Therapeutic Implications of Antibacterial Resistance in Community-Acquired Respiratory Tract Infections in Children

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Abstract

The global spread of antibacterial resistance has important implications for the current and future management of bacterial respiratory tract infections in children. Data suggest that emerging resistance to commonly prescribed antibacterials, such as macrolides and trimethoprim-sulfamethoxazole, is beginning to impact the treatment of these infections, which include acute otitis media, tonsillitis/pharyngitis and community-acquired pneumonia. There is, therefore, a need for additional agents that are active against common respiratory tract pathogens, including resistant strains and are suitable for use in children. Infection control measures to curb the clonal spread of antibacterial resistance are also extremely important.

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Introduction

Infections of the respiratory tract are the most common type of infectious disease managed by healthcare providers and are responsible for significant morbidity and mortality. For example, acute respiratory tract infections (RTIs) are the single largest cause of death in children worldwide, causing two to four million deaths per year, with the highest incidence in developing countries [1, 2]. RTIs also pose a substantial socioeconomic burden as approximately three-quarters of all outpatient antibacterial prescriptions are for RTIs. Appropriate prescribing for RTIs is becoming increasingly challenging due to the global spread of antibacterial resistance among common RTI pathogens [3, 4].

Appropriate prescribing is particularly important for childhood RTIs, as children are more likely than adults are to become infected with resistant strains. Risk factors for infection with resistant strains of *Streptococcus pneumoniae* include: age < 12 years (particularly < 2 years), daycare attendance (child or family member) and recent treatment with certain antibacterials. Children are more likely than adults to receive a prescription for antibacterials [5–11]. Most antibacterial-resistant strains are clonally spread, steadily endemic and easily transmitted, especially among children.

This review discusses antibacterial resistance among common community-acquired RTI pathogens and the implications for current and future management of childhood RTIs, particularly acute otitis media (AOM), community-acquired pneumonia (CAP) and tonsillitis/pharyngitis.

Respiratory Tract Infections in Children

Upper RTIs, particularly AOM and tonsillitis/pharyngitis, are among the most common childhood illnesses, second only to the common cold [12, 13]. While not potentially life-threatening, these infections can cause significant morbidity and potentially serious sequelae. AOM is the most frequent reason for antibacterial prescribing in children in the developed world. Indeed, around 75% of children will have at least one AOM episode before their third birthday [14]. In developed countries, the highest incidence of AOM is seen in children aged < 2 years [14–16]. Classic complications of untreated bacterial AOM include mastoiditis, lateral sinus thrombosis and chronic suppurative otitis media. Tonsillitis/pharyngitis is most frequent in school-age children. Complications of untreated bacterial tonsillitis/pharyngitis include direct invasion of adjacent respiratory sites, suppurative complications and, rarely, rheumatic fever/glomerulonephritis [17].

CAP is a potentially more serious childhood RTI. The annual incidence of CAP in children aged < 5 years is 34 to 40 cases per 1,000 in Europe and North America, higher than at any other time of life except in adults > 75 to 80 years of age [18, 19]. In the developing world, CAP is more common and often more severe than in developed countries and is also frequently fatal in children [20, 21]. Prompt and appropriate therapy of bacterial CAP is essential in the treatment of severe disease and bacteremia.

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Respiratory Tract Pathogens

The main causative agents of acute community-acquired RTIs in children are summarized in table 1.

Table 1
Main causative agents of acute community-acquired respiratory tract infections in children.[a]

Indication	Causative agents
Acute otitis media	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* Respiratory viruses (e.g. respiratory syncytial virus)
Tonsillitis/pharyngitis	*Streptococcus pyogenes* Respiratory viruses (e.g. respiratory syncytial virus) *Mycoplasma pneumoniae*[b] Other viruses (e.g. Epstein-Barr virus, adenovirus, coronavirus, enteroviruses)
Community-acquired pneumonia	*Streptococcus pneumoniae* *Mycoplasma pneumoniae*[c] *Chylamydophila (Chlamydia) pneumoniae*[c] *Haemophilus influenzae*[d] *Moraxella catarrhalis*[d] Respiratory viruses (e.g. respiratory syncytial virus)

