Revised WHO classification and treatment of childhood pneumonia at health facilities

• EVIDENCE SUMMARIES •

World Health Organization

Revised WHO classification and treatment of childhood pneumonia at health facilities

EVIDENCE SUMMARIES

World Health Organization

WHO Library Cataloguing-in-Publication Data

Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries.

1.Pneumonia – drug therapy. 2.Child. 3.Health Facilities. 4.Guideline. I.World Health Organization.

ISBN 978 92 4 150781 3 (NLM classification: WA 320)

This document is derived from previously published WHO guidelines on the management of childhood pneumonia and is not a guideline per se. References for the guidelines are: [1] Integrated Management of Childhood Illness (IMCI). WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241548083/en) AND [2] Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012 (http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en).

Designed by minimum graphics
Printed in Switzerland

Contents

Executive Summary

In the early 1980s, the global burden of childhood mortality due to pneumonia led the World Health Organization (WHO) to develop a pneumonia control strategy suitable for countries with limited resources and constrained health systems. Management of pneumonia cases formed the cornerstone of this strategy. Simple signs were identified to classify varying severities of pneumonia in settings with little or no access to diagnostic technology; the classifications determined the appropriate case management actions. Children with fast breathing were classified as having "pneumonia" and were given an oral antibiotic (at that time oral cotrimoxazole) to take at home for five days. Children who had chest indrawing with or without fast breathing were classified as having "severe pneumonia" and were referred to the closest higher-level health facility for treatment with injectable penicillin. Children who had any general danger signs were classified as having "severe pneumonia or very severe disease". These children received a first dose of oral antibiotic and were then urgently referred to a higher-level health facility for further evaluation and treatment with parenteral antibiotics.

These pneumonia classification and management guidelines had been developed based on evidence generated in the 1970s and early 1980s, and were incorporated into the original version of Integrated Management of Childhood Illness (IMCI). In the intervening time, new evidence has emerged which prompted the development of revised guidelines.

Research results provided solid scientific evidence to guide and support the revision of the pneumonia guidelines. During two related consultations, a panel of experts assessed the new evidence according to the GRADE methodology ("Grading of Recommendations, Assessment, Development and Evaluation"). The consultations aimed to summarize the new WHO recommendations for policy and practice, to review GRADE evidence profiles, and to discuss the factors that determined the strength of the recommendations. The first consultation resulted in updated recommendations for preventing and managing pneumonia in HIV-infected and -exposed infants and children; these were published in 2010.[1] The second resulted in updated recommendations for managing pneumonia in non-HIV affected infants and children, published in 2012.[2]

The revisions include changing the recommendation for the first-line antibiotic and re-defining the classification of pneumonia severity. The data show that oral amoxicillin is preferable to oral cotrimoxazole for the treatment of "fast breathing pneumonia" and is equivalent to injectable penicillin/ampicillin in cases of "chest indrawing pneumonia". Hence, in a programmatic context, the distinction between previously defined "pneumonia" (fast breathing) and "severe pneumonia"

---

[1] Integrated Management of Childhood Illness (IMCI). WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241548083/en).

[2] Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012 (http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en).

(chest indrawing) loses its significance. The new classification is therefore simplified to include only two categories of pneumonia; "pneumonia" with fast breathing and/or chest indrawing, which requires home therapy with oral amoxicillin, and "severe pneumonia", pneumonia with any general danger sign, which requires referral and injectable therapy.

Dosages for pneumonia treatment at health facilities have been revised to reflect three age bands: 2 months up to 12 months (4–<10 kg); 12 months up to 3 years (10–<14 kg); 3 years up to 5 years (14–19 kg). Dosages and age bands for treatment of fast breathing pneumonia by community health workers (CHWs) have not changed.

National child health programmes will benefit from the revised recommendations and are encouraged to incorporate them into their existing guidelines for care at health facilities. The recommendations concerning the use of amoxicillin should also be included in guidelines for integrated community case management (iCCM). Programmes should recognize the importance of these revisions, which will result in a substantially lower need for referral, and in better treatment outcomes. Local adaptations may be required, particularly the arrangements to include amoxicillin as the first-line therapy; facility-level health workers will also need to be re-trained in the new system of classification and treatment.

The purpose of this document is to provide a summary of WHO-approved recommendations,[1,2] and the evidence supporting them, and to assist national child health programmes in revising their guidelines to conform to the new recommendations.

The revised recommendations are:

Recommendation 1

Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

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

Recommendation 2

Children age 2–59 months with chest indrawing pneumonia should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily for five days.

Recommendation 3

Children aged 2–59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

— Ampicillin: 50 mg/kg, or benzyl penicillin: 50 000 units per kg IM/IV every 6 hours for at least five days
— Gentamicin: 7.5 mg/kg IM/IV once a day for at least five days

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

Recommendation 4

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV-infected and -exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

Recommendation 5

Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.

Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and -exposed children over 1 year of age with chest indrawing or severe pneumonia.

Introduction

Pneumonia continues to be the biggest killer worldwide of children under five years of age. Although the implementation of safe, effective and affordable interventions has reduced pneumonia mortality from 4 million in 1981 (*1*) to just over one million in 2013 (*2,3*), pneumonia still accounts for nearly one-fifth of childhood deaths worldwide.

Case management is a cornerstone of pneumonia control strategies (*4*). It consists of classifying the severity of illness using simple clinical signs such as fast breathing, chest indrawing and general danger signs,[3] and then applying the appropriate treatment. Treatment includes home care advice, antibiotics for home therapy, or referral to a higher-level health facility.

The recommendations for the management of pneumonia in health facilities have recently been modified (*5–7*). The revisions are a result of new evidence generated from research carried out in the last decade including in those low- and middle-income countries with the largest burden of pneumonia mortality. Integrated Management of Childhood Illness (IMCI) at health facility level has been updated accordingly. Integrated Community Case Management (iCCM) by lay community health workers (CHWs) has not been changed.

The original guidelines classified the respiratory symptoms of children 2 to 59 months of age into four categories (*8,9*). Children with cough and cold who did not have signs of pneumonia were classified as "no pneumonia", and their caregivers were advised on appropriate home care. Children with fast breathing were classified as "pneumonia" and were given an oral antibiotic (at that time oral cotrimoxazole) to take at home for five days. Children who had chest indrawing with or without fast breathing were classified as "severe pneumonia" and were referred to the closest health facility for treatment with injectable penicillin. Children who had any general danger signs were classified as "severe pneumonia or very severe disease". These children received a first dose of oral antibiotic and were then urgently referred to a health facility for further evaluation and treatment with parenteral antibiotics.

Data shows that the majority of childhood pneumonia deaths are due to severe pneumonia/severe disease (*10*); management of these cases requires early identification, prompt referral and the availability of good-quality higher-level care. However, in many low-resource settings, referral is difficult and often does not take place (*11–15*). On the basis of this information, WHO undertook a review of the evidence, with the aim of developing a simplified approach that could increase the number of children receiving correct treatment for pneumonia.

[3] Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

In two consultations, experts updated recommendations for 1) preventing and managing pneumonia in HIV-infected and -exposed infants and children (*9*) and 2) for managing pneumonia in non-HIV-affected infants and children (*5*). The recommendations were published in 2010 and 2012 respectively.

