

Prevention of COVID-19 among older adults receiving pneumococcal conjugate vaccine suggests interactions between *Streptococcus pneumoniae* and SARS-CoV-2 in the respiratory tract

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KEY POINTS

- After adjusting for risk factors and other exposures, adults aged ≥65 years who received 13-valent pneumococcal conjugate vaccine (PCV13) experienced lower incidence of COVID-19 diagnosis, hospitalization, and death.
- Antibiotic receipt transiently attenuated the association between PCV13 receipt and COVID-19 diagnosis.

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ABSTRACT

Introduction: While secondary pneumococcal pneumonia occurs less commonly after COVID-19 than after other viral infections, it remains unclear whether other interactions occur between SARS-CoV-2 and *Streptococcus pneumoniae*.

Methods: We probed potential interactions between these pathogens among adults aged ≥ 65 y by measuring associations of COVID-19 outcomes with pneumococcal vaccination (13-valent conjugate and 23-valent polysaccharide; PCV13, PPSV23). We estimated adjusted hazard ratios (aHRs) using Cox proportional hazards models with doubly-robust inverse-propensity weighting. We assessed effect modification by antibiotic exposure to further test the biologic plausibility of a causal role for pneumococci.

Results: Among 531,033 adults, there were 3,677 COVID-19 diagnoses, leading to 1,075 hospitalizations and 334 fatalities, between 1 March-22 July, 2020. Estimated aHRs for COVID-19 diagnosis, hospitalization, and mortality associated with prior PCV13 receipt were 0.65 (95% confidence interval: 0.59-0.72), 0.68 (0.57-0.83), and 0.68 (0.49-0.95), respectively. Prior PPSV23 receipt was not associated with protection against the three outcomes. COVID-19 diagnosis was not associated with prior PCV13 within 90 days following antibiotic receipt, whereas aHR estimates were 0.65 (0.50-0.84) and 0.62 (0.56-0.70) during risk periods 91-365d and >365 d following antibiotic receipt, respectively.

Discussion: Reduced risk of COVID-19 among PCV13 recipients, transiently attenuated by antibiotic exposure, suggests pneumococci may interact with SARS-CoV-2.

KEYWORDS

COVID-19; SARS-CoV-2; *Streptococcus pneumoniae*; pneumococcal conjugate vaccine; older adults; polymicrobial infection

INTRODUCTION

Bacterial-viral interactions in the upper and lower airways influence the natural history of numerous respiratory virus infections. A substantial proportion of influenza-associated respiratory disease involves the bacterium *Streptococcus pneumoniae* (pneumococcus; [1]) likewise, incidence of severe pneumococcal infections closely tracks the incidence of influenza and other respiratory virus infections [2]. A canonical explanation for this observation is that virus-induced inflammation in the upper airway impairs innate (monocyte or cytokine) responses to pneumococci [3], facilitating the acquisition of pneumococcal carriage and a loss of control over progression to secondary bacterial pneumonia [4].

However, both epidemiological and experimental studies reveal viral-bacterial interactions arising at earlier stages of the clinical course. Individuals shedding respiratory viruses—including influenza virus, respiratory syncytial virus (RSV), adenoviruses, endemic human coronaviruses (HCoVs), and human rhinoviruses [5–11]—have higher-density pneumococcal carriage than individuals without respiratory virus infection. Additionally, pneumococcal carriers have diminished mucosal antibody responses to influenza virus challenge [12], and higher likelihood of both acquiring respiratory viruses and thereafter experiencing acute respiratory symptoms [13]. Whereas these interactions have been shown to promote transmission of both pneumococci and viruses [14,15], clinical implications including impacts on viral disease pathogenesis remain less clearly understood [16].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19), has rapidly achieved pandemic spread and has caused substantial morbidity and mortality in the United States (US) and worldwide. While available data have shown limited burden of secondary bacterial pneumonia among individuals with severe COVID-19 illness [17], the contribution of respiratory microbiota to SARS-CoV-2 infection and pathogenesis has not been widely investigated [18,19]. In one study of invasive pneumococcal disease (IPD) patients, concomitant SARS-CoV-2 infection and IPD was associated with 7-fold higher odds of death in comparison to IPD without SARS-CoV-2 infection; further, SARS-CoV-2 infection within 28 days after IPD was associated with 4-fold higher mortality [20].