[a] for a fuller account of the range of pathogens responsible for these infections, please consult the text and supporting references; [b] may play a role in teenagers; [c] mainly older children and adolescents (5–15 years); [d] not common causative agents of community-acquired pneumonia in the developed world

Acute Otitis Media

Over 70% of AOM cases are of bacterial origin [12]. *S. pneumoniae* is the most common bacterial pathogen of AOM, followed by *Haemophilus influenzae* and *Moraxella catarrhalis*. *S. pneumoniae* causes 40 to 50% of bacterial AOM infections and is the least likely of the pathogens to resolve without treatment [16, 22]. *Streptococcus pyogenes* is a less frequent cause of AOM (accounting for < 10% of cases) [23], but has been associated with serious clinical sequelae, including perforation [24]. Viruses also have a role in AOM, with respiratory syncytial virus being the most commonly identified viral pathogen in middle ear fluid [25].

Tonsillitis/Pharyngitis

Viruses are responsible for the majority (up to 85%) of cases of tonsillitis/pharyngitis [26]. Group A β-hemolytic streptococci (GABHS; *S. pyogenes*) is the most important and frequent bacterial cause of tonsillitis/pharyngitis and is responsible for 15 to 30% of all cases [17, 26]. GABHS is uncommon in children < 4 years old, but is responsible for up to 65% of cases in children ≥ 4 years of age [27]. *Mycoplasma pneumoniae* may also play a role in teenagers [17]. It is important to differentiate streptococcal from viral tonsillitis/pharyngitis, as streptococcal tonsillitis/pharyngitis is associated with the potentially serious complications listed previously. In addition, antibacterial therapy is ineffective in viral infection.

Community-Acquired Pneumonia

A microbiologic diagnosis is often difficult to obtain with CAP in children. In an estimated one-half to two-thirds of cases, a specific etiology cannot be demonstrated using culture, antigen detection or serologic techniques [28, 29]. Viruses account for 14 to 35% of childhood CAP infections [28, 29]. *S. pneumoniae* is the most frequently implicated bacterial pathogen across all age-groups, being responsible for around one-third of infections in children [28, 29]. Together, atypical and intracellular pathogens (*M. pneumoniae*, *Legionella pneumophila*, and *Chlamydophila* [*Chlamydia*]) are implicated in ~ 15% of CAP cases. *M. pneumoniae* and *C. pneumoniae* can affect all age-groups, but are particularly common among children [30–32]. *M. pneumoniae* is thought to mainly affect older children and adolescents (5 to 15 years), but has been isolated from children as young as two years of age [30–32]. The age range for *Chlamydia pneumoniae* infection is similar, however, its causal role in CAP can be difficult to demonstrate due to the frequency of occurrence of oropharyngeal colonization [32]. *L. pneumophila* infection is infrequent among children and is most common in adults > 30 years of age [30]. *H. influenzae* and *M. catarrhalis* are less common causes of CAP in children [28, 29, 33].

Age is a predictor of the likely causative pathogens in childhood CAP [29]. Viruses are most commonly found in younger children. In children of any age, when a bacterial cause is found, it is most commonly *S. pneumoniae*, followed in older children by *M. pneumoniae* and *C. pneumoniae*. Mixed bacterial or bacterial/viral CAP is relatively rare.

Antibacterial Resistance

Antibacterial resistance among the common bacterial respiratory tract pathogens (*S. pneumoniae, H. influenzae, and M. catarrhalis*) is now a global concern [3, 4] (Figure 1). Worldwide surveillance studies between 1996 and 1997 [3] revealed erythromycin (minimum inhibitory concentration [MIC] ≥ 0.5 mg/l) and trimethoprim–sulfamethoxazole (TMP-SMX; trimethoprim MIC > 1/19 mg/l) resistance among *S. pneumoniae* isolates was 22% and 30%, respectively. Penicillin resistance was 25% (10% intermediate [MIC 0.12–1 mg/l], 14% resistant [MIC ≥ 2 mg/l]). However, these overall prevalences masked considerable variations between countries. For example, < 10% of *S. pneumoniae*

