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Symptom Experience and Influenza-Like Illness in a Military Population

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SYMPTOM EXPERIENCE AND INFLUENZA-LIKE ILLNESS IN A MILITARY POPULATION

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Disclosure

The views expressed herein are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

Abstract

AIMS: The primary objective of this study was to identify if symptom presentation expressed over the course of an influenza-like illness (ILI) can predict virus type by use of unsupervised machine learning. The secondary objective was to describe clinical characteristics of strain specific coronavirus. Finally, examine the psychometric properties of the Canadian Acute Respiratory Illness and Flu Scale (CARIFS).

BACKGROUND: ILI outbreaks have been a significant source of non-battle injury among military personnel. Many different viruses cause ILI, and it is difficult to determine which virus is causing the illness. Recent studies have examined the etiology and epidemiology of ILIs. Other studies have examined influenza virus symptom severity either a dichotomous or liner-sum analysis. No studies to the researcher's knowledge have examined ILI symptoms through an unsupervised learning analysis, and few studies have examined self-reported outpatient ILI reported symptoms over an extended time frame.

METHODS: This is a secondary analysis of data collected over a four year period by the Acute Respiratory Infection Consortium (ARIC), from an otherwise healthy military population. The symptom data was captured on visit days and by a symptom diary patients filled out at home using a symptom severity instrument designed for this study.

FINDINGS: Clustering by unsupervised machine learning was unable to predict virus type based on physical symptom presentation over the course of ILI. It did identify patient attributes, like sex and age that caused patients to experience symptoms differently. Additionally, clinical similarities and differences were noted between the four common human coronavirus strains. The strain HKU1 tended to have higher

systemic symptom scores and higher gastrointestinal symptom severity score over the course of illness when compared to the other strains. Finally, the psychometric properties of CARIFS revealed many strengths and limitations for its use in research. The CARIFS should be reexamined using current knowledge of symptom management to increase the validity of the instrument.

IMPLICATIONS: The results demonstrated how individuals experience physical symptoms differently making it difficult to predict the viral strain causing ILI. Future research should focus on the development of symptom instruments using the theoretical underpinnings of the symptom management theory.

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Chapter 1

Introduction

Overview

Through history, influenza virus subtypes have been responsible for pandemics across the world (United States Department of Health and Human Services, n.d.; Rogers, 2010; Simonsen et al., 2013). In 2009, a military humanitarian mission was cancelled due to an influenza outbreak on the main ship (BBC News, 2009). Many viruses cause influenza-like illnesses such as, influenza A and B, coronavirus, rhinovirus, adenovirus, and they tend to be highly contagious. The symptom presentation of the viruses can vary with the illness, but they also have many common overlapping symptoms. For instance, respiratory syncytial virus (RSV) tends to cause more severe lower respiratory systems, while rhinovirus has a greater effect on the upper respiratory system; but, they share some common symptoms such as cough (Walsh & Hall, 2010; Turner, 2010). The presentation ILI symptoms varies based on virus; therefore, it is possible to predict the type of virus affecting an individual.

Background and Significance

Theoretical Framework

The Symptom Management Theory (SMT) is the theoretical framework that guided this study. The concept of SMT was initially introduced as the Symptom Management Conceptual Model in 1994 by Larson and colleagues. This model focused on identifying the underlying cause of a symptom and managing the total symptom experience, instead of focusing on the cause of a symptom alone. The model was later

revised in 2001 by Dodd and colleagues as more of a dynamic process where symptoms experienced and changes in strategy needed to occur over time. In 2008 the framework was renamed Symptom Management Theory, and was introduced as a middle range theory by Humphreys and colleagues. An underlying principle in the development of SMT is the nurses' involvement. Larson and colleagues stressed the importance for nurses to take the lead in developing a symptom model because they are more involved in the management of patient symptoms. The Symptom Management Theory has a bidirectional conceptual relationship among symptom experience, symptom management, and symptom outcomes (Landers, 2014).

Approximately twenty years ago symptom research was focused on a single symptom, such as pain, or known associated symptoms as stomach pain and diarrhea. With the development of the Symptom Management Conceptual Model leading to the SMT, symptoms are now looked at as a multidimensional process relying on not only one symptom experienced, but taking into account other factors, such as environment, health and illness, and different types of symptom outcomes (Dodd et al, 2001). Dodd and colleagues (2001) defined symptoms as subjective experiences echoing individual changes in sensations and biopsychosocial and cognitive functioning. Many recent studies have utilized SMT to guide their symptom research in the fields of HIV, cancer, and constipation focusing on symptom experience with self-care outcomes. A study by Dodd, Cho, Cooper, and Miaskowski (2010) was supported by the concepts of SMT, and reported symptoms are experienced in clusters. The study examined specific symptom clusters in women receiving chemotherapy with symptom severity assessed at different

time points over the course of treatment. Lenz, Rugh, Milligna, Gift, & Suppe (1997) indicated symptoms have a reciprocal link between physiologic, psychologic, and situational factors, and multiple symptoms are multiplicative, not additive.

Symptom Management Theory is divided into three key components: symptom experience, symptom management strategies, and patient outcomes (see figure 1). All three components of SMT are within the three domains of nursing science: person, environment, and health and illness. For the purpose of this research study, the SMT component of interest was symptom experience, specifically perception and evaluation of symptoms. Symptom experience is defined as the intensity, misery, and occurrence of symptoms as they are produced (Armstrong, 2003). According to SMT, symptom experience is evaluated within the three domains of nursing science (Humphreys et al, 2014). With the strict inclusion/exclusion criteria of the data collected for the research study, the researcher made the assumption that the three domains of nursing science were equal across the population.

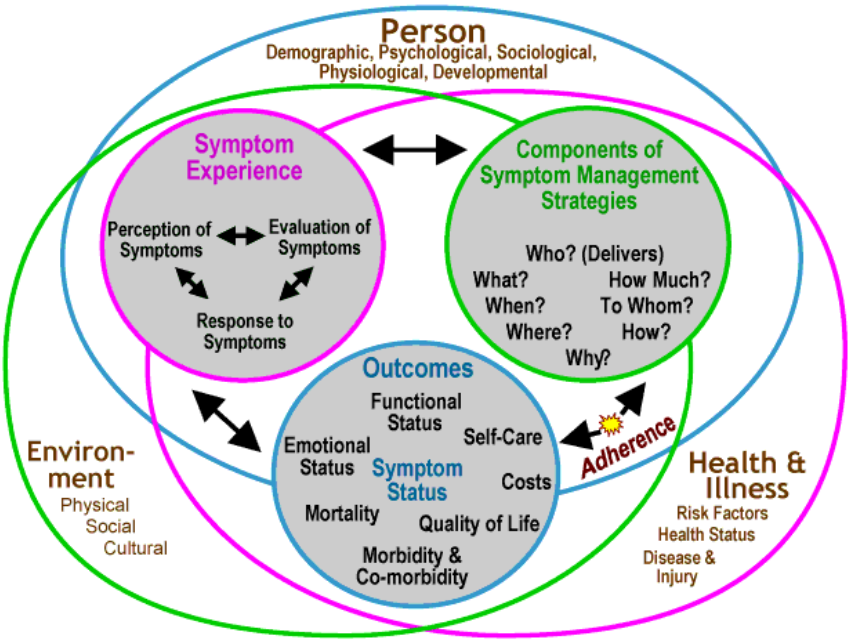

FIGURE 1- Theoretical framework for study: Symptom Management Theory From "Nursing theory and concept development or analysis: Advancing the science of symptom management," by Dodd, M.J., Janson, S., Facione, N., Faucett, J., Froelicher, E.S., Humphreys, J…, Taylor, D., 2001, *Journal of Advanced Nursing, 33*(5), 668-676. Copyright 2008 by John Wiley and Sons.

Influenza-like illness

Currently, based on symptomatology, there are a multitude of different definitions as to what classifies an illness as influenza or influenza-like. The World Health Organization (WHO) defines influenza-like illness as an acute respiratory infection with onset in the last 10 days with cough and measured fever, but they do not provide a clear definition on the diagnosis of influenza (World Health Organization, 2014). The International Classification of Health Problems in Primary Care (ICHPP-2) states the

diagnosis of influenza can be made if six of the nine influenza-like symptoms occur: sudden onset, cough, chills, fever, weakness, headache, myalgia, no physical signs other than redness of nasal mucous and throat, and influenza close contacts (Govaert, Dinant, Aretz & Knottnerus, 1998). The Center of Disease Control and Prevention (CDC) defines influenza-like illness as a fever, cough and/or sore throat with the presence of a sick contact or potential epidemic, and leaves the diagnosis of influenza vague, based on symptoms alone (Center for Disease Control and Prevention, 2015).

In the literature, a variety of diagnostic criteria exists to classify an illness as influenza-like. Common themes to the diagnosis of influenza-like illness include fever, sudden onset, cough, and potential for other symptoms typically related to influenza. For the purpose of this study, influenza-like illness is defined as: a fever over 100.4 ℉ and respiratory symptoms (cough, sputum production, shortness of breath, chest pain) and/or sore throat.

Viruses associated with ILI

There are over 200 different viruses that produce influenza-like symptoms (Eccles, 2005). A recent systematic review of studies examining the concept of influenza-like illness identified people who presented with ILI symptoms, and the common viruses experienced were: adenovirus, coronavirus, influenza A/B, human metapneumovirus, parainfluenza, picorna virus, respiratory syncytial virus (RSV), and rhinovirus (Thomas, 2014). Research continues to grow in the area of being able to distinguish viruses based on patient symptomatology (Puzelli et al., 2009). The frequency of the virus type causing influenza-like illness depends on the seasonality of

data collected, location, and age group. The most common viruses to cause ILI symptoms are: adenovirus, rhinovirus, influenza A/B, coronavirus, RSV, and human metapneumovirus (Puzelli et al., 2009; Thomas, 2014).

Adenoviruses are common with over 100 identified across all species with the infection being self-limiting. Adenoviruses are known to cause respiratory tract infection, ocular disease, and gastrointestinal tract disease (Rhee & Barouch, 2010). Rhinoviruses account for approximately 40% of all cases of upper respiratory infection. Rhinovirus infections are typically classified as the 'common cold,' causing symptoms mostly concentrated in the upper respiratory tract (Turner, 2010).

The influenza virus is divided into types, A and B. Influenza type A is known to cause global pandemics with high mortality in the younger population, while influenza B typically does not result in pandemics and occurs in older adults or high-risk population. Clinical manifestations of influenza are: fever, sore throat, cough, and malaise, and there is a vaccine developed yearly to help prevent the illness (Treanor, 2010).

Respiratory syncytial virus (RSV) infections tend to attack the lower respiratory system, and is the most frequent cause of bronchiolitis in infancy and influenza-like symptoms in the adult population. The clinical manifestations of RSV differ by the age group infected with young children experiencing bronchiolitis, pneumonia, and some upper respiratory tract symptoms, while older children and adults present mostly lower respiratory tract symptoms and pneumonia (Walsh & Hall, 2010). Human metapneumovirus (hMPV) is a newly discovered virus, first described in 2001, and causes severe lower respiratory tract disease, ranking second to RSV in children. The

clinical manifestations are similar to RSV and pneumonia with the most common symptoms associated with it being fever, nasal congestion, and cough (Falsey, 2010).

Coronaviruses are known to cause upper respiratory symptoms in humans, and cause 15%-35% of the influenza-like illnesses reported in clinics (McIntosh & Perlman, 2010). The severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses have been the focus of many coronavirus studies, while the common human sub-types have not. The four common types of coronavirus are known to cause upper respiratory symptoms similar to influenza, but few studies have examined the characteristics of the different strains (McIntosh & Perlman, 2010).

ILI Symptoms

When people experience influenza-like illness symptoms, it is common for them to diagnose themselves with a 'cold' or the 'flu' (Eccles, 2005). ILI symptom experience varies, but the most common reported symptoms include: fever, cough, rhinorrhea, and sore throat. Because symptom experience is subjective, it is difficult to determine which virus is the cause of ILI without laboratory testing.

The progression of symptom experience differs from person to person, but most literature agrees ILI typically starts with a fever and progresses to upper respiratory tract symptoms (Eccles, 2005; Tyrrell, Cohen, & Schlarb, 1993). There are some ILI viruses that cause systemic and gastrointestinal symptoms in addition to the respiratory tract symptoms. Although people with ILI characterize the symptom experience as the worst part of the illness, these symptoms may actually help them overcome the illness with the release of more cytokines (Eccles, 2005).

