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# Influenza in the US Military: An Overview

Jose L Sanchez[1] and Michael J Cooper[2]

1 Armed Forces Health Surveillance Branch, Public Health Division, Defense Health Agency, 11800 Tech Road, Silver Spring, MD 20904, USA
2 Respiratory Program Initiatives, Global Emerging Infections System, Armed Forces Health Surveillance Branch, Public Health Division, Defense Health Agency, 11800 Tech Road, Silver Spring, MD 20904, USA

**Corresponding author:** Jose L. Sanchez

toti.sanchez@us.army.mill

MD, MPH, Armed Forces Health Surveillance Branch, 11800 Tech Road, Suite 218, Silver Spring, MD 20904, USA.

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## Abstract

Circulation of influenza strains in the military has been responsible for clusters of illness among military personnel in the United States and remote areas where they operate, although not usually associated with a high degree of morbidity [1,2]. During the latest 5-year period (2007-2012) for which there is published data by the AFHSC, influenza was found to be responsible for as many as 7,000 to 25,000 cases per week in the MHS, of which 3,000 to 16,000 (40 to 65 percent) involved military personnel [3]. Since 2009, pH1N1 has continued to circulate worldwide; [4] it resurged in the US from November 2013 through February 2014, causing an increase in laboratory-confirmed influenza associated hospitalizations in all age groups [5].

Since summer-fall of 2014, drifted H3N2 viruses have begun to predominate causing an increase in laboratory-confirmed influenza associated hospitalizations among both US civilian and military personnel in the winter of 2014-2015 and through December 2015 [1,6]. These drifted H3N2 viruses have also been associated with increased mortality, especially among those older than 64 years [7-9].

**Keywords:** US military; Influenza; H1N1; H3N1; Armed forces

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## Clinical Aspects

Seasonal influenza viruses (H1N1, H3N2 and B subtypes) have a very short incubation period (median, 2 days; range, 1 to 4 days), but may be longer (up to 8 to 9 days) in infections caused by other avian influenza viruses (AIVs) [10,11]. Viral shedding begins approximately 24 to 48 hours prior to symptom onset, peaks within 48 to 72 hours, and can continue for up to a week after symptom resolution, especially in non-immune individuals. Hospitalized adults may shed infectious virus for a week or longer after illness onset. Viremia rarely occurs in uncomplicated influenza except in cases of H5N1-infected patients, in whom detection of viral ribonucleic acid (RNA) in the blood is associated with a worsened prognosis.

Most persons with symptomatic influenza virus infection have uncomplicated illness with sudden onset of fever, cough, headaches, and malaise, all of which resolve over 3 to 5 days, although cough and fatigue may persist longer. Some adults may also experience diarrhea [12]. Although most persons with influenza virus infection will not develop critical illness, those who are pregnant [13,14], obese [13,15], suffer from chronic renal or liver disease, [16] or suffer from diseases of the circulatory system [16] are at a greater risk of respiratory complications and mortality. Deterioration in clinical status occurs rather rapidly after 4 to 5 days of symptom onset with development of acute respiratory distress syndrome (ARDS) characterized by hypoxemia, shock, and multiorgan dysfunction, [17,18] an illness that results from an intense inflammatory host response to the virus [19]. Influenza infections may also be complicated by secondary bacterial pneumonia, especially *Staphylococcus aureus* (including methicillin-resistant *S. aureus,* or MRSA), *Streptococcus pneumoniae*, or *Streptococcus pyogenes*, in up to 20 to 30 percent of cases [19]. Influenza-like illnesses are usually associated with clusters among non-immune recruits (early in basic training, prior to the development of vaccine-induced immunity) and among older individuals in whom vaccine-derived immunity has waned.

In the recent past, mortality due to influenza viruses has been very low, although an influenza pandemic in 1918-1919 was associated with high mortality [1]. Only nine influenza-associated deaths among US military personnel have been documented during the past 16 years (1998–2014), three of these nine occurred during the 2009–2010 pandemic period (Potter R, personal communication). This relatively low mortality level

 

is most likely an accurate reflection of influenza viruses' low virulence among military personnel because of the availability of real-time, systematic, standardized military data collection systems which appropriately and promptly evaluate influenza (or other pathogen)-related mortality.

## Diagnosis

Influenza viruses can be readily isolated in tissue culture from nasal swab specimens, nasal aspirates, or combined nose and throat swab specimens [20,21]. As with adenoviruses, the time required to detect influenza viruses in cell culture can be shortened to one to two days by employing shell vial centrifugation culture (SVCC) systems followed by fluorescent antibody staining. Immunologic detection of influenza antigens in respiratory samples can be used for rapid diagnosis, and a large number of such rapid influenza diagnostic tests (RIDTs) are commercially available [22] They can provide results at bedside (within 15 minutes or less), thus, results are available in a clinically relevant time period to inform clinical decisions. Unfortunately, RIDT sensitivities have varied widely (10 to 80 percent) compared to viral culture or molecular detection and are largely dependent on the type of sample as well as on the patient's age and phase of illness [22]. RIDT sensitivity is lower in adults and elderly patients than in young children, whose nasal secretions may contain larger quantities of virus [23,24]. Similarly, sensitivity is likely to be higher early in the course of illness (within 48 to 72 hours of onset), when viral shedding is maximal. Thus, care should be exercised when utilizing RIDTs later in the course of illness as sensitivity can be low as viral shedding decreases [25]. RIDT specificity, on the other hand, has been very good ranging from 85% to 100%, thus, they are good tests for "ruling-in" rather than "ruling out" influenza infection, especially when influenza activity is high in the community [22]. Two recent FDA-cleared assay systems that rely on instrument optics to determine an objective result, as opposed to a subjective read by the operator, hope to improve performance of RIDTs [26].

