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Effectiveness of Pneumococcal Conjugate Vaccines Against Community-acquired Alveolar Pneumonia Attributable to Vaccine-serotype *Streptococcus pneumoniae* Among Children

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(See the Editorial Commentary by Klugman and Rodgers on pages e1434–5.)

Introduction. *Streptococcus pneumoniae* is a leading cause of pneumonia among children. However, owing to diagnostic limitations, the protection conferred by pneumococcal conjugate vaccines (PCVs) against pediatric pneumonia attributable to vaccine-serotype pneumococci remains unknown.

Methods. We analyzed data on vaccination and nasopharyngeal pneumococcal detection among children <5 years old with community-acquired alveolar pneumonia (CAAP; "cases") and those without respiratory symptoms ("controls"), who were enrolled in population-based prospective surveillance studies in southern Israel between 2009 and 2018. We measured PCV-conferred protection against carriage of vaccine-serotype pneumococci via the relative risk of detecting these serotypes among vaccinated versus unvaccinated controls. We measured protection against progression of vaccine serotypes from carriage to CAAP via the relative association of vaccine-serotype detection in the nasopharynx with CAAP case status, among vaccinated and unvaccinated children. We measured PCV-conferred protection against CAAP attributable to vaccine-serotype pneumococci via the joint reduction in risks of carriage and disease progression.

Results. Our analyses included 1032 CAAP cases and 7743 controls. At ages 12–35 months, a PCV13 schedule containing 2 primary doses and 1 booster dose provided 87.2% (95% confidence interval: 8.1–100.0%) protection against CAAP attributable to PCV13-serotype pneumococci, and 92.3% (–0.9%, 100.0%) protection against CAAP attributable to PCV7-serotype pneumococci. Protection against PCV13-serotype and PCV7-serotype CAAP was 67.0% (–424.3%, 100.0%) and 67.7% (–1962.9%, 100.0%), respectively, at ages 36–59 months. At ages 4–11 months, 2 PCV13 doses provided 98.9% (–309.8%, 100.0%) and 91.4% (–191.4%, 100.0%) against PCV13-serotype and PCV7-serotype CAAP.

Conclusions. Among children, PCV-conferred protection against CAAP attributable to vaccine-targeted pneumococcal serotypes resembles protection against vaccine-serotype invasive pneumococcal disease.

Keywords. pneumonia; pediatric; *Streptococcus pneumoniae*; pneumococcal conjugate vaccine; vaccine effectiveness.

Pneumonia remains the leading cause of death among children under 5 years old globally [1]. Prior to implementation of pneumococcal conjugate vaccines (PCVs) [2, 3], the bacterial pathogen *Streptococcus pneumoniae* (pneumococcus) was the most prominent etiology of severe pneumonia cases among children [4]. In addition to revealing 76–100% efficacy against invasive pneumococcal disease (IPD) involving vaccine-targeted serotypes [5–7], prelicensure randomized controlled trials of PCVs among children identified 6–35% efficacy against all-cause nonbacteremic pneumonia meeting differing case definitions [8]. Substantial reductions in incidence of community-acquired pneumonia have occurred among children following implementation of PCVs [9–11], providing further evidence of the etiologic significance of pneumococci in childhood pneumonia and suggesting specific PCV-conferred protection against this condition.

Because pneumonia accounts for a majority of all severe pneumococcal morbidity and mortality among children [12], understanding PCV effectiveness against this endpoint is crucial to quantifying the public health impact and economic value of vaccination programs. Whereas the specific etiology of invasive pneumococcal infections can be revealed by pneumococcal detection in blood or cerebrospinal fluid, no gold standard exists for microbiological diagnosis of the majority of pneumonia cases among children, which

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typically present without bacteremia [13]. Commensal respiratory bacteria such as pneumococci frequently colonize the nasopharynx of healthy children [14]. As such, detecting these organisms in upper respiratory tract specimens from pneumonia cases does not allow specific determination of disease etiology. Collection of lung aspirates poses risks while offering limited diagnostic yield, whereas alternatives such as sputum induction may allow for contamination with colonizing upper respiratory-tract organisms [15]. Although urinary antigen detection enables pneumococcal pneumonia diagnosis among adults, assays are reactive for children experiencing pneumococcal colonization, limiting their specificity [16]. These challenges have prevented assessment of PCV effects against microbiologically specific endpoints in studies of nonbacteremic pneumonia among children [17].

Recent observational studies of pneumonia and diarrhea have leveraged microbiological data from disease cases and asymptomatic controls to infer pathogen-specific etiologic fractions [2, 18] and to support analyses of risk factors associated with etiologically specific disease endpoints [19, 20]. Informed by statistical methods from these studies [21], we reanalyzed data from paired prospective studies of children in southern Israel with and without respiratory illness. We aimed to assess PCV effectiveness against community-acquired alveolar pneumonia (CAAP) attributable to vaccine-serotype pneumococci.

METHODS

Study Setting

Studies were undertaken at the Soroka University Medical Center, the only hospital and emergency department serving the Negev region of southern Israel, where socioeconomically distinct Jewish and Bedouin (Arab) populations live side by side. The Bedouin population is in transition from a nomadic lifestyle to permanent settlements and largely resides in scattered settlements distinguished by larger household sizes, higher rates of crowding, and relative poverty, in comparison to living conditions of the Jewish population. Despite their geographic proximity, contact between Jewish and Bedouin children is rare. Over 90% of children from both populations receive comprehensive healthcare from the same public-sector facilities. In comparison to Jewish children, Bedouin children acquire pneumococci at earlier ages and experience higher pneumococcal carriage prevalence throughout childhood [14], as well as higher incidence of CAAP [22] and IPD [23].