Symptom severity experience is subjective, and can build off previous illness knowledge. Due to the variety of symptoms people experience with influenza-like illnesses, it is difficult to advise people when to seek treatment with symptoms because they may be conflated with other ailments. People have reported not taking the diagnosis influenza seriously, and continued their daily life activities, while other strongly recommended seeing a healthcare provider as soon as possible and were worried about being a vector for the virus (Jutel & Banister, 2013).

ILI Symptom Measurement

The scale used for capturing symptom severity of ILI for this project came from the Acute Respiratory Infection Consortium (ARIC). ARIC used the scale in their longitudinal influenza-like illness research, specifically in the military population (Chen et al, 2015). During the development of ARIC's protocol, the researchers could only identify one validated ILI symptom severity tool, the Canadian Acute Respiratory Illness and Flu Scale, but it was specifically designed for children (Jacobs et al, 2000). Therefore, ARIC developed their own symptom severity scale utilizing aspects from four similar non-validated symptom severity scales they termed: Hayden I, Hayden II, Keech, and ICCSQ (Devoulyte & Sullivan, 2003; Hayden, Fritz, Lobo, Alvord, Strober, & Straus, 1998; Keech, Scott, & Ryan, 1998; Treanor et al., 2000).

The scale created by ARIC has 20 symptoms which people with ILI rank on a four point scale, and are broken down into four subscales: systemic, upper respiratory, lower respiratory, and gastrointestinal. The 20 question symptom scale is written in layman's terms, such as 'earache', not 'otalgia', so that it would be filled out more

accurately. The four point symptom severity scale is similar to the Hayden I and II scale where 0=none, 1=mild, 2=moderate, and 3= severe. Recently the ARIC group has developed and validated a new ILI symptom measurement instrument, Flu-PRO, utilizing the symptom data from this project (Powers et al., 2013; Powers et al, 2016).

ILI and the Military

A person's age, physical state, and current immunological status can have an effect on ILI symptoms experienced. Many studies focus on ILI symptomatology in the older adult or young child population, as they are considered the most vulnerable. However, historically military members have been vulnerable to influenza outbreaks with ILI being the leading cause of outpatient reported illness in the military (Gray, Callahan, Hawksworth, Fisher, & Gaydos, 1999).

The United States military population is unique since they are generally young, healthy individuals. Active duty military members must have constant readiness to protect and serve the United States, and must be continuously aware of their health and fitness state; but, they are a high-risk group for ILI due to their occupation and other factors, such as living arrangements.

Some members of the United States military live in barracks or in close-living conditions, which can increase the transmit ability of a virus. Some may also live with their family who work with the outside community where a virus outbreak could be occurring. Additionally, active duty military members tend to have an increase in psychological stress and difficulty maintaining personnel hygiene depending on where they are stationed for service (Gray et al., 1999; Kocik et al. 2014; Padin et al., 2014).

Other Factors influencing ILI symptoms

Immunologically, the response to a viral infection differs based on a person's gender due to genetic and hormonal differences. The WHO examined the effects of an influenza virus infection on gender globally, and noted a difference in symptom experience and mortality rates in some regions of the world (World Health Organization, 2010). In the Netherlands a study compared day to day symptom experience in males to females. Overall females had higher summed symptom scores and greater symptom reporting when compared to the males (Gijsbers van Wijk, Huisman, & Kolk, 1999).

People who smoke or are former smokers are known to have a decrease in their lung function due to the components of cigarette smoke, including carcinogens. During an outbreak of influenza A in 1979, an Israeli military unit was studied to identify the effects of smoking on disease severity and susceptibility on female recruits. The data showed women recruits who smoked reported more severe influenza-like illness and high rates of contraction of illness (Kark & Lebiush, 1981). Another study examined the effects of smoking on U.S. Army recruits in 1982 with results showing those who smoked were more likely to be seen for an upper respiratory tract infection (Blake, Abell, & Stanlet, 1988).

Body mass index (BMI) is a measure of body fat based on a person's weight and height for the adult population. Many obesity-related factors have potential to affect the outcome of infectious diseases such as, obstructive sleep apnea, decreased pulmonary volumes, decreased wound healing, and dysregulated immune responses in the lung (Huttunen & Syrjanen, 2013). Several studies found high BMI values are a risk factor for

illness severity during the 2009 influenza A pandemic (Louie et al., 2011; Yu et al., 2011).

Studies have shown a person's ethnicity can influence symptom presentation in many diseases, including viral illnesses (Corley, D.A., Kubo, A., & Zhao, W., 2007; Pattermore, Asher, Harrison, Mitchell, Rea, & Stewart, 1989; O'Connor et al, 2003). CDC reports indicated self-reported ILI were lower in Hispanics and non-Hispanic blacks and higher in American Indians during the 2009 influenza pandemic. Additionally, minorities had higher rates of hospitalizations when compared to non-Hispanic whites (Dee et al, 2011). A pediatric population-based surveillance study of several ILI viruses noted patients who were Hispanic and non-Hispanic black had higher rates of hospitalizations (Iwane et al, 2004).

Statement of the Problem

The review of literature identifies the need for further understanding of ILI symptom experience, especially in the young adult/ military population. Studies predicting virus types based on patient reported ILI symptoms limited. Most of the studies predicting virus type focus on the patient having or not having influenza without consideration of the other viral types. Additionally, there is a gap in knowledge regarding symptom experience in the military population, which is unique compared to the general population.

Another gap in knowledge identified was classifying the symptom experience in people experiencing the more common forms of human coronavirus. A majority of the literature currently focuses on the more severe forms, SARS and MERS. Further

examining the common forms of coronavirus may lead to better understanding of future mutated forms of the virus.

Purpose of the Study

The purpose of the study is to explore and characterize ILI and symptom experience in a military population, and determine if symptom presentation can predict virus type. This study is a secondary analysis of data collected from an observational, longitudinal military cohort study designed to determine the etiology, epidemiology, and clinical characteristics of ILI. Secondary data analysis studies are useful because they allow researchers to examine data in other ways than originally intended with bigger numbers for analysis, but can also be limiting because further data collection from participants involved is difficult to complete. This design method is appropriate for the purpose of this study because the use of already collected data will provide more variables for analysis and larger numbers for a more thorough analysis.

Specific Aims of the Three Papers

This dissertation consists of three manuscripts written for publication in various journals. The manuscripts are formatted per the guidelines of the journal for potential publication. The specific aims for each paper are:

1. Identify if symptom presentation over the course of influenza-like illness (ILI) can predict virus type in an otherwise healthy military population using unsupervised machine learning; Identify sub-populations with similar symptom experience.

2. Describe the strain specific clinical characteristics of coronavirus among an otherwise healthy US military population.
3. Examine the psychometric properties of one of the few validated instruments examining disease severity of ILI, the Canadian Acute Respiratory Illness and Flu Scale (CARIFS).

Summary

During the 2014-2015 influenza season, the CDC's outpatient illness surveillance reported ILI activity being at or above the baseline measure for 20 weeks, which made it the longest season for reported ILI activity (Center for Disease Control and Prevention, 2015). Symptom experience is a subjective measure, which makes it difficult to identify the type of virus that may be causing the symptoms. Utilizing the military database to analyze ILI symptoms that active duty and their beneficiaries experience will provide the ability to characterize and understand them.

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Chapter 2:

Symptom Experience and Influenza-like Illness in a Military Population

Abstract

Background

Of over 350,000 samples were collected from the 2012-2013 flu season, only 21% were positive for an influenza virus. ILI outbreaks are a significant source of non-battle injury among military personnel and may lead to mission cancellations. Prior studies of influenza symptom severity used dichotomous or linear sum analysis but few examined symptoms over the course of the illness. No studies to the researcher's knowledge have examined ILI symptoms through an unsupervised machine learning analysis.

Aims

The primary objective is to identify if symptom presentation over the course of influenza-like illness (ILI) can predict virus type in an otherwise healthy population using unsupervised machine learning. The secondary aim is to identify sub-populations with similar symptom experience.

Methods

The Acute Respiratory Infection Consortium (ARIC) conducted a prospective longitudinal study from 2009-2014 to determine the etiology, epidemiology, and clinical characteristics of ILI. The sample population (n=1590) was healthy active duty military members, healthy retirees, and their dependents from five US treatment facilities. Subjects recorded symptoms on days 0, 3, and 7 using a tool designed for this study. Nasopharyngeal samples were collected for virus identification. This analysis only includes cases with complete visit data (n=699).

Unsupervised machine learning algorithm k-means clustering analyzed the data in two ways. In both approaches, patients were clustered by the individual symptom score for every visit to capture severity and illness progression. In the first analysis, patients of all virus types were clustered with patients without a viral diagnosis. The other analyses clustered patients diagnosed with the most prominent viruses (influenza A, rhinovirus, and coronavirus) separately.

Results

The primary analysis was unable to predict virus type or differentiate those with and without a virus based on patient symptom experience using a variety of scoring approaches. The secondary analyses with rhinovirus (n=101), influenza A (n=107), and coronavirus (n=51) each yielded at least one symptom cluster with a statistically significant difference based on non-symptom features using one-way ANOVA or chi square testing. The clustered rhinovirus data showed the most statistically significant differences amongst the clusters in the attributes: sex, BMI, age, smoking history, and military status. The clustered influenza A data showed a statistically significant difference in clusters based on sex and ethnicity. The clustered coronavirus data only showed some differences amongst clusters in regards to sex, which was expected as the data set was well distributed. Overall the patients in the different virus clusters experienced symptoms differently compared to the total population for virus type.

Background

The most common cause of illness and visits to healthcare providers in the United States (US) are influenza-like illnesses (ILI). The annual cost associated with ILI in the US is estimated to be over 12 billion dollars. An ILI is defined as having an acute respiratory infection with fever and presence of sick contact, and is typically caused by a contagious virus (Center for Disease Control and Prevention, 2015; World Health Organization, 2014). The Center of Disease Control and Prevention (CDC) established a surveillance network called, U.S. Outpatient Influenza-like Illness Surveillance Network (ILInet), which continuously monitors ILI in the outpatient setting. The network allows information about the rate of ILI infections across the US be monitored (Center for Disease Control and Prevention, 2015).

Historically, there have been several ILIs that reached pandemic levels with the most notable being the Spanish Flu of 1918, which affected the global population, but in the US the hardest hit population was the military (Gray, Callahan, Hawksworth, Fisher, & Gaydos, 1999). During World War I, the US military suffered more deaths from the influenza outbreak of 1918-1919 than combat casualties. The poor environmental conditions the service members endured, combined with a delay in enacting quarantine procedures, led to the high number of infections and morbidity (Byerly, 2010).

Military

Almost one hundred years later, ILI outbreaks still affect military readiness. In 2009 the United States Department of the Navy had to cancel a planned humanitarian mission to the Pacific because of an outbreak of influenza on the USS Dubuque (BBC

News, 2009). Although the active duty military population are known to be healthy, young and active; they are still at higher risk for ILI due to their housing and working environment (Gray, Callahan, Hawksworth, Fisher, & Gaydos, 1999).

Many enlisted members continue to live in close quarters such as barracks. Some live off base with their family, but others live in close knit military communities. Most members share common areas daily, such as the mess hall, gym, or even stair wells. Additionally, depending on a service members' duty station, they may experience an increase in psychological stress and/or difficulty maintaining personal hygiene, therefore, decreasing their ability to fight off an infection (Gray et al., 1999; Kocik et al. 2014; Padin et al., 2014). All these situations put the current active duty members at an increased risk for an ILI outbreak.

ILI is the leading cause of outpatient reported illnesses in the military (Gray, Callahan, Hawksworth, Fisher, & Gaydos, 1999). Most ILI research studies focus on population extremes, such as young children or older adults, or those people with underlying conditions. Most members of the US military do not meet these descriptions, so it is important to understand how ILIs affect this population due to them having to be constantly ready to deploy.

Symptom Experience

Symptoms are subjective experiences stimulating changes in a person's feelings and biopsychosocial factors; therefore, people's experience of symptom severity may vary (Dodd et al, 2001). Several studies have examined the symptom experience of participants with ILI to predict the diagnosis of influenza, but they did not yield

satisfactory results (Peltola, Reunanen, Ziegler, Silveinnonen, & Heikkinen, 2005; Puzelli et al, 2009). The symptoms of cough and fever during the influenza season were found to be better predictors of influenza, but study limitations are the lack of a uniform method of symptom measurement.

