Prior Pneumococcal and Influenza Vaccinations and In-hospital Outcomes for Community-Acquired Pneumonia in Elderly Veterans

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BACKGROUND: Studies of adults hospitalized for community-acquired pneumonia (CAP) reported better outcomes associated with prior pneumococcal vaccination (PV), suggesting potential additional benefits of PV in hospitalized CAP patients. Influenza (flu) vaccination (FV) could independently/additively improve CAP outcomes in hospitalized patients.

OBJECTIVE: To examine the effect of prior PV and FV on in-hospital outcomes in elderly veterans hospitalized for CAP.

DESIGN: Retrospective cohort study.

SETTING AND PATIENTS: A total of 6,723 elderly veterans who were admitted to Veterans Affairs hospitals for CAP between October 1, 2002 and September 30, 2003.

INTERVENTION: PV in the 5 years and FV in the 1 year before admission.

MEASUREMENTS: The association of prior PV and/or FV with inpatient mortality and length of stay (LOS) (primary) and risk of any bacteremia and respiratory complications (secondary) were assessed using logistic regressions and generalized linear model, controlling for patient demographic and clinical characteristics.

RESULTS: Prior PV alone was not associated with shortened LOS, or reduced risk of inpatient mortality or respiratory complications. Lower risk of bacteremia was associated with prior PV (odds ratio: 0.66; 95% confidence interval [CI]: 0.48-0.90). After adjusting for patients’ characteristics, risk of inpatient mortality was not statistically significantly different across the vaccination groups, but having had both PV and FV before CAP admission was associated with a 10% reduction in LOS (95% CI: 0.86-0.95) compared to having had neither vaccinations.

CONCLUSION: Significant survival benefit and improved in-hospital outcomes may not be expected among CAP-hospitalized elderly patients with prior PV alone. However, having both PV and FV before CAP admission may reduce LOS. Journal of Hospital Medicine 2015;10:287–293. © 2015 Society of Hospital Medicine

Community-acquired pneumonia (CAP) ranks fifth among all causes of death and is the leading infectious cause of death among persons 65 years or older (hereafter “elderly”) in the US. Of the 1.1 million short-stay hospital discharges for pneumonia in 2010, 55% were for elderly patients. The most common cause of pneumonia in elderly patients leading to hospitalization is infection with Streptococcus pneumoniae. The 23-valent pneumococcal polysaccharide vaccine is recommended (PPSV23) for all elderly persons and has been shown to reduce incidences of invasive pneumococcal bacteremia among immunocompetent elderly individuals. However, its effect on more common manifestations of pneumococcal disease, such as pneumonia, remains controversial.

Several studies examined the association between prior PV and in-hospital outcomes for CAP in adult patients. Although the effect of pneumococcal vaccination (PV) on inpatient mortality was inconclusive, the studies found shortened length of stay (LOS), lower risk of respiratory failure and other complications, faster resolution of pneumonia symptoms, and fewer intensive care unit (ICU) admissions among those with prior PV. These findings suggest potential additional benefits of PV in hospitalized CAP patients.

This study examined prior PV on in-hospital outcomes in elderly veterans hospitalized for CAP. Because PV-vaccinated patients are also more likely to have received influenza (flu) vaccination (FV), which could independently or additively improve CAP outcomes in hospitalized elderly patients, we attempted to separate out the effect of FV by stratifying patients into 4 subgroups: PV alone, FV alone, both, or neither. The priori hypothesis was that PV improves in-hospital outcomes in elderly veterans hospitalized for CAP.

METHODS

Study Cohort

This study is a retrospective cohort study of all elderly veterans admitted to any Veterans Affairs (VA) hospitals for CAP during the fiscal year 2003 (FY’03)
(October 1, 2002 to September 30, 2003). Inpatient admissions for pneumonia were defined based on the principal diagnosis of nonviral pneumonia (International Classification of Diseases, 9th Revision [ICD-9], codes 481.xx–487.0x). The principal diagnosis was defined as the “condition determined to be the reason for the admission.” To select only CAP cases, we included admissions where patients were admitted either directly or through a VA outpatient clinic. We excluded transfers from another hospital, skilled nursing facilities, intermediate care facilities, or another healthcare facility. All patients were 65 years or older on the first day of the first admission in FY’03 (index admission) and had at least 1 outpatient visit to a VA facility each year during the 5 years prior to the index admission.

