

Recommendations for treatment of childhood non-severe pneumonia



Gavin B Grant, Harry Campbell, Scott F Dowell, Stephen M Graham, Keith P Klugman, E Kim Mulholland, Mark Steinhoff, Martin W Weber, Shamim Qazi

WHO recommendations for early antimicrobial treatment of childhood pneumonia have been effective in reducing childhood mortality, but the last major revision was over 10 years ago. The emergence of antimicrobial resistance, new pneumonia pathogens, and new drugs have prompted WHO to assemble an international panel to review the literature on childhood pneumonia and to develop evidence-based recommendations for the empirical treatment of non-severe pneumonia among children managed by first-level health providers. Treatment should target the bacterial causes most likely to lead to severe disease, including *Streptococcus pneumoniae* and *Haemophilus influenzae*. The best first-line agent is amoxicillin, given twice daily for 3–5 days, although co-trimoxazole may be an alternative in some settings. Treatment failure should be defined in a child who develops signs warranting immediate referral or who does not have a decrease in respiratory rate after 48–72 h of therapy. If failure occurs, and no indication for immediate referral exists, possible explanations for failure should be systematically determined, including non-adherence to therapy and alternative diagnoses. If failure of the first-line agent remains a possible explanation, suitable second-line agents include high-dose amoxicillin–clavulanic acid with or without an affordable macrolide for children over 3 years of age.

Introduction

Each year, clinical pneumonia occurs in an estimated 156 million children aged under 5 years,¹ and causes approximately a fifth of all deaths among such children, most of whom are in low-income nations.² To reduce the morbidity and mortality of pneumonia in children, guidelines currently known as the Integrated Management of Childhood Illness (IMCI) have been developed by WHO and partners for first-level health systems. IMCI has been implemented by many organisations and reduces mortality effectively,^{3,4} although implementation can be improved.^{5,6} These guidelines include recommendations for the case management of acute respiratory illness. They indicate when referral is needed and specify appropriate antimicrobial agents when referral is not needed.

WHO recommendations for the treatment of pneumonia have provided critical guidance to first-level health-care workers worldwide, but the last major revision is more than 10 years old. The first WHO recommendations for respiratory disease case management were published in a 1981 WHO memorandum.⁷ The memorandum was aimed at encouraging a systematic approach to the management of children with possible pneumonia in resource-poor settings, based on simple algorithms and empirical treatment. Recommended agents included drugs available at the time of publication, with both intramuscular and oral drugs listed, such as procaine penicillin, ampicillin, erythromycin, co-trimoxazole, and sulfamethoxypridazine, and noted that there was as yet little experience with co-trimoxazole. Second-line agents for use in children still ill after 48 h included chloramphenicol or oxacillin.

WHO published a revised document in 1991, after much experience had been gained with the case-

management approach and empirical treatment.⁸ For treatment of non-severe pneumonia at the first-level health facility, this document recommended oral co-trimoxazole as the preferred agent, with injectable procaine penicillin and oral amoxicillin as alternatives. A 2005 technical update of the WHO IMCI guidelines recommended oral amoxicillin (50 mg/kg per dose, in two divided doses) or co-trimoxazole (8 mg/kg trimethoprim per dose, in two divided doses) for the treatment of non-severe pneumonia,⁹ if antimicrobial resistance to co-trimoxazole was high, oral amoxicillin was preferred.

During the past decade, various organisations have issued recommendations for paediatric pneumonia treatment.^{10–14} These recommendations are primarily intended for high-income to middle-income nations. New information on antimicrobial resistance, the changing epidemiology of pneumonia, and the availability of a broader range of first-line and second-line antimicrobial agents provides the impetus for updated recommendations for antimicrobial treatment of non-severe pneumonia among children assessed by first-level health providers, often with basic health training.

The WHO Department of Child and Adolescent Health and Development selected and assembled this panel to review the current literature on childhood pneumonia and to define further the most appropriate antimicrobial agents for treatment of non-severe pneumonia. Specifically, we were asked to define the appropriate first-line antimicrobial agent, treatment failure, when to change therapy, and appropriate second-line antimicrobial agents.

Methods

The international panel consisted of nine clinicians and researchers with experience in defining and treating

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National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA (G B Grant MD); Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK (H Campbell MD); Coordinating Office for Global Health, CDC, Atlanta (S F Dowell MD); Malawi–Liverpool–Wellcome Trust Research Programme and Department of Paediatrics, College of Medicine, University of Malawi, Blantyre, Malawi, and Centre for International Child Health, Department of Paediatrics, University of Melbourne, and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia (S M Graham FRACP); Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, and Medical Research Council/University of the Witwatersrand Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa (K P Klugman MD); Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK, and Menzies School of Health Research, Darwin, NT, Australia (E K Mulholland MD); Bloomberg School of Public Health, and School of Medicine, Johns Hopkins University, Baltimore, MD, USA (M C Steinhoff MD); WHO Indonesia Country Office, Jakarta, Indonesia (M W Weber Dr med habil); and Department of Child and Adolescent Health, WHO, Geneva, Switzerland (S Qazi MD)

Correspondence to:
Gavin Bayan Grant,
1600 Clifton Road NE, MS E-05,
Atlanta, GA 30333, USA
gbgrant@cdc.gov

Panel: Issues addressed by WHO panel**Aim 1**

Identify the most appropriate first-line antimicrobial agent

Aim 2

Define treatment failure

Aim 3

Clarify when it is appropriate to change therapy in children who do not need referral

Aim 4

Prescribe the most appropriate second-line antimicrobial agent for those children who fail the first-line therapy

	Strength of recommendation	Quality of evidence
Recommendation 1		
Amoxicillin as initial antimicrobial agent for the treatment of non-severe pneumonia.	Strong	High
Co-trimoxazole may be an acceptable alternative	Weak	Intermediate
Recommendation 2		
Definitions of treatment failure	Strong	Low
Recommendation 3		
Systematic assessment for treatment or referral	Strong	Very low
Recommendation 4		
Second-line antimicrobial agents	Strong	Very low
See main text for full details of recommendations.		
Table 1: Outline of recommendations		

pneumonia among children in various settings. We communicated by regular conference calls and by email. After reviewing the available evidence, we discussed issues such as interpretation of aetiological study results and antimicrobial resistance data. The initial focus was to identify appropriate first-line and second-line antimicrobial agents for the empirical treatment of non-severe pneumonia in children by first-level health-care workers. However, we determined that to address second-line therapy, a definition of treatment failure and determination of when to change therapy were required (panel).

