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Analysis of the morbidity and mortality of severe influenza infection in Clark County, Nevada for the 2010--2011 influenza season

Kindra Maureen St. Jacques
University of Nevada, Las Vegas

ANALYSIS OF THE MORBIDITY AND MORTALITY OF SEVERE INFLUENZA INFECTION IN CLARK COUNTY, NEVADA FOR THE 2010-2011 INFLUENZA SEASON

By

Kindra Maureen St. Jacques, BSN, RN

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Masters in Public Health
Department of Epidemiology and Biostatistics

Patricia Cruz Perez, Ph. D., Committee Chair

Sheniz Moonie, Ph. D., Committee Member

Timothy Bungum, Ph. D., Committee Member

Brian Labus, MPH, Committee Member

Eduardo Robleto, Ph. D., Graduate College Representative

Ronald Smith, Ph. D., Vice President for Research and Graduate Studies
and Dean of the Graduate College

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Abstract

Influenza circulates in the community in a fairly predictable manner each year; however, throughout the duration of any influenza season, influenza strains have the ability to evolve through antigenic mutations, viral reassortment, development of anti-viral resistance, and alterations in virulence. These changes are likely to cause illness among the unimmunized and can result in severe illness or death. Therefore, it is especially important to closely monitor severe influenza-associated hospitalizations and deaths. The University of Nevada, Las Vegas in collaboration with the Southern Nevada Health District (SNHD), Office of Epidemiology (OOE) analyzed data from the severe hospitalized influenza morbidity and mortality surveillance project for all residents of Clark County from October 1, 2010 through May 31, 2011. These data were analyzed using a descriptive approach to illustrate the epidemiology of severe influenza-associated hospitalizations and deaths, and an analytical approach to identify any associations between the variables of interest and the incidence of severe influenza-associated deaths. Among the study population (N= 158), the influenza strain type was found to be significantly associated with deaths (n= 25). Of the 36 cases diagnosed with influenza A (H1N1), 30.6% resulted in death; patients diagnosed with influenza B demonstrated a similar proportion of deaths at 29.6%; and influenza A (no subtype) was the most commonly diagnosed influenza strain (n= 94) in Clark County, but it had the lowest proportion of deaths at 6.4%. Vaccine status was not found to be significantly associated with death among hospitalized patients. The majority of deaths (n= 14) had an unknown vaccine status; therefore, these results are inconclusive. The length of stay

distribution for influenza-associated hospitalizations and deaths was non-normal because the majority of patients (70.4%) were admitted for ≤ 7 days. Transformed data showed that there was no statistically significant difference in the mean length of stay based on the influenza strain type. It is expected that the results of this study will help inform policy makers, hospitals, public health agencies, and other community partners in Clark County of the impact of influenza-associated hospitalizations and deaths.

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Introduction

Disease surveillance systems are an integral part of any public health agency, and because of the unpredictable nature of the virus, influenza surveillance monitoring systems are particularly essential. The influenza virus circulates in the community in a fairly predictable manner each year, typically from late fall to early spring; however, throughout the duration of any influenza season, influenza strains have the ability to evolve through antigenic mutations, viral reassortment, development of anti-viral resistance, and alterations in virulence (Bautista *et al.*, 2010). Changes in the influenza strain are likely to cause illness among the unimmunized and may result in more severe illness or death. Because of this, it is especially important to closely monitor hospitalized influenza patients, as they may be more likely to be infected with the most virulent strains of influenza. Influenza surveillance systems provide a picture of influenza as it spreads throughout a community and, most importantly, they are able to serve as warning systems for public health officials. The objective of this study was to describe the epidemiology of severe-influenza associated hospitalizations and deaths for the 2010-2011 influenza season in Clark County, Nevada.

It is well known that influenza infections can result in serious complications, or even death. The world witnessed this in the 1918-1919 "Spanish Flu" influenza pandemic in which the World Health Organization (WHO) estimates the worldwide death toll to have been at least 40 million (WHO, 2003). However, due to different and varying degrees of surveillance systems at the time of the pandemic (and today), mortality and morbidity statistics for influenza are difficult to pinpoint (Barry, 2004). In

his 2004 book entitled, *The Great Influenza,* John M. Barry cites varying reports ranging from 50 to 100 million deaths worldwide making it the "deadliest pandemic in history." Several pandemics have occurred since 1918, and it is the reminder of these tragedies of past pandemics that make surveillance monitoring systems paramount today.

Influenza viruses are prone to mutations because they replicate through ribonucleic acid (RNA) as opposed to deoxyribonucleic acid (DNA), and RNA replication lacks the "proofreading" mechanism necessary to recognize and correct mutations (www.niaid.nih.gov). The influenza virus genome is comprised of eight negative-strand RNA molecules surrounded by an outer layer (envelope) of surface glycoproteins (www.microbiologytext.com). The viral polymerase responsible for replication of the RNA molecules is prone to errors resulting in mutation(s) in the viral genome (www.microbiologytext.com). It is because of these mutations that the virus becomes unrecognizable to the human immune system and is able to infect the body (www.niaid.nih.gov).

Influenza viruses are categorized as types A, B, or C (Heymann, 2008). Influenza A viruses are the most commonly circulating strains in any given season, and are classified further into subtypes based on two viral surface glycoproteins: hemagglutinin (H), of which there are sixteen subtypes, and neuraminidase (N), of which there are nine subtypes (Heymann, 2008). Minor mutations in the surface proteins of the virus are referred to as antigenic drift, which occurs in both type A and B viruses, and accounts for seasonal variations. It is because of antigenic drift that we require "flu shots" to prepare our immune systems for the genetic alterations in the virus each year. Viral

reassortment causes major changes in the surface proteins of the virus, and this process is referred to as antigenic shift (www.niaid.nih.gov). Only influenza A viruses are capable of antigenic shift, and are responsible for widespread epidemics and pandemics. Influenza B viruses are more prone to antigenic drift, which account for the seasonal variations we see each year (www.niaid.nih.gov). Lastly, influenza C viruses result in mild human infections and are rarely responsible for significant outbreaks (Heymann, 2008).

Influenza viruses are not specific to humans; there are multiple animal species with receptors for influenza viruses and this is how viral reassortment occurs. Aquatic birds, chickens, humans, pigs, and whales are the primary reservoirs for influenza A viruses, while humans are the primary reservoir for influenza B viruses (www.niaid.nih.gov). Influenza A viruses are particularly worrisome because they can be spread from birds to pigs, from pigs to humans, and from humans to pigs (www.niaid.nih.gov). Pigs are referred to as "mixing vessels" because they have receptors for both avian and human influenza viruses (www.niaid.nih.gov). Antigenic shift occurs when two separate influenza A viruses (e.g., a human influenza A virus and an avian influenza A virus) both infect the same pig cell, replicate, and produce a new virus with a new combination of surface proteins to which the human population is susceptible.

Viral reassortment creates new strains of influenza that can spread quickly through nonimmune populations and result in widespread epidemics and global pandemics; however, pandemics occur rarely and require the alignment of various

conditions, one of which is limited immunity within a population. The more common scenario, antigenic drift, occurs seasonally where there are only slight variations in the antigenic makeup of the influenza virus. In 1997, the first known instance of an avian influenza virus (H5N1) spreading directly from fowl to humans, without viral reassortment in pigs, occurred. However, the virus was unable to transmit between humans beyond this point, and because of this fact an H5N1 pandemic has been avoided thus far (www.niaid.nih.gov). Surveillance measures, such as the one implemented by the Southern Nevada Health District (SNHD), are in place throughout the world to monitor closely for the spread of these potentially deadly viruses.