This document presents a summary of recommendations and of the research that forms the technical basis of the revised guidelines; it also suggests implications for implementation in countries. Its purpose is to assist national child health programmes in revising their guidelines to conform to the new recommendations. These revisions, implemented in countries with a high pneumonia burden, will result in a higher proportion of children receiving care at the outpatient or community levels, and a reduced number of pneumonia-related deaths.

1. Scientific basis of WHO recommendations for treatment of pneumonia

1.1 Recommendation 1

Children with fast breathing pneumonia[4] with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40 mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

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

1.1.1 The effectiveness of various antibiotics in community-acquired childhood pneumonia: a systematic review

Kabra et al (*16*) systematically reviewed literature comparing various antibiotics, in order to identify effective drug therapy for community-acquired pneumonia in children. All randomized controlled trials (RCTs) that compared at least two antibiotics for community-acquired pneumonia in children in hospital or ambulatory settings were selected.

The review showed that for treatment of pneumonia, cotrimoxazole was inferior in efficacy to both amoxicillin (clinical failure rates odds ratio (OR) 1.33; 95% CI 1.05 to 1.67) and procaine penicillin (clinical cure rates OR 2.64; 95% CI 1.57 to 4.45). Injectable penicillin in conjunction with injectable gentamicin was more effective than injectable chloramphenicol alone (re-hospitalization rates OR 1.61; 95% CI 1.02 to 2.55). Co-amoxyclavulanic acid was more effective than amoxicillin alone (cure rates OR 10.44; 95% CI 2.85 to 38.21). There were no differences between injectable penicillin and oral amoxicillin (failure rates OR 1.03; 95% CI 0.81 to 1.31); between azithromycin and erythromycin; between cefodoxime and amoxicillin; or between azithromycin and co-amoxyclavulanic acid.

The authors concluded that for treatment of ambulatory patients with community-acquired pneumonia, amoxicillin was more effective than cotrimoxazole. Moreover, in hospitalized patients, penicillin was found to be more effective than cotrimoxazole; and the combination of penicillin and gentamicin was superior to chloramphenicol. Injectable penicillin and oral amoxicillin had similar clinical failure rates.

Another systematic review (*17*) was conducted by nine clinicians and researchers with extensive experience in the field of childhood pneumonia. The review aimed to identify appropriate first- and second-line antimicrobial agents for the empirical treatment of fast breathing pneumonia in children by first-level health care providers, in addition to defining treatment failure and criteria for referral. For the first-line treatment oral amoxicillin was found to be most effective in the treatment of fast breathing pneumonia. The review suggested that treatment failure for fast breathing pneumonia should be redefined as "clinical deterioration" only, instead of changing therapy when the child's condition is the "same" on follow-up after two or three days of treatment. It was sug-

[4] Previously classified as pneumonia (IMCI Chart Booklet 2008).

gested that once classified as "treatment failure" each child should be assessed independently for referral as not all cases will mandate immediate referral. The review recommended the development of an algorithm to determine the best course of action when treatment failure occurs.

1.1.2 A three-day course of antibiotics is as effective as a five-day course in treating children with fast breathing pneumonia

A systematic review by Haider et al (*18*) reviewed three randomized controlled trials evaluating the efficacy of short-course versus long-course treatment of fast breathing pneumonia in children age 2–59 months. Two of the studies (*19,20*) examined treatment with oral amoxicillin, while the third (*21*) examined treatment with oral cotrimoxazole. All studies compared the duration of two courses of treatment, one lasting three days and the other five days, while holding the antibiotic constant. The three studies were double blind, randomized, placebo controlled trials with a total of 6210 participants. Data was available for 5763 cases. The primary outcome was clinical cure at the end of the treatment. The studies found no significant differences in clinical cure rates between the two groups (RR 0.99; 95% CI 0.97 to 1.01). Nor were there significant differences in either the treatment failure or relapse rates between groups. The review recommended a shorter course of antibiotic therapy, keeping in mind the benefits to the individual as well as to the health system, especially in settings with limited resources.

1.2 Recommendation 2

Children age 2–59 months with chest indrawing pneumonia[4] should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days.

Previous guidelines by WHO for the management of chest indrawing pneumonia in children (*22*) recommended parenteral antibiotics for at least three days. A study by Straus et al (*23*) published in 1998 found that treatment failure rate with oral amoxicillin was significantly lower than with oral cotrimoxazole (18% and 33% respectively) in children with chest indrawing pneumonia (p=0.009). It was concluded that although oral cotrimoxazole was effective in fast breathing pneumonia, it was less effective in treating chest indrawing pneumonia. Multi-country studies, using a randomized controlled trial design and an adequate sample size, were then undertaken to assess the effectiveness of oral amoxicillin in chest indrawing pneumonia. A summary of the evidence that has led to the revised recommendation is presented below.

1.2.1 Oral amoxicillin is as effective as injectable penicillin in the treatment of chest indrawing pneumonia in children in low-resource settings

A multicentre, randomized, open-label trial by Addo-Yobo et al (*24*) (APPIS Study) compared the efficacy of oral amoxicillin and injectable penicillin. The study was conducted at nine tertiary health facilities in eight developing countries and enrolled 1702 children age from 3 to 59 months with chest indrawing. Children were randomly assigned to receive either a five-day course of oral amoxicillin (n=857) or parenteral penicillin (n=845). Evaluations were carried out at 48 hours, five days and 14 days. The primary outcome of the study was clinical treatment failure at 48 hours. The study found treatment failure rates of 19% in each treatment group (n=161 penicillin; n=167 amoxicillin; risk difference -0.4%; 95% CI -4.2 to 3.3). The study described a number of advantages of oral treatment over parenteral treatment, including reduced risk of injection-related morbidity, and fewer needs for medical supplies such as needles, and suggested that oral treatment be considered as an equally effective alternative to parenteral treatment. Although this study proved the

effectiveness of oral amoxicillin, it did not fully address the issue of safety, as all enrolled children were hospitalized for 48 hours and kept under close supervision. More research was needed to test the hypothesis under a wider range of circumstances.

1.2.2 Oral amoxicillin is equally effective for pneumonia of various severities in a high-resource setting

A study in England in 2007 (PIVOT Trial) (*25*) compared oral amoxicillin and intravenous (IV) benzyl penicillin in the management of severe pneumonia. The randomized, controlled, non-blinded equivalence trial was conducted in eight paediatric centres (district general and tertiary hospitals) and enrolled children with all but the most severe cases of pneumonia. Additional exclusion criteria were: wheeze, oxygen saturation less than 85%, shock, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy, and age less than 6 months. Children were randomly assigned to a 7-day treatment of either oral amoxicillin or IV benzyl penicillin. The primary outcome was the time required for temperature to be below 38 °C for 24 continuous hours. The study found the two treatments to be equivalent, each having a median time of 1.3 days to achieve the primary outcome. While equivalence between oral and parenteral antibiotics itself was not a new development, this study was unique in the scope of varying severities of pneumonia treated. It was also the first study of its kind for children in a high-resource setting with radiologically confirmed pneumonia. The study recommended that children be treated with oral amoxicillin instead of IV benzyl penicillin, as oral treatment was both painless and non-invasive.

