

Evolving Shifts in Otitis Media Pathogens: Relevance to a Managed Care Organization

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Abstract

The microbiological landscape of acute otitis media (AOM) has been relatively constant over the past half century. Because of this stability, empiric management of AOM was a common and efficient practice. Recently, there has been a proportional shift in the microbiology of AOM, bringing the choices for empiric therapy into question. Because of this shift, managed care organizations should review their formularies to ensure that they are structured to include and promote the use of appropriate antibiotics. This article explores the background and events leading up to the shift in AOM microbiology; discusses the clinical consequences and the future implications of the shift, such as increased costs associated with treatment failures, its impact on new vaccines and new-onset AOM and related disease states, such as sinusitis; and describes why these factors should be considered by managed care decision makers in their formulary deliberations.

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Acute otitis media (AOM) is one of the most common pediatric infections and is responsible for more than one quarter of all oral antibiotic prescriptions written in the United States.¹ Children aged 7 to 24 months are most likely to develop AOM.²⁻⁴ Factors associated with an increased risk of developing otitis media include male sex, use of daycare facilities, atopy, use of pacifiers, and low socioeconomic status.^{5,6}

AOM represents a significant burden to patients, caregivers, and the healthcare system. AOM accounts for 20 million office visits per year in the United States and is responsible for 18% of ambulatory care visits among preschool children.^{7,8} The number of AOM visits has increased more than 2-fold in the last quarter of the 20th century.⁹ A conservative estimate by the Agency for

Healthcare Research and Quality gauges the total national cost of AOM to have been \$2.98 billion in 1995 dollars,⁹ whereas more aggressive estimates gauge the direct costs at \$4.1 billion with a per-patient cost of \$453 in 1992 dollars.¹⁰ Adjusting these figures to 2005 dollars using the Consumer Price Index¹¹ provides estimates of \$3.82 billion and \$5.7 billion, respectively, and a per-patient cost of \$630. The more conservative estimate, gathered in a study of AOM costs conducted by the Southern California Evidence-based Practice Center, reported an estimated 70% of the direct cost of AOM and 63% of the total cost was attributable to episodes of otitis media with effusion (OME) or chronic middle ear infections progressing from AOM. These figures suggest that effective treatments for AOM and prevention of subsequent infection could achieve significant cost savings.⁹ The economics of AOM are presented in more depth in an accompanying article in this supplement. Any practice recommendations or formulary modifications that could reduce AOM expenditures should be of interest to health plans.

Microbiology of AOM Pre-PCV-7

AOM is typically caused by 1 of 3 pathogens, *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, or *Moraxella catarrhalis*.^{5,12-18} Although these 3 pathogens are responsible for most cases of AOM, their individual incidence varies by the type of AOM infection. In the 20 years before the release of the heptavalent pneumococcal conjugate vaccine (PCV-7), US studies showed *S pneumoniae* as the main causative pathogen of uncomplicated AOM, associated with a median of 42% of cases (range 32%-48%); *H influenzae* was associat-

ed with a median of 31% of cases (range 20%-37%); and *M catarrhalis* was associated with a median of 16% of cases (range 9%-23%).¹²⁻¹⁶

The microbiology of recurrent and persistent AOM differs somewhat from uncomplicated AOM. Recurrent AOM is typically defined as 3 or more unique cases of AOM in a 6-month period or 4 episodes in a 12-month period.^{19,20} Persistent AOM is typically defined as clinical failure within 30 days of completion of an antibiotic course.²¹ A study in the 1980s of the microbiology of AOM in persistent AOM found that *H influenzae* was the dominant pathogen, representing 53% of the isolates (versus 19% for *S pneumoniae*).¹⁵ In the 1990s, 3 studies documented a shift in the persistent AOM population to *S pneumoniae* as the dominant pathogen.^{5,21,22}