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommends annual influenza vaccination for everyone ≥ 6 months of age as the most effective measure to help protect against influenza infection and its related complications (Fiore *et al*., 2010). Because circulating influenza viruses are capable of antigenic drift, annual vaccination is recommended to help boost individual immunity to protect against changes in the influenza virus from year to year (Fiore *et al*., 2010). Vaccine status was collected by the SNHD on the study population of severe influenza-associated hospitalizations and deaths. Analysis of these data will help to inform public health officials of the impact of recent immunization, or lack thereof, on severe influenza-associated deaths for the 2010-2011 influenza season. These results may help to further demonstrate the importance of influenza immunization as a public health measure to prevent severe influenza illness and its complications.

Influenza infections can range from mild to severe and affect the population throughout the entire lifespan from the newly born to the elderly. Influenza infections can be deadly, especially when they occur in susceptible populations such as the immune-deficient, pregnant women, the very young, the elderly, or people with various chronic health conditions. Individuals with asthma, chronic obstructive pulmonary disease (COPD), and/or congestive heart failure (CHF) are particularly at risk for exacerbations of these chronic conditions triggered by influenza infection (www.cdc.gov/flu). Individuals with co-morbidities such as diabetes mellitus (DM), morbid obesity, and heart disease are also considered to be high-risk for developing influenza infections (www.cdc.gov/flu). Influenza has the potential to cause varying degrees of severity of illness and its associated complications depending on the susceptibility and the immune response of the host. Severe influenza infections culminating in pneumonia, bacterial infections, and acute respiratory distress syndrome (ARDS) can require hospitalization and may be fatal. Data on underlying/chronic disease status were collected from the SNHD for this surveillance project to identify which underlying conditions were most likely to result in severe influenza-associated deaths among those hospitalized. The information from this surveillance project will help to target high-risk populations for future influenza vaccination campaigns.

National and state level surveillance programs serve several purposes. They are useful in determining the health and economic burden associated with influenza circulation and in helping to prepare for future pandemics (Thompson, Comanor, & Shay, 2006). Specific to preparations for the future, surveillance systems are especially

critical in helping to determine estimates for vaccine production, to anticipate antiviral medication use and diagnostic testing needs, and to guide vaccination programs in prioritizing immunization to those at the greatest risk for morbidity and mortality (Thompson, Comanor, & Shay, 2006). Surveillance measures help to assess the burden of influenza on the health care system, which tends to fluctuate seasonally, and depends upon which influenza strain is predominantly circulating. Decades of preceding trends of influenza-associated hospitalizations and deaths have shown a pattern of increased morbidity and mortality during seasons in which influenza A (H3N2) viruses are the predominantly circulating strains (Thompson, Comanor, & Shay 2006). Knowing this can help public health officials, hospitals, and community agencies prepare for increases in morbidity and mortality based solely on the predicted circulating influenza strain.

According to the CDC, influenza infection is not a nationally notifiable disease; however, influenza-associated mortality among children less than 18 years of age is deemed a nationally notifiable event. This is due in part to the conditions of the 2003-2004 influenza season in which an unusually high number of influenza-related deaths occurred among healthy children less than 18 years of age (Bhat *et al.*, 2005; Thompson, Comanor, & Shay 2006). Prior to that influenza season, the national estimates for pediatric influenza-associated mortality among children less than 5 years of age were approximately 92 deaths per year among children (Bhat *et al.*, 2005). During the 2003-2004 flu season, 153 influenza-associated child deaths occurred, and 63% (96) of these deaths were among children under 5 years of age (Bhat *et al*., 2005). As a result, the

CDC requested enhanced surveillance and declared influenza-associated pediatric mortality a nationally notifiable condition starting in 2004 (Bhat *et al.*, 2005).

Each state has the authority to set forth regulations, specific to their jurisdiction, determining which infectious diseases and conditions will be reported to the state by health care providers (HCPs) and medical laboratories. These can be above and beyond the infectious diseases and conditions recommended to be reportable by the Council of State and Territorial Epidemiologists and the CDC. Nevada recognizes that influenza surveillance is an important and vital component of public health; therefore, it has deemed laboratory-confirmed influenza a reportable infectious disease. The SNHD initiated surveillance of severe influenza-associated hospitalizations and deaths in Clark County for the 2009-2010 H1N1 pandemic flu season and recommenced surveillance for the 2010-2011 influenza season. Mortality statistics from the 2010-2011 severe influenza-associated hospitalizations and deaths surveillance project will help to compare Clark County's seasonal rates to data from the 2009-2010 H1N1 pandemic influenza season and to future data. It is also important to compare these data to the national estimates to serve as an early warning system for the detection of potential changes in the epidemiology of influenza.

The Epidemiology and Prevention Branch of the Influenza Division at the CDC is responsible for conducting the national influenza surveillance program (CDC, 2010). There are several components to the CDC influenza surveillance system, all of which help the CDC to: 1) detect when and where geographically influenza is active; 2) identify which influenza viruses are in circulation; 3) detect any changes or mutations in

influenza viruses; 4) monitor influenza-related illnesses; and 5) measure the impact of influenza-associated hospitalizations and deaths throughout the United States (CDC, 2010). The CDC influenza surveillance incorporates many partners in public health on national, state, and local levels through the six measures described below.

1) Viral Surveillance

The reporting of laboratory-confirmed viral surveillance of influenza is dependent upon the collaboration of several laboratory entities throughout the United States. Approximately 80 U.S. WHO Collaborating Laboratories and 60 National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories report influenza results to the CDC (CDC, 2010). The total number of specimens collected and the total number of isolated viruses is reported each week in an influenza surveillance report issued by the CDC entitled "FluView", which reports influenza activity from October through mid-May each year (CDC, 2010). Local hospital and commercial laboratories often do not report the influenza A subtype, but the U.S. WHO identifies the influenza A subtype and the age of the individual from whom the specimen originated (CDC, 2010). Several U.S. WHO and state public health laboratories, the Southern Nevada Public Health Laboratory (SNPHL) included, send a portion of their collected samples to the CDC for further characterization to assess antigenic and gene sequencing, and antiviral resistance (CDC, 2010). These measures assist the CDC in identifying novel influenza A strains, increases in virulence, viral reassortment, and antigenic drift, which can all occur during a single influenza season.

Initiated for the 2009-2010 and continuing into the 2010-2011 influenza seasons, the Southern Nevada Health District, along with the SNPHL, requested additional respiratory virus panel samples from Clark County hospitals with microbiology laboratory capabilities to act in accordance with the CDC request for viral surveillance. The goal of this enhanced surveillance is to identify changes in the epidemiology of influenza among hospitalized patients and is above and beyond Nevada's mandated influenza morbidity and mortality surveillance. Both of these surveillance systems are vital in informing policy-makers, hospitals, and clinicians about the potential burden and nature of severe influenza infections in Clark County. Additionally, the samples collected through this enhanced surveillance program help identify the causative pathogen(s) in severe influenza-associated hospitalization(s) or death(s), and as discussed earlier, provide samples to the CDC for further characterization.

