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Influenza vaccine effectiveness: Maintained protection throughout the duration of influenza seasons 2010–2011 through 2013–2014

Jennifer M. Radin *, Anthony W. Hawksworth, Christopher A. Myers, Michelle N. Ricketts, Erin A. Hansen, Gary T. Brice

Department of Operational Infectious Diseases, Naval Health Research Center, San Diego, CA 92106, USA

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ABSTRACT

Background: Factors, such as age, comorbidities, vaccine type, herd immunity, previous influenza exposure, and antigenic shift may impact the immune response to the influenza vaccine, protection against circulating strains, and antibody waning. Evaluating vaccine effectiveness (VE) is important for informing timing of vaccine administration and evaluating overall vaccine benefit.
Methods: VE was assessed using febrile respiratory illness surveillance among Department of Defense non-active duty beneficiaries from influenza seasons 2010–2011 through 2013–2014. Respiratory specimens were taken from participants meeting the case definition and tested by polymerase chain reaction for influenza. VE was calculated using logistic regression and by taking 1 minus the odds ratio of being vaccinated in the laboratory confirmed positive influenza cases versus laboratory confirmed negative controls.
Results: This study included 1486 participants. We found an overall adjusted VE that provided significant and fairly consistent protection ranging from 54% to 67% during 0–180 days postvaccination. This VE dropped to −11% (95% confidence interval: −102% to 39%) during 181–365 days.
Conclusions: Our study found moderate VE up to 6 months postvaccination. Since the influenza season starts at different times each year, optimal timing is difficult to predict. Consequently, early influenza vaccination may still offer the best overall protection.

1. Introduction

Each year roughly 5–20% of the US population is infected with influenza, resulting in an estimated 3000–49,000 deaths [1]. The best way to prevent influenza-associated disease burden is vaccination; therefore, as of 2010, influenza vaccination has been recommended for everyone in the United States, 6 months of age and older [2]. Yearly revaccination is necessary because circulating strains and/or vaccine composition change every influenza season. Additionally, previous studies have found that influenza vaccine effectiveness (VE) declines over time since vaccination in some populations does not provide significant protection in most cases after 90–120 days [3–7]. Many factors impact VE estimates and speed of decline – including age, comorbidities, herd immunity, use of adjuvants, type of vaccine administered (live attenuated or inactivated), prior natural influenza exposure, prior influenza vaccination, antigenic drift, and study design [6,8–13].

Previous studies have assessed influenza VE declines in relatively small sample sizes or from 1 influenza season [3–6,14]. Additionally, many of these studies have been conducted outside the United States, in regions that have different vaccine composition (adjuvant vs. non-adjuvanted) [6,15], and vaccine recommendations [2,16], and may also have differences in circulating strains and in the proportion of LAIV vs. IIV and quadrivalent versus trivalent vaccine which is administered. The goal of this study is to evaluate VE over time among US Department of Defense (DoD) beneficiaries during 4 influenza seasons. Gaining a better understanding of postvaccination immunity declines is important for evaluating the benefit of the vaccine and planning the timing of vaccine administration.

2. Methods

2.1. Study participants

Participants were selected from the Naval Health Research Center's (NHRC) febrile respiratory illness surveillance of DoD non-active duty beneficiaries. The surveillance sites included Naval

* Corresponding author at: Scripps Translational Science Institute, 3344 North Torrey Pines Court, Suite 300, La Jolla, CA 92037, USA.
E-mail address: radin.jennifer@scrippshealth.org (J.M. Radin).

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Medical Center San Diego, California; Naval Branch Health Clinic Kearny Mesa, San Diego, California; Naval Hospital Camp Pendleton, Oceanside, California; and Captain James A. Lovell Federal Health Care Center, North Chicago, Illinois. The case definition for febrile respiratory illness is a person presenting at an outpatient health care facility with an oral temperature ⩾38.1 °C (100.5 °F) or subjective fever, and either cough or sore throat. A convenience sample of up to 20 cases per week per site were enrolled (with sampling dependent upon study staffing hours, resulting in a near random sample) with nasal, combination nasal/throat, or nasopharyngeal swabs during influenza seasons 2010–2011 through 2013–2014. Samples were frozen and sent to NHRC for testing every 1–2 weeks along with de-identified case data. Vaccine history, including vaccine type, and date of vaccination were collected from medical records and/or recall. Cases tested positive for influenza by real-time polymerase chain reaction (qPCR), and controls tested negative for influenza. Briefly, separate qPCR assays were performed for influenza A and B using standard extraction methods and with primers provided by the Centers for Disease Control. Influenza A positive samples were further tested by CDC primers to determine subtype [influenza A (H3N2) or A(pH1N1)]. Viral culture was performed on a subset of influenza-negative samples using a rhesus monkey kidney cell line to ensure that qPCR assays remained sensitive.

This study included participants enrolled during seasonal epidemic influenza periods, which were defined as times of consistent circulation and identification of influenza positive cases. Participants with unknown influenza vaccine status or known influenza vaccine status but unknown vaccine date were excluded, as were those vaccinated <15 days or >365 days before sampling.

