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MAJOR ARTICLE

Effectiveness of the 7- and 13-Valent Pneumococcal Conjugate Vaccines Against Vaccine-Serotype Otitis Media

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Background. Despite the demonstrated impact of pneumococcal vaccine (PCV) implementation on otitis media (OM), demonstration of real-life serotype-specific effectiveness of the 7-valent and 13-valent PCVs (PCV7 and PCV13) is lacking owing to the paucity of culture-positive cases. Furthermore, prelicensure PCV13 efficacy against OM was not studied.

Methods. The study was conducted from October 2009 to July 2013. Case patients were children aged 5–35 months with OM (mostly complex OM [recurrent/nonresponsive, spontaneously draining, chronic with effusion]) from whom middle-ear fluid culture was obtained; controls were contemporary children with rotavirus-negative gastroenteritis in a prospective population-based rotavirus surveillance, from the same age group with similar ethnic distribution and geographic location. Vaccine effectiveness (VE) was estimated as 1 minus the odds ratio using unconditional logistic regression, adjusting for time since PCV implementation, age, and ethnicity.

Results. A total of 223 case patients and 1370 controls were studied. Serotypes 19F and 19A together caused 56.1% of all vaccine-type (VT) OM. VE of ≥2 PCV doses in children aged 5–35 months was demonstrated as follows: PCV7 against OM due to PCV7 serotypes, 57.2% (95% confidence interval, 6.0%–80.5%); PCV13 against OM due to PCV13 serotypes, 77.4% (53.3%–92.1%); PCV13 against OM due to the 6 additional non-PCV7 serotypes 67.4% (17.6%–87.1%); PCV13 against OM due to serotype 19F, 91.3% (1.4%–99.2%); and PCV13 against OM due to serotype 3, 89.0% (23.9%–98.4%). PCV7 and PCV13 VE against OM due to serotype 19A in children aged 12–35 months was 72.4% (95% confidence interval, 6.2%–91.9%) and 94.6% (33.9%–99.6%), respectively.

Conclusions. PCV7 and PCV13 were effective against complex OM caused by the targeted serotypes.

Keywords. pneumococcal conjugate vaccine; otitis media; effectiveness; case-control study.

Otitis media (OM) is the most common bacterial upper respiratory tract infection in infants and young children [1], peaking between the ages of 6 and 24 months [2]. It accounts for high antibiotic prescription rates, vast impact on children's quality of life and development, and substantial economic burden [3, 4].

Before pneumococcal conjugate vaccine (PCV) introduction, pneumococci accounted for approximately 30%–60% of OM cases [5–7], and serotypes included in the 7-valent and 13-valent PCVs (PCV7 and PCV13) constituted approximately 50% and approximately 80% of all pneumococcal OM, respectively [6]. In Israel and worldwide, after PCV7/PCV13 implementation, nontypeable *Haemophilus influenza*e became universally the leading pathogen [8].

The introduction of PCVs resulted in an overall OM rate reduction, with substantial differences in outcomes between various studies [9–15], largely explained by differences in study design, measured outcomes, and OM definitions. End points used to evaluate PCV impact on OM included, among others, assessment of complex OM with middle-ear fluid (MEF) culture, OM defined by *International Classification of Diseases*, clinical diagnosis, and ventilation tube insertion.

However, because no MEF cultures were obtained in most studies, PCV effectiveness (namely, direct protection against vaccine-type [VT] disease) could not be determined. Therefore, in the post-PCV era, OM studies attempted to assess PCV impact (defined as the overall all-cause OM reduction) rather than effectiveness. Furthermore, no studies have ever assessed PCV13 efficacy (defined as direct protection against VT disease in randomized clinical trials). However, determining postimplementation PCV13 effectiveness against OM can provide insights into the level of direct protection in vaccinated children in a real-world setting, where not all children are being vaccinated as planned. Furthermore, such an evaluation raises fewer concerns with regard to changes in care seeking, diagnosis practices, or the quality of the surveillance.

In southern Israel, a large prospective, population-based surveillance has been ongoing to determine the impact of PCV7 and PCV13 implementation on the incidence of OM necessitating MEF culture in young children (mostly complex OM [recurrent, nonresponsive, spontaneously draining OM, or

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chronic OM with effusion]) [11, 15]. Over the same period, we have conducted a prospective population-based study to determine rotavirus vaccine impact on hospital visits for gastroenteritis [16]. The participants in the study had similar age range and ethnic distribution as those studied for OM, providing a unique opportunity to conduct a case-control study to evaluate the effectiveness of PCV7 and PCV13 against VT-caused OM (VT-OM), using contemporary subjects with rotavirus-negative gastroenteritis as controls.