Israel introduced PCV7 in July 2009 under a 3-dose schedule with 2 primary doses at ages 2 and 4 months, and a booster dose at age 12 months (2p+1b dosing); 2 catch-up doses were recommended for all children ages <2 years. Beginning in November 2010, PCV13 replaced PCV7 without additional catch-up. Coverage of PCV7 and PCV13 reached 90% among children <5 years old by July 2012 and December 2013, respectively [24].

Study Design

We constructed a nested case-control study assessing prior vaccination and pneumococcal detection among children ages 0–59 months residing in the Negev region, who were recruited into ongoing, population-based prospective surveillance studies between July 2009 and June 2018.

Cases were enrolled in a study of CAAP [25]. Children were eligible for inclusion if they were admitted to the pediatric emergency department or were hospitalized with radiographically confirmed CAAP (according to standardized criteria [26]), as determined by chest X-ray obtained at presentation or <48 hours from admission. Nasopharyngeal specimens were collected at the earliest opportunity and generally before antibiotic treatment, and no later than 47 hours following presentation. Parents provided written informed consent for study participation. Clinical practices regarding lower respiratory infection referral, evaluation, and chest X-ray examination remained constant throughout the study period. Cases diagnosed with CAAP within the previous 28 days were ineligible.

Controls were enrolled in a concurrent study of pneumococcal colonization employing systematic convenience sampling procedures. As described previously [24], the first 4 Jewish and first 4 Bedouin children presenting each day to the emergency department for any reason, whose parents provided written informed consent for study participation, were included and received nasopharyngeal swabs. So that the control population in our analyses would not include children experiencing diseases potentially attributable to pneumococci, we excluded children whose emergency department diagnoses included upper or lower respiratory tract infection, otitis media, conjunctivitis, pneumonia, influenza, bacteremia/sepsis, or meningitis.

For assessments of vaccine effectiveness (VE), exposures of interest were receipt of 2 PCV doses (among children ages 4–11 months); receipt of 2p+1b dosing, with 1 dose administered at ages ≥10 months (among children ages ≥12 months); and receipt of 0 PCV doses (reference group for VE estimation). Outcomes of interest were detection of PCV13-targeted pneumococcal serotypes, PCV7-targeted serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), or serotypes targeted by PCV13 only (1, 3, 5, 6A, 7F, 19A; "+6PCV13 serotypes"). We assessed VE for PCV13 doses against endpoints associated with PCV13-targeted, PCV7-targeted, and +6PCV13-targeted pneumococcal serotypes, and VE of PCV7 or PCV13 (PCV7/13) doses against endpoints associated with PCV7-targeted serotypes.

In both studies, standardized demographic and risk factor data were collected including children's gestational age, exposure to cigarette smoking, and household characteristics. The number and timing of previous PCV7/13

doses were obtained from children's medical records, held at Soroka University Medical Center (SUMC), along with children's history of asthma, pneumonia, otitis media, and tympanocentesis.

The studies received ethical approval from the human subjects committee of SUMC.

Laboratory Procedures

Nasopharyngeal specimens were obtained via dacron-tipped swabs and placed in MW173 Amies transport medium, plated within 16 hours on 5% sheep blood/5.0 μg gentamicin agar media, and incubated for 48 hours at 35°C as described previously [14, 24]. Pneumococci were detected by alpha hemolysis and optochin inhibition, with confirmation by slide agglutination. One colony per plate was selected for serotyping by Quellung reaction (Statens Seruminstitut, Copenhagen, Denmark).

Statistical Methods

We conducted descriptive analyses comparing demographic characteristics and risk factor prevalence among CAAP cases and controls. We assessed differences in distributions of categorical exposures via the χ^2 statistic. We used the Student *t* test to assess differences in means of continuous variables.

We separately estimated PCV effects against vaccine-serotype carriage, and against progression of vaccine serotypes from carriage to CAAP, to define VE against CAAP attributable to vaccine-serotype pneumococci [21, 27]. In this regard, our analysis addressed vaccine "direct effects" comparing risk between counterfactually vaccinated or unvaccinated children, given the same exposure to circulating vaccine-serotype pneumococci [27]. We estimated the risk ratio of vaccine-serotype carriage among vaccinated versus unvaccinated exposure groups (RR_C) using regression models with a log-binomial link function and defined protection against vaccine-serotype carriage as $VE_C = (1 - RR_C) \times 100\%$.

We used differences in the magnitude of the association of vaccine-serotype pneumococcal detection with CAAP case status, among vaccinated and unvaccinated individuals, to estimate VE against progression (VE_P) of vaccine serotypes from carriage to CAAP. Our statistical approach centered on the hypothesis that vaccine-conferred protection against disease progression would attenuate the association of vaccine-serotype pneumococcal detection with CAAP case status [21]; we expected the excess prevalence of vaccine-serotype pneumococci among vaccinated CAAP cases (as compared to vaccinated controls) would be lower than the excess prevalence of vaccine-serotype pneumococci among unvaccinated CAAP cases (as compared to unvaccinated controls).

