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Pan-serotype Reduction in Progression of *Streptococcus pneumoniae* to Otitis Media After Rollout of Pneumococcal Conjugate Vaccines

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Background. Reductions in otitis media (OM) burden following rollout of pneumococcal conjugate vaccines (PCVs) have exceeded predictions of vaccine impact. In settings with active surveillance, reductions in OM caused by vaccine-targeted pneumococcal serotypes have co-occurred with reductions in OM caused by other pathogens carried in the upper-respiratory tract of children. To understand these changes, we investigated the progression of vaccine-targeted and non-vaccine pneumococcal serotypes from carriage to OM before and after vaccine rollout.

Methods. Nasopharyngeal carriage prevalence of pneumococcus was monitored in prospective studies of Bedouin and Jewish children <3 years old in southern Israel between 2004 and 2016. Incidence of OM necessitating middle-ear fluid culture (predominantly complex OM including recurrent, spontaneously-draining, non-responsive, and chronic cases) was monitored via prospective, population-based active surveillance. We estimated rates of pneumococcal serotype-specific progression from carriage to disease before and after rollout of PCV7/13, measured as OM incidence per carrier. We pooled serotype-specific estimates using Bayesian random-effects models.

Results. On average, rates of progression declined 92% (95% credible interval: 79–97%) and 80% (46–93%) for PCV7/13 serotypes among Bedouin and Jewish children <12 months old, respectively, and 32% (−58–71%) and 61% (−5–86%) among children aged 12-35m. For non-vaccine serotypes, rates of progression among Bedouin and Jewish children aged <12m declined 74% (55–85%) and 43% (4–68%), respectively.

Conclusions. Vaccine-targeted and non-vaccine pneumococcal serotypes showed lower rates of progression to complex OM after rollout of PCV7/13. Early-life OM episodes historically associated with vaccine-serotype pneumococci may impact the susceptibility of children to OM progression.

Keywords. otitis media; complex otitis media; pneumococcal conjugate vaccine; surveillance.

Otitis media (OM) is a multifactorial disease caused by upper-respiratory pathogens and is the main contributor to pediatric healthcare visits and antimicrobial prescribing in high-income countries [1]. Severity ranges from acute, self-limiting and possibly asymptomatic infections to complex OM, which includes recurrent, nonresponsive, and spontaneously-draining infections and chronic OM with effusion [2]. Historically, *Streptococcus pneumoniae* has been a predominant bacterial cause of OM, especially in infancy [3, 4]. Because nearly all children carry *S. pneumoniae* or other otopathogens early in life, host and bacterial factors impacting progression from colonization to infection are ideal targets for preventing disease.

Pneumococcal conjugate vaccines (PCVs) include capsular antigens from 7, 10, or 13 of the *S. pneumoniae* serotypes most commonly implicated in pneumococcal diseases. In recent decades, PCVs have been introduced to national immunization schedules in most countries, contributing to the near-elimination of vaccine-targeted pneumococcal serotypes from upper-respiratory carriage among children [5]. Whereas PCVs were licensed primarily to prevent vaccine-serotype invasive pneumococcal disease (IPD), pre-implementation randomized controlled trials also demonstrated moderate efficacy against vaccine-serotype OM [6]. In addition, several pre-implementation studies demonstrated enhanced efficacy of PCV7 against complex manifestations including recurrent and chronic ear infections, reducing the need for ventilation tubes by >30% [7–10]. These complex episodes are often secondary events following early-life pneumococcal OM associated with virulent vaccine-targeted serotypes [11, 12], and are frequently characterized by mixed-species biofilm formation involving non-typeable *Haemophilus influenzae* (NTHi) [13].

In post-licensure studies, reductions in OM incidence have in some instances exceeded the proportion of cases attributed

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to PCV7/13 serotypes in the pre-vaccine era [14]. Unlike observations of serotype replacement in pneumococcal carriage, PCV7/13 implementation has not led to proportional increases in non-vaccine serotype OM [15–18]. Declining rates of OM caused by NTHi, *Moraxella catarrhalis*, and *S. pyogenes*, and of culture-negative OM, have been reported in the only microbiologically-detailed prospective study of OM episodes before and after PCV7/13 implementation [16], in a sample enriched with complex cases. This finding corroborates pre-licensure evidence that PCVs protect against complex OM manifestations [7–10], and post-licensure reductions in OM-associated pediatrician visits, antimicrobial prescribing, and tympanostomy tube insertions reported in numerous settings [19–22].

Understanding how PCVs prevent complex OM manifestations, which may involve pathogens other than vaccine-serotype pneumococci, can inform the use of vaccines. An accumulating body of evidence suggests morphological and mucosal damage sustained in the middle ear during early-life OM predisposes children to subsequent OM progression [2]. We hypothesized that prevention of tissue damage from early-life infections historically associated with vaccine-serotype pneumococci may contribute to the declining incidence of complex OM after PCV7/13 rollout. To understand the impact of PCVs on susceptibility of children to OM progression, we investigated changes in the capacity of vaccine-targeted and non-vaccine pneumococcal serotypes to progress from carriage to OM using prospectively-gathered epidemiological surveillance data from Israel.

METHODS

Setting

We analyzed data from previously-published studies of pneumococcal carriage and OM incidence among Bedouin and Jewish children in the Negev region of southern Israel. The Bedouin population is transitioning from a nomadic lifestyle to permanent settlements, with larger family sizes, higher rates of overcrowding, and lower socioeconomic status than the nearby Jewish population [23].

