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Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease among children in the United States between 2010 and 2019: An indirect cohort study

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Lee Harrison provides service on advisory boards (Pfizer, Sanofi, GSK) and a DSMB (Merck); while LH does not receive any fees for this work he is reimbursed for occasional travel. Tamara Pilishvili reports a relationship with GSK that includes: employment. During data collection, analysis, and write-up, TP was employed by CDC. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.]

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Kristin L. Andrejko: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation. **Ryan Gierke:** Writing – review & editing, Data curation. **Jemma V. Rowlands:** Writing – review & editing, Investigation. **Jennifer B. Rosen:** Writing – review & editing, Investigation. **Ann Thomas:** Writing – review & editing, Investigation. **Zachary Q. Landis:** Writing – review & editing, Investigation. **Maria Rosales:** Writing – review & editing, Investigation. **Sue Petit:** Writing – review & editing, Investigation. **William Schaffner:** Writing – review & editing, Investigation. **Corinne Holtzman:** Writing – review & editing, Investigation. **Meghan Barnes:** Writing – review & editing, Investigation. **Monica M. Farley:** Writing – review & editing, Investigation. **Lee H. Harrison:** Writing – review & editing, Investigation. **Lesley McGee:** Writing – review & editing, Data curation. **Sopia Chochua:** Writing – review & editing, Data curation. **Jennifer R. Verani:** Writing – review & editing, Methodology. **Adam L. Cohen:** Writing – review & editing, Methodology. **Tamara Pilishvili:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Miwako Kobayashi:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

¹See e.g., 45C.F.R. part 46.102(1)(2), 21C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

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Abstract

Background: A U.S. case-control study (2010–2014) demonstrated vaccine effectiveness (VE) for 1 dose of the thirteen-valent pneumococcal conjugate vaccine (PCV13) against vaccine-type (VT) invasive pneumococcal disease (IPD) at 86 %; however, it lacked statistical power to examine VE by number of doses and against individual serotypes.

Methods: We used the indirect cohort method to estimate PCV13 VE against VT-IPD among children aged < 5 years in the United States from May 1, 2010 through December 31, 2019 using cases from CDC’s Active Bacterial Core surveillance, including cases enrolled in a matched case-control study (2010–2014). Cases and controls were defined as individuals with VT-IPD and non-PCV13-type-IPD (NVT-IPD), respectively. We estimated absolute VE using the adjusted odds ratio of prior PCV13 receipt ($1 - aOR \times 100\%$).

Results: Among 1,161 IPD cases, 223 (19.2 %) were VT cases and 938 (80.8 %) were NVT controls. Of those, 108 cases (48.4 %; 108/223) and 600 controls (64.0 %; 600/938) had received 3 PCV13 doses; 23 cases (17.6 %) and 15 controls (2.4 %) had received no PCV doses. VE 3 PCV13 doses against VT-IPD was 90.2 % (95 % Confidence Interval 75.4–96.1 %), respectively. Among the most commonly circulating VT-IPD serotypes, VE of 3 PCV13 doses was 86.8 % (73.7–93.3 %), 50.2 % (28.4–80.5 %), and 93.8 % (69.8–98.8 %) against serotypes 19A, 3, and 19F, respectively.

Conclusions: At least three doses of PCV13 continue to be effective in preventing VT-IPD among children aged < 5 years in the US. PCV13 was protective against serotypes 19A and 19F IPD; protection against serotype 3 IPD did not reach statistical significance.

Keywords

13-valent pneumococcal conjugate vaccine; Invasive pneumococcal disease; Pneumococcal infections; *Streptococcus pneumoniae*; Vaccine effectiveness; Indirect cohort

1. Background

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality among children globally [1]. Prior to the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) in 2000 in the United States, the incidence of invasive pneumococcal disease (IPD) among U.S. children aged < 5 years was 98.7 per 100,000 cases [2]. Implementation of PCV7 was associated with reductions in the burden of vaccine-

type IPD (VT-IPD) followed by increases in disease caused by serotype 19A and other non-PCV7 serotypes [3,4]. In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the routine childhood immunization schedule, and a supplemental dose of PCV13 was recommended for children aged 14–59 months who had received four doses of PCV7 [5]. In 2018–2019, the incidence of IPD among children aged < 5 years in the United States was 7.2 cases per 100,000 [6].

PCV13 was licensed using safety and immunogenicity endpoints only; thus, post-licensure vaccine effectiveness (VE) studies are critical to generate estimates of protection conferred by PCV13 against IPD and monitor vaccine protection under real-world conditions of use [7]. A post-licensure matched case-control study conducted in the United States that enrolled IPD cases and population-based healthy controls, estimated that the VE of 1 doses of PCV13 against IPD caused by PCV13-type serotypes was 85 % [8]. However, this study was conducted shortly after PCV13 introduction when many children only received one catch-up PCV13 dose as opposed to the recommended four-dose series of PCV13 (3 + 1): three primary doses before 12 months of age followed by a booster dose at 12–15 months [9]. Additionally, protection conferred from PCV13 differs by serotype, and may be lower for serotypes 3 and 19A, although the reported estimates have varied [8,10–12]. Serotype 3 has a high invasive capacity and propensity to cause severe infections; therefore, real-world serotype 3 vaccine effectiveness data remains important to monitor for establishing PCV13 impact on invasive disease [13].

Using additional years of data available post-PCV13 introduction in U.S. children, we sought to estimate effectiveness of the protection conferred by 3 doses of PCV13 against IPD caused by VT serotypes among children aged < 5 years in the United States. We additionally assessed VE by PCV13 dosing schedule and individual serotype among the most common circulating VT serotypes.

2. Methods

2.1. Data sources

We assessed PCV13 effectiveness against IPD utilizing serotyped IPD cases from Active Bacterial Core surveillance (ABCs) at the Centers for Disease Control and Prevention (CDC). ABCs is an active laboratory- and population-based surveillance system of 10 sites in the United States, either entire states or metropolitan regions [14]. Approximately 45 million residents (14 % of the U.S. population) are under surveillance. We defined cases of IPD as any isolate of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid) among residents of the catchment area. During May 1, 2010 – May 31, 2014, surveillance was expanded beyond the ABCs catchment area to include additional sites for the purpose of achieving adequate sample size for the previously published PCV13 case-control evaluation [8]. These areas included New York City, Los Angeles, the state of Utah, and expanded areas in New York State (outside of New York City, beyond the routine ABCs catchment), and Tennessee. During June 1, 2014 through December 31, 2019, all IPD cases were identified via routine IPD surveillance through ABCs.

