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Association Between Hospitalization With Community-Acquired Laboratory-Confirmed Influenza Pneumonia and Prior Receipt of Influenza Vaccination

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ABSTRACT

Importance Few studies have evaluated the relationship between influenza vaccination and pneumonia, a serious complication of influenza infection.

Objective To assess the association between influenza vaccination status and hospitalization for community-acquired laboratory-confirmed influenza pneumonia.

Design, Setting, and Participants The Etiology of Pneumonia in the Community (EPIC) study was a prospective observational multicenter study of hospitalizations for community-acquired pneumonia conducted from January 2010 through June 2012 at 4 US sites. In this case-control study, we used EPIC data from patients 6 months or older with laboratory-confirmed influenza infection and verified vaccination status during the influenza seasons and excluded patients with recent hospitalization, from chronic care residential facilities, and with severe immunosuppression. Logistic regression was used to calculate odds ratios, comparing the odds of vaccination between influenza-positive (case) and influenza-negative (control) patients with pneumonia, controlling for demographics, comorbidities, season, study site, and timing of disease onset. Vaccine effectiveness was estimated as (1 – adjusted odds ratio) × 100%.

Exposure Influenza vaccination, verified through record review.

Main Outcomes and Measures Influenza pneumonia, confirmed by real-time reverse-transcription

polymerase chain reaction performed on nasal/oropharyngeal swabs.

Results Overall, 2767 patients hospitalized for pneumonia were eligible for the study; 162 (5.9%) had laboratory-confirmed influenza. Twenty-eight of 162 cases (17%) with influenza-associated pneumonia and 766 of 2605 controls (29%) with influenza-negative pneumonia had been vaccinated. The adjusted odds ratio of prior influenza vaccination between cases and controls was 0.43 (95% CI, 0.28-0.68; estimated vaccine effectiveness, 56.7%; 95% CI, 31.9%-72.5%).

Conclusions and Relevance Among children and adults hospitalized with community-acquired pneumonia, those with laboratory-confirmed influenza-associated pneumonia, compared with those with pneumonia not associated with influenza, had lower odds of having received influenza vaccination.

INTRODUCTION

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Influenza remains an important cause of morbidity and mortality worldwide. In the United States, seasonal influenza epidemics are responsible for an estimated average of 226 000 hospitalizations and between 3000 and 49 000 deaths each year.[1,2] Pneumonia, the leading infectious cause of hospitalization and death in the United States, is a relatively common and serious complication of influenza.[3]

Vaccination is the primary strategy to reduce influenza burden. Currently, the US Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all persons 6 months or older.[1,2] Supporting evidence from randomized clinical trials, conducted mainly in outpatient settings, indicates that influenza vaccines are effective in preventing influenza-associated acute respiratory illnesses among healthy children and adults.[4,5]

Vaccine effectiveness studies based on laboratory-confirmed influenza infections and verified vaccinations are essential to evaluate the public health value of influenza vaccines and to inform vaccination policies.[6,7] Recent observational studies have consistently shown that vaccination is associated with lower odds of hospitalization for laboratory-confirmed influenza acute respiratory infections.[3,7-14]

However, whether influenza vaccines can decrease the risk of influenza-associated hospitalizations for community-acquired pneumonia remains unclear.[5,6,15] Because influenza vaccination is currently recommended for all persons 6 months or older in the United States, observational studies are the only option to assess vaccine effectiveness. We sought to determine whether influenza vaccination was associated with reduced odds of hospitalizations for laboratory-confirmed influenza-associated pneumonia.

METHODS

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The US Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study was conducted from January 2010 through June 2012.[16,17] Children and adults admitted with community-acquired pneumonia were enrolled at 8 hospitals in 4 sites: Nashville, Tennessee; Memphis, Tennessee; Chicago, Illinois; and Salt Lake City, Utah. Pneumonia was defined as evidence of acute infection, symptoms of respiratory illness, and radiologic findings compatible with pneumonia. Patients with history of recent hospitalization, children who were residents of chronic care facilities, adults who were nursing home residents and not independently functioning (defined as score >7 in the Activities of Daily Living scale[17]), and patients with severe immunosuppression were excluded.[16,17] Written informed consent was obtained from all participants, their legally authorized representatives, or both. After enrollment, research personnel collected sociodemographic characteristics (including interview self-

reported race/ethnicity), pneumonia risk factors, and health care utilization information, including vaccination history. Because children younger than 6 months are not eligible for influenza vaccination, the study was restricted to patients 6 months or older. Institutional review boards of the research sites and CDC approved the study.[16,17]

