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Influenza vaccine effectiveness in older adults compared with younger adults over five seasons

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ABSTRACT

Background: There have been inconsistent reports of decreased vaccine effectiveness (VE) against influenza viruses among older adults (aged ≥ 65 years) compared with younger adults in the United States. A direct comparison of VE over multiple seasons is needed to assess the consistency of these observations.
Methods: We performed a pooled analysis of VE over 5 seasons among adults aged ≥ 18 years who were systematically enrolled in the U.S. Flu VE Network. Outpatients with medically-attended acute respiratory illness (cough with illness onset ≤ 7 days prior to enrollment) were tested for influenza by reverse transcription polymerase chain reaction. We compared differences in VE and vaccine failures among older adult age group (65–74, ≥75, and ≥ 65 years) to adults aged 18–49 years by influenza type and subtype using interaction terms to test for statistical significance and stratified by prior season vaccination status.
Results: Analysis included 20,022 adults aged ≥ 18 years enrolled during the 2011–12 through 2015–16 influenza seasons; 4,785 (24%) tested positive for influenza. VE among patients aged ≥ 65 years was not significantly lower than VE among patients aged 18–49 years against any subtype with no significant interaction of age and vaccination. VE against A(H3N2) viruses was 14% (95% confidence interval [CI] −14% to 36%) for adults ≥ 65 years and 21% (CI 9–32%) for adults 18–49 years. VE against A(H1N1) pdm09 was 49% (95% CI 22–66%) for adults ≥ 65 years and 48% (95% CI 41–54%) for adults 18–49 years and against B viruses was 62% (95% CI 44–74%) for adults ≥ 65 years and 55% (95% CI 45–63%) for adults 18–49 years. There was no significant interaction of age and vaccination for separate strata of prior vaccination status.
Conclusions: Over 5 seasons, influenza vaccination provided similar levels of protection among older and younger adults, with lower levels of protection against influenza A(H3N2) in all ages.
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1. Introduction

Older adults (aged ≥ 65 years) are at high risk for complications from influenza, including hospitalization and death [1–3]. During 2010–2013, older adults comprised 54–70% of influenza-associated hospitalizations and 73–85% of influenza-associated deaths in the United States [4]. Influenza vaccination is the primary method of prevention of infection and has been recommended for all adults aged ≥65 years since the 1960s [5,6]. Understanding factors that contribute to differences in vaccine effectiveness (VE) by age and achieving the highest possible VE is a priority, especially for this at-risk group.

The U.S. Flu VE Network publishes estimates of influenza VE each season [7–11], including VE by age group. VE has been lower in older adults compared with younger adults in some seasons

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[7,8,10], but not others [9,12]. A prior pooled estimate of U.S. Flu VE Network data examining intra-season waning of VE did not find statistical differences in VE among adults aged <60 and ≥60 years [13]. A recent meta-analysis has shown that although the vaccine is generally effective in adults aged ≥65 years, VE was often lower as compared with younger adults, particularly in seasons when A (H3N2) was the predominant circulating virus [14].

Most of these prior studies have only assessed VE in single seasons, or in single large age groups. We hypothesized that the effectiveness of standard dose inactivated influenza vaccines would be lower among older adults compared with younger adults. We pooled 5 seasons of data from the U.S. Flu VE Network to describe and compare VE among adults aged ≥65 years with adults aged 18–49 years.

2. Materials and methods

2.1. US Flu VE Network

We used data from sites participating in the U.S. Flu VE Network Study [7–9,11] from the 2011–12 through 2015–16 influenza seasons. The network enrolled patients aged ≥6 months who presented to outpatient providers for an acute respiratory illness (ARI) of ≤7 days duration with cough (or fever/feverishness in the 2011–12 season) during periods of local influenza circulation across five sites. Interviews were performed at enrollment to collect demographic data and self-reported current health status. Oral and nasal swab specimens were collected and tested for influenza by reverse transcription polymerase chain reaction (RT-PCR) [7]. Patients with inconclusive RT-PCR results and those with two influenza viruses detected were excluded. Patients were considered to have high-risk medical conditions [15] based on ICD-9 or ICD-10 codes corresponding to a high-risk condition in the electronic medical record in the year before enrollment. At selected sites, patients without vaccination documented in the medical record or vaccine registry were considered vaccinated if plausible date and location of vaccination were provided by self-report. Receipt of prior season vaccination was obtained only from medical records or state immunization information systems. Patients who received influenza vaccines other than standard dose inactivated vaccines were excluded. We limited this analysis to enrolled patients aged ≥18 years.

