Impact of Pneumococcal Conjugate Vaccination on Otitis Media: A Systematic Review

Sylvia Taylor,[1] Paola Marchisio,[2] Anne Vergison,[3] Julie Harriague,[4] William P. Hausdorff,[1] and Mark Haggard[5]

[1]GlaxoSmithKline Biologicals, Global Vaccine Development, Wavre, Belgium; [2]Department of Maternal and Pediatric Sciences, University of Milan and Fondazione IRCCS Cá Granda-Ospedale Maggiore Policlinico, Italy; [3]Pediatric Infectious Diseases, Infection Control and Epidemiology Unit, Université Libre de Bruxelles, Belgium; [4]4Clinics, Paris, France; and [5]Multi-Centre Otitis Media Study Group, Department of Experimental Psychology, University of Cambridge, United Kingdom

Acute otitis media (AOM) is a leading cause of visits to physicians and of antibiotic prescriptions for young children. We systematically reviewed studies on all-cause AOM episodes and physician visits in which impact was attributed to pneumococcal conjugate vaccines, either as efficacy or effectiveness. Of 18 relevant publications found, most used the 7-valent pneumococcal conjugate vaccine (7vCRM). The efficacy of 7vCRM against all-cause AOM episodes or visits was 0%–9% in randomized trials and 17%–23% in nonrandomized trials. In observational database studies, physician visits for AOM were already declining in the 3–5 years before 7vCRM introduction (mean change, −15%; range, +14% to −24%) and continued to decline afterward (mean, −19%; range, +7% to −48%). This vaccine provides some protection against OM, but other factors have also contributed to the recent decline in OM incidence. Future effectiveness studies should thus use better-controlled methods to estimate the true impact of vaccination on AOM.

By the age of 3 years, more than two-thirds of children experience ≥1 episode of acute otitis media (AOM), and about half experience ≥3 episodes [1]. AOM is a leading cause of physician visits and antibiotic prescriptions. Pathogenic bacteria are isolated from middle ear fluid in up to 70% of cases [2], with *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* together representing 60%–80% of bacterial cases [3–5]. Vaccines against these pathogens thus offer potential public health gains.

Use of the 7-valent (7vCRM; Pfizer) pneumococcal conjugate vaccine (PCV) in infants became widespread over the last decade [6]. Two PCVs with higher valency were recently licensed and are gradually replacing 7vCRM. The 10-valent PCV (PHiD-CV; GlaxoSmithKline Biologicals) includes 3 additional serotypes and uses an *H. influenzae* protein D carrier [7]. The 13-valent PCV (13vCRM; Pfizer) includes the same serotypes as PHiD-CV, plus another 3 [8].

7vCRM has dramatically reduced invasive pneumococcal disease (IPD), with >90% efficacy in clinical studies [9] and virtual elimination of vaccine-type IPD in immunized cohorts [10]. However, the impact on AOM, a polymicrobial mucosal disease, is less clear. A previous meta-analysis of efficacy trials [11] did not include observational database studies, and the 2 types of results need to be reconciled. Accumulation of effectiveness results for new vaccines takes some years, so OM policy decisions must still be based partly on 7vCRM effectiveness data.

METHODS

Search Strategy

PubMed was searched for articles in English, French, German, and Italian published between January 1998 and September 2010, using the terms "*S. pneumoniae*," "pneumococcal conjugate vaccin*," "vaccine," "acute otitis media," "otitis media," "efficacy," "effectiveness," "effect(s)," "impact," "visit(s)," "episode(s)," "claims," "trends," "retrospective," and "observational" combined with "All child: 0–18 years." Potentially relevant publications were screened for (1) original study, (2) assessment of PCV efficacy/effectiveness against all-cause AOM episodes or physician visits, and (3) a study population of children aged ≤12 years. Publication bibliographies and recent reviews were examined for further articles. Publications were noted but data not used in evidence tables if they focused specifically on hospitalizations/severe complications, recurrent AOM, and OM with effusion; used schedules other than 3 + 1 or 2 + 1; provided only data after administration of both PCV and the 23-valent pneumococcal polysaccharide vaccine; or calculated cost-effectiveness without providing new effectiveness data.