Vaccine rollout in southern Israel has been described elsewhere [24]. Briefly, PCV7 was introduced to the national immunization program in July, 2009 with catch-up campaigns among children <2 years old. PCV13 replaced PCV7 in November, 2010, and coverage among children <3 years old surpassed 90% in 2012. Consistent with previous analyses [16], we defined the pre-vaccine era as July 2004-June 2008, and the era of widespread PCV13 use as July 2013-June 2016; the majority of children included in our carriage and OM surveillance datasets received vaccine doses as recommended (2-dose primary series and booster at 1y; Table S1).

Surveillance Data

Over 95% of children in the Negev region receive care from Soroka University Medical Center (SUMC). Data from all OM episodes at the hospital necessitating middle ear fluid (MEF) culture were compiled through ongoing prospective, population-based epidemiological surveillance. Indications for MEF culture included, but were not limited to, previous OM or tube insertion, high-grade fever or toxic appearance, and spontaneous drainage, as described elsewhere [16]. Because these indications have not changed during the study period, the data represent incidence of severe OM manifestations before and after vaccine rollout. Census data supplied child-years at risk in Jewish and Bedouin birth cohorts [23].

Two studies provided carriage prevalence before PCV7 implementation (Table 1). In the first, 1125 swabs were collected from PCV7-unvaccinated Jewish and Bedouin children ages 12-35m enrolled in a hepatitis A vaccine trial; swabs were taken during blood draws at scheduled visits [25]. In the second study, 1602 swabs were collected from unvaccinated Jewish and Bedouin children ages 2–30 months enrolled in a pre-implementation trial of PCV7 dosing schedules [26].

Following PCV7 implementation, the first four Jewish and first four Bedouin children presenting each day to the emergency department at SUMC submitted nasopharyngeal swabs for pneumococcal carriage [24]. To ensure pneumococcal carriage was unrelated to the cause of the visit, we excluded swabs from children whose diagnoses included fever, OM, pneumonia, lower or upper respiratory infections, suspected viral infections including influenza, conjunctivitis, asthma, sepsis/bacteremia, and meningitis (n = 3321 of 6905). The most common diagnoses for the remaining 3584 swabs were gastroenteritis (n = 1987) and urinary tract infection (n = 182). Because this left us with a carriage sample enriched with visits occurring during the summer, when carriage may be lower [26], we performed a sensitivity analysis including all swabs when estimating carriage prevalence.

Bacteriological procedures for *S. pneumoniae* identification were consistent for the carriage and OM studies, and have been detailed previously [27]. Serotypes were determined by the Quellung reaction (antisera from Statens Serum Institut, Copenhagen, Denmark). Original studies received ethics approval from SUMC. Secondary analyses were exempted by the institutional review board at Harvard-Chan School of Public Health.

Progression Rate

We measured progression rate as the rate of OM incidence divided by carriage prevalence for each serotype, with units of (cases/year)/carrier. We stratified measurements for children <12 and 12–35 months old by Jewish/Bedouin ethnicity, and compared between the pre-PCV7 and PCV13 eras within these strata. We generated estimates in a Bayesian framework to propagate uncertainty in measurements. We detail the procedure in the online supplement (**Text S1**). Briefly, for each age/ethnic/temporal stratum, we generated Gamma-distributed rates of pneumococcal OM incidence, and fitted log-normal

Table 1. Data Sources

Variables measured	Measurement details	Coverage	Citation
Pneumococcal OM incidence	All episodes of OM submitted for MEF culture among Bedouin and Jewish children presenting for care at Soroka University Medical Center	5092 episodes	[16]
Nasopharyngeal pneumococcal carriage prevalence	Unvaccinated Bedouin and Jewish children sampled at scheduled visits, ages 2-30 months, enrolled in a PCV7 dosing study	769 children submitting 1602 swabs	[26]
	Unvaccinated Bedouin and Jewish children ages 7-35 months	322 children submitting 1125 swabs	[25]
	Bedouin and Jewish children ages 0-35 months presenting to the emergency department for reasons other respiratory or invasive illnesses	3584 swabs	[24]
Resistance to neutrophil-mediated killing[a]	Survival of pneumococcal serotype in a complement-independent *in vitro* surface killing assay	14 serotypes[b]	[28]
Magnitude of anionic surface charge[a]	(Negative) zeta potential of fixed-density suspension of pneumococcal serotype in phosphate-buffered saline	48 serotypes[b]	[29]
Capsular size[a]	Zone of exclusion of fluorescent dextran molecules around pneumococcal serotype diplococcus	15 serotypes[b]	[28]
IPD case-fatality ratio	Serotype-specific 30-d mortality during invasive pneumococcal disease	37 serotypes[b]	[31]
Metabolic efficiency	Inverse of number of carbons per capsular polysaccharide repeat unit of pneumococcal serotype	54 serotypes[b]	[28]
Invasiveness	Proportion of carriage events leading to invasive pneumococcal disease	36 serotypes[b]	[30]

Abbreviations: IPD, invasive pneumococcal disease; MEF, middle ear fluid; OM, otitis media; PCV, Pneumococcal conjugate vaccines.