2.2. Study design and inclusion criteria

We estimated VE using the indirect-cohort method, in which we compare vaccination status of IPD caused by PCV13 (VT) serotypes (cases) to that of IPD caused by non-PCV13 vaccine type (NVT) serotypes (controls). [15]. Children with IPD residing within ABCs surveillance areas aged 2–59 months on the date of pneumococcal culture, with a serotyped pneumococcal isolate and verified pneumococcal vaccination history were eligible for inclusion in the analysis. Pneumococcal isolates were serotyped at the Minnesota Department of Health or CDC *Streptococcus* laboratory by Quellung reaction, polymerase chain reaction, or whole genome sequencing (2015–2019) [16]. The primary advantage of the indirect-cohort method over other observational study designs (eg. case-control) is by eliminating the need to enroll a separate control population. Instead, the study can be conducted entirely using IPD cases ascertained through routine surveillance, so long as vaccination history is routinely collected and all IPD cases are serotyped. The indirect cohort method provides reliable estimates of VE under the assumption that implementation of the vaccine product does not influence the risk of NVT-IPD [10,15,17].

2.3. Outcomes

The primary outcome was IPD caused by serotypes included in PCV13 (4, 6B, 9 V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A, and 6C). Due to known cross-protection with 6A antigen, serotype 6C was considered a PCV13 serotype [18]. All other serotypes, including non-typeable pneumococcal cases, were defined as NVT controls. Secondary analyses estimated serotype-specific VE among the most common VT serotypes.

2.4. Exposures

The primary exposure was receipt of 3 doses of PCV13 given at or after 2 months of age regardless of prior PCV7 receipt compared to receipt of no pneumococcal vaccines among children age-eligible to have received three doses (< 12 months). Persons who received only PCV7 doses were excluded from the primary analysis (Table S1). Exposure to 1 PCV13 doses, regardless of prior PCV7 receipt, which was assessed in the previous case-control study, was also evaluated. Secondary exposures included PCV13 receipt as categorized by various dosing schedules. Pneumococcal doses given at least 4 weeks after the previous dose of PCV7 or PCV13, and at least 2 weeks before the culture date to allow sufficient time for an immunologic response, were considered valid. For analyses of VE by pneumococcal dosing schedule, doses received before 12 months of age were considered primary series, and any doses received at 12–59 months of age were considered booster doses.

During May 1, 2010 – May 31, 2014, pneumococcal vaccination history was ascertained as part of the previously published case-control study described elsewhere [8]. In brief, study personnel determined pneumococcal vaccination history by referencing written vaccination records and state immunization registries and contacting providers from whom the child may have received vaccinations.

For June 1, 2014 onward, ABCs personnel obtained pneumococcal vaccination history through medical chart review. If vaccination data were unavailable from medical chart review, sites were instructed to attempt up to 10 calls per case to verify pneumococcal

vaccination records. If the caregiver or guardian of the case-patient did not answer the phone or could not provide vaccination data, study personnel attempted to contact the primary care provider. Study personnel indicated which source of vaccination data was used to obtain vaccination history (i.e., medical chart review, registry, or primary care provider). Participants were excluded from the analysis if no source was available to obtain vaccination history.

Following methods established in the previously published case-control study, any PCV dose given prior to March 15, 2010 was assumed to be PCV7. Doses received on or after January 1, 2011 were considered to be PCV13. For doses received during March 15, 2010 through December 31, 2010, lot numbers were referenced to differentiate between doses of PCV7 and PCV13 [8].

2.5. Statistical analysis

We used a logistic regression model to estimate the adjusted odds ratio (aOR) for receipt of 1 or 3 doses of PCV13 versus no PCV doses comparing VT-cases and NVT-controls. VE was estimated as $(1 - \text{aOR}) \times 100\%$. We adjusted models for potential confounders identified using a directed acyclic graph including age group, race/ethnicity, sex, state, calendar year, report of any immunocompromising conditions, and report of any chronic conditions including asthma. Models were stratified by time period (May 1, 2010 – May 31, 2014 [Early PCV13 implementation period]; June 1, 2014 – December 31, 2019 [Late PCV13 implementation period]; and May 1, 2010 – Dec 31, 2019 [Full study period]).

We conducted a sensitivity analysis in which IPD cases caused by vaccine-related (VR) serotypes were excluded from the primary analysis; VR serotypes included 23B, 9N, 23A, 6C, 7A, 7B, 7C, 9A, 9L, 18F [11]. To address the possibility of bias arising from inclusion of immunocompromised children, for whom pneumococcal vaccination recommendations differ, we also conducted a sensitivity analysis excluding immunocompromised children [9].

For the full study period (May 1, 2010 – Dec 31, 2019) we estimated VE by PCV13 administration schedule: 1 + 0 (one PCV13 dose received prior to 12 months of age), 2 + 0 (two PCV13 doses received prior to 12 months of age), 3 + 0 (three PCV13 doses received prior to 12 months of age), 2 + 1 (two PCV13 doses received prior to 12 months of age and one PCV13 dose after 12 months of age), and 3 + 1 (three PCV13 doses received prior to 12 months of age and one PCV13 dose after 12 months of age). To estimate VE by schedule of PCV13 receipt, each model was restricted to the sub-set of the study participants who were age-eligible to receive a given schedule. Therefore, for the assessment of the 1 + 0, 2 + 0, and 3 + 0 schedule, models were restricted to participants, 2, 4, and 6 months of age, respectively, corresponding to U.S. dosing schedules. For the assessment of the 2 + 1 and 3 + 1 schedules, models were restricted to participants 12 months or older.

For the assessment of serotype-specific VE among serotypes unique to PCV13 (19A, 3, 7F), participants were considered vaccinated with PCV13 if they had received 1 or 3 doses of PCV13, regardless of prior PCV7 receipt. Given that PCV7 should not provide protection against PCV13 unique serotypes, for this secondary analysis we allowed non-PCV13 unique

serotype cases who had received PCV7 to be included in the reference group for the analysis of serotype 19A, 3, and 7F VE.

