Effectiveness of Monovalent 2009 Pandemic Influenza A Virus Subtype H1N1 and 2010–2011 Trivalent Inactivated Influenza Vaccines in Wisconsin During the 2010–2011 Influenza Season

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Background. The 2009 influenza A virus subtype H1N1 (A[H1N1]pdm09) did not exhibit antigenic drift during the 2010–2011 influenza season, providing an opportunity to investigate the duration of protection after vaccination. We estimated the independent effects of 2010–2011 seasonal trivalent inactivated influenza vaccine (TIV) and A(H1N1)pdm09 vaccine for preventing medically attended influenza A virus infection during the 2010–2011 season.

Methods. Individuals were tested for influenza A virus by real-time reverse transcription polymerase chain reaction (rRT-PCR) after a clinical encounter for acute respiratory illness. Case-control analyses compared participants with rRT-PCR–confirmed influenza A virus infection and test-negative controls. Vaccine effectiveness was estimated separately for monovalent pandemic vaccine and TIV and was calculated as 100 × [1 – adjusted odds ratio], where the odds ratio was adjusted for potential confounders.

Results. The effectiveness of TIV against influenza A virus infection was 63% (95% confidence interval [CI], 37%–78%). The effectiveness of TIV against A(H1N1)pdm09 infection was 77% (95% CI, 44%–90%). Monovalent vaccine administered between October 2009 and April 2010 was not protective during the 2010–2011 season, with an effectiveness of −1% (95% CI, −146% to 59%) against A(H1N1)pdm09 infection.

Conclusions. Monovalent vaccine provided no sustained protection against A(H1N1)pdm09 infection during the 2010–2011 season. This waning effectiveness supports the need for annual revaccination, even in the absence of antigenic drift in A(H1N1)pdm09.

Keywords. case-control studies; effectiveness; epidemiology; influenza; vaccine.
the H1N1 component in the 2010–2011 trivalent influenza vaccine [4]. In the United States, A(H3N2) was the predominant virus during the 2010–2011 season, but A(H1N1)pdm09 and influenza B virus also circulated widely [5]. A(H1N1)pdm09 did not exhibit antigenic drift during the 2010–2011 influenza season [6–8]. These circumstances provided an opportunity to investigate cumulative protection and waning effectiveness of influenza vaccines, independent of substantial antigenic variation.

Studies in Europe have suggested that receipt of monovalent A(H1N1)pdm09 vaccine during the 2009–2010 pandemic season and receipt of 2010–2011 seasonal trivalent influenza vaccine during the 2010–2011 season conferred greater protection against real-time reverse transcription polymerase chain reaction (rRT-PCR)–confirmed A(H1N1)pdm09 infection during the 2010–2011 season, compared with receipt of either vaccine alone [9, 10]. In these studies, receipt of adjuvanted monovalent vaccine during the pandemic did not provide significant protection against A(H1N1)pdm09 infection in 2010–2011 in the absence of seasonal vaccination, suggesting declining immunity to A(H1N1)pdm09 across seasons [9, 10]. The implication of these findings for immunity to influenza virus in the United States is unclear. Influenza vaccines containing adjuvant(s) have been widely used in Europe, but the Food and Drug Administration (FDA) has not licensed any pandemic or seasonal adjuvant-containing influenza vaccines in the United States.

The objective of this study was to assess the independent and combined effects of unadjuvanted monovalent A(H1N1)pdm09 vaccine (received between October 2009 and April 2010) and 2010–2011 seasonal trivalent inactivated influenza vaccine (TIV) for prevention of medically attended infection due to influenza A virus (A[H1N1]pdm09 or A[H3N2]) during the 2010–2011 influenza season. We assessed vaccine effectiveness for monovalent inactivated A(H1N1)pdm09 vaccine (MIV) and monovalent live-attenuated A(H1N1)pdm09 vaccine (MLV) separately. We prospectively enrolled and tested patients from a population cohort and estimated vaccine effectiveness by use of methods similar to those used to study influenza vaccine effectiveness in previous seasons [11, 12].