Mortality and Hospitalization Estimates

Estimating the mortality and hospitalization rates attributable to influenza is an important, albeit difficult task. Influenza prevention and control strategies are based on these estimates, as are preparations for seasonal influenza circulation and future pandemics (Thompson *et al.,* 2009). Influenza deaths affect the population differently based on age, underlying or chronic disease status, vaccine status, and/or by influenza strain type (Thompson *et al.*, 2009). Several methods of statistical analyses have been used to make these estimates, each with advantages and disadvantages. The estimates and rates of influenza morbidity and mortality for this analysis are obtained from the

CDC, which has done extensive research into the topic and uses the statistical methods employed by Thompson *et al*. (2010) in the Morbidity and Mortality Weekly Report (MMWR).

2) Mortality Surveillance

Typically, influenza mortality rates are concentrated among children less than 2 years of age, adults 65 years of age and older, and among persons of any age with co-morbidities that increase their risk of influenza infection (e.g., asthma, COPD, immunosuppression, etc.) (Fiore *et al.*, 2010). Thompson *et al*. (2010) conducted a long-term analysis of influenza mortality trends from the 1976-1977 through the 2006-2007 influenza seasons. Death certificates were reviewed for an underlying cause of death from pneumonia and influenza causes (considered to be the lower limit of the range) and/or from respiratory and circulatory causes (considered to be the upper limit of the range) (Thompson *et al.*, 2010). Deaths ranged from a high of 48,614 (2003-2004 influenza season) to a low of 3,349 (1986-1987 influenza season), and the mortality rate ranged from 16.7 to 1.4 deaths per 100,000 throughout the study period (Thompson *et al.*, 2010). These trends help to show that the mortality rate varies significantly from season to season based on which influenza strain is predominantly circulating. Overall, during the study period, influenza A (H3N2) strains were responsible for the highest rates of influenza mortality, and seasons in which H3N2 was the predominately circulating strain had 2.7 times higher influenza-associated mortality rates in comparison to seasons in which it was not (Thompson *et al.*, 2010). Influenza mortality

surveillance systems, such as the one described above, are helpful in estimating the burden of influenza on the nation and predicting when mortality rates will exceed the expected epidemic thresholds, such as during H3N2 dominant seasons. However, influenza mortality surveillance systems alone do not give a complete picture of the impact influenza can have on a community and its resources.

Mortality surveillance also occurs through the review of death certificates indicating influenza or pneumonia as the cause of death, or a contributing factor/underlying condition to the cause of death. Death certificates are monitored and classified by age group in over 122 reporting cities throughout the United States (CDC, 2010). The previous five years of pneumonia and influenza deaths are calculated using a regression model, and this estimate is considered to be the "seasonal baseline" to which the number of weekly deaths is compared (CDC, 2010). The "epidemic threshold" is reached when the number of reported weekly deaths exceeds 1.645 standard deviations above the baseline estimate (CDC, 2010). Rates above this threshold serve as an indicator of elevated influenza mortality above what is expected, suggesting that more aggressive monitoring or other public health interventions may be warranted.

Finally, as discussed earlier, the CDC recommended that influenza-associated pediatric mortality became a nationally notifiable event in 2004. On the occasion of an influenza-related pediatric death, an "Influenza-Associated Pediatric Deaths Case Report Form" is completed by the local or state public health agency. This report includes detailed information regarding demographics, the circumstances of death, the type of influenza testing conducted, any medical care received, clinical diagnoses and

complications, medication and therapy history, and influenza vaccine history. This information is then submitted to the CDC by the state public health department. Excluding the 2009-2010 H1N1 pandemic season, the CDC (2010) reported a range of 46 to 153 pediatric deaths from 2004 through the 2010-2011 influenza season. The CDC reported unusually high pediatric mortality rates (N= 345) as a result of the H1N1 pandemic (CDC, 2010). Influenza can be quite harmful to children, especially those under 5 years of age (CDC, 2010); therefore, it is not difficult to understand why pediatric mortality surveillance is a critical function of public health.

3) Hospitalized Surveillance

Hospitals, public health entities, pharmaceutical companies, diagnostic partners, and key policy-makers all rely on morbidity and mortality estimates to help guide their business practices and interventions. These entities rely specifically on severe hospitalized influenza surveillance systems to make critical decisions regarding the allocation of important resources (e.g., medical supplies, vaccine stockpiles, antiviral medication stockpiles, and nursing, physician, and support staffing in hospitals, emergency departments, and clinics). Influenza-related hospitalizations are difficult to identify because influenza can exacerbate pre-existing chronic health conditions; therefore, the admitting or discharge diagnosis may not be attributable to influenza even though it was paramount in the progression of events leading to hospitalization or death.

Currently, there are two reporting systems that collect and submit data to the CDC to help estimate the number of influenza-associated hospitalizations that occur throughout an influenza season. The first is the Influenza Hospitalization Network (FluSurv-NET), which collects data in counties from the 10 states participating in the Emerging Infections Program (EIP) and from six other states (CDC, 2010); Nevada is not one of these 16 reporting states. Reported cases are defined as patients of all ages with confirmed laboratory testing performed as part of their inpatient care (CDC, 2010). The second reporting system is the Aggregate Hospitalization and Death Reporting Activity (AHDRA) in which state and local health authorities voluntarily participate by submitting weekly aggregate reports of the number of laboratory-confirmed hospitalizations and deaths (CDC, 2010). Although these systems do not depict an all-inclusive portrait of influenza-associated hospitalizations, they are useful in identifying trends that could help to direct state and local public health interventions and help to make key decisions involving resource allocation.

Thompson *et al.* (2004) estimated the annual influenza-associated hospitalizations in the United States based on age, hospital discharge category, and influenza type. The authors obtained data from the National Hospital Discharge Survey (NHDS) for the 1979-1980 through the 2000-2001 influenza seasons, and this information was weighted to obtain the national estimates of hospitalization rates per influenza season. The International Classification of Diseases (ICD), 9th edition, Clinical Modification (ICD-9-CM) discharge codes for pneumonia and influenza hospitalizations (low), and respiratory and circulatory hospitalizations (high) were analyzed. The ICD

codes were categorized as either the "primary" if they were the first diagnosis listed, or as "any" if they were listed anywhere on the discharge summary.

Yearly averages for the study period ranged from 94,735 (primary) to 133,900 (any) of pneumonia and influenza hospitalizations. For respiratory and circulatory hospitalizations, average rates were higher: 226,054 (primary) and 294,128 (any). As with the mortality statistics discussed earlier, Thompson *et al.* (2004) found that seasons in which the predominately circulating strain was influenza A (H3N2) displayed higher rates of hospitalization in comparison to seasons in which influenza B and influenza A (H1N1) strains predominated. The summary of their findings is listed in Table 1.

