MAJOR ARTICLE

Impact of the Pneumococcal Vaccine on Long-Term Morbidity and Mortality of Adults at High Risk for Pneumonia

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Background. There is debate surrounding the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV). We determined whether PPV was associated with reduced mortality or additional hospitalization for vaccine-preventable infections in patients previously hospitalized for community-acquired pneumonia (CAP).

Methods. From 2000 through 2002, adults with CAP admitted to the hospital in Edmonton, Alberta, Canada, were enrolled in a population-based cohort. Postdischarge outcomes during 5 years were ascertained using administrative databases. The primary outcome was the composite of all-cause mortality or additional hospitalization for vaccine-preventable infections. Proportional hazards analysis was used to determine the association between PPV use and outcomes.

Results. A total of 2950 patients were followed up for a median of 3.8 years. The mean patient age was 68 years; 52% were male. One-third ($n = 956$) received PPV: 667 (70%) before and 289 (30%) during hospitalization. After discharge, 1404 patients (48%) died, 504 (17%) were admitted with vaccine-preventable infections, and 1626 (55%) reached the composite outcome of death or infection. PPV was not associated with reduced risk of the composite outcome (589 [62%] vs 1037 [52%] for those unvaccinated; adjusted hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.79–1.04). Results were not altered in sensitivity analyses using propensity scores (adjusted HR, 0.91; 95% CI, 0.79–1.04), restricting the sample to patients 65 years or older (adjusted HR, 0.90; 95% CI, 0.77–1.04), or considering only those who received PPV at discharge (adjusted HR, 0.84; 95% CI, 0.71–1.00).

Conclusions. One-half of patients discharged from the hospital after pneumonia die or are subsequently hospitalized with a vaccine-preventable infection within 5 years. PPV was not associated with a reduced risk of death or hospitalization. Better pneumococcal vaccination strategies are urgently needed.

The clinical, societal, and economic burden of community-acquired pneumonia (CAP) is high. In North America, CAP affects 5–20 per 1000 adults per year [1, 2], with 20%–40% requiring hospitalization [3]. Hospitalization for CAP is associated with significant mortality; in-hospital mortality occurs in ~10% of admitted individuals [4, 5], and in those who survive hospitalization, more than 50% die within 5 years [6]. There is also substantial morbidity associated with CAP; for example, one-sixth of individuals who are hospitalized with CAP will be subsequently hospitalized with pneumonia within 5 years [6].

Efforts to prevent CAP are therefore critically important. Current guidelines recommend vaccinating individuals at increased risk of CAP with the 23-valent polysaccharide pneumococcal vaccine (PPV) [7] because the bacterium *Streptococcus pneumoniae* causes at least 30%–50% of all cases of CAP [8]. Although it is generally accepted that PPV prevents uncommon but serious episodes of invasive pneumococcal disease [9, 10], there is considerable debate regarding the clinical effectiveness of PPV for actually preventing pneumonia. Indeed, most observational studies and randomized, controlled trials suggest that PPV is relatively ineffective in preventing pneumonia [10, 11], although there is

Received 8 December 2009; accepted 20 March 2010; electronically published 26 May 2010.

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Clinical Infectious Diseases 2010; 51(1):15–22

1058-4838/2010/5101-0003$15.00
DOI: 10.1086/653114

limited evidence suggesting the vaccine might reduce in-hospital death or the need for intensive care unit admission in those who develop CAP [4, 12]. The impact of PPV on pneumococcal-related morbidity and mortality in high-risk patients, such as those who have survived an episode of pneumonia-related hospitalization, is even less well characterized. The only randomized, controlled trial evaluating the efficacy of PPV in preventing additional episodes of CAP was inconclusive, likely because it was underpowered [13, 14].

To our knowledge, no study has examined the effectiveness of PPV in individuals at perhaps the greatest risk of pneumonia: those patients who have survived an episode of hospitalization for CAP. Thus, we sought to determine whether PPV is associated with reduced mortality or additional admissions to the hospital for potentially vaccine-preventable infections in a cohort of individuals at high risk of CAP during 5 years of follow-up. We hypothesized that PPV should improve the morbidity and mortality of patients at high risk of developing pneumococcal-related infections, such as pneumonia, meningitis, or severe sepsis.