METHODS

Source Population

The source population included residents of the Marshfield Epidemiologic Study Area (MESA), a dynamic, population-based cohort of approximately 54,000 people in a 14–zip code area surrounding the Marshfield Clinic campus in Marshfield, Wisconsin [13]. Within this area, Marshfield Clinic data systems capture >97% of residents, 99% of deaths, and 90% of outpatient visits [13]. The effectiveness of influenza vaccines against medically attended rRT-PCR–confirmed influenza has been estimated in this population since the 2004–2005 influenza season [11, 12].

Individuals were eligible to participate in this study if they had at least 12 months of continuous residency in MESA (individuals <12 months old were eligible if they resided in MESA since birth) and had a healthcare encounter for acute respiratory illness during the 2010–2011 influenza season. Infants <6 months of age were not eligible because influenza vaccines are not licensed for this age group. During the 2009–2010 pandemic, the Advisory Committee on Immunization Practices (ACIP) recommended that target groups (ie, pregnant women, persons who live with or provide care for infants aged <6 months, healthcare and emergency medical services personnel, children and young adults aged 6 months–24 years, and persons aged 25–64 years who have medical conditions that put them at higher risk for influenza-related complications) be vaccinated first, followed by vaccination of the rest of the population as vaccine availability increased [14].

Individuals were classified as having a high-risk medical condition if they had ≥1 visit to the Marshfield Clinic during 2010 that involved a prespecified International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for a high-risk condition. These included diagnoses in the following chronic disease categories: cerebrovascular, cardiac, pulmonary, renal, liver, neurological/musculoskeletal, metabolic, circulatory system, diabetes mellitus, immunosuppressive disorders, and malignancies. A full list of specific codes is available on request.

Influenza Vaccination Status

Vaccination status was determined by a real-time, Internet-based registry used by all providers serving the population (information available at: http://www.recin.org). Recent validation demonstrated that this registry captured 95% of all influenza vaccinations received by patients enrolled in a study during a previous season [15]. Vaccination status was a time-dependent variable, and participants were considered immunized if a dose of vaccine was received ≥14 days before symptom onset. The ACIP recommends that children <9 years old receive 2 doses during their first season of vaccination [16], and partially vaccinated children were excluded from the analysis.

Enrollment and Sample Collection

Study recruitment was initiated on 17 January 2011, when there was evidence of initial influenza virus transmission in the community. Enrollment continued for 12 weeks, ending on 8 April 2011. Members of the study cohort were recruited after an inpatient or outpatient medical encounter for acute respiratory illness with subjective fever or cough. Trained research coordinators screened and obtained consent from participants and collected swab specimens for influenza diagnosis after the clinical encounter was complete. Combined nasal
and oropharyngeal swab specimens were obtained by research coordinators from all participating patients. Physicians and clinical staff were not involved in patient recruitment or sample collection. Individuals with an illness duration of >7 days (at the time of the encounter) were excluded because of the increased potential for false-negative test results [17].

Research coordinators used an electronic appointment system to screen chief complaints and identify potential study participants in primary care departments (including departments of pediatrics, family practice, internal medicine, and urgent care) on weekdays, evenings, and weekends. If the chief complaint indicated respiratory symptoms or febrile illness, the patient was approached to determine eligibility and interest. Patients were also screened and enrolled if they were seen in the emergency department or admitted to an acute care hospital contiguous with Marshfield Clinic (St. Joseph’s Hospital). Most patients with acute respiratory illness who were not approached during the medical encounter were identified using electronic diagnostic codes entered by the clinician (ICD-9-CM codes 382.0, 382.4, 382.9, 460–466, 480, 483–486, 487, 490, 780.6, 786.2), contacted the following day, and invited to participate. A swab specimen was collected from those who met eligibility criteria and consented to participate.

Each participant (or parent) completed an interview to assess onset date and illness symptoms. Patients could be re-enrolled with a new illness after a 14-day exclusion period to allow for recovery from the first illness. The Marshfield Clinic Research Foundation Institutional Review Board reviewed and approved this study, and all participants or parents gave written informed consent for influenza virus testing.

