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Effectiveness of Nonadjuvanted Monovalent Influenza A(H1N1) pdm09 Vaccines for Preventing Reverse Transcription Polymerase Chain Reaction–Confirmed Pandemic Influenza Hospitalizations: Case-Control Study of Children and Adults at 10 US Influenza Surveillance Network Sites

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During 2009–2010, we examined 217 patients hospitalized with laboratory-confirmed pandemic influenza in 9 Influenza Hospitalization Surveillance Network sites and 413 age- and community-matched controls and found that a single dose of monovalent nonadjuvanted influenza A(H1N1)pdm09 vaccine was 50% (95% confidence interval, 13%–71%) effective in preventing hospitalization associated with A(H1N1) pdm09 virus infection.

Keywords. influenza; influenza vaccines; vaccine effectiveness; hospitalization; pandemic/prevention & control.

The 2009 influenza A(H1N1) pandemic, which began in 2009 and continued into 2010, resulted in increased hospitalizations in the United States and globally [1, 2]. A recent review reported that monovalent A(H1N1)pdm09 vaccines were 69% effective in preventing medically attended influenza during the pandemic [3]. Studies focused specifically on hospitalization have reported estimates of vaccine effectiveness (VE) that ranged from 49% to 90% [3–6]; however, to date, no estimate of VE against these outcomes in the United States has been published.

METHODS

We identified patients with community-acquired, laboratory-confirmed A(H1N1)pdm09 infections through the Influenza Hospitalization Surveillance Network (FluSurv-NET) within the Centers for Disease Control and Prevention’s (CDC) Emerging Infections Program. FluSurv-NET conducts population-based surveillance of influenza-associated hospitalizations among children and adults from select counties in 9 states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee) that represent approximately 7.3% of the US population [1, 7]. Although A(H1N1) pdm09 vaccine was initially only available to priority groups [8], enrollment for this study started after vaccine became available to the general population and at least 10% of the local population was estimated to be vaccinated (November–December 2009; Supplementary Figure). Cases were patients aged >6 months residing in a FluSurv-NET catchment area who tested positive for A(H1N1)pdm09 influenza by reverse transcription polymerase chain reaction (RT-PCR) assay from respiratory specimens collected shortly before (1%) or upon (99%) admission to the hospital for an acute respiratory illness; 86% of specimens were collected within 7 days of illness onset. Patients in long-term care facilities and those with nosocomial infections were not enrolled.

For each RT-PCR-confirmed hospitalized influenza case, 2 community controls matched by age group and county of residence were enrolled. Persons who had not been hospitalized for a respiratory illness from 1 October 2009 until the hospital admission date of a corresponding case were eligible for enrollment. Control children were matched on differing age bands depending on age (children aged 7–23 months were matched ±2 weeks of the case’s birth; those aged 24–59 months were matched ±2 months of the case’s birth; children aged 5–13
years were matched in 3- or 4-year age bands, ie, 5–7 years, 8–10 years, 11–13 years, and 14–17 years; and adults were matched in 5-year age bands, with the exception of a single 18–24 years age band). Controls were recruited from individuals identified through birth certificate registries (for children aged <5 years) or lists of random landline telephone numbers (for those aged ≥5 years). Structured telephone interviews (forms available upon request) were conducted with cases after hospital discharge and their matched controls; guardians were available upon request) were conducted with cases after hospital discharge and their matched controls; guardians were interviewed for participants aged <18 years. Participant characteristics, vaccination status and date, and the presence of medical conditions associated with increased risk of influenza complications [9] were collected from telephone interviews, from reviews of medical records at primary care providers, and through review of hospital records for hospitalized cases. Receipt of at least 1 dose of vaccine was documented by medical record or by self-report (if date and location of vaccination could be provided). High-risk conditions and vaccination status were documented by self-report only for the 35% of cases and 34% of controls for whom medical records were unavailable.

Immunization was defined as receipt of any monovalent A (H1N1)pdm09 vaccine ≥14 days before illness onset for the case; for matched controls, the illness onset date of their corresponding case was used. VE was estimated as 100% × (1 – odds ratio [ratio of odds of being immunized among the cases to the odds of being immunized among the controls]) using conditional logistic regression models. The following covariates in our adjusted models were similar to those used in other recent pandemic VE studies [5, 6, 8]: age, race, ethnicity, region, high-risk medical condition, and month of index-case illness onset. Other covariates were considered for inclusion in the model as confounders if they were related to both vaccination and influenza status or if they affected the VE point estimate by >5%.

We estimated that 78 cases were needed to achieve 80% power (α = .05) to detect a VE of 60% with 2 controls per case and a vaccination rate of 30% among controls.

Each participating site submitted a protocol for evaluation by their state institutional review board (IRB), and IRB approval was obtained if required.