Search strategy

A literature search was done to generate a foundation for recommendations. The results for appropriate first-line and second-line antimicrobial agents (webtable) were similar those obtained by a Cochrane review.¹⁵ Evidence was collected with a focus on publications from January, 1991 (the date of the last recommendations) through September, 2008, by searches of PubMed, EMBASE, and the Cochrane Central Registrar of Controlled Trials, in addition to bibliographies of relevant articles and the

author's records. Search terms were "pneumonia", "child", "childhood", "pediatric", "paediatric", "antibiotic", "trial", and "cohort", and was limited to available articles in English or an English abstract that included children with pneumonia under age 5 years in the study. For the selection of antimicrobial agents, 36 articles that assessed more than one antimicrobial agent and the seven articles that assessed different durations or doses of antimicrobial agents by use of a randomised controlled trial were included in the review. Articles were excluded if no treatment failure data were available as an outcome or if they exclusively enrolled children with very severe pneumonia. If an article presented results of children with a spectrum of diagnosis (eg, sinusitis, otitis media, and pneumonia) only results for children with pneumonia were included, if possible. These articles provide the basis, along with the panel's experience, for the recommendations.

Development of recommendations

Initial recommendations were drafted and then circulated to a broader group of reviewers for comment. The broader group included experts with experience in the treatment and epidemiology of pneumonia, as well as representatives from the WHO regional offices. Table 1 outlines the recommendations developed, with strength of each major recommendation and the quality of supporting evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.^{16,17} The GRADE quality of evidence categories include high, intermediate, low, and very low, and was determined by the panel's review of the literature. The studies available for this review, with few exceptions, were observational in nature rather than blinded randomised trials, and therefore, the GRADE quality of evidence was rarely higher than intermediate. After the review by the broader group, the strength of each recommendation was determined by the panel members.

Recommendation 1

Amoxicillin is the preferred initial antimicrobial agent for the treatment of non-severe pneumonia. The dose of amoxicillin is 50 mg/kg per day in two divided doses for a 3-day treatment course in areas with low HIV prevalence, and 5 days in areas of high HIV prevalence. In some situations, such as where local evidence clearly indicates infrequent resistance, co-trimoxazole (8 mg/kg trimethoprim in two divided doses) may be an acceptable alternative.

Rationale and evidence summary

Pneumonia is, strictly speaking, a pathological diagnosis, determined by clinical means. Radiological consolidation is commonly used as a surrogate, but is often not feasible at first-level health facilities.¹⁸ Pneumonia definitions used in the IMCI guidelines were developed and

See Online for webtable

validated to identify children with specific treatment needs,⁷ such as those needing antimicrobial therapy or referral to higher levels of care. Non-severe pneumonia is diagnosed in a child with cough or difficulty breathing accompanied by tachypnoea, defined as a respiratory rate of at least 40 breaths per min in a child aged 12–59 months, or at least 50 breaths per min in an infant aged 2–11 months. Use of these criteria identifies 80% of children with pneumonia who need antimicrobial therapy.⁷ Children aged 2–59 months require immediate referral if they have signs of severe or very severe pneumonia (lower chest indrawing or central cyanosis), stridor when calm, or IMCI-defined danger signs (inability to drink or breastfeed, convulsions, persistent vomiting, lethargy, or unconsciousness). Children aged less than 2 months with pneumonia have, by definition, severe pneumonia due to their higher risk for mortality, and thus require referral.

Identification or prediction of the likely organisms that cause pneumonia is the most important step in determining appropriate antimicrobial therapy. Despite the importance of understanding the aetiology of pneumonia, few recent studies have been done in resource-poor settings,^{19,20} or in areas with high HIV prevalence.^{21,22} The most useful studies that have been done generally use one of two approaches: vaccine probe methods or comprehensive diagnostic testing protocols.

Vaccine probe studies may provide the best possible estimates of pathogen-specific pneumonia burden because they are not limited by insensitive diagnostic testing practices.²³ However, these studies are extremely costly and generally estimate only the role of vaccine-type strains of the pathogen and often focus on severe or hospitalised pneumonia cases. By contrast, studies that incorporate a wide range of diagnostic tests offer the possibility of detecting many pathogens. The diagnostic tests used, however, are often insensitive and sometimes not specific, which limits data quality.²⁴

Directly obtaining specimens from the site of infection by lung aspiration before antimicrobial administration, potentially a gold-standard approach in children, produces positive results in 62% of appropriately selected cases, according to a review of 13 studies.²⁵ Although this approach produces a relatively high yield, it is limited to peripheral lobar pneumonias that may selectively decrease the yield of several pathogens and therefore may not be representative of all severe pneumonia.

The results of aetiological studies require cautious interpretation because estimates of the proportion of pneumonia caused by the different pathogens do vary. The sensitivity of culture-based techniques for identifying bacteria is compromised by previous antimicrobial administration, which is often not assessed. If antimicrobial exposure before culture is common, the measured results in culture-based studies may significantly underestimate those organisms that are sensitive to

commonly prescribed antimicrobial agents, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and overestimate organisms such as *Staphylococcus aureus*.