Among adults, 13-valent pneumococcal conjugate vaccine (PCV13) reduces nasopharyngeal carriage acquisition and density [21,22] for targeted pneumococcal serotypes, in addition to preventing invasive disease and non-bacteremic pneumonia [23,24] involving these serotypes. In contrast, 23-valent pneumococcal polysaccharide vaccine (PPSV23), also recommended for US adults ages ≥65y to prevent IPD, has not been found to confer strong protection against mucosal endpoints such as pneumococcal carriage and non-bacteremic pneumonia [25]. Randomized controlled trials among children and adults [26–29] have found PCVs to confer 23–49% protection against pneumonia associated with respiratory viruses, including HCoVs [27,28], supporting the etiologic involvement of pneumococci in virus-associated respiratory disease. To probe the potential for similar interactions between SARS-CoV-2 and pneumococci, we compared COVID-19 outcomes in a cohort of US older adults who had received and had not received PCV13.

Methods

Cohort

The Kaiser Permanente Southern California (KPSC) healthcare system provides comprehensive care to roughly 19% of the Southern California population. Members are enrolled through employer-provided health insurance plans, pre-paid plans, and state- and federally-sponsored insurance programs. Electronic health records including member demographics, services (including vaccination), and diagnoses are tracked from outpatient, emergency department, and hospital settings. Care received out of network is captured through insurance claim reimbursements, enabling

near-complete medical care ascertainment for KPSC members. We included individuals ages ≥ 65 years as of 1 March 2020 and thus eligible for PCV13 receipt, who were KPSC members for at least one year before this date. The KPSC Institutional Review Board provided ethical approval.

Outcomes and exposures

We assessed time to each of the following endpoints: any COVID-19 diagnosis, defined as a positive result of a molecular test for SARS-CoV-2 infection or a clinically-confirmed COVID-19 diagnosis; COVID-19 hospitalization, defined as a new inpatient admission between 7 days before and 28 days after a COVID-19 diagnosis; and fatal COVID-19 hospitalization, defined as death within 60 days of the admission date for a COVID-19 hospitalization. We excluded observational admissions lasting < 24 hours from our definition of COVID-19 hospitalization.

The primary exposure of interest for our study was receipt of PCV13 (with or without PPSV23) concordant with Advisory Committee on Immunization Practices (ACIP) guidelines at ages ≥ 65 y. We excluded cohort members who received PCV13 and PPSV23 at intervals discordant with 2015 ACIP guidelines [30], which stipulated the timing of PCV13 dosing as follows: ≥ 1 year before PPSV23 for immunocompetent individuals or ≥ 8 weeks before PPSV23 for immunocompromised persons; or ≥ 1 year after the most recent PPSV23 dose for individuals previously vaccinated with PPSV23 (owing to the reduced immunogenicity of PCV13 when administered shortly after PPSV23 [31]). We updated vaccination status for individuals who received PPSV23 or PCV13 during the follow-up period, excluding person-time contributed during the first 30 days after receipt of any PCV13 or PPSV23 dose to allow for time to onset of immunity.

To mitigate confounding due to differences in risk status, contact patterns and SARS-CoV-2 exposure, and healthcare utilization associated with vaccination, covariates included in our analyses were age group (defined in 5-year bins), sex, race/ethnicity, current or former smoking, body mass index, history of comorbid conditions, prior year healthcare utilization (across outpatient, emergency, and inpatient settings), median household income within individuals' residential census tract, and prior receipt of any zoster vaccine as well as 2019-2020 seasonal influenza vaccine. Comorbid conditions were defined by International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for prior diagnoses of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, renal disease, moderate or severe liver disease, asthma, obstructive sleep apnea, HIV/AIDS, immunocompromising conditions, organ transplant, malignancy or metastatic solid tumor, rheumatologic or inflammatory disorders, and depression. We encoded missing information on race/ethnicity, body mass index, smoking, and median census tract household income as a distinct exposure category, as the occurrence of missing data was informatively associated with healthcare utilization and history of vaccination. To assess effect modification, we also recorded dates of any oral or intravenous antibiotic receipt among cohort members.

Statistical analysis

We measured the association between PCV13 receipt and COVID-19 outcomes via the adjusted hazard ratio (aHR), estimated via Cox proportional hazards regression with doubly-robust inverse propensity weighting for PCV13 exposure [32]. We computed stabilized weights for cohort members that were inversely proportional to their propensity of having received PCV13, based on demographic and clinical attributes, using a logistic regression model defining any PCV13 receipt as the outcome. Covariates listed above were the predictors. We controlled for all covariates included the treatment model in the outcome models.