Biological, psychological, and social factors can contribute to a person's symptom experience. Studies have shown a person's history of smoking can have an effect on ILI susceptibility and severity most likely stemming from the structural changes in the lungs caused by the smoke inhalation (Arcavi & Benowitz, 2004; Blake, Abell, & Stanlet, 1988; Kark & Lebiush, 1981). A person's body mass index (BMI) is a risk factor for worse illness severity as demonstrated recently with the H1N1 outbreak; people with higher BMIs tended to have worse symptom severity (Louie et al., 2011; Yu et al., 2011). Additionally, a Canadian study noted, a positive association between increased BMI and rates of respiratory hospitalizations during the influenza season (Kwong, Campietelli, & Rosella, 2011).

Gender can also influence the response of a viral infection due to genetic and hormonal differences. There is a gender difference between symptom severity and influenza infection outcome with females having higher morbidly and mortality rates (World Health Organization, 2010). Gijsbers van Wijk, Huisman, & Kolk (1999) studied daily symptom experience in males and females, and noted females had a higher summed symptom scores. A person's ethnicity can also influence symptom presentation. During the 2009 H1N1 pandemic, the CDC noted self-reported ILI was lower in Hispanics and non-Hispanic blacks and higher in American Indians with higher rates of hospitalizations

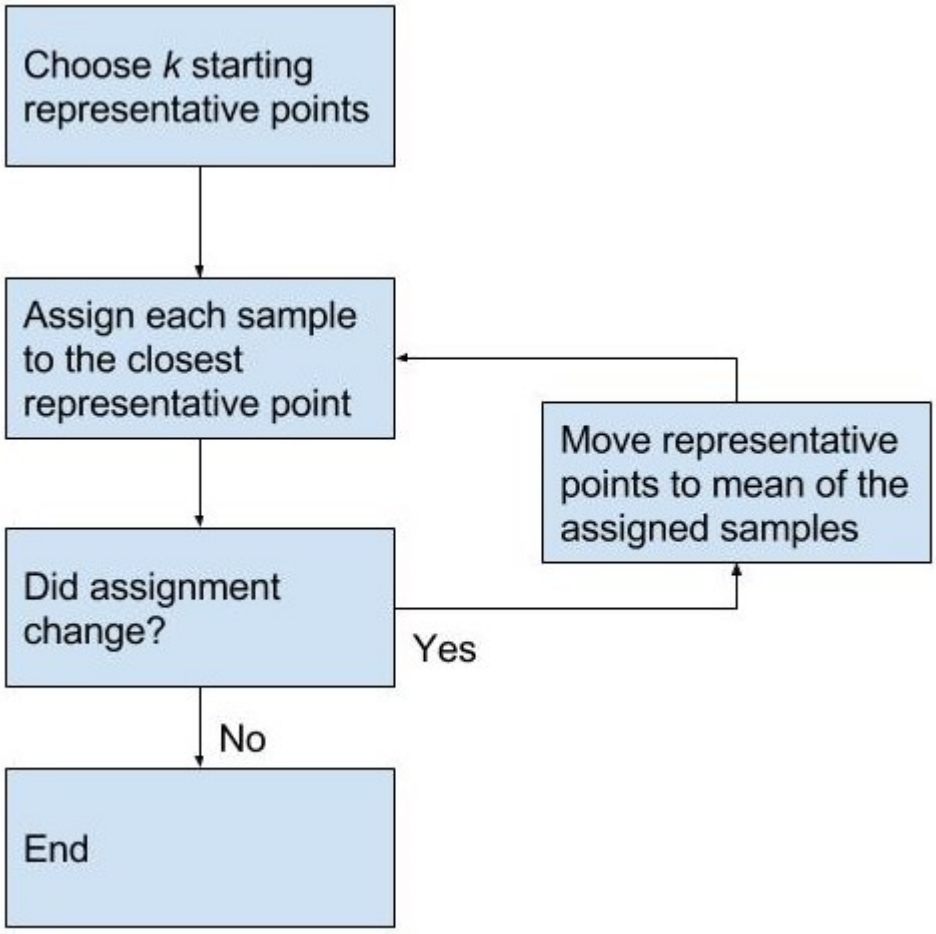
for minorities when compared to non-Hispanic whites (Dee et al, 2011). A pediatric population-based surveillance study of several ILI viruses noted patients who were Hispanic and non-Hispanic black had higher rates of hospitalizations (Iwane et al,2004).

Unsupervised Machine Learning

Unsupervised machine learning is a process that detects patterns in data with minimal human guidance. One of the most common approaches to unsupervised learning is called clustering, wherein samples are grouped together based on similarity. The resulting clusters can be used for classification, population segmentation, or be further analyzed for common features. This paper employs a technique called *k*-means clustering, which is described below.

K-means clustering (MacQueen, 1967) is one of the simplest, but also one of the most widely-used and easily understood forms of unsupervised learning. While there are numerous extensions and improvements to the algorithm, the most basic approach starts by randomly selecting *k* points to serve as representative points of each cluster. Then, all samples in the data set are assigned to one of these points, based on similarity. Next all *k* representative points are moved to the mean of all the sample points that were assigned to them. This process of assigning points to clusters and updating the means of those clusters is repeated until the points assigned to a mean are unchanged, i.e. the algorithm has convergence, or a fixed number of reassignments occurs. The value of *k* in *k*-means clustering must be provided by the experimenter and is typically based on domain knowledge or discovered through experimentation with several values (see figure 1).

Figure 1: Graphical representation of K means clustering process



This clustering algorithm has been applied to many problem domains such as image segmentation (Ng et al, 2006), feature learning (Coates, 2012), and user classification (Lingras, 2004). Some notable medical applications of *k-means clustering* include predicting the recurrence of breast cancer (Belciug et al, 2010) and detection of Alzheimer's disease (Escudero et al, 2011).

Studies examining patient reported ILI symptoms to predict virus type are limited, especially related to virus types other than influenza. Most research focuses on the

influenza virus and symptoms, and not the other common viruses identified as sources of ILI. The military population is a unique population when compared to the general population, and there is limited knowledge regarding symptom experience in the military. Additionally, there are no studies to the authors' knowledge that utilize unsupervised machine learning to identify if symptom severity can predict ILI virus type.

Objectives

The primary objective is to identify if symptom presentation over the course of influenza-like illness (ILI) can predict virus type in an otherwise healthy military population using unsupervised machine learning. The secondary aim is to identify subpopulations with similar symptom experience.

Methods

Study Design

A secondary analysis of symptom severity data from a prospective ILI study conducted by the Acute Respiratory Infection Consortium (ARIC) whose methods for data collection have previously been reported (Chen et al, 2015). This study received exempt status approval from the University of San Diego. Below is a summary of the methods ARIC utilized for its prospective study.

Overview of ARIC study

The ARIC conducted a longitudinal study for the purpose of determining the etiology, epidemiology, and clinical characteristics of ILI among healthy active and retired military personnel and their beneficiaries. The study data was collected from 2009-2014 from five US military treatment facilities across the United States. The study

was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of Health Sciences (IDCRP-045), and written informed consent was obtained prior to data collection.

Population

Patients aged 0-65 years who presented to the clinic within 72 hours of influenza-like illness (ILI) symptoms were included into the study. ARIC defined ILI symptoms as having a self-reported fever above 100.4F with at least one of the following upper respiratory symptoms: cough, shortness of breath, chest pain, sputum production, sore throat). Patients with a history of chronic disease such as, COPD, uncontrolled asthma, diabetes, immunodeficiency, heart disease, neuromuscular disease, or renal disease were excluded from the study.

Demographic and patient history data were captured at enrollment. Nasopharyngeal samples were collected for virus identification analysis. Symptom data was captured prospectively on visit days 0, 3, 7, 28, and by a take-home seven-day symptom diary.

Symptom severity and virus identification tools

Clinical symptom severity was captured by a symptom severity instrument created for this study. The instrument was modified from several ILI symptom severity instruments, and included rating 20 symptoms. The patients were instructed to rate their severity on an ordinal scale with 0=none and 3= severe on daily basis in their seven day symptom journal and at all scheduled study visits. The symptoms on the instrument were: decrease in appetite, earache, runny nose, eye pain, sore throat, cough, breathing

difficulty, dizziness, hoarseness, chest pain, muscle ache, sneezing, joint pain, fatigue, headache, chills, abdominal pain, nausea, vomiting, and diarrhea.

The nasopharyngeal swabs collected were analyzed by multiplex assays (xTAG Respiratory Viral Panel, Luminex, Austin, TX pr PLEX-ID Viral IC Spectrum, Abbott, Chicago, IL). The multiplex assays detected the presence of the following viral respiratory pathogens: influenza A and B, adenovirus, rhinovirus, coronavirus, respiratory syncytial virus, parainfluenza virus, bocavirus, coxsackievirus/echovirus, and metapneumovirus.

Sample used in current study

Participants aged 0-65 with complete symptom severity measurements for visits 0, 3, and 7 were included in analysis. Any cases with incomplete symptom severity measures and/or a co-detection of another respiratory virus were excluded from analysis. People with bacterial co-infections were not excluded because the study focused on viral illnesses. Only the symptom visit data, demographic information, and viral diagnosis were needed for the analyses.

Data Analysis

Descriptive statistics were used to create and analyze the dataset for this study. Basic demographic information such as, age, sex, geographic location, ethnicity, military rank, and BMI were analyzed to determine distribution of data.

Primary Objective

All eligible patients were clustered together according to symptom expression on visit days 0, 3, and 7. The symptoms were analyzed as separate entities, and not grouped

for a total score or system scores. The distribution of viral diagnosis for each cluster was then compared to the distribution of the entire population to determine if any of the resulting clusters represented a specific virus type or group of virus types. Groups that were different were further analyzed to determine what unique symptom expressions caused them to cluster together and could potentially be associated with one or more viruses. Because it was unclear if different viruses may express similarly (and therefore cluster together) clustering was run with *k* values ranging from 5 to 10 clusters.

Secondary Objective

Patients were grouped together based on viral diagnosis to correct for symptoms that may be specific to a particular virus type. Only three viruses, influenza A, coronavirus, and rhinovirus, had sufficient numbers to perform meaningful clusters. The patients in each group were clustered on symptom expression, and compared based on demographic information (sex, military status, age, BMI, smoking, ethnicity) to determine if any clusters represented how a specific group may experience an illness. Patients with these viruses were clustered with *k* set to five for rhinovirus and influenza A and four for coronavirus due to the smaller sample set for coronavirus.

The distribution of attributes for each cluster were then compared to the distribution of the entire population for that virus. Groups with different attributes had Chi square test or one-way ANOVA test performed (based on variable type) to identify if there were any statistically significant differences between the clustered groups based on symptom data that caused them to cluster together. If statistical significance was found in a cluster, Bonferroni post-hoc analyses were performed.

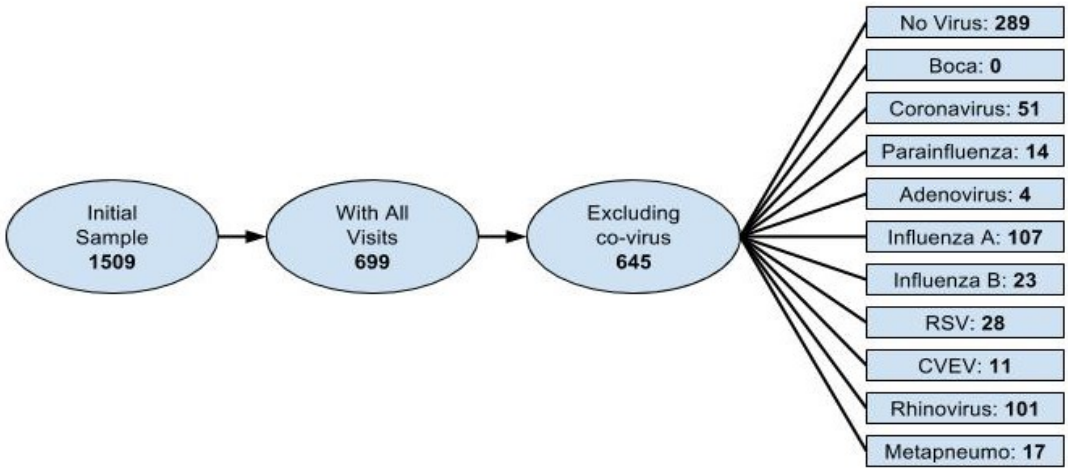
All statistical analyses were performed using SPSS software, version 22 (IBM corporation). Clustering was performed with scikit-learn version 0.17.1's implementation of K-Means Clustering on Python 2.7.6, with default parameters except for the number of clusters which were varied as part of the experiments.