### Data Source

Data were drawn from Veterans Health Administration medical SAS datasets (SAS Institute Inc., Cary, NC). Demographic characteristics, inpatient and outpatient care utilization, and related medical diagnoses and procedure codes were extracted from national patient data extracts. Selected lab test results were drawn from the Decision Support System national extracts. This study was approved by institutional review boards at the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System.

### Prior Vaccination Status

Prior PV status was determined within 5 years prior to the index admission using: ICD-9 codes V06.6, V06.8, and V03.82, ICD-9 procedure code 99.55, or Current Procedure Terminology (CPT) codes 90732 and 90669.16 This 5-year time frame was chosen for 2 reasons: (1) the Centers for Disease Control and Prevention (CDC) recommends a second dose for elderly persons if the first dose was before age 65 years and more than 5 years have passed; (2) effectiveness of PV decreases over time in elderly persons, especially after 5 years since vaccination. Consistent with the CDC’s vaccination recommendation, patients with no record of prior PV were classified as “not vaccinated.” Prior FV status was determined in the year before the index admission using: ICD-9 code V04.8, ICD-9 procedure code 99.52, or CPT codes 90655–90660.16 Based on prior vaccinations, patients were classified into 4 groups: PV alone, FV alone, both, or neither.

### Outcome Variables

The primary outcomes were LOS and inpatient mortality. LOS, measured in days, was the duration of a hospital stay from admission to discharge, censored at death or transfer, the occurrence of which was ascertained via the discharge type field. Inpatient mortality was defined as death from any cause that occurred before discharge or transfer. The secondary outcomes were respiratory complications and any bacteremia identified via the diagnosis field of discharge records (see Supporting Information, Appendix Table A.1, in the online version of this article for a list of ICD-9 codes).

### Covariates

Covariates included patients’ demographic characteristics (age, gender, race, marital status) and Charlson Comorbidity Index scores. Comorbidities were...
identified during the year prior to the index admission using ICD-9 diagnoses codes based on Deyo et al. adaptation.\textsuperscript{19} Additionally, we included prior admission for CAP within the year preceding index admission, the number of outpatient visits (excluding mental health visits; ICD-9 codes 290.xx–319.xx) within the year preceding index admission, and acute respiratory conditions experienced within 30 days preceding index admission. Development of bacteremia and respiratory complications may increase LOS, and risk of mortality and were adjusted in the regression models for these outcomes.

Race

Missing race in VA administrative data is a well-documented problem.\textsuperscript{20} When available, missing race was imputed using information reported during a patient’s other inpatient stays available in our data as follows. We first imputed it using the most frequently reported race category. If unavailable, race was imputed by the most recently reported race category whenever available. This imputation algorithm reduced the proportion of patients with missing race information in our data to from 76% to 20%. Remaining patients with missing race information after imputation were analyzed as a separate category.

Pneumonia Severity Index Score

For patients with available lab values, we constructed an abbreviated pneumonia severity index (PSI) score adapted from Escobar et al.\textsuperscript{21} The original PSI score developed by the Pneumonia Patient Outcomes Research Team (PORT) is a validated clinical prediction tool that permits risk stratification with regard to the likelihood of adverse outcomes in CAP patients.\textsuperscript{22} Calculation of the PORT score requires information on patient’s physical examination and radiographic findings at admission,\textsuperscript{22} which was unavailable to us. Escobar et al. developed and validated an abbreviated form of the PORT score (PSI-E) in CAP patients that does not incorporate physical examination and radiographic findings.\textsuperscript{21} We calculated the PSI-E developed by Escobar et al. with the exception that arterial pH and PaO\textsubscript{2} test results were omitted because they were not available in the VA lab result files for the years we examined.