RESULTS

From 5 December 2009 to 30 April 2010, a total of 329 hospitalized patients with RT-PCR–confirmed A(H1N1)pdm09 infection were identified as potential study cases; 24 pediatric and 88 adult patients were excluded either because they did not give consent (n = 107) or because vaccination status could not be confirmed (n = 5). Enrolled cases were similar to all eligible cases with respect to age and onset month (data not shown). Only 1 matched control was enrolled for 10% of the cases (21 of 217).

Compared with community controls, hospitalized influenza cases were more likely to be non-white, Hispanic, and unmarried; have less education and lower incomes; lack private healthcare insurance; be obese; and have high-risk medical conditions (Table 1). Among cases, the proportion immunized differed by age; among controls, Hispanics and those with a high-risk medical condition were more likely to be immunized; no other significant association between participant characteristics and immunization status was observed.

Among 217 hospitalized influenza cases, 14% were immunized compared to 22% immunized among 413 community controls. The crude VE against A(H1N1)pdm09 for prevention of hospitalization was 38% (95% confidence interval [CI], 4%–61%) for all ages. The VE adjusted for age, race, ethnicity, region, high-risk respiratory condition, and month of index case illness onset was 46% (11%–67%). Potential confounding was observed for education, insurance status, and presence of a nonpulmonary high-risk medical condition. Adding these to the multivariate model resulted in a fully adjusted VE of 50% (95% CI, 13%–71%). Hispanic ethnicity, lower education, lack of healthcare insurance, and pulmonary and nonpulmonary high-risk medical conditions were all statistically significant contributors in the final multivariate model (data not shown).

In secondary stratified analyses, the adjusted VE for those with 1 or more high-risk medical condition was 54% (95% CI, 16%–75%), and the VE point estimate for those without a high-risk condition was similar at 46% (95% CI, –89% to 84%), although confidence intervals were wide given the small number of cases without a high-risk condition. In sensitivity analyses, VE estimates were unchanged when those vaccinated 7–13 days prior to the illness onset of the index case were considered immunized.

DISCUSSION

We estimated that during the winter wave of the 2009 influenza A(H1N1)pdm09 pandemic in the United States, a single dose of monovalent nonadjuvanted A(H1N1)pdm09 vaccine was 50% (95% CI, 13%–71%) effective in preventing hospitalization associated with A(H1N1)pdm09 virus infection. This finding is similar to the adjusted VE of 56% (23%–75%) against medically attended A(H1N1)pdm09 influenza reported by a US study with the same vaccine options in which 9% of the cases were hospitalized [8]. Our VE point estimate of 50% was consistent with VE estimates in an Australian study of hospitalization and unadjuvanted pandemic vaccine that used a test-negative control design (VE = 49%; 95% CI, 13%–70%) [6], but was substantially lower than the inpatient VE reported by a European study of adjuvanted pandemic vaccine that used a test-negative control design (VE = 90%; 95% CI, 48%–100%) [5].

The strengths of this study include case ascertainment through population-based surveillance and confirmation of
Table 1. Characteristics of Hospitalized Influenza Cases and Nonhospitalized Age- and Community-Matched Controls and the Percentage of Monovalent A(H1N1)pdm09 Immunized

