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Brief report

Mid-season influenza vaccine effectiveness 2011–2012: A Department of Defense Global, Laboratory-based, Influenza Surveillance System case–control study estimate

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ABSTRACT

Mid-season influenza vaccine effectiveness (VE) was estimated using data from surveillance conducted by the Department of Defense Global, Laboratory-based, Influenza Surveillance Program at the United States Air Force School of Aerospace Medicine. Respiratory specimens from geographically diverse military members and dependents who sought medical care 2 October 2011–3 March 2012 were analyzed by viral culture and real-time reverse transcriptase-polymerase chain reaction; influenza viruses were typed and sequenced. Controls were influenza test-negative. Overall, vaccine type and subtype-specific VE were estimated using logistic regression. Adjusted VE (95% confidence interval) was: overall 77 (57–87)%; live attenuated vaccine (LAIV) 74 (48–87)%; trivalent inactivated vaccine (TIV) 75 (48–88)%. H3 component-specific VE was: overall 77 (52–89)%; LAIV 78 (47–91)%; TIV 74 (38–89)%; data were insufficient for separate H1 and B estimates. Both vaccine types showed moderate to high VE, indicating significant protection against circulating influenza strains.

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1. Introduction

The Department of Defense (DoD) conducts active, laboratory-based, sentinel influenza surveillance at the U.S. Air Force School of Aerospace Medicine (USAFSAM) [1–3]. Since annual influenza vaccination with U.S.-licensed vaccine is mandatory for U.S. forces, a large proportion of respiratory specimens are from vaccinated individuals. The Vaccines and Related Biological Products Advisory Committee of the Food and Drug Administration (VRBPAC), meets annually in late February to determine components for the next season's U.S. vaccine, and requests and considers DoD surveillance with vaccine effectiveness (VE) data in addition to civilian surveillance.

The first influenza VE study was conducted in U.S. military during 1943–1944 [4]. Several end-of-season VE and related studies involving military populations have been published in the past decade [5–8]. No mid-season VE study with U.S. military populations has been published. A collaborative study between USAFSAM and the Armed Forces Health Surveillance Center, evaluated 2010–2011 VE using several case–control selection strategies [5]. Estimates were adjusted for age, gender, month of specimen collection, and vaccination in previous seasons. VE was calculated for each component (A/H1, A/H3, and B) and for trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV). Low to moderate VE was found; some but not all estimates were significant. The best suited of three methods from that study was chosen for this study.

Five civilian studies published in surveillance literature have estimated mid-season VE for the last two seasons in Europe using case–control methods (2010–2011, 42–72%; 2011–2012, 43–55%) [9–13]. Estimation of mid-season vaccine type-specific VE was not attempted and only one [12] included sequence analysis (48 viruses).

2. Methods

The study population included active duty military and beneficiaries with specimens collected 2 October 2011–3 March 2012. All specimens (nasal wash, nasopharyngeal swab) were tested by real-time reverse transcriptase-polymerase chain reaction (PCR) and culture at USAFSAM. Program methods – enrollment, questionnaire, specimen collection, transport, culture, molecular testing and sequencing – have been previously described [1–3]. Cases were

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positive for influenza by PCR or viral culture or both. Controls were influenza culture and PCR negative; 57 controls were positive for other respiratory viruses. Individuals with multiple specimens collected less than 14 days apart were included for the first case-defining instance.

Vaccination status and type (TIV or LAIV) were obtained from three sources: a questionnaire, the Air Force Complete Immunization Tracking Application, and the Defense Enrollment Eligibility Reporting System. Individuals were considered vaccinated if immunized at least 14 days before specimen collection. For age < 9 years, evidence of one vaccination with 2011–2012 season vaccine was accepted as being vaccinated. Individuals with unknown vaccination status were excluded (16 influenza-positives and 242 negatives).

Case and control demographic and other categorical variables were compared using chi-square tests. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. Adjusted models included variables differing significantly between cases and controls and potential confounders. VE was calculated as (1 – OR). VE estimates were calculated for the A/H3 component (there were insufficient numbers of A/H1 and B cases for separate analysis during the study period) and for TIV and LAIV. Analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC, USA) (Table 1).

3. Results

Influenza circulated in all geographic regions; A/H3 was the dominant circulating virus for the study period; both A/H3 and A/H1 activity began later than usual this season. We identified 145 eligible cases (114 A/H3, 17 A/H1, and 14 B) and 622 eligible controls with known vaccination status. Ninety-one cases (62.8%) (29 TIV, 62 LAIV) and 401 controls (64.5%) (127 TIV, 252 LAIV, 22 unknown type) were vaccinated. Enrollment of controls remained steady throughout the study period; case enrollment followed influenza activity trends (Fig. 1).

There were statistically significant ($p < 0.05$) differences between cases and controls by age group, geographic region, and time period but not gender ($p = 0.35$) or beneficiary status ($p = 0.06$). Age distribution was bimodal (peaks in young children and 18–35 year olds) and similar between cases and controls with the exception of young children; 15.8% of controls were under 5 years of age but only 6.2% of cases. USNORTHCOM accounted for 80% of controls but only 31% of cases (Table 1). USEUCOM and USCENTCOM were combined in the analysis because of small numbers; all USEUCOM specimens were submitted from Turkey. Adjusted models included age group (<5, 5–17, 18–28, 29–35, 36+), geographic region (USNORTHCOM, USEUCOM/USCENTCOM, USPACOM), time period and gender. Models and effects of adjustment are shown in Fig. S1 (online supplementary material).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.01.022.

