

The Impact of Vaccination on Rhinosinusitis and Otitis Media

Michael S. Benninger · Ryan Manz

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Abstract Routine childhood vaccination has affected frequency and bacteriology of acute otitis media (AOM) and acute bacterial rhinosinusitis (ABRS). Routine influenza vaccination moderately reduces AOM, and the *Haemophilus influenzae* type b vaccine likely had a minor role in AOM and ABRS. The conjugated pneumococcal vaccine has drastically reduced invasive pneumococcal disease and caused a moderate decrease in AOM and, likely, ABRS. The vaccine serotypes of *Streptococcus pneumoniae* have been all but eliminated, but other serotypes have emerged as potential causes of invasive disease. Antibiotic resistance in pneumococcal disease seems to have decreased. A decrease in the overall prevalence of *S. pneumoniae* may have resulted in an increased incidence of *Staphylococcus aureus* as a pathogen in AOM and ABRS due to the concept of bacterial interference.

Keywords Vaccines · Vaccination · Rhinosinusitis · Sinusitis · Otitis media · Pnevna · Bacterial interference

Introduction

Acute Bacterial Rhinosinusitis

Nasal and sinus symptoms are among the most common reasons for physician office visits. These symptoms can

have infectious or noninfectious causes. Rhinosinusitis is “a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses” [1]. It is further identified by the length of time that the inflammation persists. Although inflammation can be the result of many causes, much interest has focused on infectious causes. Most infectious causes of rhinosinusitis are secondary to viruses that are usually self-limited, but about 0.5%–2.0% of patients with acute rhinosinusitis develop acute bacterial rhinosinusitis (ABRS), an infection that lasts less than 4 weeks and involves the mucosa of the nose and paranasal sinuses [1]. This disease process has been estimated to effect three of every 1,000 people in the United States each year, with some individuals experiencing multiple episodes per year. ABRS is more common in adults than children, and the incidence seems to be increasing [2, 3, 4].

Streptococcus pneumoniae (20%–45%) and *Haemophilus influenzae* (22%–35%) are traditionally the predominant organisms in ABRS in adults [2]. *S. pneumoniae* (30%–43%), *H. influenzae* (20%–28%), and *Moraxella catarrhalis* (20%–28%) are traditionally reported as the predominant organisms in ABRS in children [2]. *Staphylococcus aureus* has often been considered a contaminant in the past, but a recent meta-analysis suggests that *S. aureus* is a true pathogen in about 10% of cases of ABRS in adults [3, 4].

Chronic rhinosinusitis (CRS) is also a common entity, affecting up to 30 million patients each year [1]. The definition of CRS is rhinosinusitis lasting for longer than 12 weeks in duration [1]. Although ABRS is almost always infectious in etiology, CRS is associated with several conditions that result in inflammation in the nose and sinuses. Although infectious agents may play a role in many patients, a direct correlation between viruses, fungi, and bacteria has been difficult to substantiate.

M. S. Benninger (✉) · R. Manz
Head and Neck Institute, The Cleveland Clinic,
9500 Euclid Avenue, A-71,
Cleveland, OH 44139, USA
e-mail: benninm@ccf.org

R. Manz
e-mail: manzr@ccf.org

Acute Otitis Media

Acute otitis media (AOM) is also a very common respiratory tract infection that is more commonly reported in children than adults. In fact, AOM is one of the most common infections in children, with 80%–90% of children experiencing one episode by age 2 years [5]. *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are the three most common bacteria traditionally cultured from middle ear fluid that is aspirated or spontaneously draining in the setting of AOM [6].

Antibiotic Resistance

Antibiotic-resistant strains are a concern in AOM and ABRS. About 40% of *S. pneumoniae* isolates have been found to be resistant to two or more of the antibiotics tested, and more than 28% were resistant to three or more antibiotics, whereas up to 70% of nontypeable *H. influenzae* isolates have been found to be β -lactamase positive [7, 8].

