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Risk Factors Associated With Severe Acute Respiratory Infections Cases

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This is to certify that the doctoral dissertation by

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Abstract

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Abstract

The close proximity of the United States to the Mexican border poses a concern for communicable diseases because of the high flow of population movement. The purpose of this retrospective, quantitative study was to identify risks associated with respiratory diseases using an analysis of archived data from the Severe Acute Respiratory Illness (SARI) surveillance program. Based on the epidemiologic triangle theory, demographic and etiologic factors were analyzed to examine any associations with SARI in this population. Between 2010 and 2012, 798 subjects enrolled in this program, with 336 (42.1%) testing positive for respiratory pathogens. Chi square analysis determined that age (X^2 (4, $N = 786$) = 255.361, $p < 0.001$), clinic location (X^2 (3, $N = 780$) = 290.841, $p < 0.001$), and race/ethnicity (X^2 (4, $N = 762$) = 1456.701, $p < 0.001$) showed significant associations with SARI in the population. The logistic regression model showed that the youngest age group (0-4) had the highest risk of developing SARI compared to other age groups (5-24 *OR* = 0.521, 95% *CI* [0.311-0.871]; 25-49 *OR* = 0.377, 95% CI [0.224-0.636]; 50-64 *OR* = 0.211, 95% CI [0.118-0.376]; >65 *OR* = 0.225, 95% CI [0.143-0.356]. African Americans were also at higher risk of developing SARI compared to Hispanic Americans (*OR* = 3.997, 95% CI [1.272-12.558]. This study promotes positive social change by informing efforts to increase vaccination and health literacy, improve the accessibility and availability of preventive health care in low socioeconomic communities, and promote healthy lifestyles among at-risk groups. These steps will improve the overall health of the communities along the U.S.-Mexico border region.

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Chapter 1: Introduction to the Study

Background

One of the biggest concerns of the modern era is the effect of communicable diseases on the global population and ensuring that proper surveillance is practiced in order to keep communicable diseases at bay. Proper enhancement of respiratory disease surveillance permits the assessment of multiple determining factors that affect disease activity (Ortiz et al., 2009). These factors include the differences in effectiveness of disease control measures, such as social distancing and vaccination between developed and underdeveloped communities. Disease surveillance efforts must be sensitive to the real number of cases through adequate surveillance techniques employed. Surveillance can include accurate case definitions and effective surveillance protocols, especially in certain regions of the United States such as the U.S.-Mexico border, where there is an increased population movement and incidence of communicable diseases.

There was a significantly increased incidence of vaccine-preventable diseases in major U.S. counties within 100 kilometers from the border between 1990 and 1998 (Weinberg et al., 2003). There are a number of factors that contribute to the increase in incidence of acute respiratory illness (ARI) seen along this region of the United States, such as poor health care facilities and services that would provide the necessary preventative and medical care for the population living along the surrounding communities. In addition, some of the lowest socioeconomic communities lie along the U.S.-Mexico border region, which spans over 2,000 miles from the southern tip of Texas to the Pacific Coast in California (Weinberg et al., 2003). The unique composition of the population residing along the communities of this region often times live below the poverty level, with much of the general population having a lower educational attainment when compared with the rest of the United States (Joseph, 2010). For example, the average yearly income of the Hispanic American population (the country's largest minority group) living along the border communities is only $14,560, which is far below the national average income of $50,000 (Joseph, 2010). Due to the high poverty level in this region, the population is medically underserved, leading to higher uninsured rates and inequitable health conditions.

Another factor that increases the incidence of communicable diseases in this region is the failure to meet the necessary vaccination coverage for children under the age of 5 years. According to the California Department of Public Health (CDPH, 2011), the number of kindergarten students with personal belief exemptions for the recommended vaccines during childhood nearly tripled in San Diego from 1.09 to 3.15% between 2000 and 2010. This decline in vaccine coverage in children has led to an increasing incidence of pertussis cases in San Diego that reached epidemic levels in 2010 (CDPH, 2011). Despite the United States' nationwide Healthy People 2020 Initiative to increase vaccination coverage, by March of 2011 only 43 % of the people across all age groups in the United States were shown to be immunization-covered (Centers for Disease Control and Prevention [CDCc], 2011). Another factor that can contribute to low vaccination coverage among the population is the availability and convenience of getting the vaccine to the population living in low socioeconomic status (SES; Lin et al., 2006). Korschun (2011) found that the disparities in minority and low SES people were largely due to the limited availability of vaccines in community clinics and the increasing costs of getting the recommended vaccines, which make it much more difficult for people living in these communities to receive them.

Other factors that contribute to the low vaccination coverage include fear and negative perceptions that vaccines may actually cause other diseases. These factors prevent many people, especially parents, from getting the vaccines for themselves and their children. For example, there are prevalent myths that vaccines may revert back to the virus' wild type, thereby causing the disease that the vaccinations were designed to protect them, despite several studies to the contrary (Tosh, Boyce, & Poland, 2008). Other concerns are fueled by misconceptions about vaccines, such as opting out of immunizations because of a belief that they are not necessary due to the diseases disappearing. Many members of the U.S. general public, especially parents, have reasoned that improved hygiene and sanitation in developed countries have eliminated vaccine-preventable diseases, making vaccines unnecessary (CDCc, 2011). Religion also has a strong potential to affect how people decide whether vaccinations are necessary. For example, more parents are filing for vaccine exemptions on the basis of religious and personal beliefs in order to refuse mandated childhood immunizations for school entry. According to Shelton, Snavely, de Jesus, Othus, and Allen (2011), 48 out of 50 U.S. states allow some form of nonmedical exemptions; exemption rates are as high as 15-18% in some geographic clusters or communities, thereby significantly increasing the percentage of unvaccinated children attending public schools in the United States.

Researchers have shown the effectiveness of immunizations against infectious diseases, not just coverage for those who receive them. By offering protection for those who are not vaccinated, a term often referred to as herd immunity a secondary protection can manifest when the majority of the population is vaccinated (Hoke, Hawksworth, & Snyder, 2012). In the United States alone, the total number of reported pertussis cases prior to the introduction of the whole cell pertussis vaccine into the population during the 1950s was approximately 200,000 annually (Bamberger & Srugo, 2008). After the introduction of the pertussis immunization program, the incidence of reported pertussis cases gradually declined to a low of 1,010 reported cases in 1976 (Bamberger & Srugo, 2008). Despite the effectiveness of such immunization programs, the contributing factors to vaccine nonuse has produced an overall vaccination coverage of the U.S. population far below the objective value presented in the Healthy People 2020 Initiative (Health and Human Services [HHS], 2012).

Despite the growing concerns of increasing incidence of communicable diseases seen along U.S. border counties, there are no established infectious disease surveillance systems implemented to address the border population (Arizona Dept. of Health Services [AZ DHS], 2013). In addition, there are no accurate depictions of the true incidence rates of the communicable diseases because of differences in surveillance case definitions between the United States and Mexico for reporting certain diseases (Weinberg et al., 2003). The result of these factors is an inaccurate description of the communicable disease incidences between the two countries due to incomplete and/or limited border surveillance data, therefore diminishing the usefulness and understanding of the epidemiology of infectious diseases along these regions, as well as effective preventive measures in trying to minimize its impact.

An active disease surveillance system that is both accurate and consistent is needed to effectively control and prevent the spread of communicable diseases across geographical boundaries. This need is especially acute in the context of U.S. counties bordering Mexico. In 1997, the CDC and the Mexico Secretariat of Health agreed to an initiative that would establish a standardized, binational surveillance system for infectious disease epidemiology. Designated as the Border Infectious Disease Surveillance (BIDS), the program allowed both countries to bridge the surveillance gap through sharing of experiences in both syndromes and laboratory-based efforts of local, state, and national public health officials and laboratory scientists (Weinberg et al., 2003).

In 2010, new program was developed as a part of the larger BIDS program spearheaded by the CDC and the Mexico Secretariat of Health. The Severe Acute Respiratory Illness (SARI) surveillance program was developed specifically to increase the surveillance for people with influenza-like illness (ILI) from both viral and bacterial etiology (McCotter et al., 2011). The World Health Organization (WHO) defines ILI as someone who has a temperature of 100.5°C or higher, cough, and/or sore throat without known cause other than influenza (Ortiz et al., 2009). By general standards set forth by both public health agencies, case definitions for severe acute respiratory illness (SARI) fall into two categories depending on the age of the person. For a person who is over 5 years of age, the case definition for SARI includes ILI and hospital admission. Under the age of 5-years-old, the case definition is ILI, clinically suspected of having pneumonia and requiring hospital admission.

Problem Statement

Acute respiratory infections are among the most common types of illnesses among persons of all ages, with approximately 2 million deaths occurring annually worldwide in mostly elderly and younger children (Kammerer et al., 2011). The majority of both morbidity and mortality from acute respiratory illnesses fall among people living in low SES communities, where there is a lack of necessary access to preventive and medical services (Joseph, 2010). With a span of over 2,000 miles, the U.S.-Mexico border includes a unique composition of communities often living below the poverty level. In addition, the U.S.-Mexico border is one of the highest traffic border in the country, with approximately 90 million international land border crossings occurring in 2005 alone, accounting for over 30% of all international entries into the United States (Waterman et al., 2009). Furthermore, the San Ysidro border crossing alone hosts over 41 million northbound crossings occurring every year (Weinberg et al., 2003). This high traffic can pose a serious concern for introducing communicable diseases into the population living along the border region.

The high volume of population movement across the U.S.-Mexico border can be attributed to different factors, including tourists visiting regularly to shop, visits to family members, legal migrant workers, and entrepreneurs who seek to do businesses along the border communities. From an epidemiologic perspective, the high volume of population movement across the international border presents a concern over the spread of numerous infectious communicable diseases. Because infectious diseases are not limited by geographical borders, this region of both countries poses a high risk zone for transmitting communicable diseases, especially within communities of low SES as they pose the highest disease susceptibility due to the lack of proper medical and preventive care.

It is important to examine land border crossings from an infectious disease epidemiologic perspective because the migration of people carries the possibilities of spreading of communicable diseases from a population of low to high susceptibility (Heymann, 2008). Some of the people who are traveling in and out of the country are potential carriers of a disease, even though they might seem asymptomatic. In a study in Tanzania, Quintero et al. (2011) showed that 35% of healthy children under the age of 5 were asymptomatic carriers of *Streptococcus pneumoniae,* a pathogen that causes significant morbidity and mortality worldwide. In addition, the incidence of pertussis in adolescents and adults in United States has steadily increased since the 1980s (Bamberger & Srugo, 2008). These factors suggest that a significant portion of border crossers carrying infectious diseases without being aware of this.

Over the past 15 years alone, the incidence of reported cases of pertussis in the United States has risen to an alarming rate, from 1.4 to 12.3 per 100,000 to about 26.5 per 100,000 in 2004 (Bamberger & Srugo, 2008). Furthermore, in 2008 alone, there were more than 13,000 reported cases of pertussis to the CDC nationwide, with the majority of these cases belonging to the adolescent and adult age groups. The number of reported cases of pertussis in the United States increased nearly 19-fold in 2004 for the 10-19 age group, and 16-fold in those over the age of 20 years old (Tartof et al., 2013). Based on these studies, it is clear that there is an upward trend of pertussis cases from previous years, which is of great concern epidemiologically especially in poorer communities that lack adequate vaccine coverage in children.

The burden of communicable diseases is more severe in younger children, compared to members of older age groups. The WHO reported recently that there were around 48.5 million cases of pertussis annually worldwide, with as much as 295,000 case fatalities occurring each year (Ghanaie et al., 2010). Although the disease can occur at any age, most of the cases of serious pertussis disease and fatalities occur in infancy, especially in preterm and nonimmunized infants (Ghanaie et al., 2010). In a 10-year pertussis surveillance program in Sweden, infants between the ages of 3 and 5 months had an incidence rate of 264 per 100,000 for unvaccinated infants, while infants 5 months and older had an incidence rate as low 24 to 95 per 100,000 (Nilsson, Lepp, von Segebaden, Hallander, & Gustafsson, 2012). Although the rate decreases with age, the incidence rate among adolescents between the ages of 11 to 18 years went from 1.7 per 100,000 in 1994 to 5.5 in 2009 (Schoff, Cohn, & Clark, 2012). As shown, it is the youngest children that are most at risk for both morbidity and mortality associated with pertussis in the U.S.

For influenza, border surveillance has reported an elevated rate when compared with the national average. According to Kammerer et al. (2011), about 25% of all border samples tested were positive for influenza between 2004 and 2009. When compared with the national statistics from CDC, the national average for influenza during the same time ranges from 13 to 18 % (CDCb, 2014). There is an increased rate of influenza infection around the communities along the U.S.-Mexico border region, which poses an epidemiology concern for the rest of the country.

Populations from poor and developing countries, such as Kenya and Mexico, are not the only ones susceptible to communicable diseases. Researchers have indicated significant travel-related illness in children who routinely travel internationally with their parents and families. Hagmann et al. (2010) demonstrated that a significant number of children from developed countries were hospitalized within 7 days after returning from visiting family and relatives abroad. Among the children studied, roughly 11% who were hospitalized due to some type of respiratory disorders had previously traveled from Europe and North America to countries in Africa and Asia. Increasing the vaccination rates of children in poor and developing countries can lower the incidence of transmission of communicable diseases among traveling children by lowering the chances of such transmission from occurring.

Several factors can play a role in the spread and acquisition of communicable diseases. From low SES to age dependency, the differences in the composition of many communities can have different factors that affect how the communicable diseases are introduced and spread into the surrounding populations.

Purpose of the Study

Due to the different demographic profiles that exist along the U.S.-Mexico border region, it is imperative that more studies are conducted to identify and/or determine whether there are significant associations between factors such as SES, education attainment, age, and/or vaccine history among people who are enrolled in the SARI surveillance program. The intention of this quantitative study was to explore and correlate the demographic information collected from the SARI surveillance program to each of the potential respiratory pathogens identified. I gathered previously collected data from SARI cases enrolled in the surveillance program and used this information to construct an accurate and descriptive profile of the study population for use by public health officials in the prevention of the acute respiratory diseases.

Research Question and Hypotheses

The primary research question guiding this study was “Is there an association between possible demographic (age, gender, location, etc.) and etiologic factors (such as vaccine history), clinical symptoms present during enrollment, and the incidence of severe acute respiratory illness among SARI cases along the United States-Mexico border region?”

The null hypothesis for the study was that there is no statistically significant association between demographic and etiologic factors, and the incidence of SARI cases among the population living along the U.S.-Mexico border. The alternate hypothesis was that there is a statistically significant association between the risk factors and the SARI cases enrolled in the surveillance program.

