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Effectiveness of Pneumococcal Conjugate Vaccination Against Virus-Associated Lower Respiratory Tract Infection Among Adults: A Case-Control Study

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Background. Interactions of *Streptococcus pneumoniae* with viruses feature in the pathogenesis of numerous respiratory illnesses.

Methods. We undertook a case-control study among adults at Kaiser Permanente Southern California between 2015 and 2019. Case patients had diagnoses of lower respiratory tract infection (LRTI; including pneumonia or nonpneumonia LRTI diagnoses), with viral infections detected by multiplex polymerase chain reaction testing. Controls without LRTI diagnoses were matched to case patients by demographic and clinical attributes. We measured vaccine effectiveness (VE) for 13-valent (PCV13) against virus-associated LRTI by determining the adjusted odds ratio for PCV13 receipt, comparing case patients and controls.

Results. Primary analyses included 13 856 case patients with virus-associated LRTI and 227 887 matched controls. Receipt of PCV13 was associated with a VE of 24.9% (95% confidence interval, 18.4%–30.9%) against virus-associated pneumonia and 21.5% (10.9%–30.9%) against other (nonpneumonia) virus-associated LRTIs. We estimated VEs of 26.8% (95% confidence interval, 19.9%–33.1%) and 18.6% (9.3%–27.0%) against all virus-associated LRTI episodes diagnosed in inpatient and outpatient settings, respectively. We identified statistically significant protection against LRTI episodes associated with influenza A and B viruses, endemic human coronaviruses, parainfluenza viruses, human metapneumovirus, and enteroviruses but not respiratory syncytial virus or adenoviruses.

Conclusions. Among adults, PCV13 conferred moderate protection against virus-associated LRTI. The impacts of pneumococcal conjugate vaccines may be mediated, in part, by effects on polymicrobial interactions between pneumococci and respiratory viruses.

Keywords. pneumococcal conjugate vaccine; influenza; respiratory syncytial virus; parainfluenza virus; human metapneumovirus; pneumonia.

Streptococcus pneumoniae (pneumococcus) is among the most prominent causes of lower respiratory tract infections (LRTIs), including pneumonia, and is associated with elevated disease severity in both bacteremic and nonbacteremic cases [1, 2]. Pneumococcal conjugate vaccines (PCVs) are of importance to the control of pneumococcal diseases globally. Numerous countries have implemented routine immunization with PCVs among children to reduce pediatric burden of vaccine-serotype invasive pneumococcal disease and acute otitis media [3]. In addition, PCVs protect against nonbacteremic pneumonia associated with vaccine-targeted serotypes among children [4] and adults [5, 6] and have reduced the incidence of all-cause LRTIs, including pneumonia under real-world conditions of use [7–9].

Pneumococcal disease incidence varies in association with seasonal transmission of respiratory viruses [10], suggesting that bacterial-viral interactions play an important role in pathogenesis. Secondary pneumococcal infections are well known to cause severe outcomes following influenza and other viral infections [11]. However, interactions between pneumococci and respiratory viruses also occur at earlier stages in the clinical course of viral and bacterial illnesses. Pneumococcal carriage in the upper airway is associated with a higher likelihood of detection or higher-density shedding of influenza virus, respiratory syncytial virus (RSV), human rhinoviruses, and both endemic human coronaviruses (HCoVs) and severe acute respiratory syndrome coronavirus 2 [12–19]. Pneumococcal carriers have a higher likelihood of acquiring respiratory viruses [20] and have diminished mucosal antibody responses to viral infections [12, 21]. Interventions targeting pneumococci may thus offer ancillary benefit by preventing disease typically attributed to viral pathogens. In a prelicensure randomized trial among children

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in South Africa, an investigational 9-valent PCV prevented 33% of virus-associated pneumonia cases among human immunodeficiency virus–negative children [22]. However, it remains unclear whether adult PCV recipients derive similar benefit [23].

The use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been recommended since 1984 for all US adults aged ≥65 years and high-risk adults aged 18–64 years to prevent invasive pneumococcal disease [24]. In 2014, the Advisory Committee on Immunization Practices (ACIP) extended these recommendations to state that all adults aged ≥65 years should receive 13-valent PCV (PCV13) in series with PPSV23 to prevent nonbacteremic pneumonia associated with PCV13-targeted serotypes [25]. Updated recommendations in 2019 called for PCV13 administration on a shared clinical decision-making basis for healthy adults aged ≥65 years, while in 2021, all adults aged ≥65 years and high-risk adults aged 18–64 years were recommended to receive 20-valent PCV as a stand-alone immunization or PCV15 followed by PPSV23 [26]. To probe the vaccine-preventable disease burden associated with pneumococcal-viral interactions among adults, we undertook an observational study evaluating PCV13 effectiveness against virus-associated LRTI among adults.

METHODS

Setting

Kaiser Permanente Southern California (KPSC) is a prominent healthcare provider, enrolling roughly 19% of the population of southern California through employer-provided, prepaid, and federally sponsored insurance plans. Our study population comprised adult KPSC enrollees (aged ≥18 years) between 2015 and 2019. Electronic health records capture all diagnoses, immunizations, prescriptions, and services provided across within-network outpatient, emergency, hospital, and virtual settings for KPSC members. Care received outside of KPSC is captured through insurance claim reimbursements.

Design and Case Definition

We used a case-control framework comparing the history of PCV13 receipt among patients with LRTI, from whom specimens were collected and results obtained for multiplex panel-based polymerase chain reaction assays, and among matched controls without LRTI diagnoses during the same season. Within KPSC, viral testing was ordered on the basis of clinical judgment, most commonly for patients seen in inpatient settings (compared with outpatient or emergency department settings), although clinicians could order tests for patients seen in any setting (**Supplementary Table 2**).

Case patients were individuals receiving any LRTI diagnosis (according to codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification*) between 1 January 2016 and 31 December 2019, who tested positive for infection with any of the study end point viruses: influenza A and B viruses, RSV, HCoVs (including the 229E, HKU1, NL63, and OC43 subtypes), parainfluenza viruses (types 1–4), adenoviruses, human metapneumovirus (HMPV), and enteroviruses (including rhinoviruses). These represented the shared targets of multiplex (17–20 pathogen) viral panel testing assays used at KPSC during the study period. While tests limited to influenza A/B viruses and RSV were also available to physicians, the use of such tests was uncommon (9.1% of all viral testing over the study period) and mostly restricted to outpatient settings; we thus excluded from the analysis any patients who did not receive panel tests that included all study end point viruses.

If multiple viruses were identified, case patients were considered to be associated with each virus detected and contributed data to each virus-specific analysis. We defined single-virus detections as case patients with one of the study end point viruses detected and negative results for all other study end point viruses, without any positive detections of these other viruses within a 30-day window before and after the date of the initial LRTI diagnosis. We included only case patients with new-onset infection (without LRTI diagnoses in the preceding 30 days) who had been enrolled in KPSC health plans continuously for ≥12 months (allowing for enrollment gaps of ≤30 days) before their diagnosis to enable ascertainment of prior-year history of LRTI and other risk factors.

We considered LRTI cases without pneumonia diagnoses within 30 days after an initial nonpneumonia LRTI diagnosis to be nonpneumonia LRTI cases, and we considered cases in patients not hospitalized within 30 days after their initial LRTI diagnosis date to be outpatient-attended cases. Cases with any pneumonia diagnosis or new inpatient admission within these time windows were classified as pneumonia and hospitalized cases, respectively.

We also considered an end point of virus-negative LRTI. For these analyses, we sampled a 20% random subset of all case patients whose tests yielded negative results for all study end point viruses and who did not have viruses detected on any other test within 30 days before or after the initial LRTI diagnosis.