All analyses were conducted in R Statistical Software (version 4.2.1). This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.¹

3. Results

The study included 1,161 children aged 2–59 months with IPD, including 524 children enrolled from a previous post-licensure case-control study of PCV13 VE conducted during the early PCV13 implementation period and 637 children identified through routine surveillance during the late PCV13 implementation period; 61 were excluded because vaccination history could not be verified (Fig. 1; Figure S1). For the full study period, there were 223 cases of IPD caused by PCV13 VT serotypes (VT-cases), and 938 cases of IPD caused by NVT serotypes (NVT-controls) (Table 1; Figure S2).

During the full study period, three VT serotypes (19A, 3, and 19F) were responsible for 90.1 % (201/223) of VT-IPD; serotype 19A was the most common VT-serotype causing IPD, responsible for 43.0 % (96/223) of VT-IPD throughout the study period, followed by serotype 3 and serotype 19F (Figure S2, Table S2). Whereas serotype 19F was responsible for 3.8 % during the early implementation period, 19F was responsible for 34.4 % of cases of VT-IPD during the late PCV13 implementation period (Fig. 2). The majority of NVT disease was caused by serotypes 22F and 33F (Figure S2; Table S3).

Among the 1,161 participants included, 176 VT-cases (78.9 %; 176/223) and 885 NVT-controls (94.3 %; 885/938) had received 1 dose of PCV13 regardless of prior PCV7 receipt; 47 VT-cases (21.1 %; 47/223) and 53 NVT-controls (5.7 %; 53/938) had received no PCV doses (Table 2; Table S4). For the primary analysis assessing VE of 3 PCV13 doses, we excluded 353 participants (68 VT cases and 285 NVT-controls) who received 1 or 2 doses of PCV13. Therefore, among the 808 participants included in the primary analysis (297 during the early PCV13 implementation period and 511 during the late PCV13 implementation period), 108 VT-cases and 600 NVT-controls had received 3 doses of PCV13 (Table 2).

For the full study period, effectiveness against VT-IPD afforded by 3 doses of PCV13 versus no doses of any pneumococcal vaccine was estimated to be 90.2 % (95 % confidence interval: 75.4–96.1 %) (Table 2). Point estimates of PCV13 VE for 3 doses were higher in the late PCV13 implementation period (90.5 % [68.1–97.2 %]) as compared to the early PCV13 implementation period (86.5 % [28.0–97.3 %]); however, the confidence intervals overlapped. For the early and late PCV13 implementation period, upon exclusion of VR serotypes from the analysis, VE of 3 doses of PCV13 was estimated to be 90.6 % (32.5–98.6 %) and 88.0 (57.6–96.5 %), respectively. VE of 3 doses for the full study period excluding children with at least one immunocompromising condition was 88.0 % (74.9–94.3

Appendix A. Supplementary data
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2024.04.061>.

VE for 1 dose for the full study period was 81.7 % (69.1–89.1 %). In a sensitivity analysis including participants who received 1–2 doses in a separate exposure category, VE estimates were similar (90.2 % [75.4–96.1 %]).

VE for a single primary dose of PCV13 (1 + 0), two primary doses of PCV13 (2 + 0), and three primary doses of PCV13 (3 + 0) were 58.3 % (9.7–80.3 %), 58.2 % (–35.1–86.8 %), and 87.6 % (67.9–95.2 %), respectively (Table 2). VE among participants who received three primary doses and a booster dose (3 + 1 schedule) or two primary doses and a booster (2 + 1) was 92.4 % (78.2–97.2 %) and 99.9 % (78.2–100.0 %), respectively.

For the full study period, 3 doses of PCV13 were highly effective for serotype 19A (86.8 % [73.7–93.3 %]), serotype 7F (94.5 % [13.5–99.6 %]), and serotype 19F (93.8 % [69.8–98.8 %]) (Table 3). However, VE for 3 doses of PCV13 against serotype 3 had a lower point estimate and was not statistically significant: 50.2 % (–28.4–80.5 %). Owing to limited number of cases during the early PCV13 implementation period VE of 1 PCV13 dose against serotype 19F could not be estimated; however, VE of 1 PCV13 dose against 19F during the late PCV13 implementation period was 94.1 % (80.1–98.2 %) (Table 4).

4. Discussion

Receipt of 3 doses of PCV13 conferred strong protection against VT-IPD among U.S. children aged 2–59 months. This aligns with recent estimates of PCV13 effectiveness from a multi-center indirect cohort study conducted in Europe during a similar time period, 2012–2018 [11] and the previously published case-control study in the United States [8]. VE increased with increasing number of primary doses among schedules without a booster although the confidence intervals overlapped, and the effectiveness of schedules with a booster dose (2 + 1 and 3 + 1) were both > 90 %. During the full study period, three VT serotypes (19A, 3, and 19F) were responsible for the majority of VT-IPD; we estimated significant VE for serotypes 19A, 19F, and 7F, but VE was not significant for serotype 3. Non-PCV13 types 22F and 33F were the most common NVTs contributing to IPD, both of which are included in higher valency PCVs [6,19].

While this study was not adequately powered to address serotype-specific VE for all VT serotypes, we did not find evidence of significant PCV13 protection against serotype 3 disease, adding to the real-world evidence suggesting PCV13 may not provide adequate protection against disease caused by this serotype [20]. In clinical trials, the serotype 3 immune response was lower than the other additional five PCV13 serotypes (i.e., serotypes included in PCV13 but not PCV7) [21]. Serotype 3 has unique capsular properties compared to other pneumococcal serotypes including a thick capsule, high invasive capacity, and resistance to opsonic killing, all of which may contribute to lower VE [22–25]. As higher valency and PCVs using new or different technology are implemented in the United States, it will be important to continue to monitor and evaluate VE against serotype 3 [19].