Table 1: Influenza-associated hospitalizations by predominant influenza type and subtype from the 1979-1980 through the 2000-2001 influenza seasons (Thompson *et al.*, 2004)

National Hospital Discharge Survey (NHDS) Codes	Hospitalization Rates per 100,000 person-years		
	Influenza A (H1N1)	Influenza B	Influenza A (H3N2)
Pneumonia and influenza (primary)	22.6	37.7	43.5
Respiratory and circulatory (primary)	55.9	81.4	99.0

Overall, age trends showed that the lowest rates of hospitalizations occurred among the 5 to 49 years age group, and hospitalization rates showed a positive correlation with age, especially among those over the age of 85 (Thompson *et al.*, 2004). Children 5 years and under displayed annual averages of 18.5 (primary) to 26.3 (any) documented pneumonia and influenza hospitalizations per 100,000 person-years; and 107.9 (primary) to 113.9 (any) documented respiratory and circulatory hospitalizations

per 100,000 person-years (Thompson *et al.*, 2004). Hospitalization rates climb steadily after the age of 65, increasing dramatically with each 5-year increment; rates peaked with those 85 years of age and greater (Thompson *et al.*, 2004). Persons over the age of 85 displayed annual averages of 628.6 (primary) to 777.3 (any) documented pneumonia and influenza hospitalizations per 100,000 person-years; and 1194.9 (primary) to 1669.2 (any) documented respiratory and circulatory hospitalizations per 100,000 person-years (Thompson *et al.*, 2004). The extremes of age (< 5 years and > 65 years) showed the greatest rates for all categories (both primary and any listed pneumonia and influenza, and respiratory and circulatory hospitalizations) of influenza-associated hospitalizations.

Using mortality statistics from the same study period, the authors calculated the relative risk of influenza-associated hospitalization in comparison to influenza-associated death. These results showed that children under 5 years of age are 270 times more likely to experience influenza-associated hospitalization compared to influenza-associated death, while adults ages 50-64 were at a much lower risk (relative risk= 11) for hospitalization than death (Thompson *et al*., 2004). According to the CDC (2010), an estimated 20,000 children under 5 years of age are hospitalized annually as a result of influenza. These data stress the importance of yearly immunization for influenza, especially among this age group, and for those in direct contact with or care of young children.

In the same study, Thompson *et al.* (2004) also found that the median length of hospital stay was correlated with patient age and diagnosis. Length of stay data are critical to resource allocation decisions for hospitals. The national length of stay results

by age group are summarized in Table 2. The SNHD surveillance data provide length of stay based on influenza type, which may help to further delineate how influenza-associated hospitalizations impact Clark County's hospitals.

Table 2: National annual median length of stay (days) by age group and diagnosis for influenza-associated hospitalizations (Thompson *et al*., 2004)

Primary hospitalizations diagnoses	Length of stay (days) by age group							
	< 5	5-49	50-64	65-69	70-74	75-79	80-84	≥ 85
Pneumonia and influenza	3	4	6	6	6	7	7	7
Respiratory and circulatory	3	3	4	5	5	5	6	6

4) Outpatient Illness Surveillance

A database of more than 3,000 HCPs throughout the nation reports information on over 25 million outpatients yearly through the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) (CDC, 2010). This information is collected weekly and identifies the number and age of people seeking outpatient care meeting the following CDC criteria for Influenza-like Illness (ILI): 1) body temperature greater than 100˚F, and 2) a cough and/or sore throat in the absence of a known cause other than influenza (CDC, 2010). This information is then weighted and compared to regionally determined baseline data (CDC, 2010). The reported outpatient ILI activity level by state is displayed on the "ILI activity indicator map" to provide a national indicator of influenza transmission and activity throughout the duration of the influenza season (CDC, 2010). The SNHD, OOE collects a frequency count of laboratory-confirmed influenza cases

received from outpatient settings and from patients who are hospitalized for less than 24 hours.

5) Geographic Spread

The State and Territorial Epidemiologists Reports are submitted weekly to provide a more adequate geographic representation of national influenza activity (CDC, 2010). This information is displayed in the form of a geographical map of the United States released each week to show the progression of disease throughout the duration of each influenza season. Each state classifies and reports their weekly activity based on the following criteria as defined by the CDC (2010):

1. **No activity:** No reported increase in the number of cases of ILI and no laboratory-confirmed cases of influenza.

2. **Sporadic:** Reports of small numbers of laboratory-confirmed influenza cases or a single laboratory-confirmed influenza outbreak, but no increase in cases of ILI.

3. **Local:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in one region of the state.

4. **Regional:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least two, but less than half, the regions of the state with recent laboratory evidence of influenza in those regions.

5. **Widespread:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state with recent laboratory evidence of influenza in the state.

Since the 2009 H1N1 pandemic, and with these surveillance functions in mind, the SNHD, OOE has conducted a severe hospitalized influenza morbidity and mortality surveillance program to describe the epidemiology of influenza in Clark County, Nevada. The SNHD severe influenza-associated hospitalizations and deaths surveillance project

most closely resembles the viral, morbidity, and mortality surveillance components of the CDC national influenza surveillance program. In this study, we conducted a secondary analysis of these surveillance data to examine severe influenza-associated hospitalizations and deaths, and to address the following research questions and hypotheses.

Research Questions

Among severe influenza-associated hospitalizations:

1. Will the strain of influenza be associated with death?
2. Will vaccine status be associated with death?
3. Will there be a difference in the length of stay based on the influenza type?

Hypotheses

Hypothesis #1. Among severe influenza-associated hospitalizations:

H_o: Influenza strain type will not show an association with severe influenza-associated deaths.

HA: Laboratory confirmation of influenza A (H1N1) will show a positive association with severe influenza-associated deaths.

This hypothesis is based on the worldwide prevalence of influenza A (H1N1) for the 2009-2010 influenza season and the fact that it is still the predominately circulating strain in Europe (WHO, 2011). This hypothesis will be tested using Chi-square analysis

to determine if influenza strain type(s) (categorical predictor variable) is/are associated with death (dichotomous outcome variable).

Hypothesis #2. Among severe influenza-associated hospitalizations:

H_o: Vaccine status will not be associated with severe influenza-associated deaths.

HA: Lack of seasonal influenza vaccination for the 2010-2011 influenza season prior to hospitalization will show a positive association with severe influenza-associated deaths.

This hypothesis is based on the fact that the lack of recent influenza immunization results in susceptibility to infection due to the highly mutagenic nature of influenza viruses. The influenza vaccine is updated and developed each year using surveillance systems to identify and predict circulating strains (CDC, 2010). If the population is unimmunized to these strains, they are more susceptible to infection, especially those who have risk factors for influenza infection. This hypothesis will be analyzed using Chi-square analysis to determine if vaccine status (categorical predictor variable) is associated with death (dichotomous outcome variable).

Hypothesis #3. Among severe influenza-associated hospitalizations and deaths:

H_o: The type of influenza strain will have no effect on the average length of hospital stay.

HA: Influenza type A viruses will result in a longer average patient length of stay in comparison to influenza type B viruses.

This hypothesis is based on the fact that influenza B viruses are prone to antigenic drift and, typically, cause mild illness in comparison to influenza A viruses, which are capable of antigenic shift and generally result in more severe illness (www.niaid.nih.gov). It is predicted that influenza B viruses will not be associated with severe influenza illness and the average length of stay will be shorter in comparison to patients with influenza A viruses. This hypothesis will be tested using an analysis of variance (ANOVA) to compare the length of stay (continuous outcome variable) among severe influenza-associated hospitalizations and deaths categorized by influenza strain type (categorical predictor variable). Mean differences will be compared between the groups, and post-hoc analyses will be conducted should the overall model show significance.