Results

Demographics

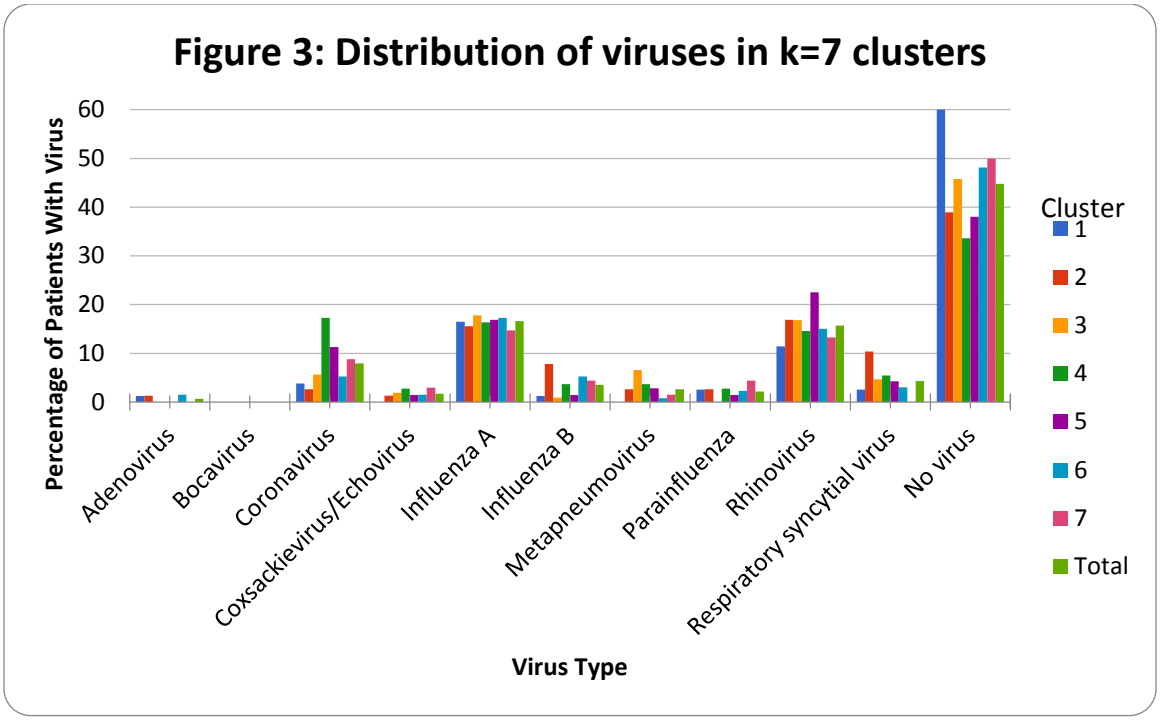
ARIC had a total of 1590 patients with viral diagnosis data, but over 50% of those patients had missing symptom data for their visits. For that reason, a subsample of 699 was mined that included only patients who had complete symptom data for visits 0, 3, and 7. The sample was amended further to exclude patients with viral co-infections to reduce the possibility of symptom interaction. A total of 645 patients' data was used for analysis (see fig. 2).

Figure 2: Sub-sample distribution by virus type



Predicting virus type

The goal of the first experiment was to determine if a particular ILI virus has universal symptom expression among all patients, allowing it to be uniquely identified by physical symptoms alone. After initial analysis, only the k=7 clustering demonstrated promising differences (see figure 3). Detailed analysis of this clustering revealed that all clusters were not significantly different than the population ($p > 0.05$ for all clusters and virus types) except for a one cluster (cluster 3, fig. 3) had a statistically significant difference ($p<.000$) and coronavirus percentage (17.3%) when compared to the overall population (7.9%). However, this cluster contained eight total virus types, some with similar percentages (16.4% influenza A and 14.5% rhinovirus); thus, it would not be very helpful in an absolute diagnosis. An ideal cluster distribution would be heavily skewed towards one or two virus types. Overall, this experiment was unable to predict virus type or differentiate those with and without a virus based on individual patient symptom experience using a variety of scoring approaches.



Symptom Experience

The second experiment attempts to identify if different patient attributes may cause them to experience a virus differently. For example, people who smoke are more likely to have compromised lung function; therefore may present with more severe respiratory symptoms when compared to a non-smoker with the same illness.

There were a total of nine viruses in the data set, but only three had sufficient numbers to run the analysis: rhinovirus (n=101), influenza A (n=107), and coronavirus (n=51). The patient attributes examined were: age, military status, BMI, sex, smoking history, and ethnicity. Each clustering by virus type yielded at least one symptom cluster with a statistically significant difference based on patient attributes.

Five out of the six attributes in the clustered rhinovirus data had statistically significant differences (see table 1). Bonferroni post-hoc analyses identified which

aspects of patients within the clusters were attributing to the differences. Analyses showed that cluster 2, as seen in table 1, had statistically significant differences in military rank, more likely a dependent ($p<.000$), smoking status, non-smoker ($p<.01$), BMI, underweight BMI, ($p<.000$), and age, less than 12 ($p<.000$). The underweight BMI was expected with this cluster due to the group being mostly patients under 12; therefore, it is difficult to use this attribute. Cluster 4 demonstrated statistical significant difference in sex, more females ($p<.000$), and cluster 3 had significant statistical difference in smoking history ($p<.000$).

Examining the median symptom scores per cluster implies a younger population (as seen in cluster 2) with rhinovirus do not have as severe of symptoms as adults and experience eye pain (see table 4); or, females (as seen in cluster 4) present with more severe upper respiratory symptoms (table 4).

The clustered influenza A data showed a statistically significant difference in clusters based on sex and military status (see table 2). Bonferroni post hoc analyses though revealed only cluster 3 had statistical significant difference in sex ($p<.000$), while cluster 4 was approaching a statistically significant difference in military status. Examining the median symptom scores for cluster 3 (see fig. 4), infers females have lingering coughs and runny noses with initial headache presentation when compared to the population total.

The clustered coronavirus data only showed a statistically significant difference in clusters in regards to sex (table 3), but Bonferroni post hoc analysis revealed clusters 3 and 4 were only approaching statistically significant differences. Examining the median

scores for the clusters show cluster 4, which was all female, tended to express worse upper respiratory symptoms, while cluster 3 (mostly males) tended to express worse systemic scores when compared to the total population (see figure 4).

Table 1: Rhinovirus attributes by cluster

	Total N=101	Cluster1 N (%)	Cluster2 N (%)	Cluster3 N (%)	Cluster4 N (%)	Cluster5 N (%)	p^a
Age (yrs)							
0-12.9	13	0 (0)	12(71)	0 (0)	0 (0)	1 (3)	.000
13-17.9	1	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	
18-34.9	63	10(67)	3(18)	21(81)	5(62)	24(68)	
35-65	24	5(33)	1 (6)	5(19)	3(38)	10(29)	
Sex							
Male	65	9(60)	10(59)	19(73)	0 (0)	27(77)	.001
Female	36	6(40)	7(41)	7(27)	8(100)	8(23)	
Ethnicity							
White	70	9(60)	11(65)	16(61)	7(87)	27(79)	.369
Black	13	2(13)	5(29)	2 (8)	1(12)	3 (9)	
Asian	6	1(7)	0 (0)	4(15)	0 (0)	1 (3)	
Other	11	3(20)	1 (6)	4(15)	0 (0)	3 (9)	
History of Smoking							
Yes	39	8(53)	2(12)	18(6)	1(13)	10(29)	.000
No	62	7(47)	15(88)	8(21)	7(87)	25(71)	
Body Mass Index							
<18.5	11	0 (0)	9(53)	19(73)	0 (0)	1 (3)	.000
18.5-24.99	25	3(20)	4(23)	7(27)	5(63)	6(17)	
25-29.99	39	7(47)	1 (6)	19(73)	2(25)	20(57)	
>30	24	5(33)	2(12)	7(27)	1(12)	7(20)	
missing	2	0 (0)	1 (6)	0 (0)	0 (0)	1 (3)	
Military Status							
Active Duty	74	11(73)	4(2%)	24(9%)	6(75)	29(83)	.000
Dependent	23	3(20)	13(77)	1 (4)	1(12)	5(14)	
Retired	4	1(7)	0 (0)	1 (4)	1(13)	1 (3)	

Table 2: Influenza A attributes by cluster

	Total N=107	Cluster1 N (%)	Cluster2 N (%)	Cluster3 N (%)	Cluster4 N (%)	Cluster5 N (%)	p^a
Age (yrs)							
0-12.9	7	1(11)	5(15)	0 (0)	0 (0)	1 (6)	.100
13-17.9	1	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	
18-34.9	66	3(33)	18(55)	9(56)	25(78)	11(65)	
35-65	33	5(56)	9(27)	7(44)	7(22)	5(29)	
Sex							
Male	69	3(33)	26(79)	4(25)	25(78)	11(65)	.000
Female	38	6(67)	7(21)	12(75)	7(22)	6(35)	
Ethnicity							
White	69	9(100)	18 (5)	12(75)	20(63)	10(59)	.384
Black	22	0 (0)	6(18)	3(19)	7(22)	6(35)	
Asian	9	0 (0)	6(18)	0 (0)	3 (9)	0 (0)	
Other	6	0 (0)	2 (6)	1 (6)	2 (6)	1 (6)	
Missing	1	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	
History of Smoking							
Yes	35	3(33)	10 (3)	4(25)	11(33)	7(41)	.898
No	72	6(67)	23(70)	12(75)	21(66)	10(59)	
Body Mass Index							
<18.5	11	0 (0)	4(12)	0 (0)	1 (3)	1 (6)	.132
18.5-24.99	25	2(22)	10(30)	3(19)	10(31)	7(41)	
25-29.99	39	3(34)	8(2%)	10(63)	5(16)	4(24)	
>30	24	2(22)	7(21)	2(12)	14(44)	5(29)	
missing	9	2(22)	4(1%)	1(6)	2 (6)	0 (0)	
Military Status							
Active Duty	74	2(22)	18(54)	10(63)	27(84)	12(71)	.031
Dependent	23	6(67)	11(33)	5(31)	4(13)	4(23)	
Retired	4	1(11)	4(12)	1 (6)	1 (3)	1 (6)	

Table 3: Coronavirus attributes by cluster

	Total N=51	Cluster1 N (%)	Cluster2 N (%)	Cluster3 N (%)	Cluster4 N (%)	p^a
Age (yrs)						
0-12.9	0	0 (0)	0 (0)	0 (0)	0 (0)	.404
13-17.9	3	0 (0)	0 (0)	3(18)	0 (0)	
18-34.9	41	11(85)	13(81)	13(76)	4(80)	
35-65	7	2(15)	3(19)	1 (6)	1(20)	
Sex						
Male	22	7(54)	4(25)	11(65)	0 (0)	.020
Female	29	6(46)	12(75)	6(35)	5(100)	
Ethnicity						
White	30	8(61)	9(56)	9(53)	4(80)	.996
Black	11	2(15)	4(25)	4(23)	1(20)	
Asian	3	1 (8)	1 (6)	1 (6)	0 (0)	
Other	6	1 (8)	2(13)	3(18)	0 (0)	
Missing	1	1 (8)	0 (0)	0 (0)	0 (0)	
History of Smoking						
Yes	16	5(39)	6(38)	4(24)	1(20)	.718
No	35	8(61)	10(62)	13(76)	4(80)	
Body Mass Index						
<18.5	11	1 (8)	1 (6)	0 (0)	0 (0)	.132
18.5-24.99	25	5(38)	8(50)	7(41)	1(20)	
25-29.99	39	1 (8)	6(38)	5(29)	2(40)	
>30	24	6(46)	1(6)	4(24)	2(40)	
Missing	9	0 (0)	0 (0)	1 (6)	0 (0)	
Military Status						
Active Duty	44	12(92)	13(81)	14(82)	5(100)	.206
Dependent	7	1 (8)	3 (1)	3(18)	0 (0)	
Retired	0	0 (0)	0 (0)	0 (0)	0 (0)	

