Effectiveness of Influenza Vaccine for Preventing Laboratory-Confirmed Influenza Hospitalizations in Adults, 2011–2012 Influenza Season

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During the 2011–2012 influenza season, we enrolled hospitalized adults with acute respiratory illness and tested each for influenza using reverse transcription polymerase chain reaction. Influenza vaccination was verified in 35% (6/17) of adults with influenza-associated hospitalizations compared to 64% (97/152) of test-negative controls; adjusted vaccine effectiveness was 71.4% (95% confidence interval, 17.1%–94.9%).

Keywords. influenza vaccine; older adults; effectiveness.

Annual influenza vaccine has been recommended for US adults at high risk for influenza complications since 1960 [1]; universal vaccination has been recommended since 2010 [2]. Two recent reviews [3, 4] both reported that there is little evidence to support vaccine effectiveness against serious influenza complications for adults. Clinical trials have been too small to evaluate influenza complications, and most observational studies have not used laboratory-confirmed influenza as an outcome. The case-positive, control-negative study design is an efficient method to determine vaccine effectiveness that assures appropriate classification of cases and identifies controls with risk factors for both acute respiratory illness and propensity to seek medical care similar to those of influenza-positive patients [5, 6].

Our previous study used the case-positive, control-negative method to estimate inactivated influenza vaccine effectiveness in adults aged ≥50 years hospitalized with respiratory illness over 3 consecutive influenza seasons (2006–2009) [7]. Although none of the individual estimates of vaccine effectiveness were statistically significant, pooling the annual estimates of 56%, 56%, and 73% yielded an estimate of 61% (interquartile range, 18%–82%), consistent with moderate protection.

During the 2011–2012 influenza season, we enrolled hospitalized adults with respiratory symptoms, and tested each for influenza using reverse transcription polymerase chain reaction (RT-PCR) assays. We estimated vaccine effectiveness using the case-positive, control-negative design.

METHODS

Study Design

We enrolled adults aged ≥18 years hospitalized for acute respiratory illness in 1 academic and 3 community hospitals 4–5 days per week when influenza virus was circulating, as defined by the detection of influenza in the academic hospital laboratory in 2 consecutive weeks and continued through the end of April 2012. Eligibility criteria included admission diagnosis of pneumonia or influenza, or an admission diagnosis of an acute circulatory or respiratory disease plus at least 2 of the following: temperature ≥38°C (100°F) or <36°C (96.8°F), or new onset/increase in chronic cough, dyspnea, chills, headache, myalgia, or sore throat. Patients with symptoms for >10 days, previously enrolled or treated with antivirals were excluded. Patients were approached consecutively based on symptoms at the time of admission and without knowledge of prior vaccination status. Institutional review board approval was obtained for all participating hospitals.

Influenza Vaccination Status

Self-report of influenza vaccination was verified by contacting vaccine providers. Provider confirmation of vaccination was considered the gold standard. Vaccination status categories included "not vaccinated" (verified and self-reported not vaccinated) and "vaccinated" (verified only). Patients with unknown or unverified vaccination status, or vaccination within 14 days of symptom onset, were excluded from the primary analysis. A sensitivity analysis included patients with self-reported vaccination that was not verified.

Laboratory Methods

Nasal and throat swabs specimens were combined in lysis buffer, and tested for influenza virus by real-time RT-PCR

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using primers and probes designed by the Centers for Disease Control and Prevention (Stephen Lindstrom, written communication, September 2008). To assure specimen quality, samples were also tested for ribonuclease P (RNase P) and if absent in 3 consecutive tests, RT-PCR negative results were categorized as indeterminate and excluded from analyses. All laboratory testing was completed by staff blinded to subject and vaccine exposure.

Identification of Cases and Controls

Participants with positive RT-PCR on duplicate testing were cases, and those who tested negative for influenza by RT-PCR but positive for Rnase P were controls. Participants with indeterminate laboratory results were excluded from all analyses.

Definitions and Covariates

Covariates obtained by self-report or chart review included age in years, sex, race (black, nonblack), any underlying medical conditions (diabetes mellitus, chronic heart or kidney disease, cardiovascular disease, asthma, and chronic obstructive pulmonary disease), smoking, immunosuppression (human immunodeficiency virus, corticosteroid use, or cancer), and timing of admission relative to the onset of influenza season. All of these covariates were considered as potential confounders and were included in all adjusted analyses. Additional information was collected on hospital course and discharge diagnoses as a surrogate for reason for admission.