Taking OR_1 and OR_0 as the odds ratio (OR) of vaccine-serotype detection associated with CAAP case status, among vaccinated (1) and unvaccinated (0) exposure groups, we defined:

$$VE_P = \left(1 - \frac{OR_1 - 1}{OR_0 - 1}\right) \times 100\ \%\ ,$$

as derived previously [21]. We estimated OR_1 and OR_0 using logistic regression models. To correct for confounders potentially associated with risk of CAAP and vaccination or pneumococcal detection, models yielding adjusted estimates of RR_C, OR_1, and OR_0 controlled for the following covariates: calendar time (to account for PCV7/13-attributable reductions in vaccine-serotype circulation), seasonality (using sine and cosine terms with 12-month oscillations), child age, ethnicity, gestational age <37 weeks, history of pneumonia and asthma diagnoses, number of siblings, and maternal age.

We defined VE against CAAP attributable to vaccine-targeted serotypes (VE_D) as:

$$\begin{aligned} VE_D &= (1 - (1 - VE_C)(1 - VE_P)) \times 100\% \\ &= \left(1 - RR_C \times \frac{OR_1 - 1}{OR_0 - 1}\right) \times 100\%. \end{aligned}$$

RESULTS

Enrollment and Sample Characteristics

The primary CAAP study enrolled 5941 cases among 3704 Bedouin and 2237 Jewish children; complete vaccination data were available from case report forms for all children (Supplementary Table 1). In total, 4305 of 5941 (72.5%) consented CAAP cases were hospitalized for their illness. Because specimen collection typically occurred after radiographic confirmation of illness, children treated as outpatients were unlikely to be available at the healthcare centers for nasopharyngeal sampling (Supplementary Table 2); hospitalized children thus represented 96.6% of CAAP cases included in our analyses. Among those enrolled, 1032 (691 Bedouin and 341 Jewish) children had cultures obtained (Table 1). Cases included in the study thus represent a severe spectrum of disease, with greater likelihood of prior asthma and pneumonia diagnoses, and household cigarette exposure, in comparison to all enrolled CAAP cases (Supplementary Table 2).

Of 13 102 children visiting the emergency department who were enrolled in the carriage study, 7756 did not receive diagnoses related to respiratory symptoms or invasive bacterial infections (Supplementary Table 1). Complete data were available on pneumococcal carriage and PCV receipt for 7743 of these children, including 4503 Bedouin and 3240 Jewish children; we considered these children to comprise the control group.

Over half of the children in both the case and control groups were male (Table 1). Whereas controls were enrolled in equal numbers throughout the calendar year, most CAAP cases were

Table 1. Enrollment and Risk Factor Profile Among CAAP Cases and Eligible Controls

		All Children			Bedouin Children			Jewish Children		
Attributes		CAAP Cases	Controls	*P*[a]	CAAP cases	Controls	*P*[a]	CAAP Cases	Controls	*P*[a]
Total enrollment		1032	7743		691	4503		341	3240	
Hospitalization										
	Admitted inpatient	997 (96.6)	…		681 (98.6)	…		316 (92.7)	…	
Ages										
	0–3 months	119 (11.5)	1358 (17.5)		99 (14.3)	956 (21.2)		20 (5.9)	402 (12.4)	
	4–11 months	326 (31.6)	2137 (27.6)		225 (32.6)	1310 (29.1)		101 (29.6)	827 (25.5)	
	12–35 months	413 (40.0)	3099 (40.0)		246 (35.6)	1649 (36.6)		167 (49.0)	1450 (44.8)	
	36–59 months	174 (16.9)	1149 (14.8)	.01	121 (17.5)	588 (13.1)	.002	53 (15.5)	561 (17.3)	.48
Season										
	March–May	235 (22.8)	1867 (24.1)		163 (23.6)	1103 (24.5)		72 (21.1)	764 (23.6)	
	June–August	108 (10.5)	2162 (27.9)		80 (11.6)	1290 (28.6)		28 (8.2)	872 (26.9)	
	September–November	155 (15.0)	1840 (23.8)		94 (13.6)	1029 (22.9)		61 (17.9)	811 (25.0)	
	December–February	534 (51.7)	1874 (24.2)	<.001	354 (51.2)	1081 (24.0)	<.001	180 (52.8)	793 (24.5)	<.001
Sex										
	Male	564 (54.7)	4264 (55.1)	.83	370 (53.5)	2572 (57.1)	.08	194 (56.9)	1692 (52.2)	.11
Health status										
	Gestational age <37 weeks	138 (13.4)	724 (9.4)	<.001	97 (14.0)	407 (9.1)	<.001	41 (12.0)	317 (9.8)	.24
	Prior asthma diagnosis	118 (11.5)	392 (5.1)	<.001	68 (9.9)	119 (2.6)	<.001	50 (14.8)	273 (8.5)	<.001
	Prior pneumonia diagnosis	205 (20.1)	643 (8.3)	<.001	142 (20.8)	285 (6.3)	<.001	63 (18.6)	358 (11.1)	<.001
	Prior otitis media diagnosis	398 (45.3)	2559 (37.2)	<.001	262 (45.9)	1460 (37.2)	<.001	136 (44.3)	1099 (37.4)	.02
	Prior tympanocentesis	32 (3.3)	179 (2.3)		17 (2.6)	85 (1.9)		15 (4.5)	94 (2.9)	
Exposures										
	Cigarette smoking in household	525 (51.5)	3703 (49.5)	.25	386 (56.5)	2274 (53.0)	.09	139 (41.2)	1429 (44.8)	.23
	Mother's age, years; mean (±SD)	30.0 (±6.0)	29.4 (±5.9)	.007	29.2 (±6.1)	28.1 (±6.0)	<.001	31.6 (±5.5)	31.2 (±5.3)	.26
	Father's age, years; mean (±SD)	33.4 (±7.3)	33.2 (±7.4)	.37	33.1 (±7.7)	32.6 (±8.0)	.13	34.2 (±6.4)	34.1 (±6.2)	.82
	Number of siblings; mean (±SD)	2.9 (±2.3)	2.3 (±2.2)	<.001	3.3 (±2.4)	2.8 (±2.4)	<.001	2.0 (±1.7)	1.5 (±1.4)	<.001
	Persons sharing bedroom with child; mean (±SD)	2.1 (±0.9)	2.2 (+1.0)	.003	2.4 (±0.8)	2.6 (±0.8)	<.001	1.6 (±0.9)	1.7 (±1.0)	.12
PCV7/13 doses										
	0	245 (23.7)	1496 (19.3)		170 (24.6)	1017 (22.6)		75 (22.0)	479 (14.8)	
	1	165 (16.0)	960 (12.4)		133 (19.2)	641 (14.2)		32 (9.4)	319 (9.8)	
	2	319 (30.9)	2417 (31.2)		203 (29.4)	1361 (30.2)		116 (34.0)	1056 (32.6)	
	3	288 (27.9)	2744 (35.4)		180 (26.0)	1442 (32.0)		108 (31.7)	1320 (40.2)	
	≥4	15 (1.5)	126 (1.6)	<.001	5 (0.7)	42 (0.9)	.001	10 (2.9)	84 (2.6)	.002
PCV7/13 schedule										
	2 doses (children ages 4–11 months)	207 (63.5)	1676 (78.4)	<.001	131 (58.2)	967 (73.8)	<.001	76 (75.2)	709 (85.7)	.009
	3-dose series including booster dose (children ages ≥12 months)	281 (66.3)	2691 (84.4)	<.001	176 (66.7)	1413 (84.2)	<.001	105 (65.6)	1278 (84.6)	<.001

