Antibiotic Use for Community Acquired Pneumonia (CAP) in Neonates and Children: 2016 Evidence Update

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# Table of Contents

1. Introduction .................................................................................................................................... 3  

2. Key Facts about Community Acquired Pneumonia in Children ...................................................... 3  
   2.1 Definition............................................................................................................................. 3  
   2.2 Aetiology ............................................................................................................................. 3  
   2.3 Epidemiology....................................................................................................................... 4  
      Burden of Disease .................................................................................................................. 4  
      Prevalence of *S. pneumoniae* .......................................................................................... 4  
      Prevalence of *M. pneumoniae* ......................................................................................... 4  
   2.4 Diagnostics .......................................................................................................................... 4  
   2.5 Current WHO Guideline and Rationale ............................................................................... 5  

2 Methods .......................................................................................................................................... 5  

3.1 Findings: New Evidence .................................................................................................................. 6  
   3.1.1 New Antibiotics................................................................................................................... 6  
   3.1.2 New Interventions............................................................................................................... 6  
   3.1.3 Changing Epidemiology ....................................................................................................... 6  
      Issues in Surveillance ............................................................................................................. 6  
      Effect of PCV13 Vaccine on Serotype Selection ...................................................................... 7  
      Effect of PCV13 Vaccine on Disease Severity ......................................................................... 8  
   3.1.4 New Efficacy Data ............................................................................................................... 8  
   3.1.5 New Safety Data .................................................................................................................. 9  
   3.1.6 Antimicrobial Resistance ..................................................................................................... 9  
      Resistance in *S. Pneumoniae* ............................................................................................. 10  
      Resistance in *M. pneumoniae* .............................................................................................. 10  
   3.1.7 New Acceptability and Feasibility Data ............................................................................. 11  
   3.1.8 Emerging Issues ................................................................................................................. 11  
      Trial Design ............................................................................................................................ 11  
      Dosing and Formulation .......................................................................................................... 12  
      Potential reconsideration of Current Dosing Age-Bands .......................................................... 13  
      Pharmacokinetics ..................................................................................................................... 15  
      Duration of Treatment: Intravenous to Oral Switch ................................................................. 15  
      Role of Antimicrobial Treatment on Resistance ..................................................................... 16  
      Targeting Antibiotics in Primary Care Settings for High Risk Children ...................................... 16  
   3.1.9 Summary of International Guidelines ............................................................................... 16  

3.2 Findings: Costs of treatment ........................................................................................................... 17  

3.3 Findings: Ongoing clinical trials .................................................................................................... 18  

4 Conclusion ..................................................................................................................................... 20  

5 References .................................................................................................................................... 21
1. Introduction

This review summarises the most up-to-date evidence for the empiric antibiotic treatment of community acquired pneumonia in neonates and children. For this update, special focus has been placed on publications since the release of the previous report ‘Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries’ in 2014 (1). As the 2014 Guideline was both very recent and a major revision of guidance, this review has both summarised the recent literature and discusses the emerging challenges in this area.

Current 2014 WHO CAP drug and dosage recommendations are summarized in the table below:

| 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 (40–110 kg) | 1 tab twice a day x 5 days (80 tabs) |
| IMCI tool for professional health workers at health facilities: revised | Fast breathing and chest indrawing pneumonia | 2 months up to 12 months (40–110 kg) | 2 tabs twice a day x 5 days (20 tabs) |

Figure 1 Current recommendations for doses of oral amoxicillin (Adapted from World Health Organization. Revised WHO classification and treatment of childhood pneumonia at health facilities–Evidence summaries)

2. Key Facts about Community Acquired Pneumonia in Children

2.1 Definition

Community acquired pneumonia (CAP) refers to pneumonia that is acquired in the community as compared to the healthcare system. Updated clinical classification is addressed in Section 2.5.

2.2 Aetiology

The most common causes of bacterial pneumonia in children are *S. pneumoniae* and *Haemophilus influenzae* type b (Hib). Pathogens considered ‘atypical’ are *Chlamydia pneumonia*, *Mycoplasma pneumoniae*, or *Legionella spp.* Prevalence differs both regionally and by age group. Pneumonia affects children and families everywhere, but is most prevalent in South Asia and sub-Saharan Africa (1).

Aetiological studies of CAP in children are complicated by the low yield blood cultures, inadequate sputum specimens, and infrequent workup with lung aspiration and bronchoalveolar lavage. Quantification of aetiology is further complicated by limited microbiological workup in the community, seasonality, mixed infection, and viruses and commensal bacteria in samples. The PERCH (Pneumonia Etiology Research for Child Health) project is a multi-country, case-control study examining the aetiology of pneumonia in children 1-59 months of age. Enrollment of cases and controls ended in January 2014. The main findings are projected to be published in 2017. (http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch/)

*Streptococcus pneumoniae* is the most common bacterial cause of community acquired pneumonia in childhood. It is widely considered the leading cause of CAP, though proportions vary by region. It is responsible for about one-third of radiologically confirmed pneumonia in children aged <2 years. *Haemophilus influenzae* type b (Hib) is a major pathogen, though proportions vary regionally and with vaccine coverage (2). Children with mycoplasmal (or chlamydial) pneumonia may be over-represented in hospital-based studies because of failure of penicillin-related antibiotic treatment in the community. Less common, severe infection is caused by *Staphylococcus aureus*, especially following influenza. Fungal infection by Pneumocystis jiroveci (PCP) is particularly important in young children with AIDS.
Furthermore, children with milder atypical pathogens may recover without antibiotic intervention. One-third of cases of CAP represent a mixed infection with viruses (3).

Viruses commonly associated with CAP are RSV, parainfluenza and influenza in the community and in hospital. Other viruses isolated in children with pneumonia include adenovirus, rhinovirus, herpes simplex virus, enteroviruses, human metapneumovirus, human bocavirus and coronavirus. Overall, viruses account for 30 to 67% of CAP cases in childhood and are more frequently identified in children aged <1 year than in those aged >2 years (3).

Causative pathogens also vary by age. Overall, viruses alone are found as a cause in younger children in up to 50%. In older children, when a bacterial cause is found, it is most commonly *S. pneumoniae* followed by mycoplasma pneumonia (3).

### 2.3 Epidemiology

#### Burden of Disease

Pneumonia is the single largest infectious cause of death in children worldwide accounting for 15% of all deaths of children under 5 years old. For HIV-negative children pneumococcal infection is responsible for around 11% of all deaths in this age group (1). Nearly one in 500 children under the age of 5 years is hospitalised each year for community acquired pneumonia (CAP) (4). However, only 54% of children with symptoms of pneumonia are taken outside the home for care (5). There are signs of progress for the 75 countries included in *Countdown to 2015* (5). In this group, the number of deaths due to pneumonia in children under 5 has declined from 21% in 2000 to 16% in 2015 (5). Nonetheless, community acquired pneumonia remains an issue of profound economic and social importance to children and communities worldwide.

**Prevalence of *S. pneumoniae***

*S. pneumoniae* is the leading cause worldwide of community-acquired pneumonia, Pneumococci are commonly found in asymptomatic nasopharyngeal carriage, where the prevalence varies by age and region. The asymptomatic carriage state is responsible for much of the transmission within populations, such as day-care centres (6).

**Prevalence of *M. pneumoniae***

In the United States, pneumonia is the leading cause of hospitalization amongst children. Pneumonia caused by *Mycoplasma pneumoniae* is considered an atypical bacterial pneumonia because of its differing course, radiological findings and treatment. Jain et al (2015) conducted active population-based surveillance for community acquired pneumonia in hospitals in three American cities. 87% of the 1272 children ages 19 months to 12 years had received three or more doses of pneumococcal conjugate vaccine. Of 2222 children with radiographic confirmation of pneumonia and laboratory workup, 8% had *M. pneumoniae* isolated and 4% had *S. pneumoniae* isolated. *M. pneumoniae* was more common among children 5 years of age (19%) or older than among younger children (3%). Annual incidence of hospitalization with pneumonia was 15.7 cases per 10 000 children (95%CI 14.9 – 16.5). When looking at estimated annual incidence of specific pathogens, *M. pneumoniae* 1.4 per 10 000 (95%CI 1.2 - 1.6) and *S. pneumoniae* 0.5 per 10 000 (95%CI 0.4 – 0.6) (7).