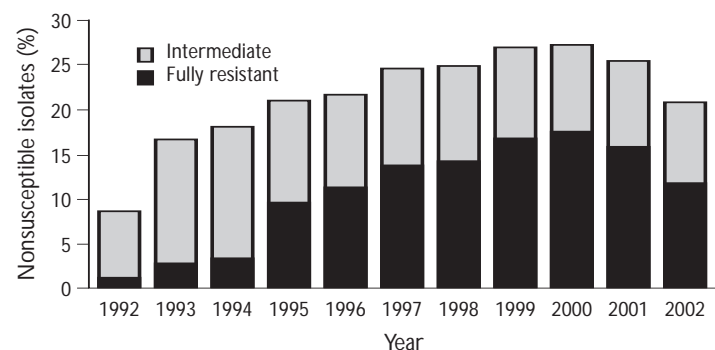
This shift was attributed to the increase in the incidence of penicillin nonsusceptible *S pneumoniae* (PNSP) (Figure 1). In fact, studies performed in the United States during the 1990s showed that PNSP accounted for 31% to 70% of the *S pneumoniae* recovered from children with recurrent or persistent AOM.^{5,17,18} This phenomenon was global, as data from France,²³ Spain,²⁴ and Israel²⁵ showed that PNSP accounted for 77% to 90% of the *S pneumoniae* recovered from children with refractory AOM during this time period.

On the basis of the data available in the 1980s and 1990s, managed care organizations and public health agencies structured empiric AOM treatment recommendations to provide coverage for *S pneumoniae*, especially PNSP, as the primary pathogen and *H influenzae* and *M catarrhalis* as the secondary and tertiary pathogens, respectively.

PCV-7 Vaccine: Impact on the Incidence of AOM

In February 2000, PCV-7 was introduced in the United States and recommended for the active immunization of infants and toddlers.²⁶ Although initially recommended for the prevention of invasive disease, PCV-7 also had a favorable impact on preventing infections by pneumococcal strains responsible for AOM. The 7 pneumococcal serotypes in the vaccine (4, 6B, 9V, 14, 18C,

Figure 1. Penicillin Nonsusceptible *S pneumoniae*, United States, 1992-2002



19F, and 23F) are commonly found in AOM, 5 of which are PNSP strains (6B, 9V, 14, 19F, and 23F).^{2,3,27,28} As the efficacy of PCV-7 immunization against AOM-causing serotypes became known, the AOM indication was added to the labeling of PCV-7.²⁶

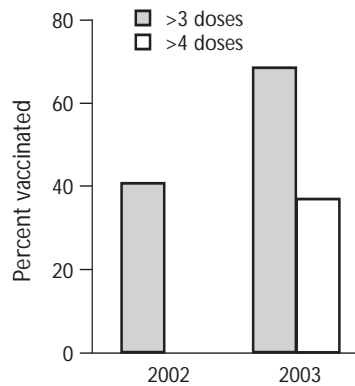
Based on the assumption that 20% of AOM cases were caused by vaccine-type serotypes, and that the vaccine would prevent 80% of those infections, Fireman et al predicted an overall 16% reduction in AOM.²⁰ Using somewhat different assumptions, Pelton and Klein estimated a 15% to 20% reduction in AOM.⁴

Although these predictions were mathematically sound, the initial clinical trials of PCV-7 vaccination found an overall reduction of 6% to 8.9%.^{19,20,29,30} However, of more interest to health plans and payer groups were the observed reductions in recurrent AOM and otologic surgical procedures, both of which can be far costlier than uncomplicated AOM. The study performed in the Northern California Kaiser Permanente system observed a 10% to 26% reduction in recurrent AOM and a 24% reduction in tympanostomy tube placement in children who received the PCV-7.²⁰