Control Selection

For each case patient, we selected up to 50 eligible controls at random who did not receive any LRTI diagnosis within 1 year after the matched case patient's diagnosis date, or before the control's date of death or disenrollment, whichever was earlier. Because case patients were considered to have experienced new-onset LRTI if they had not received a previous LRTI diagnosis within 30 days, individuals with LRTI diagnoses ≤30 days before the onset date for the case patients were excluded as controls. Matching criteria included age (±1 year), sex, race/ethnicity, history of any LRTI diagnosis in the year before the case patient's diagnosis date, ACIP pneumococcal disease risk group designation (**Supplementary Table 3**), and prior receipt

of adult vaccinations other than PCV13. Vaccine exposures used for matching included PPSV23 and zoster vaccination (live or recombinant) and receipt of seasonal influenza vaccine (live or inactivated) within the same respiratory season, defined over a July–June timetable.

Exposure Definition

The primary exposure was prior receipt of PCV13 under ACIP-concordant frameworks. We excluded case patients and controls who received PCV13 before 2015 (when the vaccine became broadly available to US adults) and those who received PCV13 in series with PPSV23, conflicting with recommended dosing sequences [27] (PPSV23 ≥1 year after PCV13 for immunocompetent individuals or ≥8 weeks after PCV13 for immunocompromised individuals; or PCV13 ≥1 year after PPSV23).

Statistical Analysis

We used logistic regression to estimate the adjusted odds ratio (aOR) comparing prior PCV13 receipt among case patients and controls; we measured vaccine effectiveness (VE) for PCV13 as (1 – aOR) × 100%. Models adjusted for all matching variables as well as risk factors including body mass index, history of smoking, comorbid medical conditions (listed in **Table 1**), and prior-year healthcare use across outpatient, emergency department, and inpatient settings.

Our primary analyses assessed VE for PCV13 against LRTI with ≥1 virus identified in any clinical setting. We also assessed VE against LRTI diagnoses associated with each virus individually, as well as diagnoses associated with single detections of each virus and virus-negative LRTI diagnoses. We repeated these analyses, stratifying for case patients with diagnoses of pneumonia or nonpneumonia LRTI and for case patients who were or were not hospitalized. Each of these analyses was restricted to case patients who met the applicable end point definition and their matched controls, for case patients with any virus detection, those with detections of specific viruses, and those who were virus negative.

We conducted additional exploratory analyses within various population subgroups. These included individuals designated by ACIP as being "at risk" or "at high risk" for pneumococcal disease (based on the presence of comorbid conditions or immunocompromised/immunosuppressed status, respectively) versus those "at low risk" (immunocompetent individuals without ACIP-recognized "at risk" or "high-risk" medical comorbid conditions; **Supplementary Table 3**). We also repeated analyses among individuals aged ≥65 years only, who received PCV13 according to age-based recommendations. To verify that protection was attributable to PCV13 and not to other vaccines, we repeated analyses within the subset of individuals who had received PPSV23 (because 88% of PCV13 recipients had also received PPSV23, analyses within PPSV23-unvaccinated strata were not possible). We also repeated analyses, matching case patients and controls on their frequency of outpatient visits over the preceding year (in bands of 5 visits) and their history of any inpatient admission and emergency department presentation in the preceding year. For influenza A/B virus–associated end points, we likewise repeated analyses separately in strata of individuals who received or had not received any seasonal influenza vaccine in the applicable season (defined on a July–June yearly timetable).

To verify the biological plausibility of our findings, we also assessed VE for seasonal influenza vaccines against LRTI end points associated with influenza A or B virus. Here we applied the same statistical framework used in our primary analyses but instead matched individuals on their history of PPSV23, zoster vaccine, and PCV13 receipt in addition to age, sex, race, prior-year LRTI, and ACIP risk stratum.

RESULTS

Eligible adult KPSC enrollees experienced 413 953 new-onset LRTI diagnoses during follow-up, with 292 945 (70.8%), 62 225 (15.0%), and 58 783 (14.2%) of these case patients receiving care in outpatient, emergency department, and inpatient settings, respectively (**Supplementary Table 2**). Viral panel testing was more common for severe cases; 40 283 (9.7% of 413 953) cases received tests, including 6353 outpatient-diagnosed cases (2.2% of 292 945), 11 330 emergency department-diagnosed cases (18.2% of 62 225), and 22 600 hospitalized cases (38.4% of 58 783). Analyses included 13 856 patients with ≥1 virus detected and 3560 with negative results for all viruses assessed, as well as 279 772 matched controls (**Tables 1** and **2**). Attributes of case patients and matched controls are presented for each virus-associated or virus-negative end point in **Supplementary Tables 4–12**; comparisons of characteristics among case patients with each virus detected, or no viruses detected, are presented in **Supplementary Table 13**.

In total, 11 715 case patients (67.3% of 17 416) and 189 812 controls (67.8% of 279 772) received PCV13 (**Table 1**). Among both groups, PCV13 recipients tended to be older than nonrecipients (within both the 18–64- and ≥65-year age strata), with higher prevalence of comorbid conditions, higher rates of healthcare use in the preceding year, and higher uptake of other adult vaccinations (**Supplementary Table 14**). Controlling for these differences, we estimated that the VE of PCV13 against LRTI diagnoses with any positive viral detection was 23.4% (95% confidence interval [CI], 17.9%–28.6%; **Table 3**). Statistically significant protection was apparent for case patients associated with each virus except RSV (VE, 0.5% [95% CI, –23.3% to 19.7%]) and adenoviruses (–46.1% [–194.6% to 27.5%]), with VE point estimates spanning from 16.1% (for influenza A virus-–positive patients) to 43.4% (for influenza B virus–positive patients). Estimates were similar in analyses limited to case patients with a single virus detected. We estimated a VE of 30.0% (95% CI, 19.9%–388%) against virus-negative LRTI.