1.2.3 It is safe to treat chest indrawing pneumonia at home with oral amoxicillin

Hazir et al (*26*) (NO-SHOTS Study) carried out a randomized, open-label equivalency trial at seven sites in Pakistan, comparing hospitalization with parenteral ampicillin to home treatment with oral amoxicillin. Children with chest indrawing pneumonia were randomized to treatment in hospital (n=1012) with two days of injectable ampicillin followed by three days of oral amoxicillin (80–90 mg/kg/day), or were sent home with a five-day twice daily course of oral amoxicillin (n=1025). The primary outcome was clinical treatment failure. Follow-up assessments were conducted at 1, 3, 6, and 14 days after enrolment. At day 6 there were 87 (8.6%) treatment failures in the hospitalized group and 77 (7.5%) treatment failures in the home-treatment group (risk difference 1.1%, 95% CI – 1.3–3.5). In addition to finding equivalence between the two treatments, the authors suggested that in cases of chest indrawing pneumonia without underlying complications, home treatment with a short course of high-dose oral amoxicillin was preferable to parenteral treatment because of the associated reduction in referral, admission, and treatment costs as well as the reduced invasiveness of oral treatment.

1.2.4 Home therapy with oral amoxicillin is effective in a range of settings

To test whether the interpretation that chest indrawing pneumonia can be treated safely and effectively at home was generalizable across communities and geographic regions, a multicentre observational study was conducted in Bangladesh, Egypt, Ghana and Viet Nam (*27*). Outcome was ascertained on a total of 823 children age 3 to 59 months old, with chest indrawing pneumonia, who were given oral amoxicillin (80–90 mg/kg/day) twice daily for five days. Follow-up at home was carried out on days 1, 2, 3 and 6 to assess treatment failure, and at the health facility on day 14 to assess relapse. Overall treatment failure was 9.2%, varying from 6.4% in Ghana to 13.2% in Vietnam. The common reasons for failure were persistence of chest indrawing at day 6 (3.8%),

abnormally sleepy or difficult to wake (1.3%) and central cyanosis (1.3%). The authors concluded that among children with chest indrawing pneumonia treated at home with oral amoxicillin, clinical treatment failure and adverse event rates did not differ across geographic areas. This argues in favour of the option of home-based therapy of chest indrawing pneumonia in a wide variety of settings.

In these studies, the children with chest indrawing pneumonia were identified and treated on an outpatient basis by qualified doctors, and were followed up either in an outpatient facility or at home. This made it difficult to generalize to situations where pneumonia is treated within the community, by CHWs who may have little or no formal education. Data were needed to assess the effectiveness of community case management of chest indrawing pneumonia.

1.2.5 Efficacy of higher dose (80–90 mg/kg/day) vs. lower dose (45 mg/kg/day) of amoxicillin

1.2.5.1 Amoxicillin is more effective when given in higher doses

The major parameter determining the *in vivo* efficacy of many antibiotics is the duration of time that serum level exceeds the mean inhibiting concentration (MIC), and studies have demonstrated the effect of increasing concentrations of antimicrobials on their bactericidal activity. A clinical review and other reports showed that for *Streptococcus pneumoniae* and *Haemophilus influenzae* in patients with otitis media (*28–34*), serum levels must be above the MIC for more than 40% of the time the child is in treatment in order to achieve a bacteriological cure rate of 85% to 100%. The review also showed that amoxicillin and cefuroxime provided adequate duration above the MIC for penicillin-intermediate resistant strains. In contrast, for penicillin-resistant strains, only amoxicillin provided levels above the MIC for more than 40% of the dosing interval. The review also showed that a four-fold higher dose given every eight hours results in a much higher peak/MIC ratio than a dose administered every two hours.

The evidence-based practice guidelines of the American Academy of Pediatrics and the American Academy of Family Physicians for the treatment of community-acquired pneumonia recommend an amoxicillin dose of 75–100 mg/kg/day (*35*). This recommendation was based on extrapolation from microbiology studies on acute otitis media (AOM). Amoxicillin can be given in a twice-daily regimen.

The main causal organisms of AOM and childhood pneumonia are *S. pneumoniae* and *H. influenzae*. Keeping in mind the penicillin-intermediate and penicillin resistant strains of these organisms, the revised guidelines recommend 80mg/kg/day of amoxicillin in two divided doses for the treatment of chest indrawing pneumonia.

1.2.5.2 Amoxicillin can be given twice instead of thrice daily for children with fast breathing and chest indrawing pneumonia

Fonseca W et al (*36*) compared levels of oral amoxicillin in a 15 mg/kg/body weight/dose given thrice daily with a regimen of 25 mg/kg/dose twice daily in 66 children age 3 to 59 months. Amoxicillin concentrations were determined by high performance liquid chromatography after the first daily dose on days 1 and 3. For amoxicillin, the mean area under the concentration time curve after the 25 mg/kg/dose was 54.7 µg/ml x h, whereas after the 15 mg/kg/dose it was 24.9 µg/ml x h. The study concluded that oral amoxicillin twice daily is a feasible alternative to thrice daily dosing. It was suggested that in order to lengthen the time above the MIC at higher concentration levels, a 30 to 40 mg/kg/dose twice daily should be considered instead of the 25 mg/kg/dose used in this study.

Valtonen M et al (*37*) compared the clinical efficacy and side effects of amoxicillin (40 mg/kg/day) in two groups of children randomly assigned to a regimen of either two or three doses per day. In the group with two daily doses, 82% of the patients with otitis media were cured; in the group with three daily doses this figure was 86%. Side effects were equal in both groups. The trial concluded that "the same total daily dose of amoxicillin given either three times daily or two times daily is comparably effective and tolerated in children with acute respiratory infections".

Daschner FD et al (*38*) compared the effects of giving amoxicillin (50 mg/kg/day) twice or four times per day in 34 children with respiratory tract infections. Peak and trough antibiotic concentrations were determined. Eradication of bacteria, clinical improvement and side effects were compared in both groups. The authors concluded that the same total daily dosage of amoxicillin given either twice or four times daily was equally effective and safe.

The Catchup study group (*39*) compared the clinical effectiveness of twice-daily oral amoxicillin with twice-daily oral cotrimoxazole in 1459 children with fast breathing pneumonia in a randomized, double blind trial in seven outpatient departments and one community health service in Pakistan. 730 children were randomly assigned to receive a 25 mg/kg/dose of amoxicillin, and 741 to receive 4 mg/kg trimethoprim plus 20 mg/kg sulphamethoxazole (cotrimoxazole). Treatment failure in the amoxicillin group was 16.1% as compared to 18.9% in the cotrimoxazole group (OR 0.83, 95%CI 0.63–1.08, p=0.160). The authors concluded that both amoxicillin and cotrimoxazole provided equally effective therapy for fast breathing pneumonia in twice-daily dosing regimens.

Hazir et al (*26*) compared high dose oral amoxicillin (80–90 mg/kg/day) with injectable penicillin in children with chest indrawing pneumonia, using a twice-daily regimen. This study showed that amoxicillin given two times a day was effective in treating children with chest indrawing pneumonia.

These studies demonstrate that amoxicillin given in a twice-daily dosage regimen is as effective as regimens of three- or four-times daily, provided that the total daily dosage of amoxicillin is the same. A twice-daily schedule has advantages for caregivers and programmes as it may result in improved adherence.

1.3 Recommendation 3

Children aged 2–59 months with severe pneumonia[1] should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

- **Ampicillin: 50 mg/kg, or benzyl penicillin: 50 000 units per kg IM/IV every six hours for at least five days**
- **Gentamicin: 7.5 mg/kg IM/IV once a day for at least five days**

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

One systematic review (*40*) that included two large randomised controlled trials (RCT) comparing beta-lactam and gentamicin versus chloramphenicol for very severe pneumonia showed high-quality evidence that ampicillin/penicillin and gentamicin reduce clinical failure rates compared to

[1] Previously classified as very severe pneumonia (Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources. First edition. Geneva: World Health Organization; 2005).

chloramphenicol. There was moderate-quality evidence of a trend towards reduced death rates for treatment with ampicillin/penicillin and gentamicin compared to chloramphenicol.

