



## Risk factors for severe outcomes among members of the United States military hospitalized with pneumonia and influenza, 2000–2012



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### ABSTRACT

**Background:** The progression from hospitalization for a respiratory infection to requiring substantial supportive therapy is a key stage of the influenza severity pyramid. Respiratory infections are responsible for 300,000–400,000 medical encounters each year among US military personnel, some of which progress to severe acute respiratory infections.

**Methods:** We obtained data on 11,086 hospitalizations for pneumonia and influenza (P&I) among non-recruit US military service members during the period of 1 January 2000 through 31 December 2012. From these, we identified 512 P&I hospitalizations that progressed to severe episodes using standard case definitions. We evaluated the effect of demographic and occupational characteristics, co-morbid conditions, and history of influenza vaccination on the risk of a hospitalized P&I case becoming a severe case. We also evaluated the risk of a severe outcome and the length of time since influenza vaccination (within 180, 60, and 30 days).

**Results:** The median age of subjects at the time of the P&I episode was 32 years (range, 28–40) and subjects were predominantly male (89.5%). In a univariate analysis, demographic risk factors for a severe episode included service in the US Air Force (RR = 1.6 relative to US Army, 95%CI 1.3–2.1), US Coast Guard (RR = 2.1, 1.2–3.7) or US Navy (RR = 1.4, 1.1–1.8). Being born in the US and recent influenza vaccination (within 180 days of episode) were protective against developing severe disease. Among co-morbid conditions, univariate risk factors for severe disease included chronic renal or liver disease (RR = 4.98, 95%CI 4.1–6.1), diseases of the circulatory system (RR = 3.1, 95%CI 2.6–3.7), diabetes mellitus (RR = 2.3, 95%CI 1.5–3.6), obesity (RR = 1.6, 95%CI 1.2–2.1), cancer (RR = 1.6, 95%CI 1.3–2.0), and chronic obstructive pulmonary disease (RR = 1.4, 95%CI 1.1–1.7). Although many of the risk factors found to be significant in univariate analysis were no longer significant under a multivariate analysis, receipt of any influenza vaccine within 180 days of episode remained protective (RR = 0.81, 95%CI 0.67–0.99), while serving in the US Coast Guard (RR = 1.9, 95%CI 1.1–3.4) or US Air Force (RR = 1.5, 95%CI 1.2–2.0), presence of renal or liver disease (RR = 3.6, 95%CI 2.9–4.6), and diseases of the circulatory system (RR = 2.2, 95%CI 1.8–2.8), remained significantly associated with a higher risk of developing severe disease.

**Conclusions:** In a large cohort, after adjusting for many possible risk factors, influenza vaccination was protective against severe episodes among P&I hospitalizations. The service-specific (US Coast Guard or US Air Force) increased risk may represent some differences in data (e.g., coding or reporting practices) as opposed to genuine differences in physiological outcome. Our findings suggest that renal and liver disease as well as diseases of the circulatory system may contribute to influenza severity in this population independently of age and other potential comorbidities. These findings provide additional evidence for the prioritization of specific risk groups within the US military for influenza vaccination

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## 1. Introduction

The burden of influenza in the United States (US) is significant, typically affecting the very young and old, those with chronic health conditions and pregnant women. Among the general population, many aspects of respiratory diseases, particularly influenza, are well studied and monitored through the US Centers for Disease Control and Prevention surveillance systems [1]. Historically, military populations have been at high risk of acute influenza-related respiratory illnesses, especially among recruits and during fall–winter months [2,3]. The living, environmental, and physical conditions of US military personnel have been shown to compromise the immune systems of recruits leading to higher levels of respiratory disease when compared to non-military recruits [2,4,5]. The burden of severe illness due to influenza in the US military population as a whole, however, is largely unknown.

During the 1918 influenza pandemic, the US military experienced attack rates as high as 25% and case fatality rates averaging 5% (ranging from 1 to 8%) [6]. During the 2009 pandemic, attack rates among military personnel measured during clusters of infection among specific military units ranged from as low as 3% [7] and as high as 70% [8]. In confined settings, such as aboard navy ships, serologic attack rates of influenza among US and foreign military crew have been estimated to be between 30 and 50% [9,10]. Estimates of the proportion of the US military infected with influenza, risk factors for severe outcomes among those infected with influenza, and trends in incidence and cross-protective immunity are important for understanding the burden of influenza in this unique cohort.

