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Influenza Vaccination and Respiratory Virus Interference Among Department of Defense Personnel During the 2017–2018 Influenza Season

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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.

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], [3], [4], [5], [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], [8], [9], [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.

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