Because covariate adjustment may not completely remove bias in the presence of unmeasured confounding [33], we corrected for the association of COVID-19 outcomes with receipt of zoster vaccination (defined as receipt of any live or recombinant zoster vaccine dose, for which there are similar age-based recommendations among US older adults) as a negative control exposure. While not hypothesized to confer specific protection against COVID-19 outcomes, we expected that zoster vaccine receipt could be associated with COVID-19 outcomes through unmeasured confounding pathways that would also affect analyses of PCV13, such as an association between vaccine uptake and personal protective measures against COVID-19 (e.g. mask-wearing, avoidance of social gatherings, etc.). Using the method of Sanderson and colleagues [33], we adjusted estimates for the association of zoster vaccine receipt with COVID-19 outcome via the formula aHR_P/aHR_Z , where aHR_P and aHR_Z were adjusted hazard ratio estimates for PCV13 and zoster vaccine exposures, respectively. We considered findings to be statistically-significant if the 95% confidence interval around aHR_P/aHR_Z excluded one; here, statistical significance indicated that the magnitude of effect associated with pneumococcal vaccination exceeded the estimated negative control effect size.

Effect modification by antibiotic exposure

Finally, to assess the hypothesis that associations with PCV13 receipt were mediated by presence of pneumococci in the respiratory tract, we assessed differences in effect size estimates across strata defined according to individuals' history of antibiotic exposure. While direct verification of individuals' pneumococcal carriage status was not possible in this retrospective study, we hypothesized that no effects of PCV13 would be evident during risk periods immediately following antibiotic treatment, as persistence of pneumococci in the upper airway following antibiotic treatment would be unlikely [34]. Our analyses used a case-control framework, defining cases as individuals who experienced COVID-19 diagnosis over the duration of the study period, and controls as individuals who did not. We estimated adjusted odds ratios (aOR) for predictors of case status using logistic regression models applying stabilized inverse propensity weights (as defined above) for PCV13 receipt. We quantified the negative control-corrected association of PCV13 with COVID-19 outcomes as aOR_P/aOR_Z , consistent with our primary analyses, for the aORs associated with receipt of PCV13 (P) and zoster (Z) vaccines. Owing to the low incidence of COVID-19 (<1% in the study cohort over the follow-up period) the odds ratio provided a suitable approximation for the hazard ratio [35].

We defined separate strata for cases who experienced COVID-19 diagnoses within 1-30, 31-60, or 61-90 days following receipt of any antibiotic (defined by the date of receipt for antibiotics with a single administration, or the last day of antibiotic supply for multi-day prescriptions); cases who never received antibiotics during the study period; and cases who received antibiotics in a remote risk period 91-365 days before their COVID-19 diagnosis. Stratification of controls for antibiotic receipt was unnecessary as the risk ratio of control status among unvaccinated and vaccinated persons—a factor in the odds ratio—approaches 1 at low risk of infection ($p \rightarrow 0$):

$$\lim_{p \rightarrow 0} \frac{1 - [1 + a_0(\alpha - 1)]p}{1 - [1 + a_1(\alpha - 1)]vp} = 1,$$

where a_1 and a_0 are the prevalence of antibiotic receipt among controls who received and did not receive PCV13, respectively, v is the risk ratio of COVID-19 given PCV13 receipt (and conditioned on antibiotic exposure status), and α is the risk ratio of COVID-19 diagnosis given antibiotic receipt.

RESULTS

The study cohort comprised 531,033 individuals aged ≥ 65 years enrolled in KPSC health plans, among whom there were 3,677 COVID-19 cases, 1,075 COVID-19 hospitalizations, and 334 fatal COVID-19 hospitalizations from 1 March to 22 July, 2020. In total, 451,068 cohort members received PCV13 at ages ≥ 65 years. On average, recipients of PCV13 were older than non-recipients, had higher prevalence of comorbid conditions associated with risk of pneumonia and COVID-19, and had higher rates of healthcare utilization in the preceding year (**Table 1; Table S1**). Incidence rates of COVID-19 diagnosis, hospitalization, and fatal hospitalization were higher among individuals with each comorbid condition included in analyses, with the exception of malignancy, metastatic solid tumor, and HIV infection (for which the sample size was small; **Table S1**). Reweighting of the cohort according to the inverse propensity of PCV13 receipt balanced the distribution of confounding variables between recipients and non-recipients (**Fig. 1; Table S2**).

