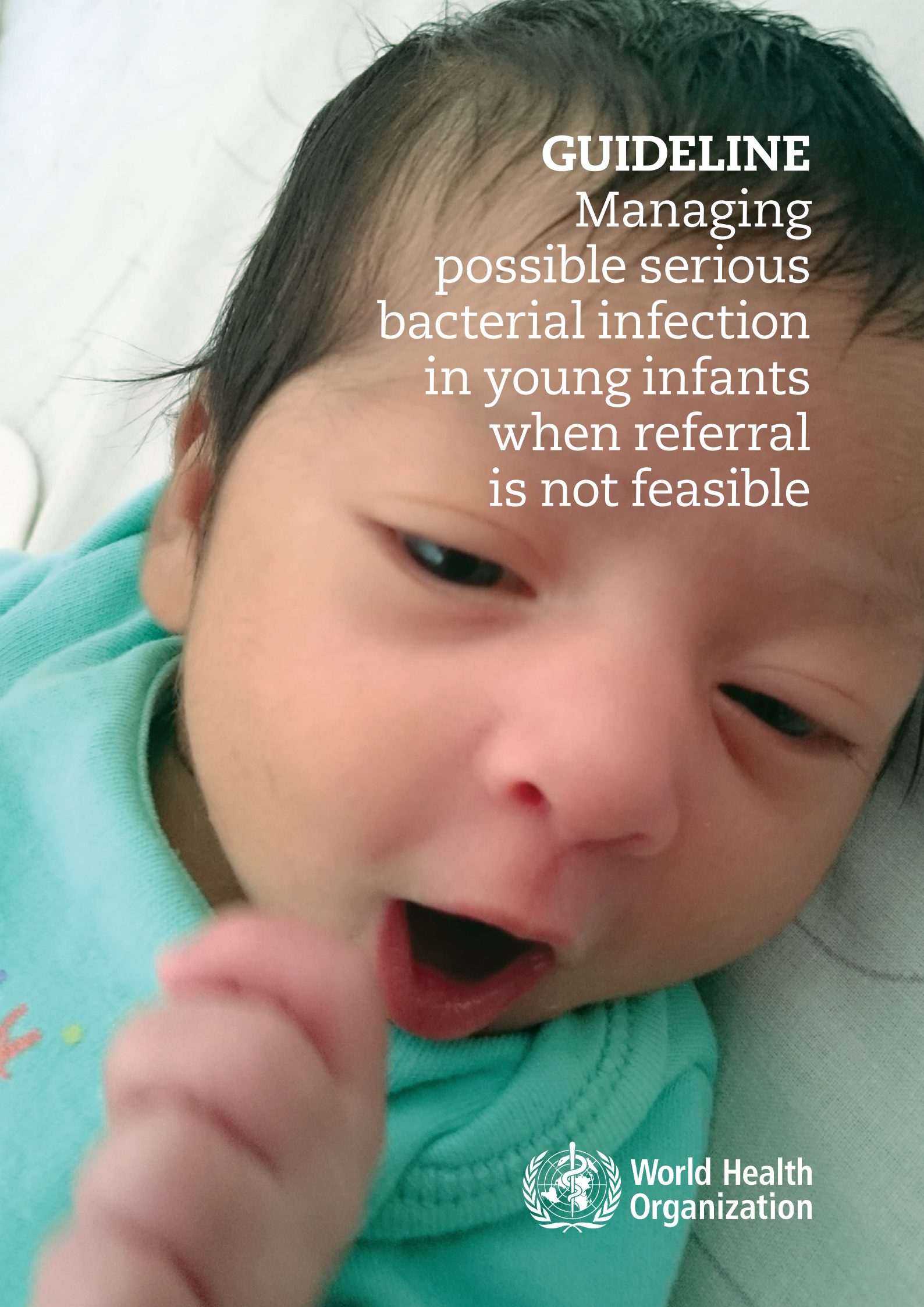

GUIDELINE
Managing possible serious bacterial infection in young infants when referral is not feasible

World Health Organization

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Contents

Abbreviations and acronyms

AMR	antimicrobial resistance
CHW	community health worker
CI	confidence interval
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IM	intramuscular
IMCI	Integrated Management of Childhood Illness
MCA	Department of Maternal, Newborn, Child and Adolescent Health
PICO	Population, Intervention, Control, Outcome
PSBI	possible severe bacterial infection
RD	risk difference
RR	relative risk
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization

Definitions of key terms

Clinical severe infection: In a young infant (0–59 days old), at least one sign of severe infection, i.e. movement only when stimulated, not feeding well on observation, temperature greater than or equal to 38 °C or less than 35.5 °C or severe chest in-drawing.

Critical illness: In a sick young infant, presence of any of the following signs: unconscious, convulsions, unable to feed at all, apnoea, unable to cry, cyanosis, bulging fontanelle, major congenital malformations inhibiting oral antibiotic intake, active bleeding requiring transfusion, surgical conditions needing hospital referral, persistent vomiting (defined as vomiting following three attempts to feed the infant within 30 minutes, and the infant vomits after each attempt).

Fast breathing: In a young infant (0–59 days old), a respiratory rate of greater than or equal to 60 breaths per minute.

Fast breathing pneumonia: In a young infant (0–59 days old), a respiratory rate of greater than or equal to 60 breaths per minute as the only sign of possible infection.

Few events: Fewer than 50 events in the control arm *(1)*.

Neonate: An infant between 0 and 28 days old.

Possible serious bacterial infection: A clinical syndrome used in the Integrated Management of Childhood Illness package referring to a sick young infant who requires urgent referral to hospital. The signs include:

- not able to feed since birth or stopped feeding well (confirmed by observation)
- convulsions
- fast breathing (60 breaths per minute or more) among infants less than 7 days old
- severe chest in-drawing
- fever (38 °C or greater)
- low body temperature (less than 35.5 °C)
- movement only when stimulated or no movement at all.

Sick child: Illness in a child 2–59 months old.

Sick young infant: Illness in an infant 0–59 days old.

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Home visits by community health workers to improve identification of serious illness and care seeking from a health facility in newborns and young infants from low- and middle-income countries

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Feasible, acceptable and cost-effective models of service delivery for neonates and young infants aged 0–59 days with possible serious bacterial infection: a systematic review

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Cost and cost-effectiveness of the management of possible serious bacterial infection in young infants: a systematic review

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Executive summary

Every year, about 2.8 million children die in the first month of life, with 98% of these deaths occurring in developing countries. The current WHO recommendation for management of infections in neonates and young infants (0–59 days old) is referral for hospital treatment with a seven to 10 day course of a combination of two injectable antibiotics – penicillin or ampicillin plus gentamicin. However, existing evidence demonstrates that in resource-limited settings many young infants with signs of possible serious bacterial infection (PSBI) do not receive the recommended inpatient treatment because such treatment is not accessible, acceptable or affordable to families. While increasing hospital-based treatment by improving availability and access is imperative, providing effective treatment for young infants with severe infection at first-level health facilities when families do not accept or cannot access referral would increase access to potentially lifesaving care for these infants. Although previously there has been little evidence to evaluate the safety and efficacy of providing care to young infants with PSBI at lower level facilities, a body of research has been conducted over the past decade to inform the creation of evidence-based guidelines. Evaluating data from recently completed studies, it is now possible to develop global clinical and programmatic guidance on management of PSBI where referral for treatment is not feasible.

This guideline, developed by a panel of international experts and informed by a thorough review of existing evidence, provides recommendations on the use of antibiotics for neonates and young infants (0–59 days old) with PSBI in order to reduce young infant mortality rates. This guideline is intended for use in resource-limited settings in situations when families do not accept or cannot access referral. It seeks to provide programmatic guidance on the role of community health workers (CHWs) and home visits in identifying signs of serious infections in neonates and young infants. It also seeks to provide clinical guidance on the simplest antibiotic regimens that are both safe and effective for outpatient treatment of clinical severe infections and fast breathing (pneumonia) in children 0–59 days old.

This guideline will not replace the WHO-recommended inpatient management as the preferred treatment option for young infants who have clinical severe infection or critical illness. Close follow-up is essential for young infants managed on an outpatient basis where referral is not possible.

To develop these recommendations, a WHO Steering Committee and an 18-member Guideline Development Group (GDG) of experts was convened. GDG members each declared their interests, and no conflicts of interest were identified. The group developed a series of priority questions, and WHO commissioned independent institutions to conduct systematic reviews for each question. Based on these reviews, the WHO Steering Committee developed an initial set of draft recommendations. Members of the GDG then reviewed and evaluated the quality of the evidence identified through the systematic reviews using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (www.

gradeworkinggroup.org) and revised and finalized the guideline recommendations. The final recommendations, which were approved by the WHO Guidelines Review Committee, appear in the summary of recommendations below.

The target audience for this guideline includes: 1) national policy-makers in health ministries; 2) programme managers working in child health, essential drugs and health worker training; 3) health care providers and clinicians managing sick children at various levels of health care, including public and private practitioners; and 4) development partners providing financial and/or technical support for child health programmes.