METHODS

Patients and setting. As previously described in detail [6], from 2000 through 2002, a total of 3415 CAP patients older than 17 years admitted to all 6 hospitals in the greater Edmonton metropolitan region in Alberta, Canada, were enrolled in a clinical registry and treated according to a validated clinical pathway [15, 16]. The region is one of the largest integrated health systems in Canada, serving >1 million people. CAP was defined as the presence of ⩾2 signs or symptoms of CAP (cough [productive or nonproductive], pleuritic chest pain, shortness of breath, temperature >38°C, and crackles or bronchial breathing on auscultation), plus radiographic evidence as determined by the treating physician. Patients were excluded if they had tuberculosis or cystic fibrosis, were immunocompromised, or were pregnant. Written consent was obtained, and the Health Research Ethics Board of the University of Alberta approved the study.

Six trained research nurses used standardized abstraction forms to prospectively collect the data, which included age, sex, comorbidities, number of prescription medications, smoking status, pneumococcal and influenza vaccination history, premorbid functional status, nursing home residence, the presence of advanced directive, and the pneumonia severity index (PSI) score [17]. Up-to-date influenza vaccination was defined as present if appropriate for the given year. Once discharged from the hospital, all patients were followed up for up to 5 years through linkage to provincial administrative databases. These databases maintain current demographic, vital statistics, and health services data for all residents of the province. All hospitalizations are identified and classified according to *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM)* (Canadian version) [5, 6]. Diagnostic coding is conducted by trained health records personnel, and accuracy is routinely validated through provincial and federal agencies [5, 6].

Exposure. The exposure of interest was PPV status, collected by trained research nurses who did not have knowledge of study outcomes or our hypotheses. In Alberta, PPV is widely available for a small copayment to any patient and free for older patients (age, ⩾65 years), those with chronic disease, nursing home residents, or those who could not afford to pay out-of-pocket.

We considered exposed patients as those who received PPV before initial CAP hospitalization and at the time of discharge. Vaccination history before the index hospitalization was ascertained through multiple methods, including patient and proxy interview, medical record review, contact with primary care physicians, and records from the regional office of community health [4, 6]. Although a history of vaccination was obtained, the information collected simply recorded whether the patient had received PPV, not necessarily when the vaccine had been administered. PPV at the time of discharge from the hospital was prospectively documented by research nurses who followed up hospitalized patients. We were unable to ascertain information on PPVs provided after hospital discharge.

In September 2002, the province implemented a second PPV strategy using the universal 7-valent pneumococcal conjugate vaccine [18]. Only children aged <2 years qualified for this new vaccine; adults were not eligible and did not receive this vaccine.

Outcomes. Our primary outcome of interest was a composite of all-cause mortality or additional hospitalization for relevant infections (sepsis, meningitis, pneumonia, sinusitis, otitis media, and mastoiditis) potentially prevented by PPV [10]. Collectively, we considered these infections to be potentially preventable by PPV, although we did not have any data regarding microbial cause after the patient was discharged from the hospital. That said, *S. pneumoniae* is the most common organism to cause serious pneumonia and meningitis and is consistently among the top 3 causes of community-acquired bacteremia [19, 20]. We expected the proportion of nonpneumococcal infections to be balanced between vaccinated and nonvaccinated patients because PPV should not affect the incidence of nonpneumococcal infections.

Hereafter, we collectively refer to this set of infections requiring hospitalization as part of our composite outcome. Secondary outcomes analyzed separately were all-cause mortality, infection requiring additional hospitalization, and additional hospitalization for pneumonia. For additional hospitalizations, the most responsible discharge diagnosis was used to classify

the event according to *ICD-9-CM* or *ICD-10-CM* discharge codes (Appendix A, Table A1). These codes have been previously used and validated in administrative database studies to evaluate infection-related outcomes [6, 21].