1.3.1 Penicillin/gentamicin vs chloramphenicol at high altitude

The first of these RCTs (*41*), conducted in the highlands of Papua New Guinea (1600–1800 m above sea level), included 1116 children aged 1–59 months with WHO-defined very severe pneumonia (modified to include heart failure as a danger sign). Enrolled children had a median oxygen saturation of 71%. Five hundred and fifty-nine (559) children were treated with 100 mg/kg/day chloramphenicol; 557 children were treated with penicillin (200 mg/kg/day) plus gentamicin (7.5 mg/kg/day). Duration of treatment was 14 days. Measured outcomes were: death, treatment failure by day 5, and readmission. More children in the penicillin/gentamicin group required a change of antibiotic (60 versus 49), while 147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes ($p = 0.11$, not significant). Thirty-six children treated with chloramphenicol and 29 treated with penicillin and gentamicin died (difference not significant). More children treated with chloramphenicol presented again with severe pneumonia within one month of hospital discharge ($p = 0.03$), as compared to those treated with penicillin and gentamicin.

1.3.2 Penicillin/gentamicin vs chloramphenicol at low altitude

The second of the RCTs (*42*) was a multi-country study, with 80% of children residing at sea level. Children aged 2–59 months were enrolled: 479 were randomized to receive chloramphenicol (75 mg/kg/day), and 479 to receive ampicillin (200 mg/kg/day) and gentamicin (7.5 mg/kg/day). Median oxygen saturation on admission was higher than for the Papua New Guinea study (88%) (*41*). Duration of treatment was 10 days. More children in the chloramphenicol group required a change in antibiotic (45 versus 26). Measured outcomes were death or treatment failure by days 5, 10, and 21. More children failed treatment with chloramphenicol at day 5 (16% versus 11%; relative risk 1.43, 95% CI 1.03 to 1.97) as well as at days 10 and 21. There was a trend towards reduced death rates in children treated with ampicillin plus gentamicin, but this was not significant.

1.3.3 Ceftriaxone as second-line treatment

Although there were no data on the use of ceftriaxone in the treatment of pneumonia with general danger signs, the WHO Guidelines Development Group recognized the need to include ceftriaxone as a second-line treatment for children with severe pneumonia with general danger signs, especially for hospital care.

1.4 Recommendation 4

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV-infected and -exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

While there has been no randomized controlled trial designed on the basis of an a-priori hypothesis to examine the efficiency of antibiotic regimens or case management, a subgroup analysis was conducted in one randomized controlled trial in which oral amoxicillin was compared with paren-

teral penicillin for chest indrawing pneumonia in children (*43*). The response rates with the two regimens were comparable, but the treatment failure rate was significantly higher for HIV-infected infants at day 14 (40.7% versus 24.3%; OR, 2.8; 95% CI 1.35; 3.5).

Therefore, it was recommended that HIV-infected or -exposed children with chest indrawing pneumonia be hospitalized and treated as patients with severe pneumonia (pneumonia with general danger signs).

1.5 Recommendation 5

Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with severe or very severe pneumonia.

Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and -exposed children over 1 year of age with chest indrawing or severe pneumonia.

Two reviews led to this decision, that was based on those guidelines previously approved by the WHO Guidelines Review Committee (*9*). One review examined the evidence for the management of pneumonia in HIV-infected children (*44*). The second review, which evaluated etiological agents for pneumonia (*45*), was comprised of nine descriptive studies, two post-mortem studies, and 15 analytical studies, of which five were post-mortem.

In a cohort study of HIV-infected children in Malawi (*46*), the incidence of severe pneumonia was high, mostly in children older than two years. No cases of PCP were diagnosed in this age group. In autopsy studies in South Africa and Zimbabwe (47,48) the mean age of all 46 cases of PCP was reported to be 3–4 months. The findings of these and subsequent autopsy and clinical studies in the region provided consistent evidence that most cases of PCP occur in young infants. Of 130 autopsy cases of PCP reported, only 5% were in children over 12 months of age.

In the 1990s, data reported from Europe, Thailand and the United States of America also showed that the peak prevalence of PCP in children was in infants under 12 months of age, with the highest prevalence under 6 months (*49,50*). A report from Ireland and the United Kingdom showed that, before 1998, 27% of HIV-infected infants had PCP or cytomegalovirus as a first indicator; 91% of these were young infants (*51*).

Based on the systematic review, the WHO Guidelines Development Group recognized the importance of covering clinically suspected PCP in infants younger than 1 year of age and thus recommended empirical treatment with cotrimoxazole of all HIV-infected and -exposed children under one year of age.

1.6 Additional information on implementing the management of pneumonia at community level

1.6.1 Management of pneumonia at community level

According to the WHO/UNICEF joint statement on management of pneumonia in community settings (*52*), an important strategy to increase access to quality care for pneumonia is to train and deploy CHWs to assess and treat children with pneumonia. There is strong scientific and programmatic evidence to support the effectiveness of this approach.

Two large-scale studies, in Bangladesh and Nepal, assessed the ability of volunteer CHWs with intensive basic training and close supervision to properly diagnose and treat pneumonia. Hadi et al (*53*) showed that the sensitivity, specificity, and overall agreement rates in pneumonia diagnosis and treatment were significantly higher among those health volunteers in Bangladesh who had intensive basic training and routine supervision than among those who had not. Ghimire et al (*54*) showed a significant trend towards a decrease in the proportion of pneumonia and severe pneumonia cases from 2004 to 2006 in districts of Nepal where the volunteers were given special training to manage pneumonia.

In addition, numerous countries implement community case management of childhood pneumonia. For example, the Gambia has a nationwide programme addressing pneumonia in the community (*52*). In Honduras, pneumonia treatment has been incorporated into the national integrated community child care programme where community volunteers – in addition to their other responsibilities – provide treatment for pneumonia and diarrhoea in more than 1800 communities (*52*). In 2008, the government of Malawi initiated activities to deliver community-level treatment of common childhood illnesses including suspected pneumonia. By September 2011, 3296 health surveillance assistants (HSAs) had been trained, and 2709 village health clinics were functional. Evaluation has shown that HSAs are able to treat sick children with a quality similar to that provided by professional health personnel in fixed facilities. Monitoring data also showed that communities were utilising the HSA services (55). Large-scale, national-level programmes supporting CHWs to treat illness including childhood pneumonia are also implemented in Ethiopia and Pakistan.

The current WHO/UNICEF tools for CHWs recommend oral amoxicillin in two daily doses. Because the CHW is not expected to treat chest indrawing pneumonia, these guidelines will retain two age bands and will not be revised at the present time. Some data from Asia (*56,57*) shows that CHWs can manage chest indrawing pneumonia with oral amoxicillin. However, current CHW guidelines will not be changed until more evidence becomes available from additional regions and countries.

1.6.2 Community management of chest indrawing pneumonia

Two studies have shown that CHWs, when properly trained and supported, can effectively and safely treat chest indrawing pneumonia at home with oral amoxicillin.