2015 WHO Recommendations on managing possible serious bacterial infection in young infants 0–59 days old when families do not accept or cannot access referral care

No.	Recommendation	Strength of recommendation	Quality of evidence
1	**Community health workers and home visits for postnatal care** At home visits made as part of postnatal care *(2)*, community health workers should counsel families on recognition of danger signs, assess young infants for danger signs of illness and promote appropriate care seeking.[a]	Strong	Moderate
2	**Infants 0–6 days with fast breathing as the only sign of illness** Young infants 0–6 days old with fast breathing as the only sign of illness should be referred to hospital. If families do not accept or cannot access referral care, these infants should be treated with oral amoxicillin, 50 mg/kg per dose twice daily for seven days, by an appropriately trained health worker.	Strong	Low
3	**Infants 7–59 days with fast breathing as the only sign of illness** Young infants 7–59 days old with fast breathing as the only sign of illness should be treated with oral amoxicillin, 50 mg/kg per dose twice daily for seven days, by an appropriately trained health worker. These infants do not need referral.	Strong	Low
4	**Young infants 0–59 days old with clinical severe infection** Young infants 0–59 days old with clinical severe infection whose families do not accept or cannot access referral care should be managed in outpatient settings by an appropriately trained health worker with one of the following regimens:[b]		
	Option 1: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for seven days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. Close follow-up is essential.	Strong	Moderate
	Option 2: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for two days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. Close follow-up is essential. A careful assessment on day 4 is mandatory.	Strong	Low
5	**Young infants 0–59 days old with critical illness** Young infants 0–59 days old who have any sign of critical illness (at presentation or developed during treatment of clinical severe infection) should be hospitalized after pre-referral treatment *(3)*.[c]	Strong	Very low

[a] If birth is in a health facility, mothers and newborns should receive care in the facility for at least 24 hours. If at home, first postnatal contact should be as early as possible within 24 hours. At least three additional postnatal contacts are recommended for all mothers and newborns on day 3 (48–72 hours), between days seven to 14, and six weeks after birth.

[b] Option 1 is the preferred option, but where the health system does not allow this to be implemented, option 2 could be considered. The GDG felt that option 2 likely would be easier to deliver, have more equitable access, have higher adherence, be more affordable and have similar effectiveness. It is expected that individual countries will adapt the recommendations to suit the local social, cultural and economic contexts. Countries are encouraged to hold key stakeholder discussions to inform the decision-making on use and introduction of the recommendations into national programmes.

[c] Give first dose of both ampicillin (50 mg/kg per dose) or benzyl penicillin (50 000 units/kg per dose) and gentamicin (5–7.5 mg/kg per dose) intramuscularly.

Scope and purpose of the guideline

This guideline, developed by a panel of international experts and informed by a thorough review of existing evidence, contains a number of recommendations on the use of antibiotics for neonates (0–28 days old) and young infants (0–59 days old) with PSBI in order to reduce young infant mortality rates. The guideline is intended for use in resource-limited settings in situations when families do not accept or cannot access referral care. The goal of the guideline is to provide clinical guidance on the simplest antibiotic regimens that are both safe and effective for outpatient treatment of clinical severe infections and fast breathing (pneumonia) in children 0–59 days old. In addition, the guideline seeks to provide programmatic guidance on the role of CHWs and home visits in identifying signs of serious infections in neonates and young infants.

This guideline will help health care providers make appropriate management decisions about sick young infants whose families cannot access referral care. They will also guide national policy-makers in health ministries, programme managers, and development partners and will inform revisions to current WHO training and reference materials such as the *Integrated Management of Childhood Illness (IMCI) Chart Booklet (3)* and the *Pocket Book of Hospital Care for Children: guidelines for the management of common illnesses (4)*.

This guideline is intended for resource-limited settings in the context of primary health care only. It is intended for the use of professionally trained health workers only and not for lay CHWs (with the exception of recommendations specific to CHWs). This guideline requires appropriate training of health care workers, supplying them with necessary equipment, job aids and medicines and providing adequate supervision and oversight. Monitoring of the programme will be needed for ensuring success and identifying and documenting adverse events of medicines (e.g. gentamicin toxicity), and community perceptions should be closely monitored. In addition surveillance for antimicrobial resistance (AMR) should be strengthened.

This guideline will not replace the WHO-recommended inpatient management as the preferred treatment option for young infants who have signs of severe infection (4). Close follow-up is essential for young infants managed on an outpatient basis where referral is not possible.

Background

Every year, about 2.8 million children die in the first month of life, with 98% of these deaths occurring in developing countries (5). Neonatal infections, including sepsis and meningitis, are estimated to cause over 420 000 deaths each year, with 136 000 attributed to pneumonia (6). The current WHO recommendation for management of infections in neonates (0–28 days old) and young infants (0–59 days old) is referral for hospital treatment with at least a seven-day course of a combination of two injectable antibiotics – benzylpenicillin or ampicillin plus gentamicin (3,4). However, existing evidence demonstrates that in resource-limited settings many young infants with signs of severe infection do not receive the recommended inpatient treatment because such treatment is not accessible, acceptable or affordable to families (7–14). Non-compliance with referral for hospitalization means that these infants receive no treatment, resulting in unnecessary, potentially preventable infection-related newborn deaths. While increasing hospital-based treatment by improving availability and access is imperative, if effective treatment for young infants with severe infection could be provided at first level health facilities or at the community level when families do not accept or cannot access referral care, many more infants could access potentially lifesaving care.

Research studies in India and Bangladesh have shown that it is possible to treat neonates 0–28 days old with signs of severe infection with injectable gentamicin in combination with oral cotrimoxazole or injectable procaine penicillin in the community when referral is not accepted by families (8,9). A subsequent study from Pakistan showed that the efficacy of a procaine penicillin-gentamicin combination was much higher than that of cotrimoxazole-gentamicin (10). No data were available from Africa. Whereas the Asian studies provided proof of principle, the proposed treatment was difficult to deliver in programmatic settings. Simpler regimens combining oral and intramuscular antibiotics or involving a switch from injectable to oral antibiotics after the first two to three days of treatment might be easier to deliver at outpatient level in resource-limited health systems.

Objective of guideline

While referral for hospital care continues to be the preferred method for the management of neonates and young infants with PSBI, a guideline for first level health facilities or community-based management of common life-threatening infections is needed to facilitate timely case management in cases where referral is either not accepted or not accessible. While previously there was little evidence to evaluate the safety and efficacy of providing care to young infants with PSBI at lower level facilities, a body of research has been conducted over the past decade to inform the creation of an evidence-based guideline. This includes a group of research projects supported by the Bill & Melinda Gates Foundation and the United States Agency for International Development, which Save the Children's Saving Newborn Lives programme and WHO conducted in five countries in South Asia

and sub-Saharan Africa. As these studies have now been completed, a review was undertaken to develop global clinical and programmatic guidance on management of PSBI where referral for treatment is not possible or not accessible.

Target audience

The target audience for this guideline includes: 1) national policy-makers in health ministries; 2) programme managers working in child health, essential drugs and health worker training; 3) health care providers and clinicians managing sick children at various levels of health care, including public and private practitioners; and 4) development partners providing financial and/or technical support for child health programmes.

Population of interest

This guideline focuses on management of neonates (0–28 days old) and young infants (0–59 days old) in resource-limited settings who have clinical signs of PSBI and whose families do not accept or cannot access referral care for treatment. Clinical signs of PSBI are defined as:

- fast breathing (respiratory rate ≥ 60 breaths/minute)
- severe chest in-drawing
- fever (temperature ≥ 38 °C)
- hypothermia (temperature < 35.5 °C)
- no movement at all or movement only on stimulation
- feeding poorly or not feeding at all
- convulsions.

As previously noted, hospitalization remains the first priority for care for these infants. ***This guideline only applies in cases where hospitalization is not accepted or not accessible.***

Justification for this age category

The WHO Global Acute Respiratory Infection Control Programme, launched in the late 1980s, used the age categories of up to 2 months and 2 months up to 59 months for management of children with acute respiratory infection and pneumonia. The signs and management of infants with pneumonia 29–59 days of age were similar to infants 0–28 days, as opposed to children 2–59 months of age *(15)*. IMCI, which was first launched in 1997, used the same age cut-offs because the signs and management of PSBI in infants 29-59 days were similar to infants 0–28 days of age, as opposed to the signs and management in children 2–59 months of age *(3)*.

This guideline provides recommendations for outpatient treatment for t*wo subgroups of young infants with PSBI*, based on increasing clinical severity. The subgroups are defined as:

- **Fast breathing pneumonia:** A young infant (0–59 days old) with a respiratory rate of ≥ 60 breaths per minute as the only sign of possible infection.
- **Clinical severe infection:** A young infant (0–59 days old) with at least one sign of severe infection (i.e. movement only when stimulated, not feeding well on observation, temperature ≥ 38 °C or < 35.5 °C or severe chest in-drawing).

Priority questions

In order to identify and evaluate the evidence for outpatient treatment, the WHO Steering Committee developed four main priority questions on the safety and effectiveness of simpler antibiotic regimens for treatment of PSBI in young infants. Each was described in terms of its characteristics: population, intervention, control and outcome (PICO). Simpler antibiotic regimens were defined as regimens with fewer injections than the reference treatment of intramuscular penicillin and gentamicin for at least seven days (i.e. 14 injections). This could be one antibiotic injection for seven days with or without an oral antibiotic (i.e. seven injections), initiating treatment with intramuscular treatment and switching to an oral antibiotic after two to three days (i.e. two to six injections) or oral antibiotic treatment alone (i.e. no injections).