Table 1. Characteristics of Case Patients and Matched Controls

Characteristic	All Participants Analyzed, No. (%)		Participants Stratified by Clinical Syndrome of Case Patient, No. (%)[a]				Participants Stratified by Case Patient's Hospitalization Status, No. (%)[a]			
			Nonpneumonia LRTI		Pneumonia		Nonhospitalized		Hospitalized	
	Case Patients (N = 17 416)	Matched Controls (N = 279 772)	Case Patients (n = 4644)	Matched Controls (n = 93 270)	Case Patients (n = 12 772)	Matched Controls (n = 186 502)	Case Patients (n = 7634)	Matched Controls (n = 151 035)	Case Patients (n = 9782)	Matched Controls (n = 128 737)
Age, y										
18–64	5254 (30.2)	79 712 (28.5)	1934 (41.6)	36 189 (38.8)	3320 (26.0)	43 523 (23.3)	2845 (37.3)	52 388 (34.7)	2409 (24.6)	27 324 (21.2)
65–69	1833 (10.5)	27 140 (9.7)	448 (9.6)	8372 (9.0)	1385 (10.8)	18 768 (10.1)	734 (9.6)	14 091 (9.3)	1099 (11.2)	13 049 (10.1)
70–74	2192 (12.6)	38 457 (13.7)	560 (12.1)	12 193 (13.1)	1632 (12.8)	26 264 (14.1)	880 (11.5)	19 441 (12.9)	1312 (13.4)	19 016 (14.8)
75–79	2239 (12.9)	38 565 (13.8)	525 (11.3)	12 526 (13.4)	1714 (13.4)	26 039 (14.0)	884 (11.6)	18 786 (12.4)	1355 (13.9)	19 779 (15.4)
80–84	2431 (14.0)	38 788 (13.9)	546 (11.8)	11 807 (12.7)	1885 (14.8)	26 981 (14.5)	946 (12.4)	19 631 (13.0)	1485 (15.2)	19 157 (14.9)
85–89	1851 (10.6)	28 121 (10.1)	366 (7.9)	6954 (7.5)	1485 (11.6)	21 167 (11.3)	751 (9.8)	13 263 (8.8)	1100 (11.2)	14 858 (11.5)
≥90	1616 (9.3)	28 989 (10.4)	265 (5.7)	5229 (5.6)	1351 (10.6)	23 760 (12.7)	594 (7.8)	13 435 (8.9)	122 (10.4)	15 554 (12.1)
Sex										
Male	8101 (46.5)	128 430 (45.9)	1886 (40.6)	36 867 (39.5)	6215 (48.7)	91 563 (49.1)	3427 (44.9)	67 530 (44.7)	4674 (47.8)	60 900 (47.3)
Female	9315 (53.5)	151 342 (54.1)	2758 (59.4)	56 403 (60.5)	6557 (51.3)	94 939 (50.9)	4207 (55.1)	83 505 (55.3)	5108 (52.2)	67 837 (52.7)
Race/ethnicity										
White, non-Hispanic	7957 (45.7)	137 804 (49.3)	1886 (40.6)	41 134 (44.1)	671 (47.5)	96 670 (51.8)	3204 (42.0)	69 376 (45.9)	4753 (48.6)	68 428 (53.2)
Black, non-Hispanic	1944 (11.2)	26 553 (9.5)	584 (12.6)	10 231 (11.0)	1360 (10.6)	16 322 (8.8)	897 (11.8)	15 357 (10.2)	147 (10.7)	11 196 (8.7)
Hispanic	5444 (31.3)	87 464 (31.3)	1564 (33.7)	31 619 (33.9)	3880 (30.4)	55 845 (29.9)	2544 (33.3)	49 264 (32.6)	2900 (29.6)	38 200 (29.7)
Asian	1753 (10.1)	26 485 (9.5)	520 (11.2)	9567 (10.3)	1233 (9.7)	16 918 (9.1)	831 (10.9)	16 080 (10.6)	922 (9.4)	10 405 (8.1)
Pacific Islander	175 (1.0)	662 (0.2)	46 (1.0)	238 (0.3)	129 (1.0)	424 (0.2)	82 (1.1)	378 (0.3)	93 (1.0)	284 (0.2)
Other/unknown	102 (0.6)	741 (0.3)	39 (0.8)	459 (0.5)	63 (0.5)	282 (0.2)	62 (0.8)	569 (0.4)	40 (0.4)	172 (0.1)
ACIP risk stratum[b]										
Normal risk	3164 (18.2)	52 804 (18.9)	1251 (26.9)	24 264 (26.0)	1913 (15.0)	28 540 (15.3)	1860 (24.4)	36 467 (24.1)	1304 (13.3)	16 337 (12.7)
At risk	897 (46.5)	132 832 (47.5)	2129 (45.8)	43 996 (47.2)	5968 (46.7)	88 836 (47.6)	3558 (46.6)	71 985 (47.7)	4539 (46.4)	60 847 (47.3)
High risk	6155 (35.3)	94 136 (33.6)	1264 (27.2)	25 010 (26.8)	4891 (38.3)	69 126 (37.1)	2216 (29.0)	42 583 (28.2)	3939 (40.3)	51 553 (40.0)
BMI										
Underweight	306 (1.8)	3380 (1.2)	51 (1.1)	142 (1.1)	255 (2.0)	2338 (1.3)	96 (1.3)	1751 (1.2)	210 (2.1)	1629 (1.3)
Normal weight	2704 (15.5)	49 481 (17.7)	671 (14.4)	16 692 (17.9)	233 (15.9)	32 789 (17.6)	1193 (15.6)	27 297 (18.1)	1511 (15.4)	22184 (17.2)
Overweight	2828 (16.2)	62 852 (22.5)	806 (17.4)	21 039 (22.6)	2022 (15.8)	41 813 (22.4)	1347 (17.6)	33 963 (22.5)	1481 (15.1)	28 889 (22.4)
Obese	1893 (10.9)	38 133 (13.6)	587 (12.6)	13 259 (14.2)	1306 (10.2)	24 874 (13.3)	911 (11.9)	20 847 (13.8)	982 (10.0)	17 286 (13.4)
Morbidly obese	1751 (10.1)	26 932 (9.6)	481 (10.4)	9759 (10.5)	1270 (9.9)	17 173 (9.2)	762 (10.0)	14 797 (9.8)	989 (10.1)	12 135 (9.4)
Unknown	7934 (45.6)	98 994 (35.4)	2048 (44.1)	31 479 (33.8)	5886 (46.1)	67 515 (36.2)	3325 (43.6)	52 380 (34.7)	4609 (47.1)	46 614 (36.2)
Smoking history										
Current smoker	1063 (6.1)	14 364 (5.1)	294 (6.3)	4961 (5.3)	769 (6.0)	9403 (5.0)	409 (5.4)	7766 (5.1)	654 (6.7)	6598 (5.1)
Former smoker	7183 (41.2)	106 352 (38.0)	1576 (33.9)	31 193 (33.4)	5607 (43.9)	75 159 (40.3)	2791 (36.6)	53 471 (35.4)	4392 (44.9)	52 881 (41.1)
Never smoker	8483 (48.7)	140 666 (50.3)	2554 (55.0)	49 302 (52.9)	5929 (46.4)	91 364 (49.0)	4069 (53.3)	77 748 (51.5)	4414 (45.1)	62 918 (48.9)
Unknown	687 (3.9)	18 390 (6.6)	220 (4.7)	7814 (8.4)	467 (3.7)	10 576 (5.7)	365 (4.8)	12 050 (8.0)	322 (3.3)	6340 (4.9)
Comorbid conditions										
MI	2159 (12.4)	24 536 (8.8)	447 (9.6)	6353 (6.8)	1712 (13.4)	18 183 (9.7)	737 (9.7)	11 357 (7.5)	1422 (14.5)	13 179 (10.2)
Hypertension	11 622 (66.7)	184 700 (66.0)	2689 (57.9)	54 261 (58.2)	8933 (69.9)	130 439 (69.9)	4596 (60.2)	92 215 (61.1)	7026 (71.8)	92 485 (71.8)