**Laboratory Methods**

Swabs were placed in M4 viral transport medium and refrigerated or kept on ice until delivery to the Marshfield Clinic Research Foundation laboratory on the same day. Samples were routinely processed within 1 day after collection, and samples obtained on weekends were tested on Monday. Nucleic acid was extracted from samples by using the Roche MagNA Pure Total Nucleic Acid Kit (Roche Diagnostics, Indianapolis, IN), and rRT-PCR was performed using the LightCycler Real-Time PCR System (Roche Diagnostics, Basel, Switzerland). The US Centers for Disease Control and Prevention Influenza Division provided sequence information for rRT-PCR primers and probes. The TaqMan-based rRT-PCR assay detects 2 highly conserved influenza virus genes: the matrix gene of influenza A virus and the nonstructural gene of influenza B virus. A human RNase P gene served as a positive control for human nucleic acid. Virus subtyping by rRT-PCR was performed on all samples with a test result positive for influenza A virus.

**Calculation of Vaccine Effectiveness**

Influenza vaccine exposure during 2 periods (the 2009–2010 pandemic period and the 2010–2011 season) was defined as a 6-level variable incorporating different combinations of MIV, MLV, and TIV. Exposure categories included receipt of MIV only, receipt of MLV only, receipt of TIV only, receipt of MIV plus TIV (MIV + TIV), and receipt of MLV plus TIV (MLV + TIV). The referent group of unvaccinated individuals did not receive any of the 3 vaccines. The number of participants who received 2010–2011 seasonal live-attenuated influenza vaccine was insufficient to generate separate vaccine effectiveness estimates, and these subjects were excluded. Patients were also excluded if they received both MIV and MLV or if they received a pandemic vaccine of unknown type.

The primary outcome was medically attended influenza A virus infection confirmed by rRT-PCR during the 2010–2011 season. The vaccine effectiveness was estimated as [1 - adjusted odds ratio] × 100, where the odds ratio is based on the odds of vaccine receipt among cases (ie, patients with laboratory confirmed influenza) vs the odds of vaccine receipt among controls (ie, patients with medically attended acute respiratory illness who were rRT-PCR-negative for influenza A virus). In addition, estimates of vaccine effectiveness were generated for the outcomes of A(H1N1)pdm09 infection and A(H3N2) infection. Patients testing positive for influenza B virus were excluded.

Study participants were identified prospectively throughout the study period, independent of vaccination status. Because this study design approximated incidence-density sampling, the odds ratio provided a valid estimate of the incidence rate ratio, even though the outcome (influenza A virus infection) was not rare [18]. Logistic regression models were adjusted for sex, age category (<9 years, 9–17 years, 18–49 years, and ≥50 years), date of enrollment (in 3-week intervals), high-risk status, and receipt of 2009–2010 seasonal vaccine. The Firth penalized maximum likelihood estimation [19] was used to estimate the effectiveness of each vaccine exposure category against A(H1N1)pdm09 infection, since no cases of A(H1N1)pdm09 infection were identified among patients vaccinated with both MLV and TIV. A 95% confidence interval (CI) was calculated for each vaccine effectiveness estimate, and if the interval excluded 0%, the vaccine effectiveness estimate was considered statistically significant. All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC).

**RESULTS**

Of 6113 patients initially screened after a clinical encounter during the 2010–2011 season, 3208 (52%) were ineligible for the study, 1095 (18%) declined to participate, and 1810 were enrolled and tested for influenza A virus. Among ineligible patients, 1552 (48%) had an illness that exceeded the maximum duration of 7
days, and 1381 (43%) did not meet symptom criteria. The latter group included individuals without an acute respiratory illness and individuals with respiratory symptoms that did not include fever (subjective) or cough. An additional 261 patients were excluded because they either tested positive for influenza B virus (n = 26), were partially vaccinated children (n = 137), received live-attenuated 2010–2011 influenza vaccine (n = 84), received both MIV and MLV during the pandemic (n = 10), or received a pandemic vaccine of unknown type (n = 4). Of the 1549 patients included in the analysis, 177 (11.4%) tested positive for influenza A virus by rRT-PCR; 82 (5.3%) were positive for A(H1N1)pdm09, and 95 (6.1%) were positive for A(H3N2). No influenza virus coinfections were found. Weekly counts of cases and controls are shown in Figure 1.

