The Acute Respiratory Infection Consortium: A Multi-Site, Multi-Disciplinary Clinical Research Network in the Department of Defense

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ABSTRACT Introduction: Acute respiratory infections (ARI) result in substantial annual morbidity among military personnel and decrease operational readiness. Herein, we summarize the research efforts of the Infectious Disease Clinical Research Program (IDCRP) related to ARIs. Methods: The ARI Research Area of the IDCRP was established in response to the 2009 emergence of pandemic influenza A/H1N1. That year, IDCRP investigators deployed the ARI Consortium Natural History Study (ARIC NHS), a multi-centered, longitudinal observational study to assess etiology, epidemiology, and clinical characteristics of influenza-like illness (ILI) and severe acute respiratory infections (SARI) in the U.S. military. The success of this initial effort spurred implementation of several new initiatives. These include the FluPlasma trial, designed to evaluate the efficacy of hyperimmune anti-influenza plasma for the treatment of severe influenza; the self-administered live-attenuated influenza vaccine (SNIF) trial, which assessed the immunogenicity and acceptance of a self-administered live-attenuated influenza vaccine in military personnel; the Study to Address Threats of ARI in Congregate Military Populations (ATARI), a prospective study of ILI transmission, etiology and epidemiology in recruits; and the Flu Breath Test (FBT) study, a preliminary study of exhaled volatile organic compounds (VOC) in influenza patients. In addition, the InFLUenza Patient-Reported Outcome (FLU-PRO) survey, a daily diary to measure influenza symptoms during clinical trials, was developed. Lastly, the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) study, a two-year randomized trial designed to compare the effectiveness of the three types of licensed vaccines, launched in Fall 2018. Results: The on-going ARIC NHS has enrolled over 2000 ILI and SARI cases since its inception, providing data on burden and clinical manifestations of ARI in military personnel and their families. The FluPlasma 2 trial concluded subject enrollment in 2018. Preliminary results from ATARI study show a high frequency of respiratory viruses circulating during the first two weeks of recruit training. Based on assessment of FLU-PRO responses, which were found to be reliable and reproducible, the survey may be a useful tool in clinical trials and epidemiological studies. The Flu Breath Study will complete enrollment in 2019. Findings from PAIVED are intended to provide evidence needed for assessing influenza vaccination policy in the military. Conclusions: The ARI burden in the armed services remains significant every year and the threat is dynamic given emergent and evolving threats, such as influenzas. With strong successes to date, future initiatives of the ARI Research Area will focus on interventional studies, ARI transmission dynamics in congregate military settings, and determinants of risk of pandemic influenza and other emergent respiratory viruses.

INTRODUCTION

Acute respiratory infections (ARI) have compromised military readiness and threatened the health of U.S. military personnel since the Revolutionary War where approximately one-third of soldiers were hospitalized from various respiratory illnesses.[1] During the 1918 influenza pandemic, an estimated 46,640 deaths among U.S. military members were due to influenza and its complications.[2] Between the First and Second World Wars, a number of health promotion strategies were implemented, including healthier living conditions and quarantine, which contributed to the reduction of ARI-related morbidity and mortality in World War II.[2] In the following decades, outbreaks of adenovirus infection occurring almost exclusively in military recruits were identified.[3] Soon thereafter, the Walter Reed Army Institute of Research (WRAIR) and the National Institutes of Health developed a live-attenuated adenovirus vaccine. Routine immunization of recruits resulted in ~50–60% declines in overall ARI, and by the early 1970s, vaccination for adenovirus became standard.[4]

Service members are at heightened risk for ARI because missions often require living/working under stressful and

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doi: 10.1093/milmed/usz174

crowded conditions, in environments where respiratory infections are endemic, and have inadequate access to hygiene. In these military training/deployment settings, the person-to-person transmission of respiratory pathogens is enhanced. Between 2012 and 2014, ARIs were responsible for up to 400,000 clinical visits each year, affecting more than 500,000 active-duty personnel and resulting in up to 95,000 lost duty days. Influenza alone accounted for ~13,400 hospital bed days annually from 2011–2013. In particular, the rate of respiratory illness among deployed military personnel was ~69% in Iraq and ~40% in Afghanistan with performance being affected in 34% of cases between 2005 and 2006.[5]