Calculations

Where necessary, rates were recalculated as the number of cases per 1000 person-years (PY). For observational database studies, pre-PCV rate changes were calculated as the difference between estimates reported for the first study year and the last year before PCV introduction, and post-PCV rate changes were calculated as the difference between estimates for the last year before PCV introduction and the last study year. Average rates for the periods before and after 7vCRM introduction were not calculated because consistently decreasing trends were seen in most studies. However, if rates were only reported for certain years combined [12–15], these data were used. Unpublished estimates were obtained directly from study investigators [13, 16] or approximated from figures [17]. For Poehling et al, the only available estimates for post-PCV changes were based on ratios of rates for <2 versus 3–5-year-olds [18]. For De Wals et al, we used the published post-PCV change adjusted by time-series regression [19].

RESULTS

Of 306 candidate publications identified (Figure 1), 18 met inclusion criteria; 7 were clinical trials (Table 1), with some multiple publications; and 8 were observational database studies (Table 2). Five trials were randomized and double blinded: 3 were on 7vCRM [3, 9, 20], 1 was on the 7-valent vaccine candidate conjugated to the outer membrane protein complex of *Neisseria meningitidis* serogroup B (7vOMPC; Merck) [21], and 1 was on the 11-valent prototype version of PHiD-CV (11Pn-PD; GlaxoSmithKline Biologicals) [4]. Two
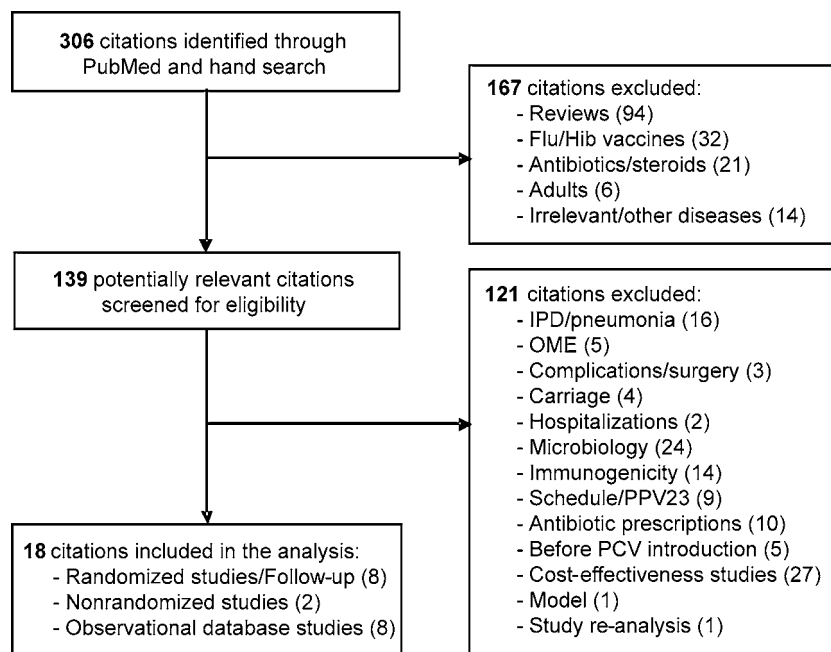

Figure 1. Flow chart of the publications evaluated for inclusion in the analysis. Flu, influenza virus; Hib, *Haemophilus influenzae* type b; IPD, invasive pneumococcal disease; OME, otitis media with effusion; PCV, pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

