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Association of Pneumococcal Conjugate Vaccine Use With Hospitalized Pneumonia in Medicare Beneficiaries 65 Years or Older With and Without Medical Conditions, 2014 to 2017

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IMPORTANCE The association of 13-valent pneumococcal conjugate vaccine (PCV13) use with pneumonia hospitalization in older adults, especially those with underlying medical conditions, is not well described.

OBJECTIVE To evaluate the association of PCV13 use with pneumonia, non–health care–associated (non-HA) pneumonia, and lobar pneumonia (LP) hospitalization among US Medicare beneficiaries 65 years or older.

DESIGN, SETTING, AND PARTICIPANTS This cohort study with time-varying exposure assignment analyzed claims data from US Medicare beneficiaries 65 years or older enrolled in Parts A/B with a residence in the 50 US states or the District of Columbia by September 1, 2014. New Medicare Parts A/B beneficiaries within 6 months after their 65th birthday were continuously included in the cohort after September 1, 2014, and followed through December 31, 2017. Participants were censored if they died, changed enrollment status, or developed a study outcome. Most of the analyses were conducted from 2018 to 2019, and additional analyses were performed from 2021 to 2022.

EXPOSURES Use of PCV13 vaccination 14 days or more before pneumonia hospitalization.

MAIN OUTCOMES AND MEASURES Discrete-time survival models were used to estimate the incidence rate ratio (IRR) and number of pneumonia hospitalizations averted through PCV13 use. The adjusted IRR for the association of PCV13 vaccination with pneumonia hospitalization was used to estimate vaccine effectiveness (VE).

RESULTS At the end of follow-up (December 2017), 24 121 625 beneficiaries (13 593 975 women [56.4%]; 418 005 [1.7%] Asian, 1 750 807 [4.8%] Black, 338 044 [1.4%] Hispanic, 111 508 [0.5%] Native American, and 20 700 948 [85.8%] White individuals) were in the cohort; 4 936 185 (20.5%) had received PCV13 only, and 10 646 220 (79.5%) had not received any pneumococcal vaccines. More than half of the beneficiaries in the cohort were younger than 75 years, White, and had either immunocompromising or chronic medical conditions. Coverage with PCV13 increased from 0.8% (September 2014) to 41.5% (December 2017). The VE for PCV13 was estimated at 6.7% (95% CI, 5.9%-7.5%) for pneumonia, 4.7% (95% CI, 3.9%-5.6%) for non-HA pneumonia, and 5.8% (95% CI, 2.6%-8.9%) for LP. From September 2014 through December 2017, an estimated 35 127 pneumonia (95% CI, 33 011-37 270), 24 643 non-HA pneumonia (95% CI, 22 761-26 552), and 1294 LP (95% CI, 797-1819) hospitalizations were averted through PCV13 use.

CONCLUSIONS AND RELEVANCE The study results suggest that PCV13 use was associated with reduced pneumonia hospitalization among Medicare beneficiaries 65 years or older, many of whom had underlying medical conditions. Increased PCV13 coverage and use of recently approved higher-valent pneumococcal conjugate vaccines may avert additional pneumonia hospitalizations in adults.

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Supplemental content

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Introducing the pneumococcal conjugate vaccine for use among children has been associated with significantly reduced incidence rates of pneumococcal disease, not only among children who were directly targeted for vaccination, but also among older children and adults who were not targeted for vaccination, by preventing the transmission of vaccine-type pneumococci.[1] Three years after the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced among US children in 2013, the incidence of invasive pneumococcal disease, defined as identification of pneumococcus from a normally sterile site, declined by 58% to 72% among US adults.[2] In 2014, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of PCV13 in series with a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) for all US adults 65 years or older.[3] This recommendation was supported by findings from a large randomized clinical trial in adults 65 years or older in the Netherlands (CAPITA trial) that reported that PCV13 provides protection not only against invasive pneumococcal disease (75% vaccine effectiveness [VE]), but also against vaccine-type noninvasive pneumococcal pneumonia, defined as pneumonia with no identification of pneumococcus from a normally sterile site (45% VE).[4] In adults, pneumococcal pneumonia contributes the largest proportion of pneumococcal disease burden. The reported efficacy against the first episode of all-cause community-acquired pneumonia from this trial was 5.1% (95% CI, −5.1 to 14.2). However, continued PCV13 use among children was expected to be associated with further reduced remaining burden of adult pneumococcal disease that was associated with serotypes contained in PCV13 and decrease the effectiveness of PCV13 in preventing pneumococcal disease in adults. Routine PPSV23 use for US adults 65 years or older had been recommended since 1984, but data on PPSV23 effectiveness against noninvasive pneumococcal pneumonia were considered to be inconsistent.[3]