Since the beginning of the 21st century, there has been the need to reintroduce the adenovirus vaccine for military trainees, respond to transient outbreaks of Severe Acute Respiratory Syndrome (SARS) coronavirus in civilian populations, manage a novel pandemic North American H1N1 influenza, and closely monitor the periodic emergence of different highly virulent avian influenza viruses and Middle East Respiratory Syndrome Coronaviruses (MERS-CoV). All these events remind us that ARIs pose considerable risk to public health, national security, and military readiness;[5–8] both from the threat of sudden catastrophic epidemics, and importantly from the persistent burden and readiness impact exerted by more ubiquitous respiratory pathogens that result in "non-severe" but temporarily disabling illness.

CONTINUED EPIDEMIOLOGIC SURVEILLANCE AND LABORATORY INFRASTRUCTURE

The U.S. military has well-established, well-positioned programs for the surveillance, identification, and characterization of ongoing and novel respiratory disease threats around the world, which are integrated with programs run by the Centers for Disease Control and Protection (CDC) and World Health Organization (WHO).[9,10] The main support and driving force behind the modern military surveillance system is Armed Forces Health Surveillance Branch Global Emerging Infections Surveillance (GEIS) section. The GEIS collaborates with Department of Defense (DoD) laboratories and sponsors population and laboratory-based surveillance of respiratory infection, including severe acute respiratory infections (SARI) to provide epidemiology, clinical severity, and burden of disease estimates in active-duty relevant population.

While the military has displayed strong surveillance and diagnostic capabilities for respiratory disease research, it was recognized that knowledge gaps existed in the clinical characteristics of ARI among military personnel. During the 2009 H1N1 pandemic, support from the National Institute of Allergy and Infectious Diseases (NIAID), Biomedical Advanced Research and Development Authority, the U.S. Navy Bureau of Medicine and Surgery, and GEIS led to the establishment of the Acute Respiratory Infection Consortium (ARIC), which is a multi-site, multi-disciplinary clinical research network for the study of ARI, overseen by the Infectious Disease Clinical Research Program (IDCRP), Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences (USU). Herein, we summarize ARIC and other ARI-related research efforts of the IDCRP over the past 10 years (2009–2019).

MEETING THE CURRENT CHALLENGES – THE PURPOSE OF THE ARIC PROGRAM

The goals of ARIC are to study the distribution and determinants, clinical features, and burden of influenza-like illness (ILI) and SARI in active-duty service members and DoD beneficiaries. In addition, this clinical research platform can be leveraged to evaluate the effectiveness of ILI prevention and control strategies in these military populations. The major objectives are to provide data for monitoring and responding to threats posed by respiratory pathogens, to improve the effectiveness of control strategies, and to contribute performance data on detection tools needed for routine surveillance of respiratory infections in military populations. Evaluations of novel diagnostic platforms, as well as conduct of clinical trials for treatment of SARI, have been conducted on the research platform established by the consortium.

The Acute Respiratory Infection Consortium Natural History Study (ARIC NHS)

The ARIC NHS is an on-going, multi-site longitudinal observational study focused on assessing the etiology, epidemiology, and clinical characteristics of ILI and SARI in the U.S. military, providing the foundation for a randomized control trial. The case definition for ILI is: 1) Measured fever of ≥38°C (100.4 °F) or subjective fever orchills/night sweats, and 2) cough or shortness of breath or difficulty breathing or sore throat, with onset within the past 7 days. The case definition for SARI is the same, but with the added requirement of overnight hospitalization, a proxy for illness severity. The ILI and SARI case definitions in the ARIC NHS are derived from those developed by the WHO,[11] with the only difference being that IDCRP's definition limits symptom onset to 7 days (vs 10 days in the WHO definition) prior to clinical presentation to improve the likelihood of pathogen detection using polymerase-chain reaction (PCR)-based assays.