Although the limitations listed above are numerous, successful treatment ultimately depends on targeting the causative agents. Therefore, despite these limitations,

	Estimated percentage*	Comments
Bacterial (20–50%)		
<i>Streptococcus pneumoniae</i>	17–37%	Estimates based on proportion of radiographically confirmed pneumonia prevented by vaccination with 7-valent and 9-valent vaccine (vaccine probe studies), ^{21,26,27} and supported by lung aspiration studies ²⁵
<i>Haemophilus influenzae</i>	0–31%	Increasing use of highly efficacious vaccine against disease by <i>H influenzae</i> type b may decrease its role as a pathogen Non-type b may play a greater role in non-severe pneumonia than type b ²⁸ Found to be a significant cause of pneumonia in all vaccine probe studies, ^{29–31} except one, ³² and in lung aspiration studies ²⁵
<i>Staphylococcus aureus</i>	1–33%	Presents clinically as a severe, necrotising pneumonia with rapid progression ²⁵
Non-typhoidal salmonellae	0–28%	Bacteraemia may present with features consistent with a clinical diagnosis of pneumonia ^{33–35} Estimates are based on studies from tropical Africa ^{33,36} Associated with non-severe pneumonia in some malaria-endemic regions of Africa ³⁴
<i>Mycoplasma pneumoniae</i>	5%	Limited diagnostic capacities in low-income countries ^{37–40} Proportion of pneumonia associated with infection increases with age, the greatest burden is in children aged >3 years ⁴¹ Assumption that infections do not cause significant morbidity or mortality lacks evidence to be either validated or invalidated ^{42,43}
<i>Chlamydia pneumoniae</i>	3–10%	Limited diagnostic capacities in low-income countries ^{37–39} Proportion of pneumonia associated with infection increases with age, the greatest burden is in children aged >3 years ⁴¹ Poor quality serological data for very young children ⁴⁴
<i>Moraxella catarrhalis</i>	0–9%	Often not the focus of pneumonia microbiological studies ⁴⁵
<i>Klebsiella pneumoniae</i>	0–4%	One study noted a higher proportion of 14% in children with previous antimicrobial use ⁴⁵ Rare exception in malnourished children ⁴⁶
Viral (9–64%)		
Respiratory syncytial virus	1–39%	Particularly important in young infants ⁴⁷
Influenza viruses	0–22%	Important cause throughout age range ⁴⁷ Increasingly documented in the tropics ⁴⁸
Adenoviruses	0–54%	Limited diagnostic testing and use of poor or insensitive tests ⁴⁷
Parainfluenza viruses	0–46%	Occurrence in alternating years means that single-year studies have limited value ⁴⁹
Human metapneumovirus	2–8%	Recent but well-documented cause of pneumonia ^{50–53}
Others (including bocavirus, coronaviruses, and rhinoviruses)	4–30%	Recent PCR-based studies more consistently identify new viruses, but their significance remains to be defined ^{54–56}
*These estimates of aetiological burden have wide ranges. Variation may be real, due to increased proportions of aetiologies due to high HIV prevalence, as well as seasonal (eg, influenza) and geographical (eg, <i>Salmonella</i>) variability. However, the primary source of variability may be due to measurement, either enrolment criteria (hospitalised versus outpatient enrolment), inadequate diagnostic testing of blood cultures with low yield (eg, blood culture), or misclassification (eg, urine antigen testing). Previous antimicrobial administration also may result in underestimation of some agents, and poor laboratory quality can also play an important part. ⁵⁷ Zero percentages (except in the case of <i>Klebsiella</i>) are often due to lack of diagnostic testing and the use of poor or insensitive tests, which are the important reasons for failure to consistently identify these pathogens, although in some cases true seasonal or geographical variations may contribute.		
Table 2: Common pathogens that cause pneumonia in otherwise healthy children aged 2–59 months		

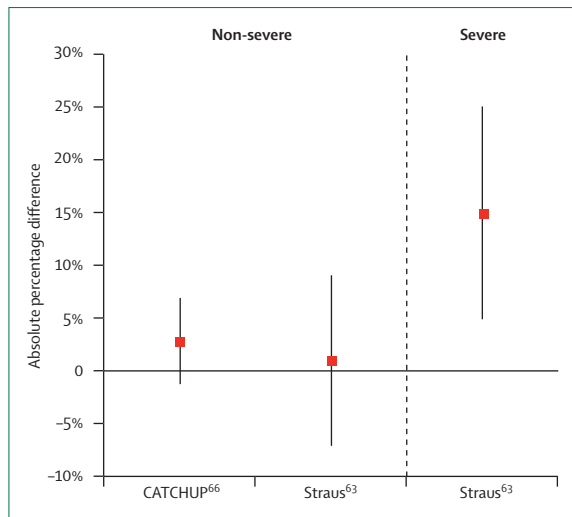


Figure 1: Absolute percentage difference in treatment failure among children with pneumonia treated with co-trimoxazole versus amoxicillin
Analysis of two studies done in Pakistan and their pooled results given with 95% CIs. Straus et al⁶³ showed a significant difference in the proportion of children with severe pneumonia who were treatment failures from 33% failing co-trimoxazole to 18% failing amoxicillin. The CATCHUP group⁶⁶ showed 19% of children failing co-trimoxazole and 16% failing amoxicillin.

estimates of the common pathogens that cause pneumonia in children are required to determine appropriate empirical antimicrobial therapy. Whereas these recommendations are for non-severe pneumonia, it is important to remember that aetiological studies usually enrol hospital inpatients with severe pneumonia. The common bacterial and viral causes of pneumonia pathogens are shown in table 2. Estimates include rather broad ranges of the plausible aetiological fractions. Most studies lack comprehensive investigation of viral causes of pneumonia, but in the studies that do provide such estimates, approximately 25% (range 9–64%) of pneumonia acquired in the community has a positive viral diagnostic test.^{50–53} Identification of a virus does not necessarily imply that the pneumonia is exclusively caused by that virus, because viral and bacterial agents may coexist, making the role of each pathogen uncertain.^{58–61}

These recommendations for non-severe pneumonia are limited by the lack of data on the causes of pneumonia among children treated outside hospital, as described above. However, an important goal of treatment for non-severe pneumonia is to prevent the progression to severe pneumonia. Therefore, directing antimicrobial therapy for non-severe pneumonia towards the pathogens known to cause severe pneumonia is believed to be appropriate.