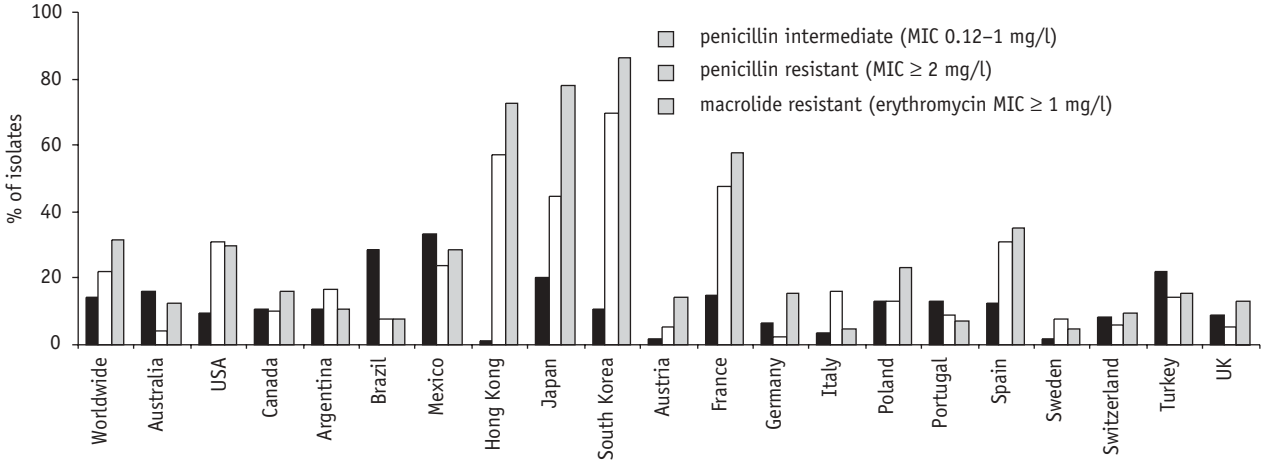

Figure 1. Worldwide prevalence of penicillin and macrolide resistance among isolates of *Streptococcus pneumoniae* (adapted from [4]); (MIC: minimum inhibitory concentration).

isolates from Germany and Austria displayed resistance to erythromycin, whereas around 40% of isolates from France and 70% of isolates from Hong Kong were erythromycin resistant. The prevalence of penicillin resistance also varied considerably between countries. β-lactamase production (resulting in resistance to certain β-lactam antibacterials) among *H. influenzae* and *M. catarrhalis* was 13% and 92%, respectively.

More recent global surveillance studies (1999–2000) revealed overall erythromycin resistance of 32% and penicillin resistance of 36% (14% intermediate, 22% resistant) among *S. pneumoniae*; and β-lactamase production among isolates of *H. influenzae* and *M. catarrhalis* was 16% and 95%, respectively [4]. *S. pyogenes* remains sensitive to penicillin, but macrolide resistance among group A streptococci has emerged and is spreading worldwide, with global resistance levels currently reported at ~9% [4]. Again, considerable variation in the prevalence of macrolide and penicillin resistance among *S. pneumoniae* isolates, as well as macrolide resistance among isolates of *S. pyogenes*, was observed between countries [4], consistent with data from other national and international surveillance studies [3, 4, 34–43].

Multidrug resistance is a serious problem. Erythromycin-resistant strains of *S. pneumoniae* are frequently cross-resistant to other macrolides (such as clarithromycin and azithromycin) and are also resistant to penicillin and other antibacterials (such as certain aminopenicillins, cephalosporins and TMP-SMX) [3, 4]. Similarly, penicillin resistance is often associated with cross-resistance to other β-lactams and co-resistance to other agents such as macrolides and particularly TMP-SMX [3, 4] (Figure1). For example, 90% of penicillin-resistant *S. pneumoniae* strains isolated worldwide between 1996 and 1997 were resistant to TMP-SMX and 50% of penicillin-resistant isolates were resistant to the macrolides, tetracycline and chloramphenicol. Multidrug-resistant pneumococci pose a clinical challenge across all age-groups, especially in AOM and CAP.

