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Effectiveness of the Influenza Vaccine in Preventing Hospitalizations of Patients with Influenza Community-Acquired Pneumonia

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Abstract

Introduction: Influenza vaccination is the primary strategy for prevention of influenza infection. Influenza infection can vary from mild or even asymptomatic illness to severe community-acquired pneumonia (CAP). Although many national and international investigators and organizations report annual estimates of influenza vaccine effectiveness for prevention of influenza infection in the community, few studies report estimates for the prevention of hospitalizations due to influenza CAP, the most severe form of the infection. The objective of this study is to determine the effectiveness of the influenza vaccine for prevention of hospitalization in patients with influenza-associated CAP.

Methods: This was a test-negative study using data from the first two years of the University of Louisville Pneumonia Study, a prospective, observational study of all hospitalized patients with pneumonia in Louisville, Kentucky from 6/1/2014 – 5/31/2016. Univariate and multivariate logistic models were used to evaluate the association between vaccine status and influenza-associated/non-influenza-associated CAP hospitalization. Unadjusted and adjusted vaccine effectiveness estimates were calculated.

Results: A total of 1951 hospitalized patients with CAP were included in the analysis, and 831 (43%) reported having received the influenza vaccination for the influenza season by the time they were hospitalized. A total of 152 (8%) cases of influenza-CAP were confirmed in the study population, with 63 (8%) cases confirmed in vaccinated individuals. The unadjusted vaccine effectiveness was not significant, with a point estimate of 5% (95% CI: -33%, 32%). After adjusting for potential cofounders, vaccine effectiveness was also found to not be significant with a point estimate of 8% (95% CI: -30%, 35%).

Conclusions: In conclusion, we found that, over the 2014/2015 and 2015/2016 influenza seasons, influenza vaccine was not effective for prevention of hospitalization with CAP due to influenza. More effective vaccines are necessary to prevent the most serious forms of influenza.

Introduction

Influenza vaccination is the primary strategy for prevention of influenza infection, with the United States Advisory Committee on Immunization Practices (ACIP) recommending vaccination for individuals ages 6 months and older [1, 2]. Influenza infection can vary from mild or even asymptomatic illness to severe community-acquired pneumonia (CAP) [3]. Although most individuals recover from influenza infection, young children, older adults, and individuals with other chronic medical conditions may experience more serious illness and increased mortality [4-6].

Due to rapid mutations and other variations in influenza viruses year to year around the world, annual vaccination is necessary to provide immunologic protection from infection. Even in the absence of direct matches between the circulating influenza viruses and the antigens included in the vaccine, it is thought that a reduction in severity may be conferred through the vaccination [7-9]. Due to these factors, it is of medical and

public health interest to understand the effectiveness of the vaccine each season for prevention of various outcomes.

Vaccine effectiveness, not be confused with vaccine efficacy, is a clinical approach to determining how effective a vaccine is in reducing a disease in a real-life population. Although there are several study designs to assess vaccine effectiveness, retrospective case-control analysis of vaccination rates are commonly employed. Vaccine efficacy is primarily measured in prospective, randomized clinical trials. These trials involve selected populations that may not be generalizable to the population at large [10].

Although many national and international investigators and organizations report annual estimates of influenza vaccine effectiveness for prevention of influenza infection in the community, few studies report estimates for the prevention of hospitalizations due to influenza-CAP, the most severe form of the infection [11-13].

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The objective of this study is to determine the effectiveness of the influenza vaccine for prevention of hospitalization in patients with influenza-CAP and to determine how well the estimated effectiveness in the general population estimates the effectiveness in hospitalized patients with CAP.

Methods

Study Design & Study Patients: This was a test-negative study using data from the first two years of the University of Louisville Pneumonia Study, a prospective, observational study of all hospitalized patients with pneumonia in Louisville, Kentucky from 6/1/2014 – 5/31/2016 [14].

Subjects: Patients were only eligible for inclusion in this analysis if they 1) were hospitalized during the influenza season in each study year (January, February, March, October, November, December), and 2) had a reverse-transcriptase polymerase chain reaction (RT-PCR) and/or rapid influenza diagnostic testing (RIDT) performed during hospitalization. Patients were considered vaccinated if they self-reported receiving any influenza vaccination for that influenza season prior to their hospitalization.