MATERIALS AND METHODS

This is a nested case-control study within an ongoing prospective, population-based active epidemiological surveillance program [15]. The current analysis covers the period between October 2009 and July 2013, evaluating vaccine effectiveness (VE) of PCV7 and PCV13 against culture-positive VT-OM. The study was approved by the Soroka University Medical Center (SUMC) Ethics Committee.

Setting and Study Population

The study was conducted in the Negev district (southern Israel). During the study period, the mean annual birth cohort was 16 000; about 95% of the Negev's children are born and receive medical services at the SUMC, the only medical center in the region. All MEF cultures obtained in the hospital setting, and >85% of those obtained in the community are processed by the SUMC bacteriology laboratory.

In the Negev district, 2 ethnically and socioeconomically distinct populations live side by side. The Jewish population, mostly urban, is largely similar to developed country populations, whereas the Bedouin population, transitioning from nomadic to a western lifestyle, resembles developing world populations. The Bedouin population is characterized by higher birth rates, crowding, and lower socioeconomic level than the Jewish population [17], with higher rates of infectious diseases and associated conditions, including pneumococcal disease, carriage, and hospitalizations for respiratory infections [9, 18–21]. Both populations follow the same National Immunization Plan (NIP).

Definition of Case Patients and Controls

All children 5–35 month old who were residents of the Negev region, with recorded PCV vaccination status and presenting between October 2009 and July 2013. were eligible to be included in this study.

Case Patients

OM episodes were diagnosed by a clinic or hospital pediatrician, a family physician, or an otolaryngologist [15]. Tympanocentesis was performed by otolaryngologists, as described elsewhere [15]. Culture-positive VT-OM episodes (based on tympanocentesis or spontaneous drainage of pus for <7 days) were included. VT-OM cases were stratified based on the serotypes causing OM (PCV7 serotypes [VT7]: 4, 6B, 9V, 14, 18C, 19F, and 23F; 6 additional serotypes in PCV13 [added-VT6]: 1, 3, 5, 6A, 7F, and 19A).

Controls

Study controls were children presenting to the SUMC's pediatric emergency room with rotavirus-negative gastroenteritis. They were part of a prospective hospital-based, population-based observational study [16]. This study (the "Rota study") included children with diarrhea (>2 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting). [16] Rotavirus-positive children were not included among the controls, because they may be affected by whether they receive vaccination generally.

Study Period

The OM surveillance program was initiated in 1998 and has been ongoing [15]. The Rota study took place from April 2006 through July 2013 [16]. For the current study, the period from October 2009 through July 2013 was chosen. During this period, PCV7 and PCV13 were sequentially implemented in the NIP, with vaccine coverage levels allowing enrollment of both vaccinated and nonvaccinated children in the study (Supplementary Figure 1).

PCV7 and PCV13 Vaccine Uptake

PCV7 was licensed in Israel in mid-2007. In 2008–2009, it was subsidized by the Health Maintenance Organizations with an uptake of about 40% among the Jewish population, but no uptake among the Bedouin population. PCV7 was included in the Israeli NIP in July 2009 (at ages 2, 4, and 12 months), with a catch-up campaign in children aged <2 years [10]. In November 2010, PCV13 replaced PCV7, without further catch-up.

Vaccine uptake evaluation methods were described elsewhere [22]. By June 2011, approximately 80% of 7–11-month-old children received ≥2 PCV7 doses and 36% of 24–35-month-old children received ≥3 PCV7 doses. By December 2012, approximately 90% and 87% received ≥2 and ≥3 PCV13 doses, respectively.

Bacteriology

Swab samples of MEF aspirates or draining pus were placed in MW173 Amies transport medium, plated, and processed within 16 hours, as described elsewhere [11, 15]. Pneumococci were serotyped by the Quellung reaction, with antiserum from Statens Serum Institut, Copenhagen, Denmark. One colony was typed per culture.

Data Collection

For both case patients and controls, demographic and clinical data were prospectively obtained from the medical charts, the

child's physician, or parents, included age, sex, ethnicity, and visit or admission date. Individual vaccination status (number and dates of doses and type of PCV) were retrieved from the vaccination centers' databases. For the case patients, information was retrieved on MEF culture date and the serotypes causing OM.

Statistical Methods

Demographic characteristics and vaccination status were compared between case patients and controls using Pearson χ^2 or the Student *t* tests, as appropriate. The statistical significance threshold was $P < .05$. Data were analyzed using SPSS 25.0 software [23].

VE was estimated using unconditional logistic regressions adjusting for time (months) since PCV implementation, age (within each age group) and ethnicity, and expressed as 1 minus the odds ratio (OR) (and 95% confidence interval [CI]) for receiving 1 and ≥2 doses versus 0 doses: VE = [1 − OR]*100%. VE was estimated separately for children receiving PCV7, PCV13, or mixed PCV7 and PCV13.