Laboratory Confirmation of Influenza Virus Infections

Nasopharyngeal and oropharyngeal swabs were collected from each patient at enrollment, placed into transport medium, and delivered to the site research laboratories. Samples were stored at −70°C and then tested in batches for influenza and other respiratory viruses using CDC's real-time reverse-transcription polymerase chain reaction (RT-PCR) protocols.[16,17] To ensure integrity of the samples, the presence of human RNaseP, a housekeeping gene, was required for evaluable samples. Laboratory personnel conducting the RT-PCR testing were blinded to the patients' vaccination status and study hypotheses.

Cases and Controls

For this case-control study, a case was a patient hospitalized for pneumonia whose nasopharyngeal/oropharyngeal swabs collected within 72 hours of admission tested positive for influenza by RT-PCR with a cycle threshold value of less than 40. A control was a patient hospitalized for pneumonia who tested negative for influenza.[3,7-14,18] Only patients with verified influenza infection status were included in the study.[19,20]

Influenza Vaccination Status

The study exposure was verified influenza vaccination status for the current influenza season. Detailed influenza vaccination history was collected in the study interview, and medical records were reviewed for verification. We also obtained vaccination information from state vaccination registries and from health care providers and pharmacies. Vaccination status included receipt of monovalent vaccines (2009-2010 season) or trivalent inactivated or live attenuated influenza vaccines (2010-2011 and 2011-2012 seasons). Per ACIP recommendations, children younger than 9 years were considered vaccinated if they had received (1) 2 vaccine doses for the current influenza season, with a time between doses of 28 days or longer and the second dose more than 14 days before their disease onset, or (2) 1 or more vaccine doses in the prior influenza seasons and 1 dose for the current season more than 14 days before their disease onset. Children 9 years and older and adults were considered vaccinated if they had received any influenza vaccine for the current season more than 14 days before their disease onset.[1,2] Partially vaccinated children and patients of any age whose influenza vaccination history could not be verified were excluded.

Influenza Seasons

To ensure a proper evaluation of the association between influenza pneumonia risk and prior influenza vaccination, we restricted our analyses to periods of influenza activity at each site, based on CDC surveillance data.[21] We defined the beginning of the influenza season as the first week of continuous influenza activity with 2 or more positive tests for influenza virus identified in each of 2 consecutive weeks by the respective regional surveillance system. The season ended on the last of 2 consecutive weeks with less than 2 positive tests detected per week.[22] Study enrollment was conducted from January 2010 through June 2012 and thus included part of the 2009-2010 season and the complete 2010-2011 and 2011-2012 influenza seasons. (See eTable 1 and the eFigure in the Supplement for additional details.)

Statistical Analyses

We examined associations between potential confounders (identified a priori) and verified vaccination status as well as laboratory-confirmed influenza pneumonia. Potential confounders included age, sex, race/ethnicity, family composition (eg, presence of young or school-aged children), smoking status, insurance status, use of oxygen supplementation at home, timing of admission relative to disease onset, timing from beginning of the influenza season to admission (because disease risk may vary during the seasons), specific influenza season, and presence of immunosuppressive conditions (including also cancer [except skin cancer] and HIV infection [with CD4 counts ≥200/mm^3]) and other chronic medical conditions associated with influenza-associated complications, including cardiopulmonary disease, diabetes mellitus, chronic liver/kidney disease, and neurological disease.[1-3,8]

We compared the odds of influenza vaccination during the current season more than 14 days before disease onset between influenza cases and controls using a multivariable logistic regression model and calculated odds ratios adjusted for relevant confounders. Influenza vaccine effectiveness (%) was estimated as (1 – aOR) × 100,[11,12] where aOR was the adjusted odds ratio for influenza vaccination from the final regression model.