Table 4: Change in symptom score amongst clusters against total population

Influenza A						Rhinovirus						Coronavirus				
CLUSTER	1	2	3	4	5	CLUSTER	1	2	3	4	5	CLUSTER	1	2	3	4
DECREASEAPP_D0	-				-	DECREASEAPP_D0		-		-		DECREASEAPP_D0	-			
DECREASEAPP_D3						DECREASEAPP_D3	-			-		DECREASEAPP_D3		+		+
DECREASEAPP_D7						DECREASEAPP_D7						DECREASEAPP_D7				
SHORTBREATH_D0	-		-		-	SHORTBREATH_D0	+	-	-		-	SHORTBREATH_D0			-	+
SHORTBREATH_D3	+					SHORTBREATH_D3	+			+		SHORTBREATH_D3				+
SHORTBREATH_D7	+					SHORTBREATH_D7						SHORTBREATH_D7				
CHEST_PAIN_D0	+	+				CHEST_PAIN_D0	+			+		CHEST_PAIN_D0				+
CHEST_PAIN_D3	+					CHEST_PAIN_D3						CHEST_PAIN_D3				
CHEST_PAIN_D7						CHEST_PAIN_D7						CHEST_PAIN_D7				
CHILLS_D0	-		-		-	CHILLS_D0	+		-	-	+	CHILLS_D0		-		
CHILLS_D3						CHILLS_D3						CHILLS_D3				
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COUGH_D0						COUGH_D0				+		COUGH_D0				
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EARACHE_D0						EARACHE_D0						EARACHE_D0	+			+
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EYEPAIN_D7						EYEPAIN_D7						EYEPAIN_D7				
FATIGUE_D0						FATIGUE_D0	+			-		FATIGUE_D0			+	+
FATIGUE_D3	-					FATIGUE_D3						FATIGUE_D3				
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HOARSENESS_D0						HOARSENESS_D0	-					HOARSENESS_D0	-	-		
HOARSENESS_D3	-				-	HOARSENESS_D3	-	-				HOARSENESS_D3	-	-		
HOARSENESS_D7						HOARSENESS_D7						HOARSENESS_D7				+
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JOINTPAIN_D3					+	JOINTPAIN_D3	+			+		JOINTPAIN_D3			+	
JOINTPAIN_D7						JOINTPAIN_D7						JOINTPAIN_D7				
MUSCLEPAIN_D0						MUSCLEPAIN_D0		-	-	-		MUSCLEPAIN_D0		-		
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MUSCLEPAIN_D7						MUSCLEPAIN_D7						MUSCLEPAIN_D7				
NAUSEA_D0						NAUSEA_D0	+	+			+	NAUSEA_D0		+		

NAUSEA_D3						NAUSEA_D3						NAUSEA_D3				
NAUSEA_D7						NAUSEA_D7						NAUSEA_D7				
RUNNYNOSE_D0		+	+			RUNNYNOSE_D0				+		RUNNYNOSE_D0				+
RUNNYNOSE_D3					-	RUNNYNOSE_D3			-	-		RUNNYNOSE_D3				
RUNNYNOSE_D7			+			RUNNYNOSE_D7					-	RUNNYNOSE_D7				
SNEEZING_D0	-	-	-		-	SNEEZING_D0				+		SNEEZING_D0			-	
SNEEZING_D3						SNEEZING_D3		-	-			SNEEZING_D3			-	
SNEEZING_D7						SNEEZING_D7						SNEEZING_D7				+
SORE_THROAT_D0				+		SORE_THROAT_D0						SORE_THROAT_D0				
SORE_THROAT_D3	-				-	SORE_THROAT_D3						SORE_THROAT_D3				
SORE_THROAT_D7						SORE_THROAT_D7						SORE_THROAT_D7				
**Symptoms vomiting, diarrhea, & abdominal pain were removed because no differences seen																

Discussion

This is the first study to the author's knowledge that analyzed individual symptom scores through unsupervised machine learning. A majority of ILI symptom research focuses on determining if a patient's symptoms can distinguish influenza from the other ILI viruses (Michiels, Thomas, Van Royen, & Coenen, 2011; Call, Vollenweider, Hornung, Simel, & McKinney, 2005; Monto, Gravenstein, Elliott, Colopy, & Schweinle, 2000). We attempted to differentiate all the viruses based on symptom score, but the technique was unable to predict virus type based on physical symptom scores. Some differences in symptoms among virus types were anecdotally observed, but only one cluster (cluster 3, fig 3) showed statistical significance. A larger sample size may reveal more statistically sound differences.

In the literature, symptom data for viral prediction tends to be analyzed as either a dichotomous response or sum of scores response (Treanor et al, 2000; Monto et al, 2000; VanWormer, Sundaram, Meece, & Belongia, 2014). We used the individual symptom scores at the initial visit and visit days 3 and 7 to provide the algorithm more data to

analyze differences. For instance, if only a sum of scores was analyzed, the differences in fever or cough may have been missed.

The use of unsupervised machine learning provides further evidence that physical symptom experiences vary by person. This concept was reinforced by the results of the second objective, which showed individuals experience symptoms differently based on individual characteristics. For instance, the study showed that a younger population seems to present with less intense symptoms for rhinovirus, or women present with more intense upper respiratory symptoms for influenza A compared to men. Healthcare providers need to take into account outside factors like environmental, biological, or social that are influencing symptom severity for ILI.

Limitations

There are several limitations to this study. One major limitation of the analysis was the limited availability of patient data. This study was a secondary analysis of previously collected data; therefore, data quality could not be controlled. While the original dataset had over 1500 patients with viral diagnosis, over half were missing symptom reported visit data for the analysis period. Additionally, another 51 patients were eliminated from the sample due to viral co-infections, which could have introduced bias. A more controlled and larger data set would greatly improve the analysis of this data.

Because the population used for this study was military personnel and their families, these results cannot be generalized to the general public as the military population is unique. Additionally, data from the 'no virus' group was difficult to use for comparison

because the patients in that group most likely had some kind of bacterial or viral illness that could not identified using ARIC's biological analysis techniques.

Another aspect of the study that may have limited the results is how symptom severity was measured. The instrument used to capture symptom severity was created for the purpose of this study, and not psychometrically evaluated although the scale was derived from other published scales. Research on symptom experience and the findings from this study's second objective have shown symptoms are not just physical but may be affected by other sociodemographic characteristics (Armstrong, 2003; Macintyre, 1993). The Symptom Management Theory by Dodd et al, indicates there are three components to symptom presentation: symptom experience, symptom management strategies, and patient outcomes. Additionally, domains outside of the individual, such as a person's environment, health history, and biopsychosocial perspective, influence symptom perception. Because the instrument concentrated on physical symptoms, the results could be biased because outside factors were unmeasured.

Future Research

As this was a novel approach of data analysis using a common unsupervised learning method, *k*-means clustering, further analysis with more sophisticated clustering methods should be performed. With the results of the secondary analysis demonstrating the difference in symptom presentation by sex, age, ethnicity, future studies should look at outside factors that may influence symptom presentation of ILI.

Unsupervised machine learning could become a proven technique to help identify patterns in medical research. Its technique could open new avenues of patient data

analysis and may reveal knowledge and factors that may not be obvious using traditional statistical approaches. The use of it in the medical world needs to increase to further the knowledge and provide better care for the patients.

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Chapter 3:

Clinical characteristics of strain specific human coronavirus among adolescents and adults

Abstract

The increase use of diagnostic tests for influenza-like illnesses has revealed the symptomology of human coronaviruses can be more severe than previously understood. The clinical presentation between the four common human coronavirus strains varies in severity, especially among gastrointestinal symptoms.

Introduction

Coronaviruses (CoV) are RNA viruses that are ubiquitous in mammals, ranging from bats to humans. Four human coronaviruses have been described with increasing frequency in humans, although human infection with animal coronaviruses does occasionally occur, sometimes with drastic consequences as with the SARS and MERS outbreaks. Despite the publicity and high case fatality rate of those outbreaks, circulation of the human coronaviruses (HKU1, OC43, NL62 and 229E) is worldwide and infection in humans is common[1-5]. As with human rhinoviruses, coronavirus were traditionally difficult to diagnose and were generally thought to cause uncomplicated upper respiratory tract infections (URI). With the increasing use of rapid diagnostic tests for a wide range of respiratory pathogens, including human coronaviruses (hCoV), emerging data have demonstrated that human coronaviruses can cause more significant illness than initially thought[6,7]. There are very few data on whether unique type-specific clinical syndromes might occur. Using a prospective cohort study of otherwise healthy adolescents and adults with influenza-like illness, we sought to describe the similarities and differences in clinical presentation of hCoV infections.

Methods

The Acute Respiratory Infection Consortium (ARIC) was established in July 2009 as a multi-site clinical research network to study ILI among otherwise healthy military personnel and their beneficiaries. The aim of ARIC was to describe the natural history of ILI among healthy people, through an observational/ longitudinal cohort study to determine the etiology, epidemiology, and clinical characteristics of ILI at five US-based

military treatment facilities across the United States. A secondary analysis of their data symptom severity data from patients with diagnosed coronavirus was performed. ARIC methods for data collection have previously been reported[15], but below is a summary of the methods utilized for ARIC's prospective study.

From 2009-2014 otherwise healthy subjects aged 0-65 who presented to one of the five military clinics within 72 h of ILI symptom were enrolled. ILI was defined as having a fever (temperature over 100.4F) with at least one of the following respiratory symptoms: cough, shortness of breath, sputum production, chest pain and/or sore throat. People with a history of diabetes (type 1 and 2), COPD, uncontrolled asthma, immunodeficiency, and/or chronic neuromuscular, cardiac, renal disease were excluded. From this cohort, we identified participants ages 13-65 who had laboratory confirmed coronavirus only by excluding those cases with a co-detection of another respiratory virus.

Demographic information and clinical symptoms were collected by interview at enrollment. A nasopharyngeal specimen was collected for virus identification. Participants returned to clinic at days 3±1, 7±2, and 28±7 for collection of symptom data and additional tests.

Additionally, clinical symptom severity was recorded by the participants utilizing a 7-day symptom diary, as previously described. Briefly, symptom severity was characterized by the sum of 4-point symptom scores in four categories: upper respiratory (earache, runny nose, sore throat, and sneezing), lower respiratory (cough, breathing difficulty, hoarseness, and chest pain), systemic (muscle ache, fatigue, headache, and

chills), gastrointestinal (nausea, vomiting, and diarrhea), and total severity (the above 15 symptoms).

The nasopharyngeal swabs underwent multiplex testing at the Naval Health Research Center (San Diego, CA, USA) for detection of the following viral respiratory pathogens: influenza virus, adenoviruses, respiratory syncytial virus, parainfluenza virus, and human metapneumovirus and human CoVs. Participants aged 13-65 years old with corona virus types HKU1, OC43, NL63, and 229 E without co-detection of another virus were included in the final analysis.

Statistical Analysis

Descriptive statistics were used to identify the differences in demographics, geographic location, and potential risk factors by corona virus type. Severity of clinical symptoms were assessed by system composite score and total score for each strain type. Fischer exact test were utilized for categorical variables, and Kruskal-Wallis test were used to examine clinical symptoms for the different corona strains. Analyses were performed using SPSS software, version 22 (IBM corporation).

The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of Health Sciences (IDCRP-045) and written informed consent was obtained.

Results

Between 2009 and 2014, CoV was detected in approximately 12% of the enrolled ARIC participants. Of the 111 positive participants, 29 (26.1%) were excluded because they were under the age of 13 years (n=15) or had a viral co-detection (n=14). The 82

remaining cases were included for analysis and sub-categorized into the four different types of CoVs. The 82 cases had a mean age of 28 years with a range of 13 years-49 years, and included 71 (87%) adults, 42 (51%) females, and 69 (84%) active duty military members. The study population ethnicity was 60% Caucasian, 24% African-American, 5% Asian, and 11% other. Among the 82 cases, 23 (28%) had 229E, 18 (22%) had NL63, 28 (34%) had OC43, and 13 (16%) had HKU1 (see figure 1). The prevalence of the type of CoV did not differ by demographic characteristics, with the exception of the 2010-2011 flu season, which had fewer cases of diagnosed CoV compared to the other seasons (p=0.046).