Theoretical Foundation

The infection and spread of communicable diseases occur when a suitable environment is present for susceptible hosts to interact or come in contact with an infectious agent. The epidemiologic triangle model explains the mechanism for infection and spread of diseases as consisting of an external agent, a susceptible host, and a proper environment that allows the interaction of both host and infectious agent (CDCa, 2012). According to this model, diseases do not occur randomly in any given population at any given environment, occur as a result of all three aspects of the epidemiologic triangle being present. Certain things from each aspect of the triangle are required, such as susceptibility of hosts and virulence of the pathogens, as well as geographic and climate factors that promotes the proper interaction between host and agent. .In any given population, there are certain factors (e.g., demographic and etiologic) that are present and permit the spread of communicable diseases, which is why it is important that these risk factors be identified in order for proper prevention.

Nature of the Study

For this epidemiologic study, I conducted a quantitative, retrospective analysis in order to assess the multiple variables previously collected during enrollment of subjects into the SARI surveillance study. When the participating clinic sites were presented with potential subjects for this earlier, the patients were evaluated for inclusion into the study by trained research assistants using SARI case definitions described previously. Once they met these case definitions for SARI, they were assisted in completing a case report form where the enrolled subjects answered various categorical variables. These variables include the age and nationality of the subjects enrolled, gender, flu vaccine status, as well as current symptoms experienced when presented to the clinic. These variables will be further discussed and/or defined in the following sections of the study. Afterwards, nasopharyngeal and throat samples were taken from each of the enrolled subjects and were immediately placed in ultra-low (-80°C) freezers until the samples were shipped to the laboratory in dry ice for testing. The details of how these samples were tested will be further discussed in the methodology section of the study.

Definitions

Bacterial culture: A general set of testing methods that include isolating bacteria in nutrient rich agar and using biochemical tests for identification (Weinstein et al., 1997).

Influenza immunization: An influenza vaccine available yearly that is specific for the predicted circulating strains. The yearly vaccination is comprised of two components of influenza A (H1N1 and H3N2) and an influenza B that is decided by the CDC and other public health agencies based on influenza data from previous years (Morbidity and Mortality Weekly Review [MMWR], 2013).

Influenza-like illness (ILI): A clinical definition set forth by WHO as someone who has a temperature of 100.5°C or higher, cough, and/or sore throat without known cause other than influenza (as cited in Ortiz et al., 2009)

Polymerase chain reaction (PCR): Molecular procedures for identifying respiratory pathogens that use molecular methods of amplifying pathogenic genome for proper identification (Post & Elhrich, 2000).

Respiratory illness: Respiratory distress that is caused by both viral (such as influenza and adenovirus) and bacterial (such as *Streptococcus pyogenes and Streptococcus pneumoniae*) pathogens (Kammerer et al., 2011).

Severe acute respiratory illness (SARI): An ongoing respiratory disease surveillance program conducted between the CDC and the Operational Infectious

Diseases (OID) of the Naval Health Research Center (NHRC) situated in San Diego, CA (Kammerer et al., 2011).

United States-Mexico border region: For the purposes of this study, this term refers to the communities located along the U.S. side of the U.S.–Mexico border, spanning across multiple states that include California, Arizona, New Mexico, and Texas.

Viral culture: A general set of testing methods that include isolating viruses in mammalian cell lines and identifying pathogens using viral specific immunofluorescence staining procedures (Weinberg et al., 2004).

Scope and Delimitations

Because the purpose of the study was to identify potential risk factors present in the population living along the United States-Mexico border region, retrospectively evaluating the SARI cases collected thus far permits for such factors to be acknowledged. The subjects that were included in this surveillance study were all living within a few miles from the border, and some were frequent border crossers for various reasons. Their close proximity to the border regions of the country allows for the interaction of populations between the two neighboring countries, in which introduction and spread of communicable diseases are practically common. In addition, the impact of the low SES among the people living in these communities along the border permits researchers to address the impact of their status to the underlying health disparities that are seen among this population group, such as the availability of the yearly influenza vaccinations and their probability of acquiring influenza-related illnesses.

The populations subjected to the SARI surveillance are only those that live in close proximity along the U.S. side of the border; therefore, this population does not represent the general population of the entire country. Consequently, whatever conclusions might be generated from this study cannot be used to construct inferences for the population of the entire country, as well as populations from communities of different locations and status. Because of the differences in the availability and accessibility of health care in more affluent communities , the same conclusions drawn from this study cannot be used to represent other populations aside from those belonging to the mentioned communities.

Limitations

Upon the presentation of potential subjects to any of the participating clinical sites, some of the variables collected by the research assistants during enrollment rely on the recollection of subjects' memories. This includes questions such as whether they had received the influenza vaccine within 1 year or the type of influenza immunization they have received (either traditional vaccination or intranasal injection). Furthermore, other questions included in the questionnaire are the frequency of visits across the border, as well as whether they have experienced the clinical symptoms during their current illness. Because of these limitations, the research assistants assessing for potential subjects and collecting variables and laboratory samples are highly trained individuals who can explain and help in completing the questionnaire form that comes along with laboratory samples for each subject enrolled.

Many of the subjects seeking medical attention to these clinic sites have limited a capability of communicating due to a language barrier. Because the clinic sites are in close proximity to the U.S.-Mexico border, many of them are able to communicate in Spanish language, but communications in English can be difficult. Some sites have addressed this issue by having research assistants who are fluent in the Spanish language, or they may have someone in the clinic staff that can translate to the potential subjects. In any case, the language barrier can be a significant limitation in the ability to collect accurate data from the subjects being enrolled into the study.

Bias can also be introduced in the study with the rapid flu tests and laboratory testing performed in the laboratory. Although not all enrolled people are subjected to rapid flu testing done onsite in the clinics, some of them are screened for influenza during their visits. The clinic sites employ rapid flu testing using a fluorescent immunoassay from Quidel (San Diego, CA) called Sofia Influenza A+B FIA. This rapid on-site influenza assays have an overall sensitivity and specificity for influenza A of 94% and 95% and for influenza B of 89% and 96%, respectively (Lewandrowski et al., 2013). Although these kits have shown a high degree of both sensitivity and specificity, incorrect sample collection and method of use can alter the accuracy of the assay.

Moreover, the various laboratory testing occurs at the Naval Health Research Center, San Diego after they receive the frozen samples, which can also alter the results. First, improper collection and storage of samples to be sent to the laboratory can affect the results of tests performed. The incorrect method of collecting nasopharyngeal samples, as well as using incorrect transport medium, can limit the ability to accurately obtain results. Proper storage of collected samples until shipment is also important to preserve the integrity of the samples. When samples are not going to be shipped the same day, they are to be stored in -80°C ultra-low freezers onsite until they are shipped in dry ice. To address this issue, all research assistants are properly trained on the methods of collection, storage, and shipment of samples.

Along with the specimens are laboratory requisition forms that contain collected information from each subject enrolled. Because these are paper-based forms, it may require some data cleaning prior to running statistical tests in order to obtain accurate results. Because a few of the collected variables are not dichotomous (yes/no) when scanned into the database, it might need to be cleaned so that all inputs match, such as spelling or capitalizations. Precise scanning forms using the teleform software might cause a few irregularities when uploading scanned data that might require manual corrections. These corrections are done when samples are being checked in for laboratory testing by trained laboratory personnel, who manually correct them by referencing the actual forms. Although minimal, these irregularities might cause the analyses of the data to be inaccurate if not corrected properly.

The most important part of the study is the clinical testing of all collected samples from the sites. Improper methods of testing the samples, both cultural and molecular methodologies, can affect the outcome if not performed properly. Because all samples are tested using culture methods for bacterial and viral, as well as molecular methods, using polymerase chain reaction (PCR) technology, it is important that they must be tested accurately. This is addressed through the accreditation of all laboratory testing by the

College of American Pathologists (CAP), a medical society that is recognized worldwide for assuring the quality of all laboratory practices. Its rigorous qualifications and inspections allow laboratories to maintain high quality practices through routine on-site inspections every 2 years in order to assess the laboratories' compliance with their rules and guidelines. Examples of these rules and guidelines include training records of all personnel performing the testing, as well as records of all quality control measures (both reagents and equipment) performed in order to maintain high standards in laboratory practices. In addition, all laboratories participate in biannual proficiency testing of all accredited tests with a passing score of 80 % or higher. These proficiencies consist of receiving unknown samples in which the laboratories must perform laboratory testing to determine the identification of certain pathogens, if any. When laboratories fail to achieve the passing score, they are required to evaluate the problems in laboratory protocols in order to identify what went wrong, as well as corrective actions required in order to amend them.

Significance

Knowing potential risk factors of any diseases will allow public health officials to employ practices and policies that will not only address the treatment, but also enable them to use preventive measures in order to minimize the exposure and likelihood of acquiring these diseases. This is especially true in communities similar to those found in the border region areas, where low SES communities often lack the necessary public health infrastructures and access to quality health care. It is important that existing practices used by public health officials be aligned and/or adjusted so that the problem with communicable diseases is addressed in this unique population, especially children and elderly who are at the highest risks for communicable diseases. Proper prevention practices, such as vaccinations, will allow public health officials and health care professionals to combat the spread of these morbid diseases in the most susceptible populations worldwide. Because there are millions of communities that reflect socially and economically those found in communities along the U.S.-Mexico border region, similar preventive measures that proven effective can be employed in order to address the same concerns regarding the spread of communicable diseases in their own communities.

The lack of adequate medical facilities in these communities have prevented public health officials from obtaining an accurate count of communicable diseases, thereby potentially underestimating the true incidence of diseases along this region of the country. By identifying these risk factors, they can model and utilize improved case definition through better understanding of certain diseases and pathogen, which will ultimately allow for a more accurate epidemiologic surveillance capacities along these border communities.

Summary

The population living along the U.S.-Mexico border includes a distinct composition of people that allows for unique epidemiologic surveillance studies. These communities live below the poverty levels, with millions of border crossers due to tourism and occupational opportunities; this situation offers a unique opportunity for the transmission of communicable diseases from one population to another. The interactions that occur between the distinct populations along the border regions enable certain diseases to be introduced, as described by the epidemiologic triangle of communicable diseases. Its unique hosts and suitable environment gives these pathogens the opportunity to interact and infect susceptible hosts, thereby allowing the disease cycle to continue.

The proper identification of potential risk factors must be determined in order to reduce the probability of interactions occurring between hosts and diseases. Using the knowledge gained from such studies, public health officials can introduce new and/or amend existing policies that will minimize the impact of diseases in susceptible populations. However, in order to advance with the study, it is important to understand previous similar studies done with homologous population. Using the knowledge from previous studies, a better understanding of the problem with communicable diseases in this population can be used to formulate a unique study that would help identify gaps in the knowledge, which will be highlighted in the following chapter. Following the theoretical foundation of the epidemiologic triangle, potential factors can be identified that might contribute to the incidence of severe acute respiratory illnesses being seen today.

Chapter 2: Review of Literature

Introduction

Acute respiratory infections are among the most common types of illnesses among people of all ages, with approximately two million deaths occurring annually worldwide among mostly elderly and younger populations (Kammerer et al., 2011). It is especially important to address this in communities along the United States-Mexico border because of the vast amount of population movement occurring annually from one country to another. In 2005, approximately 90 million international land border crossings occurred, accounting for over 30% of all international entries into the mainland United States (Waterman et al., 2009). The San Ysidro border crossing is one of the busiest U.S. border crossings on the U.S.-Mexican border, with an estimated 41 million northbound crossings from as tourism, visiting family members, legal migrant workers, and people seeking entrepreneurial business visits along border communities (Weinberg et al., 2003).

The high volume of population movement along the U.S. border poses an epidemiological threat to U.S. communities living along the border because of the significantly elevated capacity of spreading communicable diseases from one side of the border to another. According to the U.S. National Notifiable Diseases Surveillance System, between 1990 and 1998 there were significantly increased incidences of vaccine-preventable diseases in major U.S. counties that lie within 100 kilometers from the border (Weinberg et al., 2003). The severe acute respiratory infection (SARI) surveillance program organized by both Centers for Disease Control and Prevention (CDC) and Mexico Secretariat of Health in 2010 was designed in part to address this problem.

However, at the time of this study there was only a very limited number of extant studies designed determine potential risk factors for acute respiratory diseases among the population living along the border communities.

These factors showed a strong need for a retrospective study for identifying potential risk factors is necessary to provide important information that could be utilized to increase the preventive capacities of local health officials. Through quantitative research, it allowed the identification of potential demographic and etiologic risk factors for SARI. In this chapter, I covered methods for literature search strategy, discussed the theoretical prospective for the study and individual risk factors associated with the study. This permits public health officials to identify and fill gaps in health care prevention by examining relationships between respiratory diseases and identified factors that might increase people's risks of acquiring these types of diseases.

Literature Search Strategy

Working in a research and surveillance laboratory funded by the federal government, it allowed me to have unlimited access to wide selection of paid subscriptions for scientific literatures. Because of this advantage, searching for previous literature related to the topic using these search engines was made possible. I was also able to take advantage the center's on-site library; if an article was inaccessible online, I submitted requests that allowed me to obtain both electronic and paper-based copies of the articles requested. I used search engines from the U.S. National Library of Medicine (NIH), which includes PubMed Central and Medline; Oxford Journals; Cambridge Journals; JSTOR; and PlosOne. With these search engines, some of the key terms used in searching for articles include *SARI*, *communicable diseases in United States-Mexico border*, *diseases and SES communities*, *vaccine coverage in U.S. and Mexico*, *epidemiologic triangle of diseases*, *adenovirus vaccine in military population*, and *BIDS study CDC*. In addition, certain key terms to search for general information such as population and poverty information from credible sources such as government (state and federal) was conducted using the google.com and scholar.google.com search engines.

Most of the searches were filtered so that peer-reviewed literature within the past 5 to 6 years was included as the primary basis for this literature review. However, a few articles were included outside this perimeter, but only to support key ideas and theories such as susceptibility of infants and elderly to certain communicable diseases. These literature searches allowed me to determine of the gap in the knowledge being addressed in this study, as well as theoretical foundation needed to determine which factors are to be explored which will all be discussed further in the following sections.

Theoretical Foundation

The theoretical foundation for this study was the epidemiologic triangle model, one of the simplest models of infectious disease causation. According to this model, the main factors in causing a disease are grouped into a triangle consisting of an external agent, a susceptible host, and a suitable environment that permits the interaction between the host and disease agent (Ferng, 2013). The transmission of communicable diseases does not occur randomly in any given population, but with the help of numerous factors that work synergistically to allow this specific event to occur. When the proper interaction occurs between the host and agent under suitable environment, this allows the transmission of infectious diseases from infected to susceptible hosts, thereby spreading the communicable diseases into the population. Many factors within the epidemiologic triangle can influence the interaction of host and diseases from occurring. These factors include environmental or host specific, from geographical and climate factors (Altizer, Ostfeld, Johnson, Kutz, & Harvell, 2013), to genetic factors and immunological status (Zhernakova, van Diemen, & Wijmenga, 2009) of the hosts or population. Any combination of these factors, both environmental- and host-specific, provides the necessary conditions that permit the spread of infectious respiratory diseases into the population (Gould & Higgs, 2009).