Impact of PCV-7 on the Microbiology of AOM

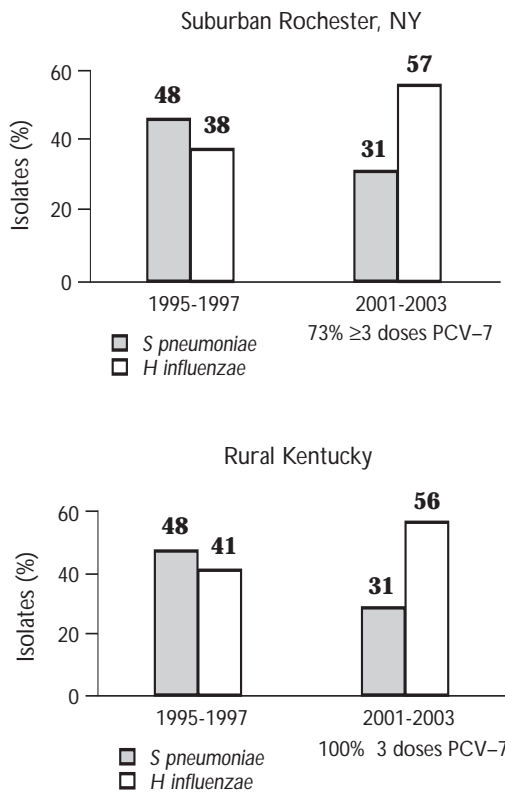
According to the National Immunization Survey, 40.8% of US children aged 19 to 35 months had at least 3 PCV-7 vaccinations in 2002; this number rose to 68.1% in 2003 (Figure 2).³¹ A number of vaccine shortages prevented vaccination in the full population,

Figure 2. PCV-7 Vaccination by Population, 19 to 35 Months of Age, 2002-2003



Source: Reference 31.
PCV-7 indicates heptavalent pneumococcal conjugate vaccine.

Figure 3. PCV-7 Vaccination by Population, 19 to 35 Months of Age, 2002-2003

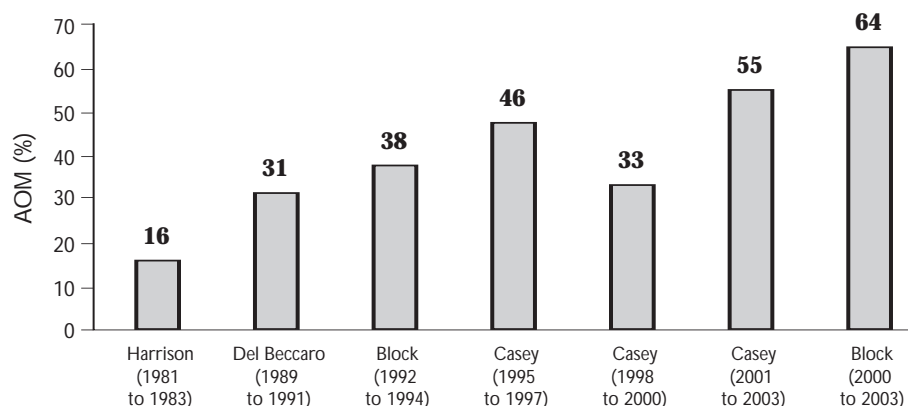


Sources: References 21 and 22.
AOM indicates acute otitis media; PCV-7 indicates heptavalent pneumococcal conjugate vaccine.

and many patients only received 2 doses of PCV-7 instead of the recommended 3 to 4 doses.³² Researchers found that children receiving only 2 doses of PCV-7 experienced a lesser reduction in otitis visits compared with those receiving 3 doses (6.5% reduction versus 7.8% reduction), and children who did not receive a third PCV-7 dose gradually lost the benefit of vaccination throughout the first year of life.²⁰ Fortunately, this shortage was resolved, and it is expected that the majority of the recommended pediatric population will receive the full complement of PCV-7 vaccinations in the future.