This research was conducted in compliance with all applicable federal and international regulations governing the protection of human subjects in research (Protocol NHRC.2007.0024). Participants gave written informed consent or parental informed consent if underage. Since all specimens in this study were collected previously and were de-identified for the purposes of this study, the NHRC institutional review board committee classified this study as minimal risk, exempt from full committee review.

2.2. Statistical analysis

Chi-squared and analysis of variance tests were used to compare the characteristics of cases and controls (Table 1). VE was calculated using logistic regression and by taking 1 minus the odds ratio (OR) of being vaccinated multiplied by 100 in the cases versus controls. The following variables were assessed in the adjusted VE model: age group (0–4 years, 5–24 years, 25–49 years, 50–64 years, and ⩾65 years), gender, influenza season (2010–2011, 2011–2012, 2012–2013, 2013–2014), and calendar season (November–December, January–February, March–June). Confounders (>10% change in OR) or variables with $P < .05$ in the multivariate model were left in the final adjusted model. The final model adjusted for age group (0–4, 5–24, 25–49, 50–64, and >64 years), calendar season, and influenza season. Overall VE estimates were also stratified by participants who were 0–14, 15–30, 31–60, 61–90, 91–180, and 181–365 days postvaccination. Additionally, age group (0–4, 5–24, and ⩾25 years), type of vaccine (inactivated influenza vaccine [IIV] versus live-attenuated influenza vaccine [LAIV]), influenza subtype, influenza season, and month stratifications were run for 15–90, 91–180, and 180–365 days postvaccination (Supplementary Table 1 and Figs. 1–3). SAS version 9.3 was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina).

3. Results

During the 4 influenza seasons examined for our study, 1720 participants meeting the febrile respiratory illness case definition were enrolled, with 198 were excluded due to incomplete vaccination history, 36 were excluded due to vaccination <15 days before diagnosis, 5 excluded due to vaccination >365 days after diagnosis. Among the remaining 1481 participants, 387 (26%) were cases (influenza qPCR positive), and 1094 (74%) were controls (influenza negative). Viral culture testing of a subset of qPCR-negative samples showed that qPCR sensitivity remained high (>99%) throughout the study. Twenty-four percent of the cases and 48% of the controls were vaccinated. Among those vaccinated, mean vaccination days were similar for cases (119 days) and controls (108 days) ($P = .063$). The percentage of participants receiving IIV vaccination was very similar in both groups, with 76% among cases and 79% among controls ($P = .471$). There were some differences in the proportion of cases versus controls across influenza seasons, likely suggesting differences in flu severity or vaccine match from season to season. The majority (53%) of the cases occurred in the 5–24 year age group. Both cases and controls had similar percentages of men and women ($P = .965$; Table 1).

Table 1
Descriptive characteristics among cases (influenza positive) and controls (influenza negative), excluding those <15 days or >365 days postvaccination, $n = 1481$.

Characteristic	Cases, $n = 387$ (%)	Controls, $n = 1094$ (%)	p value
Age group (years)			<0.001
0–4	72 (19)	400 (37)	
5–24	206 (53)	436 (40)	
25–49	67 (17)	161 (15)	
50–64	37 (10)	86 (8)	
>64	5 (1)	11 (1)	
Sex (% Men)	173 (45)	490 (45)	0.965
Influenza vaccine (% Yes)	91 (24)	521 (48)	<0.001
Mean ± SD vaccination days	119 ± 56	108 ± 52	0.063
Influenza vaccine type (% IIV)	69 (76)	407 (79)	0.471
Influenza season			<0.001
2010–2011	76 (20)	118 (11)	
2011–2012	94 (24)	211 (19)	
2012–2013	137 (35)	294 (27)	
2013–2014	80 (21)	471 (43)	
Calendar season			0.002
November–December	83 (21)	199 (18)	
January–February	199 (51)	487 (45)	
March–June	105 (27)	408 (37)	

Abbreviations: IIV, inactivated influenza vaccine; SD, standard deviation.

Age, influenza season, and calendar season were all statistically significant in the multivariate logistic regression model. Age group was the only variable that was also a confounder. During the 0–14, 15–30, 31–60, 61–90, and 91–180-day intervals, overall VE estimates were fairly constant, with VE estimates fluctuating from 53% to 67% and remaining significant. After 180 days, overall adjusted VE estimates dropped to −16% (95% confidence interval [CI]: −117% to 38%) (Supplementary Table 1 and Fig. 1).

Stratified analyses by vaccine type, age group, and influenza subtype revealed no significant differences between adjusted VE during the 15–90 and 91–180 days postvaccination time periods, with a marked decrease in VE after 180 days. Exceptions were seen in 2 subgroups (25 years of age and older; A/pH1N1 subtype) that did not show a marked decrease in VE point estimates after 180 days, although confidence intervals were wide for these intervals (Supplementary Table 1 and Fig. 1).

Our study found slightly lower adjusted VE point estimates later in the influenza season (March, April, May) compared with early in the influenza season (December, January, February), as the ratio for percent influenza positive between unvaccinated and vaccinated groups became incrementally smaller until being nearly identical in May (Fig. 2).

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