The Expert Committee endorsed the inclusion of amoxicillin and phenoxy methylpenicillin as first-choice therapy options and of amoxicillin + clavulanic acid or doxycycline as second-choice therapy in mild to moderate CAP. For severe CAP in adults, the Expert Committee endorsed the inclusion of ceftriaxone or cefotaxime in combination with clarithromycin (EML) as first-choice and amoxicillin + clavulanic acid in combination with clarithromycin as second-choice therapy. For severe CAP in children, the Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid; ceftriaxone or cefotaxime (EMLc); and gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin (EMLc).

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community rather than within the health-care system. Patients of advanced age or with comorbid conditions or greater severity of illness are more likely to be hospitalized. Although there is consensus that Streptococcus pneumoniae is the most common bacterial cause of CAP, the need for so-called “atypical coverage” of pathogens such as Chlamydia pneumoniae, Mycoplasma or Legionella with antibiotics such as macrolides or fluoroquinolones has been controversial. The emergence of macrolide and fluoroquinolone resistance in the community has created concern, and the need for these medicines in addition to antibiotics with antipneumococcal coverage has been debated. The following summary considers the CAP syndrome review conducted by the McMaster Group, and the review of CAP guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.
with chloramphenicol (RR 0.71; 95% CI 0.51–1.00) (9). The failure rate, however, was lower with ampicillin and gentamicin.

Children with very severe pneumonia showed no significant decrease in mortality with antibiotic therapy for pneumonia in children in low- and middle-income countries. Amoxicillin and against the inclusion of oral third-generation cephalosporins on the EML.

The pooled estimate of two studies involving children with mild to moderate illness was also demonstrated in a recent non-inferiority cluster RCT (6). The trial randomized patients to beta-lactams, a combination of beta-lactams and atypical antibiotics, or to fluoroquinolones. The 90-day mortality was 9.0%, 11.1% and 8.8%, respectively. Compared to the beta-lactam strategy, the risk differences (RD) for 90-day mortality were 1.9% (90% CI −0.6 to 4.4) with the beta-lactam/macrolide strategy and −0.6% (90% CI −2.8 to 1.9) with the fluoroquinolone strategy. The results indicated non-inferiority of the beta-lactam/macrolide strategy. These data are of particular relevance, because it does not appear that adding atypical antibiotics to beta-lactam antibiotics makes a clinically important difference, at least for patients presenting with mild to moderate CAP. Whether atypical coverage is required for CAP has been an important concern; another question is whether there is a difference between fluoroquinolones and macrolides.

A review of 5 RCTs for inpatients addressed this question and reported no difference between fluoroquinolones and macrolides for mortality (RR 1.14; 95% CI 0.84–1.55). However, only one study compared a beta-lactam with a beta-lactam plus a macrolide. The width of the confidence intervals exceeds that specified by the applicants for similarity (i.e. within 5%) and these results therefore do not contribute to antibiotic selection. Although there was no difference in overall adverse events between the groups, gastrointestinal events were less common in the atypical group (RR 0.70; 95% CI 0.53–0.92). A 2015 review (16 RCTs; 4809 participants) reported no difference in mortality between fluoroquinolones and beta-lactam/macrolide combinations (RR 0.99; 95% CI 0.70–1.40), but wide confidence intervals limited inferences (5). However, a reduction in clinical failure with fluoroquinolones was reported (RR 0.72; 95% CI 0.57–0.91). Overall, while these findings may be useful in helping clinicians to select antibiotics, the large number of antibiotics being compared was not considered by the applicants to be helpful for informing selection of antibiotics for the EML.