To summarize the evidence, the following questions about infants whose families do not accept or cannot access referral care for treatment were formulated as the basis for systematic reviews:

1. *Among all neonates 0–28 days old*, can home visits by CHWs compared to no home visits successfully identify newborns with serious illness and improve care seeking from a health facility?
    a. **Population:** Neonates 0–28 days old.
    b. **Intervention:** Home visits by CHWs.
    c. **Control:** No home visits by CHWs.
    d. **Outcome:** Identification of newborns with serious illness and improvement in care seeking from a health facility.
2. *Among neonates (0–6 days old) and young infants (7–59 days old) presenting with fast breathing as a single sign of PSBI*, are simpler antibiotic regimens, delivered at outpatient and/or community level, as effective as a combination of injectable penicillin and gentamicin for at least seven days as measured by rates of mortality and clinical deterioration (development of signs of severe infection or critical illness), within two weeks of starting treatment?
    a. **Population:** Neonates (0–6 days old) and young infants (7–59 days old) presenting with fast breathing as a single sign of PSBI.
    b. **Intervention:** Simpler antibiotic regimens delivered at outpatient and/or community level.
    c. **Control:** A combination of injectable penicillin and gentamicin for at least seven days.
    d. **Outcome:** Mortality and clinical deterioration within two weeks of starting treatment.
3. *Among neonates and young infants (0–59 days old) with suspected/confirmed clinical severe infection*, can simpler antibiotic regimens, delivered at outpatient and/or community level, be as effective as a combination of injectable penicillin and gentamicin given for at least seven days in achieving comparable rates of mortality, clinical deterioration (i.e. development of any sign of critical illness) and persistence of signs of severe infection within two weeks of starting treatment?

a. **Population:** Neonates and young infants (0–59 days old) with suspected/confirmed clinical severe infection.

b. **Intervention:** Simpler antibiotic regimens delivered at outpatient and/or community level.

c. **Control:** A combination of injectable penicillin and gentamicin given for at least seven days.

d. **Outcome:** Mortality, clinical deterioration and persistence of signs of severe infection within two weeks of starting treatment.

4. *Among neonates and young infants (0–59 days old) with signs of critical illness*, are simpler antibiotic regimens delivered at outpatient and/or community level, as effective as a combination of injectable penicillin and gentamicin for at least seven days as measured by rates of mortality, clinical deterioration (i.e. development of a new sign of critical illness) and persistence of signs of severe infection, within two weeks of starting treatment?

   a. **Population:** Neonates and young infants (0–59 days old) with signs of critical illness.

   b. **Intervention:** Simpler antibiotic regimens delivered at outpatient and/or community level.

   c. **Control:** A combination of injectable penicillin and gentamicin for at least seven days.

   d. **Outcome:** Mortality, clinical deterioration and persistence of signs of severe infection, within two weeks of starting treatment.

Systematic reviews addressing each of the above-mentioned priority questions were conducted, which informed the evidence presented in this document. In addition two other priority questions for systematic reviews were formulated to provide context and additional information on the possible treatments for outpatient care among infants whose families do not accept or cannot access referral care for treatment:

1. *Among neonates and young infants (0–59 days old) who have signs of PSBI*, who are managed with simpler antibiotic regimens delivered at outpatient and/or community level, what are the total costs/cost-effectiveness of treatment with simpler effective antibiotic regimens (defined as having equivalent or better reductions in mortality, clinical deterioration, non-recovery and relapse), compared to a combination of injectable penicillin and gentamicin for at least seven days?

   a. **Population:** Neonates (0–28 days old) and young infants (0–59 days old) who have signs of PSBI.

   b. **Intervention:** Management with simpler antibiotic regimens delivered at outpatient and/or community level.

   c. **Control:** Combination of injectable penicillin and gentamicin for at least seven days.

   d. **Outcome:** Total costs/cost-effectiveness of treatment with simpler effective antibiotic regimens.

2. *Among neonates and young infants (0–59 days old) who have signs of PSBI*, who are managed with simpler antibiotic regimens delivered at outpatient and/or community level, compared with a combination of injectable penicillin and gentamicin for at least seven days, what are the feasible, acceptable, effective and cost-effective *models of service delivery*[1] and what are the health system requirements for all these models?

    a. **Population:** Neonates and young infants (0–59 days old) who have signs of PSBI.

    b. **Intervention:** Management with simpler antibiotic regimens delivered at outpatient and/or community level.

    c. **Control:** A combination of injectable penicillin and gentamicin for at least seven days.

    d. **Outcome:** Feasibility, acceptability, effectiveness and cost-effectiveness of models of service delivery.

The results of these last two systematic reviews are not presented directly but rather informed the discussions that led to the recommendations that follow.

Outcomes evaluated

For each priority question two critical and two important outcomes were evaluated. The two **critical outcomes** were: 1) death within two weeks of starting treatment for PSBI; and 2) treatment failure by day 8 after starting treatment, defined as clinical deterioration after starting treatment for PSBI including death, need for hospitalization/referral, need to change antibiotics, new signs of clinical infection or persistence of signs of illness. The two **important outcomes** were: 1) clinical relapse (defined as emergence of any sign of infection within two weeks after the disappearance of all signs of clinical PSBI); and 2) adherence to treatment (defined as compliance or adherence to treatment as specified in the study methods). Summaries of all outcomes, but only the GRADE tables for the critical outcomes, are presented, as these were the focus of the GDG.

[1] These could include: 1) self-referral, with treatment in outpatient health facilities; 2) use of CHWs to identify sick young infants and refer them to outpatient clinics for care; and 3) use of CHWs to identify and treat young infants at the community level.

Methodology

The WHO Steering Committee organized a meeting in Geneva on 7–8 October 2013 to discuss the results of the recently concluded research. The participants were WHO Staff, WHO Steering Committee members and GDG members (described below). The GDG decided there was adequate evidence to update the WHO guideline on management of PSBIs in young infants where families do not accept or cannot access referral. The GDG then developed the priority questions (as listed above) and WHO commissioned independent institutions to conduct systematic reviews of each question.

Evidence retrieval, assessment and synthesis

The evidence retrieval process for the priority questions followed the standard outlined in the WHO *Handbook for Guideline Development (16)*. A list of reviewers is provided in the **Acknowledgements**. A protocol for each systematic review was developed and included the search terms and strategy, and the PICOs used to define the inclusion and exclusion criteria. The detailed search strategy for each priority question was agreed upon after a series of discussions with the Steering Committee and lead investigators of each systematic review. Each review includes a flow diagram showing the numbers of studies excluded and included. Medline and EMBASE databases were used to identify peer-reviewed publications. The WHO International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials, the International Standard Randomised Controlled Trial Number Register, and ClinicalTrials.gov were searched for on-going studies. The quality of the evidence for each priority question was assessed using the GRADE methodology (www.gradeworkinggroup.org). The quality of the evidence for treatment interventions was graded as high, moderate, low or very low based on the definitions in the GRADE guide *(17)*. The GRADE tables were prepared using the GRADE profiler software, where appropriate. The reviews are available on file and will be published. Based on these reviews, the WHO Steering Committee proposed an initial set of draft recommendations.

WHO Steering Committee

A Steering Committee, with members from the Department of Maternal, Newborn, Child and Adolescent Health (MCA), oversaw the guideline review process. WHO staff are listed in the **Acknowledgements**.

Guideline Development Group

WHO convened an 18-member GDG consisting of internationally recognized experts. A list of members is provided in the **Acknowledgements**. Members of the group were tasked with reviewing and evaluating the quality of the evidence identified through the systematic reviews using the GRADE methodology (described below) and revising and finalizing the guideline recommendations.

Peer Review Group

The duties of the Peer Review Group were to review the recommendations and supporting documentation developed by the GDG. The list of members, from various countries and disciplines, with their affiliations is provided in the Acknowledgements.

Management of conflicts of interest

All of the members of the GDG were required to sign and submit a Declaration of Interests prior to their participation in the meetings. The WHO Steering Group reviewed the Declarations prior to the GDG meeting to determine whether a conflict existed that might have precluded or limited anyone's participation. While no conflicts of interest were declared requiring any action, the interests declared are given in Annex I.

Grading the quality of evidence

The GRADE methodology was used by the GDG to evaluate the quality of the evidence. This methodology is a widely-used approach for separating the quality of evidence from the strength of recommendations *(17)*. The Cochrane Collaboration and WHO *(16)* have adopted it as standard for developing systematic reviews and recommendations. GRADE tables summarize details about the studies reviewed, including study outcomes, limitations, possible inconsistency, indirectness, imprecision and other factors that might impact judgements on the quality of evidence. GDG members then used the information to define the overall quality of evidence as very low, low, moderate or high as defined in Table 1.

Table 1. Definition of quality of evidence using the GRADE methodology

Quality	Definition
High	Further research is unlikely to change confidence in the estimates of the effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate
Low	Further research is very likely to have an important impact on the confidence of the effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Decision-making process

The WHO Steering Committee in Geneva convened a GDG meeting from 19–21 November 2014. Each member of the GDG was provided with a copy of the commissioned systematic reviews.