Table 1. Continued

Characteristic	All Participants Analyzed, No. (%)		Participants Stratified by Clinical Syndrome of Case Patient, No. (%)[a]				Participants Stratified by Case Patient's Hospitalization Status, No. (%)[a]			
			Nonpneumonia LRTI		Pneumonia		Nonhospitalized		Hospitalized	
	Case Patients (N = 17 416)	Matched Controls (N = 279 772)	Case Patients (n = 4644)	Matched Controls (n = 93 270)	Case Patients (n = 12 772)	Matched Controls (n = 186 502)	Case Patients (n = 7634)	Matched Controls (n = 151 035)	Case Patients (n = 9782)	Matched Controls (n = 128 737)
CHD	4119 (23.7)	32 874 (11.8)	827 (17.8)	7980 (8.6)	3292 (25.8)	24 894 (13.3)	1329 (17.4)	14 796 (9.8)	2790 (28.5)	18 078 (14.0)
PVD	9515 (54.6)	120 295 (43.0)	2055 (44.3)	32 740 (35.1)	7460 (58.4)	87 555 (46.9)	3598 (47.1)	57 870 (38.3)	5917 (60.5)	62 425 (48.5)
CVD	2169 (12.5)	23 514 (8.4)	449 (9.7)	6080 (6.5)	1720 (13.5)	17 434 (9.3)	811 (10.6)	11 075 (7.3)	1358 (13.9)	12 439 (9.7)
Asthma	3699 (21.2)	35 465 (12.7)	938 (20.2)	11 009 (11.8)	2761 (21.6)	24 456 (13.1)	1524 (20.0)	18 279 (12.1)	2175 (22.2)	17 186 (13.3)
CPD	7406 (42.5)	64 770 (23.2)	1701 (36.6)	19 000 (20.4)	5705 (44.7)	45 770 (24.5)	2832 (37.1)	32 205 (21.3)	4574 (46.8)	32 565 (25.3)
DM (uncomplicated)	2031 (11.7)	37 347 (13.3)	557 (12.0)	12 550 (13.5)	1474 (11.5)	24 797 (13.3)	944 (12.4)	20 214 (13.4)	1087 (11.1)	17 133 (13.3)
DM (complicated)	5282 (30.3)	80 792 (28.9)	1115 (24.0)	22 462 (24.1)	4167 (32.6)	58 330 (31.3)	1950 (25.5)	38 022 (25.2)	3332 (34.1)	42 770 (33.2)
Renal disease	6066 (34.8)	85 530 (30.6)	1225 (26.4)	22 478 (24.1)	4841 (37.9)	63 052 (33.8)	2158 (28.3)	39 754 (26.3)	3908 (40.0)	45 776 (35.6)
Moderate/severe liver disease	192 (1.1)	1594 (0.6)	42 (0.9)	416 (0.4)	150 (1.2)	1178 (0.6)	59 (0.8)	745 (0.5)	133 (1.4)	849 (0.7)
Cancer	1440 (8.3)	17 665 (6.3)	260 (5.6)	4911 (5.3)	1180 (9.2)	12 754 (6.8)	534 (7.0)	8332 (5.5)	906 (9.3)	9333 (7.2)
Tumor	627 (3.6)	8131 (2.9)	119 (2.6)	2190 (2.3)	508 (4.0)	5941 (3.2)	220 (2.9)	3725 (2.5)	407 (4.2)	4406 (3.4)
Rheumatic or connective tissue disease	979 (5.6)	9252 (3.3)	209 (4.5)	2711 (2.9)	770 (6.0)	6541 (3.5)	351 (4.6)	4436 (2.9)	628 (6.4)	4816 (3.7)
Hypothyroidism	2650 (15.2)	41 360 (14.8)	618 (13.3)	12 172 (13.1)	2032 (15.9)	29 188 (15.7)	1033 (13.5)	20 409 (13.5)	1617 (16.5)	20 951 (16.3)
HIV/AIDS	30 (0.2)	300 (0.1)	12 (0.3)	100 (0.1)	18 (0.1)	200 (0.1)	14 (0.2)	135 (0.1)	16 (0.2)	165 (0.1)
Organ transplant	225 (1.3)	1157 (0.4)	44 (0.9)	312 (0.3)	181 (1.4)	845 (0.5)	74 (1.0)	526 (0.3)	151 (1.5)	631 (0.5)
Other immune deficiency or suppression	2036 (11.7)	17 186 (6.1)	413 (8.9)	4822 (5.2)	1623 (12.7)	12 364 (6.6)	699 (9.2)	8219 (5.4)	1337 (13.7)	8967 (7.0)
Depression	3846 (22.1)	49 011 (17.5)	935 (20.1)	14 860 (15.9)	2911 (22.8)	34 151 (18.3)	1535 (20.1)	24 486 (16.2)	2311 (23.6)	24 525 (19.1)
LRTI or pneumonia in prior year	11 898 (68.3)	113 161 (40.4)	1407 (30.3)	19 567 (21.0)	10 491 (82.1)	93 594 (50.2)	4157 (54.5)	44 532 (29.5)	7741 (79.1)	68 629 (53.3)
Prior-year healthcare use										
Outpatient visits, no.										
0–9	2361 (13.6)	62 364 (22.3)	820 (17.7)	25 440 (27.3)	1541 (12.1)	36 924 (19.8)	1348 (17.7)	39 127 (25.9)	1013 (10.4)	23 237 (18.0)
10–19	3246 (18.6)	73 154 (26.1)	949 (20.4)	24 771 (26.6)	2297 (18.0)	48 383 (25.9)	1593 (20.9)	40 072 (26.5)	1653 (16.9)	33 082 (25.7)
20–29	3120 (17.9)	53 085 (19.0)	849 (18.3)	16 708 (17.9)	2271 (17.8)	36 377 (19.5)	1374 (18.0)	27 587 (18.3)	1746 (17.8)	25 498 (19.8)
30–39	4266 (24.5)	55 247 (19.7)	1076 (23.2)	16 391 (17.6)	3190 (25.0)	38 856 (20.8)	1760 (23.1)	27 386 (18.1)	2506 (25.6)	27 861 (21.6)
≥40	4423 (25.4)	35 922 (12.8)	950 (20.5)	9960 (10.7)	3473 (27.2)	25 962 (13.9)	1559 (20.4)	16 863 (11.2)	2864 (29.3)	19 059 (14.8)
ED visits, no.										
0	8534 (49.0)	196 436 (70.2)	2381 (51.3)	69 221 (74.2)	6153 (48.2)	127 215 (68.2)	4007 (52.5)	109 867 (72.7)	4527 (46.3)	86 569 (67.2)
1	4044 (23.2)	48 426 (17.3)	1101 (23.7)	14 814 (15.9)	2943 (23.0)	33 612 (18.0)	1724 (22.6)	24 716 (16.4)	2320 (23.7)	23 710 (18.4)
2	2031 (11.7)	17 789 (6.4)	522 (11.2)	4935 (5.3)	1509 (11.8)	12 854 (6.9)	851 (11.1)	8561 (5.7)	1180 (12.1)	9228 (7.2)
≥3	2807 (16.1)	17 121 (6.1)	640 (13.8)	4300 (4.6)	2167 (17.0)	12 821 (6.9)	1052 (13.8)	7891 (5.2)	1755 (17.9)	9230 (7.2)
Inpatient admissions, no.										
0	12 415 (71.3)	243 263 (87.0)	3613 (77.8)	83 491 (89.5)	8802 (68.9)	159 772 (85.7)	6019 (78.8)	134 024 (88.7)	6396 (65.4)	109 239 (84.9)
1	2921 (16.8)	26 036 (9.3)	653 (14.1)	7309 (7.8)	2268 (17.8)	18 727 (10.0)	1069 (14.0)	12 481 (8.3)	1852 (18.9)	13 555 (10.5)
2	1140 (6.5)	6635 (2.4)	207 (4.5)	1592 (1.7)	933 (7.3)	5043 (2.7)	315 (4.1)	2909 (1.9)	825 (8.4)	3726 (2.9)
≥3	940 (5.4)	3838 (1.4)	171 (3.7)	878 (0.9)	769 (6.0)	2960 (1.6)	231 (3.0)	1621 (1.1)	709 (7.2)	2217 (1.7)