Bari et al (*56*) aimed to compare community management of children with chest indrawing pneumonia by lady health workers (LHWs), using oral amoxicillin, to the standard of care: a first dose of cotrimoxazole followed by referral. Twenty-eight clusters in the Haripur district of Pakistan were randomly assigned equally in a 1:1 ratio to either intervention or control. Children age 2 to 59 months with chest indrawing pneumonia were included. In the intervention clusters, LHWs provided mothers with oral amoxicillin (80–90 mg/kg/day in two divided doses) for five days, and gave specific guidance on its use. In the control clusters, LHWs gave the first dose of oral cotrimoxazole and referred the child for standard care to the nearest health facility. The primary outcome was treatment failure by day 6. A total of 1995 children participated in the 14 intervention clusters and 1477 in the 14 control clusters. Treatment failure rates were significantly reduced in the intervention clusters (165 [9%] vs241 [18%], risk difference –8.9%). Most of the risk reduction was in the occurrence of fever and chest indrawing on day 3 (–6.7%, –10.0 to –3.3). Two deaths were reported in the control clusters and one in the intervention cluster. It was concluded that community case management by LHWs could result in appropriate treatment for children with chest indrawing pneumonia, reduce delays in initiating treatment, and reduce costs for families and health systems.

Similar evidence on the management of severe pneumonia by LHWs was generated in a cluster-randomized controlled trial in Matiari district of rural Sindh, Pakistan (57). Public-sector LHWs undertook community management of chest indrawing pneumonia. In the intervention clusters children with suspected pneumonia were screened by LHWs, and identified cases of chest indrawing pneumonia were prescribed oral amoxicillin (90 mg/kg per day in two doses) for five days at home. Children in control clusters were given one dose of oral cotrimoxazole and were referred to their nearest health facility for further management. In both groups, follow-up visits at home were conducted at days 2, 3, 6, and 14 by the LHWs. The primary outcome was treatment failure by day 6 after enrolment. 2341 children in the intervention clusters and 2069 children in the control clusters participated in the study. Treatment failure by day 6 was 8% in the intervention group and 13% in the control group. After adjusting for clustering, the risk difference for treatment failure was –5.2% (95% CI –13.7% to 3.3%). Two deaths by day 6 and one between days 7 and 14 were recorded; no serious adverse events were witnessed. The authors concluded that properly trained LHWs were able to satisfactorily diagnose and treat chest indrawing pneumonia at home in rural Pakistan. This strategy could effectively increase access to care for pneumonia in settings where referral is difficult, and could become a key component of community detection and management strategies for childhood pneumonia.

2. Costs of treating pneumonia using the revised recommendations

One potential barrier to access to case management in low-resource settings is the cost of treatment. Understanding the relevant costs can help public sector programmes and ministries of health reduce them by rationalizing the use of available resources and focusing on those interventions with the greatest public health benefit.

A number of studies carried out in countries with a high burden of childhood pneumonia compared the cost of pneumonia therapy at household, outpatient and hospital levels. The general conclusion is that costs of hospitalization are far greater than the costs of home therapy.

2.1 Household treatment costs for pneumonia

Sadruddin et al (*58*) compared household costs for chest indrawing pneumonia cases referred to a health facility with those managed directly by LHWs in Pakistan. Data on direct and indirect costs were collected through interviews and record reviews. The average household cost of each LHW-managed case was US$ 1.46, while the average cost for a referred case was US$ 7.60. After excluding the cost of the antibiotic provided, the cost per case came to US$ 0.25 for each LHW-managed case and US$ 7.51 per referred case; this is a 30-fold difference. The authors concluded that expanding the treatment of chest indrawing pneumonia to community level could significantly reduce household costs, improve access to treatment, and ultimately prevent many deaths.

2.2 Outpatient treatment costs for pneumonia

Chola et al (*59*) collected data on annual economic and financial costs from urban health centres in Zambia in 2005–06. The average cost of providing outpatient services was US$ 3 per visit, while the cost per outpatient visit for childhood pneumonia was US$48. In a study in the Northern Areas of Pakistan, Hussain H et al (*60,61*) calculated that the average cost of treating childhood pneumonia was US$ 13.44.

2.3 Inpatient treatment costs for pneumonia

Chola et al (*59*) calculated the cost of inpatient treatment in Zambia to be US$ 18 per bed day; for childhood pneumonia this increased to US$ 215 per bed day. Hussain et al (*60,61*) calculated that in northern Pakistan each in-patient episode of pneumonia cost the health system US$ 71; each in-patient case of severe pneumonia cost US$ 235. Outpatient costs averaged US$ 13 and US$ 86 respectively for pneumonia and severe pneumonia. The same authors showed that, when the provider costs (excluding inpatient care) and household costs were added together, the total societal average cost per episode was US$ 22.62 for fast breathing pneumonia, and US$ 142.90 for chest indrawing pneumonia (*60,61*). It should be clarified here that the costs quoted in the latter example are per episode of illness; thus they are slightly higher than the cost per visit cost shown in the earlier paper.

A cost minimization analysis from eight paediatric centres in England (*62*) published in 2010 concluded that treatment of community-acquired pneumonia with oral amoxicillin could result in savings of between £ 473 and £ 518 per case.

2.4 Comparison of inpatient costs for pneumonia at different tiers of health facilities

Madsen et al (*63*) looked at the health-care provider cost and household cost of the treatment of severe pneumonia in infants and young children admitted to secondary and tertiary level health-care facilities in Vellore, India. The total cost to the health system for one episode of hospitalized childhood pneumonia treated at secondary level was US$ 84.0 (INR 3524); an episode treated at tertiary level cost US$ 147.0 (INR 6158). At both levels the greatest single cost was the hospital stay itself, comprising 74% and 56% of the total costs respectively.

Ayieko et al (*64*) calculated the costs of treatment for childhood pneumonia at different tier hospitals in Kenya. A sensitivity analysis was conducted using WHO-CHOICE values for cost per bed day. From the provider perspective the mean cost per admission for childhood pneumonia at the national hospital was US$ 177.0, at district hospitals was between US$ 54.1 to US$ 99.3 and at mission hospitals ranged from US$ 43.4 to US$ 142.2. In public sector hospitals, households provide partial subsidies to the provider costs through payment of user fees; within the private sector the total amount of provider costs may be passed on to households. The authors suggested that these findings could be used in cost effectiveness analysis of health interventions.

3. Flexible Solid Oral Dosage: Dispersible formulations of amoxicillin

Amoxicillin has been recognized as a "priority essential" medicine by WHO and UNICEF (*65*). The dosage of amoxicillin is based on the child's weight. There is a potential risk of microbial resistance with under-dosing, and of toxicity with over-dosing. It is therefore crucial that the paediatric formulation have flexibility for dose adjustment, while at the same time remaining within the effective therapeutic range. One of the current challenges is the suitability of existing formulations of amoxicillin for children in resource-constrained settings. The use of solid preparations often involves breaking an adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. There is a widespread expectation from both end-users and clinicians that medicines for children should be liquid, as it is generally believed that children prefer this formulation. In addition, liquid formulations make weight-based dosing much easier. However, the accurate administration of a liquid medicine is not assured even if the dose is correctly calculated. There is evidence that measuring spoons and other devices supplied with liquid medicines are not always accurate and that significant under- or over-dosing can occur (*66–68*).

