there were limited data on dose of antibiotics. Based on current clinical practice, the GDG's guidance on antibiotic dosing is provided in **Table 3.1**.

Table 3.1 Antibiotic dosing for serious bacterial infections in infants

A. Non-hospital settings

A.2 Critical illness in young infants aged 0–59 days in non-hospital settings

Ampicillin IM/IV for a total of at least 10 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 10 days

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

A.3 Clinical severe infection in young infants aged 0–59 days in non-hospital settings

Amoxicillin oral for a total of at least 7 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 7 days, or 2 days if 7 days is not possible

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

A.4 Fast breathing as the only clinical sign of illness in young infants aged 0–6 days in non-hospital settings

Amoxicillin oral for at least 7 days

- 50 mg/kg/dose every 12 hours

A.5 Fast breathing as the only clinical sign of illness in young infants aged 7–59 days in non-hospital settings

Amoxicillin oral for at least 7 days

- 50 mg/kg/dose every 12 hours

B. Hospital settings

B.2 Suspected sepsis in young infants aged 0–59 days in hospital settings

Ampicillin IM/IV for a total of at least 10 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 10 days

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

Table 3.1 continued

B.3 Suspected staphylococcal sepsis in young infants aged 0–59 days in hospital settings

Cloxacillin IM/IV for a total of at least 10 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 10 days

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

B.4 Suspected meningitis in young infants aged 0–59 days in hospital settings

Ampicillin IM/IV for a total of at least 3 weeks

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Or

Cefotaxime IM/IV for a total of at least 3 weeks

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 6 hours (> first week of life)

Or

Ceftriaxone IM/IV for a total of at least 3 weeks

- 100 mg/kg once a day (whether starting in the first week of life or later)

Plus

Gentamicin IM/IV for a total of at least 3 weeks

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

Note: Give ampicillin plus third-generation cephalosporin plus gentamicin (i.e. triple therapy) if *Listeria monocytogenes* is suspected.

B.5 Suspected pneumonia in young infants aged 0–59 days in hospital settings

Ampicillin IM/IV for a total of at least 7 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 7 days

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

B.6 Suspected staphylococcal pneumonia in young infants aged 0–59 days in hospital settings

Cloxacillin IM/IV for a total of at least 7 days

- 50 mg/kg/dose every 12 hours (first week of life)
- 50 mg/kg/dose every 8 hours (> first week of life)

Plus

Gentamicin IM/IV for a total of at least 7 days

- 5 mg/kg once a day (first week of life)
- 7.5 mg/kg once a day (> first week of life)

4. Implementation

The recommendations should be adapted to the needs of different countries, local contexts, and individual families and infants. The GDG proposed implementation considerations for each recommendation and also reflected on adoption, adaptation and implementation to ensure availability, accessibility, acceptability and quality of care, in accordance with a human rights-based approach. Providers of services for infants with infections must consider the needs of, and provide equal care to, all individuals and their newborns.

Health policy considerations for the adoption and scale-up of recommended interventions for the care of infants with SBI:

- A firm government commitment to scale-up and increased coverage of these interventions is needed, irrespective of social, economic, ethnic, racial or other factors. National support must be secured for all recommendations, not just for specific components.
- To set the policy agenda, to secure broad anchoring and to ensure progress in policy formulation and decision-making, representatives of training facilities and the relevant medical specialties and professional societies should be included in participatory processes at all stages, including prior to an actual policy decision, to secure broad support for scaling up.
- To facilitate negotiations and planning, situation-specific information on the expected impact of implementation of the recommendations on service users, health workers and costs should be compiled and disseminated.