The host is the first important factor in the epidemiologic triangle because it describes the influences, behaviors, or genetic factors that increase the susceptibility of certain people to the causative agent (Ferng, 2013). These risks include factors such as age and gender, immunologic status, ethnicity, and behavioral factors that can all play major roles in determining how susceptible a particular population is to a disease agent. For example, certain respiratory diseases have been shown to be more age and gender specific under permissible conditions. For example, the incidence of ARI was found to be the greatest among children and elderly living in under-developed countries (Tupasi et al., 1990). In addition, there is a significant increased risk of lower respiratory illness (LRI) among young boys compared to girls, a trend that is shown to be the opposite among children with upper respiratory infection (URI; Koch et al., 2002). The greatest risk for both LRI and URI are among children between the ages of 6 to 11 months old with declining risks in older age groups, possibly be due to factors such as cessation of breast-feeding and attendance of child-care centers. Age-related susceptibility to certain respiratory illness are due to numerous factors such as under-developed immune systems among younger children, as well as weakened or immunocompromised elder population because of the presence of chronic and debilitating diseases that affects their immune responses (Koch et al., 2002).

The second contributing factor to the epidemiologic triangle consists of environmental factors physical (climate and geography), biological (insect vectors), socioeconomic (health services availability), and cultural factors (Ferng, 2013). Overcrowding and poor access to proper medical services can increase the chances of acquiring infectious diseases among vulnerable populations (Korschun, 2011). A perfect example of how overcrowding can increase the spread of communicable diseases in a given population is the military recruit training centers. Because certain viruses are able to stay viable for a few hours, viruses are easily spread through direct contact or through fomites touched by infected recruits or personnel. According to Kajon et al. (2010), the close proximity of recruits to one another in their daily training tasks increases the risk of a novel and emerging adenovirus type 14 in all 8 training sites surveyed.

This problem was evident with the recent reinstatement of the live, oral adenovirus vaccine for types 4 and 7 into the military recruit population. When the production adenovirus vaccine was halted during the late 1990s, there were evidences of markedly increased incidence of febrile respiratory illness (FRI) in subsequent years at basic training sites (Hoke et al., 2012). In addition, reports of outbreaks and deaths associated with adenovirus were identified during the years following the cessation of vaccine production. In March of 2011, after exhaustive efforts by both military surveillance centers and Barr Pharmaceuticals (makers of the current vaccine), a two-tablet live adenovirus vaccine was approved by the United States Food and Drug Administration (FDA) for market sales, and introduced to new incoming recruits (Hoke et al., 2013). Ever since the introduction of the vaccine, there was a remarkable decrease in the incidence of adenovirus 4 and 7 related FRI in recruit populations.

Furthermore, population movement from one location to another can affect the host specificity of certain diseases, more particularly when disease carriers move to a more susceptible population. Asymptomatic carriers of respiratory disease etiology are prime candidates for spreading these diseases (Ortiz, et al., 2009). According to Erdem et al. (2010), a high rate of asymptomatic Group A streptococcal (GAS) pharyngeal carriers exist among children surveyed in both Hawaii and American Samoa, where high rates of acute rheumatic fever exists. In addition, rhinitis, which is common in preschool children, was found to be associated with nasal bacterial colonization and respiratory viruses in what many dubbed as asymptomatic children (Fernanda et al., 2013).

Certain cultures bounded by geographical locations can also affect the ability of transmissible diseases within the population. For example, in countries where gender equality is uncommon, specific factors not often found in developed countries are more likely to permit the transmission of diseases in certain population. Courtwright and Turner (2010) concluded that cultural factors affect the transmissibility of communicable diseases because gender roles within certain cultures often increase their exposures, or limit their treatment options. Courtwright & Turner (2010), for example, concluded that in traditional cultures, women who remain at home have lower exposure rates than men to some diseases that might be present in the general population. Furthermore, women with infectious diseases are often hindered by fear and stigma from seeking medical attention, thereby putting themselves and their children in precarious situations.

A prime example of the epidemiologic triangle in action is the 2002 global outbreak of severe acute respiratory syndrome (SARS) that had started in China. A previously unrecognized animal strain of coronavirus, the SARS virus affected over 8,000 people in 25 countries across five continents, with about 774 case-fatalities by the end of 2003 (Peiris, Guan, & Yen, 2004). This novel virus was phylogenetically distinct from previous strains of human coronavirus, which explains its virulence across the globe; most of the people were immunologically susceptible to the virus, which caused it to spread more widely. Tourists from all over the world who visited China contributed to the global outbreak of SARS virus across continents including Europe and North America (Peiris et al., 2004). A more recent issue stems from the novel coronavirus that originated in the Middle East, which many experts claim to be more dangerous than the 2002 SARS virus. Dubbed as the MERS-CoV, there has been a total of 64 laboratory confirmed cases of MERS-CoV infection across countries in the Middle East, with 38 deaths associated from the virus (MMWR, 2013). The mortality rate of MERS-CoV was shown to be about 40%, which is higher than SARS with a 10% mortality rate (MMWR, 2013).

In relation to the present research study, the unique nature of the existing population living along the United States-Mexico border allows for completion of the epidemiologic triangle, thereby increasing the risk of transmission of communicable diseases. Both host susceptibility and environmental factors play a dramatic role in the occurrences of highly communicable diseases in this region of the country. Although presently unknown, certain host factors such as age, gender, and immunologic status, as well as environmental factors including population migration, lack of proper health services, and other socioeconomic factors, can play a significant role in the prevalence of respiratory illnesses in this region. It is imperative that both host and environmental risk factors be determined in order to help public health officials reduce the incidence of respiratory illnesses in this part of the country, as well as utilize the same preventive practices in other parts of the world that have similar population dynamics.

Risk Factors for SARI

Age Group

Since the initiation of the program in 2010, there has been limited understanding in what risk factors affect SARI patients in relation to the respiratory diseases acquired. However, there have been numerous studies that have tried to determine the contribution of different respiratory diseases to different populations who have been affected by SARI. For example, Iwane et al. (2011) had compared the severity of human rhinovirus (HRV) associated with hospitalization among young children residing in three geographic areas of the U.S. They saw that there was four-fold increased rates detected among children two years or older that were hospitalized compared to the control (asymptomatic) group. Similar trend was seen for children who tested positive for other viruses such as respiratory syncytial virus (RSV), parainfluenza virus, and influenza virus, which were hospitalized after presenting severe acute respiratory illness. In short, they developed a model that had shown no significant difference in clinical indicators of severity across different species of HRV, as well as between HRV and other respiratory pathogens that cause severe respiratory illness (Nascimento et al., 2010). Nevertheless, the analyses only occurred among children's age, which makes other risk factors unidentified by this study. There was no significant data on other demographic categories such as availability of medical services and vaccination data from children (both hospitalized and control groups) that were analyzed.

Disparity in the proportion of people that have access and availability to the yearly influenza vaccine can also affect the rate of acute respiratory distress in many different populations. Since its development during the 1950s, it has been shown to have about 70–90% effectiveness in preventing influenza illness among healthy adults (Coady et al., 2008). In addition, children seem to be the most susceptible to acquiring influenza illness because of their under-developed immune system (Koch et al., 2002). It has been shown that roughly 42% of all preschool and school-aged children are prone to getting sick from influenza yearly because it is easily transmitted from one child to another (King et al., 2006).

Furthermore, researchers had indicated that over half of the influenza hospitalizations were among children for whom the available vaccines are recommended and encouraged for (Hassan, Lewis, Davis, Gebremarian, & Dombkowski, 2009). It has been estimated that the average influenza hospitalization costs during the flu season had been around $76.5 million annually, with over half of these costs were from the children between the ages of 6 months to 18 years old (Gooskens et al., 2009). There have been many studies conducted with the effort to explore the potential reasons for this disparity. The New York Academy of Medicine had determined that many of the parents of the unvaccinated, frequently ill children had fewer reminders and recommendations from their primary care physicians, as well as availability and convenience of getting the immunizations (Lin et al., 2006). In addition, some studies have also shown that people belonging in low socioeconomic communities have far less access to hospitals and clinics that offer free or inexpensive preventive care than those from higher socioeconomic levels (Korschun, 2011; Egede & Zheng, 2002).

The elderly population is also at high risk of acute respiratory illness given their declining health status. There are numerous factors that can contribute to this such as weakened immune system with the presence of chronic illness, medications, and poor access to preventive health clinics (Felkin et al., 2012). This means that acute respiratory illness-induced morbidity and mortality is often high in individuals who are 65 years or older, which has been increasing over the past several decades. In fact, pneumonia and influenza cause an average of 36,000 deaths every year in USA, with almost 90% occurring in elderly populations (Cohen, Agree, Ahmed, & Naumova, 2009). This is a growing concern because with the population expected to have increased lifespan, the likelihood of these elderly becoming exposed to diseases increases as well. Diseases are of great concern because elderly people often have longer recovery time, slow and poor response to treatments, and increased susceptibility to infectious diseases (Larbi et al., 2013). All of these factors have significant effects on how elderly people react and cope with numerous infectious diseases.

Furthermore, the interactions between children and elderly people, such as grandparental caregiving, can significantly contribute to the spread of influenza and other diseases due to direct and indirect health effects (Cohen et al., 2009). They concluded that direct health effects for weakened immunity include increased exertion, exposure to stress, and loss of sleep; while indirect effects include reduced time for personal care and overall lifestyle changes. This is especially true with influenza because of the availability of preventive vaccinations. When children are vaccinated against influenza, the elderly have indirect protection from it because it decreases their chances of exposure, and vice versa (Cohen et al., 2009; Fine, Eames, & Heymann, 2011).

Geographic Location

Geographic location is another factor associated with respiratory infection. One study had conducted surveillance efforts in response to the pandemic influenza virus in 2009 in order to monitor the swine-origin influenza virus across Mexico into the Texas border community. McCormick et al. (2010) had developed a more practical, real-time surveillance protocol and response system by using daily data analyses, geographical information system (GIS) mapping of cases, and utilizing absence reports of schools for outbreak management. McCormick and colleagues were able to predict and prevent possible outbreak areas of the community through efforts such as door-to-door newsletter about prevention and treatment of influenza, as well as non-pharmaceutical interventions of the disease. Although the surveillance effort presented here were extensive, it was isolated only in one community.

Different communities might have different resources depending on the socioeconomic status of the communities; therefore some of the techniques and equipment employed in this study might not be as readily available to other communities. In addition, efforts presented may only support an ongoing outbreak of diseases, which may not be the case for other respiratory diseases. It is much more effective to prevent the disease from occurring from the start, which can be accomplished by addressing risk factors that allow the disease to spread into the community.

Along with the geographical location of each population, their behavioral patterns regarding infectious diseases are also dictated by where the populations are situated. People who live in rural areas are often not in direct contact with many people on a daily basis; hence their likelihood of exposure is much lower compared to heavily populated areas (Funk, Salathe, & Jansen, 2010). These people are more prone to quarantine practices themselves during illness from everyone else in order to reduce the spread of the disease because of ease and space availability. Inversely, people living in populated cities and urban communities are less likely to practice similar measures of prevention due to its fast paced lifestyles and inadequate spaces for quarantine measures (Meentemeyer, Haas, & Vaclavik, 2012). Lifestyles of those living in urban cities often carry out daily tasks, such as work, school, and chores, even when they are presented with respiratory symptoms indicative of illness. In addition, the close proximity of people living in urban cities makes it much easier for communicable diseases to spread (Hoke et al., 2012). This offers a much better scenario for the possible spread of communicable diseases, which is often seen during influenza seasons. This scenario is also true for migrant workers, much like the ones living along the border region, who often travel far in order to earn a living. This poses a less than ideal setting for disease prevention because of their ability to either carry out or bring diseases into local communities (Strand et al., 2007).

Immunization

Immunizations are another factor that affects how the population reacts to infectious diseases. Since this area of the country consists of high risk groups associated with elevated rates of acute respiratory distress, which includes people of racial and/or ethnic minorities, undocumented immigrants, and homebound elderly, whom all might not have routine access to health care nor have proper health care providers (Coady et al., 2008). For example, during the 2004-2005 influenza season, the vaccination rate in the United States among the general population was only about 42%, which falls short of the 80% objective set forth by CDC (Chen et al., 2009; Healthy People, 2011). In fact, researchers had recently demonstrated that African Americans and Hispanic Americans were shown to be the lowest percentage in the population being vaccinated in 2011, with a coverage rate of 40.5% and 43.5%, respectively (Seste et al., 2011). Much of these people belonging in the unvaccinated group were those from the high-risk groups, specifically people who are over the age of 50 years and immune-compromised people with chronic medical conditions.

However, not only do socioeconomic disparities contribute to this growing problem. In fact, there have been numerous studies that demonstrated various reasons for the low immunization rates, not only for influenza virus, but overall recommended immunizations for children and adults. One study by Jones et al. (2004) had shown that the people surveyed showed a decline in immunizations because of the fear of catching the very same diseases they were designed to protect. These fears stem from the myth that the vaccine virus might revert back to the virus' wild type form, thereby causing the recipients to become sick, even though various clinical trials have not seen such reversions from occurring (Tosh et al., 2008). In addition, many of the people surveyed also reported concerns with adverse effects such as fever, muscle aches, nausea, and chills due to the components of the vaccine even if very few reported cases of adverse effects were reported after receiving them (Tosh et al., 2008).

Aside from the fear from adults and parents, another potential reason for low vaccination coverage is the perception that vaccines are now obsolete. This leads to more and more parents opting out of their children getting the recommended immunizations because the parents think that vaccines are really not necessary any longer. Examples of these misconceptions include diseases are already disappearing because of better hygiene and sanitation, and the fact that these vaccine-preventable diseases are virtually eliminated from the country so there's no need for them anymore (CDCc, 2011). What these parents fail to recognize is the importance of the protection offered by the immunizations, not only to the ones getting them, but also to those who aren't. The vaccines not only protect children who routinely get immunizations, but also those people around them are offered some level of protection. This term is called herd immunity, which means that the people who aren't vaccinated are somewhat protected from the disease because they have a lower likelihood of coming across it (Fine et al., 2011). An example of the loss of herd immunity is the growing incidence of whooping cough seen in the country (Boyles, 2005). According to Boyles (2005), experts had indicated that one major reason for the increasing pertussis cases in the adolescent-aged group is the declining immunity, which often times are mistaken as a minor cough-related condition. Because less and less are sero-protected from the whooping cough, these adolescents have a much higher chances of coming across someone who carries the pathogen. In turn, this increases the likelihood of acquiring the disease, especially to the younger ones who have weaker immune systems.