We estimated VE for PCV7 and PCV13 against OM caused by VT7, as well as PCV13 effectiveness against OM caused by PCV13-unique serotypes (serotypes included in PCV13, but not in PCV7 [added-VT6]) and all serotypes included in PCV13 (VT13). In addition, effectiveness of mixed PCV7/PCV13 or any PCV schedule was assessed against VT7. Analyses of VE were done by age groups: <1 year (5–11 months), 1–3 years (12–35 months), and the entire cohort, <3 years (5–35 months).

Pneumococcal vaccine doses were counted when received ≥14 days before the episode date. During the PCV7 period, a small group of children participated in a study on PCV13 and therefore were excluded from PCV7 analysis, but they were included in the PCV13 VE analysis for the added-VT6. For VE analysis of PCV13 against VT7, children who received any PCV7 dose were excluded. Children who received PCV7 or PCV13 in a 3 + 1 schedule for any reason were excluded from the analysis.

RESULTS

Throughout the study, 507 pneumococcal OM episodes were identified in children 5–35 months old. Of those, 248 were VT-OM episodes. After exclusion of episodes with missing data and those not fulfilling inclusion criteria, 223 VT-OM episodes were included in the final analysis (Figure 1); of these, medical history was available in 175 (78.5%), and 131 of 175 (74.9%) had ≥1 of the following: antibiotic treatment in last month, ≥3 previous OM episodes or ≥1 previous tympanocentesis (Supplementary Table 1). The serotype distribution in VT-OM is presented in Table 1 and Supplementary Figure 2. Overall, serotypes 19F (49.3% of VT7) and 19A (59.6% of added-VT6) were the most common serotypes causing VT-OM. For controls, 1370 rotavirus-negative gastroenteritis episodes were included in the final analysis.

Demographic Characteristics and Vaccination Status

The mean age (standard deviation) of the study population was 13.7 (7.4) months, with similar age distributions in case patients and controls (Table 2). Overall, 53.4% of episodes were in male case patients. Significantly higher proportion of controls than case patients were Bedouin children. The age at PCV vaccination was generally similar in case patients and controls. Nevertheless, the ages at first and second doses were slightly higher in controls than in case patients receiving the third PCV7 dose (Supplementary Table 2).

Effectiveness Against OM Caused by VT7

A single dose of any PCV was not effective at any of the age groups (Supplementary Table 3). Administration of ≥2 doses of any PCV gave generally a higher point effectiveness compared with 0 doses, but was significant only for PCV7 at age 5–35 months (57.2%) (Table 3 and Figure 2). Because the most prevalent serotype among VT7 was serotype 19F, we attempted to examine the VE of PCV7 and PCV13 against this serotype. Administration of ≥2 PCV7 doses resulted in a VE point estimate against serotype 19F, similar to that of the overall VT7, but this did not reach statistical significance (Table 3 and Figure 3). In contrast, ≥2 PCV13 doses showed a significant and high VE (although with a wide 95% CI range) against serotype 19F for the 5–35-month age group (91.3%). The number of children 12–35 months old with OM due to serotype 19F (19F-OM) and with 1 or ≥2 PCV13 doses was too small, not permitting VE calculation.

Effectiveness of PCV13 Against OM Caused by Added-VT6 and Overall VT13

A single PCV13 dose was not effective against OM due to added-VT6 (added-VT6-OM) or due to VT13 (VT13-OM) (Supplementary Table 3 and Figure 2). The effectiveness of ≥2 PCV13 doses against added-VT6-OM for the age groups 12–35 and 5–35 months was 93.3% and 67.4%, respectively (Figure 2 and Table 3). For overall VT13-OM, ≥2 doses were effective for ages 5–11 and 5–35 months (76.9% and 77.4%, respectively)

We did a separate subanalysis of VE against OM due to serotype 19A (19A-OM) since 19A was by far the most prevalent serotype among the added-VT6 (Table 1 and Supplementary Figure 2). Both PCV7 and PCV13 were effective after ≥2 doses for children aged 12–35 months (Table 3 and Figure 3). We also did a separate subanalysis for PCV13 VE against serotype 3 (Table 3 and Supplementary Figure 3). Following ≥2 PCV13 doses, a point effectiveness of >80% was reached for both 5–11- and 5–35-month age groups, reaching significance for age groups 5–35 months.