Table 1. Continued

Characteristic	All Participants Analyzed, No. (%)		Participants Stratified by Clinical Syndrome of Case Patient, No. (%)[a]				Participants Stratified by Case Patient's Hospitalization Status, No. (%)[a]			
			Nonpneumonia LRTI		Pneumonia		Nonhospitalized		Hospitalized	
	Case Patients (N = 17 416)	Matched Controls (N = 279 772)	Case Patients (n = 4644)	Matched Controls (n = 93 270)	Case Patients (n = 12 772)	Matched Controls (n = 186 502)	Case Patients (n = 7634)	Matched Controls (n = 151 035)	Case Patients (n = 9782)	Matched Controls (n = 128 737)
Adult vaccinations										
Prior PCV13	11 715 (67.3)	189 812 (67.8)	2599 (56.0)	53 783 (57.7)	9116 (71.4)	136 029 (72.9)	4613 (60.4)	93 236 (61.7)	7102 (72.6)	96 576 (75.0)
Prior PPSV23	15 045 (86.4)	241 928 (86.5)	3566 (76.8)	72 477 (77.7)	11 479 (89.9)	169 451 (90.9)	6142 (80.5)	122 948 (81.4)	8903 (91.0)	118 980 (92.4)
Prior zoster vaccine	4938 (28.4)	82 655 (29.5)	1184 (25.5)	25 770 (27.6)	3754 (29.4)	56 885 (30.5)	2042 (26.7)	42 785 (28.3)	2896 (29.6)	39 870 (31.0)
Seasonal influenza vaccine[c]	13 482 (77.4)	193 207 (69.1)	3324 (71.6)	62 137 (66.6)	10 158 (79.5)	131 070 (70.3)	5727 (75.0)	100 644 (66.6)	7755 (79.3)	92 563 (71.9)

Abbreviations: ACIP, Advisory Committee on Immunization Practices; BMI, body mass index; CHF, congestive heart failure; CPD, chronic pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; ED, emergency department; HIV, human immunodeficiency virus; LRTI, lower respiratory tract infection; MI, myocardial infarction; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PVD, peripheral vascular disease.

[a]Controls were matched to case patients on the basis of age (within ±1 year), sex, race/ethnicity, ACIP risk stratum, history of LRTI/pneumonia in the year before each case patient's diagnosis date, and receipt of other adult immunizations (PPSV23, zoster vaccination, and seasonal influenza vaccination). Despite matching on these variables, imbalance may occur owing to differences in the number of eligible controls identified for each case patient. All factors listed in **Table 2** are controlled for in analyses estimating vaccine effectiveness. For LRTIs, diagnosis codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification*, are provided in **Supplementary Table 1**).

[b]Definitions for the ACIP risk strata are presented in **Supplementary Table 3**.

[c]Receipt of seasonal influenza vaccine was defined for controls as receipt at any time within the applicable respiratory virus season for the case patient's diagnosis date (defined on a July–June timetable) and for case patients as receipt within ≤180 days before the diagnosis date (to capture periods when the vaccine was likely to provide clinical protection and appropriate strain coverage).

We estimated VEs of 21.5% (95% CI, 10.9%–30.9%) and 24.9% (18.4%–30.9%) against nonpneumonia LRTI and pneumonia, respectively, with any positive viral detection (**Table 4**). Point estimates similarly suggested greater protection against pneumonia than nonpneumonia LRTI end points for case patients with influenza A, parainfluenza viruses, and HMPV identified. We estimated VEs of 18.6% (95% CI, 9.3%–27.0%) and 26.8% (19.9%–33.1%) against nonhospitalized and hospitalized LRTI episodes, respectively, with any virus detected (**Table 5**). Point estimates suggested greater protection against hospitalized than against nonhospitalized episodes associated with influenza A, HMPV, and enteroviruses. We did not identify evidence of protection against LRTI associated with RSV or adenoviruses for any of the end points considered.

We estimated a VE of 31.8% (95% CI, 21.7%–40.7%) against virus-negative pneumonia cases (**Table 4**). While we did not identify evidence of protection against virus-negative, nonpneumonia LRTI, it should be noted that such cases represented a small subset (9.2%) of all virus-negative cases, limiting comparability to virus-associated end points. We estimated VEs of 29.5% (95% CI, 12.4%–43.3%) and 30.7% (17.7%–41.7%) against nonhospitalized and hospitalized virus-negative LRTIs, respectively (**Table 5**).

Analyses of subsets to individuals who received PPSV23 (**Supplementary Table 15**) and those aged ≥65 years (**Supplementary Table 16**) yielded similar conclusions, with higher point estimates of protection against most end points. Among individuals <65 years old, 79.1% of PCV13 recipients were immunocompromised, while a further 18.1% were immunocompetent but had major medical comorbid conditions regarded by ACIP to be associated with pneumococcal disease risk (**Supplementary Table 3**). We obtained lower estimates of VE for PCV13 within these strata (17.9% [95% CI, 11.5%–23.8%] for virus-associated LRTI; **Supplementary Table 17**), than among immunocompetent individuals without comorbid conditions (52.3% [42.5%–60.5%]; **Supplementary Table 18**). Such differences should also be considered when comparing our primary estimates with those for the subgroup who had received PPSV23, because 89.4% of PPSV23 nonrecipients (vs 20.0% of PPSV23 recipients) were aged <65 years and thus prioritized for PCV13 receipt on the basis of immunocompromised status or major medical comorbid conditions potentially associated with reduced VE.

Our primary results were also confirmed in analyses that matched case patients and controls for healthcare use, defined by their frequency of outpatient visits and history of any emergency department presentations and inpatient admissions in the year preceding each case patient's diagnosis date (**Supplementary Table 19**). However, the limited availability of eligible matches for case patients with high rates of healthcare use restricted this analysis to a healthier subgroup, within which 17.8% of participants were immunocompromised (compared with 31.3% of the primary analysis population).

Table 2. Respiratory Virus Detections Among Case Patients Included in the Analysis

Respiratory Virus Detected	All LRTI and Pneumonia Cases Analyzed, No. (%) (N = 17 416)[a]	LRTI and Pneumonia Cases by Clinical Syndrome, No. (%)		LRTI and Pneumonia Cases by Patient's Hospitalization Status, No (%)	
		Nonpneumonia LRTI (n = 4644)	Pneumonia (n = 12 772)	Not Hospitalized (n = 7634)	Hospitalized (n = 9782)
Any virus detected, by specific virus identified					
Influenza A	3956 (22.7)	1974 (42.5)	1982 (15.5)	1905 (25.0)	2051 (21.0)
Influenza B	1141 (6.6)	607 (13.1)	534 (4.2)	588 (7.7)	553 (5.7)
RSV	1462 (8.4)	320 (6.9)	1142 (8.9)	562 (7.4)	900 (9.2)
HCoVs (229E, HKU1, OC43, NL63)	975 (5.6)	204 (4.4)	771 (6.0)	416 (5.4)	559 (5.7)
Parainfluenza viruses (1–4)	1259 (7.2)	328 (7.1)	931 (7.3)	539 (7.1)	720 (7.4)
Adenoviruses	172 (1.0)	37 (0.8)	135 (1.1)	80 (1.0)	92 (0.9)
HMPV	1460 (8.4)	184 (4.0)	1276 (10.0)	602 (7.9)	858 (8.8)
Enteroviruses	3431 (19.7)	643 (13.8)	2788 (21.8)	1533 (20.1)	1898 (19.4)
Any respiratory virus	13 856 (79.6)	4297 (92.5)	9559 (74.8)	6225 (81.5)	7631 (78.0)
Single virus detected					
Influenza A	3693 (21.2)	1859 (40.0)	1834 (14.4)	1793 (23.5)	1900 (19.4)
Influenza B	1030 (5.9)	557 (12.0)	473 (3.7)	546 (7.2)	484 (4.9)
RSV	1283 (7.4)	284 (6.1)	999 (7.8)	504 (6.6)	779 (8.0)
HCoVs (229E, HKU1, OC43, NL63)	743 (4.3)	125 (2.7)	618 (4.8)	314 (4.1)	429 (4.4)
Parainfluenza viruses (1–4)	1174 (6.7)	305 (6.6)	869 (6.8)	504 (6.6)	670 (6.8)
Adenoviruses	128 (0.7)	24 (0.5)	104 (0.8)	60 (0.8)	68 (0.7)
HMPV	1353 (7.8)	171 (3.7)	1182 (9.3)	564 (7.4)	789 (8.1)
Enteroviruses	3149 (18.1)	572 (12.3)	2577 (20.2)	1412 (18.5)	1737 (17.8)
No virus detected (negative for all)[b]	3560 (20.4)	347 (7.5)	3213 (25.2)	1409 (18.5)	2151 (22.0)

Abbreviations: HCoVs, human coronaviruses; HMPV, human metapneumovirus; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

[a]Totals do not necessarily reflect the true prevalence of each virus (or no viruses) among case patients, as we drew a 20% sample of virus-negative case patients. For LRTIs, diagnosis codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification,* are provided in **Supplementary Table 1**).