Study Definitions and Measurements: **Community-Acquired Pneumonia (CAP):** A patient was defined as having CAP when the following 3 criteria were met: 1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a attending radiologist's reading; 2) at least 1 of the following: a) new cough or increased cough or sputum production, b) fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F), c) changes in leukocyte count (leukocytosis: >11,000 cells/µL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/µL); and 3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2 [14].

Hospitalization with influenza-CAP: A hospitalized patient with CAP testing positive for an influenza virus of any subtype using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) or Rapid Influenza Diagnostic Testing (RIDT) during hospitalization.

Hospitalization with Non-Influenza-CAP: A hospitalized patient with CAP testing negative for an influenza virus of any subtype using RT-PCR or RIDT during hospitalization.

Influenza Vaccine Status: Influenza vaccine status for the influenza season of hospitalization was defined via self-report as documented in the medical record.

Confounding Variables: The following variables were considered as potentially confounding the relationship between vaccine status and hospitalization with CAP: age, race, sex, and history of the following social and medical factors: neoplastic disease, congestive heart failure (CHF), renal disease, diabetes, alcoholism, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV), and current smoking status.

Statistical Analysis: Comparisons between those with and without influenza vaccination were made using descriptive statistics: frequencies with percentages as well as medians with interquartile ranges for categorical and continuous variables, respectively. Statistical associations between variables were made using Chi-Squared tests and Mann-Whitney U-tests. P-values of less than 0.05 were considered statistically significant. R version 3.4.3 (R Foundation, Vienna, Austria) was used for all analyses [15].

Unadjusted and adjusted vaccine effectiveness estimates were calculated. A crude Odds Ratio (cOR) evaluating the unadjusted association between vaccine status and influenza/non-influenza-CAP hospitalization was calculated from a 2x2 contingency table of observed influenza-CAP hospitalizations by reported vaccination status. The unadjusted estimate was calculated by the following equation, $(1 - cOR) * 100$ [16, 17].

To obtain adjusted vaccine effectiveness, a multivariable logistic regression model was created to control for confounding effects in the relationship between vaccine status and influenza/non-influenza-CAP hospitalization. Based off of theoretical importance, the final model controlled for age, sex, race, neoplastic disease, CHF, renal disease, diabetes, alcoholism, COPD, HIV, and current smoking status. The adjusted odds ratio (aOR) was derived from this model and an adjusted vaccine effectiveness estimate was calculated using the following equation: $(1 - aOR) * 100$.

Post hoc sensitivity analysis included unadjusted and adjusted vaccine effectiveness for hospitalizations with no influenza-CAP coinfections, as well as sensitivity analysis for hospitalizations that did not utilize RIDT.

Human Subjects Protection: Participants in the primary University of Louisville Pneumonia Study provided their consent for inclusion in the vaccine recall ancillary study.

Results

Characteristics of Vaccinated and Unvaccinated Hospitalized Patients with and Without Influenza-Associated CAP

Table 1 outlines the characteristics of hospitalized patients with CAP by vaccine status. Hospitalized CAP patients who were vaccinated with the current year's influenza vaccine were significantly less likely to be from a Black/African American racial background (16% vaccinated vs 22% unvaccinated, P=0.002), were older (69 years vs 63 years P<0.001), smoked less (26% vaccinated vs 36%, P<0.001) and were significantly more likely to have various comorbid conditions.

A total of 1951 hospitalized patients with CAP were included in analysis, and 831 (43%) reported having received the influenza vaccination for the influenza season by the time they were hospitalized. A total of 152 (8%) cases of influenza-CAP were confirmed in the study population, with 63 (8%) cases confirmed in vaccinated individuals. There were 13 CAP-influenza hospitalizations with a bacterial coinfection. Four of these 13 coinfections were found in unvaccinated individuals.

