


Otitis Media in Fully Vaccinated Preschool Children in the Pneumococcal Conjugate Vaccine Era

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Abstract

Objectives. To evaluate the effect of pneumococcal conjugate vaccine (PCV13) on the burden of acute otitis media (AOM) and to evaluate the characteristics of AOM versus otitis media with effusion (OME) in the 2 PCV periods. **Methods.** A cohort of fully vaccinated children aged 18 to 60 months diagnosed with AOM from 2006 to 2015 was identified. Patients with otorrhea/bulging tympanic membrane were considered as true AOM, while those without bulging/otorrhea were considered to have OME. Burden of true AOM in the PCV7 and PCV13 periods and clinical features of true AOM versus OME were compared. **Results.** Of 393 episodes in our cohort, 50.8% occurred in PCV7 period. Burden of true AOM in the 2 PCV groups was similar: 26% in PCV7 versus 26.4% in PCV13 (odds ratio [OR] = 1.02, 95% confidence interval [CI] = 0.65–1.60). Factors significantly associated with OME were cold season (OR = 1.54, 95% CI = 1.04–2.4), fever (OR = 2.05, 95% CI = 1.29–3.3), and recurrence (OR = 2.24, 95% CI = 1.22–4.09). No complications of AOM were identified. Majority episodes were treated with antibiotics. **Conclusion.** Unlike the role of PCV13 in reducing invasive pneumococcal disease, its effect on reducing the burden of AOM is minimal as compared with PCV7. With regard to characteristics of AOM versus OME, findings of tympanic membrane should be used to suggest a diagnosis of AOM, instead of occurrence of fever or recurrence of AOM episodes. Using this approach would help in guiding the use of antibiotics appropriately.

Keywords

otitis media, PCV vaccine

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Introduction

Otitis media (OM) is one of the most common illnesses in the pediatric population and the leading cause of antibiotic prescription.^{1–5} More than 30% of infants develop at least one episode of OM before the age of 6 months, and about 80% by their third birthday, with more than 40% having >3 episodes.^{2–7} About 4 billion dollars are spent every year on acute otitis media (AOM)–related health care in the United States. OM is also known to have consequences beyond earache including a high socioeconomic impact, and to affect parental quality of life.^{8–14}

In 2000, the heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in the United States, which reduced the sick visit rates because of AOM by ≥20%, as well as recurrence of AOM.^{2,3,5,9,15,16} However,

a Cochrane meta-analysis of randomized controlled studies in about 48 000 children up to 12 years of age, from the United States, Europe, and Israel, had concluded that the effect of PCV7 to PCV11 in preventing AOM was modest to insignificant.¹⁷

In 2004, the American Academy of Pediatrics (AAP) guidelines for diagnosis and management of OM in children recommended watchful observation as the management of majority of the cases of OM, including mild cases of bacterial AOM.¹⁸ A study by McGrath et al,

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reported an initial reduction in antibiotics dispensed by prescription for AOM from 2001 to 2007.¹⁹ However, the same study reported a rebound increase in antibiotic dispensing similar to the pre-guideline era, suggesting that the earlier decline was not sustainable. Another study based on the US National Ambulatory Medical Care Survey also demonstrated no decrease in antibiotic prescriptions for the management of AOM.²⁰

Finally, after the introduction of the 13-valent PCV in the United States in 2010, substantial evidence was accumulated that demonstrates that routine PCV13 vaccination has further reduced the incidence of invasive pneumococcal disease in persons of all ages.²¹⁻²⁸ Little evidence is available about further reduction in incidence of pediatric AOM in the PCV13 era,^{1,29,30} as well as about reduction in complications of AOM caused by *Pneumococcus*, including acute mastoiditis, cavernous sinus thrombosis, and meningitis, to name a few.^{28,31,32}

The benefit of PCV13 in decreasing of the burden of bacterial AOM in a fully immunized population of preschool children in the United States is not yet established. The objective of our study is to determine the change in burden of AOM in the PCV13 era, compared with the PCV7 era, as well as to compare the characteristics and management of AOM in a cohort of fully vaccinated, young urban children in the 2 PCV vaccination periods.