2.2. Vaccine effectiveness analysis

As reported in previous VE reports by the U.S. Flu VE Network [7–11], we assessed VE using the test-negative case-control design [16,17], with cases defined as patients with lab-confirmed influenza and controls as patients testing negative for influenza. We calculated the odds of vaccination among influenza-positive cases compared to influenza-negative controls (OR), and VE was calculated as $[1 - \mathrm{OR}] \times 100\%$. The logistic regression model was adjusted for network site, age, sex, race/ethnicity, presence of any high-risk medical condition, self-rated general health status (excellent, very good, good, fair, poor), interval between illness onset and specimen collection (0–2 days, 3–4 days, or 5–7 days), month of illness onset, and season. Variables included in the model were decided *a priori* to compare with prior US Flu VE Network estimates. Within each age category, age in months was modeled using linear tail-restricted cubic spline functions with multiple knots, as previously described [8,9].

To test the hypothesis that adults aged ≥65 years had lower VE than adults aged 18–49 years, we used an interaction term for age group and vaccination for each model. We compared VE among adults aged 50–64 years, 65–74 years, ≥75 years, as well as combined ≥65 years, with the reference group of adults aged 18–49 years. Given wide variations in VE by type and subtype [7–11] we conducted analyses by influenza type and subtype. Influenza A categories included A(H1N1)pdm09 viruses, which predominated during the 2013–14 and 2015–16 seasons, and A(H3N2) viruses which predominated during the 2011–12, 2012–13, and 2014–15 seasons. Influenza B lineages were combined into a single influenza B category due to small numbers. We performed a secondary analysis for A(H3N2) viruses removing the 2014–15 season, when the majority of circulating A(H3N2) viruses were antigenically different than the viruses in the seasonal vaccines. For comparison with previous studies, additional sensitivity analyses included use of adults aged 50–64 years as the referent group and analysis for VE against A(H3N2) viruses restricted to patients with influenza-like illness (ARI and fever) and to those with documented vaccination status only.

Given prior reports of repeated vaccination being associated with lower VE [18–20] and the fact that the older age groups have consistently higher vaccination rates [21], we tested for a significant difference in VE by age group in stratified models by current season and immediate prior season vaccination status (vaccinated in both current and prior season vs. unvaccinated in both seasons, and vaccinated in current season only vs. unvaccinated in both seasons) for influenza A(H3N2).

We also hypothesized that if VE was lower among older adults, the relative odds of vaccine failure among enrolled vaccinated patients would be higher compared with adults aged 18–49 years. To directly compare vaccinated older and younger adults, we performed a post hoc analysis limited to individuals vaccinated in the current season. Using the same covariates, we calculated the adjusted OR of influenza among vaccinated adults aged 65–74 years, ≥75 years and ≥ 65 years, each compared to vaccinated adults aged 18–49 years as a referent group in separate models.

Statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). We tested for significant difference in VE by age group using a p value < .05 for the age-vaccination interaction term.

3. Results

3.1. Patient characteristics

From the 2011–12 through 2015–16 influenza season, the U.S. Flu VE Network enrolled 20,907 outpatients aged ≥8 years. A total of 885 were excluded from the analyses because of receipt of vaccine <14 days prior to illness onset or unknown date or location of self-reported vaccination (n = 385), receipt of high-dose influenza vaccine (n = 296) or live attenuated influenza vaccine (n = 126), inconclusive RT-PCR results (n = 47), illness onset >7 days prior to enrollment (n = 30), and co-detection of influenza A and B viruses (n = 1). Of the remaining 20,022 patients included in the analysis, 56% were aged 18–49 years, 27% were aged 50–64 years, 11% were aged 65–74 years, and 6% were aged ≥75 years (Table 1).

Compared with adults aged 18–49 years, adults aged ≥65 years were more likely to have at least one high risk condition (74% vs. 27%) and report fair or poor health status (22% vs. 13%). They also tended to seek care later in illness (5–7 days after symptom onset). Current season vaccination was more common in adults aged ≥65 years than aged 18–49 years (79% vs 40%). Of those who were vaccinated in the current season and had records available from the previous season (n = 8,658), 71% were also vaccinated in the prior season and this was highest for older adults (86% of adults aged ≥65 years vs. 60% of adults aged 18–49 years).

Overall, 15,237 (76%) tested negative for influenza and 4785 (24%) tested positive for influenza, including 2265 (47%) influenza A(H3N2), 1438 (30%) influenza A(H1N1)pdm09, 89 (2%) influenza