Adjusted overall, vaccine-specific and A/H3 component-specific VE estimates were positive and statistically significant, indicating protective effect of vaccine. While overall crude VE and 95% CI was only 7.1% (-35.1, 36.1), overall adjusted VE was 76.6% (57.5, 87.2). Adjustments for region and time period had the greatest impact on VE estimates, followed by age. Adjusting for gender had little effect. Results were similar for TIV- and LAIV-specific estimates. The following adjusted estimates and 95% CI were found: Age group <18, 62.4 (4.9–85.1)%; 18–49, 60.9 (26.9–79.1)%; ≥ 50, N/A (insufficient data, $n = 39$); TIV 75.1% (47.6, 88.1); LAIV 73.8% (48.2, 86.7); A/H3 76.9% (52.3%, 88.8%) A/H3 TIV 73.7% (37.5, 88.9); A/H3 LAIV 77.8% (47.0, 90.7). When restricted to active duty, VE estimates were higher but with larger confidence intervals. An alternate model excluding cases and controls with specimens collected prior to week 2012_2 gave a lower VE of 75.3% (55.4, 86.3%) (Table 2).

Sequences of 100 A/H3 and 15 A/H1 viruses collected from cases were compared with vaccine component strains from 2011 to 2012 Northern Hemisphere vaccines (Fig. S2, online supplementary material). Vaccinated cases did not cluster preferentially in specific clades or with specific mutations. Since only 15 2009 A/H1N1 sequences were available among the cases, clustering could not be adequately assessed for A/H1. Analyzed viruses came from 14 U.S. states, the District of Columbia, Guam, Japan, Kuwait, Kyrgyzstan and South Korea.

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Table 1
Characteristics of cases of laboratory confirmed influenza (rRT–PCR, culture, or both) and test-negative controls.

	Cases ($n = 145$) no. (%)	Controls ($n = 622$) no. (%)	p-Value
Age (years)			
<5	9 (6.21)	98 (15.76)	<0.0001
5–17	23 (15.86)	94 (15.11)	
18–28	35 (24.14)	216 (34.73)	
29–35	35 (24.14)	85 (13.67)	
36+	43 (29.66)	129 (20.74)	
Gender			
Male	96 (66.21)	386 (62.06)	0.35
Beneficiary category			
Active duty	87 (60.00)	328 (52.73)	0.0633
Child	32 (22.07)	199 (31.99)	
Spouse, retired, other	26 (17.93)	95 (15.27)	
Geographic region[a]			
USCENTCOM[b]	30 (20.69)	25 (4.02)	<0.0001
USEUCOM	0 (0.00)	15 (2.41)	
USNORTHCOM	45 (31.03)	499 (80.23)	
USPACOM	70 (48.28)	83 (13.34)	
Week of collection[c]			
2011_40–2012_01	18 (12.41)	376 (60.45)	<0.0001
2012_02–2012_03	39 (26.90)	58 (9.32)	
2012_04–2012_05	42 (28.97)	69 (11.09)	
2012_06–2012_07	30 (20.69)	63 (10.13)	
2012_08–2012_09	16 (11.03)	56 (9.00)	
Vaccinated[d]			
No	54 (37.24)	221 (35.53)	[e]
Yes	91 (62.76)	401 (64.47)	[e]
TIV	29 (20.00)	127 (20.42)	[e]
LAIV	62 (42.76)	252 (40.51)	[e]
Unknown type	0 (0.00)	22 (3.54)	[e]
Influenza[f]			
Influenza A/H3N2	114 (78.62)	NA	
2009 Influenza A/H1N1	17 (11.72)	NA	
Influenza B	14 (9.66)	NA	

Notes: USCENTCOM, U.S. Central Command; USEUCOM, U.S. European Command; USNORTHCOM, U.S. Northern Command (includes North America); USPACOM, U.S. Pacific Command;
TIV, trivalent inactivated vaccine; LAIV, live attenuated influenza vaccine; NA, not applicable.

[a] All countries are grouped regionally as defined areas of responsibility categorized by the U.S. Department of Defense.

[b] USCENTCOM study subjects had higher vaccination rates (97.7%), percent active duty (100%) and less age variability than other regions.

[c] Specimen collection/enrollment began Week 2011_40 (2 October 2011) and continued through Week 2012_9 (3 March 2012). More controls than cases were enrolled during the early part of the study period (Weeks 2011_40–2012_01). Graph 1 shows the relationship between vaccination of cases and controls and the week of enrollment.

[d] Both cases and controls were generally vaccinated before influenza activity began in the Northern Hemisphere.

[e] Vaccination status is the exposure of interest, see Table 2.

[f] Individuals with recent LAIV vaccination, positive influenza A and B PCR results, and negative culture would be considered false positives and therefore excluded (none were found in the study population).