Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season

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ARTICLE INFO

ABSTRACT

Purpose: Receiving influenza vaccination may increase the risk of other respiratory viruses, a phenomenon known as virus interference. Test-negative study designs are often utilized to calculate influenza vaccine effectiveness. The virus interference phenomenon goes against the basic assumption of the test-negative vaccine effectiveness study that vaccination does not change the risk of infection with other respiratory illness, thus potentially biasing vaccine effectiveness results in the positive direction. This study aimed to investigate virus interference by comparing respiratory virus status among Department of Defense personnel based on their influenza vaccination status. Furthermore, individual respiratory viruses and their association with influenza vaccination were examined.

Results: We compared vaccination status of 2880 people with non-influenza respiratory viruses to 3240 people with pan-negative results. Comparing vaccinated to non-vaccinated patients, the adjusted odds ratio for non-flu viruses was 0.97 (95% confidence interval (CI): 0.86, 1.09; p = 0.60). Additionally, the vaccination status of 3349 cases of influenza were compared to three different control groups: all controls (N = 6120), non-influenza positive controls (N = 2880), and pan-negative controls (N = 3240). The adjusted ORs for the comparisons among the three control groups did not vary much (range: 0.46–0.51).

Conclusions: Receipt of influenza vaccination was not associated with virus interference among our population. Examining virus interference by specific respiratory viruses showed mixed results. Vaccine derived virus interference was significantly associated with coronavirus and human metapneumovirus; however, significant protection with vaccination was associated not only with most influenza viruses, but also parainfluenza, RSV, and non-influenza virus coinfections.

Published by Elsevier Ltd.

1. Introduction

The influenza pandemic of 1918–1919, which contributed to an estimated 50 million deaths worldwide, stimulated interest in influenza vaccine research [1]. Twenty years after the pandemic began, the first influenza vaccine was administered to US soldiers in 1938 [1]. From the 2010–2011 influenza season to the 2017–2018 season, excluding for the 2014–2015 season, the influenza vaccine was shown to be effective at reducing the burden of seasonal influenza in the United States [2–6].

While influenza vaccination offers protection against influenza, natural influenza infection may reduce the risk of non-influenza respiratory viruses by providing temporary, non-specific immunity against these viruses [7,8]. On the other hand, recently published studies have described the phenomenon of vaccine-associated virus interference; that is, vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection [7–10]. There has been limited evidence that the influenza vaccine may actually be associated with the virus interference process [8,11]. Other studies have found no association between influenza vaccination and increased respiratory virus risk [10,12].

The purpose of this study is to add to the general knowledge of influenza vaccine-related virus interference by comparing rates of

non-influenza respiratory viruses to negative laboratory tests, and comparing vaccination status of influenza positive cases to controls among Department of Defense (DoD) personnel. The DoD provides a unique population for vaccination studies as mandatory vaccination against influenza is required by the DoD for all Active Duty and Reserve Component personnel [13]. This study aims to examine the relationship between specific respiratory viruses and influenza vaccination. The protocol for this study was reviewed and approved as exempt by the Air Force Research Laboratory Institutional Review Board.

2. Materials and methods

The Department of Defense Global Respiratory Pathogen Surveillance Program (DoDGRS) is a DoD-wide program established by the Global Emerging Infections Surveillance and Response System (GEIS). The program was founded in 1997 as an influenza-only surveillance program. In the 2013–2014 influenza season the program added respiratory Film Array for flu negative samples and began identifying other respiratory pathogens. Starting in the 2017–2018 influenza season, the program added Luminex Film Array capabilities to test for respiratory pathogens, and became known as DoDGRS. The Defense Health Agency/Armed Forces Health Surveillance Branch – Air Force Satellite Cell (DHA/AFHSB – AF) and United States Air Force School of Aerospace Medicine (USAFSAM) manage the surveillance program that includes global surveillance among DoD beneficiaries at 79 sentinel sites (including deployed locations) and many non-sentinel sites. Laboratory testing completed at USAFSAM and Landstuhl Regional Medical Center (LRMC) included multiplex PCR respiratory pathogen panels (including: adenovirus, *Chlmydia pneumoniae*, coronavirus, human bocavirus, human metapnumovirus, *Mycoplasma pneumoniae*, parainfluenza, respiratory syncytial virus (RSV), rhinovirus/enterovirus, and co-infections) [14,15], viral culture detecting influenza and other respiratory viruses, and influenza A/B subtyping via PCR [16,17]. Vaccination status was derived from both the Air Force Complete Immunization Tracking Application (AFCITA), a United States Air Force database containing vaccination-related data, and from surveys given to those submitting respiratory samples. If the patient had an influenza vaccination record in AFCITA for the 2017–2018 influenza season, or answered yes to being vaccinated during the season on their survey, they were identified as vaccinated. Patients who were not vaccinated for the season or who were vaccinated less than 14 days prior to specimen submittal were classified as unvaccinated.