Two studies published in 2004 have shown that PCV-7 has had a major impact on the microbiology of AOM. The nearly 60% decrease in AOM caused by *S pneumoniae* serotypes contained in the vaccine^{22,30,33} has resulted in a corresponding shift in the proportion of cases caused by *H influenzae* and *M catarrhalis*.^{21,22} These 2 recent studies, one in rural Kentucky and another in suburban Rochester, New York, simultaneously reported from very different geographic and patient population bases a significant decrease in the overall proportion of *S pneumoniae* and increase in nontypable *H influenzae* when comparing pre- and post-PCV-7 AOM microbiology^{21,22} (Figure 3). The overall proportion of *S pneumoniae* decreased from 48% to 31% in both studies,^{21,22} and nontypable *H influenzae* increased from 41% to 56% in Kentucky²² and 38% to 57% in New York.²¹ These studies demonstrate a significant proportional shift in the microbiology of AOM in the pediatric population. Gram-negative pathogens accounted for about two thirds of all AOM pathogens recovered in children who had received 3 or 4 doses of PCV-7.^{21,22} Similar shifts in AOM microbiology were seen in Finnish studies.^{30,33}

Of additional interest was the dramatic increase in beta-lactamase-producing *H influenzae*. Compared with 5 years ago, beta-lactamase-producing *H influenzae* are more common (Figure 4). Based on the results of the 2 recent studies by Block et al²⁹ and Casey and Pichichero,²¹ there was a 47% to 57% increase in beta-lactamase-producing pathogens, accounting for nearly one half of all AOM pathogens recovered in children who have received 3 to 4 doses of PCV-

Figure 4. Persistent AOM Increase in Beta-lactamase-producing *H influenzae*

Sources: Reference 14, 15, 21, and 22.

AOM indicates acute otitis media.

7. When *H influenzae* was specifically broken out, the rate of beta-lactamase-producing *H influenzae* increased by 16% to 22% in the post-PCV-7 time period.^{21,22}

In addition to the PCV-7, 2 other factors may have contributed to the shifting microbiology of AOM seen since the 1990s. In January 1998, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) released a set of guidelines calling for physicians to conscientiously distinguish AOM from OME and to defer antibiotics for OME.³⁴ It was predicted that this would result in the avoidance of up to 8 million unnecessary courses of antibiotics annually. Also, there was a pronounced decrease in the use of chemoprophylaxis against AOM by practitioners, as the benefit of chemoprophylaxis was deemed too small³⁵ to justify its use in an era of rising antibacterial resistance.

Clinical Consequences

In protecting patients from infection by PNSP strains, PCV-7 has reversed the trend of rising rates of resistant *S pneumoniae*-causing AOM that was evident throughout the 1990s. Indeed there has been a documented reduction in the incidence of invasive disease caused by PNSP³⁶⁻³⁸ and AOM.²¹ Casey and Pichichero reported a 42% decrease in the proportion of PNSP in the 3

years after the release of PCV-7 compared with a 3-year period just before the release.²¹ Based on increasing PCV-7 coverage, the odds of AOM caused by vaccine-type PNSP have been greatly reduced.

When selecting antibiotics for the empiric treatment of infectious disease, practitioners should consider the CDC principles for the judicious use of antibiotics.³⁹ The first principle is to only prescribe an antibiotic when it is likely to be beneficial to the patient. To ensure this principle, the CDC guidelines for AOM recommend the use of specific diagnostic criteria that include the presence of otorrhea of middle ear origin or presence of middle ear fluid or effusion and signs or symptoms of acute local or systemic illness.³⁹ It has been recommended that pneumatic otoscopy be used to confirm the presence of middle ear fluid or effusion.^{39,40}

Once a diagnosis has been confirmed, the antibiotic selected should have activity against the most commonly occurring pathogens. As discussed earlier, the causative pathogens implicated in AOM have changed; there has been an increase in beta-lactamase-producing *H influenzae* and a decrease in resistant *S pneumoniae*. The serotypes of *S pneumoniae* not contained in PCV-7 are typically susceptible to treatment with amoxicillin, whereas beta-lactamase-producing *H influenzae* are typically resistant to amoxicillin.^{41,42}

Given the recent changes in the microbiology of AOM, empiric treatment still focuses on the same 3 main pathogens (*H influenzae* [including beta-lactamase-producing strains], *S pneumoniae*, and *M catarrhalis*), but the change in their frequency and resistance patterns should be taken into consideration. As full penetration of the PCV-7 vaccine in pediatric populations is achieved, it is increasingly likely that the primary pathogen implicated in AOM will be *H influenzae*.²² Economic consequences of this shift could result from an increased number of treatment failures associated with inadequate coverage of the implicated pathogens. The full effect of PCV-7 on the bacteriology of AOM will become more evident in the next few years. A continued shift to *H influenzae* is expected as vaccination with the full 4-dose recommended schedule of PCV-7 is achieved.