Data Analysis

Patients’ baseline characteristics (see Covariates) were compared across the 4 vaccination groups using the Kruskal-Wallis test for continuous variables and \(\chi^2\) test for categorical variables. Multiple regression analyses were used to assess the effect of prior PV and FV on inpatient outcomes during the index admission while adjusting for covariates. LOS was analyzed using a generalized linear model (GLM) with a negative binomial distribution and a logarithmic link function,\textsuperscript{23} and incidence rate ratios (IRRs) were reported. IRRs were calculated by taking the exponential of the estimated coefficients from the GLM and are interpretable as the relative change in mean LOS associated with a 1-unit change in a predictor variable. Risk of inpatient mortality, and development of respiratory complications or bacteremia, were analyzed using logistic regressions, and odds ratios (ORs) were reported. All regression models adjusted for covariates as described earlier. In addition, we conducted propensity score matching of PV-vaccinated (n = 2937) and unvaccinated (n = 2937) patients using the GMATCH algorithm.\textsuperscript{24} Propensity scores were estimated using a logistic regression to predict prior PV based on covariates listed earlier and prior FV status. GLM or logistic regression models were applied to the matched sample, with PV as the only predictor to generate IRRs or ORs, respectively. To account for the matched nature of the data, analyses were stratified by matched pairs.\textsuperscript{25}

Sensitivity Analysis

Many sensitivity analyses were performed that: (1) included patients admitted from nursing homes or other inpatient facilities (n = 7296); (2) excluded 0-night admissions (n = 6678); (3) varied the minimum number of VA outpatient visits to 2, 3, 4, or 5 visits each year in the previous 5 years; and (4) adjusted for the abbreviated PSI score only in patients with available information (n = 3689).

Flu Season

Defining prior FV status during the previous year may have included individuals who received FV for the previous flu season (eg, a patient was admitted in December 2003, but his or her last FV was in January 2003). We conducted 2 sensitivity analyses: (1) recoded patients who were last vaccinated in the previous flu season as unvaccinated and (2) restricted to index admissions occurred during the flu season (n = 5311). A flu season was defined as from September to May of the following year.

Time Since Last PV

To determine if the effectiveness of PV varies by the years elapsed since vaccination, among those with prior PV, we further classified prior PV as within 1 year (\(\leq 1\) year), 2 years (\(>1\) but \(\leq 2\) years), 3 years (\(>2\) but \(\leq 3\) years), 4 years (\(>3\) but \(\leq 4\) years), or 5 years (\(>4\) but \(\leq 5\) years) preceding the index admission. Two-thirds of patients received PV more than 2 years ago. We re-estimated the regression models with indicators for the number of years since the last PV (as defined above, PV within 1 year preceding index admission as the reference group).

All analyses were conducted using SAS software (SAS Institute, Inc.). A 2-sided \(P\) value of <0.05 was used to determine statistical significance.
TABLE 2. Adjusted Incident Rate Ratio or Odds Ratios for In-Hospital Outcomes Among Elderly Veterans Hospitalized for Community-Acquired Pneumonia in Fiscal Year 2003

<table>
<thead>
<tr>
<th>Length of Stay (Days)</th>
<th>Inpatient Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination status</td>
<td>IRR 95% CI</td>
</tr>
<tr>
<td>PV in previous 5 Years</td>
<td>1.02 0.97-1.07</td>
</tr>
<tr>
<td>FV last year</td>
<td>0.97 0.92-1.02</td>
</tr>
<tr>
<td>Both</td>
<td>0.96 0.88-0.95</td>
</tr>
<tr>
<td>Neither</td>
<td>Ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacteremia</th>
<th>Respiratory Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination status</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>PV in previous 5 Years</td>
<td>0.67 0.43-1.03</td>
</tr>
<tr>
<td>FV last year</td>
<td>0.99 0.69-1.42</td>
</tr>
<tr>
<td>Both</td>
<td>0.72 0.48-1.07</td>
</tr>
<tr>
<td>Neither</td>
<td>Ref</td>
</tr>
</tbody>
</table>