Macrolide resistance among streptococci occurs via two main mechanisms: methylation of the macrolide target sites within bacterial ribosomal RNA (encoded by the *erm*[B] and *erm*[A] subclass *erm*[TR] genes) and drug efflux (encoded by the *mef*[A] gene) [44, 45]. *mef*(A) confers resistance only to 14- and 15-membered ring macrolides (erythromycin, clarithromycin, and azithromycin) and is associated with macrolide MICs of 1–32 mg/l (macrolide or M resistance). *erm*(B), however, confers resistance to the macrolide–lincosamide–streptogramin$_B$ group of antibacterials (macrolide–lincosamide–streptogramin$_B$ or MLS$_B$ resistance) and typically results in very high macrolide MICs (> 64 mg/l). The predominant mechanism of macrolide resistance globally in *S. pneumoniae* is *erm*(B) (56%) followed by *mef*(A) (35%) [46]. The distribution of macrolide resistance genotypes varies greatly between countries and geographic regions, however, with *mef*(A) tending to be the predominant genotype in North America and *erm*(B) tending to be the predominant genotype in Europe [46].

Although useful in determining resistance trends, international antibacterial susceptibility statistics are of little use in determining the prevalence of local drug resistance. An enormous variation in resistance levels exists between and within countries and resistant pathogens can emerge rapidly in specific localities [3, 4, 47, 48]. Clinicians should, therefore, be aware of local antibacterial resistance patterns when selecting therapy for RTIs. Given the different phenotypes and typical MIC values related to the two main macrolide resistance genotypes, clinicians should ideally be aware of local M and MLS$_B$ resistance genotype prevalences when prescribing for RTIs.

Antibacterial Resistance in Children

Recent surveillance data collected worldwide from children aged ≤ 14 years with RTIs indicated 36% of *S. pneumoniae* isolates were resistant to erythromycin and 43% of isolates displayed reduced susceptibility to penicillin (18% intermediate, 25% resistant) [49]. No erythromycin-resistant isolates were susceptible to the newer macrolides clarithromycin or azithromycin and half of the isolates were also resistant to penicillin. Macrolide and penicillin resistance was more prevalent among children ≤ 2 yearsof age than among older children. Erythromycin resistance among *S. pyogenes* isolates from children was around 10% and no erythromycin-resistant isolates were susceptible to clarithromycin or azithromycin [50]. In further surveillance studies, erythromycin resistance among *S. pyogenes* isolates from school-age patients in Italy increased two to 20-fold from 1993 to 1995 and was > 30% in one-third of the participating centers [51]. In addition, the sudden emergence and rapid clonal spread of erythromycin-resistant pharyngeal *S. pyogenes* in schoolchildren was recently reported in Pittsburgh, Pennsylvania, USA [48]. Between October 1998 and May 2000, no isolates displayed resistance, whereas 48% of isolates became resistant between October 2000 and May 2001. High rates of resistance were also found in the surrounding community. As in adults, considerable variation in the prevalence of macrolide resistance among isolates of *S. pneumoniae* and *S. pyogenes* from children is observed between and within countries [49, 50, 52–59].

As mentioned previously, children are more likely to be infected with resistant isolates than adults are. Starting soon after birth, the nasopharynx is colonized with bacterial flora. Colonization with respiratory pathogens occurs intermittently and by 12 months of age, 70% of children are colonized by at least one of the three major respiratory tract pathogens [60–62]. More than 90% of children demonstrate bacterial colonization by 3 years of age and strains carried in the nasopharynx frequently change serotype [63]. There is some evidence to suggest that colonization with bacteria may increase during viral RTIs [64, 65], which may result in secondary infections, particularly AOM. The average child has three to eight acute viral respiratory illnesses per year, compared with two to three in adults [66, 67]. In addition, antibacterials may increase carriage of potentially resistant pathogens in the nasopharynx [68].

Clinical Impact of Antibacterial Resistance in Respiratory Tract Infections in Children

Treatment options for RTIs in children have been largely limited to β-lactams and macrolides (Table 2), despite the increase in levels of resistance to these agents. To date, there has been a lack of large, well-controlled studies to assess how the global increase in antibacterial resistance affects clinical outcomes in children or adults with RTIs. However, some data suggest the increasing MICs for commonly prescribed antibacterials may impact treatment outcomes in childhood RTIs.