Planned sensitivity analyses included the following: (1) inclusion of vaccination status based on self-report to assess the statistical effect of exposure misclassification; (2) exclusion of the first influenza season (2009-2010), because our study only included part of this season; (3) redefining the influenza seasons to periods with either at least 4% or 5% of tested samples detected as positive per week in surveillance systems, to evaluate the sensitivity of our estimates to the influenza season definition; (4) restriction to cases and controls hospitalized within 7 and 14 days of symptom onset, to address concerns that influenza may be a concurrent infection and not the cause of pneumonia in patients with longer duration of symptoms prior to presentation[19,20]; (5) restriction to patients with radiologic evidence of alveolar consolidation, infiltrate, or pleural effusion, as determined by independent study radiologists, a common end point in pneumonia studies[23]; (6) considering patients who tested negative for influenza but positive for other noninfluenza viruses (including coronaviruses 229E, HKU1, NL63, and OC43; human metapneumovirus; human rhinovirus; parainfluenza viruses 1, 2, and 3; and respiratory syncytial virus) and those patients who tested negative for all study viruses as alternate controls, to assess the hypothesis that influenza vaccination may increase the risk of noninfluenza viral infections,[24,25] including pneumonia, and to assess potential differential detection of respiratory viruses[19,20,25-27]; (7) exclusion of patients who reported use of influenza antivirals prior to admission, as such use may interfere with RT-PCR detection of influenza infections[28]; (8) reanalyzing our data adjusting for propensity scores[3,8] created using variables from the main analysis and 16 additional variables for specific comorbidities, to address concerns about residual confounding; and (9) using respiratory syncytial virus–associated pneumonia as cases and excluding all influenza cases, to assess the specificity of the main findings.

Subgroup analyses included estimations by age group, presence of immunosuppressive and chronic conditions, study site, and influenza season. For these subgroups analyses, interaction terms between subgroup and vaccination status were examined. Estimates for each subgroup were calculated using linear combinations of coefficients from the regression models that included the interaction terms. Separate exploratory analyses for influenza type/subtype and influenza cases with and without co-detection of other pathogens[16,17] were also conducted.

All reported tests were 2-sided, and a *P* value less than .05 was considered significant. Statistical analyses were conducted in Stata version 13.1 and R version 3.0.2.

RESULTS

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Forty-six percent of patients enrolled in the EPIC study (2342/5109) were excluded for the following reasons: age younger than 6 months (n = 342, 7%), enrollment outside of the influenza season (714, 14%), children with partial vaccination (300, 6%), vaccination within 14 days of disease onset (115, 2%), self-reported vaccination (518, 10%), self-reported vaccination with unknown vaccination date (52, 1%), unknown vaccination status (210, 4%), and unknown influenza infection status (91, 2%). After exclusions, 2767 patients were included in this study (Figure).

Figure.

Patient Flowchart in Study of Influenza Vaccination and Influenza Pneumonia

Research sites B and D enrolled only children, site A enrolled only adults, and site C enrolled both children and adults.

[a]Influenza infection status could not be determined for 91 patients (1.8% of total enrolled), including patients without samples available for testing and patients with samples collected after 72 hours of admission or with missing data on the time of sample collection.

[b]Noninfluenza respiratory viruses.

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One hundred sixty-two of 2767 patients with pneumonia tested positive for influenza (5.9%) by RT-PCR and were defined as cases, including 62 (38%) with A(H1N1)pdm09, 51 (31%) with A(H3N2), 43 (27%) with influenza B, 4 with influenza A with no available subtype information (3%), and 2 co-infections with influenza A and B (1%). Among 162 influenza cases, 116 cases had only influenza viruses detected, 32 had a viral co-detection, and 14 had a bacterial co-detection. A total of 2605 controls were identified for comparison, including 1196 control patients who tested positive for other respiratory viruses and 1409 control patients who tested negative for all viruses tested.

Characteristics of Cases and Controls

Compared with influenza-negative control patients, influenza-positive case patients had similar age distribution but were more likely to be black and enrolled during the 2010-2011 influenza season. The distribution of influenza cases differed by study site. The prevalence of congenital heart disease and heart failure was higher among controls. Relative to cases, controls were admitted earlier during the influenza seasons. The distribution of other sociodemographic factors and comorbidities was generally similar in both groups (Table 1 and Table 2). There were 2 (1%) in-hospital deaths among case patients and 29 (1%) among control patients.