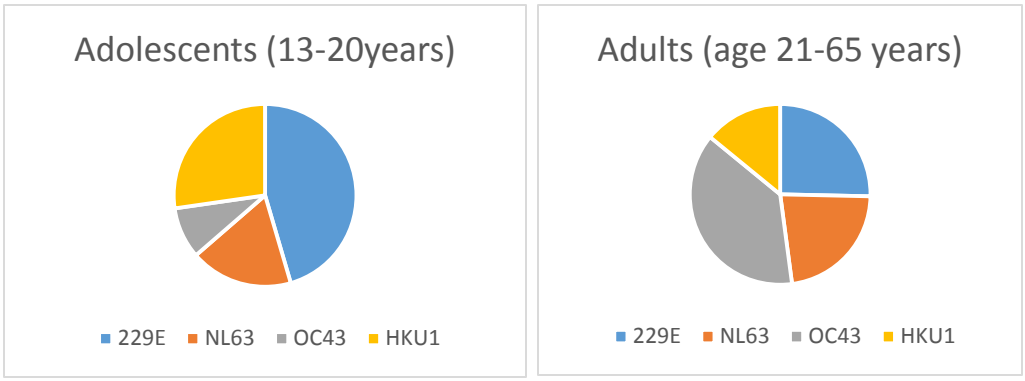
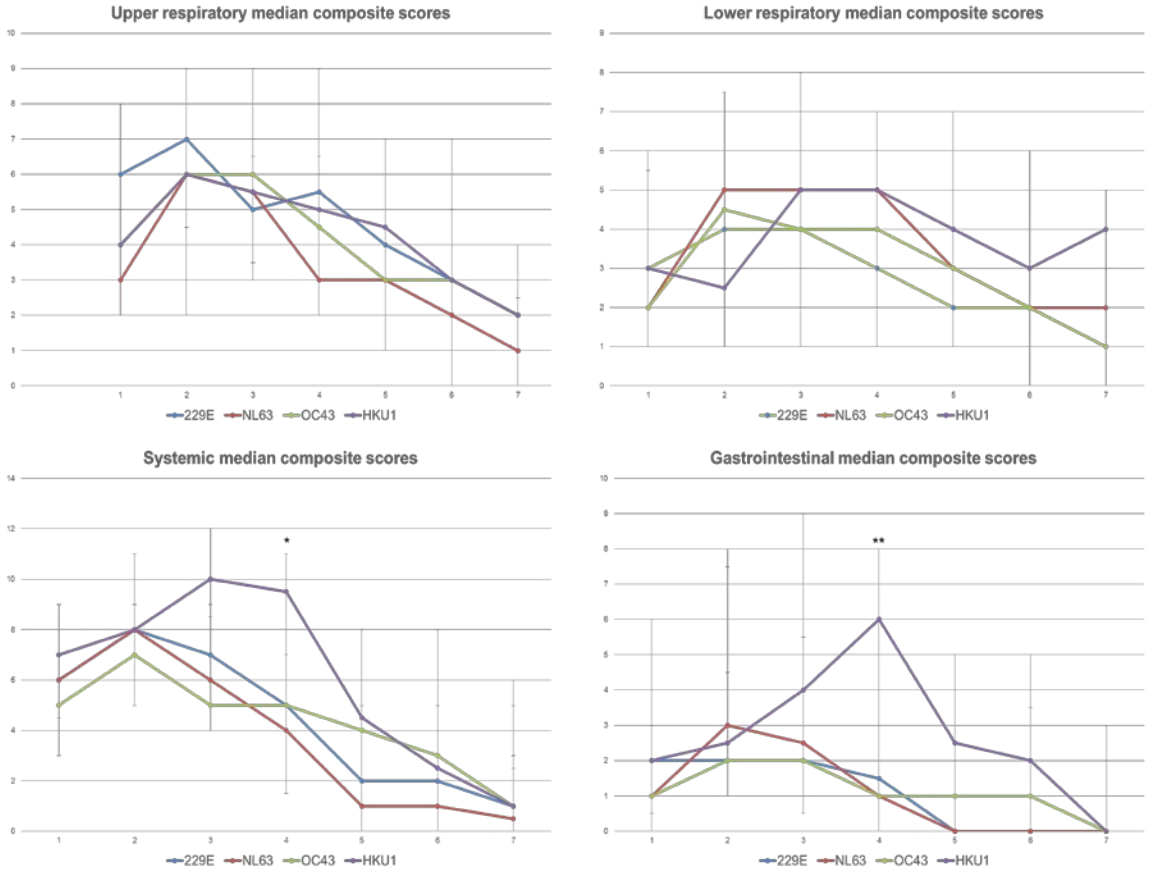


Figure 1: Distribution coronavirus strain by age

Participants with HKU1 had a trend to higher visit 1 composite scores for gastrointestinal symptoms compared to the other virus types, but were not statistically significant. The majority of participants (76%) reported persistent symptoms through day 7. The composite scores for upper respiratory, lower respiratory, systemic, gastrointestinal, and total symptoms peaked on days 3 and 4 and tended to decrease thereafter (figure 2). HKU1 had statistically significant difference in composite GI

symptom score on day 4 (p=0.05), compared to the other strain types. No other statistically significant symptom composite scores were noted, although higher systemic symptom scores for HKU1 approached significance on days 3 and 4 compared to the other virus types.

Figure 2: Symptom Severity Participant Diary
***indicates approaching statistical significance and **represents statistical significance**



Discussion

This study was the first study to compare the epidemiology and symptom severity of the four common human coronavirus strains in an otherwise healthy population. The longitudinal design of the study allowed for the prospective capture of self-report symptom severity scores utilizing a standard symptom severity instrument. In order to ensure symptoms were attributable to CoVs, all cases of viral co-detection were excluded. Subjects under 13 years old were eliminated because parental symptom reporting occurred in younger children and is difficult to compare to self-reported symptoms.

Few studies exist that describe severity differences between the CoV's in young health adults, though several have been published in children[5,6,8-10], or older adults with co-morbidities[11-13]. Lau and colleagues published the results of a prospective cohort study of hospitalized children and adults, though the mean age was between 2 and 9 years of age, depending on the CoV type[1]. Dare et al published a similar prospective cohort of mixed inpatient (64, 78%) and outpatient (18, 22%) children (34, 41%) and adults (48, 59%) and found no difference in severity between the four types[3]. A study of mixed children and adults done by Gaunt and colleagues had high rates of co-detection which were not removed from study data[14]. Our study of young healthy adolescents and adults with no co-detections found that coronavirus 229E was more prevalent in adolescents, and OC43 more so in adults. Additionally, it was noted that the HKU1 strain had higher gastrointestinal symptom severity when compared to the other virus types on days 3 and 4. HKU1 also had a trend toward more severe systemic symptoms with lingering lower

respiratory composite scores compared to the other three virus types. Previous literature has noted that HKU1 is associated with gastrointestinal symptoms than the other three viruses, but it has not been associated with more prolonged lower respiratory tract and systemic symptoms[16].

Although the strengths of this study are the prospective data collection with symptoms diary validation, multiplex testing, and 5 year time-period, it is a secondary review of a large database not designed specifically to detail CoVs. Additionally, the symptom severity diary was developed for the purpose of the original study, and was not a validated instrument. Our scale is nearly identical to that used by Hayden et al for ILI symptom severity in neuramindase inhibitor trials, although there is no agreed upon, validated scale for ILI symptom severity. The small sample size (n=82) may have prevented us from making further associations with the coronaviruses and clinical outcomes, although it is one of the largest human CoV cohorts in healthy patients to-date. Lastly, subjects were only those who sought medical care, so it cannot be assumed that it represents the entire spectrum of illness from asymptomatic through severe presentations

In summary we describe the epidemiology of symptoms in healthy adolescents and young adults in whom one of the four common species of coronaviruses was detected. Although not often attributed to CoVs, intestinal symptoms were once again described, especially with HKU-1, and trends toward differential severity and duration were observed. Coronaviruses should be considered as a potential cause of ILI, and future research on risk factors and prevention, as well as surveillance for the potential of less common CoVs is needed.

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Chapter 4:

A Critique: The Canadian Acute Respiratory Illness and Flu Scale

Abstract

Acute respiratory illness is the most common clinical childhood illness globally, and there are few instruments available that measure acute respiratory illness severity, especially in children. An instrument created to fulfill this gap is the Canadian Acute Respiratory Illness and Flu Scale (CARIFS). The CARIFS is an instrument with reported psychometric testing that measures acute respiratory tract illness disease severity. This article is a review of the psychometric properties of the Canadian Acute Respiratory Illness and Flu Scale with a focus on its strengths and limitations.

Introduction

Acute respiratory illness (ARI) is the most common clinical childhood illness globally. In 2010, there were approximately 15 million hospital admissions globally of children with acute lower respiratory tract infection (Nair et al., 2013). It is estimated the cost associated with acute respiratory illnesses in the US is over 12 billion dollars annually, and yet there are a limited number of instruments available that assess and measure acute respiratory illness severity, especially in children (Jacobs et al., 2000). One of the few available instruments available is the Canadian Acute Respiratory Illness and Flu Scale.

Background

The Canadian Acute Respiratory Illness and Flu Scale (CARIFS) was originally developed for use in research to measure ARI disease severity among children (range 0 to 12 years) by capturing health care professionals' and parents' concerns with ARI. While developed for research purposes, there is evidence it has been used by clinicians in practice (Fischer, 2014). Overall, the instrument uses a list of symptoms to measure the disease severity of ARI.

Origin of Instrument

The CARIFS was initially based upon the Kirshner and Guryatt framework for assessing health indices (1985). The development of the instrument began with item selection and face validity to reduce items as well as generate new items. Content for an initial 25 items was generated from the items of 13 other instruments (Hayden et al., 1997; Hayden et al., 1996; Barker et al., 1998; Englund et al., 1994; Hall et al., 1987;

Morley et al., 1991; Landgraf et al., 1996; Young et al., 1995; Msall et al., 1994; McCarthy et al., 1982; Pollack et al., 1996; Stein et al., 1990; Walker & Greene, 1991). While these instruments were used to extrapolate items, several had no published statistics on validity.

Following the generation of 25 items, face validity was determined using three general pediatricians and 23 parents of children with ARI. As a reminder to readers, face validity is not a psychometric test; it is a subjective form of evaluation (Waltz, Strickland & Lenz, 2016). In this case, the pediatricians and parents evaluated items by ranking the relevance of the initial 25 items that were presented to them, each on separate cards. They had the option to remove cards that had items believed to be irrelevant as well as to generate up to five new items that they regarded as important. That evaluation led to the reduction of the 25 items to 17. Only one item was added to the list (clinginess) resulting in an instrument with a total of 18 items. Next, the items were subjectively grouped into three dimensions by the instrument authors. The resulting dimensions included a) symptoms (e.g., cough, fever), b) function (e.g., not playing well, not interested), and c) parental impact (needing extra care, clinginess) (Jacobs et al., 2001). There are no published criteria available to determine what was used to group the individual items into these three dimensions.

Description of Instrument

The current version of the CARIFS contains the 18 items within the three dimensions described above. The instrument is to be completed by the parent of a child with ARI. There is no recommended time limit to be imposed for completing the

instrument. In fact, over time, there is evidence that different researchers have used different timeframes for instrument completion (Shepperd, et al., 2004; Fischer et al., 2014; Vohra et al., 2008; Whitley et al., 2001).

Scoring

The 18 items are scored on a four-point ordinal scale with 0= no problem, 1= minor problem, 2= moderate problem, 3= major problem, and not applicable= no score. A total score is then calculated by summing the individual item scores, ranging from 0 (best possible health) to 54 (worst possible health). If any item is marked as 'not applicable' then a mean score is calculated based upon the items that were answered. That mean score is then multiplied by 18 to obtain a total score (Jacobs et al., 2001). No cut-off scores have been reported in the literature for clinical or research for determining ARI disease severity; therefore, the instrument does not have norms and would not be considered standardized for clinical purposes (Waltz, et al., 2016). Finally, a parent global health assessment, a 10 cm visual analog scale (VAS), is placed underneath the CARIFS items with instructions to mark the perception of the child's health on the line with a single mark from best to worst possible health (Jacobs et al., 2001).

Psychometric Testing

The first psychometric testing for the CARIFS (diary version) was performed in three Canadian cities, Halifax, Calgary, and Toronto, during the winter of 1998. The parents of 220 otherwise healthy children, aged 0 to 12 years, with ARI symptoms in the previous 72 hours were enrolled in the study; 206 completed data collection. Inclusion criteria were a) a diagnosis of ARI with criteria for ARI being a fever above 38C, in the

past 72 hours, b) at least one upper respiratory symptom (e.g., nasal congestion, cough, sore throat), and c) at least one systemic symptom (e. g., fatigue, headache). A diary format was designed for this study. The diary contained sixteen individual CARIFS instrument sheets. Each sheet was to be completed twice daily for days 1-7 and once daily on days 10 and 14 by the parents. No recommended time frame for completing the score sheets could be located in the published literature. Therefore, some parents may have completed each sheet at the end of each day, while others may have completed all 16 sheets on the last day of data collection.

At the enrollment visit, the child's axillary temperature was recorded, and their parents rated the ARI disease severity by completing the first CARIFS instrument diary entry. The parents then completed the parent global health assessment (VAS 10 cm) part of the CARIFS for the child's current state of health (Jacobs et al., 2001). Additional testing involved physicians and nurses completing the CARIFS as well as other instruments to compare ARI symptoms between instruments.