Pathogens such as *S pneumoniae* and *H influenzae* are prominent treatable causes of severe pneumonia, and first-line antimicrobial therapy has historically been directed primarily at these pathogens. An approach that targets these two aetiological agents has been repeatedly shown to be effective at reducing pneumonia morbidity

and overall mortality through studies and clinical experience during the past 15 years.³ Altering empirical first-line treatment to better cover atypical agents, *S aureus*, non-typhoidal salmonellae, or others, might be considered on theoretical grounds based on the above-referenced studies, but such an approach lacks evidence that it would reduce morbidity or mortality.

Many studies have compared the efficacy of different antimicrobial agents for treating pneumonia in children (webtable). However, despite the large number of studies, most are limited by small sample sizes, and lack the power to conclusively show non-inferiority. These studies are also hampered by the inability to accurately and consistently define treatment failure, largely due to the limited resources available in the field.

Interpretation is also limited by the so-called “Pollyanna phenomenon”. In settings where an antimicrobial agent is compared with a standard agent, the potentially dangerous subset of bacterial cases that are the intended target of study are diluted by the inclusion of milder, self-limited, viral disease, which results in poor antimicrobial agents seeming to be more efficacious, and superior antimicrobial agents seeming less efficacious against the standard agent, as noted by Marchant and colleagues⁶² in the setting of otitis media.

The lack of bacterial endpoints complicate our understanding of the clinical relevance of antimicrobial resistance for the management of pneumonia in the community. Our perceptions of the clinical relevance of amoxicillin, macrolide, and co-trimoxazole resistance for oral outpatient management of pneumonia are all based on the failure of these oral agents to eradicate resistant *S pneumoniae* from the middle ear.⁶²

Although Straus and colleagues⁶³ suggest that co-trimoxazole has a higher failure rate in severe pneumonia treatment than amoxicillin, the role of resistance was unclear, even though resistance has been the most frequently proposed explanation. A sub-analysis did not show a significant increase in failure among co-trimoxazole-resistant *S pneumoniae* or *H influenzae* treated with co-trimoxazole.⁶³ Few pneumonia studies have described the clinical impact of co-trimoxazole resistance on the treatment of pneumonia.⁶⁴

In-vitro resistance to co-trimoxazole correlates with poor clinical outcome in the treatment of these pathogens in acute otitis media. Trials of treatment for acute otitis media have measured bacteriological failures by use of tympanocentesis, comparing middle-ear fluid cultures before and after therapy to show bacterial eradication with treatment. In one tympanocentesis study,⁶⁵ co-trimoxazole resistance resulted in higher rates of bacteriological failures for *H influenzae* and *S pneumoniae*. A caveat is that middle-ear fluid concentrations of many drugs are substantially lower than comparable lung concentrations, and therefore antimicrobial agents used in therapy for acute otitis media may perform more poorly against strains with decreased susceptibility than

antimicrobials used in pneumonia therapy. With this caveat, the available data suggest that in vitro co-trimoxazole resistance is meaningful in some clinical circumstances. This conclusion, if relevant for pneumonia, has important implications for countries where co-trimoxazole resistance is common.

First-line antimicrobial agents should be effective, reliable, widely available, and affordable in resource-poor settings. The 2005 technical update of the WHO IMCI guidelines recommended oral amoxicillin or co-trimoxazole as first-line treatment for non-severe pneumonia because of their low cost and wide spectrum of coverage.⁹

Historically, co-trimoxazole and amoxicillin have been evaluated for the treatment of non-severe pneumonia. Two studies, both done in Pakistan, have compared amoxicillin to co-trimoxazole in children aged under 5 years.^{63,66} The absolute difference in treatment failure between children with treatment failure after taking co-trimoxazole relative to amoxicillin is illustrated in figure 1. The study by Straus and colleagues⁶³ included children with both severe and non-severe pneumonia, whereas the study by the CATCHUP (Co-trimoxazole Amoxicillin Trial in Children Under 5 years for Pneumonia) study group⁶⁶ included only children with non-severe pneumonia.

The duration and dosage of amoxicillin therapy has been assessed and summarised in a WHO 2003 consultative meeting report.⁶⁷ Two clinical trials in India and Pakistan examined 3-day (short) versus 5-day (standard) amoxicillin treatment courses for pneumonia and showed equal effectiveness of the two durations.^{68,69} Shortened courses have not been as well studied in areas of high HIV prevalence, where a substantially greater burden of severe bacterial pneumonia among HIV-infected persons exists. Prudence indicates that shortening treatment to a 3-day course should be studied before being implemented in such settings. Variations of amoxicillin dose have not been well studied for the treatment of childhood pneumonia. One study of 836 children compared 3 days of amoxicillin in 45 mg/kg versus 90 mg/kg doses and did not show a significant difference in treatment failure 5 days after initiation of therapy.⁷⁰

Recommendation 2

Treatment failure is defined as the development of lower chest-wall indrawing, central cyanosis, stridor while calm, or IMCI-defined danger signs at any time during a child's illness or a persistently raised respiratory rate at 72 h (48 h in an area of high HIV prevalence).