In order to reach consensus on the most suitable formulations of medicines for children, with particular attention to conditions in developing countries, in 2006 WHO hosted a meeting of pediatricians, pharmacists, clinical pharmacologists, and representatives of the European Medicines Agency, the International Federation of Pharmaceutical Manufacturers and Associations, the Medicines for Malaria Venture, the National Institutes of Health, UNICEF, and the Bill & Melinda Gates Foundation. The group recommended that in general, the dosage forms of medicines that are likely to prove most 'suitable' particularly for developing countries are flexible solid dosage forms, such as tablets that are oro-dispersible and/or that can be used for preparation of oral liquids (for e.g. suspension or solution). Provided the product can be dispersed in breast milk from the mother, it could potentially be used for very young children (0–6 months). This type of product is feasible to manufacture in facilities that produce conventional tablets, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet product suggest that they can be more affordable than standard liquid dosage forms (*69*).

In September 2010, the UNICEF Supply Division and WHO brought together experts in paediatric medicine from academia, the pharmaceutical industry (both innovator and generic), regulators, programme managers and implementers. The meeting aimed to reach consensus on priority essential medicines for children, and to identify the steps required to ensure that these medicines are available and affordable. The group concluded, "Liquid formulations can be difficult to use and store, which can make their use impractical in some areas. Solid formulations and flexible solid oral dosage forms, such as dispersible tablets, that can be given whole to older children or dispersed in water for ease of administration to younger children are preferred" (*65*).

Based on these consultations, WHO recommended 'Flexible Solid Oral Dosage' forms as the optimum formulation for children's medicines administered orally, as they have better stability and shelf life than liquids, in addition to being less bulky to ship and store (*70*).

4. Implications for implementation

The revised recommendations present a number of advantages.

- Oral amoxicillin can be used to treat both fast breathing pneumonia and chest indrawing pneumonia (see Table).
- Pneumonia classification and management are simplified to two categories instead of three (see Figure).
- Access to antibiotic treatment closer to home is increased.
- The need for referrals to higher level facilities is decreased.
- The probability of hospitalization and thus the risk of nosocomial and injection borne diseases is reduced.
- The probability of antimicrobial resistance is diminished, due to better adherence to the simplified treatment.
- Training of health workers is simplified.

Adoption of the revised guidelines will have a number of implications for policy as well as for implementation at different levels of the health system.

4.1 Implications for policy

- National programmes will need to switch from oral cotrimoxazole to oral amoxicillin. Because of this:
  - ✔ *retraining of healthcare providers will be required (with training materials and job aids appropriately revised);*
  - ✔ *reduction in overall costs of pneumonia treatment by promoting outpatient/home therapy will help offset the additional costs of switching to oral amoxicillin from oral cotrimoxazole.*
- Combining the two previous categories of "pneumonia" (fast breathing) and "severe pneumonia" (chest indrawing) under a single classification of "pneumonia" simplifies classification. Because of this:
  - ✔ *training will be simplified;*
  - ✔ *the process of local adaptation of training materials and job aids will be easier.*
- It is crucial that the policy makers, administrators and officials of relevant programmes understand the significance of these modifications. Because of this:
  - ✔ *widespread dissemination of technical updates is of utmost importance to ensure adoption and adherence.*
- In order to pre-empt the possible over-use of antibiotics, programmes will need to invest in careful monitoring procedures. Because of this:
  - ✔ *close monitoring will be essential in areas implementing the new guidelines at large scale.*

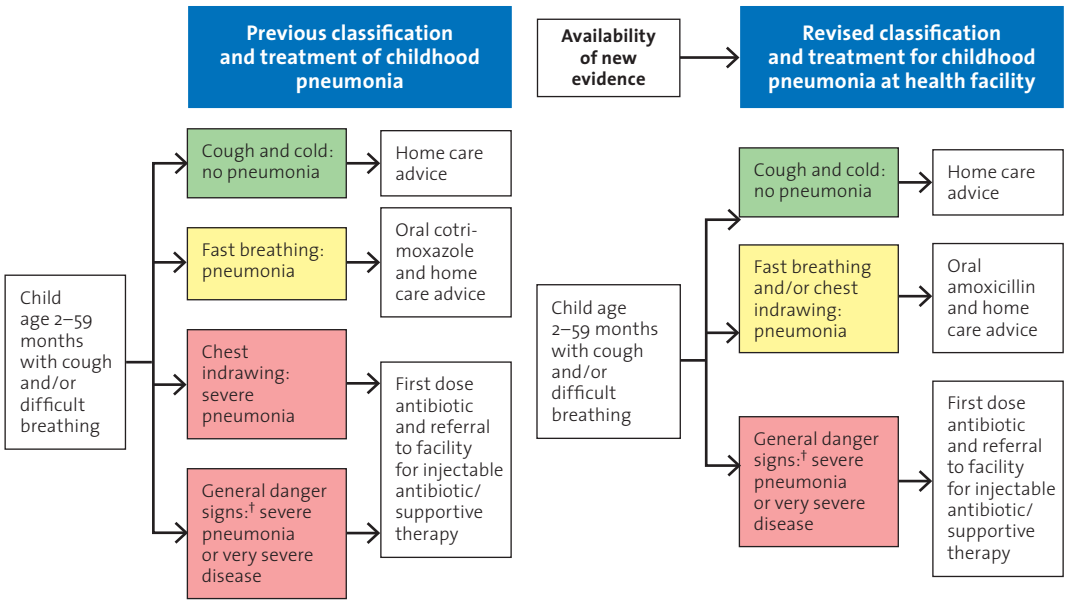
Table

Doses of amoxicillin for children 2–59 months of age with pneumonia

TOOLS	CATEGORY OF PNEUMONIA	AGE/WEIGHT OF CHILD	DOSAGE OF AMOXICILLIN DISPERSIBLE TABLETS (250 mg)
iCCM tool for community health workers: **no change**	Fast breathing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day x 5 days (10 tabs)
		12 months up to 5 years (10–19 kg)	2 tabs twice a day x 5 days (20 tabs)
IMCI tool for professional health workers at health facilities: **revised**	Fast breathing and chest indrawing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day x 5 days (10 tabs)
		12 months up to 3 years (10–<14 kg)	2 tabs twice a day x 5 days (20 tabs)
		3 years up to 5 years (14–19 kg)	3 tabs twice a day x 5 days (30 tabs)

Figure

Comparison of previous and revised classification and treatment of childhood pneumonia at health facility



† Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

4.2 Implications for implementation at community level (integrated Community Case Management)

The WHO/UNICEF joint statement *Management of pneumonia in community settings* (*52*) recommends the training and deployment of CHWs as a central strategy for increasing access to quality care for pneumonia. Research showed that educated community members could be trained to detect and manage pneumonia in their communities; large-scale studies confirmed that the sensitivity, specificity, and overall agreement rates in pneumonia diagnosis and treatment were high among health volunteers who had intensive basic training and routine supervision. This led to a substantial decrease in the proportion of severe pneumonia cases and deaths.

It has also been shown that properly trained and supervised CHWs can appropriately manage chest indrawing pneumonia with oral amoxicillin at community level, resulting in increased access to treatment and reduced costs for families. As evidence is limited, the iCCM guidelines are not currently being updated to include the management of chest indrawing pneumonia. In situations where referral is not possible, however, CHWs may treat chest indrawing pneumonia with oral amoxicillin, if local health policy allows them to do so.