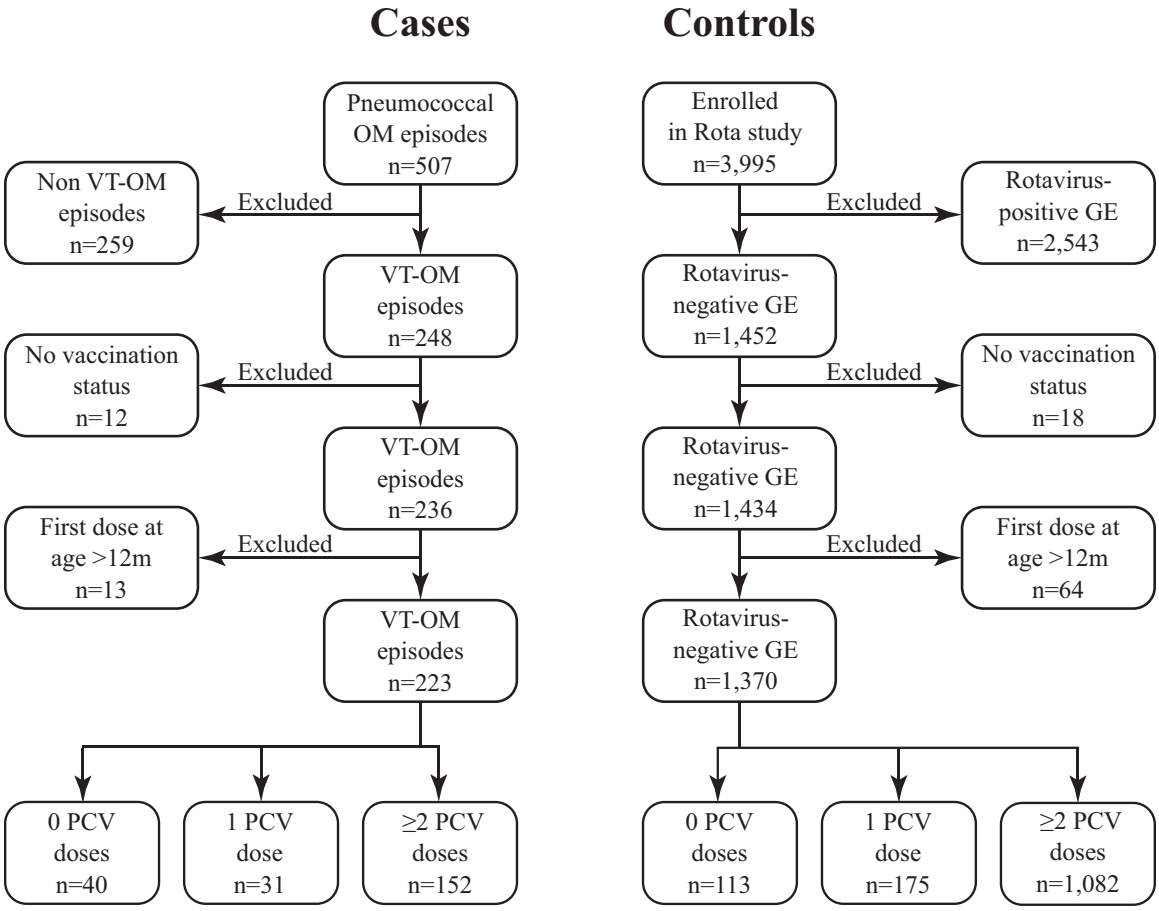

Figure 1. Flow chart of study population. Abbreviations: GE, gastroenteritis; non-VT-OM, otitis media (OM) due to non-PCV serotypes; PCV, pneumococcal conjugate vaccine; VT-OM, otitis media due to PCV serotypes.

Table 1. Vaccine Serotypes Isolated from Middle-Ear Fluid of 223 Children with Otitis Media (October 2009 to July 2013)

VT and Serotype	Children, No. (%)
VT7 (n = 79)	
19F	39 (49.3)
23F	16 (20.2)
6B	10 (12.7)
18C	6 (7.6)
14	4 (5.1)
9V	3 (3.8)
4	1 (1.3)
Added-VT6 (n = 144)	
19A	86 (59.6)
3	22 (15.3)
6A	21 (14.6)
1	6 (4.2)
5	5 (3.5)
7F	4 (2.8)

Added-VT6 serotypes included in 13-valent but not 7-valent pneumococcal conjugate vaccine (PCV).
Abbreviations: VT, vaccine type; VT7, serotypes included in 7-valent PCV.

DISCUSSION

This is the first study in which "real-life" PCV effectiveness against VT-OM was assessed using time-adjusted controls. A previous study evaluated PCV13 effectiveness against added-VT6-OM, using historical controls (children receiving PCV7 during the PCV7 era) [24], probably overestimating VE due to the additional indirect (herd) protection deriving from the reduced added-VT6 nasopharyngeal carriage, and thus reduced exposure. All other studies assessing PCV effect on OM were either prelicensure efficacy studies or postlicensure impact studies. MEF cultures are not routinely obtained, which limits serotype-specific VE studies. Furthermore, unlike PCV7, PCV13 was licensed uniquely based on noninferiority in immunogenicity compared with PCV7 [25] and therefore no efficacy data are available for PCV13. Our study provides a unique opportunity for assessing real life serotype-specific direct PCV7 and PCV13 effectiveness against VT-OM.