NOTE: All analyses have been adjusted for patient's age, gender, race, marital status, comorbidity index score, non–mental health outpatient visits, and CAP hospitalization in the previous year, and any acute respiratory conditions experienced in the previous 30 days. Analyses of length of stay and inpatient death was additionally adjusted for development of bacteremia and respiratory complications. Abbreviations: CI, confidence interval; FV, influenza vaccine; IRR, incidence rate ratio; OR, odds ratio; PV, pneumococcal vaccine.

RESULTS

In FY'03, 10,540 elderly VA patients had at least 1 inpatient admission for nonviral pneumonia. Among them, 3242 were excluded due to lack of VA outpatient visits in at least 1 of the 5 years prior to the index admission. Additionally, 574 patients were excluded because they were transferred from nursing homes or other inpatient facilities. The final sample consisted of 6723 elderly patients; among them, 1347(20%) had only PV, 1698(25%) had only FV, 1668 (25%) had both, and 2010 (30%) had neither prior to admission (see Supporting Information, Appendix 1, in the online version of this article). Table 1 compares patients' baseline characteristics and inpatient outcomes across vaccination groups. Patients with prior PV and FV had the shortest LOS and were least likely to experience respiratory complications or die during the inpatient stay. They also tended to be younger, had more frequent VA non–mental health outpatient visits in the previous year, and more medical comorbidities than other groups. Although these differences were statistically significant, the actual differences were small across the groups.

Table 2 presents findings from the adjusted regression analyses. After adjusting for covariates, having prior PV alone, FV alone, or both did not significantly affect the risk of inpatient mortality, compared to patients without records of either vaccination. However, having both prior PV and FV was associated with 10% reduction in LOS (IRR: 0.90; 95% confidence interval [CI]: 0.86-0.95; P < 0.0001). PV alone were associated with an increased risk of respiratory complications (OR: 1.23; 95% CI: 1.01-1.51; P = 0.0429) and trended toward a reduced risk of bacteremia (OR: 0.67; 95% CI: 0.43-1.03; P = 0.0673). After matching on patient characteristics including prior FV status, prior PV significantly lowered the risk of developing bacteremia (OR: 0.66; 95% CI: 0.48-0.90; P = 0.0088) but was not statistically significantly associated with the other outcomes (Table 3).

Findings from sensitivity analyses are included in the online appendices. Results were generally robust to various sensitivity analyses. However, in the analysis using the subset of patients with available lab information to define the PSI-E score, having prior FV alone was also found to be associated with reduced LOS (IRR: 0.92; 95% CI: 0.86-0.98; P < 0.05). The relationship between PV and in-patient outcomes did not vary by the time since vaccination, which is consistent with Jackson et al.¹¹

DISCUSSION

Consistent with previous findings,⁷⁻¹¹ elderly VA patients hospitalized for CAP were found to have an association between prior PV and reduced risk of bacteremia. However, no associations of prior PV alone with other in-hospital outcomes (LOS, inpatient mortality, or development of respiratory complications) were consistently found. Although, FV was not associated with a decrease in inpatient mortality in this study, having had both prior PV and FV (not necessarily given at the same time) was found to be associated with shortened LOS.

Our findings were inconsistent with 3 previous studies of prior PV on in-hospital outcomes among adult CAP patients. Those studies found shortened LOS,⁹,¹⁰ lower risk of respiratory failure and other complications,⁹ faster resolution of pneumonia symptoms,¹⁰ and fewer ICU admissions¹¹ among PV-vaccinated patients. Subanalysis of elderly patients performed in 2 of the 3 studies demonstrated a comparable survival benefit⁰ or protective effect on the composite outcome of ICU admission or death¹¹ among elderly patients.
compared to nonelderly patients. However, unlike our analysis, neither study excluded patients admitted from nursing home facilities. Our database, including patients admitted from nursing homes or other inpatient facilities, estimated a slightly more favorable effect of PV alone on inpatient mortality compared to our main analysis, although the estimate remained statistically insignificant (see Supporting Information, Appendix Table A.2, in the online version of this article).