Table 1 Patients Characteristics (n=1951)

Study Population	Unvaccinated	Vaccinated	P-value
Total No. = 1951	1120	831	
Demographics			
Male sex, Frequency(%)	496 (44)	367 (44)	0.994
Race: Black, Frequency(%)	241 (22)	131 (16)	0.002
Age, Median(IQR)*	63 (18)	69 (16)	<0.001
Social and Medical History		**Frequency (%)**	
Chronic obstructive pulmonary disease	492 (44)	409 (49)	0.023
Diabetes mellitus	326 (29)	296 (36)	0.003
Current smoker	402 (36)	218 (26)	<0.001
Congestive heart failure	265 (24)	250 (30)	0.002
HIV disease	35 (3)	13 (2)	0.04
Stroke	106 (9)	93 (11)	0.242
Neoplastic disease	105 (9)	105 (13)	0.026
Renal disease	279 (25)	254 (31)	0.007
Obesity (BMI >= 30)	408 (36)	313 (38)	0.629
Severity of Disease on Admission		**Frequency (%)**	
Need for intensive care	178 (16)	116 (14)	0.264
Altered mental status	163 (15)	116 (14)	0.76
Need for ventilatory support	133 (12)	98 (12)	>0.999
Need for vasopressors	23 (2)	14 (2)	0.672

*IQR: Interquartile range

Influenza Vaccine Effectiveness for Prevention of Hospitalization due to Influenza-Associated CAP

Table 2 outlines the observed 2x2 Contingency Table for the proportion of influenza-CAP hospitalization by vaccination status. The unadjusted vaccine effectiveness was not significant, with a point estimate of 5% (95% CI: [-33%, 32%]). After adjusting for potential cofounders, vaccine effectiveness was also not significant with a point estimate of 8% (95% CI: [-30%, 35%]).

Table 2 2x2 Contingency Table: Influenza-CAP Hospitalizations by Vaccination Status

	Unvaccinated	Vaccinated
Non-Influenza-CAP	1031 (A)	768 (B)
Influenza-CAP	89 (C)	63 (D)

Crude, Unadjusted Odds Ratio (cOR)	$= (A/C)/(B/D)$
	$= (1031/89) / (768/63)$
	$= 0.950272121 \approx .95$
Crude, Unadjusted Vaccine Effectiveness	$= (1 - cOR) * 100$
	$= (1 - .95) * 100$
	$= 5\%$

Post Hoc Sensitivity Analysis

The presence of coinfection was unlikely to alter the effectiveness of the vaccine. This was confirmed by post hoc sensitivity analysis in which the 13 CAP-influenza infections were removed from analysis. With no adjustments, vaccine effectiveness in hospitalizations with no CAP-influenza coinfections was not significant and remained insignificant after adjusting for potential cofounders. The type of influenza test used was also considered for post hoc sensitivity analysis to control for the effect of false-negative RIDT. Only hospitalizations who received RT-PCR testing were included in this analysis. Unadjusted and adjusted estimates were not significant. Post hoc sensitivity analysis suggests that the influenza vaccine effectiveness in CAP hospitalizations is not significantly affected by influenza-CAP coinfections, or the type of influenza test conducted.

Discussion

This study suggests that the seasonal influenza vaccine may not be effective for preventing hospitalizations due to influenza-CAP. One important clinical implication is that although vaccines may be a primary prevention strategy for some infections, they are not 100% effective. Populations at risk for severe disease or poor clinical outcomes, such as the young children and the elderly, may need to take increased measures to reduce the risk of influenza infection. As vaccination remains as the primary recommendation for prevention, clinicians should also recommend annual vaccinations and monitor vaccination status of all patients.

Our data contradicts the results of other studies from similar years, and vaccine effectiveness reported by the CDC during the 2014-2015 and 2015-2016 flu seasons. The CDC reports, in reference to a 2015 study conducted by Zimmerman, R.K., et al. [18], an adjusted vaccine effectiveness of 19% (95% CI: [10% - 27%]) during the 2014-2015 flu season. This is significantly higher than our suggested effectiveness in influenza-CAP hospitalizations. For the 2015-2016 flu season, the CDC reported an adjusted vaccine effectiveness from another of 48% (95% CI [41% - 55%]) [19], which is significantly higher than our suggested effectiveness in influenza-CAP hospitalizations. Similar to our study, vaccine effectiveness was calculated from the results of test-negative design from the same study years. However, conflicting results are likely due to different study populations. Reports from the CDC are based off of results from studies across all age groups, while our study is only specific to hospitalizations due to CAP.