All people submitting a respiratory specimen to the DoDGRS for the 2017–2018 influenza season were eligible for the study. The influenza season began 1 October 2017 and ended 29 September 2018. Those who submitted a sample and only tested positive for *Chlamydia pneumoniae* and/or *Mycoplasma pneumoniae* were excluded because these illnesses are bacteriological in nature, not viral. People with influenza and non-influenza coinfections were excluded because they could not be uniquely classified as either influenza or non-influenza respiratory virus. Individuals with multiple specimens collected during the season were also removed from the study as they could have had multiple different viruses over the season. Specimens where neither vaccination status could be obtained via databases nor a questionnaire was completed were excluded because vaccination status could not be confirmed. Subjects who were ill before receiving vaccination were excluded as vaccination status would therefore be unrelated to illness. Lastly, those people for whom the laboratory rejected the specimen were not included in the final study population.

Data management and statistical analyses were conducted using SAS 9.4 and SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary,

NC). Basic descriptive epidemiology was utilized to obtain counts and rates of outcomes by sex, military beneficiary category, age group, disease status, seasonality of illness, and vaccination status. In order to determine if virus interference was associated with influenza vaccination in the military beneficiary population, odds ratios and confidence intervals were calculated utilizing conditional logistic regression to compare vaccination status from two analyses. First, those with a viral respiratory illness other than influenza were compared to those with no pathogen detected (pan-negative). Next influenza positive cases were compared to three different control groups. The first control group was comprised of all controls, specifically, individuals testing negative for flu or positive for any respiratory virus other than flu. The second control group consisted of only those who were positive for respiratory viruses other than influenza. Lastly, pan-negative controls were compared to influenza cases. Unadjusted and adjusted odds ratios were calculated for the overall population, the population with AFCITA records only, and the active duty only population during the influenza season for the comparison of other respiratory illnesses to pan-negatives, as well as all three case-control comparisons. Adjusted odds ratios were calculated after modeling variables in a nested logistic regression, keeping all variables with p < 0.20 and then adding them to a full logistic model. In the full logistic model, only variables that remained significant were included in the final adjusted model. Age group remained significant in the overall population; age group and seasonality remained significant in the AFCITA confirmed vaccination group and the Active Duty population; and gender, age group, and seasonality all remained significant in all three of the case-control comparisons. Those respective variables that remained significant were included in the adjustment for the odds ratio for the total season. Individual respiratory virus outcomes were also examined and stratified by vaccination status. Odds ratios, confidence intervals, and p-values were calculated to determine if individual respiratory viruses were associated with influenza vaccination.

3. Results

For the 2017–2018 influenza season, 4041 out of 11,943 specimens tested positive for influenza (33.8%) (Data not shown). There were 3869 specimens identified as other respiratory pathogens (32.4%). The remaining 4033 specimens resulted as negative (33.8%) (Data not shown). Of the 11,943 specimens, 2474 (20.7%) specimens were excluded from our population based on the exclusionary criteria described in the Methods section, leaving a final study population of 9469 unique people (Data not shown). The study population was predominantly male, Active Duty service members, aged 18–35 years old (Tables 1 and 2). A majority of the study population was vaccinated (Tables 1 and 2). Most respiratory specimens were analyzed during the winter (December, January, and February) months (Tables 1 and 2).

Those who tested positive for a respiratory virus other than influenza had a similar breakdown for sex, vaccination status, and season of illness when compared to pan-negatives (Table 1). The other respiratory positive group had more child beneficiaries, and was overall younger than the pan-negative group (Table 1). Examining demographic characteristics stratified by vaccination status, males were more likely to be vaccinated than females (Table 2). Active Duty members were more likely to be vaccinated than people with other beneficiary statuses (Table 2). The younger aged population was more likely to be unvaccinated when compared to other age groups (Table 2). Composition of lab results (Other respiratory virus, influenza, and no pathogen detected) was distributed fairly evenly among the vaccinated population; however, unvaccinated people were more likely to have their

Table 1
Demographics by disease status.

