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Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season

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ABSTRACT

Background: Recent studies have suggested that vaccine-induced protection against influenza may decline within one season. We reanalyzed data from a study of influenza vaccine effectiveness to determine if time since vaccination was an independent predictor of influenza A (H3N2).
Methods: Patients with acute respiratory illness were actively recruited during the 2007–2008 season. Respiratory swabs were tested for influenza, and vaccination dates were determined by a validated immunization registry. The association between influenza RT-PCR result and vaccination interval (days) was examined using multivariable logistic regression, adjusting for calendar time, age and other confounders.
Results: There were 629 vaccinated participants, including 177 influenza A (H3N2) cases and 452 test negative controls. The mean (SD) interval from vaccination to illness onset was 101.7 (25.9) days for influenza cases and 93.0 (29.9) days for controls. There was a significant association between vaccination interval and influenza result in the main effects model. The adjusted odds ratio (aOR) for influenza was 1.12 (CI 1.01, 1.26) for every 14 day increase in the vaccination interval. Age modified the association between vaccination interval and influenza ($p = 0.005$ for interaction). Influenza was associated with increasing vaccination interval in young children and older adults, but not in adolescents or non-elderly adults. Similar results were found when calendar week of vaccine receipt was assessed as the primary exposure variable.
Conclusions: Identification of influenza A (H3N2) was associated with increasing time since vaccination among young children and older adults during a single influenza season.

1. Introduction

Annual influenza vaccination is a key component of influenza prevention and control efforts in the United States. In most seasons, trivalent inactivated influenza vaccine (TIV) provides moderate protection against influenza illness in healthy adults [1], and a hemagglutination inhibition (HI) titer of 1:40 or greater has been associated with clinical protection [2–4]. A systematic review of published studies found that seroprotective titers against influenza A were maintained for >4 months after immunization in almost all studies [5], but recent reports have raised concerns that vaccine induced protection against influenza illness may decline over the course of a single season [6–8].

The goal of this study was to assess evidence for waning protection against influenza A (H3N2) in a community cohort. To do this, we reanalyzed data from an observational study of influenza vaccine effectiveness that was performed during the 2007–2008 influenza season. Vaccine effectiveness against influenza A (H3N2) was 41% in the study population during that season [9]. The Marshfield Clinic Research Foundation has conducted annual assessments of influenza vaccine effectiveness in Wisconsin since 2005, but this analysis focused on the 2007–2008 season because the number of influenza A (H3N2) cases was substantially higher compared to other seasons.

2. Methods

The source population included community-dwelling residents ≥6 months old living in or near Marshfield, Wisconsin [10]. Patients

Abbreviations: HI, hemagglutinin antibody inhibition; TIV, trivalent inactivated influenza vaccine; RT-PCR, reverse transcription polymerase chain reaction; NK, natural killer; ACIP, Advisory Committee on Immunization Practices.

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in this population were screened and enrolled by trained research coordinators during or after an encounter for acute respiratory illness with symptoms of feverishness, chills, or cough. Potential participants with illness duration >7 days were excluded to minimize false negative influenza test results. Enrollment occurred in primary care departments at the Marshfield Clinic main campus, a nearby satellite clinic, and an acute care hospital.

Each participant or parent was interviewed to determine illness onset date. Nasopharyngeal (adults and adolescents) or nasal swabs (children < 12 years) were obtained and tested for influenza by reverse transcription polymerase chain reaction (RT-PCR). Participants were classified as having a high-risk health condition if they had ≥2 medical visits during 2007 with a relevant ICD-9 diagnosis code (list of codes available on request).

Enrollment in the study began on January 21, 2008 based on laboratory identification of influenza at the local clinical laboratory and the Wisconsin State Laboratory of Hygiene. Enrollment continued for 10 weeks, ending on March 28, 2008.

2.1. Laboratory methods

Swabs were placed in M4-RT viral transport media and delivered to the Marshfield Clinic Research Foundation laboratory on the same day. Samples were routinely processed within one day, and weekend samples were tested on Monday. Nucleic acid was extracted using the Roche MagNA Pure Total Nucleic Acid Kit (Roche Diagnostics, Indianapolis, Indiana), and RT-PCR was performed using the LightCycler® Real-Time PCR System (Roche Diagnostics, Basel, Switzerland). The U.S. Centers for Disease Control and Prevention provided sequence information for RT-PCR primers and probes. The TaqMan®-based RT-PCR assay detects two highly-conserved influenza genes: the matrix gene of influenza A and the non-structural gene of influenza B. A human RNase P gene served as a positive control for human nucleic acid. Virus subtyping by RT-PCR was performed on all samples with a positive influenza A result.