The goal of this article is to describe the impact of vaccination on the incidence, prevalence, and severity of rhinosinusitis and otitis media. Given the heterogeneity of CRS, the discussion primarily revolves around ABRS and AOM. The routine use of the 7-valent pneumococcal vaccine, PCNV7, has had an impact on more common diseases such as ABRS and AOM as well as on invasive disease. This article also reviews in detail the current literature and highlights the changes in pathogenicity, incidence, and bacterial resistance of ABRS and AOM after the widespread use of conjugate pneumococcal vaccine.

Overview of *Haemophilus influenzae* and *Streptococcus pneumoniae* Vaccines

Haemophilus influenzae Type b Vaccine

Since 1991, conjugate *H. influenzae* type b (Hib) vaccines have been given as part of a routine childhood vaccination regimen. This vaccination has all but eliminated *H. influenzae* meningitis and supraglottitis in vaccinated populations. Even children who do not receive vaccination but live in a widely vaccinated area are often protected by herd immunity [9]. Nonvaccine strains of *H. influenzae* still play a significant role in ABRS, AOM, and other respiratory infections.

Streptococcus pneumoniae Vaccines

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, and sepsis worldwide [10]. More

than 90 serotypes of *S. pneumoniae* have been isolated, and multiple serotypes have been shown to cause invasive disease in humans, as opposed to *H. influenzae*, in which most invasive disease was caused by Hib [11]. A 23-valent pneumococcal polysaccharide vaccine has been available and in use for many years. This vaccine is recommended for patients at high risk of invasive pneumococcal disease, including patients who are asplenic, immunocompromised, institutionalized, or older than 65 years of age. Unfortunately, this vaccine is not effective in children younger than 2 years of age, a population at high risk of invasive pneumococcal disease [11]. In the United States, seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) were responsible for more than 80% of the invasive disease caused by *S. pneumoniae* in young children prior to widespread pneumococcal vaccination [11].

In February 2000, a heptavalent conjugate pneumococcal vaccine (PCNV7) was approved for use in children younger than 2 years of age [11]. The widespread use of this vaccine has led to an impressive decrease in pneumococcal invasive disease [4, 12–14]. Additionally, the effect seems to have extended onto the nonvaccinated and adult populations via herd immunity [13, 15]. A population-based study evaluating invasive pneumococcal disease was conducted in an area with widespread and continuous use of conjugate pneumococcal vaccination in children. The rates of invasive pneumococcal disease decreased by 32% in adults 20–39 years of age, 8% in those 40–64 years of age, and 18% in those 65 years of age and older [13]. Another study of a multihospital health system showed an even more dramatic reduction in invasive pneumococcal disease, with a reduction of 68%–70% in children, 42% in adults 18–49 years of age, and 30% in adults older than 64 years of age [4, 12]. Another population-based study showed that patients who did contract an invasive pneumococcal disease had a 78% decrease in mortality after 2001 compared with patients treated before 1999 [15].

Literature Review

A MEDLINE search of the literature published between 1990 and 2010 was conducted. The search terms used were “acute otitis media,” “sinusitis,” “acute sinusitis,” “acute rhinosinusitis,” “pneumococcal vaccine,” “pneumococcal vaccination,” “*Haemophilus influenzae* vaccine,” and “Prevnar.” Articles were identified that described changes in pathogenic organisms in AOM or ABRS, changes in disease incidence, changes in severe outcomes and complications of those diseases, changes in bacterial resistance, and those articles that proposed changes in treatment after the widespread use of

vaccines. These references served as the source for this review. Once identified, the reference lists from these articles used were also reviewed to identify significant additional information, resulting in inclusion of additional articles.

Effectiveness of Vaccines in Acute Otitis Media and Acute Bacterial Rhinosinusitis

Acute Otitis Media

Many studies that evaluated the effectiveness of the PCNV7 on invasive disease also evaluated the impact on AOM. The studies that evaluated the impact on AOM were almost exclusively in pediatric populations. A randomized, double-blind efficacy trial compared conjugate pneumococcal vaccine with hepatitis B vaccine as a placebo. The number of all AOM events decreased by 6% in the PCNV7 arm compared with placebo. Additionally, culture-confirmed episodes of pneumococcal otitis media decreased by 34%, and the number of episodes caused by serotypes contained in the vaccine decreased by 57% [16]. Follow-up of this population revealed that the vaccinated group had a 3.5% rate of requiring tympanostomy tubes, while the placebo group had a rate of 5.7% [17]. This is an overall modest effect on AOM, but due to the incidence of the disease, the societal impact could be substantial. It has been estimated that with universal use in the United States, 1.2 million of the 20 million cases of otitis media could be prevented [16]. Other studies have supported these findings, with a decrease in episodes of recurrent otitis media of up to 26% [18]. Evidence also indicates that widespread pneumococcal vaccination may reduce tympanostomy tube placement by 23% [19, 20]. A recent Cochrane Database systemic review concluded that if PCNV7 is given during infancy, the overall incidence of AOM is reduced by about 7%. Vaccination of older children showed no significant effect [21••].