Table 1. Summary of the Clinical Trials Included in the Literature Analysis

Reference	Country (State, Pop)	Data	PCV	Schedule (Months)	Age (Years)	No. of Subjects	Outcome	Case Definition	Case Ascertainment	Comparison	Baseline Rate (per 1000 Pop or PY)	PCV Efficacy (% [95% CI])
Efficacy randomized clinical trials												
Black et al 2000 [9] Black et al 2002 [26] Fireman et al 2003 [25] (NCKP)	United States (CA)	RCT	7vCRM	2, 4, 6, 12–15	<3.5	~38K	Episodes Visits	AOM	Computerized diagnoses, emergency physicians and pediatricians	Control vs 7vCRM arm	... Visits: ~2000[a]	Episodes: PP: 5.8 (3.7–7.8) to 7.0 (4.1–9.7) ITT: 5.8 (3.7–7.9) to 6.4 (3.9–8.7) Visits: PP: 7.8 (5.4–10.2) to 8.9 (5.8–11.8) ITT: 7.0 (4.7–9.1) to 7.8 (5.2–10.5)
Eskola et al 2001 [3] (FinOM)	Finland	RCT	7vCRM	2, 4, 6, 12	<2	1662	Episodes	AOM	Study physician according to case definition	Control vs 7vCRM arm	1240	PP: 6 (–4 to 16)
Palmu et al 2004 [24]		FU			2–5	756						ITT: 9 (–35 to 38)
O'Brien et al 2008 [20]	United States (Native Americans)	RCT (community randomized)	7vCRM	2, 4, 6, 12–15	<2	856	Episodes	AOM	Treating physician	Control vs 7vCRM arm	1500	PP: –0.1 (–20.8 to 17.1)[b]
Kilpi et al 2003 [21] (FinOM)	Finland	RCT	7vOMPC	2, 4, 6, 12	<2	1666	Episodes	AOM	Study physician according to case definition	Control vs 7vOMPC arm	1240	PP: –1 (–12 to 10)[b]
Prymula et al 2006 [4] (POET)	Czech Republic/ Slovakia	RCT	11Pn-PD	3, 4, 5, 12–15	<2.5	4968	Episodes	AOM	Pediatrician, confirmed by ENT	Control vs 11Pn-PD arm	125	PP: 33.6 (20.8–44.3)
Nonrandomized clinical trials												
Esposito et al 2007 [22]	Italy	Observer blinded	7vCRM	3, 5, 11–12	<2.5	1555	Episodes	AOM, excluding AOM with more severe concurrent illnesses	Reported by parents, confirmed by study pediatrician	Control vs 7vCRM arm	469	PP: 17 (–2 to 39)
Adam and Fehnle 2008 [23]	Germany	Nonblinded	7vCRM	2, 3, 4, 12–15	<2	7411	Children with ≥1 episode	AOM	Treating physician	Control vs 7vCRM arm[c]	291	ITT: 19.0 (10.7–26.4); MP: 23.2 (12.9–32.3)

Abbreviations: 7vCRM, 7-valent pneumococcal vaccine conjugated to CRM$_{197}$; 7vOMPC, 7-valent pneumococcal vaccine conjugated to OMPC; 11Pn-PD, 11-valent pneumococcal vaccine conjugated to protein D; AOM, acute otitis media; CA, California; ENT, ear, nose, and throat specialist; FU, follow-up; ITT, intention-to-treat; MP, matched pair; PCV, pneumococcal conjugate vaccine; Pop, population; PP, per protocol; PY, person-years; RCT, randomized controlled trial.

[a] Recalculated for the total population. Rate per 1000 PY was originally 2650 for children aged <1 years, 2010 for children 1–2 years, and 1180 for children >2–3.5 years.

[b] A negative efficacy indicates an increased risk in the vaccine group.

[c] Most vaccinated children had underlying medical conditions, in contrast to unvaccinated children.