Methods

This is a retrospective study of OM episodes in children ages 18 to 60 months diagnosed from January 2006 to December 2015, based on electronic medical record review. The study was approved by the institutional review board and conducted at Lincoln Medical Center, Bronx, NY. The vaccination status of the patients with OM was verified through the New York State's online Citywide Immunization Registry (CIR).

The inclusion criteria were as follows: (1) age 18 to 60 months; (2) complete 4 doses PCV7 vaccination for OM events from January 2007 to December 2010; (3) complete 4 doses PCV13 vaccination for OM events from January 2011 to December 2015; (4) complete 4 doses hemophilus influenza type B (HiB) vaccination for all patients; and (5) detailed description of tympanic membrane (TM), as defined below.

The exclusion criteria were as follows: (1) age range outside the inclusion criteria; (2) comorbid conditions: sickle cell disease, immune deficiency, faltering weight or failure to thrive, nephrotic syndrome; (3) a diagnosis of otitis externa; (4) unsatisfactory description of TM; and (5) incomplete or undocumented PCV and HiB vaccination status.

For the purpose of this study, we used the following definitions:

1. *Acute otitis media*: unilateral or bilateral ear ache with or without fever associated with abnormal TM examination.
2. *True acute otitis media* (t-AOM): Documentation of bulging of the TM, presence of yellow exudate behind the ear drum, or otorrhea.
3. *Otitis media with effusion* (OME): Other TM findings or middle ear effusion, without bulging, yellow exudate or otorrhea.
4. *Recurrent OM*: 2 or more AOM episode(s) at least 3 months apart with complete resolution of TM findings in the interval period.
5. Complication of AOM:
 - a. Acute mastoiditis
 - b. Intracranial extension of infection, including bacterial meningitis, abscess, and so on
 - c. Empyema
 - d. Venous sinus thrombosis
6. *Cold season*: October to March.

We compared the burden of t-AOM among all diagnosed episodes of AOM in children fully vaccinated with PCV and HiB in the 2 time periods: 2006 to 2010 (PCV7 period) versus 2011 to 2015 (PCV13 period). We also compared demographic and clinical features and management of t-AOM versus OME. All statistical analyses were conducted using STATA 14 software. A *t* test was used for evaluating continuous variables, whereas a χ^2 test was used to evaluate categorical variables. Odds ratio (OR) and 95% confidence interval (CI) were calculated wherever possible. Multivariate analyses were carried out using logistic regression model to adjust for confounding factors of age less than 2 years, gender, presence of fever, or season. With 393 episodes, our study was adequately powered (80%). A 2-tailed $P < .05$ was used to define statistical significance and identify a change in prevalence of AOM in the 2 PCV periods $\geq 10\%$.

Results

A total of 537 episodes of fully vaccinated children aged 18 to 60 months diagnosed with AOM between January 1, 2006, and December 31, 2015, were identified (286 in PCV7 group and 251 in PCV13 group). Out of these, 144 episodes were excluded (86 in PCV7 group and 58 in PCV13 group). Thus, 393 episodes were included in our study for the purpose of analyses, 53% of which were males (200 episodes were in the PCV7 period and 193 episodes in the PCV13 period). The mean age at

Table 1. Characteristics of the Episodes of AOM in the PCV7 (2007-2010) Versus the PCV13 (2011-2015) Periods in Fully Vaccinated Children of Preschool Age.

Study Period	PCV7 Period	PCV13 Period	Total	P
Number of AOM episodes	200	193	393	—
Mean age \pm SD (months)	33 \pm 11	29 \pm 10	31 \pm 11	.0003*
True AOM: n, (%)	52, (26)	51, (26.4)	103, (26.2)	.94
Complications of AOM	0	0	0	—

Abbreviations: AOM, acute otitis media; PCV, pneumococcal conjugate vaccine.