The lack of additional benefit of atypical antimicrobials in patients with CAP with mild to moderate illness was also demonstrated in a recent non-inferiority cluster RCT (6). The trial randomized patients to beta-lactams, a combination of beta-lactams and atypical antibiotics, or to fluoroquinolones. The 90-day mortality was 9.0%, 11.1% and 8.8%, respectively. Compared to the beta-lactam strategy, the risk differences (RD) for 90-day mortality were 1.9% (90% CI −0.6 to 4.4) with the beta-lactam/macrolide strategy and −0.6% (90% CI −2.8 to 1.9) with the fluoroquinolone strategy. The results indicated non-inferiority of the beta-lactam strategy. These data are of particular relevance, because it does not appear that adding atypical antibiotics to beta-lactam antibiotics makes a clinically important difference, at least for patients presenting with mild to moderate CAP. Whether atypical coverage is required for CAP has been an important concern; another question is whether there is a difference between fluoroquinolones and macrolides. A review of five RCTs for inpatients addressed this question and reported no difference between fluoroquinolones and macrolides for mortality (RR 1.13; 95% CI 0.65–1.98) (7). The confidence intervals are relatively wide and the results do not allow either protection or harm from fluoroquinolones compared with macrolides to be inferred. Children A 2013 Cochrane review of antibiotics within an outpatient or hospital setting (29 RCTs; 14 188 children) showed that cure rates with amoxicillin were similar to those with sulfamethoxazole + trimethoprim (SMX–TMP) (odds ratio (OR) 1.03; 95% CI 0.56–1.89) (8). In this review, “cure” referred to an absence of symptoms at the end of treatment, “failure” was the presence of a sign at the end of treatment, and “relapse” was defined as recurrence of disease in follow-up of a patient after cure. Given the wide confidence intervals (i.e. >10%), these data were not considered by the applicants to inform the proposal of antibiotics for the EML. Amoxicillin resulted in better cure rates than amoxicillin + clavulanic acid (RR 10.44; 95% CI 0.29–38.2), suggesting that amoxicillin alone may be preferred. Failure rate at 21 days was greater for chloramphenicol compared with amoxicillin and gentamicin (OR 1.43; 95% CI 1.03–1.98). The applicants considered that this important evidence supported non-inclusion of chloramphenicol on the EML and inclusion of amoxicillin and gentamicin. Cure rate was significantly greater for amoxicillin compared with cefpodoxime (OR 0.20; 95% CI 0.08–0.53), which argues for the inclusion of amoxicillin and against the inclusion of oral third-generation cephalosporins on the EML. Another systematic review examined antibiotic therapy for pneumonia in children in low- and middle-income countries. The pooled estimate of two studies involving children with very severe pneumonia showed no significant decrease in death rates between ampicillin and gentamicin compared with chloramphenicol (RR 0.71; 95% CI 0.51–1.00) (9). The failure rate, however, was lower with ampicillin and gentamicin.
compared with chloramphenicol (RR 0.79; 95% CI 0.66–0.94). On this basis, and because of its potential toxicity, chloramphenicol was not proposed by the applicants for inclusion on the EML. When SMX–TMP was compared with amoxicillin, failure rates were higher for SMX–TMP (RR 1.79; 95% CI 1.13–2.84). For non-severe pneumonia, there was no difference between SMX–TMP and amoxicillin for cure rate in two RCTs (3468 children; RR 0.99; 95% CI 0.96–1.01) (10). That amoxicillin is better tolerated, with fewer side-effects, than SMX–TMP argues in favour of including amoxicillin alone on the list. Overall, these data point to beta-lactam regimens as being a key part of therapy for CAP in children, which is similar to what existing evidence suggests for adults.

As noted, the systematic reviews that were identified provided limited information on superiority. Most of the RCTs included in the reviews were non-inferiority studies but frequently did not meet the criteria for non-inferiority determined by the applicants. The RCTs did not show mortality benefit of adding a fluoroquinolone or macrolide to a beta-lactam compared with beta-lactam monotherapy. In children, amoxicillin appeared to be either equivalent to, or have better cure rates than, SMX–TMP. The greater tolerability of amoxicillin means it is preferred. Better cure rates were achieved with amoxicillin than with cephapodoxime, and there were fewer clinical failures with ampicillin and gentamicin than with chloramphenicol, making these antibiotics the preferred choices.