Table 1. Sociodemographic Characteristics of Study Patients by Influenza Infection and Vaccination Status

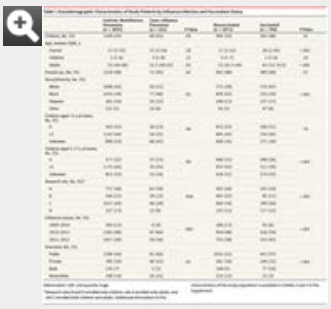

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Table 2. Clinical Characteristics of Study Patients by Influenza Infection and Vaccination Status

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Characteristics of Vaccinated and Unvaccinated Patients With Pneumonia

A total of 794 patients (29%) with pneumonia were vaccinated during current influenza seasons. Compared with unvaccinated patients, vaccinated patients were older and more likely to be white and enrolled during the 2010-2011 influenza season. The prevalence of influenza vaccination differed by study research site. The prevalence of current smoking was lower among vaccinated patients, although they were more likely to be past smokers and require home oxygen supplementation. The prevalence of chronic obstructive pulmonary disease, cardiovascular diseases, diabetes, and other chronic medical conditions was generally higher among vaccinated than unvaccinated patients. Unvaccinated patients were admitted earlier than vaccinated patients during the respective influenza seasons (Table 1 and Table 2). There were 11 (1%) in-hospital deaths among vaccinated patients and 20 (1%) among unvaccinated patients. (See eTables 2 and 3 in the Supplement for additional details.)

Association Between Prior Influenza Vaccination and Hospitalization for Influenza-Associated Pneumonia

Of 162 influenza-associated pneumonia cases, 28 (17%) were vaccinated compared with 766 of 2605 (29%) influenza-negative controls. The adjusted odds ratio comparing the odds of prior vaccination among those with influenza-positive pneumonia (cases) with the odds of prior vaccination among those with influenza-negative pneumonia (controls) was 0.43 (95% CI, 0.28-0.68; estimated vaccine effectiveness, 56.7%; 95% CI, 31.9%-72.5%). (See eTable 4 in the Supplement for additional details.)

Results from sensitivity analyses that evaluated key study definitions and assumptions were similar to the main findings. There was no significant association between influenza vaccination and respiratory syncytial virus pneumonia (Table 3).

Table 3. Sensitivity Analyses Within Study of Influenza Vaccination and Influenza Pneumonia

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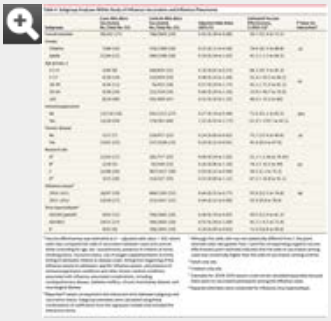
In subgroup analyses, 7 of 68 case children (10%) were vaccinated compared with 376 of 1309 control children (29%; adjusted odds ratio, 0.25; 95% CI, 0.11-0.58); whereas among adults, 21 of 94 cases (22%) were vaccinated compared with 390 of 1296 controls (30%; adjusted odds ratio, 0.59; 95% CI, 0.34-1.02). Among children aged 0.5 to 4 years, 3 of 40 cases (8%) and 266 of 850 controls (31%) were vaccinated (adjusted odds ratio, 0.16; 95% CI, 0.05-0.53). Among older children and adults, the differences in vaccination between cases and controls were more modest. Among patients without immunosuppression, 13 of 134 cases (10%) were vaccinated compared with 592 of 2212 controls (27%); whereas, among patients with immunosuppression, 15 of 28 cases (54%) were vaccinated compared with 174 of 393 controls (44%). The adjusted odds ratio of prior vaccination between cases and controls was significantly lower among patients without immunosuppression (0.27; 95% CI, 0.14-0.49) compared with patients with immunosuppression (1.22; 95% CI, 0.55-2.71).