Methods

Study Population and Inclusion Criteria

The study population consists of all residents of Clark County, Nevada who were hospitalized for ≥ 24 hours or expired between October 1, 2010 and May 31, 2011, and met the following criteria:

1. **Clinical case definition:** Abrupt onset of at least two of the following specific symptoms: body aches, dry cough, fever, headache, rhinitis, severe fatigue, and/or sore throat. Other symptoms uncommon in adults, but that might occur in children were also included, such as: diarrhea, nausea, otitis media, and vomiting; **AND**

2. **Laboratory criteria for diagnosis:** Including one of the following:

    a. Isolation of the virus by culture or detection of virus by real time reverse transcription polymerase chain reaction (*r*RT-PCR) from nasopharyngeal or throat swabs, nasal wash or nasal aspirate(s);

    b. Positive testing from a Food and Drug Administration (FDA) approved rapid diagnostic test. The rapid test is only acceptable as a screening method within the current influenza season if it has been confirmed by *r*RT-PCR or culture; however, it will be accepted as evidence of infection if the patient is hospitalized or has expired.

The diagnostic testing methods differ based on the identification method employed, the type of sample from which evidence of influenza infection is extracted, and the time required to process the results. Rapid diagnostic testing methods detect antigens specific to the influenza virus type (A or B) from any of the following specimens (dependent upon the rapid test utilized): nasopharyngeal swab/aspirate, nasal wash/aspirate, lower nasal swab, throat swab, and/or bronchioalveolar lavage (CDC, 2011). The viral subtype for influenza A viruses is unable to be identified by rapid diagnostic testing. The advantage to using rapid diagnostic testing is that results are processed in 10 to 15 minutes (CDC, 2011). There are multiple FDA approved rapid diagnostic tests available; however, none are as sensitive at detecting and/or isolating the virus as viral culture or *r*RT-PCR.

Viral culture is considered to be the "gold standard" for influenza virus testing, but can take from 2 to 14 days to isolate the virus from respiratory epithelial cells (Ruest

et al., 2003; CDC, 2011). To optimize effectiveness, initiation of antiviral medication is recommended within 48 hours of the onset of flu-like symptoms (www.cdc.gov/flu); therefore, the time period required for viral culture is one disadvantage to its use. The *r*RT-PCR is another diagnostic testing method more sensitive than the rapid antigen test. The PCR method utilizes the extraction of RNA particles from the specimen sample, and uses fluorescent primers and a probe to amplify the viral RNA particles present, allowing for detection of the target virus (www.focusdx.com). The *r*RT-PCR requires about 2-4 hours for the results to be processed, which is considerably less than the viral culture method. Both the viral culture and *r*RT-PCR methods require specimen samples from any of the following: nasopharyngeal swab/aspirate, nasal swab/aspirate/wash, throat swab, bronchioalveolar lavage, and brochioalveolar lavage sputum (CDC, 2011).

Exclusion Criteria

Subjects excluded from the surveillance project were those not admitted for greater than 24 hours, did not test positive for influenza by any of the diagnostic testing methods listed, or whose primary residence was located outside of the jurisdiction covered by the SNHD (i.e., Clark County).

SNHD Data Collection Process

As part of routine public health practice, the SNHD conducts seasonal influenza surveillance through several methods, both passive and active. The surveillance data on severe hospitalized influenza patients are collected as mandated by the Nevada

Administrative Code (NAC). According to the NAC, all HCPs and medical laboratories are required to report positive laboratory-confirmed influenza results to the SNHD. Acceptable laboratory testing results are outlined above in the influenza case definition section. Through this passive surveillance, positive influenza test results from laboratories throughout Clark County and, occasionally, from laboratories throughout the nation are reported to the OOE.

Passive surveillance also occurs in the review of the cause of death (COD) listed on all death certificates received by the SNHD. Any deaths attributed to influenza are noted and actively investigated if further information is required to assess the clinical circumstances surrounding the death. Commonly listed complications of influenza illness are cardiopulmonary arrest, pneumonia, and/or respiratory failure. The cases with these diagnoses listed as the COD or as contributing factors were further investigated to elicit influenza-related infection or involvement.

Disease Investigation and Intervention Specialist (DIIS) staff members at the SNHD further investigated each report of influenza to determine if it met the case definition for severe-hospitalized influenza morbidity or mortality. Clinically compatible cases that met the case definition criteria listed above were entered into the Microsoft SharePoint survey database. Various subject information were abstracted from patient medical records and included the following: demographics, hospitalization status, hospital name, date of admission, admission to intensive care unit status, mechanical ventilation status, date of discharge, transfer status and location of transfer, death, date of death, underlying conditions, antiviral medication, antiviral name and start date, type

and date of laboratory confirmation, name of laboratory, influenza type, and vaccine history (Appendix A). The data collection process required communication with the following entities: infection control practitioners, HCPs, and the medical records departments of all Clark County hospitals, the Clark County Coroner's Office, and various members of the community.

Study Design and Approach

In this prospective cohort study, data were collected upon receipt of laboratory-confirmation of influenza infection and admission to the hospital for greater than 24 hours. Patients were followed forward in time until either one of two outcomes occurred: discharge or death. A descriptive approach was utilized to calculate central tendencies and frequencies to depict the distribution of severe influenza-associated hospitalizations and deaths in Clark County for the 2010-2011 influenza season. An analytical approach was utilized to identify associations between the various predictor variables of interest and death among the severe influenza-associated hospitalizations.

Data Analyses

The variables collected from the severe-hospitalized influenza morbidity and mortality surveillance project from October 1, 2010 through May 31, 2011 were operationalized according to the data dictionary in Appendix A. Population-based hospitalization and mortality rates were calculated using the 2010 U.S. Census Bureau statistics for Clark County, Nevada. Hypothesis testing was performed as described

above utilizing both Chi-Square and ANOVA statistical methods. Microsoft® Excel, PASW 18 and 19, and SPSS® software were utilized for the statistical analyses.

Human Subjects

An UNLV Institutional Review Board (IRB) project proposal form was completed, and approval was granted (Protocol #1104-3806M) for this research study in May 2011. The data collection process was completed by the SNHD in accordance with mandates set forth by the NAC for the purposes of routine public health practice. The data collected from the SNHD surveillance project were de-identified of all personal patient identification information and any dates specific to birth, admission, laboratory confirmation, anti-viral initiation, discharge, and/or death. These data were recoded to coincide with the CDC MMWR calendar. Permission was granted from the SNHD, OOE to analyze this information for the purposes of this project.

Results

Population characteristics

One hundred and fifty-eight (N= 158) severe influenza-associated hospitalizations and deaths were reported to the SNHD for Clark County, Nevada from October 1, 2010 through May 31, 2011. The first reported case occurred in the week ending October 2, 2010 (week 39), and the last occurred in the week ending May 7, 2011 (week 17); the peak number of cases was reported in the week ending February 19, 2011 (week 7) (Figure 1). Males accounted for 81 cases (51.3%); females accounted

for 77 cases (48.7%). Race was obtained from the hospital medical records demographic face sheet, and subjects were categorized as follows: 9 Asian/Pacific Islander (5.7%), 27 black (17.1%), 2 Native American or Alaskan Native (1.3%), 81 white (51.3%), and 39 other (24.7%). Approximately 71% of the study population was non-Hispanic (n= 112).

Age of subjects ranged from newborn to over ninety years of age. Severe influenza-associated hospitalizations and deaths were categorized into the following age groups: 41 were < 5 years of age (25.9%), 52 were 5-49 years of age (32.9%), 20 were 50-59 years of age (12.7%), 16 were 60-69 years of age (10.1%), 19 were 70-79 years of age (12%), and 10 were ≥ 80 years of age (6.3%). The distribution of cases by age group and the ending date of the week of admission or death (in the case of those not admitted to the hospital) are displayed in Figure 1.