[a] *In vitro* measurements of serotype properties were obtained from isogenic capsular-switch mutants

[b] We list serotypes for which phenotypic data were collected in Table S2.

distributions of carriage prevalence using regression models. We sampled from the proportions of disease and carriage episodes ascribed to individual serotypes within strata using a Dirichlet distribution with a flat prior, thus retaining uncertainty in the context of sparse serotype-specific measurements. We defined the change in serotype-specific progression rate within each stratum as

$$1-\frac{\left(\frac{\textit{Post-rollout serotype-specific OM incidence in age / ethnic group}}{\textit{Post-rollout serotype-specific carriage prevalence in age / ethnic group}}\right)}{\left(\frac{\textit{Pre-PCV7 serotype-specific OM incidence in age / ethnic group}}{\textit{Pre-PCV7 serotype-specific carriage prevalence in age / ethnic group}}\right)}$$

Because our study was under-powered to measure changes for each serotype, we used Bayesian random-effects models to summarize mean changes in progression rates across vaccine-targeted and non-vaccine serotypes within each age/ethnic stratum.

Phenotypic Correlates of Progression Rate

We tested for associations between progression rate and previous measurements of phenotypic attributes to understand variation in the capacity of serotypes to cause OM (Table S2). These measurements included resistance of serotypes to complement-independent phagocytosis, measured as the proportion surviving a neutrophil surface-killing assay, and relatedly, widths and negative surface charges of the capsule (which determine susceptibility to phagocytosis) [28, 29]; efficiency with which capsules can be produced, measured by the inverse of the number of carbons per repeat unit of the polysaccharide [28]; likelihoods for serotypes to progress from carriage to IPD [30]; and likelihoods for serotypes to cause death during IPD [30, 31].

We estimated associations between log-transformed serotype-specific progression rates and phenotype in linear regression models. We fitted models separately for the age groups and time periods, controlling for Jewish/Bedouin ethnicity. Because vaccine-mediated protection could confound the association between serotype factors and progression rate after PCV7/13 rollout, we included only non-vaccine serotypes for the period after PCV13 rollout. We recovered effect size distributions by fitting models to 10,000 independent draws from posterior distributions of outcome variables.

We used the same approach to test for phenotype associations with the effect of vaccine introduction on serotype-specific progression rate. The outcome was the log-transformed rate ratio of serotype-specific progression after PCV13 rollout relative to the pre-PCV7 era. We again stratified by age and controlled for ethnicity, and conducted separate analyses for vaccine-targeted and non-vaccine serotypes.

RESULTS

Pneumococcal Carriage and OM

Incidence of pneumococcal OM episodes necessitating MEF culture declined between the pre-PCV7 period (2004–2008) and the era of widespread PCV13 use (2013–2016) among Bedouin and Jewish children in both the first and second years

of life (Table 2), as described previously [16]. Reductions in vaccine-serotype infections occurred within all age/ethnic strata. In addition, Bedouin children <12 months old experienced a 68% (95%CI: 46–84%) reduction in incidence of non-vaccine serotype OM. Incidence of non-vaccine serotype OM either increased or did not change among Jewish children aged <12m, and among Jewish and Bedouin children aged 12-35m.

Decreases in vaccine-serotype OM incidence were accompanied by proportionally smaller decreases in vaccine-serotype carriage prevalence within the <12m age group, in contrast to near-equal decreases in vaccine-serotype OM incidence and carriage prevalence during months 12-35 (Table 2). Increases in non-vaccine serotype carriage offset reductions in carriage of vaccine-targeted serotypes among Jewish children. In contrast, Bedouin children experienced net reductions in pneumococcal carriage in both age groups. The same patterns emerged in sensitivity analyses including swabs from children experiencing respiratory illness (Table S3).

Variation in Serotype-specific OM Progression

Dividing serotype-specific OM incidence by carriage prevalence provided an estimate of the rate of progression from carriage to disease. In the pre-vaccine era, serotypes that were subsequently included in PCV7/13 had higher rates of progression to OM than other serotypes: carriage of vaccine-targeted serotypes during the first year of life was associated with 3.38 (95%CrI: 1.92-6.26) and 5.99 (2.66-14.16)-fold higher rates of OM progression among Bedouin and Jewish children, respectively, compared to carriage of non-vaccine serotypes (Figure 1). At ages 12-35 months, vaccine-serotype carriage was associated with 1.47 (0.82-2.89) and 3.67 (1.76-7.26)-fold higher progression rates in these populations.

Factors associated with the capacity of serotypes to persist in asymptomatic upper respiratory colonization—including stronger negative surface charges, greater metabolic efficiency, and lower IPD case-fatality ratios—predicted higher rates of OM progression at ages <12 months before PCV7 introduction (Table 3). Serotype invasiveness was weakly associated with elevated OM progression rate (RR = 1.15, 95%CrI: 0.97-1.36) at ages <12m in the pre-vaccine era, but inversely associated with progression rate at ages 12-35m after PCV13 rollout.

Declining Progression for Vaccine-targeted and Non-vaccine Serotypes

On average, rates of progression from carriage to OM in the first year of life decreased by 92% (79-97%) and 80% (46-93%) among Bedouin and Jewish children, respectively, for serotypes targeted by PCV7/13 following introduction of the vaccines (Table 4). We estimated significant reductions for serotypes 3, 6A, 14, 19A, 19F, and 23F among Bedouin children, and for serotypes 14, 19A, and 19F among Jewish children; lower initial carriage prevalence and OM incidence among Jewish children

Table 2. Pneumococcal OM Incidence and Carriage Prevalence Before and After PCV7/13 Rollout