Although the Hib vaccine was effective in eliminating more than 99% of invasive *H. influenzae* infections [9], the Hib strain traditionally played a less significant role in AOM than invasive pneumococcal disease. Before the era of widespread Hib vaccination, studies reported Hib isolates from middle ear fluid in 5%–10% of cases of AOM [22, 23]. No reports to date have shown a decrease in incidence of *H. influenzae*-positive AOM or a decrease in the overall incidence of AOM after the widespread use of the Hib vaccine. However, it could be argued that the reduction in Hib meningitis may be related to a decrease in Hib AOM and therefore a decrease in Hib otitic meningitis, although this has not been reported in the literature.

Viral vaccines also have made a minor contribution to the prevention of AOM. Viral illness often precedes AOM, causing mucosal edema and leading to eustachian tube dysfunction. As a result, the influenza vaccine was shown in a recent meta-analysis to reduce the incidence of AOM in healthy children younger than 18 years of age from 1.4% to 0.7% per year [24••].

Acute Bacterial Rhinosinusitis

There is no strong evidence of a change in the incidence of ABRS after widespread use of conjugate pneumococcal vaccination. Furthermore, the impact of universal pneumococcal vaccination on the incidence of episodes of ABRS is more difficult to assess than the impact on AOM. ABRS can be caused by many pathogens and is often viral [2, 25]. Additionally, otoscopic examination or otorrhea is often diagnostic for AOM, where rhinorrhea, even when discolored, is less specific. Physical examination with rhinoscopy is more challenging and less reproducible than otoscopy, making ABRS more difficult to diagnose.

A clear and parallel shift has occurred on pathogens associated with ABRS and AOM, as discussed subsequently. This is not unexpected, because the pathogenic organisms are similar for ABRS and AOM. The shift in the microbiology of ABRS has been suggested to have occurred because of the involvement of the same pathogens in AOM and ABRS [4, 26]. Additionally, the middle ear and paranasal sinuses have been considered different parts of the same system as part of a concept of a unified airway. The middle ear communicates indirectly with paranasal sinuses via connections between the eustachian tube, nasopharynx, and nose [27].

This pathogen shift may have an important effect on the severity of ABRS. Benninger et al. [28] have shown that ABRS patients infected with *S. pneumoniae* have more significant symptoms and worse radiographic findings than those infected with *H. influenzae*. As discussed subsequently, substantial evidence indicates that the rate of *S. pneumoniae* ABRS has decreased, and the rates of *H. influenzae* and *M. catarrhalis* have increased. This could result in less severe symptoms and radiographic findings in patients who contract ABRS. Additionally, there have been reports of increased *S. aureus* culture rates in the setting of ABRS and AOM [29, 30]. Although *S. aureus* in ABRS was thought to be a contaminant, a recent meta-analysis of randomized clinical trials of antibiotic therapy in ABRS strongly suggests that *S. aureus* is a real pathogen and should be considered in the treatment of ABRS [3•]. If there is an increase in culture rates for *S. aureus* in ABRS in adults and children, then the positive impact of pneumococcal and *H. influenzae* vaccination

may be moderated; this may have some impact on treatment decisions [4].

The Hib vaccination has had an effect on ABRS and on periorbital cellulitis. Before the widespread use of the Hib vaccine, Hib sinusitis was the leading cause of periorbital and orbital cellulitis. After the use of Hib, the annual rate of periorbital cellulitis decreased by nearly 75%, and the number of cases with a positive culture for Hib was reduced by 70% [31].