Rationale and evidence summary

Treatment failure was previously vaguely defined as "the same" (ie, a respiratory rate persistently above the age-appropriate IMCI cut-off) or deterioration after 2 or 3 days of therapy.⁸ Deterioration is development of chest indrawing, central cyanosis, stridor when calm or IMCI-

defined danger signs. If the child does not deteriorate, these signs and symptoms are traditionally assessed at a scheduled follow-up visit 48 h after the initiation of therapy. However, on the basis of results of a study in Pakistan, 72 h may be acceptable in countries with low HIV prevalence.⁷⁰ These results should be replicated in other low-income countries, particularly those with high HIV prevalence. We believe that children who have a persistently raised respiratory rate and no indication for immediate referral should undergo a brief but systematic assessment to determine whether second-line therapy would be beneficial.

Recommendation 3

A brief but systematic assessment should be used for children who have failed therapy for non-severe

	Frequency*	Possible solution†
Wrong diagnosis		
Reactive airways/asthma	Common	Physician referral
Malaria	Geographically focused	Hospital for blood smear
Foreign body	Rare	Hospital assessment
Anaemia	Rare	Hospital assessment
Cardiac disease	Rare	Hospital assessment
Others	Rare	Hospital assessment
Host failure		
HIV/AIDS	Geographically focused	Hospital for HIV test
Malnutrition	Geographically focused	Hospital for intensive treatment
Pulmonary maldevelopment	Rare	Hospital assessment
Others	Rare	Hospital assessment
Complication		
Empyema	Uncommon	Hospital for drainage
Abscess	Rare	Hospital for radiography
Others	Rare	Hospital assessment
Non-susceptible pathogen		
Viral infection (respiratory syncytial virus, influenza, others)	Common	Observation or hospital
Tuberculosis	Geographically focused	Four drugs and hospital assessment
<i>Mycoplasma</i> , <i>Chlamydia</i>	Uncommon	Appropriate antibiotics (eg, macrolide, doxycycline, or fluoroquinolone)
Non-susceptible <i>S pneumoniae</i>	Uncommon	Appropriate antibiotics (eg, high-dose amoxicillin, ceftriaxone)
Beta-lactamase-producing <i>Haemophilus influenzae</i>	Uncommon	Appropriate antibiotics (eg, amoxicillin-clavulanic acid, ceftriaxone)
Non-typhoidal salmonellae	Geographically focused	Appropriate antibiotics in hospital
<i>Staphylococcus aureus</i>	Rare	Appropriate antibiotics in hospital
<i>Strongyloides</i> , other parasites	Rare	Ivermectin etc, in or out of hospital
Endemic fungi	Rare	Hospital assessment and anti-fungal therapy
Others	Rare	Hospital assessment

*Common agents may be responsible for at least a third of outpatient pneumonia treatment failures; uncommon agents may be responsible for a minor fraction; rare agents are probably responsible for only occasional treatment failures; globally uncommon agents may be common in certain geographic areas, although they are uncommon as causes for pneumonia treatment failure globally. Based on data from Heffelfinger et al¹² and discussions of the panel based on their clinical experience. †Note that referral to the next level facility instead of a hospital may occasionally be appropriate, depending on the resources at the facility and the suspected condition.

Table 3: Potential reasons for treatment failure for WHO-defined pneumonia at 72 h and possible solutions

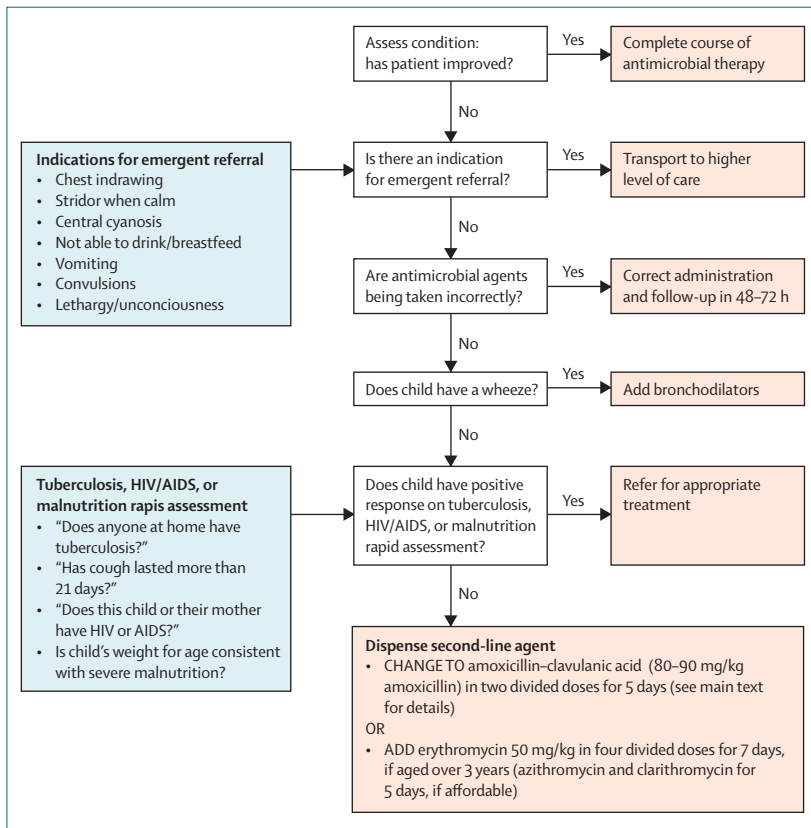


Figure 2: Example algorithm of how to systematically assess children aged >2 months and <5 years, initially diagnosed and treated with non-severe pneumonia and who returned for follow-up, in low HIV prevalence settings, based on the experience and recommendations of the panel

This assessment is intended to supplement and not to replace the clinical judgment of the first-level health worker. If Integrated Management of Childhood Illness guidelines have been followed, the child should have been assessed for malnutrition and HIV in settings with high prevalence. This figure is offered only as an example of such an algorithm that can be developed.

pneumonia as determined on follow-up by the health worker. Referral for in-patient treatment should occur, if appropriate. If immediate referral is not warranted, the assessment should determine possible causes of the failure of therapy.