Cases of serotype 19F, a serotype contained in both PCV7 and PCV13, were observed at a higher frequency during the later study period as compared to the early study period among both recipients and nonrecipients of PCV13. Comparative estimates of 19F VE by

study period are not available owing to the small number of 19F cases during the early PCV13 implementation period; however, VE of 3 doses against 19F estimated from the current study for the full study period (93 %) was similar to estimates from a U.S.-based case-control study conducted during the PCV7 era (87 %), and a recent multi-center indirect cohort study in Europe (84 %) [3,11]. However, evidence of persistent 19F carriage among children throughout the PCV13 era has been well documented across various settings despite early reports from a trial indicating PCV13 reduced 19F carriage [26–28]. Additionally, some immunogenicity studies have demonstrated lower 19F immunogenicity following PCV13 than PCV7 after the primary infant doses [29,30]. These data indicate that PCV13 provides direct protection against serotype 19F disease. However, protection against carriage is less complete. Thus, indirect effects against serotype 19F IPD could have decreased post-PCV13 introduction compared with post-PCV7 introduction. If so, this could explain the increase in 19F disease during the late PCV13 implementation period, particularly among the unvaccinated.

The majority of children enrolled in this study received four doses of PCV13 in a 3 + 1 schedule, in accordance with U.S. recommendations [31]. As such, we were not able to evaluate VE for reduced dosing schedules (e.g., 1 + 1), which have garnered global interest particularly in countries with mature PCV programs [32]. VE increased in schedules without booster doses with increasing number of primary doses, although the confidence intervals overlapped likely due to the small number of children who received PCV13 based on 1 + 0 or 2 + 0 schedules. Larger studies are needed to evaluate the impact of VE by number of primary doses. However, growing evidence regarding the two World Health Organization-recommended PCV schedules (2 + 1 or 3 + 0) suggests that administration of the booster dose is what provides durable protection leading to stronger protection among the unvaccinated population [33]. Point estimates from our schedule-specific analysis suggest VE was > 90 % for both schedules with a booster dose (2 + 1, 3 + 1). Given that the United States is one of the few countries in the world that continues to recommend a 3 + 1 PCV schedule, additional evidence that directly compares VE across vaccine schedules would help inform the discussion on a possible transition to a reduced-dose PCV schedule in United States in the future.

VE estimates of 1 PCV13 dose produced for the early PCV13 implementation period from our study (69.7 % [33.0–86.2 %]) were not statistically different from estimates produced in a previous case-control study (86 % [75.5–92.3 %]) that enrolled matched, population-based controls [8]. Point estimates of VE from the indirect cohort study were lower than the case control study; this is consistent with the expectation that case-control studies may bias VE estimates due to differential healthcare seeking behavior between cases and population-based controls [34]. In other words, vaccination coverage among controls may not represent the source population if enrolled controls are more likely to seek vaccination than the source population, resulting in biased overestimates of VE. The indirect cohort method mitigates potential selection biases that may arise due to differences in the characteristics between cases and controls as both are identified using the same case definition [15,35].

This study has limitations. First, while we attempted to adjust for confounders that may bias the causal pathway between pneumococcal vaccination status and IPD using a multivariate

model, the possibility of unmeasured confounding persists. Second, inclusion of cases with VR serotypes as NVT, for which PCVs may confer some protection, may result in underestimates of VE [11,36]. Indeed, sensitivity analyses which excluded VR serotypes resulted in higher point estimates of VE, though differences were not meaningfully different from models that included the VR serotypes. Additionally, the indirect cohort method relies on the assumption that implementation of vaccination does not influence the risk of NVT-IPD. However, given that the US has not observed significant serotype replacement following PCV13 introduction, this assumption is likely not violated [37]. Third, exposure misclassification is possible despite robust efforts by surveillance sites to obtain detailed vaccination history. Fourth, while this is one of the largest published studies of pediatric PCV13 vaccine effectiveness in the United States as of writing to our knowledge, owing to the success of PCV implementation, IPD case numbers were too small to detect significant effects for some stratified analyses. Lastly, we were unable to estimate effectiveness of alternative dosing schedules such as one primary dose with a booster dose (1 + 1) as the majority of vaccinated children had received a four-dose schedule, in accordance with U.S. recommendations [9].

In summary, 3 doses of PCV13 continues to be effective in preventing VT-IPD among children aged < 5 years in the United States, although protection against serotype 3 IPD was non-significant. Indirect cohort studies are an efficient platform in a setting with robust IPD surveillance to both estimate VE and mitigate potential bias from healthcare seeking behaviors influencing estimates from traditional case-control studies. As new PCVs become available for use in children, additional data are needed to monitor effectiveness including serotype-specific protection and differences by dosing schedule.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The authors do not have permission to share data.

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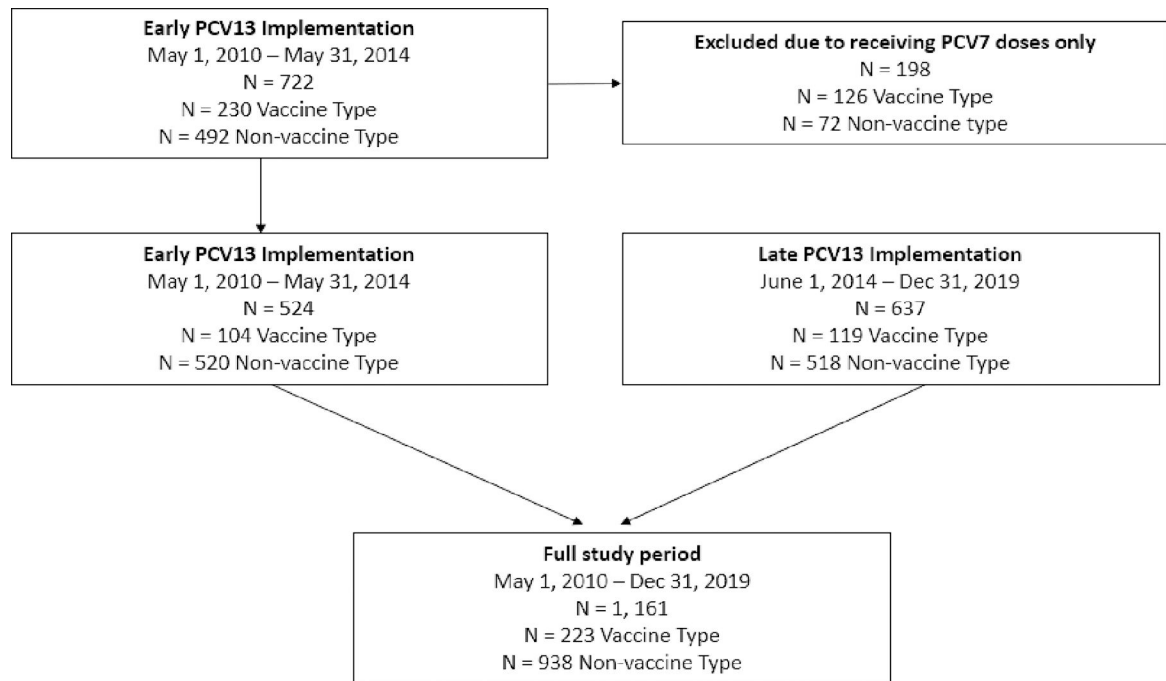


Fig. 1. Flow diagram of children included in the analytic dataset¹. ¹Cases for the late PCV13 Implementation period were enrolled from Active Bacterial Core surveillance (ABCs). Inclusion/exclusion of these cases are outlined in Figure S1. Cases from the early PCV13 Implementation period were included from a previously published case-control study.