Appropriate Antibiotic Selection

When faced with suspected AOM, most clinicians treat the infection empirically. When selecting empiric therapy, providers often make assumptions about the patient caregiver's preferences for antibiotic therapy (dose frequency, duration of therapy, suspension taste, etc); these assumptions are not always correct. In a survey comparing the opinions of 400 parents and 100 pediatricians on antibiotics, parents selected side effects as the most important antibiotic factor, whereas pediatricians ranked this as least important, selecting dosing schedule as the most important factor.⁴³ (The next article in this supplement will explore these issues in more depth and also addresses issues of adherence.) The **Table** summarizes select oral therapies approved by the US Food and Drug Administration (FDA) for use in AOM.

Aminopenicillins. Aminopenicillins (particularly amoxicillin) have long been considered first-line therapy for the treatment of AOM. High-dose amoxicillin achieves middle ear fluid concentrations that should effectively eradicate penicillin-susceptible, intermediate, and some nonsusceptible strains of pneumococci.^{41,44} However, neither high-dose nor regular-dose amoxicillin will affect

beta-lactamase-producing *H influenzae*.⁴¹ The significant presence of gram-negative organisms in fully PCV-7-vaccinated children may make amoxicillin ineffective as an AOM treatment in populations that have recently been treated with antibiotics.^{21,22} Because of its low cost and relative safety, amoxicillin is still considered first-line therapy in all major guidelines.^{22,45,46} However, if the trend toward an increased frequency of beta-lactamase-producing organisms continues, the decision to use amoxicillin as first-line therapy for AOM may need to be reconsidered.

Amoxicillin/Clavulanate. To combat the presence of beta-lactamase-producing pathogens, clavulanate has been added to amoxicillin (amoxicillin/clavulanate). Traditional dosing of amoxicillin was at 45 mg/kg/day when used alone or in combination with clavulanate. When administered at 45/6.4 mg/kg/day, amoxicillin/clavulanate achieves suboptimal eradication rates against *H influenzae*. In 2 studies, reported eradication rates were 87% and 62%.^{47,48} When the dose of the amoxicillin component was raised to the currently recommended 90/6.4 mg/kg/day, eradication rates improved to 90% to 94%.^{49,50}

High-dose amoxicillin/clavulanate has been recommended by the AAP and the CDC for the treatment of AOM in patients who have failed previous therapy with amoxicillin.^{45,46}

Cephalosporins. A number of cephalosporins have been approved by the FDA for the treatment of AOM (Table), yet most of these agents are not considered appropriate for empirical therapy of AOM today. Of those approved, 3 oral cephalosporins (cefdinir, cefpodoxime, and cefuroxime) have been shown to possess the best activity against beta-lactamase-negative and beta-lactamase-positive gram-negative pathogens (*H influenzae* and *M catarrhalis*) as well as retaining reasonable activity against intermediate-susceptible *S pneumoniae*.^{22,51-57}

One cephalosporin, ceftriaxone, has been reserved for use parenterally for patients failing oral therapy or those with recalcitrant or severe disease. More than 99% of