Accounting for zoster vaccination as a negative-control exposure, the estimated aHR for COVID-19 among PCV13 recipients, versus non-recipients, was 0.65 (95% confidence interval: 0.59-0.72; **Fig. 2; Table S3**). For hospitalization and fatal hospitalization endpoints, aHR estimates were 0.68 (0.57-0.83) and 0.68 (0.49-0.95), respectively. In contrast, receipt of PPSV23 was not independently associated with clear differences in risk of the three COVID-19 outcomes (**Fig 2; Table S4**); estimates suggested a reduction in risk of hospitalization associated with PPSV23 receipt, although this effect size did not differ significantly from the negative control association with zoster vaccination (aHR 1.02; 0.78-1.29). Individuals receiving only PCV13 experienced lower risk of each outcome than individuals receiving only PPSV23 (**Table S5**).

In analyses distinguishing risk periods according to history of antibiotic receipt, the aOR for COVID-19 among PCV13 recipients, versus non-recipients, was 0.62 (0.54-0.70) among individuals who never received antibiotics over the study period (**Fig. 3**; owing to the low incidence of COVID-19, the aOR is directly comparable to the aHR for the same outcome). In contrast, estimates of the aOR over time periods 1-30d, 31-60d, and 61-90d after antibiotic receipt were 1.12 (0.87-1.41), 1.14 (0.71-1.75), and 1.06 (0.66-1.60), respectively. Over the period 90-365d after antibiotic receipt, the aOR for COVID-19 associated with PCV13 receipt was 0.65 (0.50-0.84), suggesting differences in effect estimates shortly after antibiotic administration were not attributable to fundamental differences between individuals who received and did not receive antibiotics.

We indicate negative-control (i.e., non-causal) associations of zoster vaccine receipt with COVID-19 outcomes, used to correct for residual confounding, in **Table S6**. In contrast to the lower observed incidence of COVID-19 among zoster vaccine recipients than non-recipients, 2019-2020 seasonal influenza vaccination was not independently associated with COVID-19 outcomes in the study cohort (**Table S7, Table S8**), illustrating that our findings were not sensitive to the choice of zoster vaccination as the negative control exposure.

DISCUSSION

Within a cohort of US adults aged ≥ 65 y, receipt of PCV13 was associated with lower incidence of any COVID-19 diagnosis, COVID-19 hospitalization, and fatal COVID-19 hospitalization after correction for multiple potential sources of confounding. These results are consistent with previous findings of interactions between pneumococci and respiratory viruses [5–9], contributing to PCV efficacy against virus-associated pneumonia among both children and older adults [26–29]. Although exploratory in nature as our study used an observational design, our findings support the hypothesis that interactions with pneumococci in the upper airway contribute to SARS-CoV-2 pathogenesis in three respects. First, similarity of PCV13 effect estimates across all three outcomes suggests that protection arose from the prevention of early stages of COVID-19 pathogenesis rather than prevention of severe

post-infection sequelae, which would have led to higher effectiveness estimates against hospitalization and death. This finding is externally consistent with previous studies suggesting a low burden of secondary pneumococcal pneumonia following SARS-CoV-2 infection, in contrast to experience with other viral pathogens such as influenza [16]. Second, receipt of PPSV23—which, unlike PCV13, would not be expected to prevent pneumococcal colonization—showed little association with protection against COVID-19 outcomes. Third, recent antibiotic receipt was a modifier of the PCV13 effect estimate. Individuals who recently received antibiotics, and who would therefore not be expected to carry pneumococci, did not experience PCV13-associated protection against subsequent COVID-19 diagnosis.

Improved understanding of viral-bacterial interactions during SARS-CoV-2 infection remains necessary to validate the mechanistic basis for our findings. However, our results are in agreement with other data suggesting the pathogenicity of respiratory viruses may be modified by bacterial carriage [36]. Evidence that upper respiratory commensal bacteria promote viral infection dates at least to 1987 [37], with studies demonstrating that enzymes expressed by bacteria (including pneumococci [38]) enhance influenza virus replication and pathogenicity. More recently, blunting of innate immune responses to influenza virus during pneumococcal colonization has been demonstrated in human challenge studies [12]. Such mechanisms of interaction may account for epidemiologic observations of enhanced virus acquisition and symptoms risk among carriers of pneumococci and other respiratory commensal pathogenic bacteria [9,13]. To substantiate our findings, it remains crucial to determine whether risk of SARS-CoV-2 infection and adverse clinical outcomes differ among individuals who carry or do not carry pneumococci. Several classes of observational studies would be helpful to test this hypothesis. Epidemiological studies should evaluate interactions between pneumococci and SARS-CoV-2 by comparing the prevalence and density of pneumococcal carriage among COVID-19 cases and uninfected controls, or among individuals with SARS-CoV-2 infection who experience or do not experience symptoms. Such studies will also provide an opportunity to assess whether interactions between pneumococci and SARS-CoV-2 are serotype-specific, as reported in prior laboratory and epidemiologic studies of pneumococcal interactions with influenza and RSV [36,39–41]. Studies assessing whether pre-existing or concomitant pneumococcal colonization is associated with differential immune responses to SARS-CoV-2 could further establish whether host-mediated mechanisms of interaction between pneumococci and influenza also apply contribute to the observed association in our study [12].