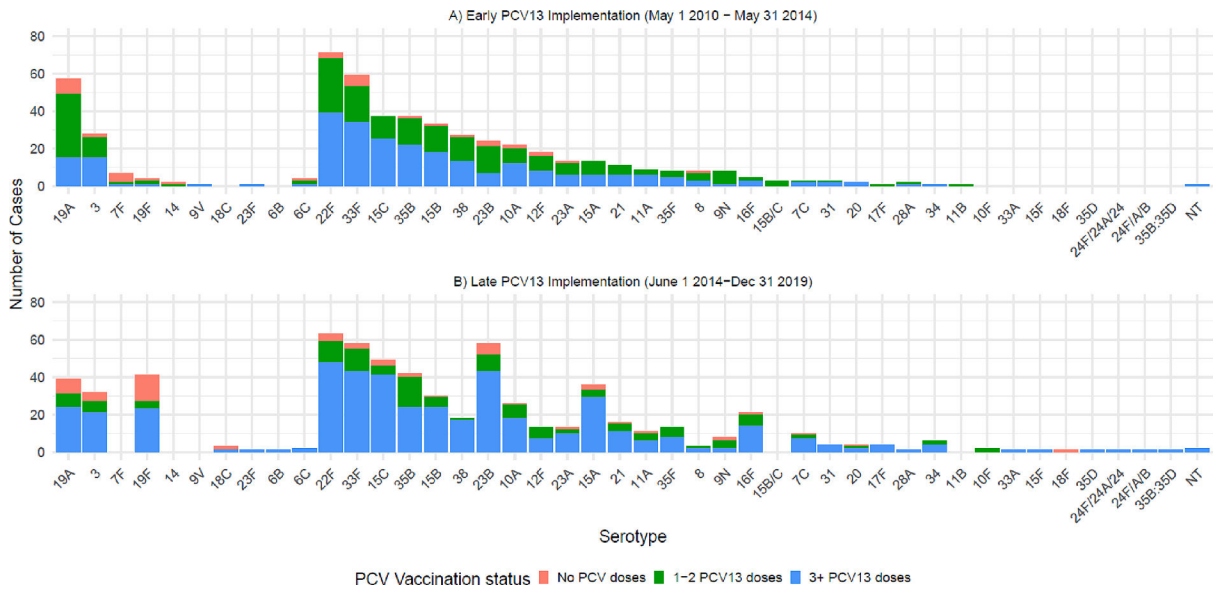


Fig. 2. Cases included in analysis stratified by serotype and receipt of PCV13.

Characteristics of study participants by VT (IPD caused by serotypes included in PCV13) and NVT IPD (IPD caused by non-PCV13 serotype) stratified by study period.

Table 1

	Full study period			Early PCV13 implementation			Late PCV13 implementation		
	May 1, 2010 - Dec 31 2019			May 1, 2010 - May 31 2014			June 1, 2014 - Dec 31 2019		
	VT	NVT	N (%)	VT	NVT	N (%)	VT	NVT	N (%)
	N = 223	N = 938	N = 104	N = 420	N = 119	N = 518			
Age group									
2–6 months	44 (19.7)	153 (16.3)	26 (25.0)	68 (16.2)	18 (15.1)	85 (16.4)			
7–11 months	26 (11.7)	166 (17.7)	15 (14.4)	80 (19.0)	11 (9.2)	86 (16.6)			
12–23 months	49 (22.0)	292 (31.1)	23 (22.1)	139 (33.1)	26 (21.8)	153 (29.5)			
24–59 months	104 (46.6)	327 (34.9)	40 (38.5)	133 (31.7)	64 (53.8)	194 (37.5)			
Sex									
Male	133 (59.6)	544 (58.0)	56 (53.8)	233 (55.5)	77 (64.7)	311 (60.0)			
Female	90 (40.4)	394 (42.0)	48 (46.2)	187 (44.5)	42 (35.3)	207 (40.0)			
Race and ethnicity									
White, non-Hispanic	89 (39.9)	418 (44.6)	35 (33.7)	175 (41.7)	54 (45.4)	243 (46.9)			
Black, non-Hispanic	58 (26.0)	274 (29.2)	21 (20.2)	118 (28.1)	37 (31.1)	156 (30.1)			
American Indian/ Alaska Native, non-Hispanic	7 (3.1)	16 (1.7)	3 (2.9)	9 (2.1)	4 (3.4)	7 (1.4)			
Asian/Pacific Islander, non-Hispanic	11 (4.9)	53 (5.7)	5 (4.8)	25 (6.0)	6 (5.0)	28 (5.4)			
Unknown race, non-Hispanic	2 (0.9)	4 (0.4)	2 (1.9)	4 (1.0)	3 (2.5)	11 (2.1)			
Hispanic	4 (1.8)	14 (1.5)	1 (1.0)	3 (0.7)	15 (12.6)	73 (14.1)			
Calendar year									
2010	16 (7.2)	28 (3.0)	16 (15.4)	28 (6.7)	--	--			
2011	23 (10.3)	111 (11.8)	23 (22.1)	111 (26.4)	--	--			
2012	22 (9.9)	99 (10.6)	22 (21.2)	99 (23.6)	--	--			
2013	26 (11.7)	128 (13.6)	26 (25.0)	128 (30.5)	--	--			
2014	29 (13.0)	113 (12.0)	17 (16.3)	54 (12.9)	12 (10.1)	59 (11.4)			