Statistical analysis. Baseline characteristics were compared using the χ^2 test or *t* test, as appropriate. The independent association between PPV status and outcomes was estimated using multivariable Cox proportional hazards models that controlled for age, sex, comorbidities, number of medications, smoking status, premorbid functional status, nursing home residence, pneumonia severity at presentation (using the PSI), the presence of an advanced directive, and up-to-date influenza vaccination. All patients were followed up after hospital discharge until the occurrence of the event of interest, death, coverage termination, or 31 March 2006 (the end of the study). Assessment of log-log survivor plots and interaction terms with time indicated no violations of the proportional hazards assumptions.

The robustness of the main results was evaluated through 3 prespecified sensitivity analyses. First, a propensity score (based on 37 demographic and clinical characteristics present before initial CAP hospitalization admission and available on request) was created using standard techniques to predict the likelihood of an individual patient receiving PPV [22]. The propensity score was entered into the models using a quintile approach, with higher quintiles predicting greater likelihood of vaccine receipt [22]. Second, we evaluated potential differences in the association between PPV use and outcomes in those aged ⩾65 years. Those older than 65 years are at a substantially higher risk for infections, including pneumonia, than the younger patients and are universally eligible for PPV under current guidelines [7]; thus, this group should be less prone to various selection biases. Last, because it is possible that the effectiveness of the PPV may be modified by the proximity of vaccine receipt, we stratified patients according to those who received PPV before initial CAP hospitalization and PPV received at the time of discharge in previously unvaccinated patients; both the short-term outcomes (ie, 1 year) and longer-term outcomes were assessed. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute).

RESULTS

Patient characteristics. Of the 3081 patients who survived their initial CAP hospitalization, we excluded 131 (3%) whom we could not link to the administrative databases, leaving a study sample of 2950 patients. The mean age (± standard deviation) was 68 ± 18 years, 52% were male, 17% were admitted from a nursing home, and most (59%) had severe pneumonia (PSI risk class IV and V) on their index admission for CAP. One-third ($n = 956$) of the cohort received PPV: 667 (70%) before the index hospitalization and 289 (30%) during the index hospitalization. Patients who were vaccinated were older, more likely to have comorbidities, and had lower functional status than nonvaccinated individuals (Table 1).

Primary outcome: composite of death or vaccine-preventable infections. During a median of 3.8 years, 1404 patients (48%) died and 504 (17%) were readmitted to the hospital with a potentially vaccine-preventable infection. By the end of the study, the primary composite outcome of all-cause mortality or additional hospitalization for infections occurred in 1626 patients (55%). In unadjusted analysis, PPV seemed to increase the risk of the primary outcome (589 [62%] for those

Table 1. Characteristics of 2950 Patients Discharged from the Hospital after an Episode of Community-Acquired Pneumonia, Stratified by Pneumococcal Polysaccharide Vaccine Use

Characteristic	Vaccinated patients (n = 956)	Nonvaccinated patients (n = 1994)	*P*
Age, mean years ± SD	75 ± 14	64 ± 19	<.001
Age group, years			
<55	81 (8)	620 (31)	<.001
55–64	87 (9)	283 (14)	<.001
65–74	225 (24)	363 (18)	<.001
75–84	328 (34)	481 (24)	<.001
⩾85	235 (25)	247 (12)	<.001
Male sex	484 (51)	1051 (53)	.29
Nursing home resident	235 (25)	273 (14)	<.001
Advanced directive	134 (14)	144 (7)	<.001
Previous comorbidities			
Cardiovascular disease	489 (51)	703 (35)	<.001
Prior cancer	145 (15)	254 (13)	.07
Chronic kidney disease	120 (13)	263 (13)	.63
Neuropsychiatric history	191 (20)	380 (19)	.55
Receipt of ⩾5 medications	189 (20)	266 (13)	<.001
Influenza vaccine	664 (69)	137 (7)	<.001
Smoking status			<.001
Nonsmoker	403 (42)	824 (41)	
Former smoker	370 (39)	591 (30)	
Current smoker	183 (19)	579 (29)	
Premorbid functional status			.004
Independent mobility	845 (88)	1838 (92)	
Wheelchair or prosthesis	73 (8)	103 (5)	
Bedridden	38 (4)	53 (3)	
Pneumonia severity index			<.001
Class I or II	100 (10)	512 (26)	
Class III	198 (21)	398 (20)	
Class IV	450 (47)	744 (37)	
Class V	208 (22)	340 (17)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. SD, standard deviation.