These concerns are especially significant today with the emergence of the novel pandemic H1N1 (pH1N1) because of the severity and widespread the virus was able to inflict on the global population. Since the novel virus is a combination of swine, avian, and human influenza virus, the majority of the people appear to be highly susceptible to this strain of influenza (Hillaire et al., 2011). However, there have been conflicting theories as to how infective the virus is to the population. Several studies have shown that some people actually show significant levels of immunity against the novel virus. A study conducted by researchers at the University of California, Davies surveyed for known human epitopes present in numerous proteins in seasonal influenza A viruses that are immunologically similar to epitopes found in the hemaglutinin and nucleoproteins of the pandemic H1N1 virus (Xing & Cardona, 2009). The researchers had concluded that the cross-reactive immunity found between these strains of influenza might have occurred from partial cell-mediated or humoral immune response from repeated exposure to seasonal influenza or annual immunizations. Alternatively, CDC had conducted a serological survey where they compared the immune reactivity of human serum, from those who have no previous vaccination, with those who had received influenza vaccinations between 2005 and 2009. CDC had found that there were no significant differences in the antibody responses to the novel virus between the two groups, thereby concluding that previous history of influenza immunization elicit little immune response to the virus (MMWR, 2009). These researchers illustrate the illusiveness of the influenza vaccine from human immune response, which further highlights the importance of maintaining current vaccination for influenza. Unlike other types of vaccines available for preventing diseases, the elusiveness of influenza through constant mutations (Xing & Cardona, 2009) makes it very difficult to control, hence the yearly vaccine recommendations by public health officials. Since similar population reside along the border region, it is important that continuous surveillance of yearly influenza is conducted in order to assess if sufficient vaccine accessibility is being provided to the residents along this region of the country.

Gender

Other potential risk factors that must be addressed are gender, pregnancy among females, and existing comorbidities that might increase the severity of respiratory diseases. A recent study of 2009 pandemic H1N1 had shown that females have a higher reported incidences and case-fatality rates to influenza, compounded with pregnancy which increases their risk from four to 10 fold higher than the general population (Klein, Passaretti, Anker, Olukoya, & Pekosz, 2010). Females are also at higher risk of acquiring acute respiratory illness because of their traditional roles in families and society. Interactions between females and their children usually occur more due to their responsibilities as mothers such as feeding and bathing, when compared with males who are often gone throughout the day with their job (Clougherty, 2010). Females are also traditionally left alone to give care for extended families such as grandparents who live with them. Occupational risks are also present in women, making them highly susceptible to various diseases. Healthcare workers, grade school teachers, and day-care workers are often held by predominantly females, which potentially lead to a gender-specific risk for communicable disease acquisition (Schlagenhauf et al., 2010).

Comorbidities

Comorbidities can greatly affect how some people react to infectious diseases, which can exacerbate or worsen the symptoms of respiratory diseases. A similar study by Klein et al. (2010) showed that medical conditions such as asthma, bronchitis, chronic respiratory disorders, and other pre-existing illnesses has profound effects on the rate and severity of respiratory illnesses. In fact, a cohort study conducted by Thornburn (2009) had shown that death associated to RSV infection had higher risk (RR 2.36) when they have pre-existing conditions during the episode of the disease. In addition, researchers had also determined a possible link between severe viral respiratory infection during infancy with persistence of wheezing and asthma into later childhood (Kusel, Kebadze, Johnston, Holt, & Sly, 2012). They had found that children who experienced RSV associated lower respiratory infections in their first year of life were more likely to report chronic wheezing and asthma at the age of 5 (Kusel et al., 2012). In addition, RSV infections among school age children with asthma also demonstrated viral illnesses lasting longer, more severe, and were more likely have an episode of loss of asthma control (Olenec et al., 2010). Furthermore, most viral upper respiratory infections in children and young adults are frequently associated with conjunctival and tympanic infections (Tregoning & Schwarze, 2010). These symptoms include earache from tenderness and bulging of tympanic membrane, tachypnea (rapid breathing), wheezing, severe cough, breathlessness, and other respiratory distress (Tregoning & Schwarze, 2010).

Not only are symptoms of severity and persistence an issue for acute respiratory illness, bacterial coinfection is also a great concern. According to Tregoning & Schwarze (2010), a good majority of the people who died from the 1918 pandemic influenza was caused by secondary bacterial pneumonia. Other studies have determined that viral infection can enhance bacterial infection in different ways: by altering physical barriers and altering immune system (Nascimento et al., 2010). For example, the neuraminidase protein in influenza virus plays a major role in the thinning of the mucus in sick people, thereby exposing the receptors along the epithelial cells for bacterial infectivity (Miller et al., 2011; Tregoning & Schwarze, 2010). This opportunistic occurrence allows for a much more severe episode of respiratory illness, especially in immune-compromised people. This is also important in infants because of their under-developed immune system. In fact, Nascimento et al. (2010) had shown that up to 40% of children under the age of two who had visited an emergency unit with acute bronchiolitis had tested positive for some form of respiratory coinfection.

This is a troubling trend given the chances of coinfection with antibiotic resistant bacteria circulating around. Because of improper prescription and use of antibiotics for the treatment of bacterial infection, this practice offers selective pressure thereby isolating resistant strains to grow and spread. It has been estimated that in 2002 alone, between 100,000 and 200,000 tons of antibiotics were prescribed and used worldwide (Andersson & Hughes, 2010). The increase in the number of antibiotic resistant bacteria allows healthcare personnel with a limited arsenal to combat bacterial infection in humans. Not only do these resistant strains slow down the treatment and recovery, it also drive up the cost of treatment since pharmaceutical companies must keep pace with them (Lenski, 1998; Casey et al., 2012). For example, researchers examining community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) had shown that about 10% of those isolated in children were resistant to clindamycin and methicillin, and one percent were resistant to trimethoprim-sulfamethoxazole (Costelloe, Metcalfe, Lovering, Mant, & Hay, 2010). With the continued misuse of antibiotics, more and more coinfections with bacterial pathogens might be seen in acute respiratory patients in clinics and hospitals (Guilherme, Ferreira, Kohler, Postol, & Kalil, 2013). Even though these studies have demonstrated that factors such as age, gender, and pre-existing conditions increase the likelihood of the severe respiratory illness, further research is needed to demonstrate the relationship between them.

Review of Literature Related to Methods

The study presented here is an archival, quantitative study utilizing secondary data previously collected by OID of the NHRC for the SARI program. The advantages of using archival data previously collected are that they are easily accessible electronically, at relatively no cost, and contain fewer errors since they were already screened and checked for input errors, without the need for active interaction with subjects (Jones, 2010). With the raw data already organized and prepared in spreadsheet formats, it makes it easier and more convenient to perform statistical analyses, thereby saving time and resources. This eliminates the chances of handling personal identifiable information (PII) and personal health information (PHI), which require a lot of measures in order to protect the confidentiality of subjects enrolled in the study (Wylie & Mineau, 2003).

There are numerous advantages for utilizing quantitative research method for this study. One advantage is that the outcome of the study can be used to make a generalization with similar populations and subpopulations if properly replicated, something that cannot be done with qualitative method. This is especially true with larger population being studied since it increases the power to reject the null hypothesis. There have been numerous studies that followed the same method for understanding the relationships between different factors and the likelihood of respiratory diseases in different populations. Feikin et al. (2012) had conducted surveillance between 2007 and 2010 for etiology and incidence of viral and bacterial acute respiratory illness among 21,000 children and adults in rural western Kenya, where they found a strong relationship between age, season, and HIV-status with respiratory diseases. Utilizing Fisher’s method for rate ratios to determine correlation between monthly rates and percent positive for pathogens, and odds ratios to compare both cases and asymptomatic groups, they had determined that influenza and *Streptococcus pneumoniae* were the most common virus and bacterial in the population, respectively. Using both rate ratios and odds ratio will allow researchers to determine whether there exist a significant differences between two populations for a particular disease or pathogen.

In another study, Miller et al. (2011) had utilized logistic regression models in order to assess for host factors on bronchiolitis among 630 hospitalized infants between 2004 and 2008. They had found that hRV was a frequent cause of bronchiolitis among infants hospitalized, including maternal atopy associated with more severe infant hRV illness. Another study by Cohen et al. (2009) had surveyed elderly between 1991 and 2004 for grandparental caregiving, income inequality and rate of respiratory infections using multiple log-linear regression models to determine any relationships between them. The researchers saw that rates of infection were higher among counties with lower median income and high levels of live-in grandparental caregivers. When regression models are used in these types of quantitative study, it offers a better analysis of various independent variables for every outcome so that relationships between each variable and outcome can be assessed.

Summary

There have been multiple studies that demonstrated relationships between host conditions, demographics, and geographic locations with the probability of acquiring respiratory diseases. In addition, the epidemiologic triangle had illustrated specific dynamics of host populations that enable the proliferation and spread of communicable diseases, traits that are reflective of the border communities. It is because of these that the following chapters would attempt to demonstrate similar relationships through retrospective quantitative analyses of SARI cases along the U.S.-Mexico border region.

Chapter 3: Research Design and Methods

Introduction

This study was a retrospective analysis of the potential risk factors for Severe Acute Respiratory Illness (SARI) subjects residing along the U.S.-Mexico border region of the country. This region has a significantly elevated probability of acute respiratory infections due to the resident population's uniqueness and the large amount of interaction with international tourists. In order to determine the actual rate of infection, effective analyses were necessary to identify risk factors including age, gender, and vaccination history for use by public health officials to reduce morbidity and mortality due to respiratory diseases. However, previous studies have not effectively identified the relationships between these risk factors and their effects on the border population.

The purpose of this qualitative, retrospective study was to directly identify these relationships in order to further understand and employ effective measures that would help minimize these risks. The goal of this study was accomplished by comparing all of the potential factors associated with the subjects enrolled previously in the SARI surveillance program from 2010–2012, and to use this information to determine their probability of being infected by specific, laboratory–confirmed respiratory diseases.

Research Design and Rationale

I selected a quantitative, retrospective study design for this epidemiological inquiry. I analyzed various independent variables to determine any correlations with matching, laboratory-confirmed respiratory disease cases. Quantitative analysis was the best fit for this study because it was designed to use statistical correlations between different independent variables in order to observe potential associations with diseases over a large population (Johnson & Christensen, 2008). As a result, the generalized findings from this study can be applied to predict inferences to similar populations. Using case-control analysis in this study was rejected because there were too many variables to compare groups in order to assess SARI outcome. In addition, because almost all subjects were exposed to similar factors, it would have been difficult to identify the control groups in this population. Because of these issues, I determined that quantitative retrospective analyses using chi-square tests and logistic regression were the best method of identifying the factors that increase the likelihood of acquiring respiratory diseases.

The independent variables tracked in this study included the subjects' age, gender, race/ethnicity, demographic location along the border, influenza vaccination status, as well as any febrile respiratory symptoms experienced during the episode of the disease. During their visit to participating clinic sites along the border, the subjects were enrolled in the SARI study by completing case report forms that gather variables, prior to them submitting a nasopharyngeal swab sample for both culture and molecular laboratory testing. Utilizing the subjects already enrolled in the SARI study was sufficient to address the research question of identifying risk factors because they are the same population exposed (Kammerer, et al., 2011). In addition, a retrospective study was more effective because of its highly accurate and more convenient since the immediate availability of data (Euser, Zoccali, Jager, & Dekker, 2009). Because the variables were already collected and sorted using a commercially available teleform processing application developed by Hewlett Packard (HP, 2012), the data were already available in spreadsheet format, allowing for better manipulation of the data for easier analyses.

Methodology

Population and Sampling

Since the study utilized archival data collected previously, part of the methodology of this study involved the process for collecting SARI cases at individual clinic sites. According to the U.S. Census, there are approximately 6.5 million people living along the 44 U.S. counties that are within 100 km from the U.S.-Mexican border (AZ DHS, 2013). However, the target population for this surveillance program consisted of subjects who were presented with severe acute respiratory illness and required hospital admission at participating clinic sites across the border region with case definition described in the previous chapters. If these individuals met the necessary case definition for the SARI study subject, they were asked if they were willing to participate in the surveillance program by trained research assistants located on site.

Between 2004 and 2009, on average the Operational Infectious Diseases (OID) laboratory collects about 300 samples yearly for those exhibiting influenza-like illnesses, with 36% of those testing positive for any types of respiratory pathogens (Kammerer, et al., 2012). Using similar estimates to conduct a post hoc power analysis for this study, utilizing approximately 600 samples collected between 2010 and 2012 gave a statistical power of about 0.99, with an effect size of 0.5 and an alpha measure of 0.05 (Soper, 2014). Only samples collected between these years for the SARI study with completed requisition forms and laboratory results were included in the study.

Procedures for Recruitment, Participation, and Data Collection

When it was determined that a subject met the case definition for severe acute respiratory illness, the research assistants provided necessary information regarding the surveillance study (AZ DHS, 2012), which included purpose of the study, level of participation from the subjects enrolled including safety, privacy act statements that explains how their information are protected, and how the nasopharyngeal samples were to be collected. Since the subjects' were sequentially assigned numbers with the 'SARI' prefix, their names and other information that might link them to the study were not collected, such as names, birth date or social security numbers (SSN). This ensured that the subjects remained anonymous throughout the study, with no necessary follow up from the program after enrollment.

Once the subjects gave consent to participate, they were then required to complete a case report form that collected the necessary information mentioned previously in this chapter. Aside from personal information, the subjects were asked to the best of their knowledge, pertinent information such as the types of symptoms they have experienced since the onset of the respiratory disease, their history of influenza vaccination, and their prior border crossing into Mexico if any. Once the form was completely filled out, the subjects were then asked to submit a nasopharyngeal swab sample, performed by trained research assistants on site, which were all sent to the laboratory for further testing. These nasopharyngeal samples were stored in Universal Transport Medium (UTM) by Diagnostic Hybrids, USA (HealthLink Inc., 2009), which contained preservatives and nutrients necessary to maintain pathogenic viability if present. Once collected, these

UTM samples were stored in ultra-low freezers that have temperatures of at least -70 degrees Celsius or lower until transported to the laboratory. Transporting frozen specimens involved overnight shipping of UTM samples with dry ice in insulated specimen shipping boxes to maintain their status until arriving in the laboratory for testing.

When the specimens arrive in the laboratory, they were immediately examined by trained laboratory personnel who ensured that the samples arrived in good condition. They were evaluated for any damage in the UTM tube that might cause sample leakage, mislabeling or missing labels, and if they were adequately frozen during shipment, all of which can affect the specimen acceptability. The shipment also contained all of the case report forms for each subject included, as well as a study requisition form that informs the laboratory of the types of testing required. These forms were then scanned through the teleform software program that automatically gathered and sorted all of the information from each form, and stored them in the laboratory database until ordered for testing by the different laboratories. It was in this in-house developed laboratory database that all of the data collected from each subject are sorted out and stored throughout the duration of the testing.