Health system or organization-level considerations for implementation:

- Derivative tools and job aids should be updated, such as *Integrated management of childhood illness: management of the sick and young infant aged up to 2 months (28)*, *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (13)*, as should lists of essential medicines at global and national levels.
- National and subnational subgroups may be established to adapt and implement these recommendations, including development or revision of existing national or subnational guidelines or protocols.
- Long-term planning is needed for resource generation and budget allocation to address the shortage of health workers and trained community health workers, to improve facility infrastructure and referral pathways, and to strengthen and sustain high-quality small and sick newborn care services.
- Implementation of the recommendations should involve pre-service training institutions and professional bodies, so that training curricula for small and sick newborn care services can be updated as quickly and smoothly as possible.
- In-service training and supervisory courses will need to be developed according to health workers' professional requirements, considering the content and duration of the courses and the procedures for the selection of health workers for training. These courses can also be explicitly designed to address staff turnover, particularly in low-resource settings.
- Standardized tools will need to be developed for supervision, ensuring that supervisors are able to support and enable health workers to deliver integrated, comprehensive small and sick newborn care services.
- A strategy to optimize the use of human resources.
- Strategies will need to be devised to improve supply chain management according to local requirements, such as developing protocols for

the procedures of obtaining and maintaining the stock of supplies, encouraging health workers to collect and monitor data on the stock levels, and strengthening the provider-level coordination and follow-up of medicines and health-care supplies required for implementation.

- Development or revision of national guidelines and health facility-based protocols is needed.
- Good-quality supervision, communication and transport links between community, primary- and higher-level facilities need to be established to ensure that referral pathways are efficient.
- Successful implementation strategies should be documented and shared as examples of best practice for other implementers.

User-level considerations for implementation:

- Community-sensitizing activities should be undertaken to disseminate information about the importance of each component of care, and infants' rights to receive care for their health and well-being. This information should provide details about the timing and content of the recommended contacts, and about the expected user fees.

Considerations for humanitarian emergencies:

- The adaptation of the recommendations should consider their integration and alignment with other emergency response strategies. Additional considerations should be made for the unique needs of families and infants in emergency settings, including their values and preferences. Context-specific tools may be required in addition to standard tools to support the implementation by stakeholders of the recommendations in humanitarian emergencies.

5. Applicability issues

A number of factors (barriers) may hinder the effective implementation and scale-up of the recommendations in this guideline. These factors may be related to the behaviours of families or health workers or to the organization of care or health service delivery. As part of efforts to implement these recommendations, health system stakeholders may wish to consider the following potential barriers:

- difficult access to health services and health workers for families and newborns, including lack of transport, geographical conditions and financial barriers;
- lack of human resources for health with the necessary expertise and skills to implement, supervise and support recommended practices, including client counselling;
- lack of infrastructure to support interventions (e.g. electricity for refrigeration, access to clean water and sanitation, access to digital interventions and devices, and physical space to conduct individual care and counselling);
- lack of time or understanding of the value of newly recommended interventions among health workers and health system administrators;
- lack of physical resources (e.g. equipment, supplies, medicines and nutritional supplements);
- lack of opportunities for continuing education and professional development for health workers;
- resistance of health workers to change from non-evidence-based to evidence-based practices (e.g. providing home visits or ensuring family involvement);
- lack of effective referral mechanisms and care pathways for families and newborns identified as needing additional care and hospital referral; and
- lack of health management information systems designed to document and monitor recommended practices (e.g. patient records and registers).

Given the potential barriers noted above, a phased approach to adoption, adaptation and implementation of the recommendations in this guideline may be helpful.

6. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research. The knowledge gaps were prioritized by the GDG by considering whether the research would: (i) contribute to improvements in care and outcomes of infants aged 0–59 days with SBI; (ii) be likely to result in significant public health impacts; (iii) inform a new recommendation or change an existing recommendation; (iv) be feasible to implement; and (v) be likely to promote equity. The full list of research gaps can be found in **Annex 4**.

7. 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 website of WHO's Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA). Technical meetings will be held between WHO and stakeholders to share the recommendations and derivative products.