Table 2. Demographic Characteristics and Vaccination Status of the Study Population, Comparing Case Patients and Controls

Variable	Case Patients, No. (%) (n = 223)	Controls, No. (%) (n = 1370)	*P* Value
Mean age (SD), mo			
All children	14.1 (7.2)	13.6 (7. 5)	.30
5–11-mo age group	8.6 (2.1)	8.1 (2.0)	.02
12–35-mo age group	19.4 (6.2)	20.1 (6.2)	.28
Ethnicity			
Bedouin n (%)	99 (44.4)	923 (67.4)	<.001
Jewish n (%)	124 (55.6)	447 (32.6)	
Sex			
Male n (%)	119 (53.4)	786 (57.4)	.26
Female n (%)	104 (46.6)	584 (42.6)	
PCV doses, no.			
Age 5–11 mo	n = 108	n = 740	
0	12 (11.1)	40 (5.4)	.02
1	23 (21.3)	158 (21.4)	.99
3	2 (1.9)	12 (1.6)	.86
≥2	73 (67.6)	542 (73.2)	.22
Age 12–35 mo	n = 115	n = 630	
0	28 (24.3)	73 (11.6)	<.001
1	8 (7.0)	17 (2.7)	.02
3	48 (41.7)	396 (62.9)	<.001
≥2	79 (68.7)	540 (85.7)	<.001
Age 5–35 mo	n = 223	n = 1370	
0	40 (17.9)	113 (8.2)	<.001
1	31 (13.9)	175 (12.8)	.64
3	50 (22.4)	408 (29.8)	.02
≥2	152 (68.2)	1082 (79.0)	<.001

Abbreviations: PCV, pneumococcal conjugate vaccine; SD, standard deviation.

We did not include children with OM caused by non-VT serotypes as controls (the indirect cohort method), because the main assumption of indirect cohort studies that the study vaccine does not influence the risk of control condition (non-VT OM), was violated [26]. Our group has previously shown that prevention of early VT-OM occurred as part of PCV7/PCV13 impact, resulting in reduction of recurrent episodes caused not only by VT serotypes but also by nontypeable *H. influenzae*, *Moraxella catarrhalis,* and non-VT pneumococci [11]. The most plausible explanation was that early VT-OM resulted in damage to the middle-ear mucosa, rendering it more susceptible to recurrent and chronic infections by organisms that are often less invasive, including non-VT serotypes [8]. Indeed, a recent analysis showed a reduced ability for progression to disease by non-VT serotypes after implementation of PCV7 or PCV13 [27].

We found that administration of ≥2 doses of either PCV7 or PCV13 during the first year of life afforded effectiveness against VT-OM. The results reached statistical significance for PCV7 against OM due to VT7, PCV13 against VT13-OM, and PCV13 against added-VT6-OM. The paucity of cases caused by VT7 or VT13 during the PCV13 period is the likely reason for not reaching statistical significance for these outcomes with PCV13, despite high point effectiveness. Administration of only 1 dose of either vaccine resulted in lower point effectiveness than administration of ≥2 doses, a difference not reaching significance, similar to the finding in the prelicensure PCV7 OM efficacy study [28].

As expected, PCV13 was highly effective against**19**-A-OM in children 12–35 months old after ≥2 doses. Surprisingly, for this age group, PCV7 appeared to be effective against serotype 19A (although with a wide CI). This was somewhat unexpected, given the sharp and impressive increase in serotype 19A disease, including OM, after PCV7 introduction, also seen in our study (Supplementary Figure 2). However, the most important determinant of serotype replacement disease is the impact of PCVs on nasopharyngeal carriage, determining the extent of exposure in the community. Because PCV7 is not effective against nasopharyngeal carriage of serotype 19A, a marked post-PCV7 replacement by serotype 19A was observed, resulting in increased 19A-OM rates. Some degree of PCV7 effectiveness against 19A-OM could potentially partially blunt this trend, still resulting in an overall 19A-OM increase.