Additional study objectives include the assessment of immunologic correlates of disease severity and genetic characterization of etiologic agents. Through the collection of clinical, microbiologic and immunologic information over a 28-day period, the study evaluates the clinical impact of ILI and SARI in this population and characterizes patterns of illness, the severity of symptoms, and differences in clinical manifestations by pathogen. Since its launch in 2009, ARIC

NHS has enrolled more than 1,900 ILI and SARI cases and findings from the studies have advanced our understanding of the control, changing distribution, and determinants of ARI in this population (Table I).

Currently, ARIC NHS comprises six study sites, which includes five major military hospitals that enroll SARI cases: Madigan Army Medical Center, Naval Medical Center Portsmouth, Naval Medical Center San Diego, Brooke Army Medical Center, and Walter Reed National Military Medical Center. A sixth study site, McWethy Troop Medical Clinic at Fort Sam Houston, enrolls outpatient ILI cases and monitors respiratory threats risk in enlisted military trainees living in a congregate setting. Trainees at Fort Sam Houston are participating in a related-study, which is an anonymous survey designed to assess ILI-related health-seeking behaviors. Collaborative ties with U.S. government, private industry, and other DoD researchers allow us to apply interdisciplinary expertise to tackle ARI research questions.

Findings of the ARIC Natural History Study

Surveillance of respiratory infections, including temporal/regional changes, and assessments of etiology provide vital data on the epidemiology, clinical severity, and burden of ARI disease estimates. Using data collected through ARIC NHS, species-specific differences in clinical severity and viral shedding were demonstrated with human rhinovirus (HRV), a major cause of ILI. In particular, HRV-A was predominant in adults, and was associated with a greater severity of upper respiratory symptoms compared to HRV-B along with a significantly longer duration of viral shedding versus HRV-C. Age-specific differences were also observed with HRV-C being more common in children versus adults.[12]

The clinical characteristics of adenovirus have also been assessed among febrile ILI patients enrolled in ARIC NHS. Over a five-year period, 3% of febrile ILI patients were positive for adenovirus with species C being the most common. Approximately half of the adenovirus cases were positive for at least one other respiratory pathogen, primarily influenza and respiratory syncytial virus. When symptoms were assessed, children positive for non-C adenovirus had a higher proportion of sore throats and hoarseness, indicating potential species-specific virulence differences, as well as variations in the host response to infection.[8] Furthermore, 12% of ILI patients enrolled in ARIC NHS were positive for human coronavirus (HCoV) with HCoV-OC43 and HCoV-229E being the most common with season-to-season variability.[13]