Pathogenicity and Serotype Shift

Acute Otitis Media

A significant shift has taken place in AOM bacteriology and pathogenicity in the time periods before and after routine immunizations. Casey and Pichichero [32] looked at three intervals (1995–1997, 1998–2000, 2001–2003) during the transition to widespread conjugate pneumococcal vaccination. They found sequential decreases in *S. pneumoniae* cultured from middle ear aspirates (48%, 44%, and 31%), with a simultaneous increase in *H. influenzae* isolates (38%, 43%, and 57%) [32]. Another study compared cultures from spontaneously draining ears in the time before and after the introduction of the vaccine. The frequency of *S. pneumoniae* decreased from 54% to 44%, while the frequency of *H. influenzae* increased from 18% to 24%. The frequency of *M. catarrhalis* increased slightly, from 10% to 12%. Importantly, *S. aureus* was only present in 8% of samples prior to widespread vaccination and was present in 18% of samples afterward. More than 50% of the *S. aureus* isolates were methicillin resistant [30].

Acute Bacterial Rhinosinusitis

Widespread use of PCNV7 has resulted in a recognizable shift in the pathogenic organisms in ABRS, as well as the colonizing organism cultured from the nasopharynx. Brook et al. [29] compared endoscopically directed cultures in adults with acute maxillary sinusitis from the 4 years prior to and the 5 years after the widespread use of the conjugate pneumococcal vaccine. *S. pneumoniae* dropped from the most common pathogen, at 46% of isolates, to the second most common, at 35%, after the use of the vaccine; *H. influenzae* increased from 36% to become the most common pathogen, at 43%. There were also modest increases in the rate of cases caused by *M. catarrhalis* and *S. aureus* [29].

In a similar study, nasopharyngeal cultures were obtained in children with acute maxillary sinusitis before

and after widespread use of conjugate pneumococcal vaccination [33•]. *S. pneumoniae* decreased from 43% of isolates to 25%, whereas *H. influenzae* increased from 35% to 41%, and *M. catarrhalis* remained stable (13%–14%). *Streptococcus pyogenes* increased from 7% to 12%, and *S. aureus* increased from 4% to 8% [33•].

Serology

The serology of *S. pneumoniae* responsible for AOM and ABRS as well as invasive pneumococcal disease has shifted. There has been a significant decrease in vaccine serotypes and an increase in serotypes not found in the vaccine [16, 34–36]. In one recent prospective study, the number of episodes of AOM attributable to serotypes contained in the vaccine was virtually absent, whereas the number of episodes attributable to other serotypes has increased to nearly 40%, almost completely replacing vaccine serotypes. The serotypes found in the vaccine are known to cause more severe and more invasive disease. It could be expected that the reduction in these serotypes might have an impact on disease severity in ABRS and AOM. This, however, has not been reported in the literature to date.

A recent review of the impact of 7-valent pneumococcal vaccine in Alaskan children showed a rather drastic shift in serology. There was a 96% decrease in the serotypes contained in the vaccine, but since 2004, there was a 140% increase in invasive pneumococcal disease by serotypes not contained in the vaccine. Serotype 19A, a nonvaccine serotype, accounted for 28.3% of invasive cases in children younger than 2 years of age [37•]. In another study, nasopharyngeal carriage rates in children who underwent pressure equalization tubes revealed nonvaccine serotypes in 50.7% of all strains isolated. Serotypes 19A and 35B account for 7% and 12% of all pneumococcal isolates, respectively. Serotype 19A was found to be resistant to all oral agents tested, and 35B was resistant to penicillin and cefuroxime [4, 38]. Serotype 19A has also emerged as an important cause of coalescent mastoiditis and a leading cause of pediatric chronic sinusitis [39, 40].

There has been speculation that this serotype replacement may reduce the long-term efficacy of the 7-valent conjugate pneumococcal vaccine against AOM [4, 36]. This has led to the development of newer conjugate vaccines containing the newly emergent serotypes [35]. The recent introduction of the 13-valent conjugate pneumococcal vaccine will provide coverage of many of the newly emerging serotypes [35], but the long-term implications of the additional serotype vaccination likely will not be seen for 2–4 years.