Acute Otitis Media

In AOM there is significant evidence showing bacteriologic success contributes to clinical efficacy [69] and it may be compromised if pathogens with reduced antibacterial susceptibility are present in middle-ear fluid and treated suboptimally, or if a nonbacterial etiology, e.g. RSV, is the cause [70, 71]. Carriers of resistant *S. pneumoniae* are more likely to have frequent episodes of AOM and are significantly less likely to respond adequately to treatment [5, 7, 72–76]. For example, bacteriologic success rates for cefaclor, cefuroxime axetil and azithromycin are seriously compromised against penicillin-resistant (but not intermediate) and erythromycin-resistant strains of *S. pneumoniae* [71, 77]. Indeed, the bacteriologic success rates for cefaclor and azithromycin against penicillin- and erythromycin-resistant strains have been shown to be equivalent to that of placebo or the spontaneous resolution rate. High bacteriologic and clinical failure rates have been observed with TMP-SMX and it has been suggested that this antibacterial is a choice for AOM unless its efficacy can be evaluated *in vitro* [78, 79].

Amoxicillin remains a commonly used first-line agent for AOM in children (Table 2), despite the increase in resistance to this an-

Table 2
Therapeutic options for acute community-acquired respiratory tract infections in children.

Indication	Antibacterial
Acute otitis media	Amoxicillin High-dose amoxicillin [a,b] Amoxicillin–clavulanate [b] Oral cephalosporins [b] Ceftriaxone [b]
Tonsillitis/pharyngitis	Amoxicillin Macrolides (erythromycin, clarithromycin, azithromycin) [c]
Community-acquired pneumonia	High-dose amoxicillin [a] Macrolides (erythromycin, clarithromycin, azithromycin) [d] Amoxicillin–clavulanate Oral cephalosporins Clindamycin Doxycycline [e]

[a] if resistant *Streptococcus pneumoniae* is suspected or involved; [b] IM, if no improvement with a first-line agent by day 3; [c] mainly used in penicillin-allergic children; [d] in children > 5 years of age to cover atypical pathogens; [e] not in children ≤ 8 years of age

tibacterial. Rising MICs for amoxicillin are reflected in the recommended switch to high-dose amoxicillin (80–90 mg/kg vs 40–50 mg/kg) when resistant *S. pneumoniae* is suspected [16]. In Europe and some centers in the United States, AOM is not treated at the first visit and antibacterial therapy only given if there is no improvement after 24 h. If no improvement is observed with a first-line agent such as amoxicillin by day 3, a switch to high-dose amoxicillin, amoxicillin–clavulanate (to cover β-lactamase production [amoxicillin–clavulanate is no more effective than amoxicillin against penicillin-resistant *S. pneumoniae*]), oral cephalosporins, or intramuscular ceftriaxone may be necessary.

Tonsillitis/Pharyngitis

In tonsillitis/pharyngitis, penicillins are commonly used, with macrolides such as clarithromycin and azithromycin often being used for penicillin-allergic children (Table 2). Apparent effects of macrolide resistance on outcomes in children with tonsillitis/pharyngitis are beginning to emerge. Treatment with azithromycin (10 mg/kg for 3 days) is associated with similar rates of clinical cure but significantly lower bacteriologic eradication rates than penicillin V (10,000 IU/kg/day for 10 days) (38% vs 81%, respectively), whereas 20 mg/kg azithromycin gives similar bacteriologic cure rates to penicillin V [80]. Furthermore, *S. pyogenes* isolates from children unsuccessfully treated with azithromycin 10 mg/kg have been found to acquire resistance during treatment [81].

Although penicillin resistance has not been observed among *S. pyogenes*, bacteriologic/clinical failure rates with penicillin are now reported to be ~ 30% [82]. Suggested reasons for penicillin failure include: lack of compliance with the dosing regimen (leading to exposure to suboptimal doses), β-lactamase production by oral flora, eradication of normal protective pharyngeal flora or lack of penetration into oropharyngeal secretions. These factors may singly or together cause treatment failure. A further potential reason for treatment failure may be strain invasiveness. An association between erythromycin resistance and cell adherence/invasiveness in streptococci isolated from children in Italy was recently shown [83–85].