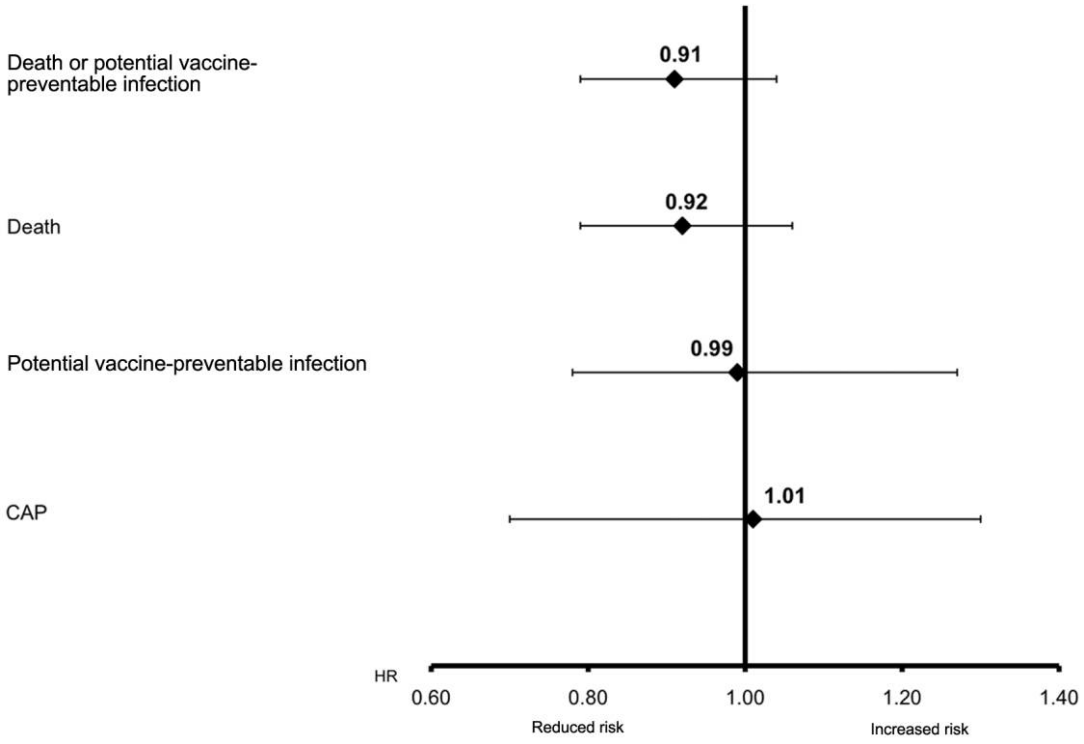

Figure 1. Adjusted hazard ratios (HRs) representing the risk of morbidity and mortality in pneumococcal vaccinated individuals compared with nonvaccinated individuals during 5 years of follow-up. CAP, community-acquired pneumonia.

vaccinated vs. 1037 [52%] for those not vaccinated; unadjusted hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.14–1.40; $P<.001$). However, after adjusting for potential confounders, we in fact found no significant association between PPV use and the composite outcome of death or infection (adjusted HR, 0.91; 95% CI, 0.79–1.04; $P = .17$) compared with those who had not been vaccinated (Figure 1).

Secondary end points: death and vaccine-preventable infections. By the end of the study, compared with the 528 deaths (55%) in the PPV group, there were 876 deaths (44%) in individuals not vaccinated ($P<.001$). Again, after controlling for numerous potential confounders, we found no statistically significant association between PPV use and all-cause mortality (adjusted HR, 0.92; 95% CI, 0.79–1.06; $P = .24$) (Figure 1).