Data are presented as number (%) unless otherwise indicated. Where data are missing, proportions are computed from all children with data available.

Abbreviations: CAAP, community-acquired alveolar pneumonia; PCV, pneumococcal conjugate vaccine; SD, standard deviation.

[a]Tests for differences in proportions use the χ^2 statistic. Student *t* test is used to compare means of continuous variables.

Table 2. Pneumococcal Detection Among CAAP Cases and Eligible Controls, Ages 4–59 Months

Detection		Number of Children (%)		
		CAAP Cases	Controls	*P*
Total sample[a]		913	6385	
Streptococcus pneumoniae detected		422 (46.2)	2869 (44.9)	.49
PCV7 serotypes				
	Any detected	94 (10.3)	341 (5.3)	<.001
	4	2 (0.2)	5 (0.1)	.48
	6B	17 (1.9)	61 (1.0)	.02
	9V	7 (0.8)	14 (0.2)	.01
	14	31 (3.4)	57 (0.9)	<.001
	18C	4 (0.4)	21 (0.3)	.82
	19F	20 (2.2)	100 (1.6)	.21
	23F	13 (1.4)	83 (1.3)	.88
+6PCV13 serotypes				
	Any +6PCV13 serotype	86 (9.4)	271 (4.2)	<.001
	1	8 (0.9)	8 (0.1)	<.001
	3	5 (0.5)	26 (0.4)	.74
	5	7 (0.8)	2 (<0.1)	<.001
	6A	22 (2.4)	83 (1.3)	.01
	7F	7 (0.8)	5 (0.1)	<.001
	19A	37 (4.1)	147 (2.3)	.002
Non-PCV13 serotypes				
	Any non-PCV13 serotype	242 (26.5)	2257 (35.3)	<.001
	6C	4 (0.4)	52 (0.8)	.31
	8	0 (0.0)	8 (0.1)	.59
	9N	6 (0.7)	68 (1.1)	.33
	10A	5 (0.5)	64 (1.0)	.25
	10B	1 (0.1)	67 (1.0)	.01
	11A	15 (1.6)	143 (2.2)	.30
	12F	7 (0.8)	31 (0.5)	.39
	15A	12 (1.3)	120 (1.9)	.29
	15B/C	37 (4.1)	278 (4.4)	.74
	16F	21 (2.3)	137 (2.1)	.86
	17F	16 (1.8)	119 (1.9)	.92
	21	12 (1.3)	103 (1.6)	.59
	23A	4 (0.4)	121 (1.9)	.002
	23B	8 (0.9)	151 (2.4)	.006
	34	5 (0.5)	74 (1.2)	.13
	35B	15 (1.6)	156 (2.4)	.17
	Nontypeable	19 (2.1)	159 (2.5)	.53
	Other non-PCV13 serotype	55 (6.0)	406 (6.4)	.75

Entries in the table indicate frequencies of nasopharyngeal detection of each pneumococcal serotype among CAAP cases and controls. *P* values for differences between CAAP cases and controls are computed using the χ^2 statistic.

Abbreviations: CAAP, community-acquired alveolar pneumonia; PCV, pneumococcal conjugate vaccine.