TABLE I. Summary of Selected IDCRP Acute Respiratory Infection Research

Study and Key Findings	Significance	Reference
H1N1 Vaccine in HIV-Infected Individuals: Only 28% of 63 HIV-infected adults developed durable protective responses to H1N1 influenza vaccine at 6 months, compared to the rate of 56% seen in 64 controls.	Monovalent H1N1 vaccine in this asymptomatic HIV+ cohort was ineffective indicating the need for a different strategy for this population.	Crum-Cianflone NF, et al.[30]
Clinical Patterns of Influenza-like Illness (ILI) Due to Human Rhinoviruses (HRV): 84 cases of HRV were genotyped in 22 children and 62 adults with ILI. Most HRV-C occurred in children. Adults with HRV-A displayed more severe symptoms and shed virus longer.	Species-specific and age-specific differences in symptoms and duration of shedding occur with the 3 main serotypes of HRV (A, B, C)	Chen WJ, et al.[12]
Use of Neuraminidase Inhibitors (NI) in the Department of Defense (DoD): NI were used for proven influenza in 23.9% of DoD members, though only 63% received NI at <48 hours of illness.	NI's use was limited, not always as early as recommended, and displayed only modest benefits in this healthy population.	Fairchok MP, et al.[16]
Self-Administration of Live attenuated Influenza Vaccine (LAIV): A phase IV open label randomized trial found similar immunogenicity (anti-hemagglutinin antibody concentrations) in 529 subjects who self-administered LAIV vs. 548 who received vaccine from healthcare workers	Self-administration of LAIV was well-accepted, equally effective, and could be an option during future needs for mass immunization.	Burgess TH, et al.[29]
Attenuation of Influenza after Vaccination: Of 111 immunized individuals with influenza, those who developed H3N2 infection had reduced disease severity, though those with H1N1 did not show a similar benefit.	Though vaccines may not protect against disease, they may attenuate severity for certain strains.	Deiss RG, et al.[31]
Validity of the Flu-PRO Symptom Screening Tool: Qualitative research validated the utility of the 37 question self-reported "Flu-PRO" symptom severity assessment tool.	Potential role for this adjunct tool in supporting rapid assessment of influenza disease severity	Powers JH, et al.[14]
Clinical Patterns of ILI with Adenovirus: Of 43 cases of adenoviral ILI, species C predominated, primarily in young children (median 3.4 years), and were less severe than A, B, or E	Unique clinical patterns are associated with specific species, and may help predict disease severity	Koren MA, et al.[8]
Phase 2 Trial Assessing Immune Plasma for Severe Acute Respiratory Infection Treatment: Patients who received plasma had fewer serious adverse effects but no overall significant impact of time to normalization of respiratory status	Immune plasma was well-tolerated by patients and demonstrated the potential for outcome improvement	Beigel JH, et al.[36]

Among SARI cases enrolled during the 2016/2017 respiratory illness season, influenza was detected in approximately 40%; however, influenza was detected in only 2% of ILI cases. In addition, bacterial and non-influenza pathogens were more frequently detected in ILI cases than in SARI cases. The results suggest that SARI cases have a greater likelihood to be associated with pathogens that cause more severe symptoms than those responsible for ILI. The findings also highlight the diversity of pathogens that may cause ILI in trainees. It is also important to note that for both ILI and SARI cases, pathogens could not be detected in half the samples using PCR-based assays.

Presently, there is no standardized method related to the evaluation of influenza symptoms. The development of such a systematic measure would have substantial value for public health in terms of use as a validated outcome measure regarding interventions to treat or prevent influenza. A standardized method could also serve as an overall measure of influenza severity. Therefore, in collaboration with NIAID and the U.S. Food and Drug Administration (FDA), we developed the InFLUenza Patient-Reported Outcome (FLU-PRO) daily diary to act as a standardized, measure scale of patient influenza symptoms to evaluate the occurrence, severity, and duration of influenza symptoms during clinical trials. Thirty-seven drafted questions[14] were finalized into a 32-item measure of influenza symptoms across six body regions (e.g., nose, throat, eyes, and chest) and evaluated using a 5-point ordinal system. Use of FLU-PRO was assessed based on information from 200 ILI patients (28% hospitalized during illness) and the questionnaire scores were found to be reliable, reproducible, and valid, indicating its usefulness in clinical trials and epidemiological studies.[15] Specifically, FLU-PRO may provide valuable insight into treatment efficacy and safety with greater precision and less bias than non-standardized metrics in FDA-regulated studies.

Data collected through ARIC NHS has also been used to examine characteristics associated with treatment and hospitalization. Among enrolled patients positive for influenza, 24% were prescribed neuraminidase inhibitors (more than half within 48 hours of symptom onset). Between patients who were and were not treated with neuraminidase inhibitors, there was no significant difference in symptoms; however, early receipt (within 48 hours) had a moderate benefit related to symptoms and duration of illness.[16] In an examination of clinical characteristics of ILI patients within the Military Health System stratified by hospitalization status, hospitalized patients were less likely to have received influenza vaccination and more likely to receive treatment with a neuraminidase inhibitor. Obesity and influenza A infection were also associated with increased risks for hospitalization. Furthermore, patients with influenza requiring hospitalization were more likely to be febrile, but otherwise presented with similar symptoms (e.g., chills, cough, and sore throat) as outpatients.[17]