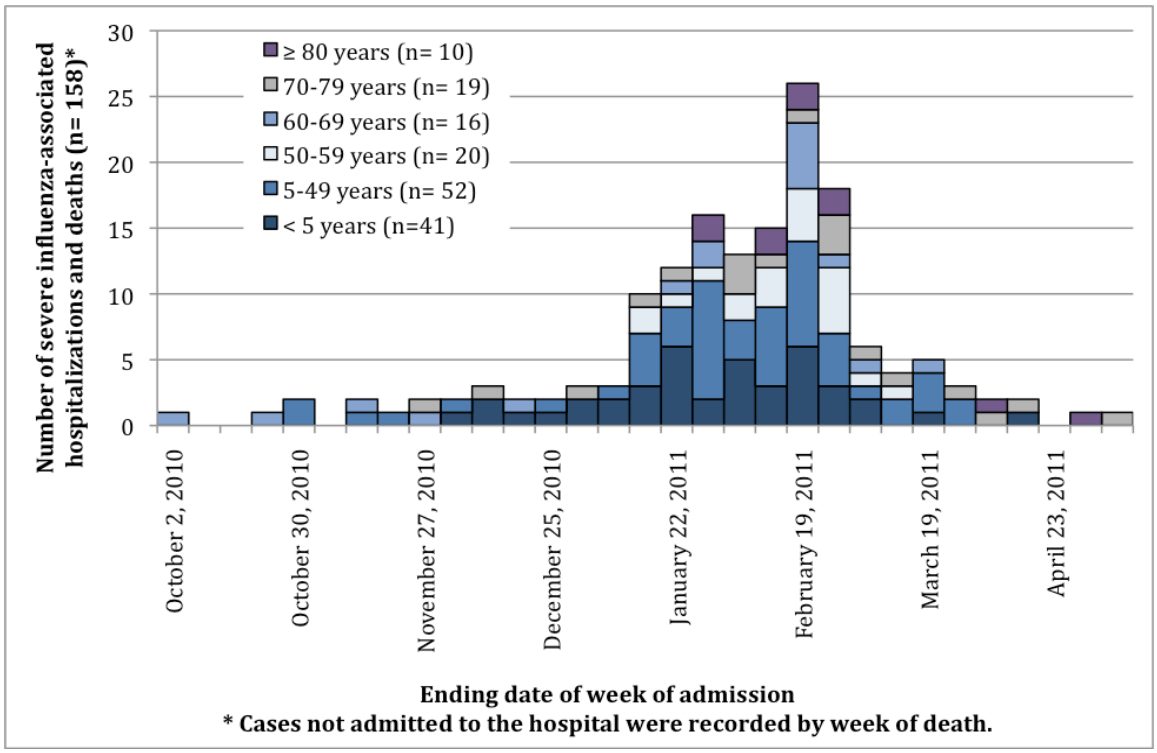

Figure 1: Severe influenza-associated hospitalizations and deaths by week and age group- Clark County, 2010-2011 influenza season

Mortality and hospitalization rates

During the study period, a total of 25 (15.8% of the study population) severe-influenza associated deaths were reported to the SNHD. The overall severe influenza-associated mortality rate for Clark County based on the 2010 census data (total population 1,951,269 residents in Clark County) was 1.28 per 100,000. Severe influenza-associated hospitalizations and deaths were further categorized by age group, and by mortality and hospitalization rates by age group (Table 3). The lowest percentage of deaths occurred among those < 5 years of age and those 70-79 years of age (n= 2, 8% for both), and the highest percentage of deaths occurred among those 5-49 years of age (n= 7, 28%). Females accounted for 68% of deaths, even though the overall study

population was normally distributed with regards to gender, 81 (51.3%) males and 77 (48.7%) females. A relative risk was calculated to determine if females were more likely to die than males, but these findings were not found to be statistically significant, RR= 2.235 (C.I. 0.972, 5.423), p= 0.059.

Table 3: Severe influenza-associated hospitalizations and deaths by age group- Clark County, 2010-2011 influenza season (N/A = not applicable)

Age groups (years)	All deaths by age group *	Mortality rate per 100,000	Hospitalizations by age group **	Hospitalization rate per 100,000
Totals (N= 158)	n= 25 (%)	1.28	n= 153 (%)	6.82
< 5	2 (8)	1.44	39 (25.5)	28.07
5 – 49	7 (28)	0.56	49 (32)	3.92
50-59	5 (20)	2.09	20 (13.1)	8.37
60-69	6 (24)	3.31	16 (10.5)	8.82
70-79	2 (8)	2.09	19 (12.4)	19.82
≥ 80	3 (12)	6.51	10 (6.5)	21.72
Gender				
Females	17 (68)	N/A	74 (48.4)	N/A
Males	8 (32)	N/A	79 (51.6)	N/A
***Includes both the deaths admitted to the hospital (n= 20) and those who were not (n= 5)** ****Includes deaths that were admitted to the hospital (n= 20)**				

To compare the 2010-2011 severe influenza morbidity and mortality rates to the national rates, the data were recalculated to reflect the same time period from October 1, 2010 through April 30, 2011 and to reflect the same age group categories utilized by the CDC (Table 4). Overall, the hospitalization rates in Clark County are significantly lower than those of the nation.

Table 4: Comparison of Clark County and U.S. national influenza-associated hospitalization rates from October 1, 2010 through April 30, 2011

Age group	Clark County, Nevada (n= 153)*	United States**
	Hospitalization rate per 100,000	Hospitalization rate per 100,000
0-4 years	28.1 (n= 39, 25.5%)	43.8
5- 17 years	2.6 (n= 9, 5.9%)	8.5
18-49 years	4.4 (n= 40, 26.1%)	10.7
50-64 years	8.5 (n= 29, 19.0%)	21.7
≥ 65 years	16.3 (n= 36, 23.5%)	62.5
***Includes deaths that were admitted to the hospital (n= 20)** ****FluSurv-NET surveillance data for the 2010-2011 influenza season (CDC, 2011)**		

According to the CDC (2011), there were 311 laboratory-confirmed deaths due to pneumonia and influenza in the U.S. during the 2010-2011 influenza season (October 3, 2010 through May 21, 2011). Of these deaths, 105 deaths were among children less than 18 years of age (CDC, 2011). In Clark County, of the 25 reported deaths, there were 3 pediatric deaths (under the age of 18) for this same time period; 2 of which were < 5 years of age. In the United States, there were 46 total pediatric deaths under the age of 5 years (CDC, 2011).

Influenza vaccination status

Vaccine status was obtained on 132 of the 158 subjects, which was 83.5% of the study population. Individuals who received the influenza vaccine prior to 2010, during, or after their hospitalization were categorized as not receiving the 2010-2011 influenza vaccine for the purposes of this study. Of the total study population (N= 158), 93 (58.9%) subjects were not vaccinated, 39 subjects were (24.7%), and 26 subjects were classified as unknown (16.5%). Of the total population with known vaccine status (n=

132), 93 (70.5%) were not vaccinated and 39 (29.5%) were. Among the non-vaccinated, 8 patients expired (8.6%), and among the vaccinated, 3 patients expired (7.7%); the remaining deaths (n= 14) had an unknown vaccine status. Chi-square analysis was run between vaccine status and death (excluding those that were unknown), and vaccine status was not found to be significantly associated with death among hospitalized patients, χ^2 (1, n= 132) = 0.030, p= 0.584. Fisher's Exact Test p-value was reported due to the small sample size. Relative risk was calculated and also found to be non-significant, RR= 0.894 (C.I. 0.192, 3.481), p= 1.00.