	Respiratory Virus Positive (n = 2880) N (column %)	No Pathogen Detected (n = 3240) N (column %)
Sex		
Male	1576 (54.7)	1770 (54.6)
Female	1304 (45.3)	1470 (45.4)
Beneficiary Category		
Active Duty	1119 (38.8)	1625 (50.1)
Child	1212 (42.1)	666 (20.6)
Other	97 (3.4)	158 (4.9)
Retiree	103 (3.6)	244 (7.5)
Spouse	308 (10.7)	485 (15.0)
Unknown	41 (1.4)	62 (1.9)
Age Group		
0–17	1237 (42.9)	685 (21.1)
18–35	1074 (37.3)	1562 (48.2)
36+	569 (19.8)	993 (30.7)
Vaccination Status		
Vaccinated	2050 (71.2)	2441 (75.3)
Unvaccinated	830 (28.8)	799 (24.7)
Season		
Winter	1770 (61.4)	1921 (59.3)
Spring	716 (24.9)	827 (25.5)
Summer	69 (2.4)	122 (3.8)
Fall	325 (11.3)	370 (11.4)

Table 2
Demographics by vaccination status.

	Vaccinated (n = 6541)	Not Vaccinated (n = 2928)
Sex		
Male	3916 (59.9)	1310 (44.7)
Female	2625 (40.1)	1618 (55.3)
Beneficiary Category		
Active Duty	2516 (55.3)	247 (8.4)
Child	1597 (24.4)	1469 (50.2)
Other	181 (2.8)	237 (8.1)
Retiree	403 (6.1)	272 (9.3)
Spouse	654 (10.0)	616 (21.0)
Unknown	90 (1.4)	87 (3.0)
Age Group		
0–17	1616 (24.7)	1522 (52.0)
18–35	3007 (46.0)	627 (21.4)
36+	1918 (29.3)	779 (26.6)
Disease Status		
Other Respiratory Virus	2050 (31.3)	830 (28.3)
Influenza	2050 (31.3)	1299 (44.4)
No Pathogen Detected	2441 (37.4)	799 (27.3)
Season		
Winter	4327 (66.2)	1912 (65.3)
Spring	1644 (25.1)	548 (18.7)
Summer	165 (2.5)	45 (1.5)
Fall	405 (6.2)	423 (14.5)

specimen resulted as influenza (Table 2). Winter was the predominate season for illness and specimen testing (Table 2). Among the study population, 4549 people had AFCITA vaccination records (48.0%) while 4920 people self-reported vaccination status via questionnaire (52.0%) (Data not shown).

Examining the population with other respiratory viruses and no virus detected, those who were vaccinated had 19% lower unadjusted odds (95% CI: 0.72, 0.91) of having other respiratory viruses compared to those who were unvaccinated (Table 3). After adjusting for age group, the odds were 3% lower (95% CI: 0.86, 1.09) of having other respiratory viruses in the vaccinated population (Table 3). The unadjusted (data not shown) were statistically significant; however, the adjusted odds did not remain statistically

significant (p = 0.60) (Table 3). Since self-reported vaccination status may not be accurate and may bias results, those with AFCITA confirmed vaccination were examined exclusively. Those who were vaccinated according AFCITA records had 5% lower unadjusted odds (95% CI: 0.68, 1.34) of having other respiratory viruses compared to those who were unvaccinated (Table 3). Adjusting for age group and seasonality increased the odds to 23% higher (95% CI: 0.86, 1.76) of having other respiratory viruses in the vaccinated population (Table 3). Neither the unadjusted odds (data not shown) nor the adjusted odds (p = 0.24) in the AFCITA population were significant. Virus interference was also examined among Active Duty only for the 2017–2018 season. Those who were vaccinated had slightly lower unadjusted odds (OR: 0.97, 95% CI: 0.73, 1.29) of having other respiratory viruses compared to those who were unvaccinated (Table 3). After adjusting for age and season, these odds increased to a 20% higher odds (95% CI: 0.89, 1.61) of having other respiratory viruses in the vaccinated population; however, the unadjusted (data not shown) and adjusted (p = 0.24) odds ratios were not statistically significant (Table 3).