Table 2. Unadjusted and Adjusted Hazard Ratios (HRs) for Death, Potentially Vaccine-Preventable Infections, and Pneumonia, According to Pneumococcal Vaccination Status ($n = 2950$)

	No. (%) of patients		HR (95% CI)		
Outcome	Vaccinated ($n = 956$)	Not vaccinated ($n = 1994$)	Unadjusted	Adjusted	P[a]
Death or infection	589 (62)	1037 (52)	1.27 (1.14–1.40)	0.91 (0.79–1.04)	.17
Death	528 (55)	876 (44)	1.36 (1.22–1.51)	0.92 (0.79–1.06)	.24
Infection	176 (18)	328 (16)	1.18 (0.99–1.42)	0.99 (0.78–1.27)	.95
CAP	164 (17)	308 (15)	1.16 (0.96–1.40)	1.01 (0.79–1.30)	.93

NOTE. CAP, community-acquired pneumonia; CI, confidence interval.

[a] P value for adjusted HR.

Table 3. Unadjusted and Adjusted Hazard Ratios (HRs) for Death, Potentially Vaccine-Preventable Infection, and Pneumonia When Pneumococcal Vaccination Is Stratified, According to Timing of Pneumococcal Vaccination

	Vaccination status before hospitalization				Vaccination status before discharge			
	No. (%) of patients				No. (%) of patients			
Outcome	Vaccinated (n = 667)	Not vaccinated (n = 1994)	Adjusted HR (95% CI)	P	Vaccinated (n = 289)	Not vaccinated (n = 1994)	Adjusted HR (95% CI)	P
Death or infection	442 (66)	1037 (52)	0.98 (0.83–1.16)	.82	147 (51)	1037 (52)	0.84 (0.71–1.00)	.06
Death	395 (59)	876 (44)	0.93 (0.77–1.11)	.42	133 (46)	876 (44)	0.91 (0.75–1.09)	.30
Infection	130 (19)	328 (16)	1.12 (0.82–1.53)	.49	46 (16)	328 (16)	0.89 (0.65–1.22)	.46
CAP	124 (19)	308 (15)	1.24 (0.89–1.72)	.20	40 (14)	308 (15)	0.83 (0.60–1.17)	.29

NOTE. Pneumococcal vaccination before the index pneumonia hospitalization versus pneumococcal vaccination received at the time of hospital discharge in previously unvaccinated patients. CAP, community-acquired pneumonia; CI, confidence interval.

Similarly, PPV was not associated with a reduced risk of additional hospitalization for potentially vaccine-preventable infections (176 [18%] vs 328 [16%] for those not vaccinated; adjusted HR, 0.99; 95% CI, 0.78–1.27; $P = .95$) (Figure 1). Among patients subsequently hospitalized for potentially vaccine-preventable infections, CAP was the most common reason (94%). Additional analyses evaluating PPV use and additional hospitalization for CAP also failed to show any significant association (164 [17%] vs 308 [15%] for those not vaccinated; adjusted HR, 1.01; 95% CI, 0.79–1.30; $P = .93$) (Table 2 and Figure 1).

Sensitivity analysis. First, propensity score–adjusted analyses (c statistic, 0.71) of the primary composite outcome yielded nearly identical results to our primary study analyses (adjusted HR, 0.91; 95% CI, 0.79–1.04; $P = .16$). Second, in analysis restricted to only those aged ⩾65 years, the results were again nearly identical to the overall cohort ($n = 1879$; adjusted HR, 0.90; 95% CI, 0.77–1.04; $P = .16$) for PPV compared with those not vaccinated. Third, analyses in which we evaluated those who received the vaccine at the time of hospital discharge ($n = 289$) also demonstrated no statistically significant association between PPV use and the composite outcome (147 [51%] vs 1037 [52%] for those not vaccinated; adjusted HR, 0.84; 95% CI, 0.71–1.00; $P = .06$) (Table 3). Similarly, there was no association between PPV and the composite outcome 1 year after vaccination in the group who received the vaccine at the time of hospital discharge (66 [23%] vs 523 [26%] for those not vaccinated; adjusted HR, 0.81; 95% CI, 0.62–1.05; $P = .11$).