Analyses

Characteristics of groups were compared using Pearson χ^2 test for categorical covariates and Wilcoxon rank-sum test for continuous variables. Unadjusted vaccine effectiveness estimates were calculated using the formula [1 – odds ratio] × 100% [8]. Because the number of cases per parameter was <3, a penalized regression model with L2 norm penalty that penalized all covariates except for vaccination status was used to avoid model overfitting [9]. The 95% confidence intervals (CIs) of adjusted odds ratios were constructed using 1000 bootstrap samples. Sensitivity analyses were performed including patients with self-reported vaccination and using a propensity score model. Data analysis was conducted using R 2.14.1 (www.r-project.org) with rms and glmnet packages.

RESULTS

Influenza viruses circulated 8 February through 11 April 2012, during which time 413 adults hospitalized with respiratory symptoms met study eligibility criteria, and 200 (48%) consented to participate. Eligible but nonenrolled and enrolled patients had similar age, sex, race, and insurance status (data not shown). Of those enrolled, 198 (99%) had adequate specimens for influenza virus testing. After excluding 7 patients vaccinated within 14 days of symptom onset, there were 191 eligible patients, 21 (11%) with confirmed influenza. Of 169 eligible participants with vaccine status verified, 17 (10%) had confirmed influenza (12 influenza A[H3N2] and 5 influenza A[H1N1] pdm09). Influenza-positive patients were more likely to be black and not vaccinated compared to influenza-negative participants (Table 1). Vaccinated patients were older (median age, 69 years vs 57 years, $P < .001$), more likely to be white, and have a high-risk condition, whereas unvaccinated patients were more likely to have influenza and to smoke ($P < .05$; Table 1).

Unadjusted vaccine effectiveness was 71.1% (95% CI, 17.3%–89.9%) for all adults and 76.8% (24.1%–92.9%) for adults ≥50 years. Adjusted vaccine effectiveness for preventing influenza-associated hospitalizations was 71.4% (95% CI, 17.1%–94.9%) for all adults and 76.8% (95% CI, 24.0%–97.9%) for adults ≥50 years. Sample size precluded determining vaccine effectiveness for younger age groups, by race or sex, or by influenza type or subtype. Including those with self-reported vaccination only (additional 28 participants) yielded a vaccine effectiveness of 69.9% (95% CI, 18.8%–92.6%). Propensity score models yielded similar results.

DISCUSSION

During the 2011–2012 influenza season, we estimated the trivalent influenza vaccine to be 71.4% (95% CI, 17.1%–94.9%) effective in preventing influenza-associated acute respiratory hospitalizations in adults; results were consistent when restricted to adults aged ≥50 years. These data add to the small number of studies that have assessed vaccine effectiveness against serious influenza complications, and this estimate is similar to those we obtained in 3 previous years [7].

Despite relatively low influenza activity in the United States during the 2011–2012 influenza season [10], 10% of enrolled adults with acute respiratory hospitalizations had laboratory-confirmed influenza. The distribution of circulating strains in our study population was similar to strains identified in the United States—86% influenza A (74% H3N2, 26% pH1N1), and 14% influenza B viruses [10]. Antigenically, 95% of circulating H1N1 and 82% of circulating H3N2 viruses were similar to vaccine strains; 49% of circulating influenza B strains were of the B Victoria lineage, of which 95% were similar to the vaccine B strain [10].

Vaccine effectiveness estimates from Europe for the 2011–2012 season were lower than our estimates. The I-MOVE study reported vaccine effectiveness for outpatient visits in persons targeted for vaccination to be 43% (95% CI, −0.4% to 67.7%) [11]. A smaller Spanish study estimated vaccine effectiveness to be 55% (95% CI, 3%–79%) [12]. In France, vaccine effectiveness was 30% (95% CI, 22%–39%) for influenza-associated