The prevalence of prior influenza vaccination was higher among patients with chronic diseases than among those without, and in both groups, vaccination in cases was lower than vaccination in controls (adjusted odds ratio point estimates, 0.54 and 0.24, respectively). Differences in vaccination by site likely reflected the age of the study populations at the sites, and the adjusted odds ratio point estimates ranged from 0.26 to 0.50 across sites. In each of the 2 complete study influenza seasons, 2010-2011 and 2011-2012, the prevalence of prior vaccination was lower among cases than among controls, and the odds ratio point estimate was 0.44 for both seasons. However, some subgroup analyses had limited precision due to small numbers (Table 4). In separate analyses that evaluated influenza pneumonia cases with and without

co-pathogen detections, the odds ratio of vaccination between cases and controls was 0.43 (95% CI, 0.25-0.73) and 0.42 (95% CI, 0.18-0.99), respectively.

Table 4. Subgroup Analyses Within Study of Influenza Vaccination and Influenza Pneumonia



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In separate assessments, the odds ratio of vaccination between cases and controls was 0.40 (95% CI, 0.19-0.87) for influenza A(H1N1)pdm09, 0.55 (95% CI, 0.28-1.09) for influenza A(H3N2), and 0.28 (95% CI, 0.09-0.83) for influenza B (Table 4).

DISCUSSION

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In this study of influenza vaccination status and influenza pneumonia, the findings indicate that the odds of influenza vaccination among cases hospitalized with influenza-associated pneumonia was lower than among noninfluenza pneumonia controls, with an adjusted odds ratio of 0.43 (95% CI, 0.28-0.68; estimated vaccine effectiveness, 56.7%) during the 2009-2012 influenza seasons. This multicenter study addressed several concerns identified in previous influenza vaccine effectiveness assessments. By performing systematic influenza testing for all patients with pneumonia, the study relied on an unbiased sample of laboratory-confirmed influenza-pneumonia hospitalizations. Patients with pneumonia were prospectively identified, minimizing concerns about outcome misclassification. To ensure a proper evaluation of the association between influenza pneumonia risk and prior influenza vaccination, the study was restricted to influenza seasons and to patients with similar propensity to require hospital care. Furthermore, vaccination information was actively collected, and only patients with pneumonia and verified influenza vaccination history were included in the main analysis.

Previous studies that used a similar design have shown that influenza vaccination is effective in preventing hospitalizations for acute respiratory illnesses associated with laboratory-confirmed influenza.[3,7-14] Although some studies had limited precision, the point estimates of effectiveness ranged from 53% to 67% among children,[10,11] from 54% to 71% among all adults,[3,12] and from 42% to 61% among adults 65 years or older.[8,13] However, few studies have examined the effectiveness of influenza vaccination in preventing complications of influenza infections, such as pneumonia. In a recent multinational randomized clinical trial of a new quadrivalent inactivated influenza vaccine in children aged 3 to 8 years, a post hoc analysis of influenza-associated lower respiratory tract illness alone yielded a vaccine efficacy estimate of approximately 80%.[29] Likewise, a recent case-control study estimated that influenza vaccination was associated with a 74% reduction in the odds of pediatric intensive care unit admission during the 2010-2012 seasons.[30]

Although previous studies focusing on the prevention of all-cause pneumonia have suggested a modest effectiveness of influenza vaccines,[15,31] using all-cause pneumonia as the outcome for influenza vaccine effectiveness assessments is problematic because influenza is responsible for only a fraction of all pneumonias and varies seasonally, resulting in an underestimation of the true vaccine effectiveness.[6,19,20,32] The current study avoided this misclassification by applying a prospective and

systematic approach for confirming influenza infections and a standardized definition of hospitalizations for pneumonia. The estimated odds ratio of vaccination between cases and controls, and derived vaccine effectiveness from this study, could be used to inform subsequent estimations of the national number of hospitalizations for pneumonia averted by influenza vaccination.[33]

Findings from subgroup analyses suggest that the odds ratio of prior influenza vaccination between cases and controls was higher in patients with immunosuppressive conditions, including cancers and HIV infection, suggesting lower vaccine effectiveness. Although several studies have described reduced immunogenicity of influenza vaccines in patients with immunosuppressive conditions, few have evaluated the vaccine effectiveness in preventing influenza pneumonia among such patients. A small, open-label randomized clinical trial of influenza vaccination among patients with multiple myeloma reported a nonsignificant reduction in all-cause pneumonia, but the number of events was small and the study included only 1 season.[34] Other observational influenza vaccine effectiveness studies have reported reductions in all-cause pneumonia in patients with immunosuppressive conditions, but these events were not confirmed influenza infections.[35] Evidence for the effectiveness of influenza vaccines in preventing pneumonia among patients with HIV infection is also limited.[36] Although these findings warrant replication in other settings, they highlight the vulnerability of older adults and patients with immunosuppressive conditions and the need for additional measures to reduce their risk of influenza infection and related complications.