Shortly after PCV7 implementation, OM caused by non-19F VT7 serotypes decreased, but 19F-OM increased (Supplementary Figure 2). This was not entirely surprising. In the PCV7 era,

Table 3. Effectiveness of 7-Valent and 13-Valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Otitis Media, Comparing 0 Versus ≥2 Doses

		0 Doses		≥2 Doses	
Comparison[a]	Effectiveness, %[b]	Case Patients, n	Controls, n	Case Patients, n	Controls, n
Age 5–11 mo					
PCV7 vs VT7	57.7 (−33.3 to 86.6)	5	29	16	195
PCV7 vs serotype 19F	52.6 (−170.9 to 91.7)	2	29	8	195
PCV7 vs serotype 19A	40.5 (−140.9 to 85.3)	3	29	24	195
PCV13 vs VT7	79.4 (−101.1 to 97.9)	1	16	4	312
PCV13 vs added-VT6	38.4 (−102.6 to 81.3)	21	117	12	312
PCV13 vs VT13	76.9 (13.8–93.8)	4	16	16	312
PCV13 vs serotype 19F	93.7 (−11.6 to 99.6)	1	16	1	312
PCV13 vs serotype 19A	44.4 (−546.1 to 95.2)	1	16	6	312
PCV13 vs serotype 3	85.2 (−10.3 to 98.0)	5	117	3	312
PCV7 and/or PCV13 vs VT7	60.0 (−31.5 to 87.8)	5	29	16	285
PCV7/PCV13 mixed vs VT7	52.4 (−504.0 to 96.2)	5	29	2	30
Age 12–35 mo					
PCV7 vs VT7	56.9 (−45.1 to 87.2)	12	69	17	146
PCV7 vs serotype 19F	57.3 (−125.1 to 91.9)	4	69	11	146
PCV7 vs serotype 19A	72.4 (6.2 to 91.9)	9	69	22	146
PCV13 vs VT7	IC	1	10	2	204
PCV13 vs added-VT6	93.3 (64.0–98.8)	31	121	5	241
PCV13 vs VT13	88.0 (−11.5 to 98.7)	6	10	7	204
PCV13 vs serotype 19F	IC	1	10	1	204
PCV13 vs serotype 19A	94.6 (33.9–99.6)	4	10	4	204
PCV13 vs serotype 3	IC	2	121	0	241
PCV7 and/or PCV13 vs VT7	45.8 (−77.8 to 83.5)	12	69	18	216
PCV7/PCV13 mixed vs VT7	96.4 (−8.4 to 99.9)	12	69	1	73
Age 5–35 mo					
PCV7 vs VT7	57.2 (6.0–80.5)	17	98	33	341
PCV7 vs serotype 19F	53.0 (−39.2 to 84.2)	6	98	19	341
PCV7 vs serotype 19A	36.5 (−43.5 to 71.9)	12	98	46	341
PCV13 vs VT7	79.9 (−37.1 to 97.1)	2	26	6	516
PCV13 vs added-VT6	67.4 (17.6 to 87.1)	52	238	17	553
PCV13 vs VT13	77.4 (35.3 to 92.1)	10	26	23	516
PCV13 vs serotype 19F	91.3 (1.4 to 99.2)	2	26	2	516
PCV13 vs serotype 19A	75.8 (−14.4 to 94.9)	5	26	10	516
PCV13 vs serotype 3	89.0 (23.9–98.4)	7	238	3	553
PCV7 and/or PCV13 vs VT7	50.7 (−12.6 to 78.4)	17	98	34	504
PCV7/PCV13 mixed vs VT7	84.3 (−10.6 to 97.8)	17	98	3	103

Added-VT6 serotypes included in PCV13 but not PCV7

Abbreviations: IC, insufficient number of case patients; PCV7, 7-valent pneumococcal conjugate vaccine (PCV); PCV13, 13-valent PCV; VT, vaccine type; VT7, serotypes included in PCV7; VT13, serotypes included in PCV13.

[a]VT7 includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; added-VT6, serotypes 1, 3, 5, 6A, 7F, and 19A; VT13, VT7 plus added-VT6.

[b]Adjusted for ethnicity, time, and age within age group.

multiple reports showed that 19F-OM persisted after PCV7 implementation, possibly related to a lower functional antibody response to this serotype compared to other VT7 serotypes, and a relatively lower efficacy against 19F-OM and carriage [28–32]. Dagan et al [33] previously showed that PCV13 was more immunogenic than PCV7 against serotype 19F, resulting in a significant superior efficacy against nasopharyngeal carriage of this serotype. Therefore, it is plausible that PCV13 had a superior impact against mucosal 19F infections, relative to PCV7.

Whether PCV13 is effective against serotype 3 is up for debate [34, 35]. Dagan et al [33] previously showed that PCV13 was not efficacious against serotype 3 carriage in infants and toddlers. However, several studies suggested that PCV13 was effective against IPD in children, and a recent meta-analysis suggested the effectiveness to be 63%–72% [35]. We found that the VE of ≥2 doses in children 5–35 old months was 89%. Our findings support the available data suggesting direct protection of PCV13 against serotype 3.

Our study was done in the presence of widely implemented vaccination with a 2 + 1 regimen (at age 2, 4, and 12 months). Recently, the United Kingdom has implemented a PCV13 1 + 1 schedule (1 dose administered in infancy with a booster in second year of life). This was based on models predicting similar herd protection with the 2 + 1 and 1 + 1 schedules [36, 37].