	Full study period			Early PCV13 implementation			Late PCV13 implementation		
	May 1, 2010 - Dec 31 2019			May 1, 2010 - May 31 2014			June 1, 2014 - Dec 31 2019		
	VT	NVT	N (%)	VT	NVT	N (%)	VT	NVT	N (%)
	N = 223	N = 938	N = 104	N = 420	N = 119	N = 518			
2015	25 (11.2)	102 (10.9)	--	--	25 (21.0)	102 (19.7)			
2016	23 (10.3)	103 (11.0)	--	--	23 (19.3)	103 (19.9)			
2017	23 (10.3)	79 (8.4)	--	--	23 (19.3)	79 (15.3)			
2018	21 (9.4)	89 (9.5)	--	--	21 (17.6)	89 (17.2)			
2019	15 (6.7)	86 (9.2)	--	--	15 (12.6)	86 (16.6)			
Underlying conditions									
Chronic conditions ¹	17 (8.5)	85 (10.1)	8 (7.7)	38 (9.0)	9 (9.5)	47 (11.2)			
Immunocompromising conditions ²	7 (3.5)	64 (7.7)	2 (1.9)	19 (4.5)	5 (5.3)	45 (10.9)			
Asthma	28 (13.5)	121 (14.2)	20 (19.2)	81 (19.3)	8 (7.7)	40 (9.2)			
PCV history ³									
No doses of any PCV ⁴	47 (21.1)	53 (5.7)	18 (17.3)	21 (5.0)	29 (24.4)	32 (6.2)			
1 dose PCV13	176 (78.9)	885 (94.3)	86 (82.7)	399 (95.0)	90 (75.6)	486 (93.8)			
1 dose PCV13, 0 PCV7 doses	145 (82.4)	768 (86.8)	56 (65.1)	283 (70.9)	89 (98.9)	485 (99.8)			
1 dose PCV13 + 1 PCV7 doses	31 (17.6)	117 (13.2)	30 (34.9)	116 (29.1)	1 (1.1)	1 (0.2)			
3 doses PCV13	108 (48.4)	600 (64.0)	35 (33.7)	223 (53.1)	73 (61.3)	377 (72.8)			
3 doses PCV13, 0 PCV7 doses	104 (96.3)	589 (98.2)	31 (88.6)	212 (95.1)	73 (100.0)	377 (100.0)			
3 doses PCV13 + 1 PCV7 doses	4 (3.7)	11 (1.8)	4 (11.4)	11 (4.9)	0 (0)	0 (0)			
PCV13 vaccination schedule Infant schedule ⁵									
1 + 0: One dose < 12 mo	27 (12.1)	86 (9.2)	18 (17.3)	30 (7.1)	9 (7.6)	56 (10.8)			
2 + 0: Two doses < 12 mo	13 (5.8)	77 (8.2)	7 (6.7)	36 (8.6)	6 (5.0)	41 (7.9)			
3 + 0: Three doses < 12 mo	24 (10.8)	217 (23.1)	13 (12.5)	100 (23.8)	11 (9.2)	117 (22.6)			
2 + 1: Two dose < 12 + 1 dose 12 mo	4 (1.8)	19 (2.0)	0 (0.0)	2 (0.5)	4 (3.4)	17 (3.3)			
3 + 1: Three doses < 12 + 1 dose 12 mo	73 (32.7)	346 (36.9)	18 (17.3)	108 (25.7)	55 (46.2)	238 (45.9)			
Toddler doses (12 mo) ⁶	0 (0.0)	12 (1.2)	0 (0.0)	4 (1.0)	0 (0.0)	8 (1.8)			

Abbreviations: **VE** = Vaccine Effectiveness; **PCV** = pneumococcal conjugate vaccine; **PCV13**- 13-valent pneumococcal conjugate vaccine; **VT** = PCV13 vaccine type serotypes, including serotype 6C due to cross protection with 6A; **NVT** = non-vaccine type, serotypes not included in PCV123.

- ¹Chronic conditions were defined a priori and include: Congestive heart failure (chronic heart disease), Cardiomyopathies (chronic heart disease), Chronic liver disease, Chronic obstructive pulmonary disease (chronic lung disease), Emphysema (chronic lung disease), Proportions are calculated out of the total number of individuals who are not missing data for chronic, immunocompromising or asthma.
- ²Immunocompromising conditions were defined a priori and include: Congenital or acquired asplenia, Sickle cell disease or other hemoglobinopathies, Chronic renal failure, Congenital or acquired immunodeficiencies, Generalized malignancy, HIV infection, Hodgkin disease, iatrogenic immunosuppression, Leukemia, Lymphoma, Multiple myeloma, Nephrotic syndrome, Solid organ transplant.
- ³The primary exposure is receipt of at least one dose of PCV13 given after 6 weeks of age, at least 4 weeks after the previous dose of PCV7 or PCV13 (if 1 dose given), and at least 2 weeks before the culture date, versus receipt of no pneumococcal vaccines. Participants who received PCV7 doses are excluded from the primary analysis. Characteristics of the study population including participants who received PCV7 only are outlined in Table S2.
- ⁴The distribution of age among children receiving zero PCV doses (N = 100) was N = 46, 2–6 months; N = 16, 7–11 months; N = 22, 12–23 months; N = 16, 25–59 months. N = 63 of the children were male. N = 51 children were white, non-Hispanic; N = 26 black, non-Hispanic; N = 16 % Hispanic; N = 7 other race/ethnicity. The proportion of participants with no doses by study year are summarized in Table S5.
- ⁵Counts may not sum to total (N = 1161) because some children did not receive their doses of PCV13 in any of these schedules and are excluded (N = 263). Participants who received PCV7 were excluded from this analysis (Table S1). Of note, the median days between a participant's fourth dose of PCV13 and their pneumococcal culture during the early and late PCV13 implementation period was 245 (range: 15–1132) and 605 (range: 14–1436), respectively.
- ⁶Represents children who received one or more doses of PCV13 at 12 months of age or older and no prior doses of PCV7. Among the N = 12 participants, 4 received one toddler dose and 8 received 2 toddler doses.

Table 2

Vaccine effectiveness by study period for the outcome vaccine-type IPD.