Counter-arguments to the above hypothesis merit consideration as well. First, prevalence of pneumococcal carriage among older adults has historically been reported at very low levels. However, recent studies using sensitive techniques of nasal wash or saliva sampling with molecular pneumococcal detection methods have found that low-density carriage is much more common than previously thought among adults [42]. Notably, roughly one third of serotypes carried by adults are PCV13 types in settings with well-established pediatric vaccination programs [43–45], indicating vaccination of young children reduces but does not eliminate PCV13-serotype circulation. While short-term effects on adult carriage were reported in a large-scale randomized trial of PCV13 in the Netherlands [46], use of traditional nasopharyngeal sampling methods was a limitation of this study. Challenge experiments have provided further demonstration of PCV13-conferred protection against vaccine-serotype carriage acquisition among adults [12,22]. Second, among children, reductions in vaccine-serotype carriage are largely offset by increases in carriage of non-vaccine serotypes following PCV13 receipt. Whether this is also true of adult carriage is uncertain, in particular because adults may be exposed to a lower force of infection than children. Previous studies have reported reduced risk of virus-associated symptoms among children receiving PCVs despite serotype replacement in carriage [13,26,28,29], further suggesting non-vaccine serotypes may differ in their propensity for viral interaction. It remains unclear to what extent our findings could be explained by

lower pneumococcal carriage prevalence among adults receiving PCV13, if serotype replacement is minimal, or by serotype-specific virus interaction, if serotype replacement is substantial.

Our study has limitations. Laboratory confirmation was recorded for 81.2% of COVID-19 diagnoses; clinically-confirmed cases may have been tested by other providers. While non-randomized PCV13 exposure was a limitation, use of inverse propensity weighting helped to mitigate confounding in our analyses. Moreover, accounting for other adult vaccine exposures reduces risk that unmeasured confounding pathways—such as an association between vaccine access and compliance with social distancing—would explain our findings. As PCV13 receipt was more common among older individuals and those with high-risk conditions, bias would be expected to suggest greater risk among PCV13 recipients than non-recipients, contrary to our results. Our findings that PPSV23 did not prevent COVID-19 outcomes, and that PCV13 effects were not evident following antibiotic receipt, are consistent with the hypothesis that protection was mediated by prevention of pneumococcal carriage. Hospitalizations and death within the specified time window surrounding COVID-19 diagnosis may have owed to other causes. Such outcome misclassification, however, would be expected to obscure vaccine effects against COVID-19 hospitalization and fatality endpoints, biasing outcomes in favor of the null hypothesis. We assumed associations of COVID-19 endpoints with zoster vaccination provided an indicator of bias due to residual confounding. While we are unaware of data demonstrating non-specific effects of zoster vaccination against COVID-19, this possibility merits fuller investigation. Exposure to children and living in group housing are key risks factor for pneumococcal carriage among older adults that were not assessed in this study, although our analyses did address other risk factors including age group, smoking status, receipt of antibiotics and PCV13, and comorbid chronic diseases [47–49]. Finally, periods immediately surrounding the timing of antibiotic receipt may have been associated with differential risk of SARS-CoV-2 infection for adults in the study, although we are unaware of a reason why this would differentially modify risk among PCV13 recipients and non-recipients.

Despite longstanding pediatric PCV13 use, circulation of vaccine-targeted serotypes continues to occur in the United States, accounting for 28% of invasive pneumococcal disease cases in 2015-16 [50]. Reductions in childhood vaccine coverage associated with the COVID-19 pandemic may accentuate the relative importance of vaccine-targeted serotypes in pneumococcal carriage and in diseases for which pneumococci play a role in the causal pathway. Efforts to understand bacterial accentuation of viral infection or pathogenicity are needed, both in the context of the COVID-19 pandemic and for other important viral pathogens such as RSV and influenza.