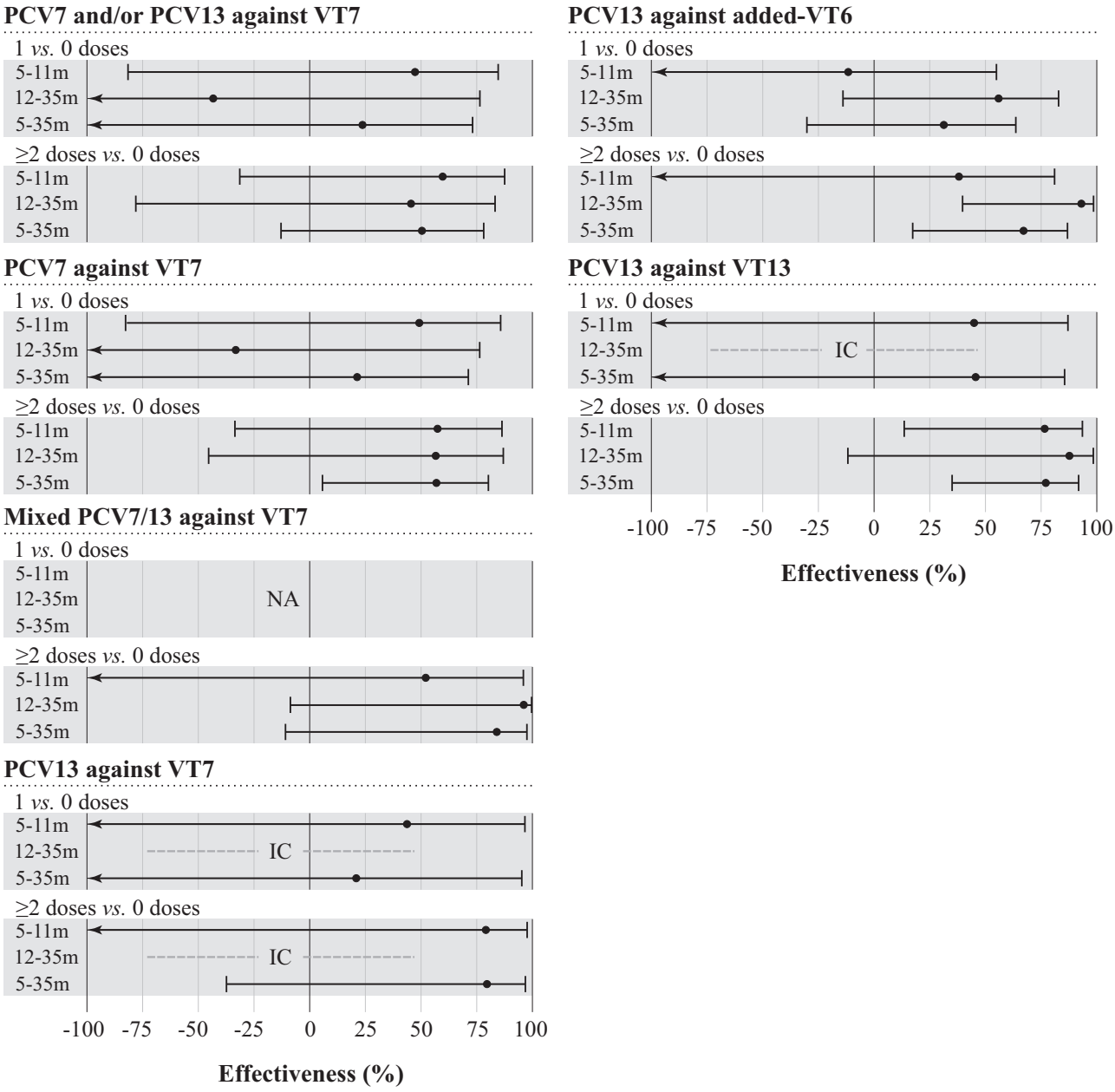

Figure 2. Effectiveness of 7-valent and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13) against otitis media (OM) caused by serotypes in PCV7 (VT7) and PCV13 (VT13). Effectiveness is expressed as percentages with 95% confidence intervals for the age groups 5–11 months, 12–35 months, and 5–35 months (all children). Children who received the first dose at ≥12 months of age were excluded. Added-VT6 serotypes included in PCV13 but not PCV7. Abbreviations: IC, insufficient number of case patients; NA, not applicable.

Given the very poor VE observed after a single PCV dose, and the known consequences of early VT-OM, the 1 + 1 regimen may result in increasing OM episodes and sequelae owing to increased early VT-OM that can occur before the booster dose [8].