The Hib vaccine has all but eliminated Hib isolates in the United States. Prior to widespread use of this vaccine, Hib was isolated in about 5%–10% of *H. influenzae* AOM and ABRS. Reports after widespread use rarely list Hib as a pathogen in AOM or ABRS. Nontypeable *H. influenzae* is the responsible pathogen in the vast majority—if not all—of the *H. influenzae*-positive AOM and ABRS cases [5, 6].

Bacterial Interference

There is growing interest in the impact of antibiotics and vaccines on the normal flora that colonize the nose and nasopharynx. The interaction between normal flora and pathogens is described as bacterial interference. Bacterial interference is a dynamic antagonistic interaction between at least two organisms that affects the life cycle of each. It has been speculated that the increase in the culture identification of *S. aureus* in isolates of ABRS and AOM in the era of post-pneumococcal vaccinations may be in part a result of this phenomenon of bacterial interference. Normal flora in the nasopharynx and pharynx tend to be more competitive in these environments and likely play a protective role against the development of AOM and ABRS, as well as against specific pathogenic organisms. In carriers of *S. pneumoniae*, the rates of *S. aureus* carriage were found to be much lower than in individuals not colonized with *S. pneumoniae* [41]. Bogaert et al. [42] have suggested that since the introduction of pneumococcal vaccination, bacterial interference may be a contributing factor in the increase in incidence of AOM caused by *S. aureus*. They found that as the colonization of the nasopharynx with serotypes of *S. pneumoniae* found in PCNV7 decreased, the colonization with *S. aureus* increased. This inverse correlation was not seen with nonvaccine serotypes [42].

An increase in the incidence of AOM and ABRS caused by *S. aureus* may be an indirect effect of the reduction of *S. pneumoniae* after the widespread use of conjugate pneumococcal vaccine. Brook et al. [29, 30, 33•] have shown in three separate studies that the incidence of positive cultures for *S. aureus* appears to be increasing in the setting of AOM and ABRS after the introduction of PCNV7. The impact of these potential interactions is not yet well-understood, but the concept of bacterial interference is becoming more important, and the impact of Hib and pneumococcal vaccination on the flora of the upper airway is not fully understood.

It has been shown that nonpathogenic organisms in the normal flora, such as *Streptococcus viridans*, α -hemolytic streptococci, nonhemolytic species, and some

Peptostreptococcus and *Prevotella* species, may interfere with growth of pathogenic bacteria. They may provide a natural defense against certain infections [43].

In a study of 132 children receiving 10 days of antibiotics immediately followed by 10 days of twice-daily treatment with α -hemolytic streptococci spray or placebo, the recurrence rate of AOM at 3 months was lower in the α -hemolytic streptococci group compared with placebo. The rate of serous otitis media recurrences among patients who did not develop recurrent AOM was lower in the α -hemolytic streptococci group [44]. Although it is difficult to know if such treatments would be effective in establishing more normal flora after changes in flora that occur following vaccination, further studies may be of value.

Other bacteria that have been studied for their potential protective role include *Lactobacillus rhamnosus* and *Bifidobacterium lactis*. In a randomized controlled trial of healthy Finnish children, one arm was given formula supplemented with these bacteria, and the other arm given unsupplemented formula. Children receiving the bacteria had a 28% decrease in episodes of AOM compared with the placebo arm. No adverse events from the probiotic supplementation were reported [45].

Antibiotic Resistance

Since the introduction and widespread use of PCNV7, many studies have shown decreased rates in antibiotic-resistant *S. pneumoniae* cultured in the setting of AOM and ABRS [6, 7, 13, 30, 32, 46–50]. In one of the more striking examples, Casey and Pichichero [32] showed a reduction in penicillin-resistant *S. pneumoniae* strains in isolates collected before versus after the use of PCNV7 from 34% to 14%. The same study showed an associated increase in the β -lactamase-producing strains of *H. influenzae* from 46% to 55% [32].

Another study noted a decrease in the rate of pneumococcal isolates nonsusceptible to penicillin in the nasopharyngeal cultures of children younger than 7 years of age with acute respiratory infections from 25% before the widespread use of PCNV7 to 12% afterward [48]. A cross-sectional survey of Alaskan children showed a decrease in the nasopharyngeal carriage of pneumococcal isolates nonsusceptible to trimethoprim-sulfamethoxazole from 44% to 16% between 2000 and 2004. However, the rate of strains resistant to penicillin remained stable at 36%. Among strains resistant to penicillin, there was an increase in the proportion of serotype 19A from 10% to 32% [47]. A summary of antibiotic resistance trends can be found in Table 1.