Influenza strain type

The largest proportion of test results were reported as influenza rapid tests (n= 86, 54.4%), followed by *r*RT-PCR (n= 67, 42.4%), both rapid test and *r*RT-PCR (n= 4, 2.5%), and viral culture (n= 1, 0.6%). The majority of testing occurred in the hospital laboratory setting (n= 91, 57.6%), and the remaining were performed either through commercial laboratories (n= 58, 36.7%), out-of-state laboratories (n= 8, 5.1%), or the SNPHL (n= 1, 0.6%). Influenza A (no subtype) was the most commonly reported strain among severe influenza-associated hospitalizations and deaths (n= 94, 59.4%), followed by influenza A (H1N1) (n= 36, 22.8%), influenza B (n= 27, 17.1%), and influenza A (H3) (n= 1, 0.6%) (Figure 2).

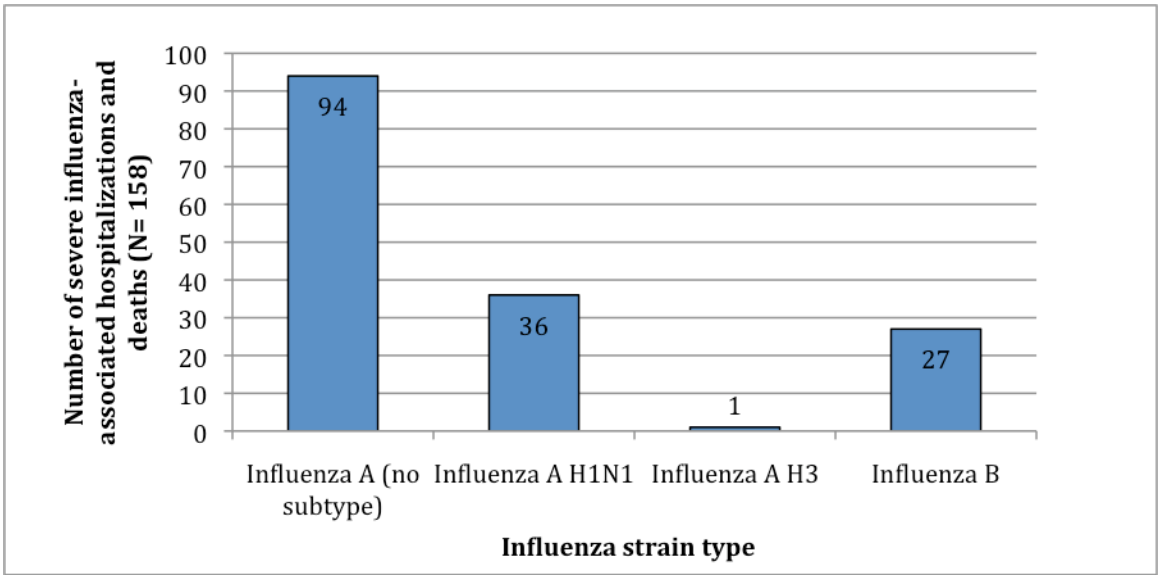

Figure 2: Total number of cases by influenza strain type- Clark County, 2010-2011 influenza season

According to a summary of the viral surveillance conducted by the CDC (2011), the predominant circulating influenza type in the U.S. for the 2010-2011 influenza season was influenza A, which was identified in over 74% of the positive laboratory-confirmed specimens received. Seventy-one percent of the influenza A virus specimens were further characterized by subtype; 62% were identified as influenza A (H3N2) and the remaining 38% were influenza (H1N1) (CDC, 2011). Influenza A (H3N2) viruses appeared to be the predominant strain during the 2010-2011 influenza season; however, both influenza A (H1N1) and influenza B (26%) were identified in significant numbers at various time periods and geographical locations throughout the season (CDC, 2011).

Influenza strain was significantly associated with deaths, G = 16.2, p= .001. Of the 36 cases diagnosed with influenza A (H1N1), 11 (30.6%) resulted in death. Patients

diagnosed with influenza B (n= 27) demonstrated a similar proportion of deaths at 29.6% (n= 8). Influenza A (no subtype) was the most commonly diagnosed influenza strain (n= 94) in Clark County; however, it had the lowest proportion of deaths at 6.4% with 6 deaths occurring among those who tested laboratory positive.

The distribution of influenza strain by the ending date of the week of admission, or death in the case of those who expired at home (n= 5), is displayed in Figure 3. Results show the week ending on February 19, 2011 (week 7) to be the peak activity of influenza-associated hospitalizations and deaths in Clark County with 26 cases reported for that week. According to the CDC (2011) summary of the 2010-2011 influenza season, national influenza activity peaked in early February as well.

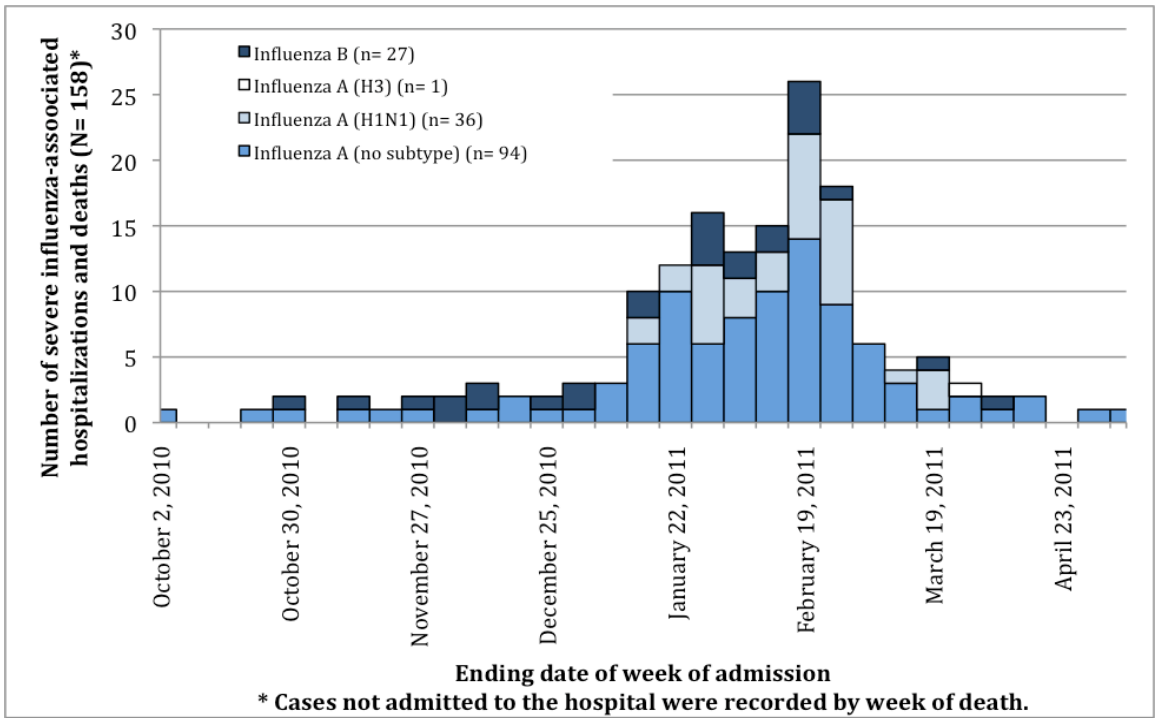

Figure 3: Severe influenza associated hospitalizations and deaths by week and influenza strain- Clark County, 2010-2011 influenza season

Hospitalization characteristics

The largest number of severe influenza-associated hospitalizations and deaths occurred at University Medical Center (n= 30, 19%), followed by Sunrise Hospital and Medical Center (n= 22, 13.9%), Summerlin Hospital and Medical Center (n= 19, 12%), and Mountain View Hospital (n= 18, 11.4%) (Table 5).