In all 3 previous studies,9–11 an overwhelming majority of PV vaccinated patients also received FV (Mykietiuk10: 90.2% in PV vaccinated vs 39.9% in unvaccinated; Fisman9: 70% vs 2.2%; Johnstone11: 88% vs 9%), making it harder to distinguish the effect of having only PV from that of having both PV and FV. By defining a separate group for having both vaccinations, we found that having both PV and FV reduced LOS relative to PV alone or having had neither vaccinations. This suggests that PV alone may not be as effective in improving inpatient outcomes as shown in the previous studies, although limitations of our study prevented us from making a deterministic conclusion.

Our findings of no beneficial effects of PV alone on in-hospital outcomes for CAP other than bacteremia in the elderly VA patients are supported by previous findings of no effect of PV on all-cause pneumonia and all-cause mortality,4,7,8 decreasing antibody response to PV,26–28 and decreasing vaccine effectiveness over time in the elderly patients.5,18 Also, in a study of patients who were previously hospitalized for CAP, PV at discharge was not associated with prevention of subsequent hospitalization for CAP or death from all causes.29

PV alone was found to be associated with an increased risk of respiratory complications using an unmatched sample, and this finding appears to be robust to several variations in the sample selection process (see Supporting Information, Appendix, in the online version of this article). This paradoxical finding may be a result of residual confounding despite our efforts to control for baseline differences in patients’ characteristics. Using propensity matching where only those with similar observed characteristics, including comorbidity burden, were compared, the result was no longer statistically significant, although still trending in the same direction.

Up until recently, PPSV23 was the only pneumococcal vaccine recommended for all elderly individuals 65 years or older. Since September 2014, 13-valent pneumococcal conjugate vaccine (PCV13) has also been recommended for all elderly persons in the United States. PCV13 became available in 2010 and was initially recommended only for routine use in children ages 2 to 59 months. Early evidence indicated some herd effect in adults associated with the use of PCV13 in children; however, the effect was not statistically significant in all age groups.30 Because at the time of the study elderly patients were not vaccinated by other pneumococcal vaccines, and PCV13 was not yet in use in children, this strengthens the findings in terms of evaluating the efficacy of PPSV23, because the association was not attenuated by the herd effect of PCV13 in children or having both PPSV23 and PCV13 in the elderly population. The recent recommendation to vaccinate all elderly adults with PCV13 was based on findings from an industry-supported placebo-controlled trial of pneumococcal vaccine naïve patients.31 It is unknown whether PCV13 is more effective than PPSV23 in elderly adults and whether giving both would have any additional benefit in the elderly population. Future studies with population wide data on PCV13 use in elderly adults are needed.

Limitations

The major limitation for generalizing to all elderly population is that we studied elderly veterans who are almost exclusively males (98%). Previous studies have found males are at higher risk of acquiring CAP,32 to die from CAP,33 to be hospitalized for CAP,34 Vaccine effectiveness was also found to be higher in women than men.35 These suggest that our finding may not generalize to female patients admitted for CAP.

Another important limitation is that if PV and/or FV are truly effective in reducing hospitalizations for pneumonia, then those who were hospitalized despite prior vaccinations potentially may have more severe disease and/or be less responsive to the vaccines than unvaccinated patients. If so, this potential selection bias would bias our results toward null, and may partially explain our insignificant findings of PV alone on inpatient outcomes and the low vaccination rates observed in this study.

By focusing on elderly patients admitted for CAP, our cohort is more homogeneous than many previous studies, given that PV was recommended for all elderly persons at the time of the study, and all patients in our study had CAP. Nonetheless, unmeasured selection bias may exist and could partially explain the lack of estimated beneficial effect. In particular, the PSI score could not be calculated for the whole sample due to lack of data availability. In a subsample of patients with available information to calculate the abbreviated PSI score, we continued to find no significant beneficial effect of PV on outcomes other than bacteremia.