### 2.4 Diagnostics

There is limited data on validated, cost-effective rapid diagnostic test for CAP in LMIC settings. Diagnosis of CAP in such settings is based on clinical criteria.

Very severe pneumonia is defined as cough or difficulty breathing plus any of central cyanosis; inability to breastfeed, drink, or vomiting everything; convulsions, lethargy, or unconsciousness; and severe respiratory distress. Severe pneumonia is defined as cough or difficulty breathing and one of lower
Non-severe pneumonia is defined as cough or difficulty in breathing accompanied by tachypnea (respiratory rate ≥ 50 breaths/minute in infant aged 2-11 months, ≥ 40 breaths/minute in child aged 12-59 months) with no signs of severe or very severe pneumonia, especially in age ≥ 2 months. The WHO definition of treatment failure includes development of signs of severe or very severe pneumonia and persistently raised respiratory rate at 72 hours (48 hours in area with high HIV prevalence).

2.5 Current WHO Guideline and Rationale

The ‘Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries’ was published in 2014. The revision integrated input from two consultations which used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation): the 2010 WHO recommendations on the management of diarrhea and pneumonia in HIV-infected infants and children: integrated management of childhood illness (IMCI) and the 2012 Recommendations for management of common childhood conditions. Evidence for technical update of pocket book recommendations. The revisions include updating the classification of pneumonia severity and changing the recommendation for the first-line antibiotic.

Community acquired pneumonia for treatment at a healthcare facility was reclassified in the 2014 guidance into three categories: very severe pneumonia, severe pneumonia and non-severe pneumonia. The new approach was designed to simplify the management of pneumonia at outpatient level, reduce the number of referrals for hospitalisation and achieve better treatment outcomes. The classification changes are summarised in Figure 2.

![Figure 2](image)

Figure 2 Comparison of previous and revised classification and treatment of childhood pneumonia (Adapted from World Health Organization. Revised WHO classification and treatment of childhood pneumonia at health facilities–Evidence summaries)

Previous to the 2014 revision, four treatment categories were defined for CAP. Children with “fast breathing” pneumonia were treated with oral cotrimoxazole. Children with “chest indrawing” pneumonia were referred to a healthcare facility and treated with injectable penicillin/ampicillin. As a result of new evidence, in the 2014 revision oral amoxicillin was preferred to oral cotrimoxazole for the treatment of fast breathing pneumonia and was equivalent to injectable penicillin/ampicillin in cases of “chest indrawing pneumonia”. Since both fast-breathing and chest indrawing pneumonias were now best treated with amoxicillin, classifications were also revised. The new classification was revised 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 antibiotic therapy.

2 Methods
A systematic search for systematic reviews and meta-analyses of antibiotic therapy for community acquired pneumonia was conducted. We searched for systematic reviews and meta-analyses published between January 1, 2013 to November 10, 2016. We applied language restrictions to English. We searched MEDLINE, Cochrane Database for Systematic Reviews and ClinicalTrials.gov. The search strategy of databases was focused on including clinical trials, controlled clinical trials, reviews, or systematic reviews in all children (0 to 18 years). Search was conducted on November 10, 2016 combining MeSH and free-text terms “Community-Acquired Infections”, “Pneumonia. Bacterial”, “community acquired pneumonia”, “antibiotics” and “Anti-Bacterial Agents”. For relevant guidelines, a search of PubMed was conducted. Screening of titles and abstracts, full-texts, as well as subsequent data abstraction, was conducted independently followed by consensus discussion.

3.1 Findings: New Evidence

3.1.1 New Antibiotics

Ceftaroline fosamil is a broad-spectrum cephalosporin antibiotic with activity against many bacteria, including *Streptococcus pneumoniae* (both penicillin-nonsusceptible and multidrug-resistant strains) and *Staphylococcus aureus* (including methicillin-resistant *S. aureus*). In a phase 2/3 study (NCT01530763), 160 patients received either intravenous ceftaroline fosamil or ceftriaxone in the treatment of paediatric patients hospitalized with CAP from a randomized, active-controlled, observer-blinded clinical trial. Ceftaroline fosamil had similar effectiveness to ceftriaxone, with high clinical cure rates at test-of-cure in the modified intent-to-treat population (94/107; 88% and 32/36; 89%, respectively). Three documented *S. aureus* infections were successfully treated in the ceftaroline group, including one caused by methicillin-resistant *S. aureus* (8). In the phase 4 study (NCT01669980), the safety and effectiveness of ceftaroline fosamil in children was evaluated in a multicentre, randomized, observer-blinded, active-controlled method. Ceftaroline fosamil was compared with intravenous ceftriaxone plus vancomycin in patients between 2 months and 17 years of age with complicated community-acquired pneumonia. Clinical response rates in the modified intent-to-treat population were 52% (15/29 patients) in the ceftaroline fosamil group and 67% in the comparator group (6/9); clinical stability at Study Day 4 was 21% (6/29) and 22% (2/9), respectively. Ceftaroline fosamil was well tolerated and showed similar clinical response rates to ceftriaxone plus vancomycin (9).

3.1.2 New Interventions

There are several interventions which are complementary to antibiotic therapy for the management of CAP. Successful efforts are being made to integrate management and global vaccination campaigns.

The WHO *Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD)* aims to address protection, prevention and treatment of both pneumonia and diarrhoea through integrated programmes in LMICs. Several identified interventions are specific to pneumonia (Reduced household air pollution; PCV, Hib and pertussis vaccination; and oxygen therapy where available). However, several interventions have been identified which are complementary for both pneumonia and diarrhoea. These are categorised as protect (breastfeeding promotion and support, adequate complementary feeding), prevent (measles vaccination, handwashing with soap, prevention of HIV) and treat (improving care seeking behaviour and referral improved case management at community and health facility levels, and continued feeding) (10).

GAVI (Global Alliance for Vaccines and Immunization) has introduced the pneumococcal vaccine to 51 countries in the 2011–2015 strategic period. Pneumococcal vaccines have been introduced to Bangladesh, Cambodia, Eritrea, Guinea-Bissau, Lesotho, Nepal, Solomon Islands, and Uzbekistan in 2015. To date, it is estimated that over 76 million children have received the pneumococcal vaccine with Gavi support. However, pneumococcal coverage with the third dose of vaccine was 35% in 2015. (11)

3.1.3 Changing Epidemiology

Issues in Surveillance
Globally, there are difficulties in surveillance due to limited laboratory capacity, harmonized diagnostic procedures and lacking surveillance networks. Mapping of AMR in under-resourced countries requires focus on specimen shipping conditions, data standardization, absence of contamination and adequate diagnostics (12).

When considering available data in resource limited settings for *S. pneumoniae*, the extent of outpatient penicillin usage correlates with level of resistance in invasive isolates. In a surveillance study of hospitalized patients in 11 Asian countries, high-level penicillin resistance was much lower than levels of resistance to erythromycin (72.7%) and MDR (59.3%). In South Africa, 18% of 20,100 isolates identified were resistant to 3 typical antibiotics. However, it is important to note that often AMR data comes from hospitals attended by wealthy patients, introducing bias. Furthermore, it is important for surveillance of pneumococcal pathogens to integrate the effects of other public health measures such as conjugate vaccinations (12).

**Effect of PCV13 Vaccine on Serotype Selection**

Widespread use of pneumococcal vaccines is altering the landscape of resistance. Infections and paediatric carriage has been reduced in classically resistant serotypes (14, 6B, 19F, 23F) which are covered by currently available multivalent PCV vaccines. Serogroups 1, 3, 7 and 19 were most common amongst pneumococcal isolates reported to EARS-Net. A large majority of isolates from serogroups 1, 3 and 7 were susceptible to both penicillin and macrolides. For serogroup 19, 52% of the isolates had decreased susceptibility to penicillin and/or macrolides (13).