Table 2. Summary of the Observational Database Studies Included in the Literature Analysis

Reference	Country (State, Prov, Pop)	Database	Age (Years)	No. of Subjects	Case Definition	Case Ascertainment	Comparison	Baseline Rate (per 1000 Pop or PY)	Pre-PCV Decrease (%)	Post-PCV Decrease (%)
Poehling et al 2004 [18]	United States (TN)	TN: Medicaid-managed care (government)	<2	TN: 442K	OM, excluding concurrent IPD/pneumonia	Any listed ICD-9 code, outpatient only	1998–2000 vs 2001–2002	1775–2019	...	4[a]
	United States (NY)	NY: Private-managed care		NY: 44K				2125–2247	...	19[a]
Poehling et al 2007 [15]	United States (TN)	TN: Medicaid-managed care (government)	<2	TN: 150K	Frequent OM	Any listed ICD-9 code, outpatient only	1998–1999 vs 1999–2000	...	TN: 16 NY: 16	
	United States (NY)	NY: Private-managed care		NY: 26K			1999–2000 vs 2001–2002			TN: −7[b] NY: 18
Grijalva et al 2006 [12]	United States	NAMCS/NHAMCS	<2	...	OM	Any listed ICD-9 code, ambulatory only	1994–1995 vs 1998–1999	1415	24[c]	
							1998–1999 vs 2002–2003			12[c]
Zhou et al 2008 [16]	United States	Employer insurance (private)	<2	20K–153K[d]	OM	First listed ICD-9 code, ambulatory only	1997 vs 1999 1999 vs 2004	2073[e]	−14[e]	48[e]
Grijalva et al 2009 [13]	United States	NAMCS/NHAMCS	<5	...	OM	Any listed ICD-9 code, ambulatory only	1995–1996 vs 1999–2000	950	23	
							1999–2000 vs 2005–2006			13
De Wals et al 2009 [19]	Canada (Quebec)	Physician claims	<5	25K–26K[e]	OM	Any listed ICD-9 code, ambulatory only	2000 vs 2007	587	...	13
Singleton et al 2009 [14] (plus Curns et al 2002 [56])	US (Native Americans)	Indian Health service database (government)	<5	775K	OM	Any listed ICD-9 code	1994 vs 1996 1996 vs 2003–2005	1380 per 1000 children	18[f]	29[f]
Sox et al 2008 [17]	United States (MA)	Physician claims (private)	≤12	...	AOM	Any listed ICD-9 code, ambulatory only	1996 vs 1999 1999 vs 2004	385	22[g]	37[g]

All studies analyzed the impact of 7vCRM on OM visits.

Abbreviations: 7vCRM, 7-valent pneumococcal vaccine conjugated to CRM197; AOM, acute otitis media; ENT, ear, nose, and throat specialist; ICD-9, *International Classification of Diseases, Ninth Revision*; IPD, invasive pneumococcal disease; MA, Massachusetts; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; NY, New York; PCV, pneumococcal conjuage vaccine; OM, otitis media; Pop, population; Prov, province; PY, person-years; TN, Tennessee.

[a] Based on comparison of relative rates for <2-year-olds vs 3–5-year-olds during 1998–2000 vs 2001–2002.

[b] A negative effectiveness indicates an increased rate of AOM.

[c] Our recalculation from the rates of AOM visits in <2-year-olds.

[d] No. of children per year.

[e] Our recalculation from yearly estimates. Zhou et al originally presented a baseline of 2173 for 1997–1999 and a 43% decrease between 1997–1999 and 2004 [16].

[f] Our recalculation from [14] and [56]. Singleton et al originally presented a 35.5% decrease between 1994–1996 and 2003–2005 [14], whereas Curns et al presented the individual OM rates for 1994–1996 [56].

[g] Our recalculation estimated from Figure 1.

7vCRM trials were nonrandomized: 1 was observer blinded [22], and 1 was open label [23].

Baseline AOM Incidence

In clinical trials, baseline AOM episode rates among children aged <2 or <2.5 years differed 10-fold, from 125 to 1500 per 1000 PY or children [3, 4, 21, 24] (Table 1). The lowest rate was from the only study requiring otolaryngological confirmation upon pediatrician referral [4]. The nonrandomized trials observed baseline rates of <500 per 1000 PY or children [22, 23].