For each draft recommendation, the WHO Steering Committee presented a synthesis of the evidence, the GRADE tables and a draft recommendation. Decision-making tables were also prepared including benefits and risks of the interventions from a public health perspective; values, preferences and acceptability to programme managers and policy-makers and health care providers; and feasibility of implementing any recommendations (including resources needed, focusing on national programmes in resource-limited or other settings). Each member was required to review the material and independently complete a written form asking them to

comment on and suggest revisions to the proposed guidance and decision-making tables. The form also required them to rate, for each recommendation: the overall quality of evidence using the GRADE methodology (independent of the rating made in the synthesis of the evidence), the balance of benefits versus harms, values that should be considered in making a recommendation, and applicability of any proposed recommendations to the populations they are intended to benefit. Finally they were asked to give their assessment of what the strength of each recommendation should be based on the criteria provided in Table 2.

Table 2. Assessment criteria for the strength of recommendations

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

The GDG then used a consensus building process to finalize the recommendations. Once each participant had completed the form detailing their opinions and proposed language, a summary of the opinions of the entire group was created by members of the WHO Steering Committee. This was presented to the GDG members in order to gauge consensus and where there were great differences. At this point the chair led a discussion on each recommendation, and the group edited the recommendations. Finally the chair of the GDG made an attempt to reach consensus among GDG members on the language for the recommendation, the quality of evidence and the strength of recommendation.

WHO staff did not express any personal opinions on the data, in the discussions or in the decisions on language, strength of recommendations or quality of evidence. At all stages of the meeting they articulated in detail the principles and guidelines of the WHO decision-making process.

In all cases except one, the committee reached unanimous agreement on the recommendations as revised by the GDG. The exception was for Recommendation 4 option 2 allowing for treatment of clinical severe infection in children 0–59 days old with intramuscular gentamicin once daily 5–7.5 mg/kg per day for two days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. One member of the GDG did not agree with this recommendation. The group decided that if consensus could not be reached, a two thirds majority would be required to put forward a recommendation. Additional efforts to address the concerns raised[1] were not successful, but as 17 of the 18 members agreed the recommendation was put forward.

[1] The dissenting member expressed his concerns in written form to the WHO Steering Committee. The GDG chair formulated a written response to the concerns raised. In order to ensure these concerns were not ignored, both documents were sent to each remaining member of the committee with a request to comment on whether they would like to change their decision or make changes to the wording of the recommendation. Each responded that they still agreed with the recommendation as drafted in the November 2014 meeting, and therefore the GDG decided not to change it.

The WHO Steering Committee then sought external peer review of the recommendations. The draft recommendations were sent to an external Peer Review Group for input on proportionality, format, clarity, consistency, level of detail, gaps, errors, implementation considerations and other general comments. The external peer reviewers made several suggestions to improve the document. The Steering Committee reviewed all suggestions and incorporated the reviewers' comments as appropriate, such as improving the evidence base for the fast breathing recommendation for young infants 0–6 days old, improving the sub-section on monitoring and evaluation, improving the general writing of text and mode of presentation and updating the list of references. The final version was approved by the GDG.

Evidence and recommendations

Review Question 1: Identification of danger signs by community health worker at home visits

The systematic review was based on the priority question: among all neonates 0–28 days old (**Population**), can home visits by CHWs (**Intervention**) compared to no home visits (**Control**) successfully identify young infants with serious illness and improve care seeking from a health facility (**Outcome**)?

Summary of evidence

Six randomized controlled trials *(14,18–22)* compared home visits by a CHW to identify young infants with serious illness (**Intervention**) to no home visits (**Control**) in children 0–59 days old (**Population**). The six studies, which are described in Grade Table 1 (Annex 2), randomized a total of 4760 infants to an intervention and 4398 to a control group. The intervention was evaluated based on improved care seeking at health facilities (**Outcome**). After pooling the data from the six trials, there was significant improvement in care seeking in the intervention arm compared to the control arm (relative risk [RR]: 1.35; 95% confidence interval [CI]: 1.15–1.58).

Considerations for recommendation development

Balance of benefits versus harms: The GDG noted that at postnatal home visits, identification of danger signs in young infants by CHWs is beneficial because it can increase early health care seeking. In addition, the specificity of diagnosis of serious illness by CHWs appears to be high (i.e. few false positives), and therefore the likelihood of unnecessary referrals is low. However, close supervision and support will still be needed to avoid missing infants with danger signs.

Values and preferences: The GDG noted that home visits for neonates 0–28 days old are already part of WHO and country strategies, and therefore it is a missed opportunity if CHWs are not trained and supported to identify PSBI and promote care seeking.

Feasibility (including resource use considerations): The GDG noted that postnatal care of newborns[1] is already recommended by WHO *(2)* but some additional costs will be required under this recommendation for training CHWs to identify sick young infants. The GDG felt those costs were worth the benefit. In addition, WHO training materials for CHWs will need to be modified.

[1] If birth is in the health facility, mothers and newborns should receive care in the facility for at least 24 hours. If birth is at home, the first postnatal contact should be as early as possible within 24 hours. At least three additional postnatal contacts are recommended for all mothers and newborns on days 3 (48–72 hours), between days 7–14 after birth, and six weeks after birth.

Community health worker recommendations

The GDG made one recommendation for young infants 0–59 days old regarding home visits by CHWs:

> **Recommendation 1:** At home visits made as part of postnatal care, CHWs should counsel families on recognition of danger signs, assess young infants for danger signs and promote appropriate care seeking.
>
> **Strong recommendation based on moderate quality evidence**

Remarks

The committee noted the following:

- CHWs should be provided with appropriate training, job aids, logistical support and close monitoring and supervision in order to be able to identify danger signs.

Review Question 2: Fast breathing as a single sign of illness

The systematic review was based on the priority question: among neonates (0–28 days old) and young infants (0–59 days old)presenting with *fast breathing as the only sign of PSBI*, whose families do not accept or cannot access referral care for treatment (**Population**), are simpler antibiotic regimens delivered at outpatient and/or community level (**Intervention**) as effective as a combination of injectable penicillin and gentamicin for at least seven days (**Control**) as measured by rates of mortality and clinical deterioration (development of signs of severe infection or critical illness), within two weeks of starting treatment (**Outcome**)?

Summary of evidence

Only one trial (the AFRINEST study *[13]*) was identified that was conducted among children 0–59 days old with only fast breathing as a sign of PSBI (**Population**) whose parents did not accept referral to hospital. The study, which is described in Grade Table 2 (Annex 2), randomized 2333 infants (2196 in the per protocol analysis reported in the GRADE tables) to either oral amoxicillin for seven days (**Intervention**) or to intramuscular gentamicin plus intramuscular procaine penicillin (**Control**). The study was a randomized controlled equivalency trial conducted in the Democratic Republic of Congo, Kenya and Nigeria with equivalency defined *a priori* as having a 95% CI on the risk difference (RD) whose limits were between +/- 5.0%. Treatments were evaluated based on the following four outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **low**. A pooled analysis across the three sites showed the incidence of treatment failure by day 8 after enrollment was 19.5% among those in the intervention arm and 22.0% among the controls. The majority of failure was due to persistence of fast breathing on day 5 (15.8% intervention versus 18.1% control) There was no significant difference between the groups (RD -2.6%; 95% CI: -6.0% to 0.8%), however, the lower limit of the CI was outside the equivalency margin (i.e. below -5.0%). These results may indicate that the new or comparative treatment could be better, but they are not conclusive. Age-specific subgroup analysis between young infants 0–6 days of age (n=802) and 7–59 days of age (n=1394) was carried out. In the 0–6 days of age group, treatment failure was

22.8% (96/421) in the intervention arm and 24.7% (94/381) in the control arm. There was no significant difference between the groups (RD -1.9%; 95% CI: -7.8% to 4.0%). However, the lower limit of the CI was outside the equivalency margin.

- **Mortality in first two weeks after enrollment:** The quality of evidence was graded as **low**. A pooled analysis across the three sites showed the incidence of death by day 15 after enrollment was 0.2% (n=4) among those in the intervention arm and 0.4% (n=4) among the controls. There was no significant difference between the groups (RD -0.02%; 95% CI: -0.5% to 0.5%) and the RD along with its 95% CI lie within the pre-specified equivalency margin indicating that the two regimens are statistically equivalent. Age-specific subgroup analysis between young infants 0–6 days old (n=802) and 7–59 days old (n=1394) was carried out. In the 0–6 day age group the incidence of death by day 15 after enrollment was 0.7% (n=3) among those in the intervention arm and 0.1% (n=1) among the controls. The RD along with the 95% CI did not lie within the pre-specified equivalency margin of +/- 0.5% (RD 0.2%; 95% CI: -0.9% to 1.3%).
- **Relapse and adherence:** A pooled analysis across the three sites showed the incidence of relapse during the second week after enrollment was 2.4% among the 914 intervention arm subjects who were initially well at day 8 and 2.2% among the 827 control arm subjects who were initially well at day 8. There was no significant difference between the groups (RD 0.2%; 95% CI -1.2% to 1.6%), and the RD along with its 95% CI lie within the pre-specified equivalency margin indicating that the two regimens are statistically equivalent. Adherence was found to be better in the intervention (98.5%) than in the control arm (90.7%) with adherence defined as receiving 100% of doses of scheduled antibiotics on all seven days or by the time of treatment failure.