The CAPITA trial did not enroll adults with immunocompromising conditions (ICs), and data on PCV13 VE in this group remain limited, even though the proportion of adults with ICs increases with age.[4,5] Additionally, determining the true burden of vaccine-type noninvasive pneumonia is challenging because of a lack of a standardized laboratory method to identify pneumococcal serotypes in noninvasive disease.[6] In US adults 65 years or older, the estimated incidence of hospitalized community-acquired pneumonia (CAP) has ranged from 847 to 3500 per 100 000 persons.[7] One study reported that approximately 5% of hospitalized all-cause CAP was due to PCV13-type pneumococci based on a urinary antigen detection assay used in research settings; however, this was still considered an underestimate of the true burden of PCV13-type disease.[8] In October 2021, ACIP recommended the use of 15-valent pneumococcal conjugate vaccine (PCV15) followed by a dose of PPSV23, or the 20-valent pneumococcal conjugate vaccine (PCV20) alone for all adults 65 years or older and adults aged 19 to 64 years with certain underlying medical conditions and other risk factors.[9] Use of PCV15 and PCV20 was licensed based on safety and immunogenicity data alone; understanding PCV13 VE against all-cause pneumonia could help inform the expected public health effect from use of PCV15 or PCV20 in adults. We evaluated the association between PCV13 and pneumonia hospitalization and estimated the number of pneumonia cases averted from PCV13 use among US Medicare Part A/B beneficiaries 65 years or older with and without underlying medical conditions during the first 4 years of routine PCV13 use in this population.

Key Points

Question Is 13-valent pneumococcal conjugate vaccine (PCV13) use associated with reduced pneumonia hospitalization in US adults 65 years or older who have a high prevalence of underlying medical conditions?

Findings In this cohort study of more than 24 million Medicare beneficiaries 65 years or older with and without underlying medical conditions across 50 US states and the District of Columbia, beneficiaries who received PCV13 had a 6.7% lower risk of pneumonia hospitalization overall, including 5.8% to 7.5% lower risk in adults with underlying medical conditions, compared with beneficiaries who did not receive any pneumococcal vaccines.

Meaning The study results suggest that new PCV13 use may be associated with reduced risk of pneumonia hospitalizations among US adults 65 years or older, including among those with underlying medical conditions.

Methods

This cohort study with time-varying exposure assignment was reviewed by the US Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy; therefore, institutional review board approval and informed consent were waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[10]

Study Cohort and Data Source

Primary data sources were the Medicare claims and enrollment databases. Information on demographic characteristics and deaths were derived from the enrollment database. Information on pneumococcal and influenza vaccinations, health covariates, and outcomes was derived from Medicare Part A (inpatient), Part B (outpatient and community settings), and Part D (prescription drug) claims. Medicare beneficiaries who met the following 3 criteria on September 1, 2014, were included in the initial cohort: (1) 65 years or older; (2) residence in the 50 US states or the District of Columbia; and (3) enrollment in Medicare Parts A and B (without enrollment in Medicare Part C). After September 1, 2014, new beneficiaries who turned age 65 years and enrolled in Medicare Parts A and B were eligible to enter the cohort, as long as enrollment in Part B started within 6 months after their 65th birthday. Beneficiaries were followed until the end of study period (December 31, 2017) or until they were censored from the cohort due to (1) death; (2) moving out of the US, or when residence became unknown; (3) changing enrollment status; or (4) experiencing any of the study outcomes. Once censored, a beneficiary could not re-enter the cohort during a later month. Each beneficiary contributed 1 to a maximum of 40 continuous person-months to

the data set (median, 17-21 person-months, depending on vaccination status and outcome). The exposure status and beneficiary characteristics (eg, age, sex, self-reported race and ethnicity, underlying health status, and state of residence) were updated monthly.

Outcomes

Outcomes of interest were identified based on inpatient claims. As the primary pneumonia outcome, we used the case definition created by Griffin et al,[11] in which hospitalized pneumonia was defined as a primary discharge diagnosis of pneumonia or a primary discharge diagnosis of meningitis, septicemia, empyema, or acute respiratory failure with a pneumonia diagnosis in any secondary position. We also evaluated 2 secondary outcomes that may be more specific for pneumococcal pneumonia. First, to exclude health care-associated (HA) pneumonia, we evaluated non-HA pneumonia, which was defined as a subset of hospitalized pneumonia cases in patients not admitted to a hospital or skilled nursing facility fewer than 30 days before pneumonia hospitalization. Second, we defined lobar pneumonia (LP) as an inpatient hospital claim with lobar or pneumococcal pneumonia in any discharge diagnosis position. *International Classification of Diseases, Ninth Revision, Clinical Modification* and *ICD-10-CM* codes used to identify these outcomes are included in eTable 1 in the Supplement.