2.2. Influenza vaccination status and dates

Vaccination status and dates were determined by a real-time, internet-based registry used by all immunization providers serving the local population (www.recin.org). The capture of the registry was validated during the 2006–2007 and 2007–2008 influenza seasons, and after adjudication it was found that the registry captured 95% of all influenza vaccinations received by study participants [11]. For this analysis, participants were considered immunized if a dose of vaccine was received ≥14 days before illness onset. Children under the age of nine were recommended to receive two doses of influenza vaccine. Partially vaccinated children who received only one of two recommended doses were excluded from the analysis. For fully vaccinated children, the most recent dose received prior to illness onset was used to determine the interval from vaccination to illness. Only trivalent inactivated vaccine was evaluated, and the Marshfield Clinic did not administer live attenuated influenza vaccine during the 2007–2008 season.

The study was approved by the Marshfield Clinic Institutional Review Board and all participants provided written informed consent.

2.3. Analytic approach

We tested the hypothesis that RT-PCR confirmed influenza A was independently associated with a longer interval from influenza vaccination to illness onset after adjustment for calendar time, age and other potential confounders. The analyses were restricted to vaccinated adults and children because a vaccination interval cannot be calculated for unvaccinated individuals. We did not attempt to directly calculate vaccine effectiveness for different vaccination intervals because it would require inclusion of the unvaccinated group, and the precision of vaccine effectiveness estimates was expected to be low for time windows before and after the epidemic peak. In contrast, the analysis of vaccination intervals allowed for detection of small differences in time from vaccination to illness onset for cases and controls after adjusting for the effect of calendar time and age.

The outcome variable was a positive RT-PCR test result for influenza A (H3N2) (cases) vs. a negative result (test negative controls). We excluded individuals with influenza B infection because there were relatively few cases of influenza B, and differences in the temporal occurrence of influenza A and B could be a source of confounding. Although the study design allowed multiple enrollments per person for distinct illness episodes, we included only the first enrollment for each person unless influenza was detected on a subsequent enrollment. In that case, we included the influenza positive enrollment and excluded other enrollments for the same person. We also repeated the primary analysis after exclusion of all individuals with multiple enrollments to ensure that results were not biased by including influenza infections that occurred during a second illness episode.

The multivariable logistic regression model assessed the association between vaccination interval (days from vaccination to illness onset) and probability of influenza. The main predictor was the interval (days) from vaccination to illness onset. The relationship between age and influenza result was nonlinear (Supplemental Figure S1), and we included covariates for age and age squared in the model. The timing of illness onset was analyzed as a series of indicator variables representing 2 week time periods in the model. Each period was compared to the referent period of weeks 7–8 (representing the peak of influenza occurrence in the community).

We examined the association between vaccination interval and influenza using two different models. A main effects model included the primary exposure (days from vaccination to illness onset) and potential confounders. These included sex, interval between illness onset and enrollment (days), and presence or absence of a high-risk health condition. Effect modification was examined with the addition of interaction terms for vaccination interval (days) and each covariate. Each interaction term was evaluated separately, and covariate and interaction terms were included in the final reduced model if they were significantly associated with influenza ($p < 0.05$) or changed the point estimate for the primary exposure by more than 10%. Since age was modeled as a continuous variable in this analysis, we used the model results to illustrate the relationship between vaccination interval and log-odds of influenza at six arbitrarily selected ages.

We performed a secondary analysis using calendar week of influenza vaccine receipt rather than vaccination interval as the exposure of interest. The model covariates were the same as in the primary analysis. All analytical procedures were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

There were 1972 enrollments representing 1955 unique patients during the 2007–2008 influenza season. For the analysis of waning protection against influenza A (H3N2), we excluded study participants with influenza B ($n = 233$), unvaccinated individuals ($n = 1088$), and five participants who received influenza vaccine within 14 days before illness onset. During this season there were an additional 17 individuals (<1%) who were enrolled twice for independent illness episodes, including 4 who were positive for influenza during the second enrollment only. The second