For countries reporting to EARSNet for 2014, serogroups 1 and 19 were the most prevalent (accounting for 13.2 % and 12.8 % of isolates, respectively), followed by serogroup 7 (11.9 %) and serogroup 3 (8.6 %). Among the most commonly reported serogroups, dual non-susceptibility to penicillin and macrolides was mainly observed in serogroups 19, 14, and 6 (by order of decreasing percentage). Single non-susceptibility to penicillins was most common in serogroups 19, 14 and 9, and single non-susceptibility to macrolides was most common in serogroups 19, 1, 14 and 6 (13).

Moore et al (2015) assessed the efficacy of pneumococcal conjugate vaccine (PCV13) by comparing rates of invasive pneumococcal disease in children before and after the introduction of PCV13 in the United States. A time-series model used to compare the reported incidence of IPD to that which would have been expected if PCV13 had not replaced PCV7. The authors determined that the overall incidence of IPD declined by 64% (95%CI 59–68) and IPD caused by PCV13 minus PCV7 serotypes declined by 93% (95%CI 91–94). It was estimated that over 30,000 cases of IPD and 3000 deaths were averted in the first 3 years after the introduction of PCV13 (14).

In a matched case-control study, Moore and colleagues (2016) further assessed the effectiveness of the PCV13 vaccine. A total of 722 cases in children aged 2–59 months with invasive pneumococcal disease were identified through active surveillance in 13 sites. 2991 controls were identified via birth registries and matched to cases by age and postal code. PCV13 serotype cases (30%) included most commonly serotypes 19A (18%), 7F (4%), and 3 (6%). Vaccine effectiveness against all PCV13 serotypes was 86% (95%CI 75.5 to 92.3), 85.6% (95% CI 70.6 to 93.5) for serotypes 19A and 96.5% (82.7 to 100) for serotype 7F. Statistically significant effectiveness against serotype 3 (79.5%, 95%CI 30.3 to 94.8) and against antibiotic non-susceptible invasive pneumococcal disease (65.6%, 44.9 to 78.7) was found. Vaccine effectiveness against all-cause invasive pneumococcal disease was 60.2% (95%CI 46.8 to 70.3) and was similar among children with (81.4%, 95%CI 45.4 to 93.6) and without (85.8%, 95%CI 74.9 to 91.9) underlying conditions (15).

Metcalf and colleagues (2016) analysed invasive pneumococcal isolates recovered from children aged <5 years through Active Bacterial Core surveillance before (2008–2009; n = 828) and after (2011–2013; n = 600) 13-valent pneumococcal conjugate vaccine (PCV13) implementation. PCR/electrospray ionization mass spectrometry and whole genome sequence (WGS) analysis was used to identify serotypes, resistance features, genotypes, and pilus types. PCV13 targeted all major 19A and 7F genotypes, and decreased antimicrobial resistance, primarily owing to removal of the 19A/ST320 complex. The strain complex contributing most to the remaining β-lactam resistance during 2011–2013 was 35B/ST558. Significant emergence of non-vaccine clonal complexes was not evident. Because of the removal of vaccine serotype strains, positivity for one or both pilus types (PI-1 and PI-2) decreased in the post-PCV13 years 2011–2013 relative to 2008–2009 (decreases of 32–55% for PI-1, and >95%
for PI-2 and combined PI-1 + PI-2). Beta-lactam susceptibility phenotypes correlated consistently with transpeptidase region sequence combinations of the three major penicillin-binding proteins (PBPs) determined through WGS analysis. Other major resistance features were predictable by DNA signatures from WGS analysis. Multilocus sequence data combined with PBP combinations identified progeny, serotype donors and recipient strains in serotype switch events. PCV13 decreased the frequency of all PCV13 serotype clones and concurrently decreased the frequency of strain subsets with resistance and/or adherence features conducive to successful carriage (16).

Effect of PCV13 Vaccine on Disease Severity

Klugman et al (2007) evaluated the link between disease severity and serotype in adults. Serotypes covered by the conjugate pneumococcal vaccine (Serotypes 9V, 14, 6B, 18C, 23F, 19F, and 4) were compared to non-vaccine serotypes. No differences were seen in disease severity or associated mortality among patients infected with PCV serotypes, compared with patients infected with non-vaccine serotypes. Invasive pneumococcal disease, older age, underlying chronic disease, immunosuppression and severity of disease were significantly associated with mortality. No association was found between nosocomial infection with invasive serotypes 1, 5, and 7 and mortality. The risk factors meningitis, suppurative lung complications and pre-existing lung disease were significantly associated with disease severity, independent of infecting serotype. Overall, host factors were more important than isolate serotype in determining the severity and outcome of invasive pneumococcal disease in adult patients (17).

3.1.4 New Efficacy Data

The KEMRI-Wellcome Trust Collaborative Research Program conducted a trial (NCT01399723) to assess whether clinical outcome following initial treatment of severe pneumonia with oral amoxicillin is as effective as the current standard benzyl penicillin. 527 children (aged 2-59 months) were recruited to an open-label, multicentre, randomized controlled noninferiority trial for treatment of severe pneumonia which was conducted at 6 Kenyan hospitals. The children were randomized to receive amoxicillin or benzyl penicillin and followed up for the primary outcome of treatment failure at 48 hours. Treatment failure was observed in 20 of 260 (7.7%) and 21 of 261 (8.0%) of patients in the amoxicillin and benzyl penicillin arms, respectively (RD, −0.3% [95%CI, −5.0% to 4.3%]) confirming noninferiority of amoxicillin to benzylpenicillin (18).

In the IndiaCLEN multicentre trial (NCT01386840), the safety and efficacy of oral amoxicillin for severe pneumonia at home or in hospital was compared. In this open labelled multicenter prospective two-arm randomized clinical trial to determine the differences in failure of treatment with a 7 day course of oral amoxicillin administered for first 48 hours in the hospital in comparison to being sent home after enrolment, in children 3 to 59 months old who have severe pneumonia. 1118 children were enrolled and randomized to home (n = 554) or hospital group (n = 564). Overall treatment failure rate was 11.5 % (per protocol analysis). The hospital group was significantly more likely to fail treatment than the home group in the intention to treat analysis. Death rates at 7 or 14 days did not differ significantly. (RD−0.0%; 95%CI −0.5 to 0.5). The median total treatment cost was INR 399 for the home group versus INR 602 for the hospital group (p < 0.001), for the same effect of a 5 % failure rate at the end of 7 days of treatment in the random subsample. Home based oral amoxicillin treatment was equivalent to hospital treatment for the first 48h in selected children and was less expensive (19).

In a Cochrane review, Lodha et al (2013) examined antibiotics for community-acquired pneumonia in children and provided recommendations for countries with high case fatalities due to pneumonia in children without underlying morbidities and where point of care tests for identification of aetiological agents for pneumonia are not available. Twenty-nine trials, which enrolled 14 188 children, comparing multiple antibiotics were included. In ambulatory settings, for non-severe CAP, amoxicillin compared with co-trimoxazole had similar failure rates (OR 1.18, 95% CI 0.91 to 1.51) and cure rates (OR 1.03, 95% CI 0.56 to 1.89). In children with severe pneumonia without hypoxaemia, oral antibiotics (amoxicillin/co-trimoxazole) compared with injectable penicillin had similar failure rates (OR 0.84, 95%
CI 0.56 to 1.24), hospitalisation rates (OR 1.13, 95% CI 0.38 to 3.34) and relapse rates (OR 1.28, 95% CI 0.34 to 4.82). In very severe CAP, death rates were higher in children receiving chloramphenicol compared to those receiving penicillin/ampicillin plus gentamicin (OR 1.25, 95% CI 0.76 to 2.07). Based on these findings, amoxicillin was recommended over co-trimoxazole in treatment of patients with CAP in ambulatory settings with co-amoxiclav and cefpodoxime as alternative second-line drugs. Oral amoxicillin for children with severe pneumonia without hypoxaemia was recommended in an ambulatory setting. For children hospitalised with severe and very severe CAP, penicillin/ampicillin plus gentamicin is superior to chloramphenicol. The other alternative drugs for such patients are co-amoxiclav and cefuroxime (20).