Once entered, each sample was simply tracked throughout the duration in the database, including the ordering of tests, any existing samples stored in ultra-low freezers, and generate laboratory reports. Similar to the individual testing performed by each of the laboratory, the in-house database is maintained vigorously using College of American Pathologists (CAP, 2013) regulations and routine inspections. All of the samples were tested by the laboratory using both culture and molecular methods (NHRC, 2012) following CAP–accredited procedures to ensure the quality of data and results. Each sample was screened for infectious respiratory pathogens that include influenza A and B, adenovirus, RSV, herpes simplex 1 and 2, parainfluenza 1-3, enterovirus, *Neisseria meningitidis*, *Haemophilus influenzae*, *Bordetella pertussis,* Group A *Streptococcus pyogenes, Staphylococcus aureus* (both susceptible and resistant to methicillin), *Streptococcus pneumoniae,* and *Mycoplasma pneumoniae*.

Once the samples were confirmed positive for any of the potential pathogens listed above, they were entered and verified into the database by two separate individuals to ensure accurate reporting. If there were any discrepancies with the entering and/or verifying of the results, the laboratory supervisor made the final decision of whether to override the tested results during the finalization of the samples, a CAP required procedure for ensuring all of the samples are reported properly. Once the results of the samples were finalized, an overall report was generated in the laboratory database in order to be sent out to proper channels (Armed Forces Health Surveillance Center, CDC, and individual training sites). In addition to the finalized reports, excel spreadsheets can also be exported from the laboratory database with all the required fields requested. This ability to export and generate workable spreadsheets with all of the data required allowed for the statistical analyses that can potentially help in addressing the research questions. The ability to gain access to these archival data using the described database can be achieved through the permission of different persons such as the department head for the Operational Infectious Diseases (OID) of the Naval Health Research Center, San Diego, CA. These permissions were obtained through the necessary permission letters written by these people, and are affixed in the appendix section once received.

Operationalization of Variables

The operationalization of the variables collected for the SARI surveillance program is outlined in Table 1. During the enrollment of the potential subjects for the study, research assistants assisted them in completing the questionnaires that contain all of the variables listed in the table prior to submitting a throat sample for laboratory testing. If the subject is a young child, either a parent or a research assistant helped to complete the questionnaires for them. Each of the section in the questionnaire required them to bubble in, using a pencil or pen, the appropriate answers for each of the question outlined. This allowed for a smooth scanning of questionnaires, from paper-based into electronic records, using the teleform program previously described.

Table 1

Operationalization of Variables Collected During SARI Enrollment

Variable	Type	Subject Input
Age group	Nominal	0-4 / 5-24 / 25-49 / 50-64 / $\geq$65
Clinic site	Nominal	Sharp Health Chula Vista / El Centro / Brawley / Arizona
Flu vaccine w/in 12 months	dichotomous	Yes / No
Race	Nominal	Hispanic / White-non Hispanic / African-American / Native American / Other
Gender	dichotomous	Male / Female
Current diagnosis pneumonia	dichotomous	Yes / No
Clinical symptoms during visit*	dichotomous	Body ache / chills / conjunctivitis / cough/ diarrhea / ear ache / headache / nasal congestion / nausea / shortness of breath / sore throat / wheezing

* Response to the clinical symptoms was dichotomous with a yes or no answer.

There were three nominal variables that are part of the questionnaire form for the study as outlined in the table below. Age group is a nominal variable that is divided into 5 different choices (*0-4, 5-24, 25-49, 50-64, >65*) according to the subject being enrolled in the study. There are four different clinic sites (*Sharp Health Chula Vista, El Centro Regional Medical Center, Brawley Medical Health, and Arizona Health Center*) that participate in the surveillance program, thereby the clinic location from where the samples were coming from is another nominal variable in this study. For every subject, the research assistants would fill out the location of the clinic where the subject is being enrolled from. The third nominal variable was the race/ethnicity of each of the enrolled subjects. On the form, the subjects were required to bubble in their race/ethnicity with the choices of *Hispanic, White-Hispanic, African-American, Native American*, or *others* if they do not fall into ones mentioned before.

There were also four dichotomous variables that each enrolled subjects must provide answers in the questionnaire before they're allowed to submit a clinical sample. Each subject was asked, to the best of their knowledge, whether they have received influenza vaccine within 12 months prior to their visit to the clinic. This means whether each person enrolled had received the recommended influenza vaccine for that particular influenza season, which is important for influenza surveillance efforts. The second dichotomous variable was the gender of each of the subjects, which they are required to answer during the questionnaire. The third variable was whether they are currently diagnosed with pneumonia, which the research assistants were required to complete once radiologic confirmation has been obtained from the clinic. The last dichotomous variable was the clinical symptoms present during their visit to the clinic. There were twelve clinical symptoms that the research assistants must ask the enrolled subjects as to whether they are currently experiencing them. These symptoms included body aches, chills, conjunctivitis, cough, diarrhea, ear ache, headache, nasal congestion, nausea, shortness of breath, sore throat, and wheezing, all of which have a *yes* or *no* response. All of these were required questions that need to be answered, to the best of the knowledge of the subject (or parent for children enrolled), as they were part of the questionnaire form for the SARI surveillance study.

Data Analysis Plan

Upon the approval from the necessary agencies for gaining access to the archived data, the statistical analyses of the different variables were performed using widely utilized statistical software called SAS/STAT (SAS Institute, 2012). To determine whether there was an association between demographic and etiologic factors with the incidence of SARI cases enrolled in the study, different statistical tests can be utilized in order to identify these factors. Using frequency analysis, major diseases were identified and used as dependent variables, or outcomes, with positive or negative responses. For independent variables with more than two inputs such as age category, race, and clinic sites, multiple logistic regression (*p*-value of 0.05 as significant) was utilized to determine the expected probability of the outcome from occurring. Using this type of regression model, the probability of testing positive for a particular pathogen were determined from each categorical input such as between different race/ethnicity and clinic locations to determine if there are significant differences between them. In addition, utilizing this type of regression model also allowed for any disease association evident within each of the age category. Lastly, chi-square analysis was also performed to determine significant differences between presence/absence of disease between each categorical variable examined (p-value of 0.05 as significant).

In addition to this, vaccine effectiveness for this population can also be assessed using odds ratio between those that had received (exposed) versus those that had not received (non-exposed), and whether they had tested positive or negative for influenza virus. In addition, risk ratio can also be utilized (with 95% confidence interval) to determine the relative risks from different exposures such as influenza vaccination within the last twelve months, or whether they have crossed the border within five days prior to presentation of the symptoms. This will allow for determination whether exposure to the vaccine would have an effect in certain disease categories, especially in influenza cases, which might be determined its relative effectiveness in prevention. Furthermore, one can determine the risk of exposures by the duration of border crossings prior to the onset of the disease.

Threats to Validity

In every research, threats to validity are always a big concern. Since the study being presented is a retrospective analysis using archival data, there were a few threats that might affect generalizability based on the outcomes of the study. One important threat was the potential selection bias of the subjects enrolled in the study because most of the people who present themselves in the participating clinic sites come from a low socioeconomic status, inferences made based on the outcome of this study can only be used in the locations that have similar socioeconomic status such as all communities living along the U.S.-Mexico border regions. In addition, reproducibility of testing over a long period of time can also be a threat to validity since variability in the testing methods might be present. This was addressed earlier with the certification of all tests by CAP, which ensured consistent and valid results are obtained through rigorous proficiencies and evaluations.

Aside from threats to external validity, there were also a few threats to internal validity that can be identified. One was the ability of the subjects enrolled to remember historical information that the research assistants collected such as the vaccination history. Furthermore, language gap between the enrolled subjects and the person collecting the data might pose a risk for the validity of the responses being collected. Both of these were addressed by having appropriate sample size in the study so that a few inconsistencies will not affect the overall outcome. Also, research assistants hired were proficient in the Spanish language, which is the most used language in this region aside from English. This ensured that the enrolled subjects fully understand every questions and instructions in order for a successful enrollment to the study. Other potential threats to internal validity, such as instrumentation variability and selection bias, had also been addressed previously. All of these were exercised in order to minimize the threats to the validity of this study.

Ethical Procedures

Ethical procedures are a significant part of all research, which is why it’s important to address these concerns before beginning any studies. It had been described within previous sections of this chapter how the data and physical specimen were collected by trained research assistants in order to address any ethical concerns. In addition, anonymity of every subject enrolled was also preserved by not collecting sensitive information that can be traced back to them such as names, birth date, and SSNs. All research assistants, as well as all laboratory personnel involved in handling specimens and records, were required to complete an annual Health Insurance Portability and Accountability Act (HIPAA) and Privacy Act through the Department of Defense Military Health System (MHS), which are the same type of training that military hospital personnel are required to complete as well (DHA, 2013). This ensured that proper practices of protecting personal identifiable information (PII) were applied throughout the course of the study. It is during these types of training that every personnel were given the tools that are necessary to maintain confidentiality of all subjects enrolled through practices such as password-protected computer access and logging off computers before leaving the station.

Aside from the annual refresher training that all personnel were required to complete in order to gain access to these information, there were other measures put in place in order to control who had access to the computers and databases that stored all of the information collected from all of the studies. Initially, since the laboratory is situated inside a military installation, all personnel must complete and submit a clearance form called Standard Form (86), which is a standard security clearance that all military personnel, government contractors, and civil workers must complete and pass before gaining access to the military base (FBI, 2013). This clearance involved a completion of the SF86 form, followed by and FBI-led background investigation to determine if the personnel were fit to receive the clearance. Only those that pass this background investigation were given access to work in the military installation.

Secondly, all of the different buildings that house computers and servers that contain the laboratory databases are secured throughout the day, with only those who are authorized would have access to them. Access to the building would only be through utilizing electronic access cards that are issued to only those that are permitted to the building. This means that personnel from another department cannot use their own access card to open doors for buildings not belonging to their own. This ensures that only those personnel who are authorize to work in the building would have access to them.

Thirdly, individuals who were given access to network computers were issued a Common Access Card (CAC) that can be used to unlock them (CAC, 2013). Each of the network computers was electronically locked, which can only be unlocked using password-protected CAC cards. In addition to gaining access inside the military base, those with SF86 clearance were issued CAC cards with individualized passwords for use of network computers. Each of the cards contained an electronic signature of its users so that access to different servers can be traced back to the users. This also pertained to the use of the laboratory database. Every time a personnel access the laboratory database, their electronic signature was automatically logged into the database including the date of access, and any procedures performed. This included when someone entering and/verifying test results into the database for each of the sample, so that any changes done will be traced back to the user.

All of these measures were put in place to ensure the safety and protection of all subjects enrolled in the study. The procedures for keeping anonymity of all enrolled subjects, technical and structural procedures for ensuring security, and proper safety and privacy training of all involved personnel would ensure that ethical and confidentiality concerns are all addressed and protected. Since this study analyzed data records that were previously collected, no such procedures involving direct research participants were required. As described previously, the confidentiality of all data was protected under multiple measures highlighted in this section. However, since the records were protected under U.S. Naval standards, none of the raw data (including any identifiable information) was allowed outside government secured computers and networks. This meant that all analyses were executed in government secured computers that contain the SAS program. Only after statistical analyses were performed, without any traceable identification from the participants, can the data be taken outside secured computers through USB or CD storage media. The data transferred afterwards were securely stored in password-protected laptop (with back up records stored in secured folders inside government secured computers) so that no public access was allowed. As per requirements of the IRB, this information will be maintained for at least 5 years following completion of the study and will be disposed of appropriately. These measures were to be put in place in order to protect the confidentiality and integrity of the data that were used in this study.

Summary

In summary, a retrospective study design was conducted to address the research hypothesis. By using archival data previously collected from the SARI surveillance study between 2010 and 2012, potential outcomes allowed for proper identification of the risk factors associated with the different respiratory diseases being seen in the US-Mexico region. Odds ratio, multiple logistic regression model, and chi-square analyses were performed in order to assess the degree of probability that demographic (age, gender, race/ethnicity, and location) and etiologic (vaccination history and clinical symptoms) factors would increase or decrease the likelihood of acquiring severe acute respiratory illnesses in this population.

Chapter 4: Data Summary

Introduction

The purpose of this study was to determine quantitatively whether there were significant demographic associations present in the US-Mexico border population with the incidence of Severe Acute Respiratory Illness (SARI) between 2010 and 2012 among persons enrolled in the surveillance program. The primary research question for this study was "Is there an association between demographic (age, gender, ethnicity, etc.) and clinical symptoms (presence of pneumonia) present during enrollment, and the incidence of SARI cases along the United States-Mexico border region?" The null hypothesis stated that there was no statistically significant association between these demographic and clinical factors, and the incidence of SARI cases in this population. Conversely, the alternative hypothesis stated that there were significant associations between these demographic and clinical factors, and the incidence of SARI cases in this population.

This chapter outlines the descriptive and demographic characteristics observed in the study population enrolled in the SARI program between 2010 and 2012, highlighting the risk variables collected during enrollment that were analyzed in this study. The statistical results of my secondary data study are presented according to the risk factors considered within the main research question. Overall, the statistical analyses performed in this study showed certain independent variables to be potential risk factors for SARI illness such as belonging to certain age groups and races/ethnicities, as well as having a history of border crossing and clinics' location along the border. In contrast, variables including sex/gender and presence/absence of pneumonia upon enrollment showed no significant association/risk factor to SARI diseases.

Data Collection

Upon obtaining the necessary permissions from the department head, I was able to collect all the raw data by performing a query search for all SARI specimens collected between 2010 and 2012 that the laboratory had done testing for from the in-house laboratory database. The search had yielded 798 subjects that included all of the information collected during enrollment, as well as their overall laboratory result, in an excel worksheet format. Since these samples were identified primarily through their assigned numbers (i.e., *SARXXXXX*), no identifying information from enrolled subjects were obtained along with their corresponding enrollment and laboratory data. This allowed the easy transfer of data, in Excel spreadsheet format, to be taken out of the database and saved in a portable USB drive. Once the spreadsheet data were obtained from the database, data clean up were performed in order to organize and standardize the inputs prior to analysis. This includes converting all “yes” and “no” data entries into “Y” and “N,” respectively. In addition, all laboratory results were also organized so that all results would match similarly in order to avoid confusion and exclusion of samples because of non-matching results.

Once all of the data were scrubbed, I added new columns for the data analyses (e.g., forming dummy variables for the different variables to be analyzed). These dummy variables include binomial responses, with “0” for a no response and “1” for a yes response, for all of the subjects’ responses to the different variables to be examined such as presence of SARI disease, age group, race/ethnicity, clinic site, gender, presence of pneumonia, and history of border crossings within five days. Once the dummy variables were established, data analyses were performed including frequency and descriptive analyses, chi-square analysis, and logistic regression models.