Evidence briefs for policy-makers, programme managers and health workers will be developed. They will focus on selected recommendations and context-specific issues, and will be developed and disseminated in collaboration with United Nations organizations, funds, programmes and partners.

The executive summary and recommendations from this publication will be translated into the six United Nations languages for dissemination through the WHO regional and country offices, and web versions will be available via the websites of the MCA Department and the WHO country and regional offices.

In addition, a number of articles presenting the recommendations and key implementation considerations will be published, in compliance with WHO's open access and copyright policies. Relevant WHO clusters, departments and partnerships, such as the Partnership for Maternal, Newborn and Child Health (PMNCH), will also be part of the dissemination process.

WHO, in collaboration with other partners, will support national and subnational working groups to adopt, adapt and implement the guideline. This will include the development or revision of existing national policies, guidelines or protocols in line with the WHO recommendations, and tools to support adaptation and implementation processes. This also includes technical support for local guideline implementers in the development of training materials and quality indicators in appropriate local languages.

8. Monitoring and evaluating the impact of the recommendations

The implementation and impact of these recommendations will be monitored at the health service, subnational and national levels, based on clearly defined criteria and indicators that are associated with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Departments of Maternal, Newborn, Child and Adolescent Health and Aging (MCA), and Sexual and Reproductive Health and Research (SRH), data on country- and regional-level adoption of the recommendations will be collected and evaluated in the short to medium term across individual WHO Member States through the WHO Sexual, Reproductive, Maternal, Newborn, Child and Adolescent Health (SRMNCAH) Policy Survey *(112)*. A full monitoring framework will be developed.

In the meantime, the GDG for this guideline suggests consideration of the following indicators, which have been adapted from current global recommended indicators *(40, 113)*, including the *Every Newborn Action Plan* (ENAP) indicators for mortality and coverage of postnatal care.

- Neonatal mortality rate – the proportion of preterm or low-birth-weight infants dying in the first 28 days after birth.
- Possible serious bacterial infection (PSBI) coverage – number of neonates identified with PSBI in outpatient or inpatient settings who received at least two days of appropriate injectable antibiotics divided by the number of neonates identified with PSBI in outpatient or inpatient settings.[1]

These indicators should be considered preliminary and will undergo further review. New indicators will be added, including those for measurement of coverage and quality of care.

1 WHO Working Group on Coverage Indicators For Small and/or Sick Newborn Care. Care for small and/or sick newborns: indicators for measurement in routine health information systems (submitted for publication in 2024).

9. Updating of the guideline

In accordance with the process for updating WHO guidelines, the "living guidelines" approach will be used *(37)*. This is a systematic and continuous process of identifying and bridging evidence gaps at least every six months following guideline publication and dissemination. A Guideline Steering Group (GSG) for maternal and newborn health recommendations will convene regularly to review WHO's current portfolio of relevant recommendations, and to prioritize new and existing questions for recommendation development and updating. The focus will be on recommendations supported by very-low- or low-certainty evidence and where new recommendations or a change in the published recommendations may be needed. When new evidence that could potentially impact the current evidence base for any of the recommendations is identified, the recommendation will be updated. If no new reports or information are identified for a particular recommendation, the recommendation will be revalidated.

Any concern about the validity of any recommendation should be promptly communicated by email to the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing (mncah@who.int). All communications will be reviewed and plans will be made to update the recommendation as needed.

WHO welcomes suggestions regarding additional questions for inclusion in future updates of this guideline; suggestions can be addressed by email to the same department (mncah@who.int).