Both the unadjusted and adjusted odds of influenza were significantly lower in the vaccinated population for all three of the control groups (Table 4). The adjusted ORs ranged from 0.46 (pan-negative comparison) to 0.51 (non-influenza virus positive comparison) (Table 4). The 95% CI for the adjusted ORs of all three comparison groups overlapped and no differences were detected among each control group when compared to influenza cases.

The odds of testing positive for individual respiratory viruses by vaccination status were also examined (Table 5). The influenza vaccine was sufficient at protecting all influenza virus results tested for at a significant level except two (Influenza B Victoria and Influenza coinfections) (Table 5). Both Influenza B Victoria and Influenza coinfections had reduced odds in the vaccinated cohort, but not at significant levels (Table 5). Examining non-influenza viruses specifically, the odds of both coronavirus and human metapneumovirus in vaccinated individuals were significantly higher when compared to unvaccinated individuals (OR = 1.36 and 1.51, respectively) (Table 5). Conversely, all other non-influenza respiratory viruses had decreased odds in the vaccinated population, including significantly decreased odds ratios in vaccinated people with parainfluenza, RSV, and non-influenza virus coinfections (Table 5). Additionally, the odds ratio in the no pathogen detected cohort was significantly higher in vaccinated versus unvaccinated individuals (OR = 1.51) (Table 5).

4. Discussion

Examining 6120 people with respiratory viruses other than influenza and pan-negative results who submitted a respiratory specimen for laboratory testing to the DoDGRS team, those who received an influenza vaccine had a decreased risk of having other respiratory pathogens identified compared to the unvaccinated group. One study in the United States found similar results [12]. The study found influenza vaccination was not associated with detection of non-influenza respiratory viruses [12]. Additionally, the laboratory data in our study showed increased odds of coronavirus and human metapneumovirus in individuals receiving influenza vaccination. The study finding similar results to our study found no association between influenza vaccination and RSV, adenovirus, human metapneumovirus, rhinovirus or coronavirus [12]. The same study did find a significant association between parainfluenza and influenza vaccination, but the association was in opposite directions when comparing children and adults [12]. In our disease specific investigation, virus interference trends were noticed for coronavirus and human metapneumovirus; however, two specific respiratory viruses (parainfluenza and RSV) showed

Table 3
Virus interference odds ratio 2017–2018 influenza season.

Total Population	Other Respiratory Viruses	Pan-Negative Respiratory Virus	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR p-Value
Vaccinated	2050	2441	0.81 (0.72, 0.91)	0.97 (0.86, 1.09)*	0.60
Unvaccinated	830	799			
AFCITA Confirmed Vaccination					
Vaccinated	1417	2979	0.95 (0.68, 1.34)	1.23 (0.86, 1.76)**	0.25
Unvaccinated	51	102			
Active Duty Only					
Vaccinated	1046	2570	0.97 (0.73, 1.29)	1.20 (0.89, 1.61)**	0.24
Unvaccinated	73	174			

* Adjusted for age group.
** Adjusted for age group and seasonality.

Table 4
Odds ratios for influenza cases versus controls using different control groups.

Cases vs All Controls	Case	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)***	Adjusted OR p-value
Vaccinated	2050	4491	0.57 (0.52, 0.63)	0.48 (0.43, 0.52)	<0.0001
Unvaccinated	1299	1629			
Cases vs Non-influenza Virus Positive Controls					
	Case	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)***	Adjusted OR p-value
Vaccinated	2050	2050	0.64 (0.57, 0.71)	0.51 (0.45, 0.57)	<0.0001
Unvaccinated	1299	830			
Cases vs Pan-Negative Controls					
	Case	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)***	Adjusted OR p-value
Vaccinated	2050	2441	0.52 (0.47, 0.57)	0.46 (0.41, 0.52)	<0.0001
Unvaccinated	1299	799			

*** Adjusted for gender, age group, and season.

Table 5
Respiratory viruses and odds ratios by vaccination status.