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Figure 1. We illustrate the distribution of demographic and clinical attributes of individuals within the cohort by receipt (blue) or non-receipt (red) of PCV13. Plots in the left-hand column illustrate cohort characteristics, as observed; individuals receiving PCV13 tended to be older, had higher prevalence of comorbid conditions, and higher rates of healthcare utilization in the preceding year than individuals who did not receive PCV13. Plots in the right-hand column illustrate cohort characteristics after reweighting of individuals according to the inverse of their propensity of PCV13 receipt (as estimated in logistic regression models defining PCV13 receipt as the outcome variable and factors listed in the **Figure** as covariates);[32] this approach reduced confounding based on differences in measured risk factors between PCV13 recipients and non-recipients. We indicate sample characteristics in **Table S1** (with reweighted estimates in **Table S3**) and indicate differences in incidence of COVID-19 endpoints associated with each risk factor in **Table S2**.

Figure 2. We present estimates of the effectiveness of any PCV13 receipt, and receipt of PCV13 and PPSV23 (relative to no pneumococcal vaccination) according to 2015 guidelines of the Advisory Committee on Immunization Practices,[30] against outcomes of **A**) any COVID-19 diagnosis; **B**) COVID-19 hospitalization; and **C**) fatal COVID-19 hospitalization. We obtain estimates using doubly robust Cox proportional hazards models applying inverse weights for the propensity of PCV13 receipt, correcting for the association of each endpoint with prior zoster vaccination as a negative control exposure. Lines (and numbers in parentheses) signify 95% confidence intervals around maximum likelihood estimates (points).

Figure 3. We present estimates of the effectiveness of any PCV13 receipt for risk periods defined by recent antibiotic exposure: no antibiotics received in the preceding 30 days (top), antibiotics received within the preceding 1-30 days (middle), and antibiotics received >60 days previously (and not within the ensuing 60 days; bottom). We obtain estimates using doubly robust Cox proportional hazards models applying inverse weights for the propensity of PCV13 receipt, correcting for the association of COVID-19 diagnosis with prior zoster vaccination as a negative control exposure. Lines (and numbers in parentheses) signify 95% confidence intervals around maximum likelihood estimates (points).

FOOTNOTES PAGE

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Conflicts of interest

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Table 1: Descriptive attributes of the study cohort.

Attribute	Number of individuals (%)	
	PCV13 received per ACIP guidelines ¹ N=451,068	PCV13 not received N=80,600
Age on 1 March 2020		
	65-69 years	96,812 (21.5)
	70-74 years	42,898 (53.2)
	75-79 years	18,982 (23.6)
	80-84 years	9,482 (11.8)
	85-89 years	5,031 (6.2)
	≥90 years	2,569 (3.2)
Sex		
	Female	21,638 (2.0)
	Male	44,662 (55.4)
Race and ethnicity		
	White, non-Hispanic	35,938 (44.6)
	Black, non-Hispanic	222,100 (49.2)
	Asian or Pacific Islander, non-Hispanic	39,483 (8.8)
	Hispanic (any race)	56,331 (12.5)
	Other, mixed, or unknown race	122,540 (27.2)
Tobacco smoking		
	Current smoker	10,614 (2.4)
	Former smoker	14,080 (3.1)
	Never smoker	156,177 (34.6)
	Unknown	261,103 (57.9)
Body mass index		
	<18.5 (underweight)	19,708 (4.4)
	18.5-24.9 (normal weight)	8,253 (1.8)
	25.0-29.9 (overweight)	129,518 (28.7)
	30.0-39.9 (obese)	162,049 (35.9)
	≥40.0 (morbidly obese)	114,448 (25.4)
	Unknown	13,786 (3.1)
Comorbid conditions		
	Myocardial infarction	23,014 (5.1)
	Congestive heart failure	22,589 (5.0)
	Peripheral vascular disease	35,647 (7.9)
	Cerebrovascular disease	181,756 (40.3)
	Hypertension	31,028 (6.9)
	Hyperlipidemia	291,730 (64.7)
	Diabetes	317,967 (70.5)
	Chronic obstructive pulmonary disease	127,981 (28.4)
	Renal disease	80,680 (17.9)
	Moderate or severe liver disease	91,274 (20.2)
	Malignancy	1,682 (0.4)
	Metastatic solid tumor	26,844 (6.0)
	Asthma	8,184 (1.8)
	Obstructive sleep apnea	45,130 (10.0)
	HIV/AIDS	31,469 (7.0)
	Organ transplant	174 (<0.1)
	Other immunocompromising condition	556 (0.1)
	Hypothyroidism	22,059 (4.9)
	Rheumatologic/inflammatory condition	66,156 (14.7)
	Depression	11,579 (2.6)
Zoster vaccination ²		
	Any zoster vaccine dose received	66,030 (14.6)
Influenza vaccination		
	Vaccinated in 2019-20 season	224,317 (49.7)
PPSV23 vaccination		
	PPSV23 ever received	9,625 (11.9)
Prior year outpatient visits		
	0-9	390,322 (86.5)
	10-19	20,617 (25.6)
	20-29	13,743 (17.1)
	30-39	404,730 (89.7)
	≥40	13,743 (17.1)
Prior year inpatient visits		
	0	98,005 (21.7)
	1	137,344 (30.4)
	2	89,508 (19.8)
	≥3	51,813 (11.5)
Prior year emergency		
	0	74,398 (16.5)
	1	43,533 (54.0)
	2	19,172 (23.8)
	≥3	8,839 (11.0)
		4,241 (5.3)
		4,815 (6.0)
		77,679 (96.4)
		2,391 (3.0)
		361 (0.4)
		169 (0.2)