[b]We analyzed data from a randomly sampled subset of all virus-negative case patients.

Table 3. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against All Lower Respiratory Tract Infection or Pneumonia End Points

	PCV13 Receipt				Matched VE (95% CI), %[a]	
	Case Patients		Controls		Adjusted for Matching Factors Only	
Respiratory Virus Detected	%	No./Total No.	%	No./Total No.		Adjusted for All Measured Confounders
Any virus detected	67.3	9324/13 856	67.8	154 409/227 887	6.4 (−.2 to 12.6)	23.4 (17.9–28.6)
Any virus detected, by specific virus identified						
Influenza A	63.6	2515/3956	62.8	44 091/70 178	−1.8 (−15.4 to 10.3)	16.1 (4.5–26.2)
Influenza B	56.5	645/1141	62.2	8365/13 455	35.5 (19.3–48.5)	43.4 (28.4–55.3)
RSV	76.3	1116/1462	78.0	18 424/23 622	−26.6 (−55.5 to −2.5)	0.5 (−23.3 to 19.7)
HCoVs (229E, HKU1, OC43, NL63)	67.9	662/975	69.7	9683/13 902	15.4 (−9.9 to 34.8)	27.4 (4.5, 44.7)
Parainfluenza viruses (1–4)	75.8	954/1259	74.7	18 396/24 616	−6.4 (−36.0 to 16.8)	17.3 (−5.7 to 35.2)
Adenoviruses	48.3	83/172	39.3	1095/2785	−63.0 (−210.3 to 14.3)	−46.1 (−194.6 to 27.5)
HMPV	69.2	1010/1460	68.9	15 040/21 834	6.3 (−15.5 to 24.0)	24.6 (6.9–39.0)
Enteroviruses	68.2	2339/3431	68.4	39 315/57 495	8.2 (−5.6 to 20.2)	28.2 (17.4–37.6)
Single virus detected						
Influenza A	63.0	2327/3693	62.6	41 171/65 754	2.1 (−11.5 to 14.1)	18.6 (7.0–28.8)
Influenza B	55.7	574/1030	61.7	7399/11 998	35.5 (18.6–48.9)	41.6 (25.4–54.2)
RSV	76.1	976/1283	78.0	15 772/20 230	−10.8 (−38.3 to 11.2)	9.8 (−13.4 to 28.2)
HCoVs (229E, HKU1, OC43, NL63)	68.8	511/743	72.4	7477/10 325	19.7 (−9.2 to 41.0)	31.5 (5.9–50.1)
Parainfluenza viruses (1–4)	75.5	886/1174	75.4	17 263/22 893	6.7 (−19.9 to 27.4)	24.4 (2.9–41.2)
Adenoviruses	45.3	58/128	36.4	782/2148	−44.2 (−233.5 to 37.7)	−32.2 (−234.0 to 47.7)
HMPV	69.0	933/1353	68.8	14 125/20 536	6.4 (−16.4 to 24.8)	24.1 (5.3–39.1)
Enteroviruses	67.8	2136/3149	68.1	35 920/52 732	14.2 (.8–25.8)	31.5 (20.7–40.8)
No virus detected (negative for all)[b]	67.2	2391/3560	68.2	35 403/51 885	19.7 (8.4–29.6)	30.0 (19.9–38.8)

Abbreviations: CI, confidence interval; HCoVs, human coronaviruses; HMPV, human metapneumovirus; PCV13, 13-valent pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; VE, vaccine effectiveness.

[a]VE is calculated for an end point of any medically attended lower respiratory tract infection (LRTI)/pneumonia for which viral respiratory polymerase chain reaction panel testing was conducted and the indicated results (pathogen detections) were obtained. Separate estimates for pneumonia and nonpneumonia LRTI end points are presented in **Table 4**, while **Table 5** presents results for hospitalized and nonhospitalized case patients. Estimates are obtained via the adjusted odds ratio of prior PCV13 receipt in case patients versus matched controls, for each end point designated according to diagnosis, hospitalization status, and respiratory virus detection, estimated using logistic regression with covariate adjustment for all measured confounders.

[b]We analyzed data from a randomly sampled subset of all virus-negative case patients.

Table 4. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Pneumonia and Nonpneumonia Lower Respiratory Tract Infection

	Nonpneumonia LRTI[a]					Pneumonia				
	PCV13 Receipt				Matched, Adjusted VE (95% CI), %[b]	PCV13 Receipt				
	Case Patients		Controls			Case Patients		Controls		
Respiratory Virus Detected	%	No./Total No.	%	No./Total No.		%	No./Total No.	%	No./Total No.	Matched, Adjusted VE (95% CI), %[b]
Any virus detected	56.6	2434/4297	58.5	51 315/87 726	21.5 (10.9–30.9)	72.1	6890/9559	73.6	103 094/140 161	24.9 (18.4–30.9)
Any virus detected, by specific virus identified										
Influenza A	56.5	1115/1974	57.8	25 171/43 530	13.3 (−5.3 to 28.7)	70.6	1400/1982	71.0	18 920/26 648	17.9 (2.3–31.1)
Influenza B	47.1	286/607	58.1	5331/9173	52.6 (34.6–65.6)	67.2	359/534	70.9	3034/4282	22.3 (−13.0 to 46.6)
RSV	70.6	226/320	72.2	4549/6297	11.9 (−38.0 to 43.8)	77.9	890/1142	80.1	13 875/17 325	−1.8 (−30.7 to 20.7)
HCoVs (229E, HKU1, OC43, NL63)	45.1	92/204	47.2	1684/3571	51.4 (6.0–74.9)	73.9	570/771	77.4	7999/10 331	23.5 (−4.1 to 43.8)
Parainfluenza viruses (1–4)	70.4	231/328	66.0	5251/7958	−1.5 (−65.9 to 37.8)	77.7	723/931	78.9	13 145/16 658	24.2 (−.6 to 42.9)
Adenoviruses[c]	48.6	18/37	29.9	254/850	…	48.1	65/135	43.5	841/1935	6.0 (−114.6 to 58.8)
HMPV	65.2	120/184	59.4	2013/3389	−25.2 (−131.6 to 32.3)	69.7	890/1276	70.6	13 027/18 445	28.1 (9.8–42.7)
Enteroviruses	53.8	346/643	54.5	7062/12958	31.8 (3.2–52.0)	71.5	1993/2788	72.4	32 253/44 537	28.6 (16.7–38.8)
Single virus detected										
Influenza A	56.1	1043/1859	57.6	23 582/40 962	13.8 (−5.6 to 29.5)	70.0	1284/1834	70.9	17 589/24 792	21.0 (5.4–34.1)
Influenza B	45.8	255/557	57.3	4814/8400	52.1 (33.3–65.6)	67.4	319/473	71.8	2585/3598	17.7 (−23.1 to 45.0)
RSV	70.1	199/284	73.2	3887/5313	29.1 (−14.0 to 55.9)	77.8	777/999	79.7	11 885/14 917	5.5 (−23.3 to 27.6)
HCoVs (229E, HKU1, OC43, NL63)	44.0	55/125	45.9	906/1975	55.3 (−12.9 to 82.3)	73.8	456/618	78.7	6571/8350	32.7 (4.8–52.5)
Parainfluenza viruses (1–4)	68.9	210/305	66.9	4859/7258	22.0 (−27.7 to 52.4)	77.8	676/869	79.3	12 404/15 635	27.5 (2.8–45.9)
Adenoviruses[c]	33.3	8/24	22.3	143/642	…	48.1	50/104	42.4	639/1506	…
HMPV	65.6	112/171	61.5	1962/3189	−19.6 (−123.5 to 35.9)	69.5	821/1182	70.1	12 163/17 347	26.5 (6.8–42.1)
Enteroviruses	53.1	304/572	53.8	6186/11 489	41.6 (15.4–59.7)	71.1	1832/2577	72.1	29 734/41 243	30.4 (18.3–40.7)
No virus detected (negative for all)[d]	47.6	165/347	44.5	2468/5544	−18.0 (−106.0 to 32.4)	69.3	2226/3213	71.1	32 935/46 341	31.8 (21.7–40.7)