CARIFS Reliability

Determining reliability is a necessary process every time instruments are administered (Waltz, et al., 2016). Initially, the CARIFS reliability was assessed using test-retest to determine its stability over time. This was determined by comparing instrument scores completed by the same person at two different times on the second day after enrollment. The morning score was compared to the evening score with a resulting correlation coefficient of 0.808 indicating acceptable reliability (Mayo, 2015).

Internal consistency is an evaluation of reliability and is determined by calculating a Cronbach alpha. This can be done for a total score as well as subscale (dimension) scores. The Cronbach alpha is a statistical test that determines if all items in a group of items (be it the entire instrument or a subscale) are measuring the same concept. A score of 1.0 would equate to perfect internal consistency reliability, at least 0.90 for clinical purposes, and 0.70-0.80 for research purposes (Mayo, 2015; Waltz, et al., 2017). Initial testing of the CARIFS was completed in a Canadian population resulting in an acceptable Cronbach alpha of 0.89 for the total score only. Using similar psychometric testing on the CARIFS, but with parents of 178 children with ARI located in the United Kingdom (UK), total score internal consistency was again acceptable at 0.85. However, somewhat lower test results were obtained for the symptom dimension (0.54), function dimension (0.77), and parental impact dimension (0.70).

Validity

Determining if the CARIFS produced valid data was accomplished through construct validity and responsiveness testing. Construct validity identifies how well the instrument items measure what they are operationally defined to measure. A number of tests of validity such as convergent validity testing can be used to determine construct validity (Waltz, et al., 2016).

Initial construct validity was determined for the CARIFS by using convergent validity testing. As part of this testing, physicians and nurses were asked to simply score the severity of the child's illness as mild, moderate or severe. Additionally, the nurses scored the child's health status by completing an adapted version of the Yale Observation

Scale (YOS). The YOS is designed to measure severity of illness in children up to three years old with fever in the emergency room department (McCarthy et al., 1982; Bang & Chaturvedi, 2009). Then the total parent CARIFS scores were compared with the a) parent VAS scores (r=0.52), b) YOS scores (r=0.48), c) child axillary temperatures at time being seen by providers (r=.29), and d) the simple assessment classifications from those physicians (r=0.36) and nurses (r=0.44). One explanation that has been offered for the weak correlation between the CARIFS scores and the axillary temperatures at enrollment (r=0.29), was that only 59% of the participants had a fever at enrollment. Shepperd et al. also approached assessing construct validity similarly except a VAS was used for physician and nurse assessments in addition to the parent VAS score. The Spearman coefficients were calculated between the CARIFS score and VAS scores from the general practitioner (r=0.13), nurse (r=0.35), and parent (r=0.40).

Sensitivity, an important concept in the clinical arena when caring for and treating patients, is defined as the ability of an instrument to detect change over time within the same patient. The smaller the amount of change an instrument can pick up, the more sensitive the instrument (Waltz, 2016). For the CARIFS it was hypothesized that the child's severity of illness would diminish over time based on the typical course of ARI, thereby setting up the perfect opportunity to measure responsiveness to change. Using an effect size approach, the change in total CARIFS scores were determined for 1) time of enrollment, 2) 8 hours post enrollment, and 3) day 3 of illness. As background, an effect size score above 0.5 indicates moderate change and above 0.8 indicates large change (Kazis, 1989). At 8 hours post enrollment the effect size was 0.5 and at day 3 of illness it

was 1.6, indicating that the CARIFS is very responsive to improvement over time. Due to few children's health declining over the course of the illness, the instrument could not be assessed for responsiveness to decline.

Instrument Strengths and Limitations

The primary strength of the CARIFS is that it was built upon the Kirshner and Guryatt process framework for assessing health indices (1985). Therefore, the methodological framework undertaken included item selection, scaling and reduction, as well as, determining the instrument's reliability, validity and sensitivity. Additionally, while not a true test of validity, face validity was determined by a large number of parents (N=23). There are several limitations to the CARIFS that should be noted by clinicians and researchers prior to utilizing the instrument.

Administration and Scoring

The instructions for administration and scoring of the CARIFS do not appear to have been standardized. An instrument should have consistent and defined administration guidelines, such as specifications and conditions (Waltz, Strickland, Lenz, 2016). In the literature, there are different versions of the administration process for the CARIFS, ranging from completing the instrument once a day for two weeks to just once during an emergency room visit. In fact, some publications on the CARIFS provided no information regarding how the instrument was administered (Whitley et al., 2001; Vohra et al., 2007; Fischer et al., 2014). Because the CARIFS does not have standard instructions for administration, users should be cautious when comparing results among referent groups (Waltz, Strickland, Lenz, 2017).

As discussed earlier, a total score for the CARIFS is obtained by summing all items, and a procedure for addressing missing data has been described above. However, established norms have not been located in the literature. While the CARIFS was created to measure disease severity of ARI, there are no identified norms for mild, moderate, or severe ARI disease severity. Without the established norms to classify the severity of ARI, it is difficult to interpret scores for clinical or research purposes.

Reliability Issues

Several forms of reliability testing were performed on the CARIFS. An instrument is considered reliable if it consistently measures the same attribute repeatedly over time. The CARIFS had several forms of reliability testing performed, as mentioned above, but the testing was not performed in a controlled or consistent manner. Instrument stability was performed using test-retest approaches. While appropriate testing, the time frames between testing were vague. Morning and evening testing (no time intervals) makes it is difficult to know if the instrument is indeed stable for any specified time interval. Additionally, it is unknown if any activities may have occurred during the time intervals that may have influenced the CARIFS score, e.g., the child was given a cough suppressant. In order to estimate test-retest reliability the CARIFS should have been administered at defined times and under standard conditions. But due to the lack of specificity in time intervals and conditions, users should proceed with caution and not assume strong instrument stability.

Internal consistency. While an acceptable total score internal consistency has been determined for clinical and research purposes, it has not been established for clinical

purposes for the three dimensions (symptoms, function, and parental impact). Additionally, because the alpha coefficient was so high, 0.89, it could be assumed that the instrument measures just one attribute (McCrae, 2011); thereby making the subscales not relevant to the measure. Prior to using the three dimensions in clinical decision-making, the internal consistency for each one should be established at higher levels. Further reliability testing should also include interrater reliability for provider groups and parental groups.

Validity Issues

While several forms of validity testing were performed on the CARIFS, questions of validity remain. As a reminder, validity refers to the extent an instrument measures what it proposes to examine. When validity is assessed, the instrument is not what is being evaluated, but rather the scores obtained from instrument. The CARIFS was developed using items from other instruments and the opinions of several parents and physicians, making validity testing extremely important.

The stated objective of the CARIFS is to measure disease severity in children with ARI. However, the instrument scoring appears to be more focused on the duration of illness. Concern exists regarding the ambiguity of the instrument: does it indeed measure disease severity or duration of illness? It may be beneficial to utilize subject matter experts with theoretical knowledge to assist in the identification of the instrument construct and face validity. Additional psychometric testing might address item-content validity in order to determine if each item is a measure of the content domain (Waltz, et al, 2017).

While issues of item-level validity exist, there may also be issues surrounding the instrument domains as well. Because criteria for determining the placement of the 18 items into the domains are not provided, use of the domain scores for clinical decision-making or research purposes should be made with caution. Factor analysis, a technique used to examine patterns of variance among items might be a first step in determining the dimensions of the CARIFS.

As described above, CARIFS convergent validity was assessed using a modified version the Yale Observation Scale (YOS). However, there was no indication of how the YOS was adapted or if any psychometric testing had been performed on the adapted scale prior to its use for convergent validity testing. If this modified version did not have validity itself, it would not serve as an appropriate measure to determine validity for the CARIFS. Additionally, there were important differences in the correlation of the overall CARIFS scores to the different provider assessment scores as well as to the axillary temperatures. Further work in establishing consistency in the instrument's validity would be recommended.

Finally, a majority of the CARIFS items focus on symptoms the child is experiencing because of ARI. The severity of symptoms of any disease can be influenced by psychological or situational factors, which the CARIFS does not measure. Several symptom-based theories, including University of California San Francisco (UCSF) Symptom Management model identify that symptoms are more than a physiological response to illness (Dodd et al., 2001). Including items such as

environmental, sociocultural, and functional health factors may change how the CARIFS would measure disease severity thereby improving validity of the data it produces.

Conclusions

Nearly every child will experience an acute respiratory illness (Simones et al, 2006). Therefore, a comprehensive way to measure the severity of that illness should exist. Instruments that measure disease severity in children with ARI are limited. The creation of the CARIFS provides an opportunity to objectively measure disease severity for both clinical care and research but should be used with caution, especially in clinical decision-making.

Instrument limitations identified in this paper are based upon questionable reliability and validity testing, therefore, further testing is recommended. It would be important to repeat reliability testing using specific time parameters for administering the instrument. Furthermore, treatments during testing procedures should be documented, and their effects considered part of testing the reliability of the CARIFS. To improve validity testing, domains should be established based on factor analysis. Including the measurement of environmental, sociocultural, and functional health factors in any revisions of the instrument may provide a more complete picture of disease severity of childhood ARI, and potentially provide an improved instrument for measuring symptoms important to parents and clinical nurse specialists.

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Chapter 5

This chapter synthesizes the information from the three aims addressed in this study, and the implications for nurses, education, and future research.

Aims

This dissertation concentrated on three different research questions, each addressed in a separate paper formatted for potential publication. The aims were:

1. Identify if symptom presentation over the course of influenza-like illness (ILI) can predict virus type in an otherwise healthy military population using unsupervised machine learning; Identify sub-populations with similar symptom experience.
2. Describe the strain-specific clinical characteristics of coronavirus among an otherwise healthy US military population.
3. Examine the psychometric properties of one of the few validated instruments examining disease severity of ILI: the Canadian Acute Respiratory Illness and Flu Scale (CARIFS).

Research Question 1: ILI and Machine Learning

I performed a secondary analysis of ILI symptomatology and virus type from a prospective study conducted by ARIC. The first objective was to identify if unsupervised learning could predict virus type based on physical symptom presentation. The second objective was to determine if I could identify subpopulations with similar symptom experience controlling for virus type.

The symptom severity data from visits on days one, three and seven were analyzed with a novel approach called unsupervised learning by k-means clustering. The clustering method identifies related cases with similar symptoms and clusters the cases together. The symptom scores reported were analyzed individually, and not by a sum of scores to provide more flexibility in cluster creation. The distribution of viral diagnosis was not equal. I observed the highest number of participants in our sub sample as not having a virus diagnosis (289), with the second highest diagnosis being influenza A (107), and the lowest being bocavirus (0).

Clustering was run with *k* values (number of clusters) ranging from 5 to 10. After review of the initial analysis, k=7 appeared to have the most favorable results. Chi square analysis showed that only one cluster had a statistically significant difference ($p<.000$) with a high coronavirus percentage (17.3%) present in the cluster when compared to the rest of the population. With only one cluster showing statistically significant results, the approach was unable to predict virus type based on individual symptom presentation.

The second objective analyzed only patient data for those diagnosed with influenza A, coronavirus, and rhinovirus because they had the largest number of patients. Three separate analyses were run, one for each viral types. The patients were clustered by symptom severity scores, as above, and then their demographic data was compared to against the populations to determine if any clusters represented a specific type of group expression. The demographic data (attributes) included: sex, military status, age, BMI, smoking history, and ethnicity. Due to varying sample sizes the

following virus cohorts were clustered with *k* sets: influenza A (n=107) k=5, rhinovirus (n=101) k=5, and coronavirus (51), k=4.

Fischer's exact tests were performed on the groups with identified different attributes. Bonferroni post-hoc analyses were performed to identify which attributes within the clusters were responsible for causing the differences. The goal was to identify if certain attributes caused a group to cluster together. Analyses revealed each virus had at least one symptom cluster with a statistically significant difference based on patient attributes. Five out of the six attributes in the rhinovirus data showed statistically significant differences (age, BMI, sex, smoking status, and military status). The coronavirus clusters only showed the attribute of sex being statistically different amongst the clusters. The clustered data for influenza A revealed statistically significant differences of the sex and military status attributes.

This research was conducted on a uniform population consisting of otherwise healthy military members, dependents, and retirees. The results of this study can be used to help further understand the characteristics of ILIs in this unique population. A strength of this research was it utilized a novel approach to analyze symptom data for ILI, and identified unique population attributes that may affect symptom presentation.

Research Question 2: Coronavirus

Strain specific differences in the four common human coronaviruses (HKU1, NL63, OC43, 229E) have not been well described in the literature. Utilizing data over a five year period from a prospective ILI study by ARIC the similarities and differences in clinical human coronavirus infections in an otherwise healthy adolescent and adult

military population were described. Demographic, geographic, and potential risk factors were analyzed by strain type using descriptive statistics. The symptom severity data for analysis was obtained from the symptom diaries the patients filled out on a daily basis. Symptom severity for days 1 through 7 were analyzed by system composite score and total score for each strain type. Data was analyzed by either Fischer's exact test (for categorical variables) or Kruskal-Wallis (for continuous variables) to examine clinical symptoms for the different corona strains.