*Student t-test, < 0.05 is statistically significant.

Table 2. Characteristics of the Episodes of t-AOM Versus Otitis Media With Effusion in Fully Vaccinated Children of Preschool Age (2007-2015).

Episodes of OM	True AOM	Otitis Media with Effusion (OME)	Total	P*
No. of episodes	103	290	393	—
Age <2 years, n (%)	37 (36)	97 (33)	134 (34)	.649
Cold season	46 (45)	161 (55)	207 (53)	.03
Fever >101.4°F	35 (34)	149 (51)	184 (47)	.002
Recurrence	15 (14.6)	80 (27.6)	95 (24)	.0009
Antibiotic use	102 (99)	282 (97.2)	384 (97.7)	.3

Abbreviations: t-AOM, true acute otitis media; OM, otitis media; AOM, acute otitis media.

*Pearson Chi square, < 0.05 is statistically significant.

diagnosis of AOM was 33 \pm 11 months in the PCV7 period versus 29 \pm 10 months in the PCV13 period ($P = .0003$). Overall, 34% of episodes occurred in children 18 to 24 months of age. t-AOM was identified in a total of 103 (26.2%) AOM episodes. The prevalence did not change significantly in the 2 PCV periods (26% in the PCV7 period vs 26.4% in the PCV13 period; OR = 1.02, 95% CI = 0.65-1.60, $P = .92$). None of the AOM episodes in both PCV7 and PCV13 periods was associated with complications (see Table 1).

When 103 episodes of t-AOM were compared with 290 episodes of the OME, there was no significant difference in the proportion of patients \leq 24 months of age between these 2 groups (OR = 1.11, 95% CI = 0.70-1.79, $P = .65$). However, episodes of OME were more frequently diagnosed during the cold season (55% vs 45%; OR = 1.54, 95% CI = 1.04-2.4, $P = .03$) than episodes of t-AOM. Episodes of OME were also more frequently associated with fever (51.4% vs 34%; OR = 2.05, 95% CI = 1.29-3.3, $P = .002$) and more frequently associated with recurrence (27.6% vs 14.6%; OR = 2.24, 95% CI = 1.22-4.09, $P = .009$). Most episodes of both OME as well as t-AOM were treated with antibiotics (97.2% and 99%, respectively; $P = .7$; see Table 2).

Discussion

We demonstrated that approximately 26% of all episodes of AOM, in both PCV7 and PCV13 periods, were

because of t-AOM. This is similar to the findings in the 2 US studies from 2003 to 2007. In a cohort of 150 children aged 1 to 8 years from Pittsburgh, PA, the prevalence of bacterial AOM was approximately 20%.³³ In another cohort of 244 children less than 3 years with middle ear infection in Galveston, TX, 34% were bacterial in etiology.³⁴ The difference in the burden of bacterial OM in these 2 cohorts might stem from the difference in the age range of the patients. To the best of our knowledge, in the PCV13 era, our study is the first to compare the burden of AOM in the 2 PCV time periods in fully immunized young children.

Principle “nature abhors a vacuum” most likely explains why PCV has only a modest effect on decreasing the incidence of AOM. It is not surprising that the 6 latest studies on the etiology of AOM in the PCV13 era conducted in the United States, Europe, and Israel have demonstrated that nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and group A β -hemolytic *Streptococcus* have dominated the scene.³⁵⁻⁴¹ Furthermore, it was recently recognized that a nonvaccine *Streptococcus pneumoniae* serotype 35B, associated with high rates of microbial nonsusceptibility to penicillin, has increasing rates among children with *Streptococcus pneumoniae* nasopharyngeal carriage, and among children with invasive and noninvasive pneumococcal infection in the United States and abroad.⁴²⁻⁴⁶