Covariates

We categorized beneficiaries into 4 mutually exclusive risk groups defined based on ACIP recommendations[12]: (1) those with ICs, (2) those with chronic medical conditions (CMCs), (3) those with ICs and CMCs (IC+CMC), and (4) low-risk individuals. Patients included in the IC group had asplenia, chronic kidney failure, generalized cancer, HIV infection, Hodgkin disease, iatrogenic immunosuppression, immunodeficiency, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, sickle-cell anemia, or solid organ transplant, but no CMC. Patients included in the CMC group had alcoholism, chronic heart/liver/lung disease, cigarette smoking, or diabetes, but no IC. Patients included in the IC+CMC group had at least 1 IC and 1 CMC. Lastly, adults with no ICs or CMCs were classified as low risk. Influenza vaccination status was assigned using all available claims data starting August 1, 2014. Beneficiaries were considered to be vaccinated against influenza if (1) they received an influenza vaccine during August to April, when the vaccine was available for that flu season, and (2) the vaccine was administered 14 days or more before the first day of hospitalization for those who developed an outcome of interest or 14 days or more before the first day of the month for those without an outcome of interest. All covariates and their definitions are listed in eTable 2 in the Supplement.

Exposure

Each month of the study follow-up, the cohort population was assigned 1 of the 4 mutually exclusive pneumococcal vaccination categories (PCV13 only, PPSV23 only, both vaccines, no vaccine) using claims data starting January 1, 2008, when vaccination status of the beneficiaries was captured consistently in the database. Vaccine doses were considered to be valid if they were administered 14 days or more before hospitalization for 1 of the pneumonia outcomes, or if they were administered 14 days or more before the first day of the month if the beneficiary did not develop an outcome that month (eMethods in the Supplement).

Statistical Analysis

We performed a descriptive analysis comparing those who received PCV13 only and those who did not receive any pneumococcal vaccines. We estimated the association between pneumococcal vaccination status and each outcome of interest (hospitalized pneumonia, non-HA pneumonia, LP) using a discrete-time logistic regression model fit with generalized estimating equations (GEEs). The model assessed each outcome for each observation month and was adjusted for all covariates identified as confounders based on potential for association with the outcome and exposure of interest (including Charlson Comorbidity score, as previously described[13,14]) (eTable 2 in the Supplement). We applied an exchangeable structure in the GEE model to account for within-participant correlation across months.

PCV13 VE

The VE was calculated as 1 minus the adjusted incidence risk ratio (IRR). The IRR was estimated as follows: (1) we calculated the marginal predictive probability (MPP) of pneumonia hospitalization using all eligible participants by plugging in the estimated parameters obtained in the GEE model described previously, assuming everyone had PCV13 only; (2) we recalculated the MPP but changed the vaccination status to no vaccine for all participants while keeping other covariate information intact; and (3) we calculated IRR as the ratio between MPPs calculated in steps 1 and 2. Steps 1 to 3 were repeated assuming everyone received PCV13 and PPSV23 in step 1, and in step 2, adults were assumed to have received PPSV23 only.

Pneumonia Hospitalizations Averted From PCV13 Use

To estimate the number of hospitalizations averted from PCV13 vaccination, we first estimated the expected number of pneumonia hospitalizations in the absence of PCV13 (with or without PPSV23) using the following formulas:

- (Observed pneumonia hospitalizations in those who received PCV13 only) divided by $IRR_{(PCV13\ only)/(no\ vaccine)}$
- (Observed pneumonia hospitalizations in those who received PCV13 and PPSV23) divided by $IRR_{(PCV13\ and\ PPSV23)/(PPSV23\ only)}$
- Subsequently, the number of hospitalizations averted was equal to the $expected_{(number\ of\ hospitalizations)}$ minus the $observed_{(number\ of\ hospitalizations)}$

We applied this procedure within strata defined by age group and risk group and then summed the stratum-specific number of hospitalizations averted. We estimated IRRs as previously described, except that to calculate the number of hospitalizations averted, we used a subset of the entire cohort that had a specific vaccination status (PCV13 only, PCV13 and

PPSV23) for the estimation steps previously described in steps 1 and 2.

We fit all models using Stata, version MP 15 (StataCorp). We used a customized Stata plug-in[15] to estimate the counterfactual marginal probabilities and risk ratios. The variances of the marginal probabilities and risk ratios were calculated via the delta method.