DISCUSSION

In this population-based cohort of patients at high risk of recurrent pneumonia, more than half died or were subsequently hospitalized with a potentially vaccine-preventable infection within 5 years of follow-up. Importantly, we found that the use of PPV did not significantly reduce the risk of death or subsequent hospitalization for potentially vaccine-preventable infections. Our findings do not necessarily support the conventional wisdom of the broader scientific community in which it has been generally accepted that the use of PPV will prevent serious pneumococcal infection [7, 10]. In fact, our results are more consistent with a recent methodologically rigorous meta-analysis of 22 trials in 101,507 patients who reported no benefit of PPV in preventing death, pneumonia, or even invasive pneumococcal disease [11].

Our results also support the only randomized, controlled trial that has evaluated the efficacy of PPV in preventing recurrent CAP in high-risk patients [14]. In this study of 691 immunocompetent adults aged 50–85 years with a history of CAP who required hospitalization (a population almost identical to the patients we analyzed), 17% of patients had recurrent CAP during the 2.5 years of follow-up, and two-thirds required admission to the hospital. The relative risk of CAP in the placebo group was 0.83 (95% CI, 0.58–1.12; $P = .31$) when compared with the vaccinated group, and vaccination did not protect against either bacteremic pneumococcal pneumonia or death [14]. However, this study has been widely considered "inconclusive" because it was relatively underpowered because of the unexpectedly low event rates in the placebo arm and an overestimated effect size [13, 14]. For example, the authors assumed that 48% of all patients in the placebo group would develop pneumonia; however, only 16% were diagnosed as having pneumonia [23]. Regardless, the results of our larger study together with these trial results suggest that the use of PPV in patients who survive an episode of hospitalization for pneumonia may not be as beneficial as commonly assumed.

The inability of PPV to protect high-risk patients from recurrent pneumococcal events has several potential explanations. Most commonly cited is the failure of the vaccine to generate a sustained antibody response. In a randomized control trial

comparing the immune response to the pneumococcal polysaccharide vaccine to that of the protein-conjugate vaccine in adults who had recovered from pneumococcal pneumonia, antibody levels to all measured serotypes returned to baseline levels 6 months after receipt of the polysaccharide vaccine [24]. Although the antibody response to the protein-conjugate vaccine stayed modestly elevated at 6 months, the antibody levels approached baseline at 1 year, despite receiving a booster with the polysaccharide vaccine at 6 months [24].

In our study, the risk of death or of developing a potential vaccine-preventable infection after hospitalization with CAP was striking; these risks highlight the need for far more effective strategies to prevent pneumococcal disease. In our study, 17% of patients were subsequently hospitalized for potentially vaccine-preventable conditions, reenforcing prior findings that CAP is a risk factor for pneumococcal disease [22, 25]. Most recurrent infections (94%) were due to pneumonia, suggesting that this particular population is at sufficiently high risk of events that we should consider them explicitly for trials (and guidelines) related to prevention of pneumonia.

Despite the strengths of this large population-based cohort analysis, our nonrandomized study may still be subject to selection bias and confounding, particularly confounding by indication. Confounding by indication may explain why PPV use appeared to increase the risk of the composite outcome in unadjusted analysis. We did, however, use several methods to reduce this potential risk. First, we adjusted for a large number of potential confounders, including variables such as functional status and pneumonia severity. Second, we conducted a sensitivity analysis that included a propensity score to reduce the potential for selection bias, which had little impact on our results. Third, in an effort to further minimize selection bias, we also restricted the cohort to those aged $\geqslant$65 years, which minimally affected our results.