The gradual dissemination of nucleic acid amplification testing (NAAT), including real-time reverse transcriptase polymerase chain reaction (rRT-PCR), in clinical laboratories has shifted the focus of laboratory diagnosis of influenza from dependency on viral culture, which takes several days, to a highly specific (>99.9 percent) and sensitive (86 to 100 percent) diagnosis available within several hours [27]. Sample processing automation, combined with user-friendly platforms for NAAT testing and information management systems, facilitates high-throughput molecular diagnostics for the detection of viral nucleic acids, including influenza A, from a variety of respiratory tract samples. Molecular assays can be used in conjunction with other diagnostic assays, and with clinical and epidemiologic information, to assist in patient management and treatment [28].

Rapid detection platforms which are US Food and Drug Administration (FDA)-cleared, such as those consisting of multiplex PCR tests for influenza, also allow the detection of other respiratory agents, either as single viruses or as co-pathogens [29-34]. Among adult patients with ARI in one study using this type of testing in the United States in 2012-2013, 5% to 8% were found to sustain viral coinfections, to include influenza, HCoVs, RSV and HRV [35]. One influenza typing kit based on the RT-PCR electrospray ionization mass spectrometry (PCR-ESI-MS) platforms allows detection of all 16 hemagglutinin and 9 neuraminidase subtypes, [36] as well as detection of drift of specific genes over time [36-39]. Because of its ability to detect newly emerging recombinant, drifted, or shifted influenza viruses, the PCR-ESI-MS typing analysis can be useful in detecting newly emerging influenza strains [40]. New PCR-based point-of-care tests have been developed and are more sensitive (>90 percent) than older RIDTs and are in wide use in the military [1,41-43].

## Treatment

The only two classes of FDA-approved antivirals are available for early treatment and chemoprophylaxis of influenza infection are the M2 inhibitors (oral amantadine and rimantadine) and the neuraminidase inhibitors (NIs; oral oseltamivir, inhaled zanamivir and oral or inhaled laninamivir, not FDA-approved) [44-47]. The ion channel protein present within the viral envelope (denominated M2 protein) is the target of the M2 inhibitors. By comparison, the NIs target the viral neuraminidase which acts on surface glycoproteins of the virus [48] The M2 inhibitors are active, *in vitro* and *in vivo*, against all strains of influenza A virus; however, they are not active against influenza B viruses, and antiviral resistance has increased since the emergence of the pH1N1 strain in 2009-2010. Therefore, they are not presently recommended for use in the United States [44].

In placebo-controlled randomized clinical trials (RCTs) oseltamivir has been found to be effective in reducing duration of influenza symptoms by 21 percent (from 123 hours down to 98 hours) as well as the risk of hospitalization by 65 percent (0.6 percent compared to 1.7 percent in placebo recipients) among adults in a recently published meta-analysis [49]. In addition to recommending influenza vaccine for preventing influenza, the CDC and the FDA recommend use of NIs for the treatment of influenza [44,50]. There are also a number of published observational studies providing data that support the efficacy of NIs (oral oseltamivir, inhaled zanamivir) for uncomplicated influenza, reducing fever and illness duration by approximately one day [51,52]. NIs have also been found to be effective in reducing mortality in patients hospitalized with pH1N1 virus infection including, but not limited to, pregnant women [50,53].

Treatment should be started within 48 hours of symptom onset and administered for at least 5 days in uncomplicated cases. Increased duration for up to 10 days, or higher dose (e.g., 150 mg twice daily in adults with normal renal function) may be necessary in the case of critically ill patients with respiratory failure or among immunocompromised patients in whom prolonged viral replication may occur in the lower respiratory tract [17,18,44,52]. Oral oseltamivir treatment begun more than 2 days after illness onset may also be of some benefit [54,55]. Fortunately, resistance is low to-date (less than 1–2 percent of isolates) among the prevailing seasonal viruses in the US and worldwide [8,56].

The US military recommends treatment only for people hospitalized with confirmed, probable or suspected disease; treatment should be implemented as soon as the clinician suspects infection and should not await laboratory confirmation

[57] The DoD also stockpiles oseltamivir and zanamivir as a contingency component of its pandemic preparedness plans (AFHSB, unpublished data). In patients with severe disease (such as pneumonia or ARDS), empirical broad-spectrum antimicrobial therapy should also be initiated to cover bacterial coinfections, with appropriate de-escalation of antimicrobials when lower respiratory bacterial cultures return with definitive results [19].