Results

In September 2014, 26.6 million beneficiaries were eligible for inclusion in the study cohort. At the end of the follow-up period in December 2017, 24.1 million beneficiaries remained in the cohort, representing approximately 49% of the US population 65 years or older. More than half were younger than 75 years, White, and had either ICs or CMCs (**Table 1**; eTable 3 in the Supplement). The proportion of those who received PCV13 with or without PPSV23 increased from 0.8% in September 2014 to 41.6% in December 2017. The median and mean months of follow-up by vaccination status are provided in eTable 4 in the Supplement. Among those who remained in the cohort in December 2017, compared with beneficiaries who did not receive any pneumococcal vaccination, those who received PCV13 only were more likely to be older (75 years or older, 51.3% vs 37.8%), have comorbidities (Charlson Comorbidity Index score ≥3, 29.4% vs 21.8%), have a higher frequency of outpatient visits (≥5 outpatient visits during the preceding year, 33.7% vs 22.8%) and hospital admissions (≥2 inpatient visits, 4.5% vs 3.5%), and have received an influenza vaccine (65.1% vs 23.2%) (Table 1). Among those who received PCV13 only, crude incidence rates per 100 000 person-months for hospitalized pneumonia, non-HA pneumonia, and LP were 131, 106, and 7, respectively; among those who did not receive any pneumococcal vaccination, the incidence rates were 137, 107, and 5, respectively (**Figure**). Hospitalized pneumonia, non-HA pneumonia, and LP incidence were higher among older age groups. Similarly, the incidence was higher among those with CMCs and ICs compared with those who did not have CMCs, ICs, or neither (Figure).

The VE for PCV13 only against hospitalized pneumonia was 6.7% (95% CI, 5.9%-7.5%) (Figure). The VE was lower among older age groups, although confidence intervals overlapped: 7.4% (95% CI, 6.2%-8.5%) in adults aged 65 to 74 years compared with 5.7% (95% CI, 4.6%-6.8%) in adults aged 85 years or older. The VE was higher for those at low risk compared with those with either ICs or CMCs: 15.1% (95% CI, 12.2%-18.1%) in adults at low risk compared with 5.8% (95% CI, 5.0%-6.7%) in adults with ICs and CMCs. Overall, PCV13 VE against non-HA pneumonia (4.7%; 95% CI, 3.9%-5.6%) and LP (5.8%; 95% CI, 2.6%-8.9%) were comparable with VE against hospitalized pneumonia; however, estimated PCV13 VE against LP in those with IC only (18.1%; 95% CI, 5.0%-31.2%) and in low-risk groups (34.6%; 95% CI, 24.6%-44.5%) was higher than estimated VE against hospitalized pneumonia and non-HA pneumonia in these subgroups. The VE comparing those who received PCV13 and PPSV23 vs those who received only PPSV23 against the outcomes of hospitalized pneumonia, non-HA pneumonia, and LP were generally smaller (3.8%, 1.8%, and 4.2%, respectively) (eTable 5 in the Supplement). Person-months of follow-up were smaller for this comparison compared with those who received PCV13 only and those who did not receive any pneumococcal vaccination, in which was associated with wider confidence intervals in some stratified analyses.

During the study period, 300 531 pneumonia, 241 279 non-HA pneumonia, and 16 810 LP hospitalizations were identified among beneficiaries who received any PCV13 vaccination (ie, with or without PPSV23), and PCV13 is estimated to have averted 35 127 pneumonia (95% CI, 33 011-37 270), 24 643 non-HA pneumonia (95% CI, 22 761-26 552), and 1294 LP (95% CI, 797-1819) hospitalizations overall (**Table 2**). The largest number of cases averted were among adults with ICs and CMCs, who had the highest pneumonia incidence (Table 2; Figure).

Discussion

In this cohort study of Medicare beneficiaries 65 years or older, we estimated a PCV13 VE of 6.7% against pneumonia in hospitalized patients. Vaccine effectiveness was lower among older age groups compared with younger age groups, as well as in adults with underlying medical conditions compared with adults without underlying medical conditions. The overall estimate was similar to the PCV13 efficacy of 5.1% (95% CI, −5.1% to 14.2%) against a first episode of community-acquired pneumonia that was reported in the CAPITA trial.[4] Adults with ICs were excluded from the CAPITA trial on enrollment, and to our knowledge, there are limited studies on PCV13 effectiveness in adults with ICs.[16] The results of the present study suggested that PCV13 was also effective against hospitalized pneumonia in adults with ICs.