Outcome	Age and ethnicity	All serotypes			Vaccine-targeted serotype			Non-vaccine serotype		
		Before rollout[a,b]	After rollout[a,b]	RR[b]	Before rollout[a,b]	After rollout[a,b]	RR[b]	Before rollout[a,b]	After rollout[a,b]	RR[b]
OM incidence	*Ages 0-11 months*									
	Bedouin	14.4 (13.1, 15.8)	1.4 (0.8, 2.1)	**0.09 (0.06, 0.15)**	11.4 (10.3, 12.6)	0.4 (0.1, 0.8)	**0.03 (0.01, 0.07)**	3.0 (2.4, 3.7)	1.0 (0.5, 1.6)	**0.32 (0.16, 0.56)**
	Jewish	11.7 (10.6, 12.9)	3.6 (2.6, 4.8)	**0.31 (0.22, 0.41)**	9.9 (8.8, 11.0)	0.9 (0.5, 1.5)	**0.09 (0.04, 0.16)**	1.8 (2.4, 3.7)	2.7 (1.9, 3.7)	1.47 (0.95, 2.25)
	Ages 12-35 months									
	Bedouin	3.1 (2.7, 3.6)	1.4 (0.9, 1.9)	**0.43 (0.29, 0.62)**	2.5 (2.1, 2.9)	0.3 (0.1, 0.6)	**0.13 (0.06, 0.25)**	0.7 (0.5, 0.9)	1.0 (0.7, 1.5)	1.58 (0.95, 2.58)
	Jewish	6.5 (5.9, 71)	2.5 (1.9, 3.2)	**0.39 (0.29, 0.50)**	5.8 (5.3, 6.5)	0.4 (0.2, 0.7)	**0.07 (0.03, 0.13)**	0.6 (0.5, 0.9)	2.1 (1.5, 2.7)	**3.27 (2.15, 5.00)**
Carriage prevalence	*Ages 0-11 months*									
	Bedouin	0.75 (0.66, 0.87)	0.41 (0.36, 0.47)	**0.54 (0.45, 0.66)**	0.39 (0.33, 0.44)	0.07 (0.06, 0.08)	**0.18 (0.15, 0.22)**	0.37 (0.32, 0.43)	0.34 (0.30, 0.39)	0.92 (0.76, 1.12)
	Jewish	0.40 (0.33, 0.48)	0.34 (0.28, 0.41)	0.85 (0.65, 1.10)	0.18 (0.15, 0.21)	0.03 (0.02, 0.03)	**0.15 (0.11, 0.19)**	0.22 (0.19, 0.27)	0.31 (0.26, 0.38)	**1.39 (1.07, 1.81)**
	Ages 12-35 months									
	Bedouin	0.79 (0.74, 0.85)	0.43 (0.38, 0.50)	**0.54 (0.46, 0.64)**	0.50 (0.47, 0.54)	0.06 (0.05, 0.07)	**0.13 (0.11, 0.15)**	0.29 (0.27, 0.31)	0.37 (0.32, 0.42)	**1.27 (1.08, 1.49)**
	Jewish	0.49 (0.42, 0.56)	0.46 (0.40, 0.53)	0.94 (0.77, 1.16)	0.32 (0.28, 0.37)	0.03 (0.02, 0.03)	**0.08 (0.07, 0.10)**	0.16 (0.14, 0.19)	0.43 (0.37, 0.50)	**2.65 (2.16, 3.26)**

Abbreviations: OM, otitis media; PCV, Pneumococcal conjugate vaccines.

[a]Incidence rates are measured per 1000 child-years at risk. Carriage prevalence is measured as a proportion and standardized for ages 6 and 24 months within the <12 and 12-35 month age groups, respectively (*Text S1*). The pre-PCV7 and PCV13 periods correspond to July 2004-June 2008 and July 2013-June 2016, respectively.

[b]All estimates (rate ratio for incidence, risk ratio for prevalence) are presented as mean (95% credible interval).