In observational database studies, baseline OM visit rates (per 1000 PY or children) were 1415–2247 for <2-year-olds [12, 18] and 610–1380 for <5-year-olds (Table 2) [14, 19]. The highest visit rates came from private insurance databases [16, 18], with lower rates in managed care (2032 per 1000 PY) than non–managed care (2429 per 1000 PY) [16].

Six database studies presented trends in baseline OM visit rates over several years before 7vCRM introduction, and all [12–15, 17] but one [16] observed substantial declines (mean change, −15%; range, +14% to −24%) (Table 2, Figure 2). For example, OM rates declined by 23%–24% over 5 years before 7vCRM introduction, in 2 US population-based surveys [12, 13]. The exception was the analysis of nationwide employers' insurance data by Zhou et al, which found a 14% increase in OM visit rates over the 2 years before 7vCRM introduction [16].

PCV Efficacy on AOM in Randomized and Nonrandomized Clinical Trials

In the 2 individually randomized trials on 7vCRM efficacy against AOM, the NCKP [9, 25, 26] and FinOM trials [3, 24], 7vCRM reduced all-cause episodes in 2-year-olds by 5.8%–7.0% and visits by 7.0%–8.9% (Table 1), achieving statistical significance in the NCKP trial. In a third, smaller, community-randomized trial among Native American infants, no effect was detected on clinically diagnosed AOM (−0.l%; 95% confidence interval [CI], −20.8% to 17.1%) [20]. In comparison, the nonrandomized trials in Italy (where parents chose whether their child received 7vCRM) and Germany (where most vaccinated children had comorbid conditions) observed 17%–23% reductions.

Only 2 publications reported efficacy of other PCVs. No efficacy of 7vOMPC was demonstrated against all-cause AOM (−1%; 95% CI, −12% to 10%) [21]. The POET trial showed 34% efficacy against all-cause AOM (95% CI, 21%–44%) for 11Pn-PD [4].

PCV Overall Impact on OM in Postimplementation Studies

The 8 observational database studies reported a 19% average reduction in OM visit rates (range, +7% to −48%) after 7vCRM introduction (Table 2). The 2 lowest estimates were in children aged <2 years receiving US governmental insurance: there was a 7% increase between 1999–2000 and 2001–2002 [15] and 4% (statistically nonsignificant) reduction between 1998–2000 and 2001–2002 [18]. The highest decrease was 48% and occurred during 1999–2004 (the decrease was 43% if the average from 1997–1999 was used) and was reported in the only study observing an increase (14%), rather than decrease, in OM rates before vaccine introduction [16].

DISCUSSION

In summary, 7vCRM efficacy against all-cause AOM episodes was an estimated 0%–9% in randomized trials and 17%–23% in nonrandomized clinical trials. Observational database
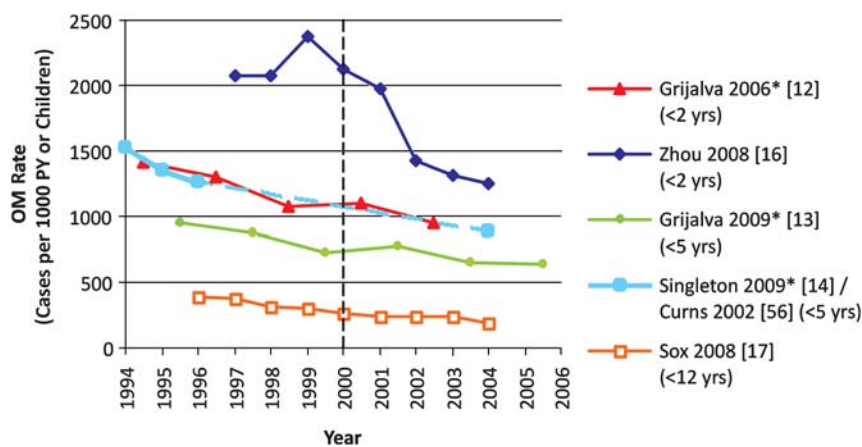