Considerations for recommendation development

Balance of benefits versus harms: The GDG concluded that the benefits of the oral regimen over the injectable regimen clearly outweigh potential harms. It also concluded there was evidence for no difference in clinical efficacy (treatment failure), serious adverse events or deaths when comparing seven days of oral amoxicillin to seven days of intramuscular procaine penicillin and gentamicin. Finally it was noted that patients given parenteral antibiotics had a lower rate of adherence with the prescribed treatment compared to those given oral antibiotics.

Values and preferences: The GDG put a high value on the benefits of oral treatment. The GDG felt that as the oral antibiotic regimen was equally as efficacious as the injectable regimen, the oral regimen was preferred because it was simpler and avoids injections. The GDG also considered that the oral regimen would be likely to be more acceptable to families, be more accessible and have greater rates of treatment completion.

Feasibility (including resource use considerations): The GDG concluded that oral treatment is feasible. The members noted that oral amoxicillin is less expensive than injectable antibiotics and could reduce the economic burden of treatment on families and health systems. They also noted that oral amoxicillin is recommended for treatment of pneumonia in children 2–59 months old and therefore should be routinely available at most health facilities. However, the GDG did conclude that

to ensure this regimen was effective, health care workers will need additional training for skill building around diagnosis and treatment, regular supplies of oral amoxicillin will be required, and the young infant component of current IMCI charts will need revision.

Fast breathing recommendations

The GDG made two recommendations for children with *fast breathing as the only sign of illness* whose families do not accept or cannot access referral, one for infants 0–6 days and one for infants 7–59 days of age.

> **Recommendation 2:** Young infants 0–6 days old with fast breathing as the only sign of illness should be referred to hospital. If families do not accept or cannot access referral care, these infants should be treated with oral amoxicillin, 50 mg/kg per dose given twice daily for seven days, by an appropriately trained health worker.
>
> **Strong recommendation, based on low quality evidence**
>
> **Recommendation 3:** Young infants 7–59 days old with fast breathing as the only sign of illness should be treated with oral amoxicillin, 50 mg/kg per dose given twice daily for seven days, by an appropriately trained health worker. These infants do not need referral.
>
> **Strong recommendation, based on low quality evidence**

Remarks

The GDG noted the following:

- These recommendations do not apply to infants with birth weight < 1500 g or those who have been hospitalized for illness in the previous two weeks because these interventions have not been tested in these populations. These infants must be treated in a hospital.
- The health care worker should counsel the caregiver to return to the health care worker immediately if the infant's condition deteriorates.
- A mandatory follow-up by the health care worker should be made on the fourth day of starting treatment (i.e. after completing three days of treatment).
- There is a higher risk of mortality in the first week of life compared to 7–59 days. Further, the causes of fast breathing in the first week of life may not be due to respiratory infection alone. The GDG therefore felt that 0–6 day old infants with fast breathing as the only sign of illness should be referred to a hospital.

Review Question 3: Clinical severe infection[1]

The systematic review was based on the priority question: among neonates and young infants (0–59 days old) with *suspected/confirmed clinical severe infection* whose families do not accept or cannot access referral care for treatment (**Population**), can simpler antibiotic regimens delivered at outpatient and/or community level (**Intervention**),

[1] In a young infant (0–59 days old), at least one sign of severe infection i.e. movement only when stimulated, not feeding well on observation, temperature greater than or equal to 38 °C or less than 35.5 °C or severe chest in-drawing.

be as effective as a combination of injectable penicillin and gentamicin given for at least seven days (**Control**) in achieving comparable rates of mortality, clinical deterioration and persistence of signs of severe infection within two weeks of starting treatment (**Outcome**)?

Summary of evidence

A total of four randomized controlled equivalency trials involving over 11 300 participants from Asia (Pakistan and Bangladesh) and Africa (Democratic Republic of Congo, Kenya and Nigeria) have addressed this issue *(10-12,23)*. They evaluated five different antibiotic regimens, each in comparison to the standard of care of seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin. The five regimens compared were:

1. intramuscular gentamicin for seven days + oral cotrimoxazole for seven days;
2. intramuscular ceftriaxone for seven days;
3. intramuscular gentamicin for seven days + oral amoxicillin for seven days;
4. intramuscular procaine penicillin + gentamicin for two days followed by oral amoxicillin for five days;
5. intramuscular gentamicin for two days + oral amoxicillin for seven days.

Below is a summary of the evidence for each regimen compared to the reference therapy. In cases where more than one study evaluated a regimen, a pooled analysis was conducted using a fixed effects model. For the pooled analyses a simpler regimen was considered 'equivalent' to the reference treatment if the 95% CI for the pooled RD was within an equivalency margin of +/- 2.5% for treatment failure and +/- 0.5% for death.

Regimen 1: Intramuscular gentamicin plus oral cotrimoxazole for seven days

Only one randomized trial from Pakistan *(10)* compared intramuscular gentamicin plus oral cotrimoxazole for seven days (**Intervention**) to seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (**Control**) in young infants 0–59 days old whose parents did not accept referral to hospital (**Population**). The study, which is described in **Grade Table 3 (Annex 2)**, assigned 144 infants to intramuscular gentamicin plus cotrimoxazole and 145 to intramuscular gentamicin plus procaine penicillin (137 and 131 in per protocol analyses). Within the study equivalency was defined *a priori* as a difference of ≤ 10.0%. Treatments were evaluated based on the following outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **moderate**. The failure rate was 9.9% in the standard of care arm and 18.2% in the intervention arm. The analysis showed significantly *higher risk* of treatment failure in the first week with the simpler treatment of intramuscular gentamicin plus oral cotrimoxazole for seven days (RD: 8.3%; 95% CI: 0.08% to 16.6%) compared to the standard of care (seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin).
- **Mortality in the two weeks after enrollment:** The quality of evidence was graded as **low**. The mortality rate was 1.5% in the standard of care arm and 7.3% in the intervention arm. The analysis showed an *increased risk* of mortality in the two weeks after enrollment associated with the simpler treatment of intramuscular gentamicin plus oral cotrimoxazole for seven days (RD: 5.8%; 95% CI: 0.9% to

10.6%) versus the reference therapy (seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin).

- **Relapse and adherence:** Information on relapse could not be estimated from the study. The rate of adherence was low overall and very similar between the two groups (60.6% intervention and 58.7% control; RR: 1.03; 95% CI: 0.85–1.25).

Regimen 2: Intramuscular ceftriaxone for seven days

Only one randomized trial from Pakistan *(10)* compared intramuscular gentamicin plus ceftriaxone for seven days (**Intervention**) to seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (**Control**) in young infants 0–59 days old whose parents did not accept referral to hospital (**Population**). The study, which is described in **Grade Table 4 (Annex 2)**, assigned 145 infants to intramuscular ceftriaxone and 145 to intramuscular gentamicin plus procaine penicillin (140 and 131 in per protocol analyses). Within the study, equivalency was defined *a priori* as a difference of ≤ 10.0%. Treatments were evaluated based on the following outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **very low**. The failure rate was 9.9% in the standard of care arm and 15.7% in the intervention arm. The analysis found no significant difference in the risk of treatment failure between the two groups in the first week after enrollment (RD: 5.8%; 95% CI: -2.1% to 13.7%).
- **Mortality in the two weeks after enrollment:** The quality of evidence was graded as **very low**. The mortality rate was 1.5% in the standard of care arm and 2.1% in the intervention arm. The analysis found no significant difference in the risk of mortality between the two groups in the two weeks after enrollment (RD: 0.6%; 95% CI: -2.6% to 3.8%).
- **Relapse and adherence:** Information on relapse could not be estimated from the study. The rate of adherence was low overall but very similar between the two groups (56.3% intervention versus 58.7% control; RR: 0.96; 95% CI: 0.78-1.17).

Regimen 3: Intramuscular gentamicin plus oral amoxicillin for seven days

Three randomized trials conducted in Bangladesh *(12)*, Democratic Republic of Congo, Kenya, Nigeria *(11)* and Pakistan *(23)* compared intramuscular gentamicin plus oral amoxicillin for seven days (**Intervention**) to seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (**Control**) in young infants 0–59 days old whose parents did not accept referral to hospital (**Population**). The three studies, which are described in **Grade Table 5 (Annex 2)**, assigned a total of 5054 (per protocol N=4729) infants to either gentamicin plus amoxicillin or to intramuscular gentamicin plus procaine penicillin. Treatments were evaluated based on the following outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **moderate**. The rate of treatment failure was 8.1% in the intervention arm and 9.9% in the control arm. Pooled analysis showed a *significantly lower* rate of treatment failure in the first week after enrollment among those given intramuscular gentamicin plus oral amoxicillin for seven days (RD: -1.8%; 95% CI: -3.4% to -0.2%) compared to those given the standard of care (seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin).