Table. Select FDA-approved Agents for Use in AOM

Compound name	Brand name	AOM indication
Amoxicillin	Various	Infections caused by <i>Streptococcus</i> sp (alfa- and beta-hemolytic strains only), <i>S pneumoniae</i> , <i>Staphylococcus</i> sp, or <i>H influenzae</i>
Amoxicillin/Clavulanate	Augmentin ES-600	For the treatment of pediatric patients with recurrent or persistent AOM due to <i>S pneumoniae</i> (penicillin MICs $\geq 2 \mu\text{g/mL}$), <i>H influenzae</i> (including beta-lactamase-producing strains), <i>M catarrhalis</i> (including beta-lactamase-producing strains) characterized by the following risk factors: antibiotic exposure for AOM within the preceding 3 months and either of the following: age of 2 years or younger or daycare attendance. Note: AOM-caused <i>S pneumoniae</i> alone can be treated with amoxicillin. Augmentin ES-600 is not indicated for the treatment of AOM caused by <i>S pneumoniae</i> with penicillin MIC at least $4 \mu\text{g/mL}$.
Cefdinir	Omnicef	Acute bacterial otitis media caused by <i>H influenzae</i> (including beta-lactamase-producing strains), <i>S pneumoniae</i> (penicillin-susceptible strains only), and <i>M catarrhalis</i> (including beta-lactamase-producing strains).
Cefixime	Suprax	Otitis media caused by <i>H influenzae</i> (beta-lactamase-positive and -negative strains), <i>M catarrhalis</i> , and <i>S pyogenes</i> .
Cefpodoxime proxetil	Vantin	AOM due to <i>S pneumoniae</i> , <i>H influenzae</i> (including beta-lactamase-producing strains), <i>M catarrhalis</i> (including beta-lactamase-producing strains), or <i>S pyogenes</i> .
Ceftibuten	Cedax	Acute bacterial otitis media caused by <i>H influenzae</i> (including beta-lactamase-producing strains), <i>M catarrhalis</i> (including beta-lactamase-producing strains), or <i>S pyogenes</i> . Note: Although ceftibuten used empirically was equivalent to comparators in the treatment of clinically or microbiologically documented AOM, the efficacy against <i>S pneumoniae</i> was $< 23\%$. Therefore, give ceftibuten empirically only when adequate antimicrobial coverage against <i>S pneumoniae</i> has been previously administered.
Cefuroxime	Ceftin	Acute bacterial otitis media caused by <i>S pneumoniae</i> , <i>H influenzae</i> (beta-lactamase-producing strains), <i>M catarrhalis</i> (beta-lactamase-producing strains), and <i>S pyogenes</i> .
Azithromycin	Zithromax	AOM in children 6 months of age and older with AOM caused by <i>H influenzae</i> , <i>M catarrhalis</i> , or <i>S pneumoniae</i> .
Clarithromycin	Various	AOM caused by <i>H influenzae</i> , <i>M catarrhalis</i> , or <i>S pneumoniae</i> .
Erythromycin Ethylsuccinate/Sulfisoxazole	Various	AOM caused by susceptible strains of <i>H influenzae</i> .
Trimethoprim	Bactrim, Septra	AOM in children due to susceptible strains of <i>H influenzae</i> or <i>S pneumoniae</i> . There are limited data on the safety of repeated use in children < 2 years of age. Not indicated for prophylactic use or prolonged administration.

FDA indicates Food and Drug Administration; AOM, acute otitis media; MIC, minimal inhibitory concentration.

penicillin-susceptible and intermediate *S pneumoniae* isolates and 85% of penicillin-resistant *S pneumoniae* isolates are susceptible to ceftriaxone administered parenterally.⁵⁶ Ceftriaxone also achieves complete eradication of *H influenzae*.^{58,59}

The 1998 CDC guidelines recommended the use of cefuroxime in addition to amoxicillin/clavulanate as a treatment option for patients failing therapy with amoxicillin.⁴⁵ The 2004 AAP/American Academy of Family Physicians (AAFP) guidelines recommend cefdinir, cefpodoxime, and cefuroxime as the preferred cephalosporins, especially if penicillin allergy is suspected.⁴⁶ Recent evidence suggests that the incidence of cross-reactivity between penicillins and cephalosporins is less than 0.5%.⁶⁰