Previous observational studies that used administrative data to estimate PCV13 VE against all-cause pneumonia reported variable results; this may be due to differences in the populations that were included. A population-based cohort study of more than 2 million adults 50 years or older in Spain did not demonstrate a protective effect of PCV13 against pneumococcal pneumonia or all-cause pneumonia, although the characteristics of those who received PCV13 were significantly different compared with those who did not receive PCV13, including a significantly higher proportion of adults with ICs among the PCV13 recipients compared with nonrecipients (42.1% vs 8.6%).[17] Effectiveness of PCV13 against all-cause pneumonia was demonstrated in other studies that were performed more recently. An insurance-based retrospective cohort study of adults 60 years or older in Germany showed lower 3-year cumulative incidence of all-cause pneumonia among those who received PCV13, with a VE of 12% (statistical significance was not reported).[18] A cohort study of more than 40 000 members of Kaiser Permanente Southern California 65 years or older reported a PCV13 VE of 8.8% (95% CI, −0.2% to 17.0%) against a first episode of pneumonia.[19] Another cohort study of more than 192 000 adults who were members of Kaiser Permanente Northern California reported a PCV13 VE of 10.0% (95% CI, 2.4%-17.0%) against hospitalized pneumonia.[20] These studies included a lower proportion of

Table 1. Characteristics of the Study Cohort at Start (September 2014) and End (December 2017) of the Follow-up Period by Vaccination Status

Characteristic	No. (%)					
	September 2014			December 2017		
	Total (n = 26 598 266)	PCV13 only (n = 155 901)	No vaccine (n = 18 852 348)	Total (n = 24 121 625)	PCV13 only (n = 4 936 1850	No vaccine (n = 10 646 220)
Age group, y						
65-69	8 148 595 (30.6)	49 589 (31.8)	6 168 847 (32.7)	7 269 859 (30.1)	1 385 235 (28.1)	4 255 828 (40.0)
70-74	6 279 961 (23.6)	35 415 (22.7)	4 062 387 (21.5)	6 042 790 (25.1)	1 017 694 (20.6)	2 358 604 (22.2)
75-79	4 734 965 (17.8)	28 843 (18.5)	3 281 813 (17.4)	4 425 178 (18.3)	964 203 (19.5)	1 585 973 (14.9)
80-84	3 495 574 (13.1)	21 236 (13.6)	2 485 249 (13.2)	3 056 821 (12.7)	750 923 (15.2)	1 127 822 (10.6)
85-89	2 424 576 (9.1)	13 734 (8.8)	1 739 978 (9.2)	2 004 255 (8.3)	509 254 (10.3)	760 239 (7.1)
≥90	1 514 595 (5.7)	7084 (4.5)	1 114 074 (5.9)	1 322 722 (5.5)	308 876 (6.3)	557 754 (5.2)
Sex						
Female	15 051 870 (56.6)	89 826 (57.6)	10 497 304 (55.7)	13 593 975 (56.4)	2 912 521 (59.0)	5 645 713 (53.0)
Male	11 546 396 (43.4)	66 075 (42.4)	8 355 044 (44.3)	10 527 650 (43.6)	2 023 664 (41.0)	5 000 507 (47.0)
Race and ethnicity						
Asian	501 740 (1.9)	3265 (2.1)	337 106 (1.8)	418 005 (1.7)	68 145 (1.4)	191 757 (1.8)
Black	2 051 205 (7.7)	10 254 (6.6)	1 555 035 (8.2)	1 750 807 (7.3)	239 121 (4.8)	1 004 541 (9.4)
Hispanic	437 024 (1.6)	1691 (1.1)	329 709 (1.7)	338 044 (1.4)	38 519 (0.8)	202 928 (1.9)
Native American	119 143 (0.4)	517 (0.3)	87 126 (0.5)	111 508 (0.5)	21 221 (0.4)	54 274 (0.5)
White	22 793 258 (85.7)	136 202 (87.4)	16 033 581 (85.0)	20 700 948 (85.8)	4 411 563 (89.4)	8 810 668 (82.8)
Other	425 124 (1.6)	2267 (1.5)	299 857 (1.6)	402 108 (1.7)	73 146 (1.5)	186 517 (1.8)
Unknown race	270 772 (1.0)	1705 (1.1)	209 934 (1.1)	400 205 (1.7)	84 470 (1.7)	195 535 (1.8)
Risk status[a]						
Low risk	7 046 294 (26.5)	29 007 (18.6)	5 545 142 (29.4)	6 168 124 (25.6)	1 046 841 (21.2)	3 636 580 (34.2)
IC	1 473 002 (5.5)	9698 (6.2)	1 026 848 (5.4)	1 451 503 (6.0)	346 335 (7.0)	559 153 (5.3)
CMC	9 967 701 (37.5)	60 139 (38.6)	6 956 264 (36.9)	8 521 792 (35.3)	1 770 899 (35.9)	3 644 421 (34.2)
IC + CMC	8 111 269 (30.5)	57 057 (36.6)	5 324 094 (28.2)	7 980 206 (33.1)	1 772 110 (35.9)	2 806 066 (26.4)
Charlson Comorbidity Index score						
0	9 947 326 (37.4)	40 465 (26.0)	7 649 996 (40.6)	9 553 769 (39.6)	1 691 883 (34.3)	5 129 870 (48.2)
1-2	8 958 777 (33.7)	58 227 (37.3)	6 167 071 (32.7)	8 046 108 (33.4)	1 792 551 (36.3)	3 195 705 (30.0)
≥3	7 692 163 (28.9)	57 209 (36.7)	5 035 281 (26.7)	6 521 748 (27.0)	1 451 751 (29.4)	2 320 645 (21.8)
Outpatient visits[b]						
0	9 065 540 (34.1)	44 617 (28.6)	7 069 170 (37.5)	7 804 454 (32.4)	1 166 759 (23.6)	4 548 901 (42.7)
1-4	10 307 950 (38.8)	65 493 (42.0)	7 010 980 (37.2)	9 355 689 (38.8)	2 104 625 (42.6)	3 668 358 (34.5)
≥5	7 224 776 (27.2)	45 791 (29.4)	4 772 198 (25.3)	6 961 482 (28.9)	1 664 801 (33.7)	2 428 961 (22.8)
Hospital admissions[c]						
0	22 463 715 (84.5)	128 401 (82.4)	16 166 618 (85.8)	20 775 017 (86.1)	4 200 759 (85.1)	9 401 818 (88.3)
1	2 736 818 (10.3)	18 088 (11.6)	1 805 787 (9.6)	2 317 144 (9.6)	515 293 (10.4)	870 599 (8.2)
≥2	1 397 733 (5.3)	9412 (6.0)	879 943 (4.7)	1 029 464 (4.3)	220 133 (4.5)	373 803 (3.5)
Pneumococcal vaccine receipt						
PCV13 only	155 901 (0.6)	NA	NA	4 936 185 (20.5)	NA	NA
PPSV23 only	7 535 351 (28.3)			3 456 550 (14.3)		
PCV13 and PPSV23	54 666 (0.2)			5 082 670 (21.1)		
No vaccine	18 852 348 (70.9)			10 646 220 (44.1)		
Influenza vaccination receipt						
Yes	NA	280 667 (77.8)	7 063 832 (39.1)	NA	3 211 428 (65.1)	2 466 406 (23.2)
No	NA	80 045 (22.2)	11 009 187 (60.9)	NA	1 724 757 (34.9)	8 179 814 (76.8)