	Exposure ^f	PCV13-type Case		Non-PCV13-type Control		Unadjusted		Adjusted ^g	
		N (%)	N (%)	N (%)	N (%)	VE (95 % CI)	VE (95 % CI)	VE (95 % CI)	VE (95 % CI)
Early PCV13 Implementation ³ (May 2010 - May 2014)	No doses of PCV	18 (17.3)	21 (5.0)	ref.	ref.	ref.	ref.	ref.	ref.
	1 dose PCV13	86 (82.7)	399 (95.0)	74.9 (51.0,87.2)	69.7 (33.0, 86.2)	ref.	ref.	69.7 (33.0, 86.2)	69.7 (33.0, 86.2)
	No doses of PCV	7 (16.7)	3 (1.3)	ref.	ref.	ref.	ref.	ref.	ref.
Late PCV13 Implementation (June 2014 - Dec 2019)	3 doses PCV13	35 (83.3)	223 (98.7)	93.3 (72.9,98.40)	86.5 (28.0,97.3)	ref.	ref.	86.5 (28.0,97.3)	86.5 (28.0,97.3)
	No doses of PCV	29 (24.4)	32 (6.2)	ref.	ref.	ref.	ref.	ref.	ref.
	1 dose PCV13	90 (75.6)	486 (93.8)	79.6 (64.7,88.3)	89.6 (77.4, 95.3)	ref.	ref.	89.6 (77.4, 95.3)	89.6 (77.4, 95.3)
Full Study Period (May 2010- Dec 2019) ⁴	No doses of PCV	16 (18.0)	12 (3.1)	ref.	ref.	ref.	ref.	ref.	ref.
	3 doses PCV13	73 (82.0)	377 (96.9)	85.5 (68.2,93.4)	90.5 (68.1, 97.2)	ref.	ref.	90.5 (68.1, 97.2)	90.5 (68.1, 97.2)
	No doses of PCV	47 (21.1)	53 (5.7)	ref.	ref.	ref.	ref.	ref.	ref.
1 + 0: One dose before 12 mo	1 dose PCV13	176 (78.9)	885 (94.3)	77.6 (65.8,85.4)	81.7 (69.1, 89.1)	ref.	ref.	81.7 (69.1, 89.1)	81.7 (69.1, 89.1)
	No doses of PCV	23 (17.6)	15 (2.4)	ref.	ref.	ref.	ref.	ref.	ref.
	3 doses PCV13	108 (82.4)	600 (97.6)	88.3 (76.9, 94.1)	90.2 (75.4, 96.1)	ref.	ref.	90.2 (75.4, 96.1)	90.2 (75.4, 96.1)
2 + 0: Two doses before 12 mo	No doses of PCV	47 (63.5)	53 (38.1)	ref.	ref.	ref.	ref.	ref.	ref.
	One dose < 12 mo	27 (36.5)	86 (61.9)	64.6 (37.0,80.4)	58.3 (9.7, 80.3)	ref.	ref.	58.3 (9.7, 80.3)	58.3 (9.7, 80.3)
	No doses of PCV	32 (71.1)	34 (30.6)	ref.	ref.	ref.	ref.	ref.	ref.
3 + 0: Three doses before 12 mo	Two doses < 12 mo	13 (28.9)	77 (69.4)	82.1 (61.9,91.7)	58.2 (-35.1, 86.8)	ref.	ref.	58.2 (-35.1, 86.8)	58.2 (-35.1, 86.8)
	No doses of PCV	29 (54.7)	28 (11.5)	ref.	ref.	ref.	ref.	ref.	ref.
	Three doses < 12 mo	24 (45.3)	216 (88.5)	89.3 (79.2,94.5)	87.6 (67.9, 95.2)	ref.	ref.	87.6 (67.9, 95.2)	87.6 (67.9, 95.2)
2 + 1: Two doses before 12 mo + 1 dose 12 mo	No doses of PCV	23 (85.2)	15 (44.1)	ref.	ref.	ref.	ref.	ref.	ref.
	2 + 1 doses	4 (14.8)	19 (55.9)	86.3 (52.1,96.1)	99.9 (78.2, 100.0)	ref.	ref.	99.9 (78.2, 100.0)	99.9 (78.2, 100.0)
	No doses of PCV	23 (24.0)	15 (4.2)	ref.	ref.	ref.	ref.	ref.	ref.
3 + 1: Three doses before 12 mo + 1 dose 12 mo	3 + 1 doses	73 (76.0)	346 (95.8)	86.2 (72.5,93.2)	92.4 (78.2, 97.2)	ref.	ref.	92.4 (78.2, 97.2)	92.4 (78.2, 97.2)
	No doses of PCV	23 (95.8)	15 (78.9)	DNC	DNC	ref.	ref.	DNC	DNC
	1 + 1 doses	1 (4.2)	4 (21.1)	DNC	DNC	ref.	ref.	DNC	DNC

Abbreviations: **VE** = Vaccine Effectiveness; **PCV** = pneumococcal conjugate vaccine; **PCV13- 13-valent pneumococcal conjugate vaccine**; **CI** = confidence interval; **ref.** = reference level; **DNC** = Model did not converge.

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- ¹ For the period specific analyses, participants were categorized as having received PCV13, regardless of prior history of PCV7. Therefore, the “exposed” may include receipt of one or more doses of PCV13, regardless of prior history of PCV7. For the schedule specific estimates, participants who received PCV7 were excluded to estimate PCV13-schedule specific VE. We outline inclusion and exclusion criteria of PCV recipients in Table S1.
- ² Logistic regression model adjusted for age group (categorical), race/ethnicity (combined variable), sex, state, calendar year, immunocompromising conditions, chronic conditions or asthma. VE for the full study period excluding children with at least one immunocompromising condition (as opposed to adjusting for immunocompromising conditions) was 81.6 % (68.3–89.1 %) for 1 doses and 88.0 (74.9–94.3 %) for 3 doses.
- ³ Exclusion of N = 68 vaccine-related serotypes (23B [N = 29], 9 N [N = 9], 23A [N = 15], 6C [N = 11], 7C [N = 4]) during this time period increased adjusted VE estimates for 1 dose(s) to 72.9 % (95 % CI: 37.5 – 88.3 %) and 3 dose(s) to 86.0 % (46.7–96.3 %).
- ⁴ Schedule specific estimates are conducted for the full study period (May 1, 2010 – Dec 31, 2019); for each schedule specific assessment stratified data sets are restricted to cases and controls who were age-eligible to have received each vaccination schedule. We conducted a sensitivity analysis limiting the population to children 2.5 months of age or older (N = 349 VT-cases; N = 1010 NVT-controls) and for the full study period estimated an unadjusted VE of 1 dose to be 76.4 % (61.6,85.6) and adjusted VE of 1 dose to be 79.6 % (63.2,88.7).