Macrolides. Erythromycin is no longer recommended for AOM because of rising levels of macrolide resistance.⁴⁵ Studies have shown that pneumococci resistant to erythromycin are also resistant to clarithromycin and azithromycin.^{61,62} For this reason the 1998 CDC guidelines do not recommend their use and the 2004 AAP/AAFP guidelines recommend their use only in the case of severe type I allergic reactions to penicillins.^{45,46}

Future Implications

Data gathered on the microbiology of AOM between 2000 and 2003 do not yet illustrate the full effect of the PCV-7 vaccine, because a significant portion of the pediatric population was not fully vaccinated during that time period (Figure 2).³¹ Because of shortages, many patients received only 2 doses of PCV-7 instead of the recommended 3 to 4 doses.³² As previously discussed, AOM protection is not sustained through the first year of life without the third PCV-7 dose.²⁰ Now that the PCV-7 shortage is over, it is expected that the majority of the pediatric population will receive the recommended 3 to 4 PCV-7 doses. Only after this has occurred can the full population impact of PCV on the microbiology of AOM be assessed.

As the percentage of the pediatric population vaccinated with PCV-7 increases, the trends of proportional increases in nonvaccine pneumococcal serotypes and *H influenzae* and *M catarrhalis* isolated in AOM may

continue, further shifting the microbiology of AOM. These continued changes may well alter the face of AOM in several ways. First, by further decreasing AOM caused by vaccine-type *S pneumoniae*, AOM outcomes should improve as suggested by the decreases in recurrent otitis and tympanostomy tube insertion after PCV-7 vaccination observed in Finland and the United States.^{19,30,33,63} Second, by increasing the rates of AOM caused by *H influenzae*, AOM may be associated with less severe inflammatory reactions and a less visually inflammatory view at otoscopy.⁶⁴⁻⁶⁸ Acute mastoiditis is a main complication of AOM that can lead to or is associated with further complications, such as epidural, subdural, extradural, cerebellar, and periosteal abscesses, cavernous or lateral sinus vein thrombosis, bacterial meningitis, labyrinthitis, petrositis, facial nerve palsy, and hearing loss. Acute mastoiditis has been associated more often with infection by *S pneumoniae*.⁶⁹⁻⁷² A shift away from *S pneumoniae* as the dominant pathogen in AOM may lead to less complications.

The increased prevalence of nontypable *H influenzae* and the reduced prevalence of antibiotic-resistant *S pneumoniae* in AOM brings into question future empiric therapy. Empiric treatment of uncomplicated AOM with amoxicillin (80-90 mg/kg/day) may be less effective in the future if the increasing rates of *H influenzae* and *M catarrhalis* as a cause of AOM continues along with a corresponding increase in the proportion of beta-lactamase-producing organisms.

Conclusion

Although the microbiological landscape of AOM was relatively constant over the past 30 years, the introduction of PCV-7 has caused an abrupt alteration since its release in the United States in 2000. This shift in the causative pathogens of AOM can have a direct effect on empiric treatment. Just as the decrease in vaccine-type pneumococcal serotypes left behind a proportional increase in nonvaccine-type serotypes, this shift has also been accompanied by a proportional increase in infections caused by *H influenzae*, bringing the risk of beta-lactamase production to the forefront as a focus on

treatment failure. As the proportion of the population vaccinated with PCV-7 increases, it is expected that this trend will continue.

Although the economic consequences of the shift in AOM pathology are still being determined, this shift should be considered by managed care when structuring their formulary. The next article in this supplement will discuss the importance of improving AOM outcomes through proper antibiotic utilization and adherence. Managed care professionals must ensure that the most appropriate agents for use as empiric treatment of AOM in the post-PCV-7 era are available and appropriately positioned within health plan formularies to encourage proper use. Given the current trends, it is expected that recognition of the shift in *H influenzae* rate by practitioners and managed care organizations may contribute to fewer AOM treatment failures, thereby containing the direct and indirect costs attributed to AOM.

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