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Annex 2. Summary of declarations of interest from the Guideline Development Group (GDG) members and how they were managed

Name	Declared interest(s)	Management of declaration(s) of interest
Narendra Arora	None declared	Not applicable
Robert Black (chair)	None declared	Not applicable
Zulifqar Bhutta	His group received funding from the Bill & Melinda Gates Foundation to independently undertake a series of systematic reviews for newborn interventions of relevance to low- and middle-income countries (LMICs) during 2023 and 2024, feeding into the Lancet Newborn series planned for 2025.	This declaration of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.
Lulu Bravo	None declared	Not applicable
Waldemar Carlo	None declared	Not applicable
Simon Cousens	He is providing statistical support to the ACTION 3 trial, which is comparing the two different doses of antenatal corticosteroids with placebo in mothers with high risk of late preterm delivery. The trial is being conducted in multiple sites across several low- and middle-income countries. He provides advice on design issues, has drafted the statistical analysis plan and is involved in producing quarterly reports for the data and safety monitoring board (DSMB). He will be involved in the final analysis of the trial data. The contract with WHO is recompense for the time he spent working on the trial.	These declarations of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.
Gary Darmstadt	None declared	Not applicable
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Name	Declared interest(s)	Management of declaration(s) of interest
Shams El Arifeen	He is employed by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). Maternal and newborn health is a priority research area for icddr,b.	These declarations of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.
Patricia Fernandez Riera	None declared	Not applicable
Patricia Hibberd	None declared	Not applicable
Zelee Hill	None declared	Not applicable
Jacqueline Ho	She has several family members who work for a generic pharmaceutical manufacturer. However, because of her roles in Cochrane and her desire for her family members' work to not have any conflict with her own work, they have nothing to do with each others' work. The manufacturer her family members work for does produce antibiotic preparations that could be administered to infants 0–59 days.	These declarations of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.
Kristina Keitel	None declared	Not applicable
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Michael Sharland	He is the clinical advisor to the neonatal and paediatric programme of the Global Antibiotic Research and Development Partnership (GARDP) (www.gardp.org). GARDP have funded research that he led at St George's University on (i) the design and conduct of a global prospective observational cohort study of babies in hospital with neonatal sepsis (Global Neonatal Sepsis Observational Study [NeoOBs]) and (ii) the global neonatal sepsis trial comparing novel combinations of older generic antibiotics (the NeoSep1 trial, an open-label randomized controlled trial [RCT] comparing novel combination and currently used antibiotic regimens for the empiric treatment of neonatal sepsis). The NeoSep1 trial includes flomoxef, which is manufactured by Shionogi, and fosfromycin, which is manufactured by InfectoPharm. GARDP have led all of the contracting work of the trial antibiotics.	These declarations of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.

Name	Declared interest(s)	Management of declaration(s) of interest
Michael Sharland (continued)	The Wellcome Trust have funded Dr Sharland's Antimicrobial Resistance, Prescribing and Consumption Data to Inform Country Antibiotic Guidance and Local Action study (ADILA study). This study aims to collect global data on antibiotic prescribing, usage and local guidance in order to inform future antibiotic prescribing to reduce antimicrobial resistance (AMR). The Medical Research Council have funded Dr Sharland's two studies that have focused on the use of antiseptic washes on babies and mothers to prevent colonization of antibiotic resistant pathogens on neonates – NeoCHG (Efficacy and safety of whole-body chlorhexidine gluconate [CHG] cleansing in reducing bacterial skin colonisation of hospitalised neonates: a pilot trial) and NeoVTAMR (Strategies to reduce vertical transmission of multi-drug resistant pathogens to neonates). The PediCAP project (Impact of oral step-down to amoxicillin or coamoxiclav and of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in severe childhood community-acquired pneumonia [CAP]: an RCT) has been funded by the European & Developing Countries Clinical Trials Partnership (EDCTP), which is studying the impact of oral step-down to amoxicillin or co-amoxiclav and of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in severe childhood community-acquired pneumonia. The trial compares amoxicillin with a novel dispersible tablet formulation of amoxicillin-clavulanate, both of which have been donated to the trial by Sandoz. He has received no personal or academic funding from Sandoz, Shionogi or InfectoPharm in relation to his work on the optimal drug and dosing of their generic antibiotics. He is the Chair of the Antibiotic Working Group of the WHO Essential Medicines List Committee that developed the WHO AWaRe (Access, Watch, Reserve) classification system for antibiotics and led to the production of the WHO AWaRe antibiotic book.	These declarations of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility.
Hoang Tran	None declared	Not applicable
Karen Walker	None declared	Not applicable