One concern with observational studies of influenza-associated hospitalizations is the control of unmeasured or poorly measured confounding factors, such as disease severity or baseline characteristics that increase the likelihood that pneumonia will require hospitalization. For example, retrospective studies of influenza vaccination and all-cause mortality have reported that indicators of poor functional status are relevant confounders, because they are associated with both likelihood of not being vaccinated and risk of death, but are rarely considered.[37] The current study used a test-positive case, test-negative control design, a design widely used for vaccine effectiveness assessments that has been shown to be superior to case-control studies of hospitalized cases with population controls, because the likelihood of hospitalization is implicitly accounted for.[19,20] In addition, the current study excluded nursing home residents with limited functional status and prospectively gathered information on risk factors for pneumonia.[19,38,39]

The study findings must be interpreted in light of several limitations. First, although an extensive evaluation of potential threats to the validity of the estimates was conducted, the observational design is vulnerable to some misclassification and residual confounding. Nevertheless, the use of a well-established design and the consistency of findings in a number of prespecified sensitivity analyses conducted to evaluate key assumptions should help reduce these concerns. Second, despite enrollment over 3 consecutive seasons, a relatively small number of influenza-associated pneumonia cases met eligibility criteria, resulting in limited precision for some subgroup analyses. Thus, the association between influenza vaccines and pneumonia among older adults remains controversial, and additional studies in this group are needed.[2,5,7] Although different types of vaccines are available and some ecological evidence suggests that influenza A(H3N2) strains are associated with higher pneumonia mortality,[40] more detailed assessments by vaccine type, specific influenza types/subtypes, or history of previous vaccination were not possible.

Third, patients missing verified vaccination status were excluded from the main analysis. However, a sensitivity analysis showed that including patients with unverified but self-reported vaccination information likely introduced misclassification and diluted the observed association. If influenza case patients who were excluded because of unknown vaccination were indeed not vaccinated, then the findings could have overestimated the true odds ratios (and underestimated the vaccine effectiveness). Fourth, although the study comprised a diverse population, it included only 4 US geographical areas, which may prevent direct extrapolation of the findings to other settings. Fifth, the study included only a few influenza seasons during which vaccine strains were generally well matched with the circulating influenza strains.[40] Sixth, it is possible that some pneumonia cases were secondary to an earlier influenza infection that could have been missed by the tests. However, this concern is most likely not of substantial importance because the median time from disease onset to hospitalization was only 3 days. Furthermore, the study focused on pneumonia hospitalizations only, and additional studies in the ambulatory setting would be useful to complement these findings.[2,7]

CONCLUSIONS

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Among children and adults hospitalized with community-acquired pneumonia, those with laboratory-confirmed influenza-associated pneumonia, compared with those with pneumonia not associated with influenza, had lower odds of having received influenza vaccination.

ARTICLE INFORMATION

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Author Contributions: Drs Grijalva and Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Grijalva, Williams, Ampofo, Pavia, Stockmann, McCullers, Arnold, Anderson, Finelli, Jain, Edwards.

Acquisition, analysis, or interpretation of data: Grijalva, Zhu, Williams, Self, Pavia, Stockmann, Arnold, Wunderink, Anderson, Lindstrom, Fry, Foppa, Finelli, Bramley, Jain, Griffin, Edwards.

Drafting of the manuscript: Grijalva, Ampofo, Stockmann, Anderson, Finelli, Jain.

Critical revision of the manuscript for important intellectual content: Grijalva, Zhu, Williams, Self, Pavia, Stockmann, McCullers, Arnold, Wunderink, Anderson, Lindstrom, Fry, Foppa, Finelli, Bramley, Jain, Griffin, Edwards.

Statistical analysis: Grijalva, Zhu, Williams, Stockmann, Finelli.

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Study supervision: Grijalva, Self, Stockmann, Finelli, Jain, Edwards.

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