Figure 2. Trends in otitis media rates among observational database studies presenting data for years before and after 7-valent pneumococcal conjugate vaccine introduction in 2000. Asterisks indicate studies for which the midpoint of the reported period was used to generate the graph. The age groups used for analysis are indicated in parentheses. Abbreviations: OM, otitis media; PY, person-years.

studies showed that OM visit rates decreased 19% on average following 7vCRM introduction, with estimates ranging widely (+7% to −48%). Before 7vCRM introduction, OM visit rates were already declining in all but one study. These findings raise several issues to be considered when appraising policy options and designing studies, as discussed below.

Variability in Efficacy Trial Results
Efficacy against all-cause AOM assessed for 3 vaccine formulations (7vCRM, 7vOMPC, and 11Pn-PD) tested in 5 randomized trials yielded point estimates ranging from −1% to 34%. Whereas some of this variability is likely due to differing vaccine composition, it is difficult to distinguish this from confounding by local variability in viral and bacterial etiology, case ascertainment, diagnosis, and care-seeking behavior. Reanalyses of POET and FinOM trials, adjusting for severity of case definition and pathogen distributions, somewhat narrowed differences in PCV efficacy estimates [27, 28], but such reconciliation is not always feasible, and conclusions have to be based on central tendency across studies.

Observed Versus Theoretical Effectiveness
Theoretical maximum effectiveness in real-life settings can be calculated by assuming no replacement with nonvaccine types, a stationary commensal profile, and 100% vaccine uptake. On the assumption that 70% of AOM episodes are bacterial [2], of which 50% are due to *S. pneumoniae* [5], of which 7vCRM serotypes represent 75% [29], and for which efficacy is 57% [3], then 7vCRM should prevent approximately 15% of the episodes of all-cause AOM (70% × 50% × 75% × 57%).

Vaccination rates of >80% would be expected to induce herd protection via decrease in nasopharyngeal carriage of vaccination serotypes [30, 31]. Although there is strong evidence for herd protection with IPD, herd protection against vaccine-type AOM in nonvaccinated age groups has not yet been directly demonstrated because tympanocentesis is not routinely performed. Dilution of vaccine-type herd protection within all-cause OM makes it hard to show, and one study failed to detect it in overall AOM visits in older children 2 years after 7vCRM implementation [19]. Near elimination of vaccine-type carriage some years after PCV use, on the assumption of maximum herd protection (with vaccine types eradicated), is a reasonable approximation. Effectiveness against vaccine types would then be 100% instead of 57%, yielding a theoretical effectiveness of approximately 26%.

The above calculations do not reflect any replacement with nonvaccine serotypes and bacteria, although some replacement is suggested in clinical studies and postintroduction surveillance [3, 32, 33]. Indeed, a recent model that used actual nasopharyngeal carriage rates in US children for both vaccine and nonvaccine serotypes, taking into account their specific abilities to cause AOM, projected a maximum theoretical effectiveness of 7vCRM against overall AOM of only 12% [34]. This suggests that estimates well beyond these theoretical limits may be substantially confounded and biased.

Variability in Baseline Incidence
Baseline AOM episode rates in clinical trials varied 10-fold. The high baseline rate in FinOM [3] is similar to US rates (900–1500 AOM episodes per 1000 children) [20, 35, 36], whereas the low rate in the POET trial is closer to those reported in other European studies (154–400 AOM episodes per 1000 PY) [37]. In general, stronger vaccine effects would be expected on samples that use tighter diagnostic definitions and, hence, lower baseline case incidence, but they face sample size challenges. This, plus possible intrinsic differences in populations or differences in healthcare uptake beyond those of diagnostic definition, suggest that one should be cautious in considering between-study comparisons of vaccines. Among the database analyses, baseline rates also varied across studies, even after taking into account age differences [12, 15, 16, 18]. Strong evidence for demographic, immunological, or microbiological differences between such populations is lacking, so such baseline rate differences are more appropriately attributed to differences in case severity or diagnostic code for case definition.