Virus	Vaccinated (%)	Not Vaccinated (%)	OR (95% CI)	P-Value
Influenza	2050 (31.3)	1299 (44.4)	0.57 (0.52, 0.63)	<0.01
Influenza A	1256 (19.2)	741 (25.3)	0.70 (0.63, 0.78)	<0.01
Influenza A H1N1	225 (3.4)	227 (7.8)	0.42 (0.35, 0.51)	<0.01
Influenza A H3N2	1023 (15.6)	512 (17.5)	0.88 (0.78, 0.98)	0.02
Influenza B	662 (10.1)	474 (16.2)	0.58 (0.51, 0.66)	<0.01
Influenza B Victoria	7 (0.1)	8 (0.3)	0.39 (0.14, 1.08)	0.07
Influenza B Yamagata	85 (1.3)	77 (2.6)	0.49 (0.36, 0.67)	<0.01
Influenza Coinfection	9 (0.1)	9 (0.3)	0.45 (0.18, 1.13)	0.09
Non-Influenza Virus	2050 (31.3)	830 (28.3)	1.15 (1.05, 1.27)	<0.01
Adenovirus	144 (2.2)	78 (2.7)	0.82 (0.62, 1.09)	0.17
Coronavirus	507 (7.8)	170 (5.8)	1.36 (1.14, 1.63)	<0.01
Human Bocavirus	69 (1.1)	34 (1.2)	0.91 (0.60, 1.37)	0.64
Human Metapneumovirus	335 (5.1)	101 (3.5)	1.51 (1.20, 1.90)	<0.01
No Pathogen Detected	2441 (37.3)	799 (27.3)	1.59 (1.44, 1.75)	<0.01
Parainfluenza	139 (2.1)	92 (3.1)	0.67 (0.51, 0.87)	<0.01
RSV	369 (5.6)	202 (6.9)	0.81 (0.68, 0.96)	0.02
Rhinovirus/Enterovirus	875 (13.4)	400 (13.7)	0.98 (0.86, 1.11)	0.71
Non-Influenza Virus Coinfection	225 (3.4)	138 (4.7)	0.72 (0.58, 0.89)	<0.01

significant protection associated with influenza vaccine receipt, and all others tested (adenovirus, human bocavirus, and rhinovirus/enterovirus) showed protection, although non-significant, associated with vaccination (Table 5).

Additional examination of virus interference was accomplished by assessing the affect that three non-influenza control groups had on vaccine effectiveness (N = 9469). The adjusted ORs for the three groups ranged from 0.46 to 0.51, having similar 95% confidence intervals, and accounting for a difference of 5% in vaccine effectiveness. The minute differences among the vaccine effectiveness of all three control groups does not support the virus interference concept.

Test-negative study designs are often utilized to calculate influenza vaccine effectiveness. This type of study recruits subjects who

have influenza-like illness, collects a respiratory specimen, performs diagnostic laboratory testing to determine the pathogen, and obtains the individual's vaccination status [18–21]. The vaccine-associated virus interference phenomenon goes against the basic assumption of the test-negative vaccine effectiveness study, that is, vaccination does not change the risk of infection with other respiratory illness. The results of this study do not support a potential for bias in test-negative influenza vaccine effectiveness studies. In a test-negative study design, patients must be sick with influenza-like illness. Since the population must be ill, if the vaccinated population is more likely to have other respiratory viruses when compared to the non-vaccinated population, then in turn they are less likely to have influenza. Bias introduced in these studies may cause an overestimate of vaccine effectiveness.

Mandatory influenza vaccination is required for all Active Duty personnel [13]. As such, vaccination effectiveness studies examining strictly Active Duty military members have previously shown to be methodologically invalid and often times have uninterpretable results [22,23]. In order to examine potential issues with mandatory vaccination, beneficiary category was included in the logistic regression model. While beneficiary category did not remain significant, and was therefore not kept in the final logistic model, Active Duty members were then separated from the rest of the population and virus interference among this population was calculated. Both the unadjusted and adjusted models did not show significant evidence of virus interference in Active Duty members; therefore, this large portion of the population does not appear to be skewing study results converse to the aforementioned vaccine effectiveness studies.

Study limitations include the assumption of a causal relationship between influenza vaccination and respiratory viruses. Perhaps there were other factors influencing rates of respiratory illnesses. Adjustment in the conditional logistic regression analysis attempted to account for some factors which could influence respiratory outcome. Additionally our study relied on self-reported vaccination status when data were unavailable in AFCITA. Missing vaccination status was especially high in non-Active Duty members of our study, as many of these patients were seen at clinics off base, and therefore not necessarily tracked in AFCITA. However, self-reported vaccination data were included to augment vaccination status when AFCITA data were unavailable. Self-reported data were assumed to be relatively accurate. To ensure self-reported data were not skewing findings, those with AFCITA records were examined exclusively for virus interference. Both the unadjusted and adjusted models did not show significant evidence of virus interference in AFCITA vaccinated personnel; therefore, vaccination record status does not appear to be skewing study results.