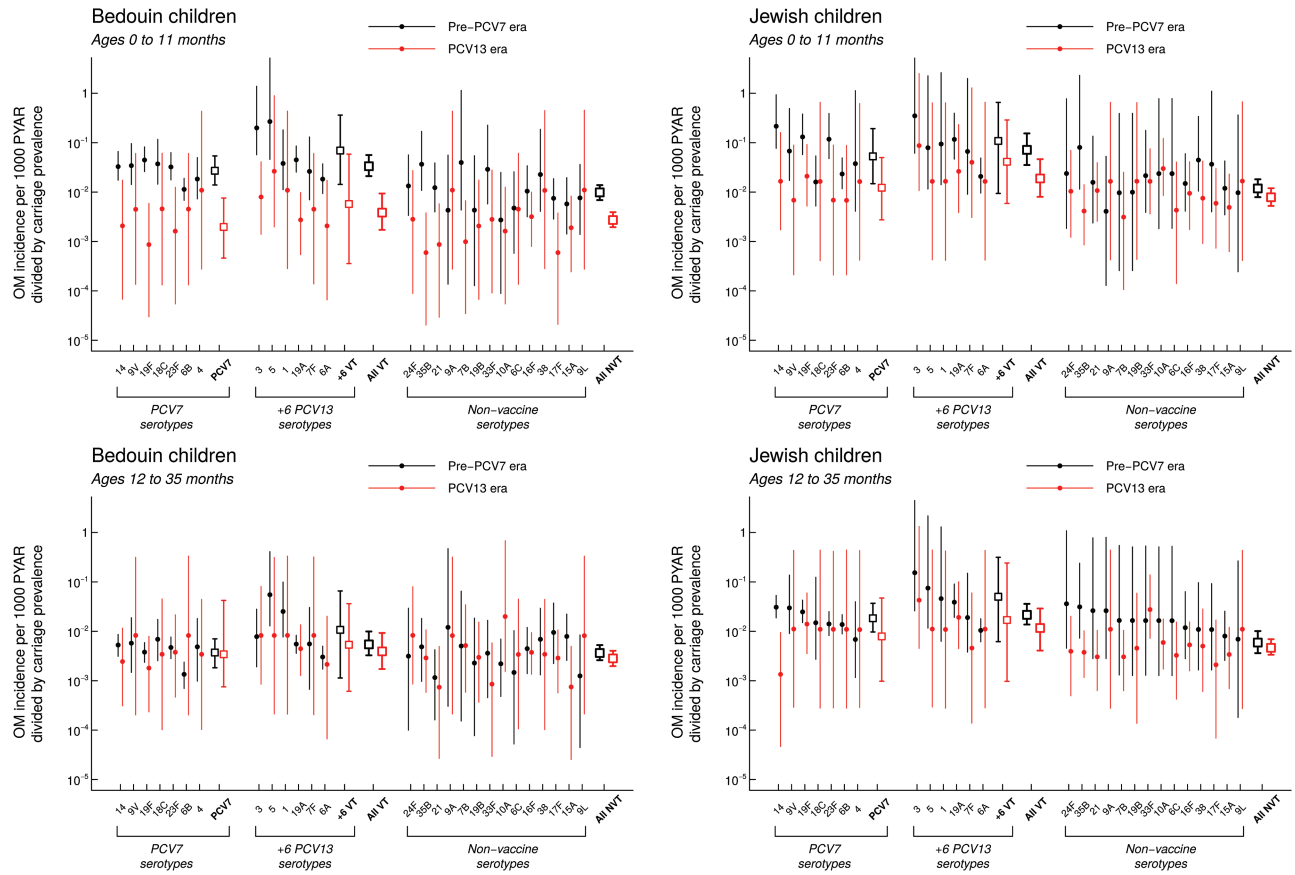

Figure 1. Serotype-specific progression rate for otitis media (OM). We illustrate measures of serotype-specific progression rates (OM incidence per 1000 person-years at risk among children, divided by carriage prevalence) with 95% credible intervals in the pre-PCV era (*black*) and era of widespread PCV13 use (*red*). Pooled estimates from Bayesian random effects models are included to the right of serotype-specific measurements, including all PCV7 serotypes, the six additional serotypes included in PCV13, all PCV13 serotypes, and all non-vaccine serotypes. Pooled estimates of NVT progression rate include all NVTs as listed elsewhere (Table S6); the 15 NVTs plotted represent those with the highest prevalence in carriage. Serotype-specific estimates with varying precision contribute differentially to pooled posterior estimates from Bayesian random effects models. Abbreviations: NVT, Non-vaccine serotype; OM, otitis media; PCV, Pneumococcal conjugate vaccines; PYAR, Person-years at risk.

reduced statistical power in serotype-specific analyses. A 98% (90-100%) reduction in progression by 19F among Bedouin children was the largest effect observed (Figure 2). In the second and third years of life, we estimated a 61% (−5-86%) average reduction in progression rate for vaccine-targeted serotypes among Jewish children, due largely to reductions in progression by serotypes 14 and 3.

Progression rate in the first year of life for serotypes not targeted by PCVs declined, on average, by 74% (55-85%) and 43% (4-68%) among Bedouin and Jewish children, respectively (Table 4, Figure 3). Serotypes 7B, 9N, 11A, 12F, 16F, 17F, 33F, and 35B each became less likely to cause disease in Bedouin children of this age group, whereas among Jewish children, we estimated significant reductions in progression

Table 3. Associations of Serotype-specific Progression Rate With Phenotypic Attributes

	Pre-PCV7 period (*all serotypes*)		PCV13 period (*non-vaccine serotypes*)	
Phenotypic attribute[a]	*Ages 0-11 months*	*Ages 12-35 months*	*Ages 0-11 months*	*Ages 12-35 months*
Resistance to neutrophil-mediated killing	0.96 (0.78, 1.15)	**0.83 (0.69, 0.97)**	0.93 (0.36, 1.98)	0.59 (0.23, 1.21)
Strength of anionic charge	**1.16 (1.01, 1.34)**	1.08 (0.92, 1.25)	1.13 (0.92, 1.38)	1.07 (0.84, 1.34)
Capsular size	0.97 (0.82, 1.14)	0.92 (0.79, 1.07)	0.93 (0.51, 1.66)	0.77 (0.42, 1.30)
Metabolic efficiency	**1.28 (1.09, 1.50)**	1.13 (0.95, 1.33)	1.15 (0.89, 1.44)	1.10 (0.85, 1.40)
IPD case-fatality ratio	**0.81 (0.70, 0.93)**	**0.81 (0.69, 0.94)**	0.82 (0.66, 1.01)	0.85 (0.68, 1.05)
Invasiveness	1.15 (0.97, 1.36)	1.00 (0.82, 1.22)	0.83 (0.66, 1.01)	**0.81 (0.65, 0.99)**

Abbreviations: IPD, invasive pneumococcal disease; PCV, Pneumococcal conjugate vaccines.

[a]Phenotype characteristics and serotypes for which data were available are summarized in Tables 1 and S2. Phenotype measurements are scaled by the standard deviation; effect size measurements reflect the fold change in progression rate associated with an increase by one standard deviation in the value of the phenotype measurement.