- **Mortality in the two weeks after enrollment:** The quality of evidence was graded as **moderate**. The rate of mortality was 1.3% in the intervention arm and 1.6% in the control arm. The pooled analysis showed no difference between the two groups in the risk of mortality in the two weeks after enrollment although the lower confidence limit was not within the pre-specified equivalency margin of +/- 0.5% (RD: -0.3%; 95% CI: -1.0% to 0.4%).
- **Relapse and adherence:** There was no significant difference in the rate of relapse between the groups, although relapse was less common among those given intramuscular gentamicin plus oral amoxicillin for seven days (1.4% intervention versus 1.9% control; RD -0.5%; 95% CI: -1.3% to 0.2%). The rate of adherence was nearly identical (93.4% intervention versus 94.0% control) between the two groups (RR: 0.99; 95% CI: 0.98-1.01).

Regimen 4: Intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days

Three randomized trials conducted in Bangladesh *(12)*, Democratic Republic of Congo, Kenya, Nigeria *(11)* and Pakistan *(23)* compared intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days (**Intervention**) to seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (**Control**) in young infants 0–59 days old whose parents did not accept referral to hospital (**Population**). The three studies, which are described in Grade Table 6 (Annex 2), assigned a total of 5066 (per protocol N=4775) infants to either intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days or gentamicin plus penicillin (or a third regimen described above). Treatments were evaluated based on the following outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **moderate**. The rate of treatment failure was 9.5% in the intervention arm and 9.9% in the control arm. The pooled analysis found no difference in the incidence of treatment failure between the two groups in the first week after enrollment (RD: -0.5%; 95% CI: -2.2% to 1.1%), and the results were within the pre-specified equivalency margin of +/- 2.5%.
- **Mortality in the two weeks after enrollment:** The quality of evidence was graded as **moderate**. The rate of mortality was 1.8% in the intervention arm and 1.7% in the control arm. The pooled analysis found no significant difference in the risk of mortality in the first two weeks after enrollment between the two groups, although the results were not within the pre-specified equivalency margin of +/- 0.5% (RD: 0.1%; 95% CI: -0.6% to 0.9%).
- **Relapse and adherence:** There was a significant reduction in the rate of relapse for those given intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days (0.8% intervention versus 1.9% control; RD: -1.0%; 95% CI: -1.7% to -0.4%) versus those given the standard of care (seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin). The rate of adherence was nearly identical between the two groups, although only two studies reported adherence data (95.2% intervention versus 94.0% control; RR: 1.01; 95% CI: 1.0–1.03).

Regimen 5: Intramuscular gentamicin for two days plus oral amoxicillin for seven days

One multi-centre trial conducted in the Democratic Republic of Congo, Kenya and Nigeria *(11)* compared intramuscular gentamicin for two days plus oral amoxicillin for seven days (**Intervention**) to seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (**Control**) in young infants 0–59 days old whose parents did not accept referral to hospital (**Population**). The study, which is described in Grade Table 7 (Annex 2), assigned a total of 1784 (per protocol N=1676) infants to either intramuscular gentamicin for two days plus oral amoxicillin for seven days or to intramuscular gentamicin plus procaine penicillin. Treatments were evaluated based on the following outcomes:

- **Treatment failure in the first week after enrollment:** The quality of evidence was graded as **moderate**. The rate of failure was 5.4% in the intervention arm and 8.1% in the control arm. The analysis showed that those given intramuscular gentamicin for two days plus oral amoxicillin for seven days had *significantly lower* incidence of treatment failure in the first week after enrollment compared to those given seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin (RD: -2.7%; 95% CI: -5.1% to -0.3%).
- **Mortality in the two weeks after enrollment:** The quality of evidence was graded as very low. The rate of mortality was 1.2% in the intervention arm and 1.3% in the control arm. There was no significant difference in the risk of mortality in the first two weeks after enrollment between the two groups, although the results were not within the pre-specified equivalency margin of +/-0.5% (RD: -0.01%; 95% CI: -1.2% to 0.9%).
- **Relapse and adherence:** There was no significant difference in the rate of relapse between the groups, although relapse was less common among those given intramuscular gentamicin for two days plus oral amoxicillin for seven days (0.8% intervention versus 1.0% control; RD: -0.2%; 95% CI: -1.1% to 0.8%) compared to those given seven days of intramuscular gentamicin plus seven days of intramuscular procaine penicillin. The rate of adherence was nearly identical between the two groups, but higher in the intervention arm (97.0% intervention versus 92.5% control; RR: 1.05; 95% CI: 1.02-1.07).

Considerations for recommendation development

Balance of benefits versus harms

The GDG concluded the following:

- Oral cotrimoxazole plus intramuscular injectable gentamicin for seven days (regimen 1) may be inferior to the reference regimen based on the higher rate of treatment failure and clearly inferior to the reference regimen based on the increased mortality.
- Intramuscular gentamicin plus oral amoxicillin for seven days (regimen 3) may be superior to the reference treatment based on the reduced treatment failure rate and non-inferior (equivalent or better) with respect to mortality.
- Intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days (regimen 4) is equivalent to the reference treatment

based on the treatment failure rate and non-superior (equivalent or worse) based on mortality.

- Intramuscular gentamicin for two days plus oral amoxicillin for seven days (regimen 5) may be superior to the reference treatment due to lower treatment failure, but is inconclusive with respect to mortality.
- None of the simpler regimens containing amoxicillin and gentamicin were associated with an increased risk of serious adverse events or deaths compared to the reference treatment.

Values and preferences: The GDG identified several benefits of simpler regimens that would make them preferable over the current standard of care. The members noted that compared to the reference treatment, which involves a total of 14 injections, simpler antibiotic regimens containing amoxicillin and gentamicin would require only two to seven injections. They concluded that families and health care providers are likely to prefer fewer injections, while policy-makers and programme managers are likely to give a high value to the simpler regimens that are easier to administer in outpatient settings.

However, the GDG also noted some drawbacks to simpler regimens. Firstly, they would require treatment to be provided by optimally trained and supervised providers to avoid injection-related complications, and regular follow-up would be needed for simpler antibiotic regimens to identify treatment failure including clinical deterioration, need for change of antibiotic therapy, no improvement by day 4 and referral for hospitalization. Secondly, in some countries there might be regulatory barriers to the new regimens if certain cadres of health workers are not permitted to administer antibiotic injections. Finally, extensive use of antimicrobial agents for young infants may lead to AMR and therefore AMR surveillance would be required. However, this risk is no greater than with the current WHO treatment recommendations.

Feasibility (including resource use considerations): The GDG noted that simpler antibiotic regimens are less expensive than the current standard treatment because they require fewer injections and have fewer human resource requirements. In addition oral amoxicillin is already recommended for treatment of pneumonia in 2–59 month old children, and therefore should be routinely available at most health facilities. However, if simpler regimens were implemented, health care workers would need training for skill building around diagnosis and treatment of PSBI, regular supplies of injectable gentamicin and oral amoxicillin would need to be ensured and changes in the young infant component of IMCI charts being used in countries would need to be made.

Clinical severe infection recommendations

The GDG made one recommendation for young infants (0–59 days old) with clinical severe infection who cannot access or refuse hospitalization, recommending two treatment options.

> **Recommendation 4:** Young infants (0–59 days) identified with clinical severe infection whose families do not accept or cannot access hospital care should be managed in outpatient settings by an appropriately trained health worker with one of the two following regimens:

Option 1: Intramuscular gentamicin 5–7.5 mg/kg *(4)* (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for seven days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. Close follow-up is essential.

Strong recommendation based on moderate quality evidence

Option 2: Intramuscular gentamicin 5–7.5 mg/kg *(4)* (for low-birth-weight infants gentamicin 3–4 mg/kg per day once daily) once daily for two days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. Close follow-up is essential. A careful assessment of the child on day 4 is mandatory for this option in order to determine if the child is improving.

Strong recommendation based on low quality evidence

For option 2, the GRADE rating by the systematic review group was moderate quality evidence for treatment failure and very low quality evidence for mortality. However, the GDG reached a consensus agreement that the overall quality was low.

The GDG made a strong recommendation for option 2 despite low quality evidence. The evidence was graded as low quality because data were available only from a single, large, multi-country study from Africa while more evidence is available for option 1 (graded as moderate quality). However there was no important difference in the key outcomes. Option 1 is the preferred option, but where the health system does not allow this to be implemented, option 2 could be considered. The GDG felt that option 2 likely would be easier to deliver, have more equitable access, have higher adherence, be more affordable and have similar effectiveness. It is expected that individual countries will adapt the recommendations to suit the local social, cultural and economic contexts. Countries are encouraged to hold key stakeholder discussions to inform the decision-making on use and introduction of the recommendations into national programmes.

Remarks

The GDG also noted the following:

- If any sign of critical illness appears at any time during treatment, the health care worker should treat the young infant as a critically ill young infant.
- If any new sign of clinical severe infection (not present initially) appears after 48 hours of treatment, the health care worker should treat the young infant as a critically ill young infant.
- If any sign of clinical severe infection is still present by day 8, the health care worker should treat the young infant as a critically ill young infant.
- The health care worker should counsel families to return to the health care worker immediately if the young infant's condition worsens.
- At each contact (for both treatment and follow-up), the health care worker should assess the baby for signs of clinical deterioration.
- Health care workers should promote exclusive breastfeeding, and the sick young infant should be kept warm if the body temperature is low.
- The GDG strongly encourages governments to set up country level surveillance for AMR to guide future antibiotic decisions.