[a]The sample included in this table excludes 119 children ages 0–3 months, who were age-ineligible for receipt of ≥2 PCV7/13 doses due to their age. We further disaggregate serotype frequencies by age group and vaccination status in Supplementary Table 3.

enrolled in the months of December–February, and few were enrolled in June–August. In comparison to controls, CAAP cases were more likely to have been born at <37 weeks gestation and were more likely to have prior asthma, pneumonia, and otitis media diagnoses. Among children 4–11 months old, 63.5% of cases had received 2 PCV7/13 doses, in comparison to 78.4% of controls ($P < .001$). At ages 12–59 months, 66.3% of cases had received a 2p+1b PCV7/13 series, in comparison to 84.4% of controls ($P < .001$).

Pneumococcal Detection

Pneumococci were detected in nasopharyngeal specimens from 46.2% of CAAP cases and 44.9% of controls ($P = .49$; Table 2). Serotypes targeted by PCV7 were detected among 10.3% of CAAP cases and 5.3% of controls ($P < .001$), whereas +6PCV13 serotypes were detected among 9.4% of cases and 4.2% of controls ($P < .001$). In contrast, serotypes not targeted by PCV13 were more prevalent among controls than among CAAP cases (35.3% vs 26.5%; $P < .001$). Individual

serotypes more prevalent among CAAP cases included 1, 5, 6A, 6B, 7F, 9V, 14, and 19A, whereas 10B, 23A, and 23B were more prevalent among controls. We further disaggregate serotype frequencies by age, vaccination status, and ethnicity in Supplementary Tables 3 and 4.

Among both CAAP cases and controls of all ages, prevalence of PCV13-serotype detection was lower among recipients of age-appropriate PCV13 series than unvaccinated children (Figure 1; Supplementary Tables 5 and 6). Our statistical analysis framework for assessing vaccine effects against pneumonia further entailed comparisons of effect sizes for the association of vaccine-serotype detection with CAAP case status among vaccinated and unvaccinated children. Among unvaccinated children, prevalence of PCV13 serotypes was higher among CAAP cases than controls at ages 12–35 and 36–59 months, whereas differences in PCV13 serotype prevalence were not statistically significant among CAAP cases and controls who received age-appropriate PCV13 series. Point estimates of the adjusted