Lassi et al conducted a meta-analysis of trials conducted in LMICs to determine the most suitable antibiotic therapy for treating pneumonia (very severe, severe and non-severe) when examining drug, duration, combination. Randomised controlled trials and quasi-RCTs that assessed the route, dose, combination and duration of antibiotics in the management of WHO-defined very severe/severe/non-severe CAP were included. Study participants included children between 2 and 59 months of age with CAP. 22 studies which enrolled 20,593 children were included in meta-analyses. Evidence from these trials showed a combination of penicillin/ampicillin and gentamicin to be effective for managing very severe pneumonia in children between 2 and 59 months of age, and oral amoxicillin to be equally effective as other parenteral antibiotics for managing severe pneumonia in children of this particular age group. Oral amoxicillin was also found to be effective in non-severe pneumonia. The review further found a short 3 day course of antibiotics to be equally beneficial as 5 day course for managing non-severe pneumonia in children between 2 and 59 months of age (21).

McCollum et al (2015) in a systematic review and expert survey review identified several candidate predictors of oral antibiotic failure not currently utilized in childhood pneumonia referral algorithms; these included excess age-specific respiratory rate, young age, abnormal oxygen saturation, and moderate malnutrition for children 2-59 months of age in resource-limited settings with WHO non-severe pneumonia (either fast breathing for age and/or lower chest wall indrawing without danger signs). An emphasis was placed on predictors not currently utilized for referral and reasonable for community health were reviewed. In nine studies meeting the inclusion criteria, oral antibiotic failure rates ranged between 7.8-22.9%. Six studies found excess age-adjusted respiratory rate (either WHO-defined very fast breathing for age or 10-15 breaths/min faster than normal WHO age-adjusted thresholds) and four reported young age as predictive for oral antibiotic failure (22).

The question of M. pneumoniae spectrum (specifically macrolide) use in CAP is commonly encountered in paediatric practice. Biondi et al (2014) conducted a meta-analysis of children with community-acquired lower respiratory tract infection treated specifically for M. pneumoniae. Sixteen articles detailing 17 studies were included. Several low-quality studies found a reduction in fever duration but the clinical impact of this effect is unclear. Meta-analysis of 5 RCTs showed a pooled risk difference of 0.12 (95% CI, 0.04 – 0.20) favouring treatment with macrolides, tetracyclines or quinolones class antibiotics which was not significant. Overall, the authors contend that there is insufficient evidence to support any conclusions about the efficacy of macrolide treatment of CAP due to M. pneumoniae in children. Future studies should highlight the potential for confounding mixed infections, timing of intervention relative to symptom onset, and testing modalities that include a combination of serology and polymerase chain reaction assays (23).

3.1.5 New Safety Data

There is no new significant findings on safety during the period covered by this evidence update.

3.1.6 Antimicrobial Resistance

Resistance in S. Pneumoniae

Resistance to beta-lactam antibacterial drugs in clinical isolates of S. pneumoniae occurs through the acquisition of mutations in the genes coding for the penicillin binding proteins (PBPs), essential components of the bacterial cell wall. The successive acquisition of multiple mutations in the different
PBPs results in increasing minimum inhibitory concentrations (MICs) for penicillin and the other beta-lactam drugs.

Further efforts are required for surveillance of antimicrobial resistance (AMR) in children. Comparison of the data for macrolide non-susceptibility for *S. pneumoniae* has found statistically significant differences between ARPEC and EARS-net resistance percentages and significant difference between adult and paediatric data (24). It is unclear whether childhood AMR patterns differ from those detected in isolates from adult patients and further research is required in this area.

Globally, larger gaps exist in the availability of penicillin non-susceptibility and resistance data with the majority of reporting coming from three WHO regions: Region of the Americas, the European Region and the Western Pacific Region. Further inconsistencies in terminology and microbiological methods complicate data synthesis.

<table>
<thead>
<tr>
<th>Data sources based on at least 30 tested isolates</th>
<th>Overall reported range of proportion resistant (R) and/or non-susceptible (NS)</th>
<th>Reported range of proportion resistant or non-susceptible resistant in invasive isolates (no. of reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African region (n=5 countries)</td>
<td>3–16 (R) or 57–60 (NS) 1–100 (R) or 9–69 NS or 0–79 b</td>
<td>3 (R) (n=1) 9–18 (NS) or 24–79 b (n=5)</td>
</tr>
<tr>
<td>Region of the Americas (n=16) from 14 additional countries</td>
<td>0–48 b 53 (non-meningitis) (NS)</td>
<td>0–48 b (n=14) 64 (meningitis) (NS)</td>
</tr>
<tr>
<td>Eastern Mediterranean region (n=3 countries)</td>
<td>13–34 (R) or 5 (NS) 0.3–64 (R) or 17–48 (NS) or 0–93 b</td>
<td>34 (R) (n=1) 2–14 (R) or 17–40 (NS) (n=10)</td>
</tr>
<tr>
<td>European region (n=71) from 2 additional countries</td>
<td>0–41 (R) or 0.9–73 (NS) 13–68 (NS)</td>
<td>0.9–61 (NS) or 32–45 b (n=27) 13 (NS) (n=1)</td>
</tr>
<tr>
<td>South-East Asia region (n=2) from 2 additional countries</td>
<td>47–48 b 0–4 (R)</td>
<td>0 (R) (n=1)</td>
</tr>
<tr>
<td>Western Pacific region (n=10) from 2 additional countries</td>
<td>17–64 (NS) or 0–47 b 0–2 44–96 (R) or 0–69 (NS)</td>
<td>44 (R) or 0 (NS) (n=2)</td>
</tr>
</tbody>
</table>

Figure 3: Streptococcus pneumoniae: Resistance or non-susceptibility to penicillin (World Health Organization. Antimicrobial resistance global report on surveillance: 2014 summary)

**Resistance in *M. pneumoniae***

Resistance in *M. pneumoniae* is based on point mutations in domain V of the 23S rRNA which reduce affinity of macrolides to the large subunit (50S) of the bacterial ribosome. In the event of non-response to beta-lactam antibiotics, typically broad-spectrum macrolides are recommended due to diagnostic uncertainty. Meyer Sauteur et al (2016) conducted longitudinal sampling of *M. pneumoniae*-positive asymptomatic children. It was shown that *M. pneumoniae* can be present in the upper respiratory tract without causing disease for up to 4 months, often in co-existence with other pathogens. Macrolide...
resistant *M. pneumoniae* (MRMP) has been observed due to selective pressure. MRMP in children may increase clinical consequences in children leading to increase in extrapulmonary manifestations, skin diseases (18%) and nervous system (7%) complications. Rates of MRMP vary greatly across the globe due in part to local prescribing practices. In some settings, such as China, MRMP rates are as high as 97% (25). Global rates of MRMP have been compiled by Meyer Sauteur and colleagues (2016) and are illustrated in the figure below.

3.1.7 New Acceptability and Feasibility Data

There is no new significant findings on acceptability and feasibility during the period covered by this evidence update.

3.1.8 Emerging Issues

The high prevalence of CAP in children means clinicians and public health experts face ongoing challenges in antibiotic prescribing for children which frame the appraisal of evidence and guide antibiotic choice.