Thus, at the **community level** the revised recommendations imply that:

— all children with fast breathing are classified as having "pneumonia" and treated with oral amoxicillin;

— children with "chest indrawing" pneumonia should be referred to a higher level. However, in situations where referral is not possible and if local health policy allows, CHWs may treat chest indrawing pneumonia with oral amoxicillin;

— dispersible amoxicillin is the preferred treatment for children.

4.3 Implications for implementation at health facility Level

The revised recommendations can be encapsulated into the following statements, each with a short description of the supporting evidence:

It is safe to treat chest indrawing pneumonia at home with oral amoxicillin. A comparison of the use of parenteral ampicillin in hospital to oral amoxicillin at home found that the two treatments were equivalent. In cases of chest indrawing pneumonia without underlying complications, home treatment with a short course of high-dose oral amoxicillin is preferable to parenteral treatment because of the associated reduction in referral, admission, and treatment costs as well as the reduced invasiveness of oral treatment.

A three-day course of antibiotics is as effective as a five-day course in treating children with fast breathing pneumonia in areas of low HIV prevalence. A systematic review of trials evaluating the efficacy of short-course versus long-course treatment of fast breathing pneumonia in children age 2 to 59 months recommended a shorter course of antibiotic therapy, keeping in mind the benefits to the individual as well as to the health system, especially in settings with limited resources.

Amoxicillin is more effective when given in higher doses. Increasing concentrations of antimicrobials improves their bactericidal activity. Clinical reviews show that, for community-acquired pneumonia, oral amoxicillin should be given in a regimen of at least 80 mg/kg/day in two divided doses.

Amoxicillin can be given twice instead of thrice daily for children. Amoxicillin given in a twice-daily dosage regimen is as effective as regimens of three- or four-times daily, provided that the total daily dosage of amoxicillin is the same. A twice-daily schedule has advantages for caregivers and programmes as it may result in improved adherence to treatment.

Dispersible amoxicillin is the most suitable formulation for children. Because the dosage of amoxicillin is based on the child's weight, and because of the risks associated with under- or over-dosing, it is crucial that the paediatric formulation have flexibility for dose adjustment. The use of solid preparations often involves breaking an adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. Liquid formulations make weight-based dosing much easier, however there is evidence that measuring devices supplied with liquid medicines are not accurate and that significant under- or over-dosing can occur. A multidisciplinary consensus supports the recommendation of 'Flexible Solid Oral Dosage' forms for children's oral medicines, as they are less costly than tablets, they have better stability and shelf life than liquids, and they are less bulky to ship and store.

Thus, at the **health facility level**, changes in the management of ARI implied by these new recommendations can be summarized as follows:

— all children with fast breathing and/or chest indrawing are classified as having "pneumonia" and treated with oral amoxicillin; the recommended dosage is 80 mg/kg for five days (40 mg/kg twice a day); in settings of low HIV prevalence the duration of treatment for 'fast breathing pneumonia' can be reduced to three days;

— only those children who have either general danger signs or who are HIV positive and have chest indrawing need to be referred to higher level facility for inpatient treatment with injectable antibiotics;

— dispersible amoxicillin is the preferred treatment for children.

4.4 Implications for implementation at hospital level

Children with chest indrawing pneumonia in settings of low HIV prevalence will be treated at the outpatient level and will no longer need to be referred for hospitalization.

References

1. Leowski J. Mortality from acute respiratory infections in children under 5 years of age: Global estimates. World Health Statistics Quarterly. 1986; 39:138–44.
2. Levels and Trends in Child Mortality: Report 2014. United Nations Inter Agency Group for Child Mortality Estimation. UNICEF, WHO, The World Bank, United Nations Population Division. New York, 2014.
3. Global Health Observatory. Proportions of child deaths by cause. (http://www.who.int/gho/child_health/en/index.html), WHO, Geneva Accessed on 24 July 2014.
4. Integrated Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization and The United Nations Children's Fund (UNICEF); 2013 (http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en).
5. Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012 (http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en).
6. Pocket book of hospital care for children: Guidelines for the management of common illnesses. Second edition. Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en).
7. Integrated Management of Childhood Illness (IMCI) (revised). Geneva, World Health Organization/ The United Nation Children's Fund (UNICEF), 2014 (http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/).
8. Chart booklet: Integrated Management of Childhood Illness (IMCI). Geneva, World Health Organization/The United Nation Children's Fund (UNICEF), 2008.
9. Integrated Management of Childhood Illness (IMCI). WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241548083/en).
10. Rudan I et al. Epidemiology and etiology of childhood pneumonia. Bulletin of the World Health Organization. 2008; 86:408–416.
11. Bang AT, Bang RA, Reddy HM. Home-based neonatal care: summary and applications of the field trial in rural Gadchiroli, India (1993 to 2003). Journal of Perinatology. 2005; 25:S108–S122.
12. The Multi-Country Evaluation of IMCI Effectiveness, Cost and Impact (MCE) – Progress Report', May 2001–April 2002, Geneva: World Health Organization; 2002 (WHO/FCH/CAG/02.16).
13. Aguilar AM et al. Mortality Survey of Bolivia: The Final Report: Investigating and identifying the causes of death for children under five. Published for USAID by the Basic Support for Institutionalizing Child Survival (BASICS) Project, Virginia, 1998.

14. Schumacher R et al. Mortality Study in Guinea: Investigating the causes of death in children under 5. Published by Save the Children and the Basic Support for Institutionalizing Child Survival (BASICS II) Project, Virginia, 2002.

15. Schellenberg JA et al. Inequalities among the very poor. Health care for children in rural southern Tanzania. Lancet. 2003; 361:561–66.

16. Kabra SK, Lodha R, Pandey RM. Antibiotics for community-acquired pneumonia in children. Cochrane Database of Systematic Reviews. 2010; (3): CD004874.

17. Grant GB et al. Recommendations for treatment of childhood non-severe pneumonia. Lancet Infectious Diseases. 2009; 9:185–196.

18. Haider BA, Saeed MA, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. Cochrane Database of Systematic Reviews. 2008; CD:005976.

19. Hazir T et al. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. Lancet. 2002; 360:835–41.

20. Agarwal G et al. Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. British Medical Journal. 2004; 328:791.

21. Consultative meeting to review evidence and research priorities in the management of acute respiratory infections. Geneva, 29 September–1 October 2003. Geneva: World Health Organization; 2004 (WHO/FCH/CAH/04.2).

22. Pocket book of hospital care for children: Guidelines for the management of common illnesses. Geneva: World Health Organization;2005.

23. Straus W et al. Antimicrobial resistance and clinical effectiveness of cotrimoxazole versus amoxicillin for pneumonia among children in Pakistan: randomised controlled trial. Lancet. 1998; 352:270–74.

24. Addo-Yobo E et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet. 2004; 364:1141–8.

25. Atkinson M et al. A multicentre randomised controlled equivalence trial comparing oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children PIVOT Trial. Thorax. 2007; 62:1102–6.

26. Hazir T et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet. 2008; 371:49–56.

27. Addo-Yobo E et al. Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: the MASS study. Tropical Medicine and International Health. 2011;16:995–1006.

28. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clinical Infectious Diseases. 1998; 26: 1–10.

29. Craig WA. Antimicrobial resistance issues of the future. Diagnostic Microbiology and Infectious Diseases. 1996; 25:213–7.

30. Howie VM, Dillard R, Lawrence B. In vivo sensitivity test in otitis media: efficacy of antibiotics. Pediatrics. 1985; 75:8–13.