Rationale and evidence summary

The literature does not describe when treatment failure should prompt a change of therapy. Treatment failure may occur for many reasons, only one of which is use of a drug to which the infecting agent is not susceptible. Many of these reasons are described in table 3, and most require assessment in hospital and specific therapies. If a child develops signs indicative of the need for immediate referral, before or after treatment is initiated, they should be referred immediately.^{7,9} We believe that children who fail to improve but do not require immediate referral should be systematically assessed before changing antimicrobial agents. This assessment can begin with the first-level health worker determining whether failure is due to inability or unwillingness to take the medicine appropriately. If the health worker believes that the child

has taken the antimicrobial agent correctly, other conditions resulting in treatment failure should be considered. If an initial assessment by the health worker indicates that these considerations are unlikely and referral is not warranted, a second-line agent should expand coverage.

This assessment by the first-level health worker may be guided by an algorithm. The efficacy of algorithms has been shown in the assessments of initial case management by acute respiratory illness guidelines.^{3,4,7} However, we are not aware of any studies that show the efficacy of an algorithm that systematically assesses a child who does not improve after therapy. Figure 2 shows an example of an algorithm developed by us, which aims to be simple for health workers to use accurately and consistently. It addresses the major causes of treatment failure, but is not a validated tool, and is offered here purely as an example.

Recommendation 4

In the setting of first-level health providers, children initially treated with amoxicillin who have a persistently raised respiratory rate and no indication for referral should receive high-dose amoxicillin with clavulanic acid (80–90 mg/kg per day amoxicillin) for second-line therapy to provide coverage for the major pathogens likely to cause severe disease. A 5-day treatment course should be prescribed for the second-line antimicrobial agents. For children over 3 years of age, an affordable macrolide or azalide (eg, 50 mg/kg erythromycin in four divided doses for 7 days) may be added to the existing regimen for a 5-day or 7-day treatment course. For children failing first-line treatment with co-trimoxazole, the recommendation is to switch to a 5-day course of amoxicillin (50 mg/kg).

Rationale and evidence summary

We define second-line antimicrobial agents as those that are used in the setting of treatment failure when no indication for immediate referral is present (ie, IMCI danger signs, lower chest indrawing, stridor, or central cyanosis) and other reasons for treatment failure have been excluded. No studies were identified that assessed second-line antimicrobial agents; therefore, second-line antimicrobial agents should logically be selected to treat organisms that fail first-line therapy. Whereas a substantial proportion of failures of first-line agents may be due to mild and self-limited viral infections, the second-line agent should ensure coverage of resistant organisms and cover a broader range of organisms that would not be treated with typical first-line agents; in some settings, coverage may be extended to include *S aureus* or non-typhoidal salmonellae.

A second-line antimicrobial agent should broaden or enhance coverage in the setting of treatment failure. Our recommendations on the best second-line antimicrobial

	Activity according to paediatric pneumonia trials*	Efficacy in vitro†72-74					Toxic effects73	Ease of administration (daily doses)73	Range of antimicrobial agent costs‡ for treatment course (US\$)75,76	Dosage
		<i>S pneumoniae</i>	<i>H influenzae</i>	<i>S aureus</i>	Non-typhoidal salmonellae	Atypical pneumonia				
Aminopenicillins										
Amoxicillin	yyy	>90%	70-90%	<40%	40-70%	<40%	..	2 or 3	0.11-0.23	One 250 mg tablet twice daily
High-dose amoxicillin	<40%	2 or 3	0.21-0.45	Two 250 mg tablets twice daily
Ampicillin	yy	70-90%	40-70%	<40%	<40%	<40%	Diarrhoea	4	0.21-0.65	One 250 mg tablet four times daily
Amoxicillin-clavulanic acid	yy	>90%	>90%	40-70%	<40%	<40%	Diarrhoea	2 or 3	0.82-3.10	Half 500 mg tablet twice daily
High-dose amoxicillin-clavulanic acid	..	>90%	>90%	40-70%	..	<40%	Diarrhoea	2 or 3	1.63-6.21	One 500 mg tablet twice daily
Penicillins										
Oral penicillin	y	40-70%	<40%	<40%	<40%	<40%	..	3 or 4	0.05-0.58	..
Intramuscular penicillin§	yy	70-90%	<40%	<40%	<40%	<40%	..	4 to 6	0.08-0.47	1 M units
Cephalosporins										
Cephalexin	..	40-70%	<40%	70-90%	<40%	<40%	..	4	0.22-0.22	Half 250 mg dose orally every 6 h
Cefaclor	..	40-70%	70-90%	70-90%	..	<40%	..	3	..	Syrup
Cefuroxime	yy	70-90%	70-90%	70-90%	..	<40%	..	2	1.25-3.44	Half 250 mg dose orally twice daily
Cefprozil	..	70-90%	40-70%	70-90%	..	<40%	..	2	..	Syrup
Cefpodoxime	..	70-90%	70-90%	70-90%	..	<40%	..	1	..	Syrup
Cefixime	..	40-70%	>90%	40-70%	..	<40%	..	1	0.20-0.20	Half 200 mg tablet daily
Ceftibuten	..	40-70%	>90%	40-70%	..	<40%	..	2	..	Syrup
Intramuscular ceftriaxone§	y	>90%	>90%	70-90%	70-90%	<40%	..	1	1.34-14.44	500 mg vial
Macrolides										
Erythromycin	yy	40-70%	40-70%	40-70%	<40%	70-90%	..	4	0.10-0.22	Half 250 mg tablet per dose
Clarithromycin	y	40-70%	40-70%	70-90%	<40%	70-90%	..	2	0.90-0.90	Syrup
Azithromycin	yy	40-70%	70-90%	70-90%	40-70%	70-90%	..	1	0.15-0.57	Syrup
Fluoroquinolones										
Ciprofloxacin	..	<40%	70-90%	70-90%	70-90%	40-70%	Possible cartilage growth	2	0.07-0.15	250 mg tablet twice daily
Ofloxacin	..	<40%	70-90%	70-90%	70-90%	70-90%	Possible cartilage growth	2	0.09-0.22	Half 200 mg tablet twice daily
Levofloxacin	..	>90%	>90%	70-90%	70-90%	70-90%	Possible cartilage growth	1	..	Half 250 mg tablet orally every 24 h
Moxifloxacin	..	>90%	>90%	70-90%	70-90%	70-90%	Serious cardiac	No paediatric dosing available
Tetracyclines										
Doxycycline	..	70-90%	70-90%	40-70%	40-70%	70-90%	Tooth discolouration (children <7 years)	2	..	5 mg/kg daily
Other agents										
Co-trimoxazole	yyy	40-70%	40-70%	40-70%	40-70%	<40%	..	3	0.03-0.09	Half 80 mg tablet orally twice daily (based on trimethoprim)
Chloramphenicol	yy	70-90%	>90%	40-70%	70-90%	40-70%	Bone marrow	4	0.11-0.23	Syrup