Table 1 Antibiotic resistance trends with patients' ages and sources of culture

Study (year)	Patients' ages	Source	Changes in resistance patterns ^a
Whitney et al. [13] (2003)	Varied	Sterile body site ^b	1999–2001: 35% reduction in penicillin-resistant <i>Streptococcus pneumoniae</i>
Block et al. [6] (2004)	7–24 mo	Middle ear	1992–2003: <i>S. pneumoniae</i> penicillin resistance decreased from 25% to 19%; <i>Haemophilus influenzae</i> β -lactamase positive increased from 23% to 36%
Black et al. [46] (2004)	Unknown	Sterile body site ^b	1998–2002: penicillin-resistant <i>S. pneumoniae</i> decreased from 29% to 20%, erythromycin from 30% to 15%, and tetracycline resistance from 39% to 14%
Casey and Pichichero [32] (2004)	2 mo–5 y and older	Middle ear	1995–2003: penicillin-resistant <i>S. pneumoniae</i> strains decreased from 34% to 14%
Huang et al. [49] (2005)	<7 y	Nasopharynx	2001–2004: penicillin-resistant <i>S. pneumoniae</i> strains remained stable at 34%–38%
Garbutt et al. [48] (2006)	<7 y	Nasopharynx	2000–2004: penicillin-resistant <i>S. pneumoniae</i> strains decreased from 25% to 12%, <i>H. influenzae</i> increased the β -lactamase-positive rate from 46% to 55%
Kyaw et al. [50] (2006)	All ages	Sterile body site ^b	1999–2004: population study showed a reduction in penicillin-resistant <i>S. pneumoniae</i> from 6.3 cases/100,000 to 2.7/100,000
Sahm et al. [7] (2007)	Unknown	Sinonasal culture	2000–2004: amoxicillin/clavulanate-resistant <i>S. pneumoniae</i> strains increased from 6.5% to 12.9% of total patient population in study
Park et al. [47] (2008)	3–59 mo	Nasopharynx	2000–2004: trimethoprim-sulfamethoxazole-resistant <i>S. pneumoniae</i> strains decreased from 44% to 16%; penicillin-resistant strains remained stable at 36% vs 37%
Brook and Gober [30] (2009)	5 mo–12 y	Spontaneous otorrhea	1993–2008: penicillin-resistant <i>S. pneumoniae</i> strains decreased from 18% to 4%; methicillin-resistant <i>Staphylococcus aureus</i> increased from 0% to 10% of total patient population in study

^a Percentages represent the percentage of total *S. pneumoniae* isolates collected, unless otherwise noted

^b Sterile body site represents any sample collected from an area that is usually sterile, such as cerebrospinal fluid or blood

Conclusions

Widespread use of infant and childhood vaccines has resulted in changes in the frequency and bacteriology of AOM and ABRS. Routine influenza vaccination has yielded a moderate reduction in the rate of AOM in healthy children. The Hib vaccine has drastically reduced the incidence of invasive disease and likely played a minor role in AOM and ABRS. The PCNV7 vaccine has had a substantial effect on invasive pneumococcal disease and a moderate effect on noninvasive disease. The vaccine serotypes of *S. pneumoniae* have been all but eliminated, and there seems to be an overall decrease in antibacterial resistance. On the other hand, as these dangerous pneumococcal strains have become less prev-

alent, other serotypes have emerged as potential causes of invasive disease. Newly developed vaccines will likely include the newly emerged invasive pneumococcal strains, as the pathogenicity of these diseases continues to evolve. The decrease in the overall prevalence of *S. pneumoniae* may have resulted in increased incidence of *S. aureus* as a pathogen in AOM and ABRS due to a change in colonization and perhaps bacterial interference. The concept of bacterial interference also suggests there may be a role in the future for the use of probiotics in prevention of AOM and ABRS.

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- Of importance
- Of major importance

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