Table 1. Patient Demographics

Demographic	Not Vaccinated (n = 65)	Vaccinated (n = 104)	Influenza Negative (n = 152)	Influenza Positive (n = 17)
Race*,**				
White	50 (77%)	94 (90%)	134 (88%)	10 (59%)
Black	14 (22%)	10 (10%)	18 (12%)	6 (35%)
Other	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Age*, y, median (IQR)	57 (47–68)	69 (59–77)	65 (54–75)	61 (52–67)
Age group*				
18–49 y	22 (34%)	10 (10%)	28 (18%)	4 (24%)
50–64 y	22 (34%)	35 (34%)	49 (32%)	8 (47%)
≥65 y	21 (32%)	59 (57%)	75 (49%)	5 (29%)
Sex, female	45 (69%)	59 (57%)	93 (61%)	11 (65%)
High-risk medical condition*,[a]	49 (75%)	96 (92%)	131 (86%)	14 (82%)
Chronic pulmonary disease	34 (52%)	60 (58%)	83 (55%)	11 (65%)
Chronic cardiovascular disease	19 (29%)	46 (44%)	60 (39%)	5 (29%)
Immunosuppression[b]	26 (41%)	38 (37%)	60 (39%)	4 (24%)
Diabetes mellitus	14 (22%)	35 (34%)	45 (30%)	4 (24%)
Kidney or liver disease	5 (8%)	6 (6%)	11 (7%)	0 (0%)
Asplenia	3 (5%)	1 (1%)	3 (2%)	1 (6%)
Current smoking	17 (26%)	14 (13%)	28 (19)%	3 (18%)
Influenza positive*	11 (17%)	6 (6%)	. . .	. . .
ICU admission	14 (22%)	17 (16%)	29 (19%)	2 (12%)
Death	1 (2%)	1 (1%)	2 (1%)	0 (0%)
Length of stay, d, median (IQR)	3 (2–5)	4 (2–6)	4 (2–6)	3 (2–5)
Vaccinated**	. . .	. . .	97(64%)	6 (35%)
Discharge diagnoses				
Pneumonia/influenza	36 (55%)	51 (49%)	78 (51%)	9 (53%)
Other acute respiratory illness	10 (15%)	20 (19%)	28 (18%)	2 (12%)
Asthma or COPD exacerbation	11 (17%)	23 (22%)	29 (19%)	5 (29%)
Cardiac disease	3 (5%)	4 (4%)	6 (4%)	1 (6%)

Discharge diagnoses (codes from the *International Classification of Diseases, Ninth Revision*) were grouped into 5 categories: pneumonia/influenza (480–482, 485–488), other acute respiratory illness (033, 034, 077, 372, 381, 382, 384, 385, 388, 460–466. 473), COPD and asthma (490–494, 496), cardiac disease (410, 411, 413,428, 785), and other (any remaining codes).

Abbreviations: COPD, chronic obstructive pulmonary disease, ICU, intensive care unit; IQR, interquartile range.

[a] History of transplant, cancer, diabetes mellitus, asplenia (functional or anatomic), cardiovascular disease, kidney disease, liver disease, pulmonary disease, human immunodeficiency virus, neurologic disease, immunosuppressive medications.

[b] Where immunosuppression is one of the following: history of transplant, human immunodeficiency virus, recent or chronic steroid use, chemotherapy, or other immunosuppressive medications.

* $P < .05$ for vaccinated compared to unvaccinated subjects.

** $P < .05$ for influenza-positive compared to influenza-negative subjects.

hospitalizations [13]. Interestingly, several sites reported a circulating H3N2 influenza strain that was antigenically different from the vaccine strain [13], which may account at least in part for the disparate results.

Our study was limited by the small number of influenza-associated hospitalizations in a single geographic area, and thus our estimate is imprecise but similar to those from the last 3 years. These estimates are for influenza complications and may be different than those for prevention of any influenza illness. Case-positive, control-negative studies attempt to avoid biases due to misclassification of influenza illness and confounding by factors associated with vaccination status. Controls are selected to be similar to cases with respect to risk of disease (acute respiratory hospitalization in this study) and propensity to seek or require care (hospitalization). Vaccination rates in our controls vs those reported for high-risk persons in Tennessee for the 2011–2012 season were similar: age 18–49 years, 31% vs 39%, respectively; age 50–64 years, 61% vs 52%, respectively; and age ≥65 years, 73% vs 75%, respectively [14]. Although we enrolled subjects with fairly broad eligibility criteria, discharge diagnoses were not associated with either influenza diagnosis or vaccination status.

These data are among the first US estimates of vaccine effectiveness for the 2011–2012 influenza season. More important,

this study adds to the evidence indicating that inactivated influenza vaccine can prevent more than half of all influenza-associated hospitalizations in older adults [7]. Influenza causes an average of 294 128 hospitalizations annually; most are in adults aged ≥50 years [15]. Given current vaccination rates and a vaccine effectiveness of 60%, more than one-third of these hospitalizations could be prevented by increasing vaccination uptake in this population.

Notes

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