The US military has played a key role in the development, deployment, and management of influenza vaccines for the US population at-large. For example, the US military led the development of influenza vaccines in the late 1930s, when Drs Salk and Francis developed the first inactivated vaccines which were used to protect US military personnel during the World War II [11]. The US military was also the first institution which established a universal influenza vaccination policy in the early 1940s, many decades before widespread immunization of healthy young people was recommended by the CDC and other international health officials [12].

The Global Emerging Infections Surveillance and Response System (GEIS), now part of the Armed Forces Health Surveillance Center (AFHSC), of the US Department of Defense was established in 1997 to provide surveillance for respiratory infections and other global emerging infections among US military personnel. Respiratory infections and illnesses remain one of the leading causes of medical encounters and lost work time of service members [13–15]. Incidence of pneumonia and influenza (P&I) typically follow a seasonal pattern with the highest incidence in the winter months of the northern hemisphere [16]. An exception was during the 2009 pandemic, when there were peaks in the spring as well as autumn months of 2009, followed by a winter peak in 2009–2010 [16]. The AFHSC has found that respiratory infections account for between 300,000 and 400,000 medical encounters annually among Service Members [17,18].

The principal objective of this study was to evaluate and quantify demographic, immunologic, occupational, and medical risk factors associated with severe P&I outcomes among non-recruit US military personnel who were hospitalized anytime between 1 January 2000 and 31 December 2012.

## 2. Methods

### 2.1. Data analyses

We obtained data on the active component US military personnel who had an inpatient diagnosis of P&I between 1 January 2000

and 31 December 2012. We further classified the P&I episodes as severe or non-severe using the criteria and ICD-9 codes presented in Table 1. We excluded individuals who were classified as a recruit at the time of the episode. Data on potentially important demographic (e.g., country of origin, race-ethnicity, age, and sex) and occupational (e.g., occupation, service, and rank) characteristics that may influence the risk of a hospitalized P&I episode becoming a severe episode were obtained for each subject.

In addition to standard demographic and occupational variables, we also investigated the potential role of other health-related comorbidities and the risk of a P&I becoming severe including pregnancy, asthma, chronic obstructive pulmonary disease (COPD), disease of the circulatory system, diabetes mellitus (DM), sickle cell disease, chronic kidney and liver disorders, cancer, and chronic immunosuppressive conditions or human immunodeficiency virus (HIV) infection. For example, we considered the presence of an encounter for asthma or DM at any time prior to an admission for P&I as a potential risk factor for a severe outcome as a result of hospitalization. Additionally, we evaluated whether prior influenza vaccination (e.g., prior vaccination [Yes/No]) and vaccination within 180 days, 60 days, and 30 days of the P&I episode influenced the risk of severe P&I. The type of vaccination including inactivated split virus vaccine (CVX code 15), inactivated whole virus Influenza virus vaccine for intramuscular or jet injection use (CVX code 16), live attenuated influenza virus vaccine (LAIV) for intranasal use (CVX code 111), and unspecified influenza virus vaccine (CVX code 88) was also evaluated for their potentially protective effects.

De-identified data was obtained from the Defence Medical Surveillance System, AFHSC, Silver Spring, Maryland [data from 2000–2012; released on 14 August 2013]. We conducted univariate analyses using generalized linear models and estimated the relative risk (RR) of a severe episode among all hospitalized P&I episodes. Variables that were statistically significant ( $p < 0.05$ ) in the univariate model were included in a multivariate model. Analyses were conducted in Stata and R. These analyses build on previous studies [15,16] by testing specific hypotheses about the factors that cause hospitalized P&I to become SARI within a multivariate statistical model. The earlier work focussed on describing the unadjusted trends in these outcomes.

### 2.2. IRB approval

IRB approval was sought and granted by the Imperial College Ethics Committee, and the project was deemed public health surveillance by the US Army Public Health Command Human Protections Administrator and the Naval Medical Research Center, Office of Research Administration.

## 3. Results

We identified 11,053 hospitalized P&I inpatient clinical episodes that occurred among 10,384 unique individuals during the 12-year study period. There were a total of 10,541 non-severe and 512 severe P&I inpatient encounters among the study population meeting the case definitions shown in Table 1. The proportion of P&I episodes by northern hemisphere influenza season are shown in Fig. 1A (primary axis). The largest proportion of severe P&I episodes over the 12-year study period was during the 2009–2010 northern hemisphere influenza season.

### 3.1. Demographic, occupational and underlying conditions

Overall, the median age of subjects experiencing an inpatient P&I episode during the study period was 32 years (range 19–72) at

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