Results

Descriptive Summary of Study Population

Between 2010 and 2012, 798 SARI subjects enrolled in the study and were tested by the NHRC laboratory (see Table 2). Of the 798 samples tested, 462 (57.9%) subjects tested negative for both viral and bacterial pathogens by both molecular and microbiology techniques. There were 284 (35.6%) subjects that had tested positive for viral pathogens, and 52 (6.5%) were tested as positive for bacterial pathogens by both laboratories.

For the age variable, the two age groups that had the most enrollment were the 0–4 and >64 age groups, with 316 (39.6%) and 197 (24.7%) enrollments, respectively. In between them, the study enrollments were 80 (10%) for 5-24 age group, 94 (11.8%) for the 25-49 age group, 99 (12.4%) for the 50–64-year-old age group. In addition, 12 people (1.5%) enrolled in the study did not have any response recorded for the age variable when they were tested. This shows that people belonging to the youngest (0-4) and oldest (>64) age group had presented to the clinic with possible acute respiratory illness more often than those belonging in other age groups.

Table 2

*Descriptive Summary of the Study Population by Variables (*N *= 798)*

Factor	Subfactor	Frequency	%
Lab Results	negative	462	57.9
	viral	284	35.6
	bacterial	52	6.5
	Total	798	100
Age	0-4	316	39.6
	24-May	80	10
	25-49	94	11.8
	50-64	99	12.4
	>64	197	24.7
	Unknown	12	1.5
	Total	798	100
Clinic	Arizona	90	11.3
	SCVH	63	7.9
	El Centro	304	38.1
	Brawley	323	40.5
	Unknown	18	2.2
	Total	798	100
Ethnicity	Hispanic	561	70.3
	White-non Hispanic	150	18.8
	Native-American	22	2.8
	African-American	16	2
	Other	13	1.6
	Unknown	36	4.5
	Total	798	100
Sex	Male	411	51.5
	Female	373	46.7
	Unknown	14	1.8
	Total	798	100
Border Cross within 5 days	Yes	133	16.7
	No	594	74.4
	Unknown	71	8.9
	Total	798	100
Current Pneumonia	Yes	444	55.6
	No	302	37.8
	Unknown	52	6.6
	Total	798	100

For the clinic variable, El Centro and Brawley clinics had the highest number of enrollments with 304 (38.1%) and 323 (40.5%) subjects enrolled in the SARI surveillance study, respectively. Arizona clinic had an enrollment of 90 (11.3%) and SCVH had 63 (7.9%) enrolled subjects. There were 18 (2.2%) study enrollments that had reported no response to the clinic variable upon enrollment and testing of the subjects.

For the ethnicity variable, the majority of the subjects enrolled in the study were Hispanics with 561 (70.3%) enrollments between 2010 and 2012. The second highest enrollment was White-non Hispanics with 150 (18.8%) subjects enrolled in the program. The rest were Native-Americans with 22 (2.8%) subjects, African-Americans with 16 (2%), and the others with 13 (1.6%). There were 36 (4.5%) enrolled in the study that reported no response to the ethnicity variable upon enrollment and testing of the subjects. Since the locations of these clinics were located near the U.S.-Mexico border region of the country, this might explain why there was a significant number of Hispanics enrolled in the surveillance program.

For the gender variable, there were about equal number of subjects from each gender enrolled in the study. There were 411 (51.5%) male subjects enrolled in the study, while 373 (46.7%) female subjects were enrolled. There were 14 (1.8%) subjects enrolled that had no response to the sex variable upon enrollment and testing of the subjects.

For the variable of whether the subjects had crossed the border within five days prior to onset of symptoms and presentation to the clinic, the majority of the subjects enrolled in the program reported not having been across the border within five days. There were 594 (74.4%) subjects who reported not having crossed the border within five days prior to disease onset, while only 133 (16.7%) had reported having been across the border within five days. Because some respiratory diseases might have longer incubation period prior to showing any symptoms, this might explain why the majority of people presented with acute respiratory illness might have responded no this question (Lessler, et al, 2009). There were also 71 (8.9%) subjects enrolled that had no response to this question on their questionnaire upon enrollment and testing of the subjects.

For the last variable of whether they currently have pneumonia upon presentation to the clinic, the majority of the subjects enrolled had answered yes during enrollment. There were 444 (55.6%) subjects that had responded yes to whether they currently have the symptoms of pneumonia when they were admitted to the clinic for treatment. In contrast, about 302 (37.8%) responded no to this question upon enrollment into the study. There were also 52 (6.6%) subjects that had no response to this question during enrollment and laboratory testing.

Analysis of SARI Cases Overall

In order to determine whether there are any significant associations between those who tested positive for SARI (both viral and bacterial) versus negative and each of the independent variables outlined in Table 2, a chi-square test for association was performed on all 798 enrolled subjects. It is appropriate that chi square statistics were performed in this analysis because it consists of two categorical variables, thereby achieving the assumptions required for this test. The outcome variable was divided into two possible outcomes, positive (whether viral or bacterial) and negative based on laboratory test results with their statistical significance evaluated at $p < 0.05$. The results of these tests are outlined in Table 3 below, along with the frequency and percentage of subjects falling into each of the independent variables.

Table 3 shows a description of the SARI cases included in this study, broken down by the independent variables assessed. It shows that all of the independent variables have significant differences within each of the variables tested, except for the sex variable. The age variable shows a statistically significant difference between those with and without severe acute respiratory illness, X^2 (4, $N = 786$) = 255.361, p <0.001. This indicates that there is an inverse trend being seen between those with and without the disease across all age group, with the youngest age group (0-4) showing the most vulnerability (60.4%) from SARI diseases, with population vulnerability declining as the population gets older. In other words, the chi-square analysis shows that the frequency of SARI cases gradually decreases as the population age increases, with only a slight dip between the 50-64 and >64 age group. This could mean that the elderly population might show a slight increase in susceptibility due to weakened immunity seen in this population group.

Table 3

Chi-Square Analysis of the Study Population by Test Variables

Factor	Subfactor	No SARI	No SARI %	SARI	SARI %	Total	X^2	*p*-value
Age	0-4	125	39.6	191	60.4	316	255.361	<0.001
	5-24	46	57.5	34	42.5	80		
	25-49	64	68.1	30	31.9	94		
	50-64	76	76.8	23	23.2	99		
	>64	146	74.1	51	25.9	197		
	Total	457		329		786		
Clinic	Arizona	59	65.6	31	34.4	90	290.841	<0.001
	SCVH	45	71.4	18	28.6	63		
	El Centro	176	57.9	128	42.1	304		
	Brawley	164	50.8	159	49.2	323		
	Total	444		336		780		
Ethnicity	Hispanic	327	58.3	234	41.7	561	1456.701	<0.001
	White-Non-Hispanic	94	62.7	56	37.3	150		
	Native-American	9	40.9	13	59.1	22		
	African-American	6	37.5	10	62.5	16		
	Other	8	61.5	5	38.5	13		
	Total	444		318		762		
Sex	Male	237	57.7	174	42.3	411	1.842	0.175
	Female	218	58.4	155	41.6	373		
	Total	455		329		784		
Border Cross within 5 days	Yes	65	48.9	68	51.1	133	292.326	<0.001
	No	359	60.4	235	39.6	594		
	Total	424		303		727		
Current Pneumonia	Yes	287	64.6	157	35.4	444	27.029	<0.001
	No	152	50.3	150	49.7	302		
	Total	439		307		746		

Note: Missing and/or unknown entries for each of the variables were not included in the analyses.

Table 3 shows a significant difference in the clinic where the subjects have presented themselves with SARI illnesses. It shows statistically significant differences among the different clinics and whether they were positive for some type of SARI disease, X^2 (3, *N = 780*) = 290.841, *p* <0.001. The clinics that showed the highest incidence of SARI illnesses are El Centro (42.1%) and Brawley (49.2%), which could potentially mean the population living along these clinic sites might be the most susceptible for some type of respiratory illnesses than the other two. However, Arizona (34.4%) and SHCV (28.6%) have fewer subjects enrolled in this study, with only 90 and 63 subjects, respectively.

The third independent variable, ethnicity, also shows significant differences in the study. The data shows statistically significant difference among the different ethnicities and whether they have SARI illnesses, X^2 (4, *N = 762*) = 1456.701, *p* <0.001. The data indicates that African-American (62.5%) and Native-American (59.1%) have the highest incidence of SARI illness when compared with the other ethnicities, with the White-non Hispanic (37.3%) having the lowest. However, the number of subjects enrolled in the study was far lower in these two groups (22 for Native-Americans and 16 for African-Americans) that this might not show the real value of incidence in this population. The Hispanics shows the highest population enrolled in the study, with 41.7% of its 561 subjects tested positive for some type of SARI illness.

The fourth variable, whether the participants had crossed the border within five days prior to onset of illness, also showed significant differences in this study. It shows a statistically significant difference whether they have crossed within five days, and tested positive for some type of SARI diseases, X^2 (1, $N = 727$) = 292.236, p <0.001. According to Table 3, there is not much difference among those crossing the border within five days and incidence of SARI illness, with 51.1% of those who have crossed had shown to be positive for some type of SARI illness, while 48.9% had tested negative. Conversely, those who reported to not have crossed within five days shows the highest percentage of non-SARI related illness, with 60.9% of 594 subjects tested negative for SARI illness. Furthermore, 235 out of 303 subjects that had tested positive for SARI illness had reported not crossing the border within five days. This could potentially mean that crossing the border within five days might not be a risk factor for SARI illness since there is an inverse trend being seen between those who have and those who have not, and the incidence of SARI illness in the population. As mentioned previously in this chapter, other factors such as incubation period of different respiratory diseases might affect the outcome of this analysis.

Whether the presence or absence of pneumonia among subjects also showed significant differences on whether they are positive for SARI illness. The data showed statistically significant difference among those with and without the presence pneumonia, X^2 (1, $N = 746$) = 27.029, p <0.001. Those who do not have current pneumonia were shown to be higher in incidence (49.7%) than those with current pneumonia (35.4%), thereby having pneumonia might not be a significant predictor for SARI illness in this population. Various factors might be present in this population that can potentially cause pneumonia other than respiratory illness, such as fungal infection (pneumocystis carinii pneumonia) and tuberculosis (Walker, et al., 2013).

The sex variable was the only independent variable in the study that showed no significant difference, X^2 (1, $N = 784$) = 1.842, $p = 0.175$. There was no statistically difference seen between male (42.3%) and female (41.6%) participants who had tested positive for some type of SARI illness in this population. This showed that sex is not a potential risk factor for [fill in the full description here].

In order to determine whether certain independent factors have an effect on the variables examined, a binary logistic regression was performed to control for these factors in the analysis of the data (Table 4). Binary logistic regression is appropriate in this matter because it fulfills all of the necessary assumptions for the test. These include having a dichotomous outcome (dependent) variable, while having one or more categorical independent variables to analyze with. Furthermore, each subject enrolled into the program was independent of others enrolled so it can be concluded that the independence of observation assumption is met for this test. In addition, even though it is possible that one subject was enrolled more than once in within the enrollment period of this study, each enrollment was considered independent and treated as such during analysis. Also, the dependent variable is both mutually exclusive and collectively exhaustive because the outcome is dichotomous, and cannot occur at the same time.

It was found that after including age, gender, race/ethnicity, and clinic location to the regression model, only the age variable showed any significance ($p \leq 0.05$) when other demographic factors were included in the analysis. From this model, it shows an odds ratio of 0.521 for the 5-24 age group, 0.377 for the 25-49 age group, 0.211 for the 50-64 age group, and 0.225 for the >64 age group when compared with the 0-4 reference age group. This can also be interpreted that the 0-4 age group is twice likely to develop

SARI illness when compared with the 5-24 age group, three times likely than the 25-49 age group, and five times likely than the two oldest age groups. In addition, the model also showed that African-Americans were four times more likely to acquire SARI illness than Hispanics (OR = 3.997, 95% CI [1.272 - 12.558].

Table 4

The Odds Ratio of SARI Diseases Associated with Study Population Belonging to Different Age Groups

Factor	Subfactor	*n*	B	*SE*	SARI Odds Ratio	95% C.I.	*p* < 0.05
Age	0 - 4	285					0.00
	5 - 24	78	-0.653	0.263	0.521	[0.311 - 0.871]	0.013
	25 - 49	84	-0.975	0.266	0.377	[0.224 - 0.636]	0.00
	50 - 64	89	-1.558	0.296	0.211	[0.118 - 0.376]	0.00
	>64	184	-1.49	0.233	0.225	[0.143 - 0.356]	0.00
	Total	720					
Race	Hispanic	526					0.098
	White – non-Hispanic	145	-0.107	0.213	1.113	[0.733 - 1.689]	0.616
	African - American	15	1.386	0.584	3.997	[1.272 - 12.558]	0.018
	Native	21	0.836	0.567	2.308	[0.759 - 7.014]	0.14
	Other	13	0.313	0.637	1.368	[0.393 - 4.763]	0.623
	Total	720					
Clinic	SCVH	61					0.902
	El Centro	275	-0.041	0.344	0.96	[0.489 - 1.884]	0.906
	Brawley	297	0.076	0.347	1.079	[0.547 - 2.131]	0.826
	Arizona	87	-0.111	0.421	0.895	[0.392 - 2.043]	0.793
	Total	720					
Sex	Male	411					
	Female	309	0.017	0.161	1.017	[0.741 - 1.395]	0.917
	Total	720					

Logistic Regression model with presence/absence of SARI disease as the outcome variable, different age groups as the independent variable, and covariates for race, sex, and clinic locations. The reference group for each variables are 0 - 4 (age group), Hispanic (race), SCVH (clinic), and male (sex). Only the age variable showed significant values of p < 0.05.

Summary

As seen in the data presented here, it can be concluded that certain groups within each independent variables have some form of association with some, or all types, of SARI illness that can be addressed. These findings, as outlined in Table 5 below, can be utilized in assessing potential risk factors to severe acute respiratory illness among the people living in the border region of the country. Based on these findings, certain actions can be recommended that might help in minimizing the incidence of SARI illness in this region of the country. However, certain limitations can also impact the outcome of this study. These impacts, recommendations, and limitations will be further discussed in the following chapter.