Annex 3. Research priorities

Diagnostic accuracy of algorithms to identify possible serious bacterial infection (PSBI)

- Test algorithms that include simple point-of-care (POC) tests such as C-reactive protein (CRP) and procalcitonin in addition to clinical signs
- Test algorithms that include World Health Organization (WHO) high and low mortality risk signs
- Test algorithms that include clinical signs and POC tests as a basis for stopping treatment, switching treatment, escalation of therapy and/or duration of therapy
- Test algorithms that include maternal risk factors
- Analyse individual patient-level data to assess which clinical signs are most predictive of mortality and sepsis
- Conduct studies comparing the accuracy of different clinical sign-based algorithms
- Test the accuracy of health worker decision tools as a basis for deciding when to commence and stop antibiotics

Sepsis

- Conduct studies to determine more accurate methods for diagnosis of early septic shock syndromes
- Conduct research to further the understanding of common bacterial pathogens that cause sepsis and their antimicrobial resistance (AMR) patterns in district hospital and community settings
- Test the effectiveness of strategies for prevention of sepsis and AMR, including skin-to-skin contact with mothers, kangaroo mother care and use of probiotics
- Determine how to expand the use of antibiotic susceptibility testing for individual infants
- Test the effectiveness of currently recommended and novel antibiotic regimens in clearly defined AMR and non-AMR settings
- Develop a set of harmonized outcome measures for clinical trials

Pneumonia

- Conduct studies to determine more accurate methods for diagnosis of bacterial pneumonia using clinical signs in addition to “fast breathing”, e.g. cough, chest indrawing, auscultation findings such as crepitations (using stethoscope but also novel auscultation devices), chest X-ray, ultrasound and other diagnostic tests
- Test the feasibility and effectiveness of using devices such as pulse oximetry, automated respiratory rate counters and POC blood tests to guide pneumonia diagnosis and therapy
- Conduct studies to determine the diagnostic accuracy of biomarkers for viral and bacterial pneumonia
- Conduct randomized controlled trials (RCTs) comparing the effectiveness of different durations of antibiotic therapy for pneumonia
- Conduct research to further the understanding of:
  - how to improve the sensitivity and specificity of clinical sign-based algorithms to diagnose bacterial pneumonia and to guide switching and stopping of antibiotics and duration of therapy
  - the pathophysiology of transient tachypnoea of the newborn
  - common bacterial pathogens that cause bacterial pneumonia and their AMR patterns in district hospital and community settings
  - the role of respiratory syncytial virus (RSV) in bacterial pneumonia (including by use of RSV vaccine probe studies)
- Develop a set of harmonized outcome measures for clinical trials

Meningitis

- Conduct studies to determine more accurate methods for diagnosis of bacterial meningitis using clinical signs in addition to bulging fontanelle, stiff neck and seizures
- Test the feasibility and effectiveness of using devices such as POC blood testing to improve the diagnosis of bacterial meningitis and to guide switching and stopping of antibiotics and duration of therapy
- Conduct research to further the understanding of common bacterial pathogens that cause bacterial meningitis and their AMR patterns in district hospital and community settings
- Develop a set of harmonized outcome measures for clinical trials

Annex 4. Summary of key details for each priority question and recommendation

For the overarching questions and framework for the evidence, please refer to **Table 1.2** in Chapter 1 of this guideline. The table in this annex provides a summary compilation of the key details for each specific priority question, as also presented in each recommendation section in Chapter 3.