Review Question 4: Critical illness[1]

The systematic review was based on the priority question: among neonates and young infants (0–59 days old) with signs of critical illness, whose families do not accept or cannot access referral care for treatment (**Population**), are simpler antibiotic regimens delivered at outpatient and/or community level (**Intervention**), as effective as a combination of injectable penicillin and gentamicin for at least seven days (**Control**) as measured by rates of mortality, clinical deterioration and persistence of signs of severe infection, within two weeks of starting treatment (**Outcome**)?

Summary of evidence

There were no comparative trials on which to base this recommendation.

Critical illness recommendations

The GDG made one recommendation for young infants 0–59 days old who have any sign of critical illness:

> **Recommendation 5:** Young infants 0–59 days old who have any sign of critical illness (at presentation or developed during treatment of clinical severe infection) should be hospitalized after pre-referral treatment with antibiotics.[2]
>
> **Strong recommendation based on very low quality evidence (standard of care)**

Remarks

Although there are no comparative trials available showing the relative efficacy and safety, in cases where hospitalization is not possible at all, critically ill children should be given one of the following treatment regimens until hospitalization becomes possible (up to seven days):

1. twice daily intramuscular ampicillin and once daily intramuscular gentamicin;
2. once daily intramuscular ceftriaxone with or without once daily intramuscular gentamicin;
3. twice daily intramuscular benzyl penicillin and once daily intramuscular gentamicin;
4. once daily intramuscular procaine penicillin and once daily intramuscular gentamicin.

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[1] In a sick young infant, presence of any of the following signs: unconscious, convulsions, unable to feed at all, apnoea, unable to cry, cyanosis, bulging fontanelle, major congenital malformations inhibiting oral antibiotic intake, active bleeding requiring transfusion, surgical conditions needing hospital referral, persistent vomiting (defined as vomiting following three attempts to feed the infant within 30 minutes and the infant vomits after every attempt).

[2] Give first dose of both ampicillin (50 mg/kg per dose) or benzyl penicillin (50 000 units/kg per dose) and gentamicin (5–7.5 mg/kg per dose) intramuscularly.

Dissemination, implementation and monitoring of guideline

Dissemination

The recommendations in this guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and non-governmental organizations. They will also be published on the WHO website. Strategic dissemination to key stakeholders will ensure that the guideline reaches the users most likely to benefit from it.

Adaptation and implementation

The first steps in implementation will be to revise all WHO publications that deal with these conditions, and/or ensure their inclusion in other relevant documents. These include the materials for the *Integrated Management of Childhood Illness (3)* and *The Pocket Book for Hospital Care of Children (4)*.

The successful introduction of evidence-based policies related to management of sick young infants into national programmes and health care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national guidelines or protocols based on this document.

It is expected that individual countries will adapt the recommendations to suit the local social, cultural and economic contexts. Countries will be encouraged to hold key stakeholder discussions to inform decision-making on the use and introduction of the recommendations into national programmes. The recommendations contained in the present guideline should be adapted into locally-appropriate documents to meet the specific needs of each country and health service. For management of 'clinical severe infection' in young infants where referral is not possible, the preferred option is the first one using seven injections. However, where the health system does not allow this to be implemented, the second option could be considered. MCA will explore using a framework for assisting policy-makers in adapting this guideline, such as the DECIDE framework *(24)*.

An enabling environment should be created for the use of these recommendations, including changes in the behaviour of health care practitioners to enable the use of evidence-based practices. Local professional societies may play important roles in this process, and an all-inclusive and participatory process should be encouraged. MCA has substantial experience of introduction of WHO guidelines and tools into national programmes.

The drugs recommended in this document are on the WHO *Model List of Essential Medicines (25)*. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community

can afford. The *Model List* is a guide for the development of national and institutional essential medicine lists.

Within this context, programme managers will need to ensure that adequate quantities of required drugs in the recommended dosages are available to health workers. These drugs would normally be provided through existing health system supply chains.

Relevant to any review of national drug lists and policy, WHO's 2014 report on global surveillance of AMR reveals that antibiotic resistance is a serious and growing problem across the world *(26)*. Countries should strengthen national plans to tackle AMR.

Monitoring and evaluation of guideline implementation

Monitoring and evaluation should be built into the implementation process, in order to provide important lessons for uptake and further implementation. With regard to monitoring and evaluation of their impact on quality of care, priority should be given to the strong recommendations.

The implementation of this guideline should involve national child health programmes collecting and reporting data on the management of sick young infants whose families do not accept or cannot access referral care. Putting this into practice may require a review of existing patient monitoring systems, including reporting tools, to ensure that the conditions are adequately addressed.

Key areas that may require monitoring include:

- diagnosis of sick young infants with suspected sepsis;
- treatment of sick young infants with suspected sepsis at first level health facilities;
- response to treatment;
- risk of side effects especially from gentamicin toxicity;
- service delivery (including the need for metrics to track coverage and quality of care and adherence to treatment protocols);
- support systems, including supplies and logistics, and supervision;
- community perceptions and acceptance.

Global and country level efforts are underway under *Every Newborn: an action plan to end preventable deaths (27,28)* through Metrics Task Teams to agree upon critical indicators for management of neonatal sepsis. The monitoring and evaluation strategy will endeavour to ensure that the existing patient monitoring tools at health facilities and communities will contain information on recognition and management of sick young infants. However, the data could be collected periodically through special surveys or programme reviews.

MCA will also monitor implementation of this guideline using indicators such as the number of requests from countries for assistance in implementation as well as requests to WHO headquarters and regional offices for monitoring and evaluation in countries applying the guideline. MCA will work with the regional offices to monitor the number of countries implementing this guideline. Additionally, MCA will monitor the number of downloads of the guideline document from the WHO, partners' and other stakeholders' websites, as well as the number of hard copies of the guidance requested and distributed through the WHO document centre.

Implications for future research

Before countries can use this guideline for policy adoption and implementation at scale, more work is needed to address these as well as operational issues. Important consideration should also be given to tracking possible harm, for example at the individual level there is a risk of increased gentamicin toxicity (e.g. ototoxicity and nephrotoxicity) particularly if blood levels are not being tracked. Innovative approaches are needed to achieve this safety tracking at lower levels of the health system. At a population level, innovative and lower costs methods are needed for tracking of potential changes in AMR.

Facilitating policy adoption and putting in place an enabling environment for implementation will require a dialogue with policy-makers and other stakeholders at country level. Programme managers will require technical support for development and implementation of operational plans in programme settings from experts with experience delivering these interventions. If policy dialogue and small-scale demonstration projects are not supported at the country level, it is less likely that this guideline will be adopted as policy and scaled-up.

To achieve scale-up WHO and UNICEF will jump-start the process through country level policy dialogue to facilitate small-scale demonstration projects for simplified management of sick young infants with suspected sepsis where referral is not possible. This will facilitate future scale-up of these lifesaving interventions. The approach will have three components.

- Policy dialogue and orientation meetings held at the national level with ministries of health and other stakeholders at the national and subnational levels to discuss limited policy adoption to set up demonstration sites in a few health facilities.
- Demonstration sites established in a few countries to demonstrate feasibility of delivering simplified antibiotic regimens to young infants with suspected serious bacterial infection where families do not accept or cannot access referral care. The innovation of this approach will be in the careful assessments and measurements of the logistical requirements for programme uptake and expansion. MCA will document the human resource requirements, the steps needed to make the supply chain for essential commodities work consistently, the level of supervision required and the ways in which that level of supervision can be produced given the limits of current supervisory systems in many areas. This implementation research should provide four country-specific assessments of the true barriers to implementation and success, and will be able to offer some grounded recommendations on overcoming those barriers. We aim to monitor the quality of programme implementation through outcomes such as whether 80% of young infants receive “adequate quality” treatment. More details are outside the scope of this document.
- Develop a partnership between demonstration sites and programme managers to provide technical assistance to initiate a pilot in other health facilities.

Plans for updating the guideline

This guideline will be reviewed and updated in January 2019. At that time the WHO Steering Committee will constitute a GDG to review the literature and update the recommendations as needed. In the interim, the WHO Steering Committee will continue to monitor any new studies, interim research results or reports of adverse events associated with this policy implementation. If relevant information becomes available that indicates urgent changes to the recommendations before January 2019, a GDG will be constituted at that time.

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ANNEX 1
Declaration of interests

The Declaration of Interest for WHO Experts forms of all the invited participants and temporary advisers for the guideline meetings were reviewed and assessed. Seven participants declared having interests that could be perceived to be a conflict of interest. The experts were asked to confirm their declarations of interest verbally at the beginning of the meeting.

1. Dr W Carlo, University of Alabama at Birmingham, USA, declared having current investments in a commercial entity, MEDNAX. MEDNAX, Inc., is a national medical group that comprises the USA's leading providers of neonatal, anaesthesia, maternal-fetal and paediatric physician subspecialty services.
2. Dr C Garg, Consultant, New Delhi, India, declared having received consulting fees from WHO.
3. Dr P Hibberd, Massachusetts General Hospital, Boston, USA, declared having received a research grant from Saving Lives at Birth.
4. Dr E Molyneux, College of Medicine, Blantyre, Malawi, declared having received a research grant from Saving Lives at Birth and a grant from GSK-Save the Children Partnership to introduce bubble continuous positive airway pressure training.
5. Dr K Mulholland, Murdoch Children's' Research Institute, Melbourne, Australia, declared having been for two years the Chair of the Technical Steering Committee for the Simplified Antibiotic Treatment trials in Bangladesh and Pakistan.
6. Dr V Paul, All India Institute of Medical Sciences, New Delhi, India, declared being an academic who takes public positions on child health issues including treatment of acute respiratory infections.
7. Dr D Vivio, United States Agency for International Development, Washington DC, USA, declared that the Agency contributed towards her travel costs in connection with this meeting.