Community-Acquired Pneumonia

The effects of antibacterial resistance on treatment outcomes in children with CAP have not been studied extensively and are difficult to define. High-dose β-lactams appear to be effective against penicillin-intermediate strains of *S. pneumoniae*, but there are conflicting data on the treatment outcome for resistant strains (MIC ≥ 2 mg/l) in both adults and children [86–91]. Although there appears to be no significant difference in response to conventional antibacterial treatment in children with penicillin-resistant *S. pneumoniae*, data are limited and the majority of children in these studies were not treated with oral β-lactam agents alone [29].

A study in Korean children with pneumococcal pneumonia found a trend towards increased clinical failure rates with increased penicillin resistance [87]. Similarly, a trend towards an increased case-fatality rate was observed in adults and children harboring strains for which the penicillin MICs were ≥ 4 mg/l [91]; patients with pneumonia and strains for which the penicillin MICs were ≥ 4 mg/l were more likely to have a poor clinical outcome. Penicillin resistance has been associated with treatment failure in children [87, 89], however, the patient numbers in these studies were small. Few data exist for macrolide-resistant isolates, but treatment failure and breakthrough bacteremia due to pneumococcal macrolide resistance in children has been reported [92]. Furthermore, case reports of macrolide treatment failure and subsequent hospitalizations in adults with CAP are accumulating [93–97].

Amoxicillin remains a preferred oral antibacterial in children < 5 years of age with CAP and across age-groups if *S. pneumoniae* is suspected (Table 2). Full/high-dose amoxicillin (80–100 mg/kg) is recommended when resistant *S. pneumoniae* is involved (or suspected) and the patient is deemed suitable for oral therapy [28, 29, 32]. Alternative treatments include amoxicillin-clavulanate, oral cepholosporins, clindamycin, or doxycycline (for children ≥ 8 years of age) [32, 33, 98] (Table 2).

Antimicrobial resistance among respiratory pathogens causing acute otitis media and CAP include *S. pneumoniae, H. influenzae* and *M. catarrhalis*. Group A streptococcus, e.g. *S. pyogenes*, is a rare cause of CAP, but is the most common cause of bacterial pharyngitis [28, 47]. Antimicrobial resistance to pneumococci is largely confined to the macrolides and TMP-SMX [38, 39, 51, 79]. Penicillin resistance among pneumococci is microbiologically classified as relative, e.g. intermediate resistance or as resistant, e.g. highly resistant. Since penicillin and β-lactams kill by time-dependent killing kinetics, any concentration above the MIC will effectively eradicate the organism. The usual therapeutic dose is concentrations > 2 mg/l, readily achieved by virtually all of the commonly used orally administered and parenterally administered β-lactams [116]. In respiratory tract infections, even highly penicillin-resistant strains are within the achievable serum and tissue concentrations of parenterally administered β-lactams. Penicillin resistance is also related to pneumococcal resistance to TMP-SMX and macrolides. It has been mentioned that the use of TMP-SMX and macrolides has been associated with inducing penicillin resistance in strains of *S. pneumoniae* [47, 48, 101].

H. influenzae is variably resistant to ampicillin but not to β-lactamase-stable β-lactams. Penicillin appears to be effective *in vitro* against *H. influenzae*, but is ineffective *in vivo*. Ampicillin is an antibiotic associated with inducing resistance, and for this reason should be used sparingly in treating infections due to *H. influenzae*, even if sensitive [116]. Amoxicillin is less likely to induce resistance in treating respiratory tract infections in children compared to ampicillin. β-lactamase-stable cephalosporins are effective

against both ampicillin-sensitive and resistant strains of *H. influenzae*.

M. catarrhalis is a potent producer of β-lactamases. Consequently, for decades, virtually all strains of *M. catarrhalis* have been β-lactamase positive and, therefore, penicillin resistant. Because *M. catarrhalis* is a relatively unimportant pathogen in the pediatric age-group, treatment of respiratory tract infections using a β-lactamase-stable β-lactam will be effective against all strains of *M. catarrhalis* [116].

Group A streptococcal resistance to penicillin is increasing. Group A streptococci are the predominant pathogens in bacterial pharyngitis, but are unimportant in otitis and pneumonia. Penicillin resistance to *S. pyogenes* is nonexistent, but there is increasing macrolide resistance to strains of *S. pyogenes. S. pyogenes* is naturally resistant to TMP-SMX and for this reason TMP-SMX should not be used to treat bacterial pharyngitis due to *S. pyogenes* [82–84].