The median age at symptom onset was 28.3 years for cases and 19.0 years for controls (P = .021, by the Wilcoxon rank sum test). The case group had a slightly higher proportion of males than the control group (Table 1). The case and control groups were similar in terms of the proportion with a comorbid condition that increased the risks of complications of influenza. The median interval from symptom onset to swab specimen collection was 3 days for both cases and controls. Controls were enrolled in each of the four 3-week categories approximately equally, and cases were predominantly enrolled in the last three 3-week categories, when influenza A virus was circulating more widely in the community (Table 1). Influenza vaccination was less common among cases, compared with controls, for 3 vaccination categories (TIV only, MIV + TIV, and MLV + TIV). Receipt of MIV only or MLV only occurred with similar frequency among cases and controls. The 2009–2010 seasonal influenza vaccine was received by 53 cases (30%) and 596 controls (43%).

The effectiveness of TIV alone against medically attended influenza A virus infection was 63% (95% CI, 37%–78%), after adjustment for potential confounders (Table 2). In contrast, neither pandemic vaccine alone (ie, MIV or MLV administered in 2009–2010) offered significant protection in the 2010–2011 season, and point estimates were close to 0. The point estimate for the effectiveness of the combination of MIV + TIV was lower than that for TIV alone (adjusted vaccine effectiveness, 51%; 95% CI, 9%–73%), while the point estimate for the effectiveness of MLV + TIV was higher than that for TIV alone (adjusted vaccine effectiveness, 79%; 95% CI, 9%–95%). However, effectiveness of either combination did not differ significantly (by the Fisher exact test) from receipt of TIV alone.

In secondary analyses, vaccine effectiveness estimates were calculated separately for prevention of A(H1N1)pdm09 infection and A(H3N2) infection (Table 2). Vaccine effectiveness against each subtype paralleled trends from the primary analysis, with TIV providing significant protection and neither pandemic vaccine alone offering protection. Vaccine effectiveness against A(H1N1)pdm09 and A(H3N2) paralleled trends from the primary analysis, with TIV providing significant protection and neither pandemic vaccine alone offering protection. In addition, compared with TIV, the point estimates for

Figure 1. Number of patients with medically attended acute respiratory illness (ARI) who were negative (controls) or positive (cases) for influenza A virus and percentage who were positive for influenza A virus, by week. Influenza A virus positivity was determined by real-time reverse transcription polymerase chain reaction analysis. Enrollment began 17 January 2011 and concluded 8 April 2011.
Table 1. Demographic Characteristics of Patients With Medically Attended Acute Respiratory Illness Who Were Positive (Cases) or Negative (Controls) for Influenza A Virus, January–April 2011

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, No. (%) (n = 177)</th>
<th>Controls, No. (%) (n = 1372)</th>
<th>P*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>44 (24.9)</td>
<td>423 (30.8)</td>
<td>.107</td>
</tr>
<tr>
<td>9–17</td>
<td>25 (14.1)</td>
<td>246 (17.9)</td>
<td></td>
</tr>
<tr>
<td>18–49</td>
<td>67 (37.9)</td>
<td>446 (32.5)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>41 (23.2)</td>
<td>257 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>84 (47.5)</td>
<td>565 (41.2)</td>
<td>.111</td>
</tr>
<tr>
<td>High-risk medical condition</td>
<td>46 (26.0)</td>
<td>402 (29.3)</td>
<td>.360</td>
</tr>
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<table>
<thead>
<tr>
<th>Interval from symptom onset to swabbing, d</th>
<th>Cases, No. (%) (n = 177)</th>
<th>Controls, No. (%) (n = 1372)</th>
<th>P*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>78 (44.1)</td>
<td>520 (37.9)</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>56 (31.6)</td>
<td>458 (33.4)</td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>31 (17.5)</td>
<td>243 (17.7)</td>
<td></td>
</tr>
<tr>
<td>7–8</td>
<td>12 (6.8)</td>
<td>151 (11.0)</td>
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<table>
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<tr>
<th>Vaccine(s) received</th>
<th>Cases, No. (%) (n = 177)</th>
<th>Controls, No. (%) (n = 1372)</th>
<th>P*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noneb</td>
<td>116 (65.5)</td>
<td>626 (45.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIV only</td>
<td>21 (11.9)</td>
<td>309 (22.5)</td>
<td>.001</td>
</tr>
<tr>
<td>MLV only</td>
<td>11 (6.2)</td>
<td>73 (5.3)</td>
<td>.621</td>
</tr>
<tr>
<td>MLV only</td>
<td>6 (3.4)</td>
<td>39 (2.8)</td>
<td>.683</td>
</tr>
<tr>
<td>MLV + TIV</td>
<td>21 (11.9)</td>
<td>265 (19.3)</td>
<td>.016</td>
</tr>
<tr>
<td>MIV + TIV</td>
<td>2 (1.1)</td>
<td>60 (4.4)</td>
<td>.038</td>
</tr>
</tbody>
</table>

Influenza A virus positivity was determined by real-time reverse transcription polymerase chain reaction analysis.