Table 4. Reduction in Otitis Media Progression Rate After Vaccine Introduction

		Vaccine-targeted serotypes			
Age group	Ethnicity	PCV7 serotypes	+6 PCV13 serotypes	All PCV7 and PCV13 serotypes	Non-vaccine serotypes
0-11 months	Bedouin children	**0.91 (0.38, 0.99)**	**0.92 (0.43, 0.99)**	**0.92 (0.79, 0.97)**	**0.74 (0.55, 0.85)**
	Jewish children	**0.85 (0.18, 0.97)**	0.70 (–1.77, 0.97)	**0.80 (0.46, 0.93)**	**0.43 (0.04, 0.68)**
12-35 months	Bedouin children	0.27 (–2.88, 0.85)	0.37 (–2.81, 0.89)	0.32 (–0.58, 0.71)	0.28 (–0.18, 0.56)
	Jewish children	0.58 (–1.59, 0.93)	0.65 (–1.63, 0.96)	0.61 (–0.05, 0.86)	0.30 (–0.31, 0.63)

Abbreviation: PCV, Pneumococcal conjugate vaccines.

Effects of vaccine introduction on progression rate presented as median (95% credible interval) and pooled from serotype-level measurements (presented in Figure 2 and Figure 3) using a Bayesian random effects model.

rate for each of serotypes 11A, 23B, and 35B (Figure 3). We did not identify strong statistical evidence for changes in progression rate among non-vaccine serotypes at older ages. Among serotypes not included in either vaccine, serotype 35B tended to show particularly large reductions in progression rate, with declines of 98% (8-100%) and 95% (46-100%) among Bedouin and Jewish children, respectively, in the first year of life, and 88% (28-99%) among Jewish children 12-35 months old.

The same changes in progression rate were evident when we did not exclude carriage isolates from children experiencing respiratory illnesses when calculating prevalence (Table S4). Since this sample had slightly higher overall carriage prevalence (Table S3), estimated reductions in progression rate tended to be

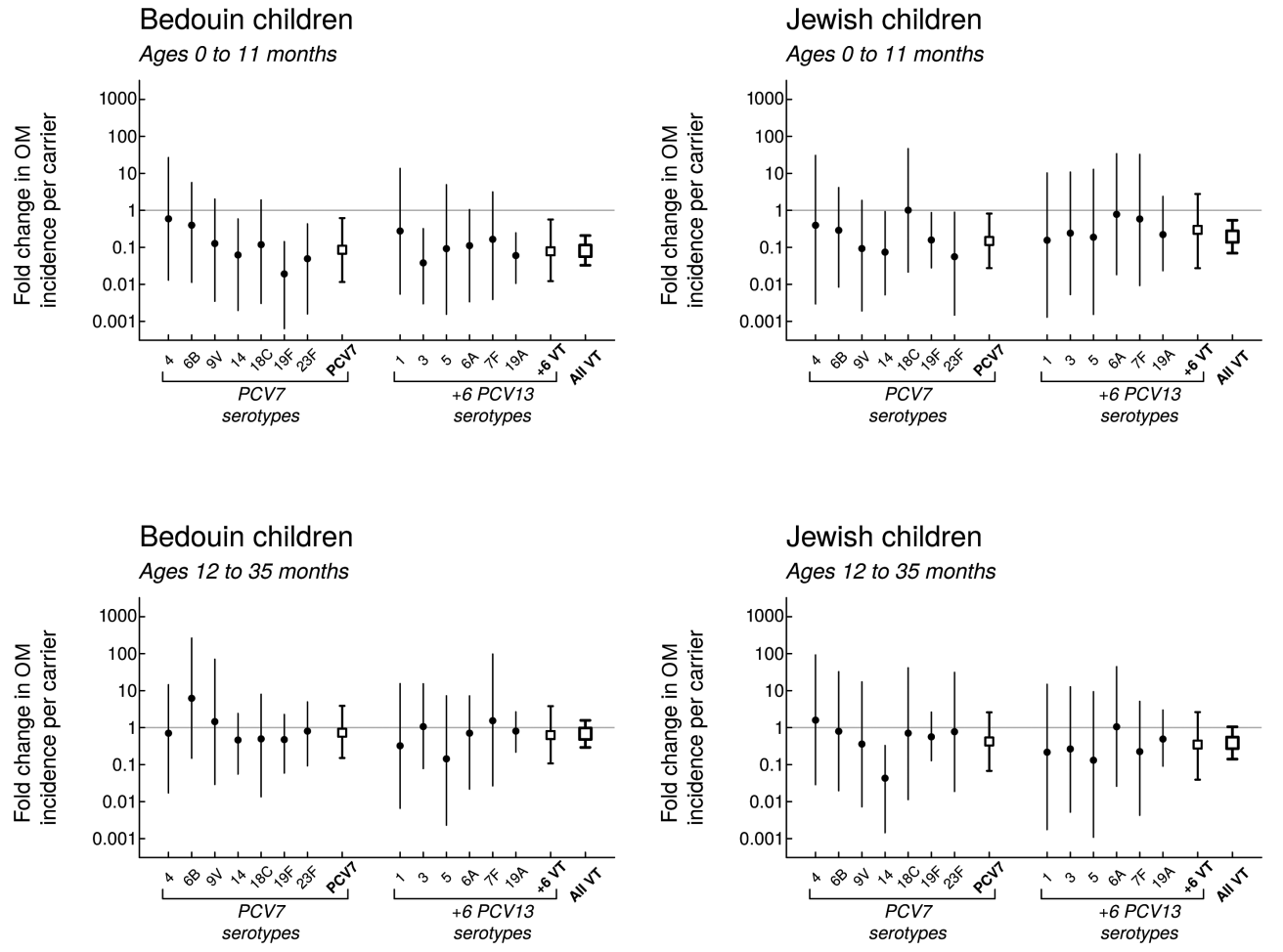

Figure 2. Reduction in progression rate for PCV7 and PCV13 serotypes. Plots illustrate medians (points) and 95% credible intervals of estimated fold changes in serotype-specific progression rate for vaccine-targeted serotypes between the pre-PCV7 era and era of widespread PCV13 use, stratified by age and ethnicity of children, as calculated from estimates of absolute progression rate presented in Figure 1. Serotype-specific estimates with varying precision contribute differentially to pooled posterior estimates from Bayesian random effects models. Abbreviations: OM, otitis media; PCV, Pneumococcal conjugate vaccines.