Guidelines

Guidelines of the British Thoracic Society (BTS) (26) and the Infectious Diseases Society of America (IDSA) for adults were summarized in the application. Currently available IDSA guidelines (which are being updated) include use of macrolides (either alone or in combination), respiratory fluoroquinolones, beta-lactams (cefotaxime, ceftriaxone, or ampicillin + sulbactam); use of antipseudomonal antibiotics when needed (piperacillin + tazobactam) or carbapenems (imipenem or meropenem); or use of an aminoglycoside. BTS recommendations include a single antibiotic, a combination of amoxicillin and macrolide, beta-lactam/beta-lactamase-inhibitor combinations and a macrolide, depending on severity of illness. For children, IDSA guidelines include amoxicillin, macrolides for outpatients and ampicillin or penicillin G (benzylpenicillin), ceftriaxone or cefotaxime, or a combination of macrolide and a beta-lactam (11). Vancomycin is recommended if methicillin-resistant Staphylococcus aureus (MRSA) is being considered. The guidelines also recommend doxycycline as an alternative first-line to macrolides as well as ceftriaxone or ampicillin + sulbactam for patients in intensive care. The BTS guidelines recommend amoxicillin as first choice for oral antibiotic therapy in children and propose amoxicillin + clavulanic acid, cefaclor, erythromycin, azithromycin and clarithromycin as alternatives (12). They suggest that macrolide antibiotics may be added at any age if there is no response to first-line empirical therapy or if either Mycoplasma or Chlamydia pneumonia is suspected or in very severe disease. They recommend amoxicillin + clavulanic acid for pneumonia associated with influenza. The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of CAP in children. This undertaking was informed by a systematic review of the current evidence of efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made with regard to antibiotic treatment of pneumonia in children: • Fast breathing pneumonia: amoxicillin oral liquid or tablets, at least 40 mg/kg twice daily (80 mg/kg per day) x 5 days; in areas with low HIV prevalence, oral amoxicillin for 3 days. • Severe pneumonia: - first-line: IM/IV ampicillin 50 mg/kg or benzylpenicillin injection 50 000 units/kg, every 6 hours for at least 5 days and IM/IV gentamicin, 7.5 mg/kg once a day for at least 5 days; - second-line: IV ceftriaxone. For HIV-infected individuals, 10 days’ therapy is recommended.

Rationale for antibiotic selection

Proposed antibiotics for CAP were based on evidence from systematic reviews and are similar to recommendations in clinical practice guidelines – with the exception of azithromycin, which is not proposed for the EML because of safety concerns reported by the FDA (2). The applicants stated that, although no systematic review evidence was found for vancomycin, its inclusion for empirical therapy when MRSA is suspected, as suggested by the guidelines, was reasonable. To minimize the occurrence of antibiotic resistance, and taking into consideration efficacy, safety, cost and availability, the application proposed the use of amoxicillin, amoxicillin + clavulanic acid, or phe noxy methylpenicillin as first-line empirical (core) therapy for mild to moderate CAP. “Targeted” antibiotics were defined in the application as those necessary in cases of more severe illness, when alternatives to first-line options are required (e.g. penicillin allergy), and in specific situations where the likelihood of a particular organism warrants use. Intravenous formulations such as benzylpenicillin, cefotaxime or ceftriaxone are proposed for inclusion on the EML as targeted antibiotics for severe CAP. Doxycycline is targeted since it is an alternative to first-line antibiotics. In settings where melioidosis is endemic, ceftriaxone can be used empirically as the third-generation cephalosporin of choice. In keeping with a fluoroquinolone-
For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the antibiotics proposed in the application and selected first- and second-choice antibiotics for community-acquired pneumonia, in line with WHO guidelines, for inclusion on the EMLc. The Committee considered the various antibiotics proposed in the application from the McMaster Group using the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML. Piperacillin + tazobactam, levofloxacin, vancomycin and ceftazidime were excluded. Recommended first- and second-choice antibiotics are reported above. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

**EML recommendations: Bacterial pneumonia**

<table>
<thead>
<tr>
<th>First choice</th>
<th>Second choice</th>
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<tbody>
<tr>
<td><strong>COMMUNITY-ACQUIRED PNEUMONIA - MILD TO MODERATE</strong></td>
<td></td>
</tr>
<tr>
<td>phenoxyethylpenicillin</td>
<td>doxycycline</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>amoxicillin + clavulanic acid</td>
</tr>
</tbody>
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**COMMUNITY-ACQUIRED PNEUMONIA - SEVERE [CHILDREN]**

- ampicillin
  - co-prescribed with gentamicin
- benzylpenicillin
  - co-prescribed with gentamicin
- amoxicillin
  - co-prescribed with gentamicin
- cefotaxime
- ceftriaxone
- amoxicillin + clavulanic acid

**COMMUNITY-ACQUIRED PNEUMONIA - SEVERE**