Abbreviations: CMCs, chronic medical conditions; ICs, immunocompromising conditions; NA, not applicable; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

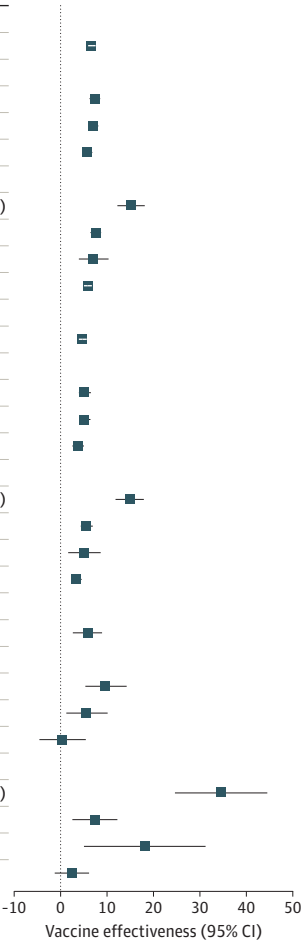
[a] Patients in the IC group had asplenia, chronic kidney failure, generalized cancer, HIV, Hodgkin disease, iatrogenic immunosuppression, immunodeficiency, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, sickle-cell anemia, or solid organ transplant but no CMCs; patients in the CMC group had alcoholism, chronic heart disease, chronic liver disease, chronic lung disease, cigarette smoking, or diabetes but no ICs; patients in the IC + CMC group had at least 1 IC and 1 CMC; and patients in the low-risk group had no ICs or CMCs.

[b] Defined as any Medicare institutional outpatient claims that did not include evidence of emergency department services (as represented by revenue center codes 450-459 or 981) during the year before the month of interest. Same-day claims were counted as 1 visit.

[c] Defined as any hospital stays in a Medicare inpatient setting during the year before the month of interest. If the discharge date of the previous stay overlapped with the admission date of the next stay, then the hospital stays were combined into 1 stay.