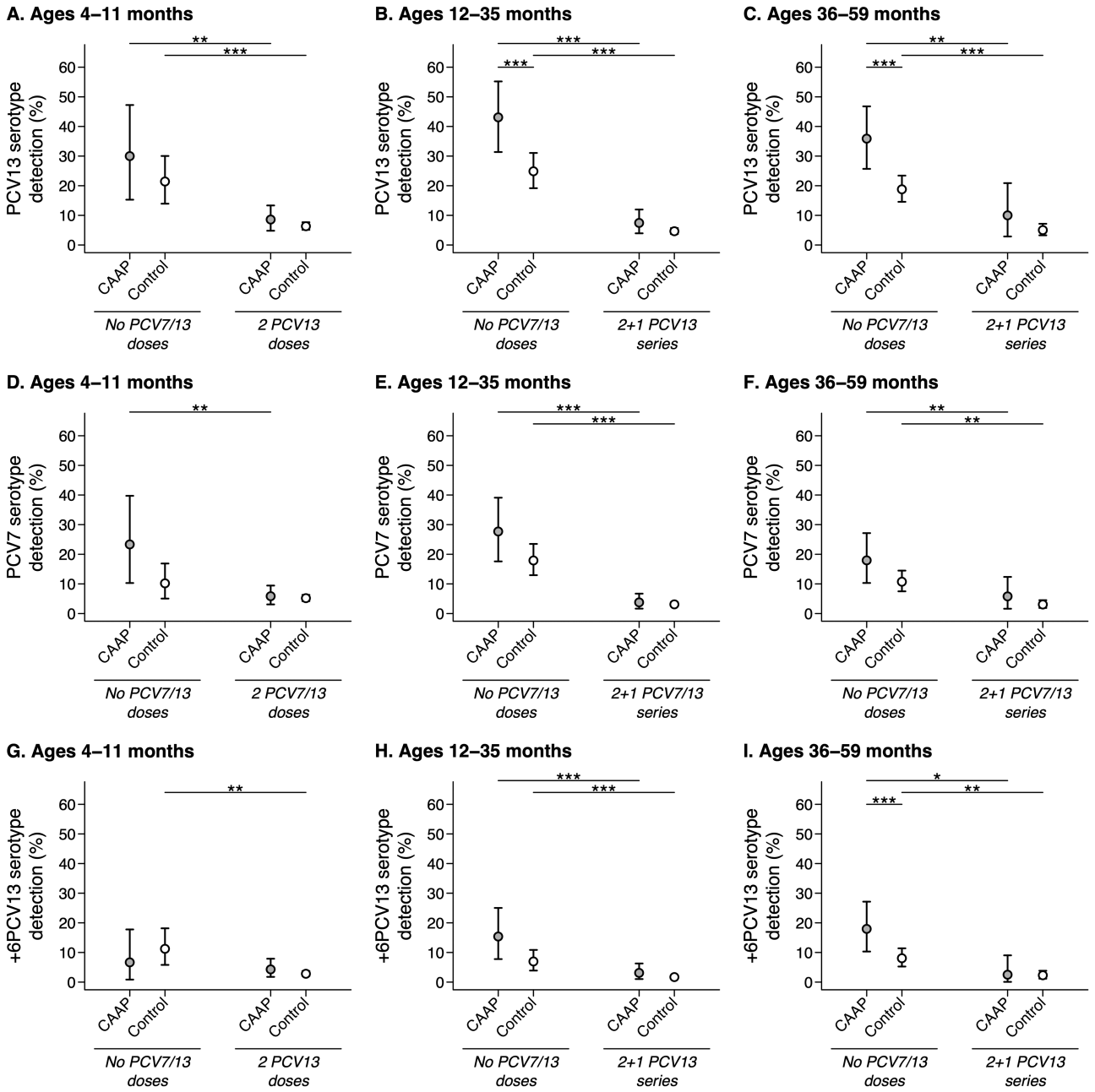

Figure 1. Detection of PCV-targeted serotypes among CAAP cases and control with differing vaccination status. We plot prevalence of detection of PCV13-targeted (*A*-*C*), PCV7-targeted (*D*-*F*), and +6PCV13-targeted (*G*-*I*) serotypes among children who received no PCV7/13 doses or recommended PCV7/13 dosing (2 doses at ages 4–11 months, *A*, *D*, *G*; 2 + 1 dosing at ages 12–35 months, *B*, *E*, *H*; and 2 + 1 dosing at ages 36–59 months, *C*, *F*, *I*). Asterisks denote significant (2wo-sided) differences between paired estimates; *: $.01 \le P < .05$: **: $.001 \le P < .01$; ***: $P < .001$. Abbreviations: CAAP, community-acquired alveolar pneumonia; PCV, pneumococcal conjugate vaccine.

relative odds of vaccine serotype detection among CAAP cases, as compared to controls, ranged from 2.46 to 3.72 among unvaccinated children ages 12–35 months, and from 1.25 to 1.78 among schedule-concordant vaccine recipients of the same ages (Table 3; Supplementary Tables 6 and 7). Differences in adjusted odds ratio estimates among vaccinated versus unvaccinated children were less consistently apparent at ages 4–11 months and 36–59 months.

Vaccine Effectiveness

Accounting for protection against carriage and disease progression involving vaccine-targeted serotypes, we estimated that a 2p+1b PCV13 series conferred 77.0% (–16.0%, 100.0%) protection against CAAP attributable to PCV13-serotype pneumococci at ages 12–59 months (Table 4). Stratifying by age, we estimated 87.2% (8.1–100.0%) protection at ages 12–35 months and 67.0% (–424.3%, 100.0%) protection at ages 36–59 months; our study was underpowered to demonstrate differences in age-specific protection. Estimates of protection against CAAP associated with PCV13-targeted serotypes at ages 12–59 months were 73.0% (–119.0%, 100.0%) among Bedouin children and 89.4% (–105.5%, 100.0%) among Jewish children.

Children ages 12–35 months who received 2p+1b schedules of PCV13 only and PCV7/13 experienced 92.3% (–0.9, 100.0%) and 95.9% (30.5–100.0%) protection against CAAP associated with PCV7-targeted serotypes. Estimates were similar in analyses addressing serotype 6A as a PCV7-targeted serotype (Supplementary Table 8). At the same ages, we estimated 81.0% (–224.5%, 100%) protection against CAAP associated with +6PCV13 serotypes, for children receiving 2p+1b PCV13 dosing (Table 4). Point estimates of protection against CAAP associated with +6PCV13 serotypes, and all PCV13-targeted serotypes, were >90% when serotype 3 was excluded from analyses (Supplementary Table 8). We did not identify marked or directionally consistent differences in effect sizes at ages 12–35 and 36–59 months within serotype strata.

At ages 4–11 months, we estimated the effectiveness of 2 PCV13 doses was 91.4% (–191.8%, 100.0%) and 86.9% (–123.5%, 100.0%), respectively, against CAAP attributable to PCV7-targeted and +6PCV13 serotypes (Table 4). We obtained similar findings for analyses considering alternative groupings for cross-reactive serotypes 6A and 6C, and those including or excluding serotype 3 (Supplementary Table 8).

DISCUSSION

We assessed PCV-conferred protection against CAAP attributable to vaccine-targeted pneumococcal serotypes among children using data from microbiologically detailed prospective surveillance studies in southern Israel. Accounting for protection against carriage of vaccine-targeted pneumococcal serotypes and progression of carried serotypes to disease, we estimated that 2p+1b PCV13 series provide 87% and 67% protection against CAAP attributable to PCV13-serotype pneumococci at ages 12–35 months and 36–59 months, respectively. We obtained similar, high point estimates of protection at ages 4–11 months. Although our analyses were not sufficiently powered to exclude the possibility of ≤0% protection within each age and serotype stratum, the consistently high VE point estimates in our study suggest PCV confers substantial protection against CAAP attributable to vaccine-serotype pneumococci among young children.