Abbreviations: CI, confidence interval; HCoVs, human coronaviruses; HMPV, human metapneumovirus; LRTI, lower respiratory tract infection; PCV13, 13-valent pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; VE, vaccine effectiveness.

[a]For LRTIs, diagnosis codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification,* are provided in **Supplementary Table 1**).

[b]VE is calculated for an end point of any medically attended LRTI/pneumonia for which viral respiratory polymerase chain reaction panel testing was conducted and the indicated results (pathogen detections) were obtained. We present results aggregated across LRTI/pneumonia end points in **Table 3**, while **Table 5** presents results for hospitalized and nonhospitalized case patients. Estimates are obtained via the adjusted odds ratio of prior PCV13 receipt in case patients versus matched controls, for each end point designated according to diagnosis, hospitalization status, and respiratory virus detection, estimated using logistic regression with covariate adjustment for all measured confounders. Estimates without adjustment for confounders that were not included in match assignment are presented in **Supplementary Table 22**.

[c]Insufficient sample size for model convergence.

[d]We analyzed data from a randomly sampled subset of all virus-negative case patients.

Table 5. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalized and Nonhospitalized Lower Respiratory Tract Infection or Pneumonia End Points

Respiratory Virus Detected	Nonhospitalized Case Patients					Hospitalized Case Patients				
	PCV13 Receipt				Matched, Adjusted VE (95% CI), %[a]	PCV13 Receipt				
	Case Patients		Controls			Case Patients		Controls		
	%	No./Total No.	%	No./Total No.		%	No./Total No.	%	No./Total No.	Matched, Adjusted VE (95% CI), %[a]
Any virus detected	60.4	3757/6225	61.7	77 678/125 931	18.6 (9.3–27.0)	73.0	5567/7631	75.3	76 731/101 956	26.8 (19.9–33.1)
Any virus detected, by specific virus identified										
Influenza A	54.9	1046/1905	55.2	23 498/42 580	4.5 (−16.1 to 21.4)	71.6	1469/2051	74.6	20 593/27 598	25.6 (11.4–37.5)
Influenza B	46.8	275/588	55.7	4992/8970	46.5 (24.3–62.2)	66.9	370/553	75.2	3373/4485	37.2 (11.8–55.3)
RSV	73.1	411/562	76.4	7960/10 420	3.0 (−38.5–32.1)	78.3	705/900	79.3	10 464/13 202	4.4 (−26.0 to 27.5)
HCoVs (229E, HKU1, OC43, NL63)	62.3	259/416	64.7	4632/7160	38.7 (2.6–61.4)	72.1	403/559	74.9	5051/6742	19.9 (−13.1 to 43.2)
Parainfluenza viruses (1–4)	71.2	384/539	70.8	9479/13 393	18.9 (−19.9 to 45.2)	79.2	570/720	79.5	8917/11 223	16.0 (−15.9 to 39.2)
Adenoviruses[b]	38.8	31/80	26.8	434/1622	…	56.5	52/92	56.8	661/1163	43.0 (−60.6 to 79.7)
HMPV	65.1	392/602	65.5	6934/10 589	17.4 (−15.6 to 41.0)	72.0	618/858	72.1	8106/11 245	25.0 (1.0–43.2)
Enteroviruses	62.6	959/1533	63.3	19 749/31 197	24.1 (4.9–39.4)	72.7	1380/1898	74.4	19 566/26 298	31.7 (18.1–43.0)
Single virus detected										
Influenza A	54.5	977/1793	55.4	22 198/40 043	7.9 (−12.6 to 24.6)	71.1	1350/1900	73.8	18 973/25 711	27.4 (12.9–39.4)
Influenza B	46.5	254/546	56.7	4630/8166	45.6 (22.5–61.80	66.1	320/484	72.3	2769/3832	36.4 (9.0–55.5)
RSV	72.8	367/504	77.1	7006/9088	18.0 (−19.5 to 43.8)	78.2	609/779	78.7	8766/11 142	6.5 (−26.0 to 30.6)
HCoVs (229E, HKU1, OC43, NL63)	65.0	204/314	70.4	3661/5202	40.8 (−2.7 to 65.9)	71.6	307/429	74.5	3816/5123	32.5 (−1.2 to 55.0)
Parainfluenza viruses (1–4)	70.8	357/504	71.6	8900/12 428	30.4 (−3.2 to 53.1)	79.0	529/670	79.9	8363/10 465	19.8 (−12.2 to 42.6)
Adenoviruses[b]	30.0	18/60	25.9	356/1372	…	58.8	40/68	54.9	426/776	…
HMPV	65.6	370/564	65.2	6499/9973	5.4 (−34.1 to 33.3)	71.4	563/789	72.2	7626/10 563	31.7 (8.6–49.0)
Enteroviruses	62.6	884/1412	63.0	17 911/28 421	25.9 (6.2–41.5)	72.1	1252/1737	74.1	18 009/24 311	35.6 (22.4–46.7)
No virus detected (negative for all)[c]	60.8	856/1409	62.0	15 558/25 104	29.5 (12.4–43.3)	71.4	1535/2151	74.1	19 845/26 781	30.7 (17.7, 41.7)

Abbreviations: CI, confidence interval; HCoVs, human coronaviruses; HMPV, human metapneumovirusPCV13, 13-valent pneumococcal conjugate vaccine; RSV, RSV, respiratory syncytial virus; VE, vaccine effectiveness.

[a]VE is calculated for an end point of any medically attended lower respiratory tract infection (LRTI)/pneumonia for which viral respiratory polymerase chain reaction panel testing was conducted and the indicated results (pathogen detections) were obtained. We present results aggregated across LRTI/pneumonia end points in **Table 3**, while **Table 4** presents separate estimates for pneumonia and nonpneumonia LRTI end points. Estimates are obtained via the adjusted odds ratio of prior PCV13 receipt in case patients versus matched controls, for each end point designated according to diagnosis, hospitalization status, and respiratory virus detection, estimated via logistic regression with covariate adjustment for all measured confounders. Estimates without adjustment for confounders that were not included in match assignment are presented in **Supplementary Table 22**. (For LRTIs, diagnosis codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification,* are provided in **Supplementary Table 1**).

[b]Insufficient sample size for model convergence.

[c]We analyzed data from a randomly sampled subset of all virus-negative case patients.