| Characteristic of Participant or of Interviewed Parent if Aged <18 y | Characteristics of Cases vs Controls | % Monovalent A(H1N1)pdm09 Immunized Among Cases and Controls |
|---------------------------------------------------------------|----------------------------------|---------------------------------------------------------------|
|                                                               | No.  (Col. %) | Nonhospitalized Controls a | PValue b | No.  (Row %) | PValue c | No.  (Row %) | PValue c |
| Total participants                                            | 217  (Col. %) | 413                        | NS       | 31  (14) | NS       | 90  (22) | NS |
| Sex, female                                                  | 120  (55) | 230 (55) | NS | 16  (13) | NS | 44  (19) | NS |
| Age category                                                  | NS | <.01 | NS | NS | NS | NS | NS |
| 7 mo–8 y                                                     | 30  (14) | 54 (13) | NS | 3  (10) | NS | 13  (24) | NS |
| 9–17 y                                                       | 8   (4) | 19 (5) | NS | 4  (50) | NS | 2  (11) | NS |
| 18–49 y                                                      | 125 (57) | 239 (58) | NS | 13  (10) | NS | 45  (19) | NS |
| 50–64 y                                                      | 47 (22) | 87 (21) | NS | 8  (17) | NS | 25  (29) | NS |
| ≥65 y                                                         | 7   (3) | 14 (3) | NS | 3  (43) | NS | 5  (36) | NS |
| Race, white                                                   | 119 (55) | 305 (74) | <.001 | 20 (17) | NS | 72 (24) | NS |
| Ethnicity, Hispanic                                          | 37 (17) | 27 (6) | <.001 | 6 (16) | NS | 10 (37) | <.05 |
| Region                                                       | NS | NS | NS | NS | NS | NS | NS |
| North (CT, MD, MN)                                           | 39 (18) | 73 (17) | NS | 6 (15) | NS | 17 (23) | NS |
| South (GA, TN)                                               | 129 (59) | 246 (60) | NS | 17 (13) | NS | 50 (20) | NS |
| West (CA, CO, NM, OR)                                        | 49 (23) | 94 (23) | NS | 8 (16) | NS | 23 (24) | NS |
| Married or living with partner d                             | 88 (41) | 203 (49) | <.05 | 15 (17) | NS | 46 (23) | NS |
| Household size (excluding self)                              | NS | NS | NS | NS | NS | NS | NS |
| 0–1                                                          | 73 (34) | 117 (28) | NS | 9 (12) | NS | 22 (19) | NS |
| 2–3                                                          | 89 (41) | 199 (48) | NS | 17 (19) | NS | 44 (22) | NS |
| ≥4                                                           | 55 (25) | 97 (24) | NS | 5 (9) | NS | 24 (25) | NS |
| Child in household                                           | 111 (51) | 230 (56) | NS | 15 (14) | NS | 55 (24) | NS |
| Education of participant/parent d                            | <.001 | NS | NS | NS | NS | NS | NS |
| High school diploma or less                                  | 100 (46) | 76 (18) | 11 (11) | 16 (21) | NS | 23 (24) | NS |
| Some college                                                 | 69 (32) | 97 (24) | 10 (15) | 23 (24) | NS | 21 (25) | NS |
| Bachelor’s degree or higher                                  | 48 (22) | 240 (58) | 10 (21) | 51 (21) | NS | 51 (21) | NS |
| Annual household income                                      | <.001 | NS | NS | NS | NS | NS | NS |
| Missing or not applicable                                    | 40 (18) | 56 (13) | 4 (10) | 14 (25) | NS | 16 (25) | NS |
| <$35 000                                                     | 84 (39) | 52 (13) | 10 (12) | 15 (29) | NS | 15 (29) | NS |
| $35 000–$69 999                                              | 52 (24) | 115 (28) | 9 (17) | 17 (15) | NS | 17 (15) | NS |
| ≥$70 000                                                     | 41 (19) | 190 (46) | 8 (20) | 21 (11) | NS | 21 (11) | NS |
| Insurance                                                    | <.001 | NS | NS | NS | NS | NS | NS |
| No insurance                                                 | 39 (18) | 22 (5) | 2 (5) | 5 (23) | NS | 16 (23) | NS |
| Medicaid/Medicare                                            | 84 (39) | 56 (13) | 16 (19) | 16 (29) | NS | 16 (29) | NS |
| Private insurance only                                       | 94 (43) | 335 (81) | 13 (14) | 69 (21) | NS | 69 (21) | NS |
### Table 1 continued.

| Characteristic of Participant or of Interviewed Parent if Aged <18 y | Characteristics of Cases vs Controls | % Monovalent A(H1N1)pdm09 Immunized Among Cases and Controls |
|-------------------------------------------------|-------------------------------------|-----------------------------------------------------------|
| | Hospitalized Influenza Cases | Nonhospitalized Controlsa | P Valueb | Hospitalized Influenza Cases | Nonhospitalized Controlsa | P Valuec |
| No. | (Col. %) | No. | (Col. %) | P Valueb | No. | (Row %) | P Valuec | No. | (Row %) | P Valuec |
| Medical home with primary provider | 180 (83) | 342 (83) | NS | 28 (16) | NS | 77 (23) | NS |
| Obese (BMI ≥30 kg/m²) | 83 (38) | 89 (22) | <.001 | 10 (12) | NS | 22 (25) | NS |
| High-risk medical conditionsg | 184 (85) | 187 (45) | <.001 | 27 (15) | NS | 49 (26) | <.05 |
| Respiratory condition | 110 (51) | 74 (18) | <.001 | 17 (16) | NS | 22 (30) | NS |
| Other high-risk condition | 154 (71) | 153 (37) | <.001 | 23 (15) | NS | 40 (26) | NS |
| Vaccination and immunization | | | | | | | |
| Monovalent A(H1N1)pdm09 vaccinationf | 54 (25) | 123 (30) | NS | 31 (57) | <.001 | 90 (73) | <.001 |
| Monovalent A(H1N1)pdm09 immunizationf | 31 (14) | 88 (21) | <.05 | . . . . . . | . . . . | . . . . |
| 2009–10 seasonal influenza vaccinationf | 87 (40) | 137 (33) | NS | 21 (24) | <.001 | 53 (39) | <.001 |

Abbreviations: BMI, body mass index; CA, California; CO, Colorado; CT, Connecticut; GA, Georgia; MD, Maryland; MN, Minnesota; NM, New Mexico; NS, not statistically significant (P > .05); OR, Oregon; TN, Tennessee.