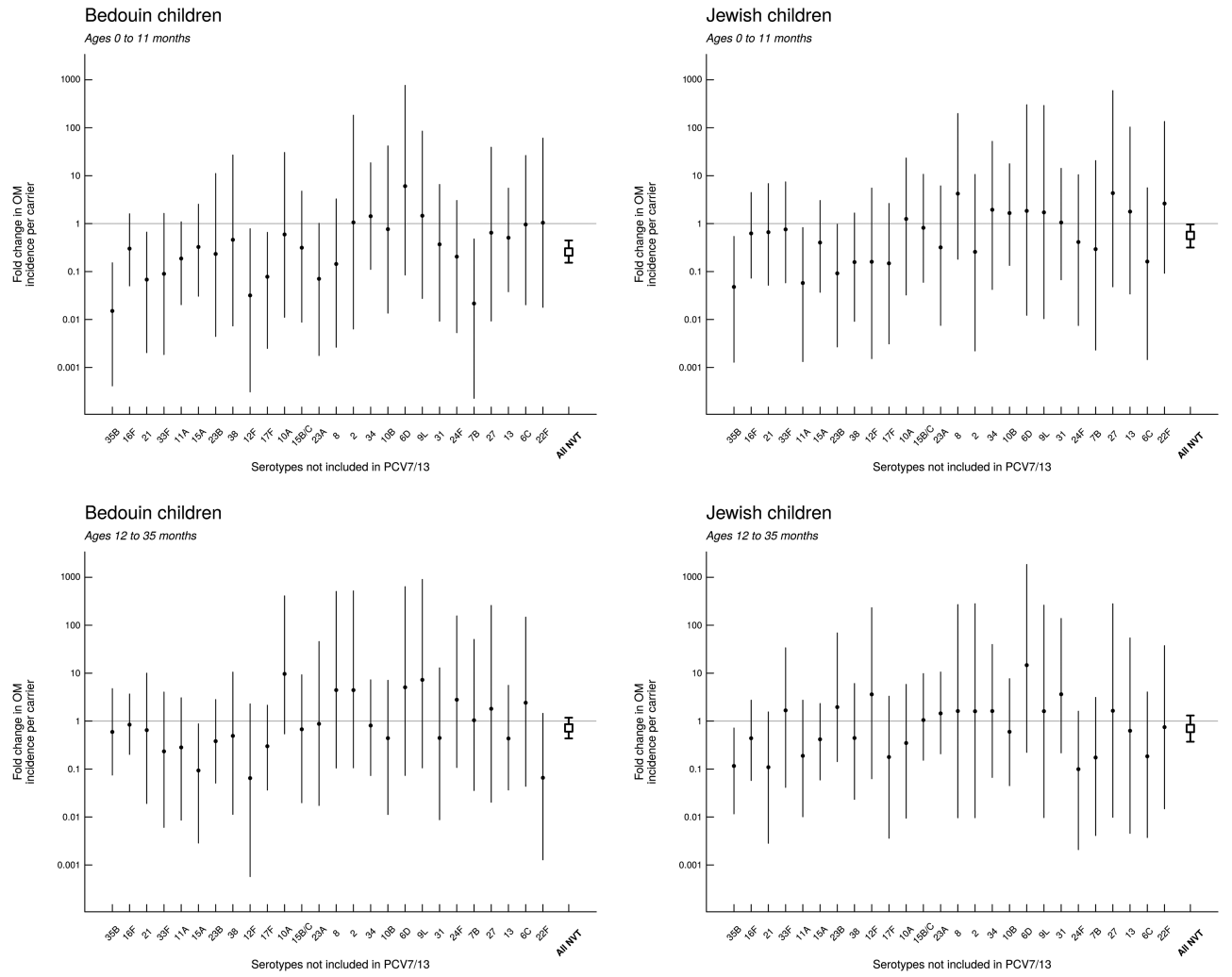

Figure 3. Reduction in progression rate for non-vaccine serotypes. Plots illustrate medians (points) and 95% credible intervals of estimated fold changes in serotype-specific progression rate for serotypes not targeted by PCVs between the pre-PCV7 era and era of widespread PCV13 use, stratified by age and ethnicity of children, as calculated from estimates of absolute progression rate presented in Figure 1. Pooled estimates of NVT progression rate include all NVTs as listed elsewhere (Table S6); the NVTs plotted represent those with the highest prevalence in carriage. Serotype-specific estimates with varying precision contribute differentially to pooled posterior estimates from Bayesian random effects models. Abbreviations: NVT, Non-vaccine serotype; OM, otitis media; PCV, Pneumococcal conjugate vaccines.

larger than estimates from the primary analyses. Reduced progression rates after PCV7/13 rollout persisted also persisted in sub-analyses restricted to respiratory virus seasons (December-March) and off-seasons (April-November; Table S5).