Abbreviations: A(H1N1)pdm09, 2009 pandemic influenza A virus subtype H1N1; MLV, monovalent inactivated A(H1N1)pdm09 vaccine; MLV, monovalent live-attenuated A(H1N1)pdm09 vaccine; TIV, 2010–2011 seasonal trivalent inactivated influenza vaccine.

* By the 2-tailed χ² test or Fisher exact test, as appropriate.

b Subjects did not receive MIV, MLV, or TIV but might have received 2009–2010 seasonal influenza vaccine.

MIV + TIV were lower and the point estimates for MLV + TIV were higher (Table 2), albeit with wide CIs. Overall, vaccines showed lower effectiveness against A(H3N2) infection as compared to A(H1N1)pdm09 infection, but CIs were overlapping.

Three sensitivity analyses were conducted. First, we restricted analyses to participants with ≤3 days from symptom onset to specimen collection, to further minimize the potential for negative rRT-PCR results and misclassification of case status. Second, we restricted the models to participants aged 2–49 years, the ages for which live-attenuated influenza vaccine is licensed [16], to ensure that vaccine exposure groups contained participants in the same age range. Finally, we included partially vaccinated children in the model, to determine whether partial vaccination influences the overall vaccine effectiveness estimate.

The vaccine effectiveness estimates for all 3 sensitivity analyses were similar to that for the primary analysis. In these analyses, receipt of TIV offered moderate protection against medically attended influenza A virus infection, whereas receipt of monovalent vaccine conferred no protection in 2010–2011 (data not shown). These findings suggest that differential misclassification of case status and age-specific differences in vaccine effectiveness did not influence the primary results. Although we were unable to estimate vaccine effectiveness separately for partially vaccinated children, we found that vaccine effectiveness estimates were similar when these children were included in the analysis.

**DISCUSSION**

We found that 2010–2011 seasonal vaccine was 63% effective for preventing medically attended influenza A virus infection in this population. The effectiveness of TIV against A(H1N1)pdm09 in the 2010–2011 season is consistent with studies in other populations [9, 10, 20], with 56% effectiveness reported for unadjuvanted A(H1N1)pdm09 vaccine against A(H1N1)pdm09 infection during the pandemic [21], and with a 4-site US study of TIV effectiveness against influenza during the 2010–2011 season [22]. However, we found that receipt of MIV alone or MLV alone did not confer protection against medically attended A(H1N1)pdm09 infection during the 2010–2011 season. Our results suggest that unadjuvanted vaccines containing A(H1N1)pdm09 provided protection against A(H1N1)pdm09 infection during the same season of vaccine receipt but that the protective effect of unadjuvanted monovalent A(H1N1)pdm09 vaccines waned from the pandemic period to the 2010–2011 season, similar to previous studies involving adjuvanted vaccines [9, 10].

The waning effectiveness of unadjuvanted monovalent A(H1N1)pdm09 vaccine that we observed is consistent with longitudinal immunogenicity studies. The major correlate of protection for influenza vaccine-induced immunity is hemagglutination inhibition antibody titer [23], and multiple serologic studies have shown that postvaccination antibody titers decline over time. For example, seroconversion and seroprotection rates decreased significantly from 1 month to 10 months after vaccination with unadjuvanted A(H1N1)pdm09 vaccine [24]. Among adults >50 years old, seroprotection rates declined rapidly over 6 months following vaccination with trivalent inactivated vaccine [25]. In addition, an immunogenicity study of inactivated vaccines against A(H1N1)pdm09 found that antibody levels for unadjuvanted vaccine 6 months after vaccination no longer met the FDA Center for Biologics
Evaluation and Research criteria [26]. Waning immune response has also been demonstrated for adjuvanted vaccines. Eight to ten months after vaccination with an AS03-adjuvanted A(H1N1)pdm09 vaccine, vaccinated individuals had only modest increases in neutralizing antibody titers and no differences in T-cell response, compared with unvaccinated individuals [27].