Point estimates of the VE for PCV13 against influenza A virus–associated end points were similar for individuals who had or had not received seasonal influenza vaccines (**Supplementary Table 20**); for influenza B virus–associated end points, estimates of PCV13 VE were greater among individuals who had not received seasonal influenza vaccines. Secondary analyses revealed protective effects of seasonal influenza vaccination against LRTI associated with influenza A or B viruses. Estimates of protection against pneumonia and hospitalized illness exceeded estimates of protection against nonpneumonia and nonhospitalized LRTI, respectively, and were greatest among immunocompetent individuals without comorbid conditions (**Supplementary Table 21**).

DISCUSSION

We identified moderate protection against virus-associated LRTI among adult recipients of PCV13. Point estimates of VE were higher for virus-associated pneumonia than for nonpneumonia LRTI, and higher for virus-associated hospitalized LRTI than for outpatient-attended LRTI. Receipt of PCV13 was protective against disease associated with each virus except RSV and adenoviruses. We identified greater protection against virus-negative episodes, consistent with the higher likelihood of a primary bacterial etiology in such cases, although caution is warranted, owing to differences in severity and clinical attributes of virus-positive and virus-negative cases. Because testing was ordered based on physicians' judgment and captured a severe subset of all diagnosed LRTI cases, estimates of protection may differ from what would be expected in samples including milder cases. With these considerations in mind, our findings suggest that PCV13-serotype pneumococci contribute to the pathogenesis of severe LRTI cases associated with respiratory viruses among adults and that the resulting burden of disease can be reduced by immunization with PCVs.

Prior case-control studies have reported that children receiving complete PCV series per local guidelines had 26%–48% lower risks of influenza-associated hospitalization, than children who did not receive PCVs [28, 29]. In intention-to-treat analyses of a prelicensure trial in South Africa, 9-valent PCV conferred 34%–51% efficacy against pneumonia associated with influenza A, endemic HCoVs, parainfluenza viruses, and HMPV among young children [22, 30, 31]. Consistent with our findings, the study did not identify strong evidence of protection against pneumonia associated with RSV (VE, 12% [95% CI, –8% to 27%]) or adenoviruses (0% [–100% to 50%]), possibly reflecting distinct interaction pathways between pneumococci and these viruses. Differences in bacterial-viral interaction pathways may also occur between children and adults. Cohort studies have reported elevated risk of secondary pneumococcal disease after RSV infection, but no commensurate increase in RSV infection risk after pneumococcal disease [32], consistent with the lagged seasonal pattern of pneumococcal disease relative to RSV [10]. Because our analysis included only new-onset LRTI episodes, lack of evidence for PCV13 effectiveness against RSV-associated LRTI in our study could also indicate that pneumococcal interactions with RSV predominantly involve secondary bacterial infections not captured by our study end point of new-onset, virus-associated LRTI.

In a randomized PCV13 trial in the Netherlands enrolling adults aged ≥65 years, which was likewise undertaken in a setting of well-established pediatric PCV use, point estimates for VE against radiologically confirmed community-acquired pneumonia associated with influenza viruses, HCoVs, and HMPV were 34%, 24%, and 11%, respectively [23]. However, the study identified only 332 virus-positive cases among 84 496 participants followed up for 4 years, yielding limited statistical power. In a previous observational study in the KPSC cohort, older adults receiving PCV13 experienced moderate (VE, 35%x) protection against COVID-19 [33]. Our study extends these earlier findings, suggesting that the benefits of PCV13 for preventing virus-associated respiratory illness among adults resemble previous observations among children [22, 30, 31].

We estimated greater VE of PCV13 against influenza B virus–associated LRTI among individuals who had not received seasonal influenza vaccines than among seasonal influenza vaccine recipients. These findings may reflect greater PCV13-preventable disease burden among individuals lacking specific viral protection. Annual US evaluations of seasonal influenza VE during the study period consistently identified greater protection against influenza B viruses than against influenza A viruses [34–36], possibly contributing to these observations. Among children, the combined use of PCVs with influenza vaccines has been found to confer greater protection against acute respiratory infections than influenza vaccination alone [37, 38]. Because most animal studies have investigated pneumococcal interactions with influenza A virus, it is unclear whether there is a biological basis for differences in PCV13 effects on LRTI associated with influenza A and B viruses.

While studies in Europe have attributed 7%–14% of all community-acquired adult pneumonia cases to PCV13-serotype pneumococci using urinary antigen detection assays [39–41], US studies have obtained lower estimates, in the range of 4%–6% [42, 43]. However, randomized and observational studies of PCV13 among older adults have consistently estimated VEs against all-cause LRTI or pneumonia end points in the range of 6%–12% [9, 44–46], suggesting that urinary antigen detection assays may generate conservative estimates of the burden of disease attributable to PCV13-targeted serotypes. While enhanced risk of secondary pneumococcal pneumonia after viral infection is well understood, facilitative relationships between pneumococci and viruses also occur in the upper airway [12–19]. Pneumococcal neuraminidase has been found to reduce neutralization of viruses in saliva [47], and pneumococcal carriers experience enhanced risk of viral acquisition

and acute respiratory infection [20]. Although our study did not include testing for other bacteria, such interactions could also contribute to the public health impact of PCV13 use. For instance, children randomized to receive 9-valent PCV experienced lower incidence of culture-confirmed pulmonary tuberculosis in South Africa [48].

Our study has limitations. Although PCV13 receipt was not randomized, detailed records on participants' medical history and exposures enabled us to control for relevant confounders. The external validity of our results is supported by findings of enhanced protection against severe disease end points, including virus-negative disease end points, and differential protection among healthy individuals versus those with comorbid conditions or compromised immunity. Our findings also resemble those from other studies [22, 30, 31] in terms of the specific viruses against which we identified or did not identify protection. It is important to note that a substantial proportion of enterovirus detections in our study may reflect rhinovirus infections, as multiplex polymerase chain reaction panels did not distinguish among viruses within this genus. Viral detection may not reveal disease etiology for all cases, although our findings were similar in analyses limited to individuals with only a single virus detected. Selection of controls without medically attended LRTI may permit outcome misclassification, for instance if some controls experienced mild respiratory illness for which they did not seek healthcare.

Finally, attributes of the various populations captured by exploratory subgroup analyses may confound between-subgroup differences in VE. For instance, although prior studies have revealed greater immunogenicity of a 7-valent PCV7 + PPSV23 series among adults aged ≥50 years than for 7-valent PCV alone [26], higher point estimates of PCV13-associated protection among PPSV23 recipients in our study may reflect the fact that most PPSV23 nonrecipients were aged 18–64 years and thus received PCV13 on the basis of risk factors that could reduce VE.

Alternative study designs, such as the test-negative design, compare prior vaccination among patients with illness attributable to a vaccine-targeted pathogen versus those with clinically identical illness without the same pathogen identified to reduce confounding based on potential associations between vaccination and healthcare seeking [49]. The fact that PCV13 prevents virus-negative pneumonia made such analyses inappropriate in this study. The risk of the aforementioned bias is reduced in analyses addressing severe end points [50], such as hospitalized LRTIs in our study. Our primary analyses were matched for receipt of other adult vaccinations and further controlled (via covariate adjustment) for healthcare-seeking behavior on the basis of prior-year outpatient, emergency department, and inpatient care interactions; findings of protection held in sensitivity analyses that also matched case patients and controls for these exposures. Collectively, these factors suggest that unmeasured confounding would be unlikely to explain our findings.

In conclusion, our study demonstrates moderate protection against virus-associated LRTI as an ancillary benefit of PCV13 use among US adults. These findings may inform implementation of next-generation (15/20-valent) PCVs covering serotypes against which herd immunity has not been established. Investigations into pathways by which pneumococci contribute to respiratory virus acquisition or disease progression among adults are warranted to inform the prevention of LRTI.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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