* Two controls who had not been hospitalized for a respiratory illness since 1 October 2009 were recruited matched by age and community. For cases aged 7–23 months, controls were within plus or minus (±) 2 weeks of the case's age at illness onset; for cases aged 24–59 months, controls were ±2 months of the case’s age. Potential controls for cases aged <5 years were selected at random from birth certificate registries and matched to the case’s zip code. For cases aged >5 years, controls were within ±7 years of the case’s age, resided in the case’s county, and were contacted from a telephone sampling list generated by Survey Sampling International (Shelton, Connecticut).

* Pearson χ² test was used to assess differences between cases and controls in the distribution of participant characteristics.

* Pearson χ² test was used to assess differences between participant characteristic groups (rows) in the percentage vaccinated; differences in vaccination by participant characteristics were tested separately with cases and then controls.

* Characteristic describes interviewed parent/caregiver when participant is aged <18 years.

* High-risk respiratory conditions included lung disease and asthma as indicated by self-report of physician diagnosis and/or a medical encounter with International Classification of Disease (ICD-9 codes available upon request. Other high-risk medical conditions were indicated by self-report of physician diagnosis and/or 1 or more medical visits for a condition associated with increased risk of influenza complications, including cancer, diabetes, and neurological disorders as well as heart, immune, and kidney disease (ICD codes available upon request). Medical conditions were determined by self-report for 35% of cases and 34% of controls with missing or unavailable medical records.

* Vaccination is defined as receipt of at least 1 dose of vaccine documented by medical record or self-report (if date and location were also provided); immunization is defined as receipt of any A(H1N1)pdm09 vaccine ≥14 days before illness onset of the case or index case if a matched control. The difference between the number vaccinated and the number immunized reflects the fact that 15 cases and 24 controls were vaccinated after the illness onset date (of the index case) and 8 cases and 11 controls were vaccinated 1–13 days before the illness onset date. Vaccination status and dates were determined by self-report for 35% of cases and 34% of controls with missing or unavailable medical records.

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influenza by RT-PCR. The study addresses a gap in knowledge regarding VE against serious influenza complications during the pandemic and the VE of nonadjuvanted vaccines, which may have fewer local and systemic reactions but can be less immunogenic in some populations [10].

Our study also has limitations. First, cases and matched controls differed on multiple characteristics. Although adjusting for potential confounders increased the VE point estimate from 38% to 50%, residual or unmeasured confounding may have biased our results in unknown ways. Second, our limited sample size resulted in VE estimates with wide confidence intervals and precluded stratification by age or consideration of site differences in a mixed-effects model. Third, our findings may have been influenced by information and selection biases, as only residents with telephone landlines could be enrolled as controls (for those aged ≥5 years) and medical history was incomplete for one-third of cases and controls. Because the proportion with missing information was similar for cases and controls, we do not expect this was a significant source of bias, but bias could have been introduced if the likelihood of recalling vaccination differed for cases vs controls with only self-report data. Fourth, information on vaccine type (inactivated vs live attenuated) and on receipt of a second recommended dose (among children aged <10 years) was not available for every subject, which likely resulted in underestimation of VE, as other studies found that VE improved after accounting for these differences [8]. Finally, similar to other VE estimates [5, 6, 8], we lacked information on medical utilization or possible infections during earlier waves of the pandemic. Natural immunity acquired from infection prior to the availability of vaccine would lead to over- or underestimating VE if those immune were more or less likely to be vaccinated, respectively.

In conclusion, our results suggest that a single dose of monovalent nonadjuvanted A(H1N1)pdm09 vaccine prevented one-half of the potential hospitalizations associated with A(H1N1)pdm09 virus infection. This finding from the FluSurv-NET, which serves geographically and economically diverse communities across the United States, confirms previous reports of the preventive benefit of the vaccine [8, 11] and adds to the evidence indicating that influenza vaccines have the potential to prevent a substantial proportion of influenza-associated hospitalizations [12].

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. W. S. serves as a consultant for Pfizer, Inc, and Dynavax Technologies; has received an honorarium from Sanofi Pasteur; and is a member of the Advisory Board for the data safety monitoring board for Merck & Co, Inc. R. I. has received royalties from a book chapter published by Blackwell-Wiley and travel expenses partially paid by the Global Pertussis Initiative (Parexel International). All other authors report no potential conflicts.

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