There are several additional limitations to consider. For example, for 70% of participants the exact timing of their PPV was relatively unknown. However, the expected duration of adequate protection from a single dose of PPV is considered at least 5–10 years [26]. Furthermore, the timing of vaccination was known for those who received it during hospitalization, and when we evaluated this subgroup, there was still no statistically significant decrease in risk in the primary composite outcome (adjusted HR, 0.84; 95% CI, 0.71–1.00). The point estimate for incident vaccination suggested somewhat greater protection than in our primary analysis (adjusted HR, 0.91), and this could potentially be interpreted as representing a dose-response relationship (statistical significance may not have been achieved simply because of the smaller sample size in this subgroup analysis). Alternately, this could simply represent chance and residual confounding. Another limitation of this study is that we considered a group of common infections to be potentially related to pneumococcal infection and thus vaccine preventable (we did not have any data related to actual microbial cause). Invariably, some of the subsequent admissions were not due to pneumococcal-specific conditions, potentially biasing the results toward the null. This is particularly true for CAP, where perhaps one-half of the cases are not secondary to *S. pneumoniae;* however, nonpneumococcal causes of CAP were likely balanced across PPV status. In addition, we considered only "serious" infections requiring hospitalizations (infections treated on a purely ambulatory basis were not included in our study). Our previous work with this cohort suggested the possibility that PPV might reduce the severity of illness without preventing it [4], and we could not capture this possibility in our data. Finally, the introduction of universal childhood vaccination with the 7-valent pneumococcal conjugate vaccine in 2002 may have altered the dynamics of so-called herd immunity [27–30]. Such a universal vaccination strategy would, however, affect both vaccinated and unvaccinated patients alike and so bias our results to the null. Although this is a potential, although unlikely, scenario because rates of invasive pneumococcal disease in adults have not decreased in Alberta since implementation [31], it would still not materially alter our major conclusion, namely, that in the current era, adults who have survived an episode of pneumonia are unlikely to obtain further protection from PPV beyond that afforded by universal childhood vaccination programs with the 7-valent conjugate vaccine.

One-half of patients discharged from the hospital after pneumonia die or are subsequently hospitalized with potentially preventable infections within 5 years. Results from our study suggest that the PPV does not, however, reduce the risk of death or hospitalization in high-risk patients previously hospitalized for CAP. What is most apparent from our work is that far better preventive efforts and PPV strategies are urgently needed in this high-risk group of patients.

Acknowledgments

Financial support. This study was funded by an establishment grant from the Alberta Heritage Foundation for Medical Research (AHFMR), grants-in-aid from Capital Health, and unrestricted grants from Abbott Canada, Pfizer Canada, and Janssen-Ortho Canada (all to T.J.M.). D.T.E. and S.R.M. receive salary support awards from the AHFMR. D.T.E. holds a New Investigator Award from the Canadian Institutes of Health Research. J.J. is funded by the McMaster University Infectious Diseases Bayer Health Care research fellowship.

Potential conflicts of interest. All authors: no conflicts.

APPENDIX A.

Table A1. ***International Classification of Diseases, Ninth Revision, Clinical Modification*** **(*ICD-9-CM*) and** ***International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM)*** **Discharge Codes Used to Determine Subsequent Hospitalization for Potential Vaccine-Preventable Pneumococcal Infections**

ICD-9-CM
Sepsis
038.0–038.9 (septicemia)
790.7 (bacteremia)
Meningitis: 320 (bacterial meningitis)
Pneumonia: 480.0–487.7 (pneumonia)
Sinusitis, otitis media, and mastoiditis
461.0–461.9 (acute sinusitis)
473.0–473.9 (chronic sinusitis)
381.0–381.4 (nonsuppurative otitis media)
382.0–382.9 (suppurative otitis media)
383.00–383.02 (acute mastoiditis)
383.1 (chronic mastoiditis)
ICD-10-CM
Sepsis
A40.0–A40.9 (streptococcal bacteremia)
A41.0–41.9 (other septicemia)
A49.9 (bacteremia NOS)
Meningitis
G00.0–G00.9 (bacterial meningitis not otherwise classified)
G01 (meningitis in bacterial disease classified elsewhere)
Pneumonia: J10–J18 (pneumonia)
Sinusitis or otitis media
J01.0–J01.9 (acute sinusitis)
J32.0–J32.8 (chronic sinusitis)
H65.0–H65.9 (nonsuppurative otitis media)
H66.0–H66.9 (suppurative otitis media)
H70.0–H70.9 (acute and chronic mastoiditis)

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