Figure. Incidence of Medicare Beneficiaries Hospitalized With Pneumonia and Adjusted Vaccine Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

	Beneficiaries who received PCV13 only			Beneficiaries who did not receive any pneumococcal vaccine			
Subgroup	Cases	Person-months of follow-up	Incidence per 100 000 person-months	Cases	Person-months of follow-up	Incidence per 100 000 person-months	Adjusted vaccine effectiveness, % (95% CI)
Hospitalized pneumonia							
Overall	162 579	123 687 910	131.4	755 467	554 062 976	136.4	6.7 (5.9 to 7.5)
By age group, y							
65-74	45 221	59 788 248	75.6	247 231	319 011 228	77.5	7.4 (6.2 to 8.5)
75-84	60 900	43 770 852	139.1	253 721	156 924 985	161.7	7.1 (6.0 to 8.1)
≥85	56 458	20 128 810	280.5	254 515	78 126 763	325.8	5.7 (4.6 to 6.8)
By risk group							
Low risk	4991	26 407 599	18.9	37 498	173 065 743	21.7	15.1 (12.2 to 18.1)
CMC	44 338	45 319 143	97.8	232 405	198 918 903	116.8	7.5 (6.4 to 8.7)
IC	4918	8 801 887	55.9	20 331	29 812 747	68.2	7.1 (3.9 to 10.3)
CMC and IC	108 332	43 159 281	251.0	465 233	152 265 583	305.5	5.8 (5.0 to 6.7)
Non-health care-associated pneumonia							
Overall	130 939	123 687 232	105.9	590 482	554 065 056	106.6	4.7 (3.9 to 5.6)
By age group, y							
65-74	36 431	59 788 021	60.9	193 340	319 011 951	60.6	5.2 (3.9 to 6.5)
75-84	48 869	43 770 597	111.6	196 659	156 925 711	125.3	5.2 (4.0 to 6.4)
≥85	45 639	20 128 614	226.7	200 483	78 127 394	256.6	3.8 (2.5 to 5.0)
By risk group							
Low risk	4625	26 407 727	17.5	35 000	173 067 287	20.2	14.9 (11.8 to 17.9)
CMC	38 183	45 319 337	84.3	194 817	198 921 394	97.9	5.6 (4.3 to 6.9)
IC	4271	8 801 964	48.5	17 081	29 813 214	57.3	5.1 (1.6 to 8.6)
CMC and IC	83 860	43 158 204	194.3	343 584	152 263 161	225.7	3.5 (2.5 to 4.5)
Lobar pneumonia							
Overall	9029	126 586 619	7.1	29 014	561 159 096	5.2	5.8 (2.6 to 8.9)
By age group, y							
65-74	2851	60 598 798	4.7	11 440	321 260 698	3.6	9.7 (5.3 to 14.2)
75-84	3375	44 890 327	7.5	9558	159 367 876	6.0	5.6 (1.2 to 10.1)
≥85	2803	21 097 494	13.3	8016	80 530 522	10.0	0.4 (-4.6 to 5.4)
By risk group							
Low risk	259	26 460 792	1.0	1824	173 203 099	1.1	34.6 (24.6 to 44.5)
CMC	2584	46 104 974	5.6	9587	200 980 248	4.8	7.4 (2.5 to 12.2)
IC	225	8 855 825	2.5	781	29 924 181	2.6	18.1 (5.0 to 31.2)
CMC and IC	5961	45 165 028	13.2	16 822	157 051 568	10.7	2.4 (-1.3 to 6.1)



Chronic medical conditions (CMCs) included beneficiaries who did not have immunocompromising conditions (ICs) and had any of the following conditions: alcoholism, chronic heart disease, chronic liver disease, chronic lung disease, cigarette smoking, or diabetes. Immunocompromising conditions included beneficiaries who did not have CMCs but had any of the following conditions: asplenia, chronic kidney failure, generalized cancer, HIV, Hodgkin disease, iatrogenic immunosuppression, immunodeficiencies, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, sickle cell anemia, or solid organ transplant.

adults with ICs (2%-7%)[18,19] or comorbidities[20] compared with the present study population, in which approximately 40% had ICs. According to the National Health Interview Survey, more than 60% of adults 65 years or older are estimated to have multiple chronic conditions (arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, current asthma, diabetes, hepatitis, hypertension, stroke, and weak or failing kidneys).[21] Therefore, our study cohort, which captured approximately half of the US population 65 years or older from all 50 US states and DC, is more likely to be representative of US adults with underlying conditions compared with those in previously published reports.

The VE estimates against all-cause pneumonia allow for estimation of the proportion of vaccine-preventable disease burden among those with all-cause pneumonia.[22] A prior study estimated that PCV13-type pneumococcal pneumonia comprised 5% of all-cause hospitalized CAP among adults 65 years or older, but the authors noted that this may still be an underestimate of the true burden of PCV13-type pneumococcal pneumonia.[8] Applying the PCV13 VE against hospitalized vaccine-type pneumonia of 45%, as reported in the CAPITA trial,[4] and assuming that PCV13-type pneumonia comprises 5% of hospitalized CAP cases, the estimated PCV13 VE against all-cause hospitalized CAP would be 2.3% (45% × 5%), which is lower than reported (5%-12%),[4,17-19] including estimates from the present study. These data suggest that there may be more pneumococcal pneumonia cases that are preventable by PCV13 than currently estimated.