Adjuvanted influenza vaccines have not been licensed in the United States. Vaccines adjuvanted with oil-in-water emulsion may enhance immunogenicity, but they have also been associated with more frequent adverse reactions [26, 28, 29]. The effect of oil-in-water emulsion adjuvants on influenza vaccine efficacy is not yet fully understood. In the United States, the estimated effectiveness of the unadjuvanted monovalent vaccine during the 2009 pandemic was 56% (95% CI, 23%–75%) [21]. Studies of adjuvanted pandemic influenza vaccines have reported similar or higher effectiveness. A recent meta-analysis of influenza vaccine effectiveness reported that the median effectiveness of 5 studies involving adjuvanted monovalent pandemic vaccine was 69% (range, 60%–93%) [30].

This study also provided an opportunity to separately assess the effectiveness of inactivated and live-attenuated monovalent pandemic vaccines for preventing medically attended influenza A virus infection during the following season, in 2010–2011. There was no evidence of protection in 2010–2011 for individuals who received monovalent vaccine alone without subsequent seasonal vaccination. This was true even when the end point was defined as medically attended A(H1N1)pdm09 infection rather than any influenza A virus infection. MLV + TIV resulted in a median effectiveness of 5 studies involving adjuvanted monovalent pandemic vaccine was 69% (range, 60%–93%) [30].

This study included all 2009–2010 seasonal trivalent inactivated influenza vaccine (TIV) recipients, who received monovalent vaccine alone without subsequent seasonal vaccination. This was true even when the end point was defined as medically attended A(H1N1)pdm09 infection rather than any influenza A virus infection. MLV + TIV resulted in a median effectiveness of 5 studies involving adjuvanted monovalent pandemic vaccine was 69% (range, 60%–93%) [30].

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is consistent with additional protection reported for receipt of monovalent A(H1N1)pdm09 and 2010–2011 trivalent vaccines in Europe [9, 10]. Previous studies have reported enhanced immune responses when live-attenuated and inactivated vaccines are received in combination [31, 32]. Because A(H1N1)pdm09 was a novel antigenic variant, it is plausible that initial vaccination with a live-attenuated vaccine produced a priming effect that led to a stronger serologic response when individuals later received seasonal inactivated vaccine. Larger studies with greater power are needed to assess the synergistic effect of live-attenuated vaccine receipt followed by inactivated vaccine receipt the following year.

Strengths of this study include prospective recruitment, use of a validated vaccination registry containing both pandemic and seasonal vaccination records, and rRT-PCR confirmation of influenza A virus infection with subtype determination. rRT-PCR is currently considered the optimal method for laboratory-based confirmation of infection in studies of influenza vaccine effects [33]. In addition, because cases and controls were identified through visits for medically attended acute respiratory illness, the study design accounted for differences in healthcare-seeking behavior between vaccinated and unvaccinated individuals [21].

This study was limited by the relatively small number of individuals who were discordant for vaccine receipt in 2009–2010 (monovalent pandemic vaccine) and seasonal vaccine receipt in 2010–2011. In addition, the point estimate for monovalent vaccine effectiveness was close to 0. These 2 factors contributed to very wide CIs for the effectiveness estimates for monovalent vaccine. We cannot rule out the possibility that unmeasured confounding or random effects (due to small sample size) led to biased estimates of vaccine effectiveness for the pandemic vaccines, although the effectiveness we observed for seasonal vaccine was similar to what has been previously reported. Although cases and controls differed in terms of median age and period of enrollment, these differences were accounted for in the models. The unadjusted and adjusted vaccine effectiveness estimates were similar, indicating that known potential confounders did not have a large effect on vaccine effectiveness. We were not able to examine differences in vaccine effectiveness by age group because of small sample sizes.

In summary, the 2010–2011 inactivated vaccine provided moderate protection against medically attended rRT-PCR-confirmed influenza A virus infection during the 2010–2011 season. We found that receipt of either inactivated or live-attenuated pandemic vaccine during the previous year did not provide protection against either influenza A virus subtype in the 2010–2011 season. These results, together with serologic studies indicating that postvaccination antibody titers decline over the course of 1 year, support the need for annual vaccination against influenza, even in the absence of substantial antigenic drift. This study also highlights the importance of research leading to the development of new influenza vaccines with a longer duration of protection.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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