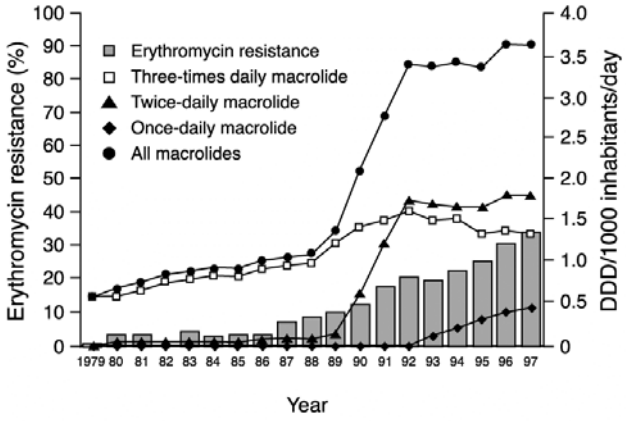

Figure 2. Correlation between macrolide resistance among *Streptococcus pneumoniae* (erythromycin minimum inhibitory concentration ≥ 1 mg/l) and macrolide consumption in Spain between 1979 and 1997 (reproduced with permission [97]); (DDD: defined daily doses).

Antibacterial Resistance: Implications for the Current and Future Treatment of Respiratory Tract Infections in Children

β-lactams remain the recommended treatment for children with RTIs. Current treatment recommendations are largely based on the fact that penicillin-intermediate strains of *S. pneumoniae* are responsive to β-lactams; fully penicillin-resistant strains of *S. pneumoniae* are currently uncommon and studies do not definitively show the impact of penicillin or erythromycin resistance on clinical outcomes. However, increasing MICs for amoxicillin have resulted in the recommendation of doubling of the dose (with or without clavulanate). Full-dose amoxicillin is also recommended for CAP caused by *S. pneumoniae* in communities where penicillin resistance is common (Table 2). Whether high-dose amoxicillin is chosen for CAP or AOM should be based on knowledge of local resistance/susceptibility patterns and patient history. Second- and third-generation oral cephalosporins, such as cefuroxime axetil or cefpodoxime, also have a high degree of activity against *S. pneumoniae*, including penicillin-resistant strains. Furthermore, in AOM, penicillin nonsusceptible *S. pneumoniae* are not well eradicated by oral cephalosporins [71, 99], which is probably secondary to limited penetration into oropharyngeal secretions.

Increases in the prevalence of macrolide-resistant strains of *S. pneumoniae* in North America and Spain over the past decade have been linked to increases in macrolide consumption [100, 101]. Macrolides with once- or twice-daily dosing regimens, rather than those given more frequently, were primarily responsible for rises in macrolide resistance rates among *S. pneumoniae* isolates in Spain [101] (Figure 2). In Finland, consumption of erythromycin was also related to an increase in the prevalence of erythromycin-resistant group A streptococci [102]. A decrease in incidence of resistance was achieved by limiting erythromycin use, but the rate of use of newer macrolides increased, so overall macrolide consumption did not change [103]. These data emphazise the importance of prescribing low-resistance-potential antibacterials at the optimal doses for preserving clinical efficacy [104], and suggest macrolides are not an appropriate first-line therapeutic option for the treatment of RTIs in children. Given the high rates of resistance to TMP-SMX, and because such strains are usually also resistant to penicillin, it has been suggested that alternative agents should be used in patients with known/suspected *S. pneumoniae* infections [78, 79, 105]. Similarly, due to resistance issues, it has been suggested that macrolides and TMP-SMX should no longer be considered appropriate second-line agents for RTIs [105]. Thus, the spread of antibacterial resistance among common respiratory pathogens has limited the choice of appropriate first- and second-line therapies for childhood RTIs.

The emergence of strains of *S. pneumoniae* with resistance to currently available antibacterials has been influenced by various factors, including the clonal spread of most resistant strains and organisms with a multidrug-resistant phenotype, have become endemic [100, 105]. The ease of transmission, as well as asymptomatic colonization, has contributed to the problem. Selective pressure from antibacterial agents, i.e. increased inappropriate antibacterial consumption of agents with a high resistance potential, has also contributed significantly to the antibacterial resistance problem [100, 103–105].