Setting	Question	PICO/PIRD details
A. Non-hospital settings		
A.1 Diagnostic accuracy of clinical signs of sepsis in young infants aged 0–59 days in non-hospital settings	Among young infants aged 0–59 days with possible serious bacterial infection (PSBI), in non-hospital settings, what is the diagnostic accuracy (sensitivity and specificity) of clinical sign-based algorithms of PSBI[a] compared with a reference standard (culture proven sepsis, physician judgement of sepsis, or mortality) in identifying infants who require treatment for PSBI?	Population – Young infants aged 0–59 days with PSBI Index test – Clinical sign-based algorithms of PSBI ascertained by any cadre of health worker Reference standard – Sepsis diagnosis (culture-confirmed or physician judgement) or mortality Diagnosis of interest – Serious bacterial infections (SBIs)
A.2 Critical illness in young infants aged 0–59 days in non-hospital settings	Among young infants aged 0–59 days with critical illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with critical illness Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability

Setting	Question	PICO/PIRD details
A.3 Clinical severe infection in young infants aged 0–59 days in non-hospital settings	Among young infants aged 0–59 days with clinical severe infection,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with clinical severe infection Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing oral amoxicillin, penicillin IM/IV or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
A.4 Isolated fast breathing in young infants aged 0–6 days in non-hospital settings	Among young infants aged 0–6 days with fast breathing as the only clinical sign of illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–6 days with fast breathing as the only clinical sign of illness Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing only oral amoxicillin or a combination of penicillin or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
A.5 Isolated fast breathing in young infants aged 7–59 days in non-hospital settings	Among young infants aged 7–59 days with fast breathing as the only sign of illness,[a] in non-hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 7–59 days with fast breathing as the only sign of illness Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing only oral amoxicillin or a combination of penicillin or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability

Setting	Question	PICO/PIRD details
B. Hospital settings		
B.1 Diagnostic accuracy of clinical signs of sepsis in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days, in hospital settings, what is the diagnostic accuracy (sensitivity and specificity) of clinical sign-based algorithms of suspected sepsis[a] compared with a reference standard (culture-confirmed sepsis or mortality) in identifying infants who require treatment for suspected sepsis?	Population – Young infants aged 0–59 days with suspected sepsis Index test – Clinical sign-based algorithms of suspected sepsis ascertained by any cadre of health worker Reference standard – Sepsis diagnosis (culture-confirmed sepsis) or mortality Diagnosis of interest – Sepsis
B.2 Suspected sepsis in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days with suspected sepsis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with suspected sepsis Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
B.3 Suspected staphylococcal sepsis in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days with suspected staphylococcal sepsis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with suspected staphylococcal sepsis Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing cloxacillin plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability

Setting	Question	PICO/PIRD details
B.4 Suspected meningitis in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days with suspected meningitis,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with suspected meningitis Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing penicillin, ampicillin, cefotaxime or ceftriaxone IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
B.5 Suspected pneumonia in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days with suspected pneumonia,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with suspected pneumonia Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing penicillin or ampicillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability
B.6 Suspected staphylococcal pneumonia in young infants aged 0–59 days in hospital settings	Among young infants aged 0–59 days with suspected staphylococcal pneumonia,[a] in hospital settings, what is the effect of alternative antibiotic regimens compared with WHO-recommended antibiotic regimens on critical outcomes? What is the effectiveness in specific strata?	Population – Young infants aged 0–59 days with suspected staphylococcal pneumonia Intervention – Alternative antibiotic regimens Comparator – WHO-recommended antibiotic regimens containing cloxacillin IM/IV plus gentamicin IM/IV Outcomes (critical outcomes) – All-cause or cause-specific mortality, morbidity (treatment failure,[b] treatment success,[b] hospitalizations, adverse events) or neurodevelopmental impairment/disability

PICO: population, intervention, comparator, outcomes; PIRD: population, index test, reference standard, diagnosis of interest.
[a] Definitions are provided in **Table 1.1** in Chapter1.
[b] As defined by the authors of the studies.

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