Trial Design

There remain significant hurdles preventing robust meta-analysis in paediatric antibiotic clinical trials. The lack of harmonisation on study design, inclusion/exclusion criteria and endpoints is a major barrier
to comparative analysis and translation into clinical practice. In a systematic review of antibiotic clinical trials in complicated clinical infection syndromes in children and neonates, Folgori et al. (2016) assessed whether standardised European Medicines Agency (EMA) and US Food and Drug Administration (FDA) guidance for adults was used in paediatrics, and whether paediatric clinical trials applied consistent definitions for eligibility and outcomes. Evaluation of 82 studies – including 24 community acquired pneumonia studies – showed that study design, inclusion and exclusion criteria, and endpoints varied substantially across the included studies.

With regards to inclusion criteria, only 12 (50%) of 24 community-acquired pneumonia studies referred to a single definition for childhood acute respiratory infections provided by WHO. Adult and paediatric CAP guidelines differ in a number of areas. Mandatory imaging is typically not an inclusion criterion for children. The effect of underlying disorders, such as asthma, are often mentioned in paediatric clinical trials but are not mentioned in adult trials. Furthermore, heterogeneity was evident when evaluating the timing of assessment of clinical endpoints in paediatric trials compared with adult European Medicines Agency guidelines.

A lack of comprehensive regulatory guidance on design and conduct hampers antibiotic clinical trials in neonates and children. To improve comparison of therapies and strategies, international collaboration among all relevant stakeholders leading to harmonised case definitions and outcome measures is needed (26). The EMA will be producing a pediatric Addendum on antibiotic trial design in 2017. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500205026.pdf)

Dosing and Formulation

There are additional complexities in defining optimal drug dosing in children as antibiotic doses need to achieve optimal clinical effectiveness, be adapted to maturational changes in pharmacokinetics, consider changes in pharmacodynamics associated with increasing antimicrobial resistance, yet still be simple and pragmatic. Daily doses at the upper end of the recommended dose spectrum may be needed to adequately treat infection when there is a high prevalence of pneumococcal penicillin resistance. However, side effects, such as diarrhea, from exceeding the recommended range may result in poor adherence (27).

Selection of formulation plays an important role in meeting the recommended doses. Solid formulations, such as dispersible tablets, can be difficult to divide sufficiently to produce exact doses for all children and splitting and crushing adult tablets can lead to inaccuracies. Liquid formulations are the most
flexible but there is increased inaccuracy with dosing of small liquid volumes. Furthermore, liquid formulations often require refrigeration and may be difficult to transport and store. Unpalatable medicines add to the complexity in children. Practically, dosing of liquids in children is dictated by the smallest volume that can be reliably measured by parents with the provided spoon or syringe. This must be balanced against the largest acceptable single dose volume for an often unpleasant tasting medicine (27).

Bielicki and colleagues simulated dose selection based on each of these key standards (exact weight, weight banded, age banded) demonstrating the strengths and weaknesses of each method. The most accurate method was to select the dose by weighing the child, but this is difficult to carry out in many settings. Weight banding often resulted in doses outside of the therapeutic range of the drug. While the simplest method of dose selection is to use age as a proxy measure for weight, in practice this is often the least accurate method. Age banded dose selection has some advantages, especially for drugs with a wide therapeutic index, when recent weight is unavailable. However, age bands need to be defined to reflect rapid changes in weight (especially during the first six months of life and around 8 to 9 years of age), accounting for weight being normally distributed around the 50th centile for age, and adapted to locally relevant weight for age standards (27).

<table>
<thead>
<tr>
<th>Total daily dose (mg/kg)</th>
<th>No (%) with total dose &lt;40 mg/kg</th>
<th>No (%) with total dose &gt;90 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exact weight</td>
<td>70 (68-72)</td>
<td>0</td>
</tr>
<tr>
<td>Weight banded</td>
<td>57 (51-65)</td>
<td>53 (6)</td>
</tr>
<tr>
<td>Age banded</td>
<td>60 (49-75)</td>
<td>74 (7)</td>
</tr>
<tr>
<td>Africa:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exact weight</td>
<td>70 (68-72)</td>
<td>0</td>
</tr>
<tr>
<td>Weight banded</td>
<td>61 (53-68)</td>
<td>83 (11)</td>
</tr>
<tr>
<td>Age banded</td>
<td>72 (58-96)</td>
<td>100 (3)</td>
</tr>
</tbody>
</table>

Figure 6 Total daily doses of amoxicillin in simulation of three dose selection approaches in 1037 children from UK and 252 from Africa (Bielicki 2015)

Practical considerations clearly influence preferences for a specific approach. The advantages and disadvantages of each approach are summarised below (Figure 8).

<table>
<thead>
<tr>
<th>Requires up to date weight of child</th>
<th>Exact weight</th>
<th>Weight bands</th>
<th>Age bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accounts for body characteristics</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Requires locally applicable weight for age data</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Allows use of commonly available measuring devices (fixed single dose)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific to recommended dosing frequency (twice or three times daily)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 7 Features of different dose selection approaches for oral antibiotic treatment in childhood (Bielicki 2015)

There is a striking lack of harmony in international paediatric antibiotic dosing guidelines. The US and much of continental Europe favour exact weight based dosing, the UK applying age banded dosing, and the World Health Organization recommending weight banded dosing. International agreement has been achieved for weight banded dosing in antiretroviral medications for HIV infection. Similar consensus is required for dosing in paediatric antibiotics (27). This is a wider issue than for CAP. Current paediatric antibiotic dosing guidelines are provided for the United States through the Red Book, in Europe by the Blue Book and in the UK by the BNF for Children. The WHO provides dosing recommendations for some clinical infections only.

**Potential reconsideration of Current Dosing Age-Bands**

A revision of age-bands could be considered at some point to ensure therapeutic levels while maintaining a twice-daily schedule. This is intended to prevent over- or under-dosing of children at
extremes of the current banding. It has been previously demonstrated (28-31) that a twice-daily dosage regimen appears to be as effective and safe as more frequent dosing. This was taken into account for the 2014 Evidence Update as a twice-daily schedule has advantages for caregivers and improves adherence.

Under the current WHO CAP dosing regimen (Table 1), a child of age 12 months (10 kg) prescribed a single 250 mg dispersible tablet would receive only 25 mg/kg/dose. This is less than the lower limit of the recommended dosing from international guidelines and pharmacokinetic studies (28). Consulting international guidelines for this age, 12 months, the Blue Book (32) recommends 15–30mg/kg/dose given three times daily with the higher dose being given in severe infections, the BNFC recommends 375mg/day and the IDSA/PIDS (33) recommend 90 mg/kg/day. In light of this, consideration could be given whether to revise this first age-band receiving a single 250 mg dispersible tablet to have an upper limit of 6 months and 7 kg (36 mg/kg/dose). The second age-band receiving two 250 mg amoxicillin tablets would then be revised to have a lower age of 6 months and now receiving around 60 mg/kg/dose. These recommendations are summarized in Table 2 below.

Furthermore, dosing recommendations for children over the age of 5 were not included in the 2014 Evidence Update. For children ages 5-12 years, the Blue Book (32) recommends 15–30mg/kg/dose given three times daily, the BNFC recommends 1500 mg/day and the IDSA/PIDS (33) recommend 90 mg/kg/day. For the adolescent age group, there is equal difficulty in balancing the dosing targets and pragmatic simplicity of guidance that would be appropriate for the CHWs in the LMIC setting.

Possible changes have been summarised into the table below, with children under 5 years always being dosed in multiples of 250 mg tablets and children over 5 years of age always receiving multiples of 500 mg tablets.