Table 5

Summary of Statistical Tests Performed Outlining Independent Variables and their Significance

Dependent Variable	Statistical Test	Independent Variables	Significant Results
Presence / Absence of SARI	Chi- Square	Age	Y
		Clinic	Y
		Ethnicity	Y
		Sex	N
		Border Cross W/in 5 Days	Y
		Current Pneumonia	Y
Presence / Absence of SARI	Binary Logistic Regression	Age	Y
		Race	N
		Clinic	N
		Sex	N

Chapter 5: Interpretation and Conclusion

Introduction

The specific population dynamic of U.S. communities living along the United States-Mexico border region creates a serious threat for communicable diseases. The majority of this region's population falls under the U.S. national poverty level and many residents are frequently medically underserved. These factors, combined with the high volume of traffic from both locals and tourists crossing the border, present a major threat of introducing communicable diseases to a highly susceptible population. Since the communities comprise of a unique and diverse demographic population, it is imperative that further studies be conducted to fully understand how communicable diseases impact this population.

It is important to examine how critical risk factors can potentially increase the likelihood of acquiring severe acute respiratory illnesses by assessing the associations of these risk factors with respiratory illnesses found in this population. This study was designed as a quantitative assessment of previously enrolled subjects in the Severe Acute Respiratory Illness (SARI) disease surveillance program, and used these data to answer certain questions regarding potential risk factors. The purpose of this study was to clearly identify and address these risk factors in order to determine effective courses of action to decrease and/or eliminate the probability of acquiring and spread of communicable respiratory illnesses in this region.

The statistical analyses for this study showed that certain independent factors have significant associations relating to SARI illness in this population. Several demographic factors such as age, ethnicity, clinic location, and history of border crossing had some level of association with certain SARI illnesses in this population, with only gender and presence and/or absence of pneumonia failing to show a correlation. How these associations are related to SARI illness is further discussed later on in this chapter.

Interpretation of the Findings

Based on the analyses performed in this study, it can be concluded that there are certain independent variables that have shown to be associated with SARI illness in this population. In the age variable, the youngest age group (0–4 years' old) was shown to be most at risk for both viral and bacterial types of SARI illness, with a declining risk, as the population gets older. This is followed by the oldest age group (>64 years) in the study, where they showed the second highest frequency of disease cases in the study population. This is evident with the declining risk as the population gets older, with the exception of an increase in the frequency among the population belonging to the oldest age group. This aligned with Medzhitov, Schneider, and Soares's (2013) finding had indicated that as humans get older, their disease tolerance also increases due to the growing resistance and tolerance of their immune system; as people age, their immune system is more and more exposed to different diseases, thereby increasing their tolerance to similar diseases. As a result, the host fitness to different pathogens generally enhances as they get older.

The youngest population segment is the most immune-naïve of all the age groups, which explains why they were identified as the most vulnerable to any type of acute respiratory diseases in the study. Infants have limited exposure to diseases prior to birth, and therefore have limited adaptive immunity and rely heavily on innate immune system for protection against infections (PrabhuDas et al., 2011). After birth, they are highly susceptible to most diseases because of the lack of exposure that builds up their immune system. Another explanation for this is the growing concern of the safety and necessity of vaccines among newborns, as discussed in the earlier chapters, leading to the drop in the vaccine coverage in the country. As discussed by Jones et al. (2004), many parents decline to have their children vaccinated due to fear of its safety and adverse effects. Others had argued that the necessity of vaccines was unwarranted due to the diseases virtually disappearing. Regardless, the growing concerns whether vaccines are even needed nowadays have led to declining immunization coverage (CDCb, 2007). This results in the number of children failing to receive all the necessary vaccines that equip them with the proper defenses against numerous diseases. In addition, this decline in coverage also increases the chances of exposure for those who aren't able to get the vaccines, such as immunocompromised people and those allergic to them (Jones et al., 2004). Herd immunity is their best chance of minimizing exposure, which is hindered when the vaccination rates are low.

Weakened immune systems are a potential explanation of the high frequency of diseases seen in the elderly population, which might be due to underlying chronic diseases present that affect their immunity (Felkin et al., 2012). Comorbidities causes predisposition to infectious diseases in all ages, but more frequently in elderly people due to immunosenescence, or decreased function of immune system (Kaye, 2011). Due to this, the combination of increased comorbid conditions and decreased activity of immune systems allow elderly people to become more prone to infections. In addition, both humoral and cellular immune responses are greatly impaired in older population, thereby decreasing their vaccine responses (Frasca et al., 2011).

In the clinic location variable, it can be noted that both El Centro and Brawley had the highest number of SARI enrollment and positive cases when compared with the other two clinic sites. This could mean that these two sites might have the highest risk of disease exposure compared to the other clinic sites. One potential reason for the differences in both the enrollment numbers and positive cases of SARI is the socioeconomic disparity along these two clinics. According to the U.S. Census Bureau (Table 6), the populations along El Centro and Brawley area show significant socioeconomic disparities when compared to the national average. Both cities show an increased unemployment rate of 11% (El Centro) and 12% (Brawley), while SCVH (8%) falls closer to the national average of 6% in 2013. Furthermore, both cities also have significantly higher number of household receiving some form of financial assistance from the government when compared with the national average. Lastly, both cities also show disparities in the number of high school graduates, household income under $20,000, and average household income when compared with the national average, while communities along SCVH falls closer to the national average. As previously explained, the socioeconomic levels of people have a direct correlation with the overall health status, such that those belonging to lower levels tend to be more medically underserved (Korscheun, 2011; Egede & Zheng, 2002).

Table 6

Demographic Data of the Population Surrounding the SARI Clinics

	El Centro	Brawley	SCVH	AZ (Sells)	National Average
Total population	42,888	25,191	81,872	1,747	316.5 million
Population per square mile	3,870	3,279	6,990	184	*unavailable*
Average family size	3.9	3.9	4	4.9	3.3
Average income	42,000	41,000	64,000	37,700	53,000
High school graduate	67%	69%	81%	68%	86%
Household with income under $20K	44%	40%	32%	49%	*unavailable*
Unemployment rate	11%	12%	8%	7%	6%
Household with public assistance	22%	22%	9%	35%	9%

*Data collected from American Community Survey, 2013; U.S. Census Bureau.

Small enrollments in the AZ clinic site might potentially be due to its location within the Tohono O'Odham Nation Indian Reservation, which comprises of 96% American Indian, 2% Caucasian, and <0.5% among other races (American FactFinder, 2013). Many American Indians still practice traditional holistic medicine for curing illnesses, therefore reliance on western medicine might not be their primary means of seeking medical treatment (Native American/Alaska Native Traditional Healing, 2014). Although they show similar socioeconomic disparities with El Centro and Brawley, their traditional ways of health and medicine might be the explanation for the low enrollment numbers in this clinic.

In the race/ethnicity variable, it was shown that both Native-Americans and African-Americans have the highest risk of any type of SARI illness. In fact, Table 4 had shown that African-Americans were four times as likely to develop some form of SARI illness than Hispanics. However, the sample size collected that had tested positive was relatively small compared to the other ethnicities so this might not truly represent the real risk associated with SARI illness. The population that had the highest number of both enrollment and positive cases was the Hispanic population, with 41.7% of the enrolled subjects tested positive for SARI illnesses. This is followed by the White-non Hispanic population, with an overall enrollment of 150 subjects and 37.3% of them showing positive cases in the study. Because both of these have the two highest numbers of both enrollment and positive cases, Hispanic and White-non Hispanic subjects were shown to be highest at risk for both viral and bacterial illness. Further studies are needed in order to fully understand how the other ethnicities would compare with both Hispanics and White-non Hispanics in relation to SARI illness incidences in this population. This might include increasing awareness of the surveillance program to these under-represented ethnic groups in order to increase their number of enrollees.

In the case of whether crossing the border within five days would be associated with SARI illness, 235 out of 303 (78%) positive cases had not crossed within the five day period prior to onset of illness. However, this might not mean crossing the borders in that period is a risk factor for SARI illness because other factors might be in play. These factors could be the length of incubation periods of certain illnesses, or the length of time from the onset of symptoms and when they decided to come to the clinic to seek medical help. As mentioned in the previous chapter, some respiratory diseases might have longer incubation period prior to onset of symptoms, which is why the majority of enrolled subjects had responded no to this question (Lessler et al, 2009). Other factors could also be socioeconomic, where the convenience of travel from small communities to the clinics might pose a problem financially. A focus group conducted by Garces, Scarinci, & Harrison (2006) had shown that there exists structural barriers to seeking medical care among immigrants such as lack of transportation, lack of proper documentation and health insurance, language barriers, and lack of knowledge of where to go for affordable care. Furthermore, sociopolitical barriers such as discrimination and fear of deportation also discourage people from seeking medical attention among the immigrant population (Bauer, Rodriguez, Quiroga, & Ortiz, 2000).

In the case of whether having the clinical symptom of pneumonia during the time of enrollment, there was an inverse trend between those who reported yes and the incidence of SARI illness in this population. It shows that more of those who had reported the presence of pneumonia had tested negative (64.6%), while only 35.4% of those who answered yes tested positive to some form of SARI illness. However, there was no difference seen among those who reported no pneumonia and the incidence of SARI illness. In addition, other factors might contribute to the increased presence of pneumonia seen in this population such as fungal infections, tuberculosis, or other types of chronic diseases that can cause pneumonia (Walker et al., 2013). In fact, the presence of comorbid conditions, including chronic respiratory and cardiovascular diseases, HIV, renal and liver diseases all can increase the risk of community acquired pneumonia between two and four fold (Torres, Peetermans, Viegi, & Blasi, 2013). Misdiagnosis of pneumonia can also be a factor in the lack of association found in this study. A retrospective study by Kanwar, Brar, Khatib, & Fakih (2007) showed that early administration of antibiotic prior to radiographic results had led to significant misdiagnosis of pneumonia between 2003 and 2005. In their study, they saw about a 60% increase in hospital admission with community acquired pneumonia diagnosis, but only <25% increase in discharge diagnosis of pneumonia. Often doctors rely solely on patient symptoms, without ordering further testing such as x-rays or blood tests, prior to prescribing proper course of treatment. Since some cases of pneumonia aren't acute infections, they are often misdiagnosed as such.

In the case of whether gender might be associated with SARI illness, there were no significant differences seen between males and females and the incidence of SARI illness in this population. It was shown in this study that the incidence of acute respiratory illness in both genders is almost equal in percentages of positive cases in the population. Therefore, it can be concluded that both genders are equally at risk of acquiring acute respiratory illness. However, no underlying factors were further identified in this study, such as pregnancy among females, which might affect the incidence of respiratory illness. Further studies are needed in order to determine the effects of these underlying factors in how gender might affect their risk from these respiratory diseases.

As stated in the previous chapters, the transmission of infectious diseases does not occur randomly in a population. Rather, they occur in a system of causation best explained by the epidemiological triangle that consists of three elements: external agent (pathogens), susceptible hosts, and suitable environment that permit interaction of the other two (Ferng, 2013). The outcome of this study highlights two of the elements (both hosts and environment) that make the population of communities along the border region highly susceptible to acute respiratory illness. As shown in this study, certain age groups and ethnicities were proven to be more at risk of acquiring respiratory illness than others based on different biological and cultural factors. Subsequently, socioeconomic factors such as low education levels and low-income households had contributed to a more suitable environment for respiratory illness to occur. Since low socioeconomic levels often are associated with poorer overall health of the people living in these communities, it promotes a foundation for susceptible communities to both acute and chronic diseases.

Limitations of the Study

As indicated in the first chapter, this study has some limitations to the generalizability, validity, and reliability of the results concluded. One of the major limitations is the subjects' recall of certain data collected upon enrollment to the surveillance program. Recall bias can greatly affect the results of any epidemiological studies because it relies on the accounts of the subjects, including the exposures to risks examined in this study. According to Raphael (1987), recall bias is introduced into the study when the accuracy of the recall regarding prior exposures is inaccurate or incorrect. These collected data would include subjects' influenza vaccine history, prior border crossings before onset of illness, and other symptoms present during the time of enrollment. If these collected data were inaccurate during enrollment, this affects the outcome of the analyses thereby misidentifying the true measure of association in the study.

Another limitation is the language barrier between the subjects and the research assistants enrolling them. These issues can pose potential problems with the subjects understanding certain questions required during enrollment, even discouraging some potential subjects from enrolling. Sarver and Baker (2000) indicated that some Latinos with limited English proficiency often reported fewer visits than English speaking patients in previous studies. In fact, they concluded that those who communicated through interpreter, or who did not have one, during hospital visits were less satisfied with their patient-provider relationship. By having research assistants who can speak Spanish fluently, the potential subjects might be more comfortable with the enrollment process, thereby increasing the chances of agreeing to the study.

There are also limitations that can happen during the testing phase of the program. Improper collection, storage, and shipment of samples can greatly affect the viability of the samples collected from the enrolled subjects, thereby affecting the outcome of the laboratory testing. Although certain precautions and steps are taken in order to preserve the integrity of the samples, there might be instances that are out of the hands of the laboratory personnel and others involved such as improper shipping conditions due to delays. In addition, improper laboratory testing can greatly affect the outcome of the results. Even though the best steps are taken to maintain good laboratory practices (through CAP compliance), there can be certain instances that might affect the outcomes such as temperature variations of equipment, viability of cells used for testing, and quality of reagents used. All of these can change the conditions from optimal, thereby affecting the outcome of the testing.

Lastly, there are also some socioeconomic and health factors, which were not collected during enrollment, that might have an effect on the probability of the subjects acquiring SARI illness. These socioeconomic factors include financial and medical disparity in acquiring adequate preventive health services and availability of proper nutrition, thereby resulting in them having higher risks of such illnesses. These factors are further explained as to how they impact the population health in the following sections.

Recommendations

There are certain recommendations that can be pursued further to better understand the effects of factors that were not considered in this study. One example is the medical history of subjects enrolled that might have an effect on the outcome of their samples tested. As mentioned before, certain chronic diseases present in the subjects might permit higher chances of disease susceptibility regardless of their age, especially in the older age groups. This would also include certain drugs they might be taking that have an effect on their overall immunity. Furthermore, vaccine histories of younger age groups can also help explain their disease susceptibility, as evident by the increasing number of parents opting out of the recommended vaccinations for their children (Jones et al., 2004; CDCb, 2007).

Another recommendation is the need to acquire an equal number of enrollments among the other race/ethnicities in order to have a better basis for comparison. In this study, the Native Americans and African Americans had very few enrollments compared to the other race/ethnicity groups, making it difficult to obtain true representation of the general population. A much higher enrollment among these two ethnic groups would be needed to form a better understanding of the real risk associated with SARI illness.

Increasing the number of days of border crossing prior to onset of illness can also help to truly evaluate whether this can play a major factor in acquiring acute respiratory illness in the border communities. As mentioned previously, certain diseases might have longer incubation period prior to onset of symptoms than five days, which affects the evaluation of this variable as a risk factor. These issues can be addressed by increasing the number of days to account for longer incubation periods.