31. Howie V. Eradication of bacterial pathogens from middle ear infections. Clinical Infectious Diseases. 1992; 14(suppl 2):S209–11.

32. Klein JO. Microbiologic efficacy of antibacterial drugs for acute otitis media. Pediatric Infectious Diseases Journal. 1993; 12:973–5.

33. Dagan R et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. Pediatric Infectious Diseases Journal. 1996; 15: 980–5.

34. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatric Infectious Diseases Journal. 1996; 15:255–9.38.

35. Lieberthal AS et al. The diagnosis and management of acute otitis media. American Academy of Pediatrics and American Academy of Family Physicians. Pediatrics. 2013; 131:e964–99. doi: 10.1542/peds.2012–3488.

36. Fonseca W et al. Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than 3 months with pneumonia. Antimicrobial Agents and Chemotherapy. 2003; 47: 997–1001.

37. Valtonen M et al. Comparison of amoxicillin given two and three times a day in acute respiratory tract infections in children. Scandinavian Journal of Primary Health Care. 1986; 4:201–4.

38. Daschner FD, Behre U, Dalhoff A. Prospective clinical trial on the efficacy of amoxicillin administered twice or four times daily in children with respiratory tract infections. Journal of Internal Medicine Research. 1981; 9:274–6.

39. Catchup Study Group. Clinical efficacy of cotrimoxazole versus amoxicillin twice daily for treatment of pneumonia: a randomized controlled clinical trial in Pakistan. Archives of Diseases in Childhood. 2002; 86: 113–18.

40. Lassi ZS et al. Systematic review on antibiotic therapy for pneumonia in children less than 59 months of age. Archives of Diseases in Childhood. 2014;99:687–93.

41. Duke T et al. Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. Lancet. 2002; 359:474–80.

42. Asghar R et al. Severe Pneumonia Evaluation Antimicrobial Research Study Group. Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2–59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). British Medical Journal. 2008; 336:80–4.

43. Jeena P et al. Amoxicillin Penicillin Pneumonia International Study (APPIS Group). Failure of standard antimicrobial therapy in children aged 3–59 months with mild or asymptomatic HIV infection and severe pneumonia. Bulletin of the World Health Organization. 2006; 84:269–75.

44. Punpanich W et al. Antibiotic and systemic therapies for pneumonia in human immunodeficiency virus (HIV)-infected and HIV-exposed children. Journal of Infection in Developing Countries. 2012; 6:109–19.

45. Punpanich W et al. Systematic review on the etiology and antibiotic treatment of pneumonia in human immunodeficiency virus-infected children. Pediatric Infectious Diseases Journal. 2011; 30:e192–202. doi:10.1097/INF.0b013e1822d989c.

46. Laufer MK. Observational cohort study of HIV-infected African children. Pediatric Infectious Disease Journal. 2006; 25:623–7.

47. Jeena PM, Coovadia HM, Chrystal V. *Pneumocystis carinii* and cytomegalovirus infections in severely ill, HIV-infected African infants. Annals of Tropical Paediatrics. 1996; 16:361–8.

48. Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. Archives of the Diseases of Childhood. 1997; 76:124–8.

49. Simonds RJ et al. *Pneumocystis carinii* pneumonia among U.S. children with perinatally acquired HIV infection. Journal of American Medical Association. 1993; 270:470–3.

50. Chokephaibulkit K. *Pneumocystis carinii* severe pneumonia among human immunodeficiency virus-infected children in Thailand: the effect of a primary prophylaxis strategy. Pediatric Infectious Disease Journal. 1999; 18:147–52.

51. Williams AJ et al. *Pneumocystis carinii* pneumonia and cytomegalovirus infection in children with vertically acquired HIV infection. AIDS. 2001; 15:335–9.

52. WHO/UNICEF joint statement. Management of pneumonia in community settings. New York/ Geneva: The United Nations Children's Fund/World Health Organization, 2004 (http://www.who.int/maternal_child_adolescent/documents/fch_cah_04_06/en).

53. Hadi A. Management of acute respiratory infections by community health volunteers: experience of Bangladesh Rural Advancement Committee (BRAC). Bulletin of the World Health Organization. 2003; 81: 183–89.

54. Ghimire M, Pradhan YV, Maskey MK. Community based intervention for diarrhoeal diseases and acute respiratory infections in Nepal. Bulletin of the World Health Organization. 2010; 88:216–21.

55. Nsona H et al. Scaling up integrated community case management of childhood illness: Update from Malawi. American Journal of Tropical Medicine and Hygiene. 2012;87:54–60.

56. Bari A et al. Community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Haripur district, Pakistan: a cluster randomised trial. Lancet. 2011; 2011;378:1796–803.

57. Soofi S et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. Lancet. 2012;379:729-37.

58. Sadruddin S et al. Household costs for treatment of severe pneumonia in Pakistan. American Journal of Tropical Medicine and Hygiene, 2012; 87:S137–43.

59. Chola L, Robberstad B. Estimating average inpatient and outpatient costs and childhood pneumonia and diarrhoea treatment costs in an urban health centre in Zambia. Cost Effectiveness and Resources Allocation. 2009; 7:16.

60. Hussain H et al. Economic analysis of childhood pneumonia in Northern Pakistan. Health Policy and Planning. 2008; 23:438–42.

61. Hussain H et al. The cost of treatment for child pneumonias and meningitis in the Northern Areas of Pakistan. The International Journal of Health Planning and Management. 2006; 21:229–38.

62. Lorgelly PK et al. Oral versus i.v. antibiotics for community acquired pneumonia in children: a cost minimization analysis. European Respiratory Journal. 2010; 35:585–64.

63. Madsen HO et al. Costing of severe pneumonia in hospitalized infants and children aged 2–36 months, at a secondary and tertiary level hospital of a not-for-profit organization. Tropical Medicine and International Health. 2009; 14:1315–22.

64. Ayieko P et al. The economic burden of inpatient pediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis. Cost Effectiveness and Resources Allocation. 2009; 7:3.

65. Priority essential medicines for child survival. Copenhagen, The United Nations Children's Fund/ World Health Organization. 2010.

66. Grießmann K et al. Dosing accuracy of measuring devices provided with antibiotic oral suspensions. Paediatric and Perinatal Drug Therapy. 2007; 8: 61–70.

67. Falagas et al. Inaccuracies in dosing with teaspoons and tablespoons. The International Journal of Clinical Practice. 2010; 64:1185–9.

68. Monk PM, Ball PA. The accuracy of a paediatric dosing device. The Australian Journal of Hospital Pharmacy. 1997; 27: 323–324.

69. Report of the informal expert meeting on dosage forms of medicines for children. Geneva: World Health Organization; 2008.

70. Priority medicines for mothers and children 2011. Ensuring access to priority medicines for mothers and children improves health and saves lives. Geneva: World Health Organization; 2011 (WHO/EMP/MAR/2011.1) (http://www.who.int/maternal_child_adolescent/documents/emp_mar2011.1/en/).

World Health Organization

For more information please contact:

Department of Maternal, Newborn, Child and Adolescent Health (MCA)
World Health Organization
20 Avenue Appia, 1211 Geneva 27, Switzerland

Tel: + 41 22 791 32 81; Fax: + 41 22 791 48 53
E-mail: mncah@who.int
Website: http://www.who.int/maternal_child_adolescent

ISBN 978 92 4 150781 3