*yyy= multiple trials with strong trial evidence, yy=some trials with good evidence, y=minimal trials and evidence. †Pharmacokinetic/pharmacodynamic (PK/PD) properties are used to help determine the susceptibility breakpoints of antimicrobial agents and therefore the agent's likely efficacy. PK/PD properties for drug classes are as follows: aminopenicillins, penicillins, and cephalosporins=time above minimum inhibitory concentration (MIC) 40%; macrolides and fluoroquinolones=area under the curve/MIC above 30. ‡Costs for non-oral medications do not include administration, syringe, or needle costs. §Treatment course was 5 days and dose was based on a 10 kg child, except intramuscular penicillin and ceftriaxone, for which cost includes only the drug cost and does not include needles and administration.

Table 4: Antimicrobial agents used for treatment of community-acquired pneumonia

agents are based primarily on efficacy data from clinical trials that assessed antimicrobial activity against the common causes of pneumonia, pharmacokinetic–pharmacodynamic properties, toxicity, tolerability, and ease of administration. Of those antimicrobial agents that were efficacious, cost was thought to be the next most important factor. Only antibacterial agents with activity against the two most important aetiological agents, *S pneumoniae* and *H influenzae*, were considered. These attributes for possible antimicrobial agents for the treatment of pneumonia are shown in table 4 from several classes of agents. The listed beta-lactam antimicrobial agents would be the most effective against resistant *S pneumoniae* and *H influenzae*, but are not active against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and non-typhoidal salmonellae. Preference is given to antimicrobial agents that are thought to be well-tolerated, and with once daily or, if necessary, twice daily dosing to increase compliance.

Although drug cost may be a critically important consideration, it may be acceptable for a second-line antimicrobial agent to be more expensive than first-line agents. Treatment course prices of US\$0.50, \$1, and \$2 were used as cut-offs to assess agent's acceptability (table 4). Appropriate second-line agents must enhance coverage not already provided by the first-line agent. Parenteral antimicrobial agents are often used in hospital settings, but are rarely used in outpatient clinics in low-income countries. The perception by some patients and providers that parenteral agents are always more effective than oral agents can be difficult to correct. Therefore, introduction of a parenteral antimicrobial agent such as ceftriaxone to peripheral settings may be impractical for these and other reasons in most situations.

If a child was initially taking co-trimoxazole at the correct pneumonia treatment dose, the preferred second-line agent would be oral amoxicillin at 50 mg/kg in two divided doses for 5 days. If the first-line agent was amoxicillin, the second antimicrobial agent choice should expand the spectrum or enhance coverage. Use of high-dose amoxicillin–clavulanic acid (80–90 mg/kg daily of divided doses of amoxicillin with a maximum of 6.4 mg/kg clavulanic acid daily) is another possibility to enhance activity against beta-lactamase-producing *H influenzae* and resistant *S pneumoniae*, but would not cover atypical bacteria.

Most oral second-generation and third-generation cephalosporin antimicrobial agents are more expensive, but have improved coverage against beta-lactamase-producing *H influenzae*. Cefuroxime and cefixime are reasonably priced, although they are not as active as high-dose amoxicillin–clavulanic acid against *S pneumoniae*.⁷² In addition, these agents do not provide coverage for *M pneumoniae* or *C pneumoniae*.

Oral chloramphenicol palmitate is a less desirable second-line agent for non-severe pneumonia. This

antimicrobial agent is bacteriostatic against a wide range of potential pathogens and bactericidal against most *S pneumoniae* and *H influenzae*, although there is some resistance to chloramphenicol. Bone-marrow toxicity includes reversible, dose-dependent suppression, as well as aplastic anaemia, the latter occurring in approximately one in 24 500 to 40 000 courses.^{77,78} Although chloramphenicol is active against a wide range of causal agents and is inexpensive, the potential for bone-marrow toxicity limits its use as a first-line agent and as a universal second-line agent. Some panel members expressed reservations about this agent because of safety concerns with its use as an oral agent for mild disease in the outpatient setting. Also important are concerns about driving resistance in settings where parenteral chloramphenicol may be the sole agent to treat meningococcal meningitis. Oral chloramphenicol may be useful in children if intramuscular antimicrobial agents are not available and immediate transportation to a higher level of care, such as a hospital, is not possible.

Although tetracycline is the appropriate drug for the treatment of some paediatric infections, the small risk of associated side-effects outweigh the potential advantages of widespread use of the drug for non-severe pneumonia treatment. Similarly, the respiratory fluoroquinolones are not optimum second-line drugs for outpatient pneumonia because of the theoretical risk of toxic effects in young children, as well as the measurable risk of promoting resistance to this valuable class of antimicrobial agents.