Table 3

Serotype specific vaccine effectiveness against IPD for 3 doses of PCV13, May 1, 2010 - December 31, 2019.

Serotype	Exposure ¹	Serotype specific Cases	Non-PCV13-type Controls	Unadjusted	Adjusted ²
		N (%)	N (%)	VE (95 % CI)	VE (95 % CI)
Serotype 19A					
	No doses of PCV13	80 (67.2)	85 (12.4)	ref.	ref.
	3 doses PCV13	39 (32.8)	600 (87.6)	93.1 (89.3,95.6)	86.8 (73.7,93.3)
Serotype 3					
	No doses of PCV13	18 (33.3)	85 (12.4)	ref.	ref.
	3 doses PCV13	36 (66.7)	600 (87.6)	71.7 (48.3,84.7)	50.2 (-28.4,80.5)
Serotype 7F					
	No doses of PCV13	24 (96.0)	85 (12.4)	ref.	ref.
	3 doses PCV13	1 (4.0)	600 (87.6)	99.4 (95.6,99.9)	94.5 (13.5,99.6)
Serotype 19F					
	No doses of PCV	8 (25.0)	15 (2.4)	ref.	ref.
	3 doses PCV13	24 (75.0)	600 (97.6)	92.5 (80.8,97.1)	93.8 (69.8,98.8)

Abbreviations: **VE** = Vaccine Effectiveness; **PCV** = pneumococcal conjugate vaccine; **PCV13**- 13-valent pneumococcal conjugate vaccine; **CI** = confidence interval; **ref.** = reference level.

¹For the assessment of Serotype 19A, 3 and 7F VE, participants who received either 7-valent pneumococcal conjugate vaccine (PCV7) or no doses of any pneumococcal vaccination were included in the reference group (No doses of PCV13). For the assessment of Serotype 19F VE, participants were included in the reference group if they received no doses of any PCV products. Persons who received PCV7 only were excluded from this analysis.

²Logistic regression model adjusted for age (categorical), race/ethnicity (combined variable), sex, state, calendar year, immunocompromising conditions, chronic conditions or asthma.

Table 4
 Serotype specific vaccine effectiveness against IPD for 1 doses of PCV13, by study period.

Exposure ¹	Serotype specific Cases		Non-PCV13-type Controls		Unadjusted		Adjusted ²	
	N (%)	N (%)	N (%)	N (%)	VE (95 % CI)	VE (95 % CI)	VE (95 % CI)	VE (95 % CI)
Early PCV13 Implementation (May 1, 2010 - May 31, 2014)								
Serotype 19A	No doses of PCV13	81 (62.3)	93 (18.9)		ref.		ref.	
	1 dose PCV13	49 (37.7)	399 (81.1)		85.9 (78.7,90.8)		76.5 (58.9, 86.5)	
Serotype 3	No doses of PCV13	17 (39.5)	93 (18.9)		ref.		ref.	
	1 dose PCV13	26 (60.5)	399 (81.1)		64.4 (32.2,81.5)		68.2 (19.6, 87.1)	
Serotype 7F	No doses of PCV13	30 (93.8)	93 (18.9)		ref.		ref.	
	1 dose PCV13	2 (6.2)	399 (81.1)		98.5 (93.4,99.6)		98.2 (89.9, 99.7)	
Late PCV13 Implementation (June 1, 2014 - December 31, 2019)								
Serotype 19A	No doses of PCV13	8 (20.5)	32 (6.2)		ref.		ref.	
	1 dose PCV13	31 (79.5)	486 (93.8)		74.5 (40.4,89.3)		88.0 (58.2, 96.5)	
Serotype 3	No doses of PCV13	5 (15.6)	32 (6.2)		ref.		ref.	
	1 dose PCV13	27 (84.4)	486 (93.8)		64.5 (2.4,87.3)		83.5 (11.3, 96.9)	
Serotype 19F	No doses of PCV	14 (34.1)	32 (6.2)		ref.		ref.	
	1 dose PCV13	27 (65.9)	486 (93.8)		87.3 (73.7,94.0)		94.1 (80.1, 98.2)	
Full study period (May 1, 2010 - December 31, 2019)								
Serotype 19A	No doses of PCV13	89 (52.7)	125 (12.4)		ref.		ref.	
	1 dose PCV13	80 (47.3)	885 (87.6)		87.3 (82.0,91.1)		77.9 (65.6, 85.7)	
Serotype 3	No doses of PCV13	22 (29.3)	125 (12.4)		ref.		ref.	
	1 dose PCV13	53 (70.7)	885 (87.6)		66.0 (42.6,80.1)		58.4 (19.0, 79.0)	
Serotype 7F	No doses of PCV13	30 (93.8)	125 (12.4)		ref.		ref.	
	1 dose PCV13	2 (6.2)	885 (87.6)		99.1 (96.0,99.8)		97.2 (86.6, 99.4)	
Serotype 19F	No doses of PCV	15 (33.3)	53 (5.7)		ref.		ref.	
	1 dose PCV13	30 (66.7)	885 (94.3)		88.0 (76.6,94.0)		92.7 (79.1, 97.3)	

Abbreviations: **VE** = Vaccine Effectiveness; **PCV** = pneumococcal conjugate vaccine; **PCV13-13**-valent pneumococcal conjugate vaccine; **CI** = confidence interval; **ref.** = reference level.

¹For the assessment of Serotype 19A, 3 and 7F VE, participants who received either 7-valent pneumococcal conjugate vaccine (PCV7) or no doses of any pneumococcal vaccination were included in the reference group (No doses of PCV13). For the assessment of Serotype 19F VE, participants were included in the reference group if they received no doses of any PCV products. Persons who received PCV7 only were excluded from this analysis.

² Logistic regression model adjusted for age (categorical), race/ethnicity (combined variable), sex, state, calendar year, immunocompromising conditions, chronic conditions or asthma.

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