Other limitations included the possibility that prior vaccination status may have been misclassified because of (1) the use of diagnosis and procedure codes to identify prior vaccination status and (2) the lack of linked Medicare data to obtain the complete medical service utilization history of the elderly patients with dual coverage. To address the second issue, we selected patients with at least 1 VA outpatient visit
each year in the previous 5 years of the index admission, hoping to identify patients who were more likely to be VA service users. In sensitivity analyses, we further restricted our data to only patients with at least 2, 3, 4, or 5 visits per year, respectively, in the previous 5 years, and the results were generally robust to these variations (see Supporting Information, Appendix Tables A.2 and A.3, in the online version of this article). Although higher vaccination rates have been reported previously (PV: 81%–89%; FV: 79%–80%) for all elderly veterans in 2003, a lower vaccination rate may be expected among hospitalized patients for CAP, if PV and/or FV are effective in reducing hospitalizations for pneumonia as reported in previous studies.\(^{36,38,39}\) The lower PV rate observed among hospitalized elderly patients in this study is similar to another study of hospitalized elderly patients (50% prior PV rate),\(^ {40}\) and is consistent with the low prior PV rates reported in other studies of CAP-hospitalized patients, which ranges from 11% to 22%.\(^ {9-11}\)

Cases of CAP admissions were identified based on principal diagnosis of pneumonia. This increased precision in the identified cases but may have underidentified CAP admissions. ICD-9 code 481.0x (influenza with pneumonia) was also used for case identification, similar to other studies\(^ {4,9,12,41};\) excluding this code only excluded a few and did not affect the findings. Relying exclusively on diagnosis codes to detect pneumonia may also lead to misclassification due to coding errors. The gold standard to confirm pneumonia was with x-ray. However, such information was not available in our data.

We did not have bacteriiological data to study the pneumococcal-specific outcomes, such as pneumococcal pneumonia or pneumococcal bacteremia, which the pneumococcal vaccine is designed to protect against. Diagnosis codes for the pneumococcal-specific outcomes have low sensitivity,\(^ {42}\) and will significantly underidentify those cases. This limitation will bias our result toward null, which may partially explain the insignificant findings.

CONCLUSIONS

In this study of elderly VA patients admitted for CAP, we did not find significant effects of prior PV on LOS, inpatient mortality, or respiratory complications. Although given the limitations of this study, we could not conclusively say that PV has no effect on these outcomes. Nonetheless, our findings and the findings of no significant protective effect on overall mortality and decreasing antibody response to vaccines in the elderly from other studies, does raise the question of whether the previously reported beneficial effects on in-hospital outcomes for CAP in adults could be generalized to elderly patients. Larger electronic medical record databases with more complete information on patients’ vaccination history are needed to confirm these findings. Nonetheless, given its protective effect against invasive diseases,\(^ {7,8}\) the economic benefits shown,\(^ {43,44}\) and relative safety, PV should still be recommended for all elderly persons, especially very old and frail nursing home residents.\(^ {45}\) However, significant survival benefit and improved in-hospital outcomes for CAP as reported in previous studies may not be expected in elderly patients with prior PV, particularly if vaccination was given more than 5 years ago. This study also supports the recommendation of FV in the elderly population. Although, FV was not associated with a decrease in inpatient mortality in this study, having both PV and FV was found to be associated with shortened LOS.

Disclosures

This study was supported by the Medical Research Endowment Fund of University of Arkansas for Medical Sciences awarded to C. Li. The funding agency had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government. All coauthors have seen and agree with the contents of the manuscript; the submission (aside from abstracts) is not under review by any other publication. All coauthors have contributed to the concept and design of the study, analysis and interpretation of data, and/or development of the manuscript. The manuscript was reviewed and revised by the coauthors to ensure that important intellectual content has been included in the final published version. C. Li is a consultant to eMaxHealth Systems on unrelated studies. The authors disclose no conflicts of interest with this study.

References