Descriptive analysis showed coronavirus strain 229E was more common in the adolescent population, while OC43 more so in adults. Demographic attributes were not statistically different among the coronavirus strains. Analysis of the system composite scores showed a peak in symptom severity at days 3 and 4, and tended to decrease thereafter. The corona strain, HKU1, did show a statistically significant difference in gastrointestinal (GI) composite scores on day 4 being higher than the other strains, and trended higher through the course of illness when compared to the other strains. The majority of participants (76%) reported lingering symptoms through day 7 of illness.

The strengths of this study was characterizing the epidemiology of symptoms of the four different coronavirus strains in an otherwise healthy adolescent and adult military population. Additionally, this study noted that GI symptoms occur with human coronaviruses, an important finding as most literature on ILI tends to overlook GI symptoms. With the recent outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which are more severe/ less common forms

of human coronaviruses, it is important to understand the epidemiology of all forms of human coronaviruses.

Research Question 3: CARIFS Critique

ILI is the most common diagnosis among children globally, but there are a very limited number of scales to capture ILI disease severity. The Canadian Acute Respiratory Illness and Flu Scale (CARIFS) is one of the very few validated scales available for research and clinics to determine ILI disease severity in children. A psychometric critique of the CARIFS was performed to evaluate its strengths and weaknesses.

Upon completion of the CARIFS critique, many strengths and limitations were noted. Some of its strengths include it being one of the few validated instruments to measure ILI disease severity and some approaches to validity and reliability testing were performed in the Canadian and United Kingdom populations. The scale also had several limitations such as, limited content validity testing, poor administration and scoring instructions, and the concern that contextual information is not captured. Some recommendations for the CARIFS would be to perform factor analysis to confirm the questions are truly measuring the outcome. Additionally, consider the development of another version of CARIFS utilizing the theoretical underpinnings of the Symptom Management Theory.

Implications for Nursing Practice

The results from this study could change how some nurses view ILI symptomatology. The knowledge that patient attributes affect symptom presentation

could change how they approach care for a patient. Additionally, the knowledge of clinical manifestation of the common coronavirus will give them more confidence in caring for people with those common strains.

Most importantly, nurses should be aware of the instruments they use for patient care, patient evaluations, and research. The psychometric critique of the CARIFS showed how an instrument that has been validated can still have numerous limitations. It is important nurses understand how instruments are made and the limitations they may have. If nurses are using instruments to influence change in nursing practice through evidence based practice research, they should perform a psychometric critique of their instruments.

Nurses are now using big data sets, such as patient charts or surveys, to answer questions on patient outcomes. The National Institute of Nursing Research (NINR) has recently added symptom science it its list of innovative questions. They seek to fund studies that address current questions in symptom science such as care models and how outside factors influence symptom management. The NINR has also focused on funding studies that can advance nursing research through data science. There are large and complex datasets available that are potentially rich sources for answering important research questions. The use of unsupervised machine learning is a unique approach to analyze complex datasets. Recent nursing literature has started to note the benefit of using unsupervised machine learning to data mine the large amounts of data that is collected with patient care (Berger & Berger, 2004; Goodwin, VanDyne, Lin, & Talbert, 2003; Meyfroidt, Guiza, Ramon, & Bruynooghe, 2009).

Implications for Future Research

This study showed how different ILI viruses can cause different symptom presentations in the population. Although, the more common approach of unsupervised learning method was used, *k*-means clustering, further analysis with more sophisticated clustering methods should be performed. Understanding how different clustering methods may be able to differentiate virus type based on symptoms presentation may provide important knowledge about the strengths of different clustering techniques as applied to symptom science. Additionally, examining the data with principal component analysis or standard regression to compare findings against unsupervised learning would help further inform the utility of this analytic approach compared to the more traditional ones. Also, comparing the analysis of the symptom score data in a variety of ways, such as the change in symptom score by day or the sum of scores to individual score, may limit the number of variables the unsupervised learning algorithm needs to consider and may produce different results. With the results of the secondary analysis demonstrating the difference in symptom presentation by sex and age, future studies should look at outside factors that may influence symptom presentation.

Future research in the field of symptoms should consider the development of instruments capturing symptom data by utilizing the theoretical underpinnings of the symptom management theory. The theory takes all aspects (social, environmental, biological) of symptom presentation into account. The critique of the CARIFS showed the importance of collecting contextual information in addition to physical data.

Most the viruses captured in this dataset have more than one strain that causes the illness. The number of patients with complete data though limited the analysis that could be performed on the different strains. The small analysis on the four common human strains of coronavirus showed there are differences between symptom presentations. Future research should focus on understanding the clinical characteristics of the different strains of viruses to further our knowledge on symptom experience.

Personal Future Research

As a nurse researcher I plan to continue to expand my knowledge and research in the field of symptomatology. Presently, I will continue working with the ARIC dataset utilizing the unsupervised learning technique to expand my knowledge on this type of data mining and knowledge of symptom presentation. I plan to use different machine learning approaches to have a better understanding of which approach works better for the type of data I am working with. I will further investigate how different attributes lead to different symptom expression in patients. I will also pursue research comparing the unsupervised learning technique and traditional statistical approaches, like regression, to understand the similarities and differences between the approaches.

For my future research, I plan to use this knowledge and integrate the study of symptomatology with genetics. I would like to study how a person's genetics can influence symptom presentation, and determine if symptoms can be prevented or 'turned off.' Additionally, I plan to advocate the need for nurses to understand the science of symptomatology. Nursing programs need to focus on the symptom management theory, so nurses have a baseline knowledge of symptomatology they can grow, and teach their

patients as well. Nurses are currently the main group of healthcare professionals focusing on the study of symptomatology, I plan to embrace that, and continue with pushing our profession forward in this field, so nurses are considered the experts on symptom management.

Implications for Nursing Education

Nurses spend more direct and indirect time with patients than doctors. They track and follow the care of a patient closely, and are typically the first to see a change in a patient's status (DeLucia, Ott, & Palmieri, 2009). It is important for nurses to be able to recognize a change in symptom severity and how different attributes may affect symptom presentation. A slight change in a patient's symptom presentation can be the beginning of a downward spiral for them. The quality of nursing care directly affects patient outcomes.

This research demonstrates the importance for nurses to be educated in the field of symptomatology. Nursing programs should have some course content focusing on the symptom management theory in order for nurses to understand the complex structure of symptom development and presentation. Symptoms typically bring attention to an underlying problem. As nurses, we have to have an understanding of these symptoms that may be warning signs to a potentially lethal problem. Nurses have to look at the overall picture according to the symptom management theory instead of just the symptom itself.

Additionally, nurses should be able to explain the importance of symptom presentation to patients. Patients should be taught about warning signs for resurgence of

conditions or the meaning behind some symptoms experienced. Nurses need to convey to patients to not necessarily treat a symptom of a chronic condition, but understand why it is happening, so treatment of the underlying problem can be addressed and not the symptom.

Conclusion

To summarize, symptomatology is a new field of study that is progressing rapidly. Medical professionals used to treat an individual symptom instead of treating the entire person. For example, if you had pain, you were prescribed an analgesic instead of determining an underlying problem such as depression, may be the etiology of the presenting pain syndrome. Because current research has shown that symptoms are multiplicative, the entire patient, biological, social, environmental, needs to be examined, not just the area of interest.

The three aims of this research have a common theme about understanding the meaning of symptom presentation. As discussed in symptom management theory, to truly understand and manage the treatment of symptoms more than just the physical symptom needs to be considered. By critiquing the CARIFS, it brought my attention to most scales used to examine symptom severity in patients with ILI do not focus on outside factors. By performing the clustering on physical symptoms only by virus type, it proved that unique attributes affect symptom presentation. Additionally, the analysis of the four common strains of coronavirus showed each strain can have a different way of presenting symptoms. This may also be true of other viruses since most of the viruses in

this study had multiple strains. Understanding symptom presentation in different strains may help with treatment management.

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Appendix A

University of San Diego

ENTERED 4/7/16

Institutional Review Board
Project Action Summary

Action Date: April 7, 2016 *Note: Approval expires one year after this date.*

Type: __New Full Review __New Expedited Review X Continuation Review __Exempt Review
____Modification

Action: _X__Approved ___Approved Pending Modification ___Not Approved

Project Number: 2015-04-240
Researcher(s): Monique Bouvier Doc SON
Dr. Mary Barger Fac SON
Project Title: Secondary Review of Acute Respiratory Infection Consortium Study Data

Note: We send IRB correspondence regarding student research to the faculty advisor, who bears the ultimate responsibility for the conduct of the research. We request that the faculty advisor share this correspondence with the student researcher.

Modifications Required or Reasons for Non Approval

None

The next deadline for submitting project proposals to the Provost's Office for full review is N/A. You may submit a project proposal for expedited review at any time.

Dr. Thomas R. Herrinton
Administrator, Institutional Review Board
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Appendix B

INFECTIOUS DISEASE CLINIC
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SAN DIEGO, CALIFORNIA 92134-5000

6500
CCS:JCA:smc
12 September 2016

MEMORANDUM

From: Principal Investigator: CDR John Arnold, MC, USN
To: Chairman, Institutional Review Board

Subj: Notification of USU ID IRB Continuing Review approval

Protocol Number: IDCRP-045
IRB Number: 351726 (USU) and 360479 (NMCSD)
Protocol Title: "The Acute Respiratory Infection Consortium (ARIC) A Multi-center Military Consortium for Clinical Research into the Natural History, Host Response, and Potential Therapy of Acute Respiratory Infection in Military Members and their Families"

Enclosures:
1) USU ID IRB Continuing Review approval letter
2) 2016 Continuing Review report

Per the terms set forth in the Department of the Navy Institutional Agreement for Institutional Review Board (IRB), we would like to inform the NMCSD Clinical Investigation Department of the USU ID IRB approval of the aforementioned protocol continuing review. The Continuing Review was approved by the USU ID IRB on September 7, 2016. CID will be notified of all future approvals from USU ID IRB. Please note that the acting IRB Chairman, CDR Arnold, is the PI on this protocol.

PI: John Arnold, CDR, MC, USN Date

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September 07, 2016

MEMORANDUM FOR TIMOTHY H BURGESS, MD, MPH

SUBJECT: USU USUHS Infectious Disease IRB (ID-IRB) (FWA 00001628; DoD Assurance P60001) Approval of Protocol IDCRP-045 for Human Subjects Participation.

Congratulations! The *Continuing Review* for your Minimal Risk human subjects research protocol IDCRP-045 [IRB# 351726; Ref# 873987] entitled, "The Acute Respiratory Infection Consortium (ARIC) - A multi-center military consortium for clinical research into the natural history, host response, and potential therapy of acute respiratory infection in military members and their families" was reviewed and approved for execution on September 7, 2016 by Kyle Petersen, DO under the provision of CFR 219.110(b)(1)Suppl. F(9). This approval will be reported to the USUHS Infectious Disease IRB (ID-IRB) scheduled to meet on October 13, 2016.

The Natural History Study will: (1) Describe the etiologic, epidemiologic, and immunologic profile of influenza-like illness (ILI) in otherwise healthy adults and children, comparing characteristics of the novel swine-origin Influenza A (H1N1) to other circulating influenza and non-influenza viral pathogens and (2) develop a scale to assess the clinical severity of ILI. Primary Objective for HIV Cohort: To describe the clinical and laboratory characteristics of ILI and H1N1 events among HIV-infected persons. The Family Transmission Study will: Characterize the transmission of influenza within families/households.

This action approves the amendment and continuation of IDCRP-045. The continuing review report indicates that there were 26 subjects enrolled since the last review with 1641 enrolled since activation of the study. This study remains active with ongoing subject participation. Investigators provided a list of adverse events and indicate no changes in the risk/benefits of participation.

Authorization to conduct protocol 351726 will automatically terminate on September 8, 2017. If you plan to continue data collection or analysis beyond this date, IRB approval for continuation is required. Please submit an application for continuing approval to the IRB Office 60 days prior to your termination date.

You are required to submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding this IRB action or questions of a more general nature concerning human participation in research, please contact Crystal Kelly at crystal.kelly.ctr@usuhs.edu or 301-319-0445.

Crystal Kelly
IRB Coordinator

Appendix C

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Nov 23, 2016

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