Implications

Since the population living along the United States-Mexico border region of the country can be diverse, it is necessary to fully understand the dynamics of this population in terms of medical health capacity. By continuously surveying and analyzing the SARI subjects enrolled in the surveillance program, health officials can actively monitor the needs of this region by identifying specific risk factors that require attention. These risk factors include the evaluation of how underlying diseases affect the susceptibility of certain age groups to acute respiratory diseases, or how the opting out of recommended vaccinations can affect the incidence of diseases in this population, especially in the younger age groups. As shown in this study, children and elderly people are the most at risk for infectious respiratory illness. Because of this, it is important that steps must be taken to minimize their risks. One important way of maintaining healthy immune system is through proper nutrition, as indicated by Chandra (1997). Chandra had mentioned that nutrition is a critical determinant of healthy immune responses to diseases, and malnutrition is the most common cause of immunodeficiency worldwide. The low socioeconomic status of households living along the border communities often leads to poor nutrition due to lack of available fresh and healthy foods.

Most low-income neighborhoods in suburbs of the United States frequently lack full service grocery stores where residents can purchase fresh fruits and vegetables; and if available, they tend to be more expensive than fast-food alternatives (Larson & Story, 2009). To combat this disparity, an emphasis on proper nutrition should be addressed in these communities through various programs. One way of achieving this is through the Child Nutrition Programs being promoted by the U.S. Department of Agriculture. These programs aim at providing nutritional meals to child and adult care institutions, day care homes, and school districts (U.S. Nutrition Assistance Programs, 2015). By making sure that such programs are being implemented in communities and school districts along the border regions of the country, many children and elderly can have access to proper nutritional meals.

Another method of combating poor nutrition is to increase access to farmers markets in the neighborhoods that have limited access to fresh fruits and vegetables. These farmers markets allow farmers to come face to face with their consumers, thereby allowing residents to have access to fresh locally grown produce. By allowing families receiving Supplemental Nutrition Assistance Program (SNAP) to purchase fresh produce in farmers' market locations, they can provide nutritional alternatives for meals and snacks. In fact, there were more than 5,170 farmers markets who are authorized to process SNAP benefits in 2014, compared to just 850 in 2008 (McGill, 2015).

Aside from nutrition, increasing health literacy, especially in elderly people, can greatly improve their overall health. According to the U.S. Department of Health and

Human Services, only 12% of adults have proficient health literacy, or basic knowledge of health information and services needed to make appropriate health decisions (Health Literacy, 2010). When adults lack proper health literacy, they often make poor decisions about lifestyles and nutrition, thereby increasing their likelihood of acquiring chronic diseases later in life (Smith et al., 2014). This is more apparent in border communities that have significant educational disparity and language barriers, where those without high school degree had reported poorer physical health than those with high school degree (Howard, Sentell, & Gazmararian, 2006). To bridge this gap, it is important that emphasis on increasing health education and health promotion in local health clinics or during doctor visits. These primary care based interventions should focus more on disease prevention, rather than just treating diseases. One of the main objectives of the Healthy People 2020 is to increase the proportion of health care workforce with geriatric certification, which will allow more doctors and nurses to promote proper preventions of long-term chronic diseases among older adults (Older Adults, 2015).

Aside from increasing health literacy for adults, it is important that health literacy regarding children be addressed as well. As mentioned previously, infants and children have under-developed immune system so getting the much needed immunization can boost their immunity against numerous infectious diseases. In previous chapters, it was highlighted that the Healthy People Initiative 2020's objective of vaccine coverage of 80% of the population fell well below, with only 43% vaccine coverage as of 2011 (CDCc, 2011). Much of them are low-income minorities who lack resources and availability of the necessary vaccinations, as well as parents who believe the unfounded negative myths regarding vaccines (Korschun, 2011; Toyce, Boyce, & Poland, 2008). To counteract this, policies should be implemented that would promote truthful facts regarding the effectiveness and safety of vaccines to parents so that they can make the proper decisions based on facts. By promoting the importance of early vaccination of children through inter-agency collaborations, such as schools and health centers, would be a great way of spreading the truths to parents and communities, coupled with free no-cost vaccines to underserved communities.

In addition, identifying locations and/or race/ethnicities that are affected more on a regular basis can be addressed by increasing medical coverage through improving infrastructures and quality of health care given in these areas. Despite the fact that low-income neighborhoods is highly correlated with poor health, more and more hospitals and family physicians are moving away from poor neighborhoods to more affluent areas (Thomas, 2014). According to Thomas (2014), since 2000 nearly two-thirds of about 230 new hospitals opened were in wealthier, suburban areas of the country.

In addition, the number of hospitals in major cities in the United States had sharply fallen from 781 in 1970 to about 426 in 2010, which is a drop of nearly 46%. In order to increase the quality of health care in such neighborhoods, it is imperative that hospitals and clinics should be built in proportional to the population in need. One way to encourage this is through incentives to both physicians and health care workers who would choose to work in low-income neighborhoods so that it would encourage them to start/maintain their practices in these locations. This permits the expansion of health screenings and educational programs that can target underserved minorities in these communities for disease prevention, rather than treatment. In addition, this would help in reducing the distance the patients would need to travel to receive medical services, a barrier previously mentioned that discourages minorities from seeking help.

Barriers to accessing quality health care are also evident in low-income neighborhoods because of numerous factors such as lack of health insurance, subpar quality and limited access to health care. The Agency for Healthcare Research and Quality (2014) acknowledged that both African Americans and Hispanic Americans tend to receive the worst quality and access to care compared to White Caucasians according to the 2010 National Healthcare Quality and Disparities Reports. To overcome this, it is important that there is an open and honest communications between doctors and patients in order to foster good working relationships that the minorities can trust. It is important for those with language barriers be able to fully understand and communicate their concerns to the doctors, and vice versa. Bridging this gap can be obtained through employing bilingual staff members, or training in communicating and interacting effectively with patients from different cultures. Lastly, expansion and availability of affordable, comprehensive health insurance, such as the Affordable Care Act, can expand health coverage to reduce the rates of uninsured minorities.

Furthermore, the constant evaluation of the SARI subjects can also identify certain areas of the program that might need enhancements in order to improve the level of surveillance of acute respiratory diseases. A better understanding of the study population can be achieved, by addressing some of the recommendations mentioned earlier in this chapter. Through better surveillances of these diseases, public health officials can properly introduce new and/or amend existing health care policies that would minimize their impact in society. Because this border region of the country is one of the busiest ports of entry, from business reasons to tourism, it is imperative that respiratory communicable diseases be limited to minimize their ability to spread across other parts of the country.

Conclusion

From the 1918 Spanish flu to the swine flu of 2009, communicable respiratory diseases have plagued mankind for many years now. Because of their adaptability to different conditions, it is imperative that we keep up with their evolution so that we can minimize the unnecessary morbidity and mortality from acute respiratory diseases. Our only chance to combat these diseases is to fully understand the behaviors of these disease agents, and how they interact with humans. By continuously studying the ever-evolving risk factors associated with SARI, we can also apply the same adaptations through better prevention practices in high-risk population. As Thomas Fuller once said, “he who cures a disease may be the skillfullest, but he that prevents it is the safest physician” (Krieger, 2001, p. 313). Understanding the mechanics of infections, especially host susceptibility and environmental impacts, can be of tremendous asset in the fight against acute respiratory illness in any population.

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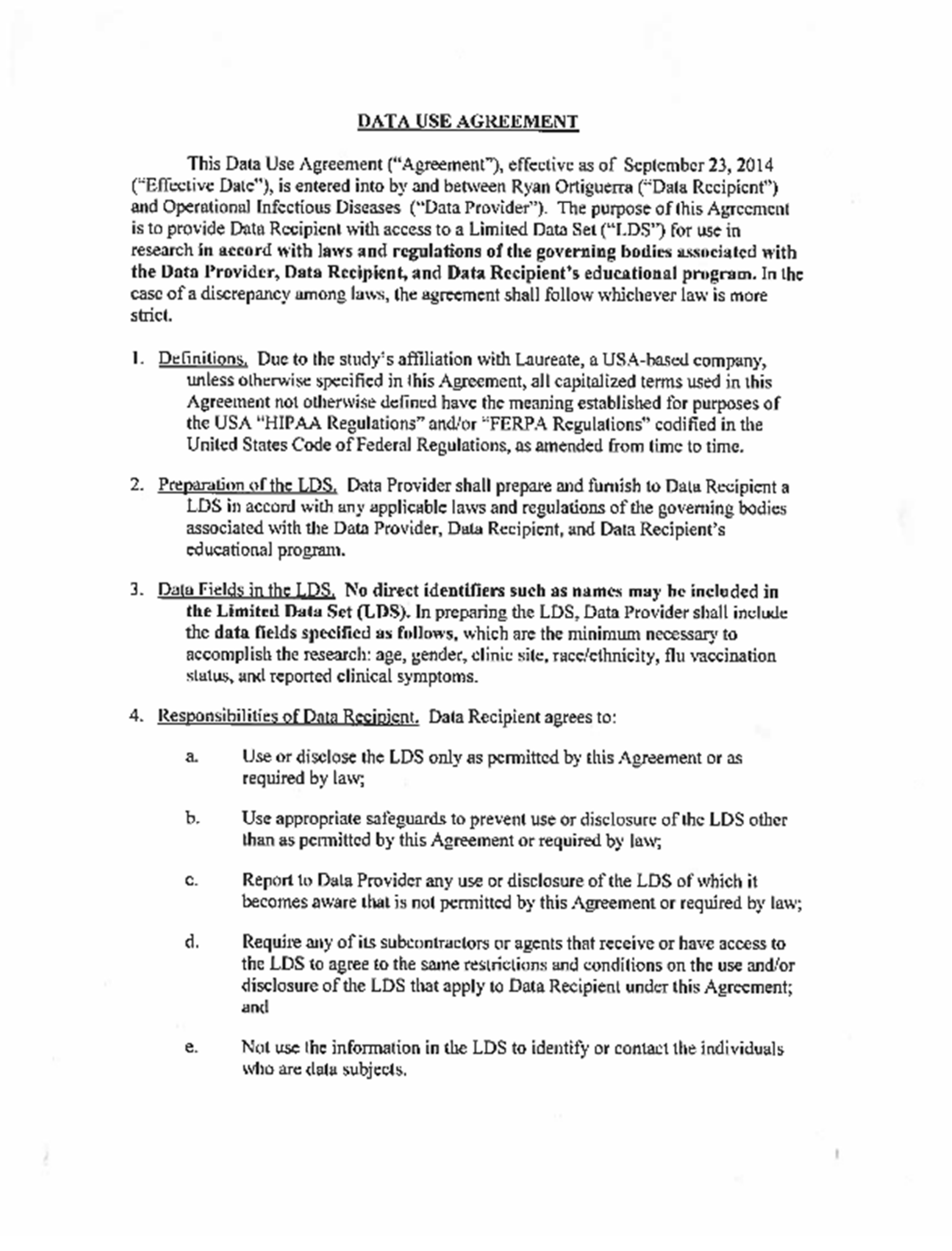
Appendix A: Data Use Agreement Form



DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of September 23, 2014 ("Effective Date"), is entered into by and between Ryan Ortiguerra ("Data Recipient") and Operational Infectious Diseases ("Data Provider"). The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research **in accord with laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.** In the case of a discrepancy among laws, the agreement shall follow whichever law is more strict.

1. Definitions. Due to the study's affiliation with Laureate, a USA-based company, unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the USA "HIPAA Regulations" and/or "FERPA Regulations" codified in the United States Code of Federal Regulations, as amended from time to time.

2. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.

3. Data Fields in the LDS. **No direct identifiers such as names may be included in the Limited Data Set (LDS).** In preparing the LDS, Data Provider shall include the **data fields specified as follows**, which are the minimum necessary to accomplish the research: age, gender, clinic site, race/ethnicity, flu vaccination status, and reported clinical symptoms.

4. Responsibilities of Data Recipient. Data Recipient agrees to:

   a. Use or disclose the LDS only as permitted by this Agreement or as required by law;

   b. Use appropriate safeguards to prevent use or disclosure of the LDS other than as permitted by this Agreement or required by law;

   c. Report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or required by law;

   d. Require any of its subcontractors or agents that receive or have access to the LDS to agree to the same restrictions and conditions on the use and/or disclosure of the LDS that apply to Data Recipient under this Agreement; and

   e. Not use the information in the LDS to identify or contact the individuals who are data subjects.

5. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS **for its Research activities only.**

6. Term and Termination.

   a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

   b. Termination by Data Recipient. Data Recipient may terminate this agreement at any time by notifying the Data Provider and returning or destroying the LDS.

   c. Termination by Data Provider. Data Provider may terminate this agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

   d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

   e. Effect of Termination. Sections 1, 4, 5, 6(e) and 7 of this Agreement shall survive any termination of this Agreement under subsections c or d.

7. Miscellaneous.

   a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in section 6.

   b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

   c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. <u>Counterparts.</u> This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. <u>Headings.</u> The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

DATA PROVIDER	**DATA RECIPIENT**
Signed: GT Brice	Signed:
Print Name: GARY T Brice, PhD	Print Name: Ryan Ortiguerra
Print Title: Director, Operational Infectious Diseases	Print Title: Doctoral Student

Appendix B: Letter of Cooperation from Research Partner

Letter of Cooperation from a Research Partner

Naval Health Research Center
Operational Infectious Diseases
McClelland and Patterson Road
Gate 4, Bldg. 330
San Diego, CA 92152

October 20, 2014

Dear Ryan Ortiguerra,

Based on my review of your research proposal, I give permission for you to conduct the study entitled "Examining Risk Factors Associated with Severe Acute Respiratory Infections (SARI)" within the Operational Infectious Diseases (NHRC). As part of this study, I authorize you to collect all necessary demographic, clinical, and laboratory data pertaining to the SARI study between 2010 and 2012. I understand that all of these previously collected data will be de-identified and use to conduct statistical examination to determine potential relationships between data collected from research participants with their laboratory confirmed results. Individuals' participation will be voluntary and at their own discretion.

We understand that our organization's responsibilities include: providing all necessary data from research participants including those collected during recruitment, and corresponding laboratory results. We reserve the right to withdraw from the study at any time if our circumstances change.

I confirm that I am authorized to approve research in this setting and that this plan complies with the organization's policies.

I understand that the data collected will remain entirely confidential and may not be provided to anyone outside of the student's supervising faculty/staff without permission from the Walden University IRB.

Sincerely,

Gary T. Brice, PhD
Email: gary.brice@med.navy.mil
Phone: 619-767-4842

Walden University policy on electronic signatures: An electronic signature is just as valid as a written signature as long as both parties have agreed to conduct the transaction electronically. Electronic signatures are regulated by the Uniform Electronic Transactions Act. Electronic signatures are only valid when the signer is either (a) the sender of the email, or (b) copied on the email containing the signed document. Legally an "electronic signature" can be the person's typed name, their email address, or any other identifying marker. Walden University staff verify any electronic signatures that do not originate from a password-protected source (i.e., an email address officially on file with Walden).