It is possible that, although we did not find the vaccine to be effective for the prevention of hospitalization due to influenza-CAP, it may be effective for other outcomes or prevention of influenza infection. Previous vaccine studies have suggested potential benefits of influenza vaccination other than preventing CAP-hospitalization. In addition to reducing the risk of CAP-hospitalizations, a 2005 cohort study of individuals 65 years and older reported a reduced risk of all-cause mortality before, during, and after flu seasons when comparing vaccinated and unvaccinated individuals [20]. Results from this study are likely due to the advantages in the study design, which were not obtainable in our study. Jackson, L.A., et al. (2006), rigorously followed members of a health maintenance organization (HMO), prospectively recording information on enrollment, immunizations, as well diagnosis in inpatient and outpatient settings, allowing for the control of multiple biases, and the assessment of multiple outcomes at different time periods.

Our study does provide supporting evidence that vaccine effectiveness varies substantially from year to year and evidence that findings from other studies may not estimate the true effectiveness in hospitalizations from influenza-CAP. It should also be noted that vaccine studies often differ in design and complexity, with no best standard or practice currently recognized. A strength of this study is the use of data from a population-based study, increasing the sample size and potentially increasing generalizability. Additionally, using a test-negative study design to estimate vaccine effectiveness offered a real-world view on how well the influenza vaccine reduced hospitalizations due to influenza-CAP and how well the target population was immunized.

This study has several limitations. Although test-negative study designs are generally simple and less costly, they are subject to many forms of bias [10]. First, not all hospitalization records reported the use of PCR diagnostics for influenza, which is a standard for laboratory confirmation of influenza virus. Although readily available and able to provide quick results, previous studies have shown that the diagnostic accuracy of a RIDT

can vary across populations [21]. Therefore, patients testing negative on a RIDT and who did not receive a PCR test may have been misclassified into the non-influenza-CAP hospitalization group. It is also believed that for some vaccines, self-reported vaccination status may not match actual vaccine receipt [22] [23]. This would bias our results through misclassification of the predictor and outcome variables. Although influenza vaccine is recommended for individuals without contraindications over the age of 6 months in the United States, actual vaccine receipt is differentially distributed between individuals with different characteristics and geographies. This may introduce bias by the way of a form of confounding by indication, necessitating other study designs or analytical approaches.

Another limitation is through the pooling of vaccine effectiveness estimates across multiple study years. It is possible that the vaccine may have been effective one year but not the next, or vice versa, leading to an overall estimate that suggested it was not effective. It is suggested that multi-season studies may be a more useful approach when trying to understand the effectiveness of repeat vaccination [24], which was not considered in this study. It is also unknown which vaccine route was obtained, potentially adding more bias to the study results. During the time of this study, individuals were still receiving Live-Attenuated Influenza Vaccine via nasal mist, which the ACIP advised against using during the 2016 – 2017 flu season due to identification of inferiority to other routes [25] . Further, the population under study is generally older. Currently, elderly individuals are recommended to receive high-dose influenza vaccine to counteract age-related immunosenescence [26, 27]. We did not collect this data, which may result in some bias in our estimates. Finally, since we did not collect data on influenza subtypes, it is possible that the vaccine is effective for various influenza A or influenza B strains in the prevention of hospitalization for influenza-CAP.

Vaccine effectiveness estimates for various outcomes should continue to be studied on an annual basis. Prospective studies have the potential to evaluate other outcomes other than hospitalization or infection. Potential mechanisms of interaction may exist between vaccine uptake and outcomes such as severity of disease, time to clinical improvement, length of hospital stay, clinical failure, and short and long-term mortality. Additional analytical approaches to counteract confounding by indication, misclassification, and geographical variations in vaccine receipt should be enhanced and utilized in future large-scale vaccine effectiveness studies.

In conclusion, we found that, over the 2014/2015 and 2015/2016 influenza seasons, influenza vaccine was not effective for prevention of hospitalization with influenza-CAP. Development of novel vaccines that enhance effectiveness for various outcomes, and are effective across multiple seasons, are needed.

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