Our estimates of protection against vaccine-serotype pneumococcal CAAP at ages 12–35 months are in close agreement with estimates of the efficacy and effectiveness of booster-containing PCV schedules against vaccine-serotype IPD at the same ages [28]. Studies of PCV efficacy and effectiveness against all-cause pneumonia have yielded varying results, in part due to differences in pneumonia case definitions across studies [29, 30]. Here we enrolled children meeting a standardized, stringently-defined CAAP endpoint to facilitate comparisons with other studies and to maintain consistent case definitions over time [26]. Owing to reductions in outpatient pneumonia during the study period, and procedures for obtaining nasopharyngeal specimens, nearly all children included in our analyses were hospitalized [9, 31]. Previous studies have reported that pneumococcal etiology is associated with greater severity of pneumonia cases among children [2]; furthermore, pneumonia cases with detection of certain invasive, vaccine-targeted pneumococcal serotypes (1, 5, 7F, 14, 19A) in the nasopharynx involve a distinct clinical phenotype featuring higher temperature and higher peripheral white blood cell count than cases with other serotypes detected or without pneumococci [32]. As such, certain vaccine-targeted pneumococci may have particular significance as causes of severe CAAP cases included in our study. Notably, whereas detection of PCV13-targeted serotypes was associated with CAAP case status in our study, detection of non-PCV13 serotypes was associated with control status. This finding of lower nonvaccine serotype pathogenicity suggests that serotype replacement in pneumococcal carriage is unlikely to fully offset vaccine impact against CAAP.

Because detection of pneumococci in the nasopharynx during pneumonia does not necessarily indicate disease etiology, our study used a population-based mathematical framework to assess PCV-conferred protection [21]. Similar approaches have been used to overcome diagnostic uncertainty in previous epidemiological studies of conditions such as pneumonia and diarrhea, for inferential objectives, and to estimate pathogen-specific etiologic fractions [2, 18]. Our ability to use carriage data to inform vaccine effectiveness against etiologically-specific disease endpoints underscores the value of simultaneous surveillance of carriage and disease within a single population.

Our study has several strengths. Risk factor data from large samples of children enabled us to control for confounders and

Table 3. Association of Pneumococcal Serotype Detection with Pneumonia Case Status Among Vaccinated and Unvaccinated Children

			Total Children					
			Vaccine Serotype Detected		Vaccine Serotype Not Detected		OR (95% CI) of Serotype Detection, for CAAP Cases Versus Controls	
Age Group	Serotype Endpoint	Exposure[a]	CAAP Cases	Controls	CAAP Cases	Controls	Unadjusted	Adjusted[b]
4–11 months								
	All PCV13							
		0 PCV7/13 doses	9	21	21	77	1.57 (0.63, 3.93)	1.26 (0.45, 3.53)
		2 PCV13 doses	14	143	149	1302	1.39 (0.77, 2.50)	1.02 (0.54, 1.95)
	PCV7 only							
		0 PCV7/13 doses	7	10	21	77	2.57 (0.87, 7.56)	2.61 (0.74, 9.13)
		2 PCV13 doses	7	49	149	1302	1.25 (0.55, 2.80)	1.41 (0.60, 3.30)
		2 PCV7/13 doses	12	86	177	1513	1.25 (0.56, 2.80)	1.41 (0.60, 3.30)
	+6PCV13 only							
		0 PCV7/13 doses	2	11	21	77	0.67 (0.14, 3.23)	0.43 (0.08, 2.35)
		2 PCV13 doses	7	39	149	1302	1.57 (0.69, 3.57)	0.76 (0.30, 1.88)
12–35 months								
	All PCV13							
		0 PCV7/13 doses	28	50	37	151	2.28 (1.27, 4.11)	2.73 (1.44, 5.18)
		PCV13 series	12	77	149	1580	1.65 (0.88, 3.10)	1.59 (0.82, 3.06)
	PCV7 only							
		0 PCV7/13 doses	18	36	37	151	2.04 (1.04, 3.99)	2.46 (1.21, 5.02)
		PCV13 series	7	49	149	1580	1.52 (0.67, 3.41)	1.46 (0.63, 3.38)
		PCV7/13 series	8	63	196	1911	1.24 (0.58, 2.62)	1.25 (0.58, 2.72)
	+6PCV13 only							
		0 PCV7/13 doses	10	14	37	151	2.92 (1.20, 7.09)	3.72 (1.32, 10.48)
		PCV13 series	5	28	149	1580	1.90 (0.72, 4.98)	1.78 (0.64, 4.94)
36–59 months								
	All PCV13							
		0 PCV7/13 doses	28	56	50	242	2.42 (1.40, 4.18)	1.98 (1.09, 3.60)
		PCV13 series	4	24	36	453	2.10 (0.69, 6.37)	1.68 (0.50, 5.66)
	PCV7 only							
		0 PCV7/13 doses	14	32	50	242	2.12 (1.05, 4.26)	1.33 (0.61, 2.89)
		PCV13 series	3	13	36	453	2.91 (0.79, 10.65)	1.76 (0.40, 7.66)
		PCV7/13 series	4	20	58	622	2.14 (0.71, 6.48)	1.18 (0.34, 4.13)
	+6PCV13 only							
		0 PCV7/13 doses	14	24	50	242	2.82 (1.37, 5.83)	3.23 (1.45, 7.21)
		PCV13 series	1	11	36	453	1.14 (0.14, 9.16)	1.51 (0.17, 13.12)

Entries in the table indicate the frequency of detection of vaccine serotypes among cases and controls with differing vaccination histories along with odds ratios for the association of detection of vaccine serotypes with CAAP case status, within strata of vaccinated and unvaccinated children. We indicate frequencies for alternative vaccine serotype groupings in Supplementary Table 6.

Abbreviations: CAAP, community-acquired alveolar pneumonia; CI, confidence interval; OR, odds ratio; PCV, pneumococcal conjugate vaccine.