department visits	0	339,108 (75.2)	69,482 (86.2)
	1	70,527 (15.6)	7,954 (9.9)
	2	22,915 (5.1)	1,945 (2.4)
	≥3	18,518 (4.1)	1,219 (1.5)
Census tract median household income	\$0-\$29,999	5,460 (1.2)	1,173 (1.5)
	\$30,000-\$49,999	67,197 (14.9)	12,848 (15.9)
	\$50,000-\$69,999	100,439 (22.3)	18,458 (22.9)
	\$70,000-\$89,999	105,416 (23.4)	18,570 (23.0)
	\$90,000-\$109,999	77,593 (17.2)	13,705 (17.0)
	\$110,000-\$129,999	52,644 (11.7)	8,538 (10.6)
	≥\$130,000	41,645 (9.2)	6,965 (8.6)
	Unknown	674 (0.1)	343 (0.4)
Receipt of antibiotics	At any point during study period	2,064 (0.5)	232 (0.3)
	≥1d before COVID-19, if ever diagnosed	1,406 (0.3)	169 (0.2)

ACIP: Advisory Committee on Immunization Practices; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine.

Values in the table show the number of individuals with each risk factor who belonged at any point during follow-up to the exposure groups. We indicate incidence of COVID-19 outcomes associated with each attribute in **Table S1**. We present reweighted estimates in **Fig. 1** and **Table S2**.

¹Receipt of PCV13 ≥1 year before PPSV23 for immunocompetent individuals, or ≥8 weeks before PPSV23 for immunocompromised individuals, or (for individuals who had previously received PPSV23) receipt of PCV13 ≥1 year after the most recent PPSV23 dose.

²Receipt of ≥1 dose of live or recombinant zoster vaccine.