Notably, no serotype showed strong statistical evidence (defined as a 95% credible interval >1) of increased progression rate following PCV7/13 rollout (Table S6). Serotype factors tended not to predict the magnitude of change in progression rate after PCV7/13 rollout (Table S7).

DISCUSSION

Reductions in OM burden following rollout of PCVs—and especially in the burden associated with complex OM—have exceeded historical forecasts of modest (8-12%) vaccine impact [32]. In a sample of OM cases necessitating MEF culture due to clinical severity, we identified that declining incidence in Israel [16] reflects diminishing risk for pneumococcal serotypes to progress from carriage to disease. Whereas PCV7/13 may mediate direct protection against progression for vaccine-targeted serotypes, we also observed declining progression rates among non-vaccine serotypes. These findings signify a changing epidemiologic relationship between pneumococcal carriage and OM following PCV7/13 introduction.

PCVs confer immunogen-mediated protection against a limited serotype repertoire. A complex set of immunological factors would therefore have to affect OM pathogenesis for PCV to elicit effects on progression of non-vaccine serotypes [18]. Historically, cohort studies have suggested that early-life infections exacerbate the future susceptibility of children to OM [33, 34]. More

recently, animal models [35, 36] and epidemiologic studies [11, 12] have clarified that damage sustained during early-life infections involving virulent pneumococcal serotypes provides a conduit for other bacterial pathogens—including less-virulent species carried at older ages—to progress to complex OM. We found that vaccine-targeted serotypes accounted for a large share of OM burden before PCV7 rollout in Israel, and had higher rates of progression to OM in comparison with non-vaccine serotypes. Vaccinating against PCV7/13 serotypes historically causing early-life infections may thus reduce all-cause OM burden by interrupting the cascade of infections predisposing children to complex OM manifestations. This benefit of early-life vaccination merits consideration in PCV13 schedules.

In our study, Bedouin children experienced reductions in pneumococcal carriage after PCV7/13 rollout, whereas 15% and 6% reductions observed among Jewish children aged 0-11m and 12-35m, respectively, were not statistically significant. Larger reductions among Bedouin children may relate to higher prevalence of PCV7/13-targeted serotypes in this community before vaccine rollout [26]. Whereas non-vaccine serotypes have replaced vaccine-targeted serotypes in carriage after PCV7/13 rollout in high-income settings, overall reductions in carriage have been reported in certain low-income populations [37, 38].

The serotype distribution of OM masks underlying variation in the ability of serotypes to progress from carriage to disease [39]. In our sample, factors associated with the capacity of serotypes to colonize the nasopharynx predicted higher rates of progression to OM at ages <12 months prior to vaccine introduction [28, 29]. These factors also predict a facilitative relationship with NTHi in carriage and complex OM [13, 40]. Prevalence of serotypes in carriage and their risk for progressing to disease both merit consideration in the formulation of next-generation anticapsular vaccines.

Shortly after PCV7/13 rollout, larger-than-predicted reductions in OM burden were interpreted cautiously due to limitations of individual observational studies [14]. Unlike previous surveillance studies, we used data gathered prospectively from a healthcare center serving nearly all children in the surrounding area. Our study is thus less likely than others to be biased by changes over time in diagnostic criteria, consultation rates, and case ascertainment. Although such factors may limit individual studies, they are unlikely to explain declines in OM-associated pediatric consultations, antimicrobial prescribing, and tube insertions since PCV7/13 introduction reported across numerous settings [14, 19–22]. In comparison to possible year-to-year variation in transmission and OM incidence, the innate capacity of serotypes to progress to OM is relatively unlikely to vary over time absent epidemiologic changes affecting host susceptibility.

High-quality epidemiological surveillance in Israel provided an opportunity to use population-based measurements of OM incidence and carriage prevalence to test the hypothesis that PCVs influence progression. However, our study has several limitations. Because complex OM infections included in our sample may concurrently involve NTHi or polymicrobial biofilms, studies using molecular diagnostic tools can establish whether the declining incidence of all-cause OM reflects changing progression rates for pathogens other than *S. pneumoniae* [16]. Such studies are also needed to determine the impact of species interactions among upper-respiratory microbiota on progression and disease risk. In addition, we used prospectively-gathered carriage data from healthy children before vaccine introduction, and from children visiting the emergency department after introduction. Nonetheless, pneumococcal carriage prevalence among eligible children visiting the emergency department after PCV7/13 rollout was equal to or lower than prevalence among healthy children prior to vaccine introduction. In case of bias, excess carriage among children visiting the emergency department would lead to conservative inferences through under-estimated changes in progression rate. Last, it is unclear to what extent the reductions we identify in complex OM incidence and progression reflect declining incidence of acute OM, versus changes in the proportion of acute episodes leading to severe manifestations. These impacts of PCV rollout on pathogen-specific OM progression should be validated and further characterized in prospective studies in settings scheduled to introduce PCVs.

Surveillance data from Israel support reductions in progression of both vaccine-targeted and non-vaccine pneumococcal serotypes from carriage to disease as a factor in declining OM burden following PCV7/13 rollout. Licensure of PCVs preceded direct evidence that the vaccines prevent the cascade of infection events predisposing children to OM progression, including episodes involving pathogens other than vaccine-serotype pneumococci. Protection against OM progression merits consideration in evaluations of vaccine impact and cost-effectiveness.

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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and Wyeth/Pfizer; and is a shareholder of Protea/NASVAX. NG-L reports no conflict. 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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