[a]We define a PCV13 series as receipt of 3 PCV13 doses and 0 PCV7 doses, including one PCV13 dose at ages ≥10 months. We define a PCV7/13 series as receipt of 3 doses of PCV7 or PCV13, including one dose of either vaccine at ages ≥10 months.

[b]Adjusted analyses control for the following confounding variables: calendar time (log-transformed), age (log-transformed), seasonality (using harmonic regression coefficients with 12- and 6-month periodicity), gestational age <37 weeks, prior pneumonia, asthma, number of siblings, and mother's age.

Table 4. Direct Effect of PCV Against CAAP Attributable to Vaccine-serotype Pneumococci

Age Group	Exposure[a]	Serotype Endpoint	Vaccine Effectiveness	
			Unadjusted (95% CI)	Adjusted (95% CI)[b]
4–11 months				
	2 PCV13 doses			
		All PCV13	73.5 (–735.6, 100.0)	98.9 (–309.8, 100.0)
		PCV7 only	89.6 (–248.3, 100.0)	91.4 (–191.8, 100.0)
		+6PCV13 only	100.0 (–708.1, 100.0)	86.2 (–123.5, 100.0)
	2 PCV7/13 doses			
		PCV7 only	84.4 (–413.8, 100.0)	86.9 (–334.1, 100.0)
12–59 months				
	3-dose PCV13 series with booster			
		All PCV13	88.2 (54.8, 99.9)	77.0 (–16.0, 100.0)
		PCV7 only	86.5 (20.9, 100.0)	73.3 (–208.7, 100.0)
		+6PCV13 only	92.3 (46.4, 100.0)	84.6 (–28.7, 100.0)
	3-dose PCV7/13 series with booster			
		PCV7 only	91.8 (45.4, 100.0)	89.8 (–56.7, 100.0)
12–35 months				
	3-dose PCV13 series with booster			
		All PCV13	90.8 (36.2, 100.0)	87.2 (8.1, 100.0)
		PCV7 only	92.9 (1.7, 100.0)	92.3 (–0.9, 100.0)
		+6PCV13 only	91.0 (–15.9, 100.0)	81.0 (–224.5, 100.0)
	3-dose PCV7/13 series with booster			
		PCV7 only	96.6 (35.3, 100.0)	95.9 (30.5, 100.0)
36–59 months				
	3-dose PCV13 series with booster			
		All PCV13	79.7 (66.4, 100.0)	67.0 (–424.3, 100.0)
		PCV7 only	60.7 (–459.5, 100.0)	67.7 (–1962.9, 100.0)
		+6PCV13 only	98.2 (–90.6, 100.0)	88.1 (–437.0, 100.0)
	3-dose PCV7/13 series with booster			
		PCV7 only	74.2 (–255.5, 100.0)	93.4 (–712.6, 100.0)

Entries in the table indicate estimates of the reduction in susceptibility to CAAP attributable to vaccine-serotype pneumococci, estimated via the reduction in risk of vaccine-serotype colonization and against progression of vaccine serotypes to CAAP (Supplementary Table 6). We present estimates for alternative vaccine serotype groupings in Supplementary Table 8.

Abbreviations: CAAP, community-acquired alveolar pneumonia; CI, confidence interval; PCV, pneumococcal conjugate vaccine.

[a]We define a PCV13 series as receipt of 3 PCV13 doses and 0 PCV7 doses, including one PCV13 dose at ages ≥10 months. We define a PCV7/13 series as receipt of 3 doses of PCV7 or PCV13, including one dose of either vaccine at ages ≥10 months.

[b]Adjusted analyses control for the following confounding variables: calendar time (log-transformed), age (log-transformed), seasonality (using harmonic regression coefficients with 12- and 6-month periodicity), gestational age <37 weeks, prior pneumonia, asthma, number of siblings, and mother's age.

secular trends in analyses of nonrandomized vaccine exposures; excluding children with respiratory symptoms from the control group further reduced the risk of misclassification. However, certain limitations should be considered. Culture-based pneumococcal detection provides lower sensitivity in comparison to molecular diagnostic approaches [33]. In our analyses, this may lead to underestimation of protection against disease progression [21]. Although CAAP cases generally had nasopharyngeal specimens collected before antibiotic treatment initiation in the hospital, some cases may have received antibiotics before presentation. We nonetheless observed a high culture-positive fraction overall among CAAP cases. We do not address the role of coinfecting pathogens including respiratory viruses in the acquisition and progression of pneumococcal carriage, although analyses control for seasonal variation in risk of disease progression [34]. Finally, compounded uncertainty from estimating vaccine effects against both carriage and disease progression led to low statistical power, particularly for the 4–11 month and 36–59 month age groups. Although our findings show in principle that PCVs confer protection against vaccine-serotype CAAP, our study was underpowered to provide precise effect size estimates.

Our study provides evidence that PCV-conferred protection against CAAP attributable to vaccine-serotype pneumococci closely resembles VE against vaccine-serotype IPD. This direct protection, together with herd effects of PCV implementation on the circulation of vaccine-targeted serotypes [35], has contributed to substantial reductions in the burden of CAAP associated with vaccine-serotype pneumococci following PCV implementation in Israel [9, 25, 32]. Estimates we provide should be considered alongside PCV efficacy and effectiveness against vaccine-serotype IPD and otitis media in assessments of the value of PCV programs, given the high incidence and mortality of childhood pneumonia globally.

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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