Azithromycin, clarithromycin, and erythromycin are reasonably priced, but the role of these agents is limited to extending the antimicrobial spectrum to atypical organisms, because these agents are relatively inactive against *H influenzae* and there is increasing resistance among *S pneumoniae*.⁷² Therefore, an affordable macrolide or azalide may be considered for a child who is not better but not worsening at time of re-assessment and is over 3 years of age, when these atypical infections are more likely. Erythromycin may be used in three or four divided doses for a 5-day treatment course at a daily dose of 40 mg/kg.³⁷ Advantages of erythromycin over azithromycin or clarithromycin include low-cost and wide availability and disadvantages include gastrointestinal disturbance and frequent dosing. Macrolides or azalides are also indicated for those who have a documented allergy to penicillin or other beta-lactam agents. Co-trimoxazole was not considered as a second-line agent because co-trimoxazole resistance in *S pneumoniae* often co-exists with penicillin resistance,⁷⁹ and, if the first-line agent used was amoxicillin, the addition of co-trimoxazole would probably not be of benefit.

These general recommendations may need to be modified for children living in areas where HIV or malaria are common, or if referral is not possible.

Countries introducing algorithms for empirical use by first-level health workers should identify such areas and consider modification of the recommendations.

Areas with a high prevalence of HIV

Special attention is required in regions where HIV prevalence has consistently exceeded 5% in at least one defined subpopulation, as is the case in much of eastern, central, and southern Africa, and certain regions of Asia and Latin America. In these high prevalence areas, HIV counselling and testing is recommended for all children aged under 10 years seen in paediatric health services.⁸⁰ The burden of HIV-associated pneumonia in such regions is substantial. One study in an area with an HIV-positive prevalence of 5% among children aged under 5 years reported that 45% of hospitalised pneumonia and 85% of pneumonia deaths occurred among HIV-positive children.⁸¹ Prophylactic co-trimoxazole has been shown to improve survival and to reduce pneumonia-related deaths in HIV-infected children and should therefore be administered.⁸²

Children presenting with pneumonia should be assessed for symptomatic HIV infection in areas where HIV is a public-health problem and should be tested if indicated by use of methods such as that described by Horwood and colleagues.⁸³ For children living in areas of high HIV prevalence, or who have clinical suspicion or a diagnosis of HIV infection, and who present with non-severe pneumonia, the recommended treatment is amoxicillin, irrespective of co-trimoxazole prophylaxis status. *Pneumocystis jirovecii* is known to be a cause of severe, progressive pneumonia, especially among children aged 2–6 months,⁸⁴ but its role in non-severe pneumonia in HIV-infected children was not evaluated as part of this review. If such a child fails first-line therapy for non-severe pneumonia, the child should be referred to hospital for management by WHO guidelines,^{85,86} including HIV testing and broad-spectrum parenteral antimicrobial agents. Finally, children in high prevalence areas without clinical suspicion or a diagnosis of HIV infection who fail to improve on first-line therapy should be treated according to the standard recommendations outlined in this review.

Malaria-endemic areas

The clinical overlap between malaria and pneumonia in children is well recognised.⁸⁷ Symptomatic malaria may have clinical features consistent with a diagnosis of pneumonia, whereas children with pneumonia may have co-incidental malaria parasitaemia.^{88,89}

Co-trimoxazole therapy for non-severe pneumonia was recommended in some countries where malaria diagnosis was unavailable at first-level facilities, in part because co-trimoxazole has some activity against both malaria and common bacterial causes of pneumonia in children.^{90,91} However, co-trimoxazole is not a first-line

anti-malaria drug, and amoxicillin, which does not have anti-malarial activity, is now preferred to co-trimoxazole as first-line therapy for non-severe pneumonia. Therefore, if a child has clinical features of non-severe pneumonia but malaria cannot be excluded, the recommended first-line therapies for malaria and pneumonia should both be prescribed. Caution should be exercised in the use of erythromycin as a second-line agent if mefloquine or halofantrine are prescribed for malaria, due to the increased risk of arrhythmia.

A complication of malaria is severe anaemia that, like pneumonia, can cause rapid breathing. In malaria-endemic regions, children presenting with rapid breathing should be assessed for severe anaemia. If laboratory assessment is not available, marked pallor may be assessed by examining the palms of the hands, nail beds, and conjunctivae. Any child with a clinical diagnosis of pneumonia who also has severe anaemia should be referred to hospital for assessment.

Areas where referral is not possible

A child who fails treatment and meets criteria for referral should be transported to and assessed at a centre that can provide more intensive therapy. However, referral is impossible in some areas. In these situations, the child should receive treatment with agents that provide broader coverage and high activity against pathogens that cause severe pneumonia. These antimicrobial agents include injectable antimicrobial agents such as ceftriaxone, penicillin/gentamicin, or chloramphenicol.

Conclusions

The WHO-recommended systematic case-management approach has greatly reduced the mortality of children with pneumonia. These updated recommendations, now identifying amoxicillin as the preferred first-line agent and specifying the approach to changing to an appropriate second-line agent in the event of treatment failure (table 1), aim to improve treatment protocols for first-level health providers for children with non-severe pneumonia. These recommendations were developed by use of the available evidence for the treatment of children with pneumonia in low-income countries. The evidence basis for some of the recommendations was limited, and more research is needed in several areas. These areas include an improved understanding of the aetiology of pneumonia in children, both severe and non-severe, using optimum diagnostic testing, a better understanding of the reasons for treatment failure, and the determination of the best systematic method for the assessment of treatment failure by first-level health workers. In the meantime, adaptation of these general recommendations to fit country-specific treatment algorithms should help to resolve some of the uncertainty surrounding the appropriate management of young children with non-severe pneumonia.

Search strategy and selection criteria

These are described in detail in the Methods section.

Conflicts of interest

We declare that we have no conflicts of interest.

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