Table 2. Estimated Number of Hospitalized Pneumonia, Non–Health Care–Associated Pneumonia, and Lobar Pneumonia Cases Averted Among Medicare Beneficiaries Through Receipt of Any PCV13 Vaccination, September 2014 to December 2017

Population	Cases averted (95% CI)		
	Hospitalized pneumonia (n = 300 531)	Non–health care–associated pneumonia (n = 241 279)	Lobar pneumonia (n = 16 810)
Overall	35 127 (33 011 to 37 270)	24 643 (22 761 to 26 552)	1294 (797 to 1819)
Overall by risk group and age group[a]			
IC + CMC			
65-74 y	6926 (6084 to 7793)	4346 (3622 to 5093)	355 (150 to 586)
75-84 y	10 170 (9124 to 11 241)	6938 (6027 to 7873)	257 (16 to 525)
≥85 y	6741 (5825 to 7681)	4547 (3745 to 5372)	−42 (−232 to 172)
IC			
65-74 y	232 (55 to 431)	176 (14 to 361)	25 (−13 to 92)
75-84 y	304 (127 to 505)	254 (91 to 442)	57 (18 to 134)
≥85 y	284 (115 to 477)	226 (70 to 406)	24 (−7 to 88)
CMC			
65-74 y	3634 (3037 to 4253)	2796 (2245 to 3370)	326 (169 to 509)
75-84 y	3795 (3190 to 4424)	2971 (2414 to 3553)	186 (44 to 355)
≥85 y	1956 (1463 to 2471)	1408 (959 to 1880)	−27 (−125 to 94)
Low risk			
65-74 y	602 (392 to 835)	574 (371 to 801)	77 (26 to 159)
75-84 y	395 (226 to 588)	359 (197 to 544)	60 (22 to 136)
≥85 y	87 (−49 to 245)	47 (−81 to 195)	−5 (−27 to 43)

Abbreviations: CMCs, chronic medical conditions; ICs, immunocompromising conditions; PCV13, 13-valent pneumococcal conjugate vaccine.

[a] Patients in the IC group had asplenia, chronic kidney failure, generalized cancer, HIV, Hodgkin disease, iatrogenic immunosuppression, immunodeficiency, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, sickle-cell anemia, or solid organ transplant; patients in the CMC group had alcoholism, chronic heart disease, chronic liver disease, chronic lung disease, cigarette smoking, or diabetes; patients in the IC + CMC group had at least 1 IC and 1 CMC; and patients in the low-risk group had no ICs or CMCs.

Limitations

This study is subject to several limitations. First, given the transition from *International Classification of Diseases, Ninth Revision (ICD-9)* to *ICD-10* in October 2015, changes in coding practices might have been associated with the sensitivity or specificity of the outcome definitions during the study follow-up. A study using an *ICD-10-CM* algorithm derived from a validated *ICD-9-CM* algorithm showed that pneumonia cases identified in the *ICD-9-CM* era might be undercounted using *ICD-10-CM*, especially in adults with pneumonia associated with chronic obstructive pulmonary disease exacerbation.[23] However, the proportion of adults with CMC was similar among those who received PCV13 and those who did not receive any pneumococcal vaccine, so undercounting of pneumonia cases would have equally affected both groups. Additionally, we adjusted for year in the model and found similar estimates during the transition period. Second, we did not report the effectiveness of PPSV23 against pneumonia because of concerns of misclassification of PPSV23 vaccination status or potential for bias. An internal validation study comparing the vaccination status of beneficiaries who were captured by the CDC Active Bacterial Core surveillance and the Medicare claims data showed that PPSV23 status is more likely than PCV13 status to be missed in the Medicare claims data (eTable 6 in the Supplement). Coverage for PCV13 was very low among adults 65 years or older before September 2014,[24,25] whereas PPSV23 has been available longer, with stable vaccine coverage. Therefore, there might have been greater opportunities to miss PPSV23 doses vs PCV13 doses, including PPSV23 doses given before age 65 years.[25] Misclassification of PCV13 vaccination status, including missing doses given outside of Medicare Part A or B settings, remains a possibility, which could bias the VE estimates toward the null. Third, as with any observational study, and especially those using administrative data, residual confounding may be present due to unmeasured factors, despite adjustment made for several potential confounders.

Conclusions

The results of this cohort study of adults 65 years or older from across the US suggest that PCV13 was effective against hospitalized pneumonia during the period when indirect effects from PCV13 use in children have been associated with reduced PCV13-type disease burden in adults. Effectiveness was also observed among adults with ICs, for whom limited data on PCV13 effectiveness exist. Use of PCV15 and PCV20 in adults has the potential to further reduce pneumococcal disease incidence in US adults, given the broader serotype coverage and expanded eligibility for PCV receipt in adults younger than 65 years.[9]

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