Figure 1

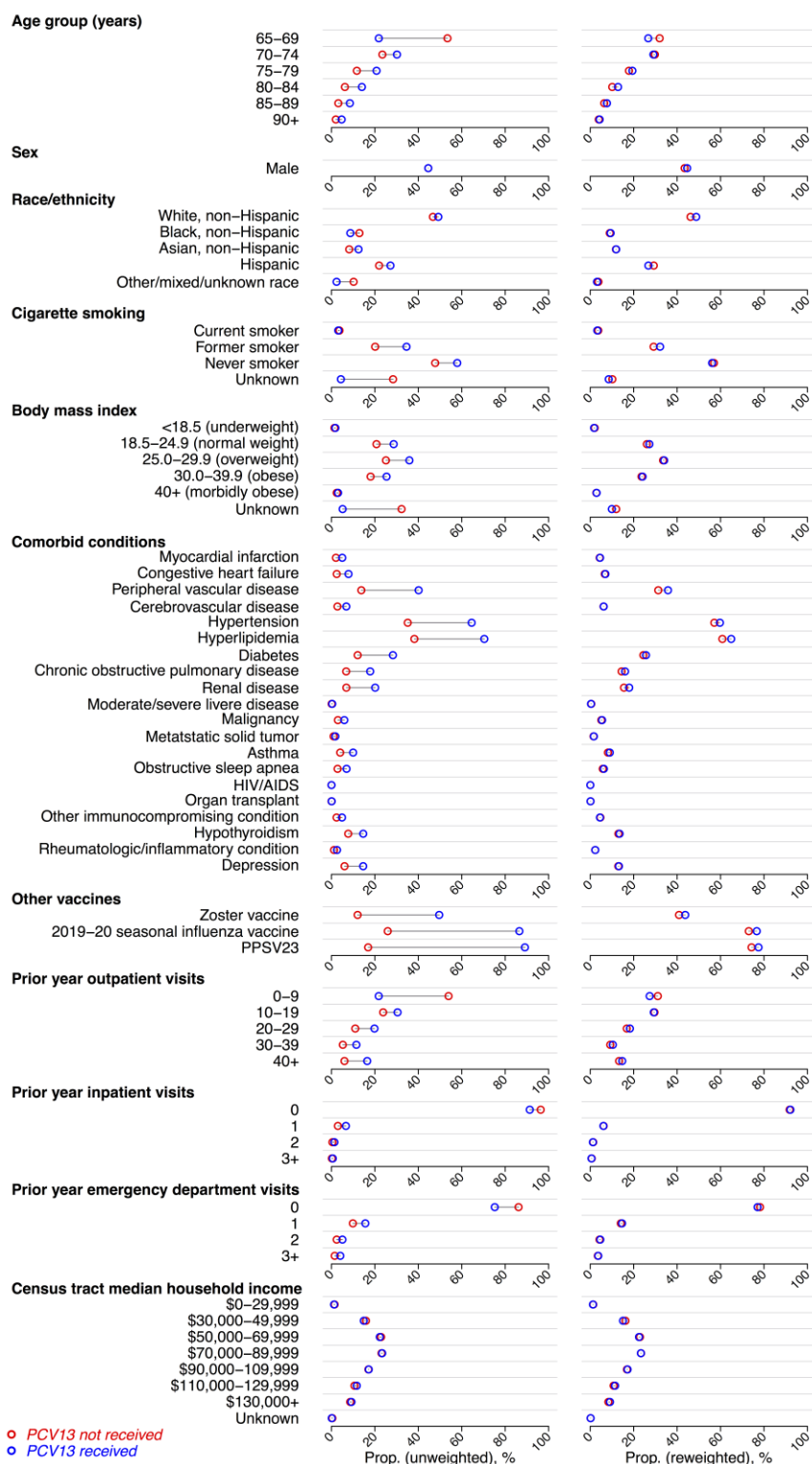
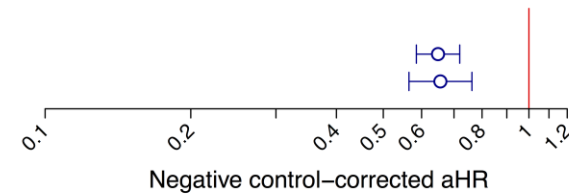


Figure 2

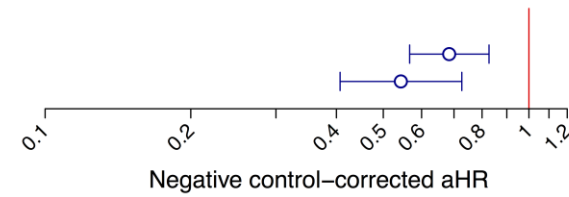
A) Any COVID-19 diagnosis

	aHR (95% CI)
PCV13	0.65 (0.59, 0.72)
PCV13 and PPSV23	0.66 (0.56, 0.76)



B) COVID-19 hospitalization

	aHR (95% CI)
PCV13	0.68 (0.57, 0.83)
PCV13 and PPSV23	0.54 (0.41, 0.73)



C) Fatal COVID-19 hospitalization

	aHR (95% CI)
PCV13	0.68 (0.49, 0.95)
PCV13 and PPSV23	0.57 (0.33, 0.97)

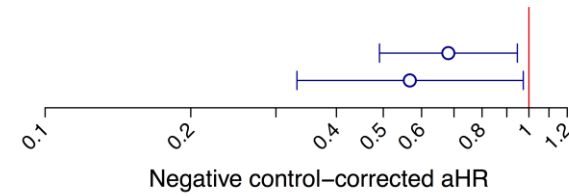


Figure 3

	<u>aOR (95% CI)</u>
No antibiotics in study period	0.62 (0.54, 0.70)
Antibiotics 1–30 days previously	1.12 (0.87, 1.41)
Antibiotics 31–60 days previously	1.14 (0.71, 1.75)
Antibiotics 61–90 days previously	1.06 (0.66, 1.60)
Antibiotics >90 days previously	0.65 (0.50, 0.84)