### Table 1: Current Dosing Regimen from 2014 CAP Evidence Update

<table>
<thead>
<tr>
<th>Age (Weight in kg)</th>
<th>Dosage of Amoxicillin Dispersible Tablets (250 mg)</th>
<th>Dose (mg/dose)</th>
<th>Max. dose in weight-band (mg/kg/dose)</th>
<th>Min. dose in weight-band (mg/kg/dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months up to 12 months (4–&lt;10 kg)</td>
<td>1 tab twice a day x 5 days (10 tabs)</td>
<td>250 mg</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>12 months up to 3 years (10–&lt;14 kg)</td>
<td>2 tabs twice a day x 5 days (20 tabs)</td>
<td>500 mg</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>3 years up to 5 years (14–19 kg)</td>
<td>3 tabs twice a day x 5 days (30 tabs)</td>
<td>750 mg</td>
<td>53</td>
<td>39</td>
</tr>
</tbody>
</table>

### Table 2: Potential adjusted Dosing Regimen

<table>
<thead>
<tr>
<th>Age (Weight in kg)</th>
<th>Dosage of Amoxicillin Dispersible Tablets</th>
<th>Dose (mg/dose)</th>
<th>Max. dose in weight-band (mg/kg/dose)</th>
<th>Min. dose in weight-band (mg/kg/dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months up to 6 months (4–&lt;7 kg)</td>
<td>1 (250mg) tab twice a day x 5 days (10 tabs)</td>
<td>250 mg</td>
<td>63</td>
<td>36</td>
</tr>
<tr>
<td>6 months up to 3 years (7–&lt;14 kg)</td>
<td>2 (250mg) tabs twice a day x 5 days (20 tabs)</td>
<td>500 mg</td>
<td>63</td>
<td>36</td>
</tr>
</tbody>
</table>
### Table 2: Recommendations for an amended dosing regimen

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage Details</th>
<th>Total Daily Dose</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years up to 5 years</td>
<td>3 (250mg) tabs twice a day x 5 days (30 tabs)</td>
<td>750 mg</td>
<td>39</td>
</tr>
<tr>
<td>(14–&lt;19 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years up to 12 years</td>
<td>2 (500mg) tabs twice a day x 5 days (20 tabs)</td>
<td>1000 mg</td>
<td>53</td>
</tr>
<tr>
<td>(19–&lt;38 kg)</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>12 years and above</td>
<td>3 (500mg) tabs twice a day x 5 days (30 tabs)</td>
<td>1500 mg</td>
<td>39</td>
</tr>
<tr>
<td>(&gt;38 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using this structure all children can be dosed with either 250 mg or 500 mg tablets and 125 mg tablets are not required.

**Total daily doses of amoxicillin are recommended to be within the range of 80–120 mg/kg/day with the daily maximum of 4g.**

Antibiotic dosing plays an important role in adverse events. Antibiotic-associated diarrhoea (AAD) is a well-recognized adverse reaction to amoxicillin. In a review of reported rates of AAD following oral penicillin treatment in paediatric clinical trials, Kuehn et al (34) quantified the evidence and elucidated the dearth of strong evidence in this field. From the pool of 7729 paediatric patients, 17.9% had AAD. For amoxicillin, the pooled rate from 6 studies was 8.1% (range 1.87% - 17.5%). However, there were no demonstrable correlation between dose of amoxicillin and rate of AAD. Importantly, there was an association of oral penicillin associated diarrhoea with age. Younger children aged 1 month to 2 years experienced higher rates of ADD (18%) than children aged 2 to 7 (4%) and those older than 7 years (2%). While AAD is important to consider, the precise mechanism and robust evidence of a dose to AAD rate response remains to be demonstrated. Further work is required to assess the role of dose and duration on AAD rates and to include diarrhoea, using a standardized definition, as an outcome measures of RCTs.

**Pharmacokinetics**

Optimisation of use of the currently available antibiotics plays an increasing role as few new drugs are becoming available in an era of antimicrobial resistance. Virtually all of the new antibiotics currently in phase I/II and III development are only for intravenous use. Available antibiotics need to be optimised with respect to MIC, efficacy and exposure to ensure adequate clinical outcomes. Despite the longstanding global use of oral amoxicillin, there have only been a few studies of its pharmacokinetics. The COMBACTE-NET group (2016) produced for the first time ever, very detailed models of oral amoxicillin/clavulanic acid tablet pharmacokinetics in 14 male patients. One group received 875/125 mg twice daily and then 500/125 mg three times daily and the other group 500/125 mg twice daily and 250/125 mg three times daily. A total of 1428 amoxicillin blood samples were collected before and after administration. AUC\(_{0-24}\) and C\(_{\text{max}}\) increased non-linearly with dose. Interestingly, oral amoxicillin absorption was non-linear and appeared to be saturable. High-dose as well as twice-daily regimens were less favourable than regimens with lower doses and higher frequency. Although it is clear that the balance between dose and frequency should be optimal to maximize antimicrobial efficacy and to minimize the risk of adverse events and the choice of dosing regimens should be rooted in robust PK/PD modelling, this level of detailed PK/PD data for amoxicillin is currently just not available for children (35).

**Duration of Treatment: Intravenous to Oral Switch**

Few studies are available to inform duration of intravenous antibiotics for children and when it is safe and appropriate to switch to oral antibiotics. Shorter antibiotic courses can potentially affect antimicrobial resistances. McMullan et al (2016) systematically reviewed antibiotic duration and timing of intravenous to oral switch for 36 paediatric infectious diseases and developed recommendations for antibiotic duration and intravenous to oral switch. The minimum intravenous and total antibiotic duration required to achieve outcomes similar to or better than those with traditional longer durations were identified. The minimum intravenous antibiotic duration was zero days, for severe or complicated CAP.
initial intravenous treatment was recommended based on expert opinion. The criterion for switch to oral antibiotic was clinical improvement. The minimum total antibiotic duration was 3 days for mild CAP and fewer than or equal to 7 days for moderate or severe uncomplicated CAP. Oral antibiotics were deemed acceptable for most children requiring hospital admission (36).

In a Cochrane review, Lassi and colleagues (2015) looked at randomised controlled trials evaluating the efficacy of short-course (two to three days) versus long-course (five days) intravenous antibiotic therapy for severe pneumonia in children aged two months to 59 months. Children with debilitating disease, HIV infection, very severe pneumonia and nosocomial pneumonia were excluded. 2352 studies were identified, however none fulfilled the inclusion criteria (37).

Role of Antimicrobial Treatment on Resistance

Malhotra-Kumar et al (2016) utilized oropharyngeal streptococci as model organisms to determine the effect of amoxicillin treatment on resistance selection in a randomized, placebo-controlled trial. Patients were prescribed amoxicillin 1 g, three times daily or placebo for 7 days. Oropharyngeal swabs obtained before, within 48h post-treatment and at 28–35 days were assessed for proportions of amoxicillin-resistant and non-susceptible streptococci. Amoxicillin resistant (ARS) and non-susceptible (ANS) proportions increased 11- and 2.5-fold, respectively, within 48h post-amoxicillin treatment compared with placebo. However, these differences were no longer significant at days 28–35 (38).

Amoxicillin use was strongly associated with increased carriage of amoxicillin-resistant bacteria. Furthermore, amoxicillin use selects for increased carriage of streptococci harbouring higher amoxicillin MICs and fitness costs. However, resistance selection in patients receiving amoxicillin was modest and short-lived, probably due to ‘fitness costs’ engendered by high-level resistance-conferring mutations (38). There is a clear need for further trials with resistance outcomes.

Targeting Antibiotics in Primary Care Settings for High Risk Children

Antibiotic prescriptions are common in young children making use of primary care services for respiratory tract infections due to the lack of certainty of disease severity and risk of poor outcome. In a large, multicentre prospective observational study the TARGET study group work to derive and validate a clinical prediction rule to identify children presenting to primary care with respiratory tract infections who are at risk of hospitalisation. Throat swab, symptom diary and a review of medical notes will be assessed to develop a clinical decision making tool (39).

Hay et al (2016) have recently published a clinical rule aimed to reduce clinical uncertainty and unnecessary antibiotic prescriptions for children seen in primary care setting by stratifying risk to very low, normal, and high risk of future hospital admission for respiratory tract infection. In a prognostic cohort study from 247 general practitioner practices in England, 8934 children (aged 3 months to 16 years) presenting with acute cough (for ≤28 days) and respiratory tract infection were recruited and included in analysis. A points-based clinical rule (one point per characteristic) consisting of short illness, temperature, age, recession, wheeze, asthma, and vomiting (mnemonic STARWAVe; AUROC 0.81, 0.76–0.85) distinguished three hospital admission risk strata: very low (0·3%, 0·2–0·4%) with 1 point or less, normal (1·5%, 1·0–1·9%) with 2 or 3 points, and high (11·8%, 7·3–16·2%) with 4 points or more (40).