Vaccination has played some role in reducing pneumococcal RTIs. The pneumococcal conjugate vaccine, which was recently licensed in some developed countries, has been shown to be highly effective in preventing invasive pneumococcal disease caused by the serotypes it covers. However, the vaccine is only modestly effective in preventing CAP and AOM [106]. Also, the high cost of this vac-

Table 3
Ideal characteristics of an antibacterial agent for the treatment of acute community-acquired respiratory tract infections in children.

Parameter	Ideal properties
Antibacterial spectrum	Coverage against: ● Common respiratory pathogens ➢ *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pyogenes* ● Penicillin-, TMP-SMX- and macrolide-resistant strains of *Streptococcus pneumoniae* ● Atypical/intracellular pathogens ➢ *Mycoplasma pneumoniae* and *Chlamydophila (Chlamydia) pneumoniae*
Tolerability	Excellent safety/tolerability profile ● Equivalent to antibacterials currently used in the treatment of children (β-lactams and macrolides) ● Good palatability ➢ Enhanced patient compliance
Pharmacokinetics/ pharmacodynamics	Pharmacokinetic/pharmacodynamic profile that permits a convenient and simple dosing regimen ● Can be taken without regard to meals ● Once-daily dosing ➢ Enhanced patient compliance ● Reduced propensity for resistance development

cine may preclude its use in developing parts of the world where CAP is most common and severe. Furthermore, there is already evidence that pneumococcal serotypes not represented in the vaccine are replacing those it covers as causes of AOM [107].

There is, therefore, a need for new agents with a high degree of activity against resistant respiratory pathogens, a low propensity to induce or select for resistance and suitable for use in children. Ideally, agents for the treatment of RTIs in children should possess a targeted spectrum of antibacterial activity, including activity against pathogens that have become resistant to currently available agents and good tolerability they should demonstrate good penetration into respiratory secretions and have a pharmacokinetic/pharmacodynamic (PK/PD) profile permitting a convenient dosing regimen (once-daily dosing) to encourage patient compliance (Table 3). Respiratory fluoroquinolones demonstrate good *in vitro* activity against resistant respiratory pathogens and have a favorable PK/PD profile [108], but these agents have had limited use in children [109].

Telithromycin, a new ketolide antibacterial, appears to be a potentially useful drug for childhood RTIs. Telithromycin has a high degree of activity against β-lactam- and macrolide-resistant strains of *S. pneumoniae* and atypical/intracellular pathogens, a low resistance potential and does not induce resistance *in vitro* [4,110–113]. In clinical trials with tonsillitis/pharyngitis, CAP, acute maxillary sinusitis, and acute exacerbations of chronic bronchitis, telithromycin was equivalent to comparator antibacterials, and the tolerability profile of telithromycin was similar to newer macrolides [110, 114, 115].

Attempts to curb the further spread of antibacterial resistance, such as encouraging appropriate antibacterial use, are extremely important in preserving the efficacy of current and future treatment strategies. Appropriate antibacterial use does not, however, simply equate with a reduction in the volume of use. It also involves encouraging the of judicious antibacterial usage through reducing overuse for viral infections and prophylaxis, preventing misuse through inappropriate choice of either antibacterial or dosage and duration of therapy and preferentially using low-resistance-potential antibacterials [104, 116–118]. Care should be taken when attempting to reduce the overprescribing of antibacterials to help curb the spread of antibacterial resistance. For example, in the Netherlands and some other north European countries, antibacterial use in AOM is recommended only if no spontaneous improvement has been observed within 24 to 72 h of diagnosis ("watchful waiting" approach) [24, 119]. This approach has, however, been associated with an increased incidence of AOM complications, such as acute mastoiditis [120].

Data from surveillance studies are increasingly important to guide appropriate prescribing as β-lactam- and macrolide-resistant strains become more prevalent. Well-designed clinical outcome studies are required, especially since reports of the selection of resistance, particularly for macrolides, are beginning to emerge [81, 97]. The most effective antibacterial resistance control strategy is likely to be the restriction of high-resistance-potential antibacterials at the formulary level [104, 116] and the preferential use of antibacterials with the lowest resistance-inducing potential at the prescribing level.

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