A shift in etiology of bacterial AOM in the PCV and HiB vaccination era may also explain why an ear infection, though very rarely, is still complicated by

mastoiditis, and extremely rarely by meningitis and other forms of intracranial extension of infection.⁴⁷⁻⁴⁹ A cross-sectional analysis of the US Kids National Inpatient Database had demonstrated a reduction in the incidence of acute mastoiditis from 8 per 10 000 hospital discharges in 1997 to 3.4 per 10 000 hospital discharges in 2009 in patients aged between 1 and 4 years.⁵⁰ Even in the Pittsburg cohort, among children treated with watchful waiting, only 1 (0.7%) developed mastoiditis.⁵¹

AOM develops with viral upper respiratory infections (URIs) and follows a seasonal variability as do the viral URIs.⁵²⁻⁵⁵ The current study showed that an episode of OME was more likely to be associated with a cold season as compared with bacterial AOM, concurring with the previously reported evidence.^{52,53,56} Contrary to previously reported association of fever with bacterial AOM, our study found that fever is more commonly associated with OME than with t-AOM.^{54,57} So, fever by itself, in a fully vaccinated child, even at the age less than 2 years, should not point toward a diagnosis of bacterial infection, and otoscopic findings should be used to diagnose AOM and guide the use of antibiotics.^{58,59}

Majority of our patients with OM were treated with antibiotics, despite physicians' awareness about the evidenced-based AAP recommendations to restrict antibiotic use for the treatment of AOM. Unfortunately, in the PCV era the rate of antibiotic use for the treatment of children with AOM remains high, despite the guidelines being published 4 years ago.^{20,51} The downside of excessive antibiotic use are adverse effects like diarrhea, vomiting, and rash,^{51,60} and more important increasing microbial resistance. Review of local practice allows us to address the overuse of antibiotics in children with OM and reinforce the AAP guidelines.

A major limitation of our study is its retrospective nature. Our classification of AOM versus OME was based on a retrospective review of charts documenting the findings of the TM appearance. There is a possibility of inaccurate documentation that might lead to a bias that cannot be excluded in our study. Moreover, TM findings could be subjective depending on a physician's expertise in using the pneumatic otoscope. A prospective study documenting the TM findings (probably a photographic evidence of TM appearance) to standardize the appearance of the TM may help in eliminating this bias. Similarly, our determination of vaccination status was based on an online database from the CIR registry. It is possible that some patients were incorrectly excluded because of the delay in data entry into the CIR database.

Another limitation of our study is the use of bulging and/or otorrhea for the diagnosis of t-AOM and to guide

the use of antibiotics. Although bulging is associated with bacterial OM, this is not always the case and patients with middle ear effusion (MEE) might also present with bulging. Thus, there is a possibility of overdiagnosing MEE as OME with our inclusion criteria. However, in that case the overdiagnosis of OME would be present in both time period groups, and thus, not affect our findings.

Also, as with all single-center studies, there is an issue with lack of reproducibility of the study findings. Still, this remains the first study in the United States determining the change in burden of AOM in fully vaccinated children in an urban population in the 2 PCV eras mentioned above.

Conclusion

In this cohort, a burden of AOM in fully immunized preschool children has not changed in the PCV13 period as compared with the PCV7 period, and remained at the rate of ~26%. Given the efficacy of PCV 13 vaccination in reducing invasive pneumococcal disease, we recommend that pediatricians still continue administering PCV 13 vaccine to their patients per the immunization schedule. None of the AOM episodes in both PCV7 and PCV13 periods in our cohort were associated with complications. Despite this fact, most patients with AOM as well as OME were treated with antibiotics. Diagnosis of AOM should only be guided by physical examination findings suggestive of t-AOM, and not by the presence of fever, nor the recurrence of AOM.

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Author Contributions

ST: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

NG: Contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SS: Contributed to design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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