3.1.9 Summary of International Guidelines

We also reviewed recently published international clinical practice guidelines. These included clinical practice guidelines from the British National Formulary for Children (BNFC), Royal College of Paediatrics and Child Health (RCPCH) and European Society for Paediatric Infectious Diseases (ESPID), Canadian Pediatric Society (CPS), British Thoracic Society (BTS) and Pediatric Infectious Diseases Society (PIDS).

The BNFC recommends benzylpenicillin with gentamicin for neonatal sepsis of all causes. For children, 1 month – 18 years, oral amoxicillin is recommended as first line for CAP and clarithromycin is recommended if there is no response to treatment. For suspected staphylococcal infection, oral amoxicillin and flucloxacillin or co-amoxiclav alone are recommended when possible. In cases where
septicaemia, complicated pneumonia, or if oral administration not possible, treatment with intravenous amoxicillin or co-amoxiclav or cefuroxime or cefotaxime should be initiated. The suggested duration of treatment is 7 days. For children 1 month–18 years with allergy to penicillin, clarithromycin is recommended for 7 days treatment (BNFC).

The Manual of Childhood Infections (2016) or ‘Blue Book’ is developed through a partnership between the Royal College of Paediatrics and Child Health (RCPCH) and the European Society for Paediatric Infectious Diseases (ESPID). For children <5 years of age, oral amoxicillin for a standard course of 5 days is the first choice antibiotic. Macrolides are recommended if either Mycoplasma or C. pneumoniae is suspected. IV antibiotics used in Europe for severe pneumonia include penicillin/amoxicillin, co-amoxiclav, cefuroxime, and cefotaxime/ceftriaxone (32).

The British Thoracic Society (2011) recommends amoxicillin as first choice for oral antibiotic therapy in all children because it is effective against the majority of pathogens which cause CAP in this group, is well tolerated and cheap. Alternatives are co-amoxiclav, cefaclor, erythromycin, azithromycin and clarithromycin. Macrolide antibiotics may be added at any age if there is no response to first-line empirical therapy. Macrolide antibiotics should be used if either mycoplasma or chlamydia pneumonia is suspected or in very severe disease. In pneumonia associated with influenza, co-amoxiclav is recommended (3).

The Canadian Pediatric Society practice points (2015) recommend that outpatients with lobar or broncho-pneumonia be treated with oral amoxicillin. Patients who require hospitalization but do not have a life-threatening illness should usually be started empirically on intravenous ampicillin. Empiric therapy with a third-generation cephalosporin is recommended for children who experience respiratory failure or septic shock associated with pneumonia. Ceftriaxone or cefotaxime are recommended for beta-lactamase-producing H. influenzae and high-level penicillin-resistant pneumococcus. For rapidly progressing multilobar disease or pneumatoceles, the addition of vancomycin is suggested empirically with de-escalation to ampicillin with subsequent oral amoxicillin. If the empyema is due to S aureus, then vancomycin. If S. pneumoniae is detected in blood or respiratory secretions and is penicillin-susceptible, treatment with either intravenous ampicillin or penicillin is recommended, followed by oral therapy with amoxicillin. Treatment for M. pneumoniae and C. pneumoniae is azithromycin for five days. In children ≥8 years of age (minimum), doxycycline is likely to be effective against such strains (41).

The European Society for Paediatric Infectious Diseases 2012 guidance recommends for children < 1 month, ampicillin/amoxicillin and aminoglycosides (gentamicin). If Listeria or enterococcus is suspected, ampicillin with an alternative of cephaparin is recommended. Third-generation cephalosporins in neonates should be avoided because of the risk of Candida. For critically ill patients antistaphylococcal penicillin and clindamycin or vancomycin are recommended. For children, 1-3 months, beta-lactam antibiotics with antistaphylococcal penicillin for critically ill are recommended. For children with no fever or severe cough, C. trachomatis and B. pertussis should be suspected and treated with macrolides. For children, children 3 months to 5 years, penicillin G or aminopenicillins are recommended to ensure adequate cover for S. pneumoniae and more atypical pathogens in this age group. For children who are not immunised, treatment with amoxiclav or third generation cephalosporin is recommended. Second generation cephalosporins may be used in areas of low penicillin resistance. For atypical pathogens, betalactams and macrolide are recommended as well as antistaphylococcal antibiotics in critically ill (42).

For children under 5 years old, IDSA/PIDS guidelines (2011) recommend amoxicillin, amoxicillin clavulate in presumed bacterial pneumonia and macrolides (azithromycin, clarithromycin or erythromycin) for presumed atypical pathogens. For children over 5 years old, amoxicillin, amoxicillin clavulante and a macrolide can be added. Doxycycline is recommended for children >7 years old (43).

### 3.2 Findings: Costs of treatment

**Cost of Management**

Zhang et al (2016) conducted a systematic review of 24 published and 10 unpublished studies including a total of 95 000 children with pneumonia from both low– and–middle income countries (LMIC) and high–income countries (HIC) covering all 6 WHO regions. The cost of management per episode of
severe pneumonia in children younger than 5 years old was US$ 4.3 (95% CI 1.5–8.7) in community, US$ 51.7 (95% CI 17.4–91.0) in out-patient facilities and US$ 242.7 (95% CI 153.6–341.4)–559.4 (95% CI 268.9–886.3) in different levels of hospital in–patient settings in LMIC. It is important to note that these figures for inpatient treatment were estimated to be 26.6%–115.8% of patients’ monthly household income in LMIC. The mean length of stay in hospital for children with severe pneumonia was 5.8 (IQR 5.3–6.4) and 7.7 (IQR 5.5–9.9) days in LMIC and HIC respectively (44).

Per year, the cost of antibiotic treatment for all children with pneumonia in 66 of the Countdown to 2015 countries has been estimated at around US$109 million. This price includes both antibiotics and diagnostics for pneumonia management (4).

Cost per Treatment Course of Antibiotic Therapy

Costs per treatment course of antibiotic therapy were calculated using the International Drug Price Indicator Guide (https://www.msh.org/resources/international-drug-price-indicator-guide) from the Management Sciences for Health (MSH). Costs were calculated using the median price buyer prices for 2014 (latest available) for a representative 20 kg child.

<table>
<thead>
<tr>
<th>Drug and Dosage</th>
<th>Strength and Dosage Form</th>
<th>Median Price</th>
<th>Cost per treatment course for 20kg child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin PO (40mg/kg bid)</td>
<td>125 mg/5 ml suspension</td>
<td>0.0090 /ml</td>
<td>US$ 2.88 (5 days) US$ 1.73 (3 days)</td>
</tr>
<tr>
<td></td>
<td>250 mg/5 ml suspension</td>
<td>0.0063 /ml</td>
<td>US$ 2.07 (5 days) US$ 1.24 (3 days)</td>
</tr>
<tr>
<td>Gentamicin INJ (7.5 mg/kg qd)</td>
<td>10 mg/ml ampoule</td>
<td>0.0942 /ml</td>
<td>US$ 7.07 (5 days)</td>
</tr>
<tr>
<td></td>
<td>40 mg/ml ampoule</td>
<td>0.0802 /ml</td>
<td>US$ 1.50 (5 days)</td>
</tr>
<tr>
<td>Ampicillin INJ (50 mg/kg q6h)</td>
<td>1 g vial</td>
<td>0.2720 /vial</td>
<td>US$ 5.44 (5 days)</td>
</tr>
<tr>
<td></td>
<td>500 mg vial</td>
<td>0.3313 /vial</td>
<td>US$ 13.25 (5 days)</td>
</tr>
<tr>
<td></td>
<td>250 mg vial</td>
<td>0.5294 /vial</td>
<td>US$ 42.35 (5 days)</td>
</tr>
<tr>
<td>Benzyl penicillin INJ (50 000 IU/kg q6h)</td>
<td>1m IU powder</td>
<td>0.3238 /vial</td>
<td>US$ 6.48 (5 days)</td>
</tr>
<tr>
<td></td>
<td>3m IU powder</td>
<td>0.2164 /vial</td>
<td>US$ 1.44 (5 days)</td>
</tr>
<tr>
<td>Ceftriaxone INJ (80 mg/kg qd)</td>
<td>1 g vial</td>
<td>0.4192 /vial</td>
<td>US$ 3.35 (5 days)</td>
</tr>
<tr>
<td></td>
<td>500 mg vial</td>
<td>0.4610 /vial</td>
<td>US$ 7.38 (5 days)</td>
</tr>
<tr>
<td></td>
<td>250 mg vial</td>
<td>0.5726 /vial</td>
<td>US$ 18.32 (5 days)</td>
</tr>
</tbody>
</table>