Changes Before Versus After Vaccine Introduction
In observational database studies, OM visit rates decreased by 19% on average after 7vCRM introduction. However, among studies also presenting data before 2000, all [12–15, 17] but one [16] observed OM visits declining by 15% on average before 7vCRM introduction. This suggests that long-term decreases in consultations before 7vCRM introduction, which are unlikely to have halted, have added to apparent postintroduction decreases. Poehling et al and Grijalva et al controlled for annual trend via differential effect by age, arriving at 4%–19% decreases due to 7vCRM [12, 18]. However, this minimizes any herd protection affecting the nonimmunized portion of the younger cohort. In addition, non–vaccine-related factors, such as age stratification of <2/≥2 years in antibiotic prescription guidelines, could affect OM visit rates over time differentially by age. De Wals et al moved in the appropriate direction by estimating a post-PCV rate with time-series regression to adjust for annual trend [19]; the raw decrease in OM claims in 2000–2007 was 25%, but the adjusted decrease attributable to 7vCRM was only approximately 13%.

To determine whether the decrease in consultations is due to 7vCRM introduction, analysis must be made over a few years and according to when and to what extent the vaccine was introduced. For example, a recent study in an Athens hospital found that, beginning in 2005, emergency department visits by children aged <15 years decreased by 38% and 48%

for all-cause and pneumococcal otorrhea, respectively [38]. However, this drop occurred 1–2 years before mass pneumococcal vaccination in Greece, at the time of (presumably low) private market 7vCRM use, and, even after the decrease, vaccine serotypes still represented the majority of pneumococcal otorrhea. Upon implementation of mass vaccination in 2006, no further drop was seen, indicating that the reduction in 2005 was largely due to nonvaccine factors.

Potential Nonvaccine Factors

Several other factors might explain why OM rates decreased before PCV introduction and continued decreasing after. First, changes in AOM perception, consultation rates, and frequency and type of antibiotic use date from the early 1990s. The increasing acceptance by parents and physicians of observation without antibiotic use ("watchful waiting"), which is officially recommended for some AOM patients [39], could reduce the apparent AOM incidence if parents do not consult physicians for mild AOM if they expect little benefit for their child. Stricter diagnostic criteria [39] may have reduced not only inappropriate antibiotic use [13] but also apparent AOM consultation rates. Second, a shift to higher antibiotic dosage or the doubling of long-acting macrolide use in US children around the same time as 7vCRM introduction [40] could have reduced relapses and, therefore, reduced the total number of AOM visits per episode, thus reducing the healthcare burden [17].

Third, awareness of vaccination status could affect care-seeking behavior. In a recent observer-blinded randomized trial in Sweden of children at risk for recurrent AOM conducted before universal PCV, receipt of 7vCRM reduced overall reported AOM episodes by 26% and AOM hospital visits by 36% [41]. Because these apparent effects are larger than the above theoretical effectiveness estimate, there may have been some differential contribution from parents seeking medical assistance depending on vaccination status, with less care-seeking for vaccinated children because of the belief that vaccine would probably prevent the more serious forms or complications of disease.

Fourth, the decline in OM rates has paralleled the decreasing exposure of children to secondhand tobacco smoke, a strong AOM risk factor [42]. Fifth, influenza vaccination can reduce AOM incidence during the influenza season by reducing viral coinfection [43]. However, influenza routine vaccination in the US began in 2004, with the sharpest increase around 2007–2008 [44], after the attributable post-7vCRM decrease in OM.