## Chemoprophylaxis

Chemoprophylaxis has also been shown to be beneficial if given for at least 7 days post-exposure. Systematic reviews have found NIs, but not M2 agents, to provide some degree of protection as chemoprophylactic agents [58] Oseltamivir (in a dose of 75 mg daily) and zanamivir (in a dose of 10 mg daily), but not amantadine, have demonstrated to be efficacious both as seasonal and as post-exposure chemoprophylaxis of influenza in households (efficacy approximately 67 to 89 percent) [59]. However, they have not been shown to prevent community-wide transmission of influenza [59,60].

In a unique study in the Singaporean military at the height of a pH1N1 epidemic in June 2009, the implementation of "ring chemoprophylaxis" (defined as geographically targeted containment by use of oseltamivir) of co-workers and same-unit members was elegantly demonstrated to be effective, in conjunction with prompt identification and isolation of infected personnel, in a restricted entry training setting. Inhaled laninamivir has also been shown to reduce secondary illness rates among household contacts (78% efficacy) in a RCT and may represent a third option for chemoprophylaxis [61].

At the present time, US military health officials do not routinely recommend "mass" or "targeted" outbreak chemoprophylaxis with NIs. However, the potential use of oseltamivir chemoprophylaxis can and should be considered by military health officials, especially if there are operational considerations which justify its use (such as circulation of a highly virulent strain, among high-risk patients during outbreaks in confined facilities or homes, among unvaccinated health care providers (HCP), in a perceived or real compromise of the military mission, or during an overwhelming epidemic) [44].

## Vaccine Effectiveness Monitoring

Continued surveillance and determination of influenza vaccine effectiveness (VE) has ongoing in the US military for many years. In collaboration with the US Centers for Disease Control and Prevention (CDC) and the FDA, the US military estimates mid-year and year-end influenza VE and these are provided at the time of the FDA's Vaccine and Related Biologic Products Advisory Committee (VRBPAC) meetings. These analyses examine VE by type of vaccine (e.g., live attenuated vaccine or inactivated vaccine), status (military members versus non-military) and age strata each year in order to track VE in these groups. Methodological and immunological issues regarding estimates of VE in US military members have surfaced and have stimulated ongoing research regarding the potential impact of a frequent vaccination (i.e., multiple vaccinations for influenza in succession over multiple years) on antigenic response to current and future vaccinations. In addition, questions regarding the possiblility of waning protection within a given influenza season suggests that later vaccinations (vaccinations closer to the peak) or multiple vaccinations within the influenza season might protect against infection more effectively. In general, it has been theorized that US military members might be different in important ways from civilian populations regarding VE and its estimation; therefore, military and dependent populations should continue to be be monitored specifically. Continued assessment of influenza VE in the US military is essential in order to continue to better inform vaccination policy decisions [62].

## Vaccine Develoment and Policy

The US military requires influenza vaccination of military recruits as well as of all personnel on active duty status on a yearly basis [1]. The goal is to exceed 90-percent immunization of all military personnel by mid-December of each year; however, delays in receipt of vaccine and other logistic and access issues are taken into consideration, and all organizations are encouraged to continue their efforts to immunize throughout the influenza season [63]. Additionally, the US military's mandatory influenza vaccination policy, which applies to all of its HCP, is based on the premise that vaccination is an important tool for enhancing patient safety and quality of care as well as a means of protecting patients and staff members [64,65]. Compliance among military HCP for 2012-2013 and 2013-2014 has been excellent with vaccination rates exceeding 95% each year [66]. By comparison, compliance rates among civilian HCP in the United States have not exceeded 75% [67].

The US military has played a key role in the development, deployment, and management of influenza vaccines for the entire nation. The US military led their development in the late 1930s when Dr's Jonas Salk and Thomas Francis developed the first inactivated vaccines which were used to protect US military personnel during World War II [68]. The US military was also the first institution which established a universal influenza vaccination policy which dates back to the early 1940s, many decades before widespread immunization of healthy young people was recommended by the CDC and other international health officials [1,69]. For many years, the CDC recommended influenza immunization only for aged and infirmed people, while the US military was immunizing the entire force. Lastly, because of the important need for their protection, US military health officials have been an active participant in the annual vaccine strain selection activities led by the FDA which, in the past, sought a military member to be part of the FDA's VRBPAC.

Even though a large proportion of US military personnel are immunized with current influenza vaccines, influenza viruses continue to affect them; [1,70] this is most likely multifactorial in nature. First, humoral-mediated immunity is transitory requiring annual immunizations [71]. This is most likely explained by distinct patterns of B-cell activation and priming resulting in lower cross-protection against heterovariant and heterosubtypic influenza strains [72]. Second, subtypes contained in annual vaccine formulations often do not match prevailing circulating

subtypes, thus, vaccine-derived immunity is non-efficacious in many cases [73] Third, even under the best of circumstances, vaccine efficacy among healthy adults is no higher than 60 to 80 percent for inactivated vaccines and much lower for live attenuated formulations, leaving many vaccinees susceptible to infection [71,74]. Lastly, military personnel often travel or are deployed to areas of the world where influenza virus subtypes differ from those subtypes included in the US-based vaccines.

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