Incidence rates of ILI for trainees are typically based on passive surveillance of those presenting to medical clinics. Such clinic-based surveillance may under-estimate the actual ILI burden because trainees with ILI may not seek healthcare due to mild symptoms or fear of missing training. Initial findings from the anonymous survey of advanced trainees regarding their health-seeking behaviors indicated 68% trainees reported ILI symptoms during training.[18] Of those reporting ILI, only 36% sought healthcare. The barriers to care-seeking in patients with ILI in a high risk, military population, are not well understood. The next phase of this study will focus on discerning the obstacles to seeking care for ILI with the overall goal of developing interventions designed to lower disease transmission in trainees.

Current plans for ARIC NHS are increasing SARI case enrollment and possible expansion to military facilities outside of the continental United States. Through these efforts along with strong collaborative ties will help to maintain the ARIC NHS as an integral multi-site platform for on-going SARI surveillance activities, which will continue to provide critical data necessary for monitoring and countering threats posed by respiratory pathogens in military populations.

Study to Address Threats of Acute Respiratory Infections among Congregate Military Populations (ATARI)

Recruits are at highest risk for respiratory infections compared to older, seasoned service members and, in particular, the rates of hospitalization are 3–4 times greater in than their civilian counterparts.[5] The high incidence of ARI among recruits is attributed to crowded living conditions, physical and mental stress, sustained environmental exposure to pathogens, and rigorous physical training, which may make recruits vulnerable to ARI outbreaks.

The ATARI study was designed to describe transmission, etiology, epidemiology, and burden of ILI among U.S. Army recruits undergoing 9-week basic combat training at Fort Benning with the goal of informing development of effective control strategies. Approximately 13% of participants experienced an ILI with coronavirus, rhinovirus, enterovirus, and influenza identified as the leading causes of symptomatic illness.[19] These same viruses also circulated widely among asymptomatic recruits. Analysis of transmission patterns, using computational modeling (in collaboration with the Harvard School of Public Health), spatial analysis and molecular fingerprinting (in collaboration with WRAIR) techniques is ongoing.

DIAGNOSTIC PLATFORMS FOR ILI/SARI ETIOLOGY

The rapid detection of respiratory pathogens has the potential for targeted use, including antimicrobial therapy, as well as

infection control measures. In 2017, the IDCRP conducted a head-to-head comparison of the performance characteristics of Biofire's FilmArray Respiratory Panel (Biofire Diagnostics, Salt Lake City, UT) and the Diatherix TEM-PCR multiplex respiratory platform (Diatherix Eurofins, LLC, Huntsville, AL) within the context of the on-going ARIC NHS.[20] The results revealed a high degree of concordance between Diatherix Eurofins TEM-PCR and BioFire FilmArray in the detection of viral respiratory pathogens.

While these comparative evaluations are necessary, they do not eliminate the need for more accurate, sensitive and rapid bench-top diagnostics for respiratory infections. Research is needed to assess whether the use of bioinformatics and other novel approaches can improve the accurate and rapid detection of ARI-associated pathogens. The development of novel diagnostic tools for influenza and other respiratory illnesses will enable rapid diagnosis leading to earlier treatment, possibly improved clinical outcomes, and lessened transmission of ARI, especially in congregate military settings

Next Generation Sequencing

While ARIs are a leading cause of morbidity in armed services personnel, a causative agent is frequently not identified using standard diagnostic tools. Given the high proportion of undiagnosed ARI cases in this population, we are collaborating with USU researchers on the Next Generation Sequencing, a novel diagnostic platform for identifying ARI etiology, for characterization of viral respiratory infections and gauging whether or not its ability to detect pathogens exceeds that of current tool diagnostic platforms. The qPCR assay developed for this study detected a previously unidentified agent (i.e., anelloviruses).[21] Further studies are needed to investigate the frequency and clinical relevance of these viruses.