Study Population

Possible differences among populations, chiefly their relative risks, cannot be overlooked in explaining the heterogeneity of results. However, convincing demonstrations are lacking. The failure of O'Brien et al to detect a statistically significant 7vCRM impact on AOM in high-risk American Indians may be due to the lack of statistical power [20]. Likewise, a favorable, although nonsignificant, vaccine effect (adjusted relative risk, 0.88 [95% CI, .69–1.13]) was found in successive cohorts of 51 nonvaccinated and 97 vaccinated (7vCRM plus a 23-valent polysaccharide booster dose) high-risk Australian aboriginal children [45]. Finally, the authors of the nonrandomized, nonblinded 7vCRM German trial [23] suggested that the achievable efficacy was possibly biased against the vaccine because more children in the 7vCRM group than the control group had a medical risk factor (66% vs 18%) or were born prematurely (40% vs 6%). The assumption behind all these studies is that high-risk, otitis-prone children generate a weaker immune response, for which there is some evidence [46]. Limited statistical power currently prevents clear conclusions, but possible differences in vaccine effectiveness between populations deserve consideration.

Diagnostic Codes Included as OM

Observational database studies identify OM cases according to broad diagnostic codes that are based often on a single clinician's judgment rather than on precise protocols and measurements. In the *International Classification of Diseases, Ninth Revision* coding system, codes 381.x refer mainly to nonsuppurative AOM, codes 382.x to suppurative AOM, and codes 383.x to mastoiditis. Code choice could greatly affect absolute OM visit count, and study-specific differences in case definition or even OM type distribution could influence 7vCRM effectiveness estimates [28, 47]. Unfortunately, no studies reported the proportions of the different codes used. Grijalva et al defined OM diagnosis as 381.x–382.x in one study [12] and as 381.x–383.x in the other [13], whereas Poehling et al used 381.0–381.4 and 382.x [15]. Zhou et al used 381.00–381.6, 382.00–382.02, 382.3, and 382.9 [16] but, unlike the other studies, only considered first-listed codes, possibly explaining why they reported the largest decrease (43%) [16]. Indeed, where AOM antibiotic use is strictly controlled, some physicians may use AOM less as a primary code, preferring a symptom-based equivalent code.

Design Considerations for Future Studies

Vaccine impact will always be assessed by large observational studies. However, one key requirement is adjustment for non–vaccine-related confounders. Adjustment for secular trends [48–50], preferably via time-series modeling [19], should always be performed. Modeling would also allow distinction between year-to-year variation (random and viral) and longer-term trends. At a minimum, projections from prevaccine trends should provide the expected null value from which an observed deviation may be taken as evidence for vaccine effect [48–50]. In addition,

measurement of time trends of other diseases could provide additional control, with the caveat that some nonvaccine trends could affect unrelated diseases differently.

The central public health questions are whether vaccination causes an overall decrease in AOM and associated healthcare burden. Tympanocentesis-based efficacy studies, even at the population level, would at least help specify how much of an overall decrease is limited to target pathogens/serotypes, but it remains unusual and ethically problematic to perform routinely, and determining vaccine effectiveness against individual serotypes necessitates large sample sizes.

PCV effects on AOM can be measured economically and with good control in case-control studies, as for IPD [51–53]. However, finding appropriate controls in a well-immunized population is difficult. The presumably present herd protection is seen as a depressed incidence in controls and is not directly measurable with this design, meaning the effect is nearer to an efficacy than to an effectiveness estimate.

Finally, the problem of quality of case definition has long been remarked in AOM studies. Some hope of reducing variability from this source is given by 2 recent high-quality randomized studies on AOM treatment that used stringent and reproducible criteria applicable to all designs except routine practice databases [54, 55].

In conclusion, observed OM visit rates have decreased by approximately 19% following 7vCRM introduction, but long-term reductions in OM visits preceding 7vCRM introduction of approximately 15% suggest that continuing influences other than PCV vaccination have caused some of the subsequent reduction. Caution is therefore needed in the report and interpretation of these data, and no single study should be quoted as representing the "true" effect of 7vCRM on AOM. Study methods need to be improved to more accurately estimate true PCV effectiveness.

Notes

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