3.3 Findings: Ongoing clinical trials

There are several clinical trials for antibiotics for the treatment of community acquired pneumonia registered on ClinTrialsGov.

A study based at Beijing Children's Hospital (NCT02775968) is investigating the population pharmacokinetics of cephalosporins and macrolide antibiotics in children for treatment of community acquired pneumonia, and aiming to correlate it with treatment effectiveness and incidence of adverse effects. The study start date is August 2016 with an estimated enrollment of 750 and completion date of October 2022 (45).

A phase 2/3, randomized, open-label, active control, multi-center study (NCT02605122) to assess the safety and efficacy of solithromycin in children and adolescents with community-acquired pneumonia is being conducted under the sponsorship of Cempra Inc. Solithromycin will be compared to the standard
A Canadian randomized controlled double-blind non-inferiority clinical trial (NCT02380352) will determine whether five days of high-dose amoxicillin leads to comparable rates of early clinical cure compared with 10 days of high-dose amoxicillin for previously healthy children with mild community-acquired pneumonia. In the experimental arm patients will be given 5 days amoxicillin 90 mg/kg/day divided three times a day followed by 5 days placebo three times a day. The active comparator arm will be given 5 days amoxicillin 90 mg/kg/day divided three times a day followed by alternate formulation 5 days amoxicillin 90 mg/kg/day divided three times a day. Estimated enrollment for the study is 270 patients with an start date of March 2016 and completion date of May 2018 (47).

The National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring a multi-center, randomized, double-blind, placebo-controlled, superiority clinical trial (NCT02891915) to test the effectiveness of short (5-day) vs standard (10-day) course therapy in children who are diagnosed with CAP and initially treated in outpatient clinics, urgent care facilities, and emergency departments. Primary objective is to compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days). The study start date is October 2016 and completion date is March 2019 with an estimated enrollment of 400 patients (48).

A Malaysian trial (NCT02258763) is being conducted to determine, in children hospitalized with pneumonia, if an extended duration of oral antibiotics (10 days) will be superior to a shorter duration (3 days) of antibiotics in improving clinical outcomes. Patients on the experimental arm will receive amoxicillin-clavulanate 22.5mg/kg/dose bd for 10 days while the comparator arm will receive amoxicillin-clavulanate 22.5mg/kg/bd for 3 days followed by another 7 days of placebo medication given at the same dose and frequency. The study was started in November 2014 with an estimated enrollment of 300 and an estimated completion date of December 2018 (49).

Two clinical trials investigating amoxicillin in childhood pneumonia are being conducted in Malawi. In a trial (NCT02760420) sponsored by Save the Children, the effectiveness of no antibiotic treatment for fast breathing, community-acquired childhood pneumonia is being compared to amoxicillin therapy. Patients in the placebo arm will be given 250 mg of placebo (dispersible tablet) in two divided doses based on age bands (500 mg/day for children 2 months up to 12 months, 1000 mg/day for children 12 months up to 3 years, and 1500 mg/day for children 3 years up to 5 years of age). The active comparator arm will receive 3 Days of 250 mg amoxicillin (dispersible tablet) DT in two divided doses based on age bands (500 mg/day for children 2 months up to 12 months, 1000 mg/day for children 12 months up to 3 years, and 1500 mg/day for children 3 years up to 5 years of age). The estimated enrollment is 2000 patients with the study running from June 2016 to September 2018 (50).

In the same setting, another trial (NCT02678195) will compare 3 days versus 5 days of treatment for chest-indrawing pneumonia. The experimental arm will receive 3 days amoxicillin and 2 days placebo while the comparator arm will receive 5 days amoxicillin. The study is slated to run from March 2016 to August 2018 with an estimated enrollment of 2000 patients (51). A one-arm safety intervention (NCT02878031) based in Nigeria will evaluate the role of community case management in the treatment of chest indrawing pneumonia with oral amoxicillin. The primary objective is to assess if community health workers can safely and appropriately manage chest indrawing pneumonia in 2-59 month old children, and refer children with danger signs. Approximately 308 children 2-59 months of age with chest indrawing pneumonia will be included in the study running from October 2016 to July 2017 (52).

In a double blind efficacy study, entitled RETAPP (NCT02372461) investigators based at Aga Khan University in Karachi, Pakistan are comparing standard amoxicillin treatment with placebo in poor urban slum settings in South Asia. The study is running from November 2014 to July 2017 with an enrollment of 2500 (53). Investigators in the United Kingdom are initiating multi-centre, randomised double-blind placebo-controlled 2x2 factorial non-inferiority trial of amoxicillin dose and duration in paediatric CAP (CAP-IT). Efficacy, safety and impact on antimicrobial resistance of duration and dose of amoxicillin treatment will
be assessed in children aged 1 to 5 years presenting to A&E or Paediatric Assessment Unit (PAU) with a clinical diagnosis of CAP in whom the decision has been made to treat with antibiotics. Participants will be randomised to four treatment groups: Shorter course and lower dose (3 days at 35-50mg/kg/day), longer course and lower dose (7 days at 35-50mg/kg/day), shorter course and higher dose (3 days at 70-90mg/kg/day), and longer course and higher dose (7 days at 70-90mg/kg/day). Expected recruitment is 2400 recruited over 2 years. (http://www.nets.nihr.ac.uk/projects/hta/138811)

4 Conclusion

The data presented above demonstrates that there is no evidence to recommend amending the current 2014 ‘Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities’, either in terms of drug choice, dosing or duration. Recent systematic reviews support the 2014 recommendations and no new trial evidence counters this view. This review has not focussed on recent aetiology studies, or other data on advances in molecular diagnostics (eg pneumococcal DNA load) predicting viral or bacterial respiratory infection. A number of CAP amoxicillin trials are underway comparing varying dose and duration regimens, although there has been limited harmonisation as yet of study design. Not all of these trials may be relevant to the LMIC setting. Few trials as yet are including AMR outcomes, making assessment of optimal treatment recommendations at a population level from an AMR perspective not currently possible.

A number of emerging themes have been identified.

1. The optimal or dosing recommendation for amoxicillin still remains unclear. There are concerns from recent adult PK data about twice daily dosing in settings of high pneumococcal resistance. Do 250 mg amoxicillin dispersible tablets cover all the paediatric dosing requirements?

2. It is unclear whether amoxicillin or broader spectrum antibiotics are most commonly being used to treat community and hospital paediatric CAP in different WHO regions. It is difficult to assess the uptake and implementation of the 2014 WHO CAP guidance.

3. There remains no globally relevant head-to-head pragmatic trial directly comparing the effectiveness of amoxicillin with an oral cephalosporin and a macrolide. Data is lacking on both clinical efficacy in the context of higher rates of both pneumococcal and mycoplasma resistance and the relative contributions of varying first line options to the selection of such resistance.

4. The optimal antibiotic management of severe pneumonia in older hospitalised children remains unclear.
5 References