Flu Breath Test

The Flu Breath Test study (in collaboration with Menssana Research Inc.) at Fort Sam Houston is investigating the use of exhaled volatile organic compounds (VOC) in the diagnosis of influenza.[22–24] Viral infections are known to increase oxidative stress. Therefore, studying the patterns of oxidative stress biomarkers in the breath, which include alkanes (e.g., 2,8-dimethyl-undecane) and methylated alkanes (e.g., 2-isopropyl-5-methyl1-heptanol), could lead to the development of non-invasive diagnostic tests for influenza. A breath test for VOCs could potentially identify early influenza cases, including infections among those who have not yet developed clinical symptoms or signs of disease. If successful, this ongoing study may enable rapid, sensitive, and specific diagnosis and treatment of patients infected with influenza. These findings will have implications for improved real-time testing of active-duty troops, including field testing of deployed service members to enable ARI infection control measures and limit the burden of influenza on active-duty personnel.

Influenza Vaccine Effectiveness

Although influenza vaccines provide variable and frequently moderate protection from infection, they remain the best strategy for the prevention of disease.[25–28] Research area investigators have conducted multiple studies focused on the response and effectiveness of vaccinations. Use of a self-administered live-attenuated influenza vaccine (SNIF) was assessed in a phase IV, open-label randomized control trial involving 1077 subjects. Seroresponse between subjects who self-administered and those who had the vaccine administered by a healthcare profession did not differ. Prior to vaccine administration, there was no preference in method; however, at follow-up, 64% of subjects who self-administered expressed a preference for that method.[29] Antibody response to the influenza vaccine among adults with HIV infections was also evaluated in one study and HIV-infected adults were less likely to generate a seroprotective response compared to adults without HIV infection. These findings indicate that despite receiving influenza vaccinations, adults with HIV infections may remain vulnerable to the disease.[30] Furthermore, the degree to which influenza vaccinations attenuate symptoms was assessed in another study involving 155 influenza-positive patients enrolled ARIC NHS (111 vaccinated). Patients who received a vaccination were significantly less likely to experience fever >-101°F or myalgias. When influenza species was considered, there was a significant reduction in symptoms among patients positive for Influenza A/H3N2 who received a vaccination; however, there was no difference in disease severity with vaccination status among patients positive for Influenza A/H1N1.[31]

Annual immunization for influenza is mandatory for DoD personnel; however, the effectiveness of influenza vaccine has been shown to be suboptimal and warrants further investigation. Vaccine effectiveness is typically estimated using the test negative design, comparing proportions of influenza vaccination among patients with and without influenza. An analysis of influenza vaccine effectiveness conducted with ARIC NHS data in 2015 showed the vaccine effectiveness was below 35%.[32] The findings were consistent with those from the CDC and other sources, highlighting the poor effectiveness of the seasonal vaccine. These data also raise concerns that repeated immunization with seasonal influenza may increase susceptibility to influenza and severe illness.[33] In some influenza seasons, attack rates appear to be higher for people who were vaccinated during both the current and the prior year's influenza seasons compared to individuals who had only been vaccinated during the current season. Elucidating the relationship between repeated vaccinations and protection would have important implications for influenza vaccination policy. To date, the results from

epidemiological studies have been conflicting. Nevertheless, examination of 155 influenza cases in the ARIC NHS (111 vaccinated) found that upper respiratory and overall symptoms were significantly less during the first two days of illness among vaccinated individuals.[31] The aim of the Influenza Vaccine Effectiveness Study is to explore the impact of repeated vaccination on influenza acquisition and severity in DoD populations based on a review of electronic medical records. Specifically, the study will assess the influence of antigenic components of the vaccine and the predominant influenza strain on vaccine effectiveness. The findings will provide preliminary data for the development of more definitive studies.