5. Conclusion

Virus interference associated with influenza vaccination has been previously investigated [7–12]. However, this study was the first virus interference study conducted among highly vaccinated DoD personnel. The study included a diverse, well dispersed population based on sex, age group, beneficiary category, and vaccination status. Additionally the population size was relatively large, and numerous respiratory pathogens were examined which were not previously individually investigated for virus interference.

The overall results of the study showed little to no evidence supporting the association of virus interference and influenza vaccination. Individual respiratory virus results were mixed, and some rebutted virus interference. Additionally those receiving the influenza vaccine were more likely to have no pathogen detected and reduced risk of influenza when compared to unvaccinated individuals. Further research is necessary to help character virus interference and validate or refute the validity of the test-negative design for influenza vaccine effectiveness.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the official policy or position of the Department of Defense, or the U.S. Government.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] National Vaccine Information Center. What is the History of Influenza Vaccine Use in America? <https://www.nvic.org/vaccines-and-diseases/influenza/vaccine-history.aspx> 2019.
[2] Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis 2012;55(7):951–9.
[3] Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis 2014;58(3):319–27.
[4] McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. J Infect Dis 2015;211(10):1529–40.
[5] Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015–2016 Season. N Engl J Med 2017;377 (6):534–43.
[6] Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2004-2018. <https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm> 22 February 2019.
[7] Suzuki M, Camacho A, Ariyoshi K. Potential effect of virus interference on influenza vaccine effectiveness estimates in test-negative designs. Epidemiol Infect 2014;142:2642–6.
[8] Cowling BJ, Fang VJ, Peiris JSM, et al. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis 2012;54:1778–83.
[9] Feng S, Fowlkes A, Steffens A, Finelli L, Cowling B. Assessment of virus interference in a test-negative study of influenza vaccine effectiveness. Epidemiology 2017;28(4):514–24.
[10] Cowling BJ, Nishiura H. Virus interference and estimates of influenza vaccine effectiveness from test-negative studies. Epidemiology. 2012;23(6):930–1.
[11] Rikin S, Jia H, Stockwell M, et al. Assessment of temporally-related acute respiratory illness following influenza vaccination. Vaccine 2018;36:1958–64.
[12] Sundaram ME, McClure DL, Belongia EA, et al. Influenza vaccination is not associated with detection of noninfluenza respiratory viruses in seasonal studies of influenza vaccine effectiveness. Clin Infect Dis 2013 September;57:789–93.
[13] Defense Health Agency. Seasonal Influenza Vaccination Program (IVP). Falls Church, Virginia: Defense Health Agency; 2018. p. 1–23. Interim Procedures Memorandum 18-005.
[14] NxTAG Respiratory Pathogen Panel [package insert]. Toronto, Ontario, Canada: Luminex; 2016.
[15] Biofire FilmArray Respiratory Pathogen Panel [package insert]. Salt Lake City, Utah, USA; 28 June 2017.
[16] CDC Influenza A Subtyping Kit (Version 2) [package insert]. Atlanta, Georgia, USA; 22 July 2016.
[17] CDC Influenza A/B Subtyping Kit [package insert]. Atlanta, Georgia, USA; 23 March 2016.
[18] Foppa I, Haber M, Ferdinands J, et al. The case test-negative design for studies of the effectiveness of influenza vaccine. Vaccine 2013;31(June):3104–9.
[19] Jackson M, Nelson J. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31(April):2165–8.
[20] Foppa I, Ferdinands J, Chaves S, et al. The case test-negative design for studies of the effectiveness of influenza vaccine in inpatient settings. Int J Epidemiol 2016;6:2052.
[21] Sullivan S, Tchetgen Tchetgen E, Cowling B. Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness. Am J Epidemiol 2016;5:345.
[22] Coleman R, Eick-Cost A, Hawksworth AW, et al. Department of defense end-of-season influenza vaccine effectiveness estimates for the 2017–2018 season. MSMR 2018;25(10):16.
[23] Cooper M. DoD Influenza Surveillance and Vaccine Effectiveness. In: Oral presentation at: The Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting; February 28, 2014; Silver Spring, MD.