External resource persons were invited to the meeting as observers and to provide technical input, but they did not participate in the decision-making processes. All declarations of interests were reviewed, and none were found to be a conflict of interest for the experts invited to this guideline development meeting. None of the above-mentioned persons chaired the meeting.

ANNEX 2

GRADE summary of findings tables

GRADE TABLE 1. Home visits by CHWs for improved care seeking from health facilities in newborns and young infants

Outcomes	Intervention and comparison intervention	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		With comparator	With intervention				
Improved care seeking from health facility *(14,18-22)*							
	Home visits by CHWs/ no home visits	**537 per 1000**	**725 per 1000** (618 to 849)	**RR 1.35** (1.15 to 1.58)	**9158** (6 studies)	⊕⊕⊕◯ moderate[a]	see footnotes

[a] Blinding was not achievable given the nature of intervention amongst the two groups. The group allocated was easily identifiable by interview with patients.

GRADE TABLE 2: Treatment of fast breathing pneumonia: oral amoxicillin for seven days versus intramuscular penicillin plus intramuscular gentamicin for seven days

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Oral amoxicillin for 7 days	IM[a] penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
1	randomized trial *(13)*	not serious	single study	not serious	serious[b]	221/1135 (19.5%)	234/1061 (22.0%)	**RD -2.6%** (-6.0% to 0.8%) 26 fewer per 1000 (from 8 more to 60 fewer)	⨁⨁◯◯ LOW	CRITICAL	The lower limit of CI crosses equivalence margins, which might indicate that the new or comparative treatment may be better, but is not conclusive
Deaths in first two weeks after enrollment											
1	randomized trial *(13)*	not serious	single study	not serious	serious[c]	4/1135 (0.4%)	4/1061 (0.4%)	**RD -0.02%** (-0.5% to 0.5%) 0 fewer per 1000 (from 5 more to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL	New regimen is EQUIVALENT to reference treatment

[a] Intramuscular
[b] 95% CI around the pooled estimate includes 1) null effect and 2) appreciable harm/benefit.
[c] Few events.

GRADE TABLE 3: Treatment of PSBI: intramuscular gentamicin plus oral cotrimoxazole for seven days versus intramuscular penicillin plus intramuscular gentamicin for seven days

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	IM gentamicin plus oral cotrimoxazole for 7 days	IM penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
1	randomized trial *(10)*	serious[a]	single study	not serious	not serious	25/137 (18.2%)	13/131 (9.9%)	**RD 8.3%** (0.08% to 16.6%) 83 more per 1000 (from 8 more to 166 more)	⊕⊕⊕◯ MODERATE	CRITICAL	New regimen is not equivalent – it is INFERIOR to reference treatment
Deaths in first two weeks after enrollment											
1	randomized trial *(10)*	not serious[b]	single study	not serious	serious[c]	10/137 (7.3%)	2/131 (1.5%)	**RD 5.8%** (0.9% to 10.6%) 58 more per 1000 (from 9 more to 106 more)	⊕⊕◯◯ LOW	CRITICAL	New regimen is not equivalent – it is INFERIOR to reference treatment

[a] Neither intervention nor outcome assessment was blinded.
[b] Outcome assessment not blinded but outcome is 'objective'.
[c] Few events.

GRADE TABLE 4: Treatment of PSBI: intramuscular ceftriaxone for seven days versus intramuscular penicillin plus intramuscular gentamicin for seven days

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	IM ceftriaxone for 7 days	IM penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
1	randomized trial *(10)*	serious[a]	single study	not serious	serious b	22/140 (15.7%)	13/131 (9.9%)	**RD 5.8%** (-2.1% to 13.7%) 58 more per 1000 (from 21 fewer to 137 more)	⊕◯◯◯ VERY LOW	CRITICAL	The upper limit of CI crosses equivalence margins, which may indicate that the new or comparative treatment may be inferior, but is not conclusive
Deaths in first two weeks after enrollment											
1	randomized trial *(10)*	not serious[c]	single study	not serious	very serious[b,d]	3/140 (2.1%)	2/131 (1.5%)	**RD 0.6%** (-2.6% to 3.8%) 6 more per 1000 (from 26 fewer to 38 more)	⊕◯◯◯ VERY LOW	CRITICAL	Wide 95% CI – equivalence cannot be commented upon

[a] Neither intervention nor outcome assessment was blinded.
[b] 95% CI around the pooled estimate includes 1) null effect and 2) appreciable harm/benefit.
[c] Outcome assessment not blinded but outcome is 'objective'.
[d] Few events.

GRADE TABLE 5: Treatment of PSBI: intramuscular gentamicin plus oral amoxicillin for seven days versus intramuscular penicillin plus intramuscular gentamicin for seven days

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	IM gentamicin plus oral amoxicillin for 7 days	IM penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
3	randomized trials *(11,12,23)*	serious[a]	not serious	not serious	not serious	192/2359 (8.1%)	235/2370 (9.9%)	**RD -1.8%** (-3.4% to -0.2%) 18 fewer per 1000 (from 2 fewer to 34 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL	New regimen is not equivalent – it is SUPERIOR to reference treatment
Deaths in first two weeks after enrollment											
3	randomized trials *(11,12,23)*	not serious[b]	not serious	not serious	serious[c,d]	31/2417 (1.3%)	39/2436 (1.6%)	**RD -0.3%** (-1.0% to 0.4%) 3 fewer per 1000 (from 4 more to 10 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL	The lower limit of CI crosses equivalence margins, which may indicate that the new or comparative treatment might be better, but is not conclusive

[a] Unclear risk of measurement bias (in two out of three studies, physicians masked to group allocation only confirmed the cases referred to them; they did not measure the outcomes in all enrolled infants).
[b] Unclear risk of measurement bias in two studies but outcome is 'objective' .
[c] 95% CI around the pooled estimate includes 1) no effect and 2) appreciable harm/benefit.
[d] Few events but sample size > 2000 per group.

GRADE TABLE 6: Treatment of PSBI: intramuscular procaine penicillin plus gentamicin for two days followed by oral amoxicillin for five days versus intramuscular gentamicin plus intramuscular procaine penicillin for seven days (reference treatment)

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	IM penicillin + gentamicin for 2 days followed by oral amoxicillin for 5 days	IM penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
3	randomized trials *(11,12,23)*	serious[a]	not serious	not serious	not serious	228/2405 (9.5%)	235/307 (9.9%)	**RD -0.5%** (-2.2% to 1.1%) 5 fewer per 1000 (from 11 more to 22 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL	New regimen is EQUIVALENT to reference treatment
Deaths in first two weeks after enrollment											
3	randomized trials *(11,12,23)*	not serious[b]	not serious	not serious	serious[c,d]	43/2405 (1.8%)	39/2307 (1.7%)	**RD 0.1%** (-0.6% to 0.9%) 1 more per 1000 (from 6 more to 9 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL	Wide 95% CI – equivalence cannot be commented upon

[a] Unclear risk of measurement bias (in two out of three studies, physicians masked to group allocation only confirmed the cases referred to them; they did not measure the outcomes in all enrolled infants).
[b] Unclear risk of measurement bias in two studies but outcome is 'objective'.
[c] 95% CI around the pooled estimate includes 1) no effect and 2) appreciable harm/benefit.
[d] Few events but sample size > 2000 per group.

GRADE TABLE 7: Treatment of PSBI: intramuscular gentamicin for two days plus oral amoxicillin for seven days versus intramuscular gentamicin plus intramuscular procaine penicillin (reference treatment)

Quality assessment						No. of patients		Effect of the intervention vs control	Quality	Importance	Interpretation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	IM gentamicin for 2 days and oral amoxicillin for 7 days	IM penicillin plus IM gentamicin for 7 days	Risk difference (95% CI)			
Treatment failure by day 8 after enrollment (assessed with: death, clinical deterioration, change of antibiotics, no improvement by day 4, etc., in the first week of enrollment)											
1	randomized trial *(11)*	not serious	single study	not serious	not serious	46/848 (5.4%)	67/828 (8.1%)	**RD -2.7%** (-5.1% to -0.3%) 27 fewer per 1000 (from 3 fewer to 51 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL	New regimen is not equivalent – it is SUPERIOR to reference treatment
Deaths in first two weeks after enrollment											
1	randomized trial *(11)*	not serious	single study	not serious	very serious[a,b]	11/890 (1.2%)	12/894 (1.3%)	**RD -0.01%** (-1.2% to 0.9%) 0 fewer per 1000 (from 9 more to 12 fewer)	⊕◯◯◯ VERY LOW	CRITICAL	Wide 95% CI – equivalence cannot be commented upon

[a] 95% CI around the pooled estimate includes 1) no effect and 2) appreciable harm/benefit.
[b] Few events.

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