Lastly, a new protocol, the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED), launched in the Fall of 2018. With questions of the effectiveness of different vaccine formulations,[34,35] this two-year, pragmatic, prospective study will compare the effectiveness of the licensed egg-based inactivated influenza vaccine to the effectiveness of two other types of licensed vaccines, the cell-culture based inactivated influenza vaccine and the recombinant influenza vaccine, in the prevention of laboratory-confirmed influenza infection in active duty members, military retirees, and other DoD beneficiaries. Presently, five military treatment facilities in the United States are participating in this protocol with plans to involve additional sites during the second year of the study. Enrollment will be restricted to adults (who are preparing to receive seasonal influenza vaccination at participating DoD sites. Nearly 11,000 subjects will be randomized to receive one of the three licensed influenza vaccines types for evaluation of effectiveness. The primary outcome is PCR-confirmed influenza infection. An immunogenicity substudy, comprising 650 volunteers, is designed to compare the effect of the three vaccine formulations on humoral and cellular immune responses.

Evaluation of current influenza vaccine effectiveness in DoD populations is intended to inform the implementation of effective influenza vaccination and prevention strategies in this highly-vaccinated population.

Severe Influenza Treatment

The U.S. military is highly susceptible to epidemics from novel strains of influenza, and effective treatment options for severe infections are limited. Also, emerging pathogens such as the MERS-CoV respiratory pathogens with the potential for significant morbidity and mortality and the ability to cause significant disruptions to military preparedness. Given the DoD's global operations, supportive care in hospitals and intensive care units may often be more constrained than that available to the general U.S. population. The assessment of novel and current ARI prevention and control strategies is crucial for mitigating the threat of severe disease. Between 2011 and 2015, IDCRP participated in a NIAID-sponsored, multi-center, randomized phase 2 trial assessing the safety and efficacy of anti-influenza plasma in the treatment of severe influenza.[36] When patients who received plasma plus standard care were compared to those who only received standard care, there was a non-significant reduction in length of hospitalization (median of 6 days versus 11; $p = 0.13$). In addition, patients who received plasma had less serious adverse effects (20% vs 38%; $p = 0.041$). Overall, there was no significant impact on the time to normalization of the patient's respiratory status with use of plasma; however, use of plasma was safe and well-tolerated by the patients and demonstrated the potential to improve outcomes with severe influenza.[36] Building on these findings, enrollment in a Phase 3 trial has been completed and data analysis is ongoing.

CONCLUSIONS

The control of ILI and SARI in armed forces personnel is an ongoing challenge for the U.S. military as influenza and clinical pneumonia remain leading causes of hospitalization, despite high vaccination coverage. Outbreaks and pandemics caused by known and emerging respiratory pathogens can result in significant morbidity and mortality, posing a considerable threat to operational readiness. The IDCRP's ARI Research Area remains committed to decreasing the impact of ARI among military populations through clinical research to improve prevention and clinical management.

FUNDING

The authors have no conflict of interest to disclose. This work was conducted by the Infectious Disease Clinical Research Program, a DoD program executed through the Uniformed Services University of the Health Sciences, Department of Preventive Medicine and Biostatistics through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been funded by a US DoD Program Project Grant (HT9404-12-1-0019), the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under Inter-Agency Agreement Y1-AI-5072, the Armed Forces Health Surveillance Branch, Global Emerging Infections Surveillance (GEIS) Section, Biomedical Advanced Research and Development Authority, and the U.S. Navy Bureau of Medicine and Surgery.

ACKNOWLEDGMENTS

We are indebted to the study team of IDCRP clinical research coordinators, laboratory personnel, and data management staff for their efforts, dedication, and contributions to the success of our projects. We wish to specifically thank Col (ret) Patrick Danaher, Dr. John Powers, Dr. Mary Fairchok, and CAPT John Arnold for their substantial contributions to the program. We also thank all of the service members who have participated in our studies, as well as our collaborators at the Naval Health Research Center, Naval Medical Research Center and the Walter Reed Army Institute of Research for their tremendous support and efforts.

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