Despite the strengths of our study, it also has some weaknesses. First, our case patients mainly had complex OM (recurrent, nonresponsive, chronic OM with effusion or spontaneous perforation of the tympanic membrane) [9, 11, 15]. It is not clear to what extent extrapolation for simple OM can be derived from our results. One study with a limited sample size from California, nested within a large PCV7 efficacy study, suggested a 66.7% efficacy against spontaneously perforated OM caused by PCV7 serotypes, efficacy than that observed against acute OM in other studies [38]. However, it is unlikely that serotype-specific effectiveness will be feasible for mild disease, not necessitating tympanocentesis or presenting with spontaneous otorrhea. In contrast, our study shows effectiveness of PCV7 or PCV13 against episodes enriched with complex OM, which were shown to be associated with the highest OM burden [39, 40].

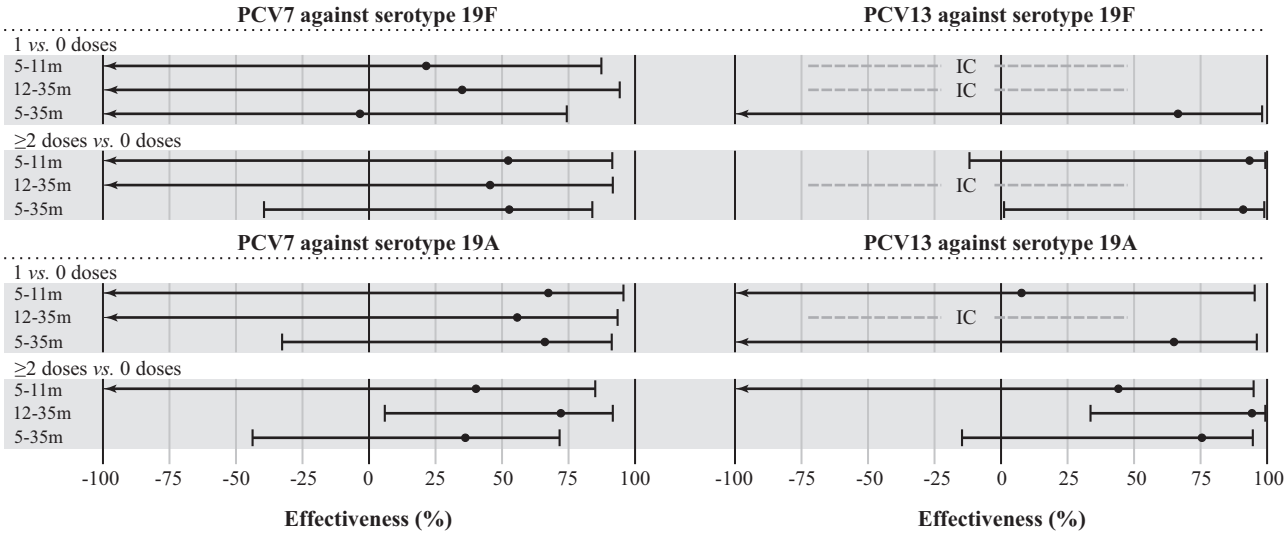

Figure 3. Effectiveness of 7-valent and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13) against otitis media caused by serotypes 19F and 19A. Effectiveness is expressed as percentages with 95% confidence intervals for the age groups 5–11 months, 12–35 months, and 5–35 months (children). Children who received the first dose at ≥12 months of age were excluded. Abbreviation: IC, insufficient number of case patients.

Second, the controls were derived from another surveillance study. However, the case patients and controls were from the same populations and same time period, and our analysis was adjusted for time, ethnic group, and age group. Third, our results derived from a single study in a single geographic location, not necessarily generalizable to other settings. However, to our knowledge, this is the only case-control study ever conducted to determine the effectiveness against VT-OM using contemporary controls, and no comparisons to other effectiveness studies can be made. Finally, for multiple analyses, the case numbers were relatively small, resulting in wide CIs, often making it difficult to draw conclusions for several subgroups. Nevertheless, this large study adds very valuable information to the limitations.

In conclusion, our study provides a unique opportunity for assessing real-life serotype-specific direct effectiveness of PCV7 and PCV13 against OM in young children. While the results with PCV7 are in line with prelicensure efficacy study, no efficacy data are available for PCV13 against OM. The results provide insight into the level of direct protection afforded by these PCVs after implementation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. R. D. has received grants/research support from Pfizer and Merck Sharp & Dohme has been a scientific consultant for MeMed, Merck Sharp & Dohme, and Pfizer and a speaker for Pfizer. S. B. S. has received speaker fees from Pfizer. B. A. V. D. B., S. B. S., and N. G. L. report grants from Pfizer and Merck Sharp & Dohme, during the conduct of the study. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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