Table 5: Distribution of severe influenza-associated hospitalizations and deaths by Clark County hospitals*

Hospitalizations/Deaths by hospital:	n= 153 (%)
Boulder City	2 (1.3)
Centennial Hills	5 (3.2)
Desert Springs	8 (5.1)
Mesa View	2 (1.3)
Mike O'Callaghan	2 (1.3)
Mountain View	18 (11.4)
North Vista	5 (3.2)
Southern Hills	2 (1.3)
Spring Valley	10 (6.3)
St. Rose De Lima	13 (8.2)
St. Rose San Martin	3 (1.9)
St. Rose Siena	8 (5.1)
Summerlin	19 (12.0)
Sunrise	22 (13.9)
University Medical Center	30 (19.0)
Other*	4 (2.5)

* Includes residents of Clark County who were hospitalized outside of Clark County.

Length of stay

Length of hospital stay ranged from 1 to 59 days (Figure 4). The length of stay distribution for influenza-associated hospitalizations and deaths (n= 153) was non-normal (Shapiro-Wilks= .645, df 152, p< .0001), leptokurtic (kurtosis= 9.951), and skewed to the right (skewness= 2.897) because the majority of patients (70.4%) were admitted for ≤ 7 days and due to the influence of extreme outliers. The mean length of stay was 7.70 days (95% C.I. 6.11, 9.30), SD= 9.943. The median and mode were calculated by influenza strain type and compared to the mean (Table 6).

Table 6: Length of hospital stay by influenza strain type (mean, median, and mode prior to log transformation)- Clark County, 2010-2011 influenza season

Length of stay (days)	Total hospitalized population	Influenza B	Influenza A (no subtype)	Influenza A (H1N1)	Influenza A (H3)
Totals	n= 153	n= 24	n= 94	n= 34	n= 1
Minimum	1	1	1	1	1
Maximum	59	22	59	34	1
Median	4	4	4	5.50	1
Mode	2	2	2	2	1
Mean	7.70	5.46	7.96	8.59	1
Standard Deviation	9.943	4.836	11.273	8.560	N/A

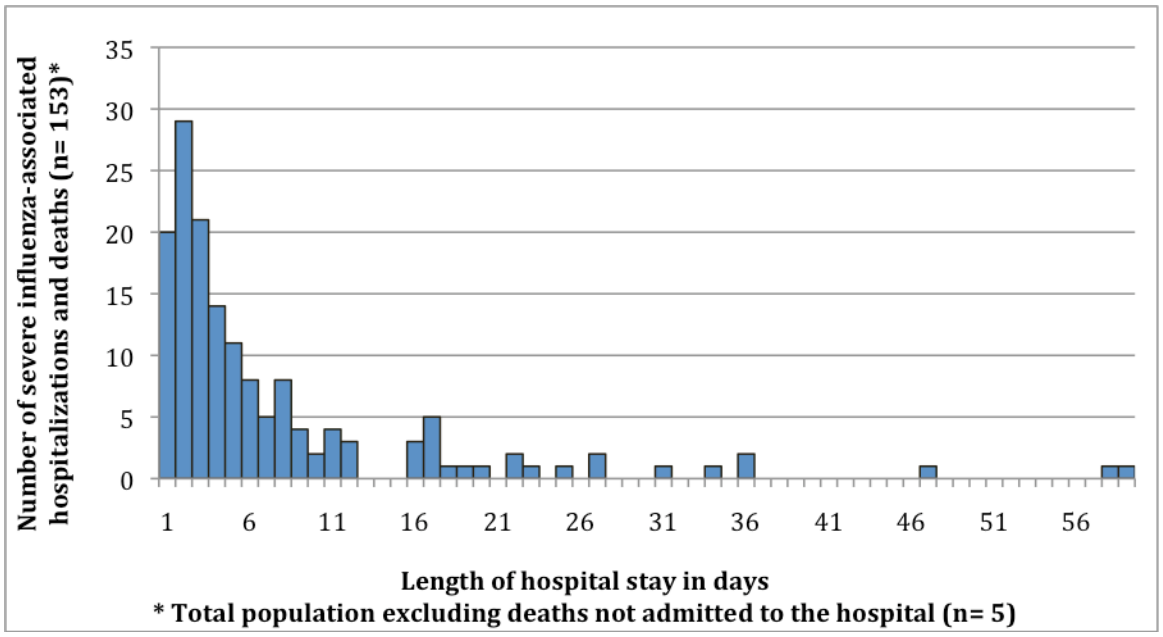

Figure 4: Distribution of length of stay for severe influenza-associated hospitalizations- Clark County, 2010-2011 influenza season

Of the 49 patients admitted to the intensive care unit (ICU), the median length of stay was 9 days (M= 14.06 days, SD= 13.936, range 1 to 59 days). The median length of stay for patients not admitted to the ICU (n= 104) was 3 days (M= 4.64 days, SD= 5.116,

range 1-36 days). As expected, a similar trend was observed among those patients that were placed on mechanical ventilation (n= 30); the median length of stay for ventilated patients was 12 days (M= 16.8 days, SD= 13.880, range 1-59). The median length of stay for non-ventilated hospitalized patients (n= 123) was 3 days (M= 5.43, SD= 7.168, range 1-58). Twenty-nine patients were admitted to the ICU and placed on mechanical ventilation with a mean length of stay of 17.2 days (SD= 13.972, range 1-59 days). Note that mechanical ventilation requires admission to the ICU, but not vice versa.

Subjects who expired outside of the hospital setting (length of stay= 0 days) and the sole patient with laboratory-confirmed influenza A (H3N2) were excluded from further analyses to avoid the influences of zero values and a small sample size, respectively; therefore, the sample was reduced to n= 152. The non-parametric equivalent of an ANOVA (Kruskal-Wallis) was employed to investigate whether or not there was a statistically significant difference in the median length of stay based on influenza strain type using a rank test. These results were found to be non-significant, p= .347. The length of stay data were log transformed to achieve a more normal distribution (skewness= 0.444, kurtosis= -0.390); afterward, all values in the data set fell within 3 standard deviations away from the mean (M= 1.500, SD= 1.00). After transformation, an ANOVA was run between the log-transformed length of stay data and the influenza strain type. These results were also found to be non-significant, F= .893, p= .412, indicating that there was no statistically significant difference in the mean length of stay based on influenza strain type. This is portrayed in the box and whisker

plots between the log length of stay and the influenza strain types (Figure 5). Note that the median length of stay does not vary significantly based on the influenza strain type.

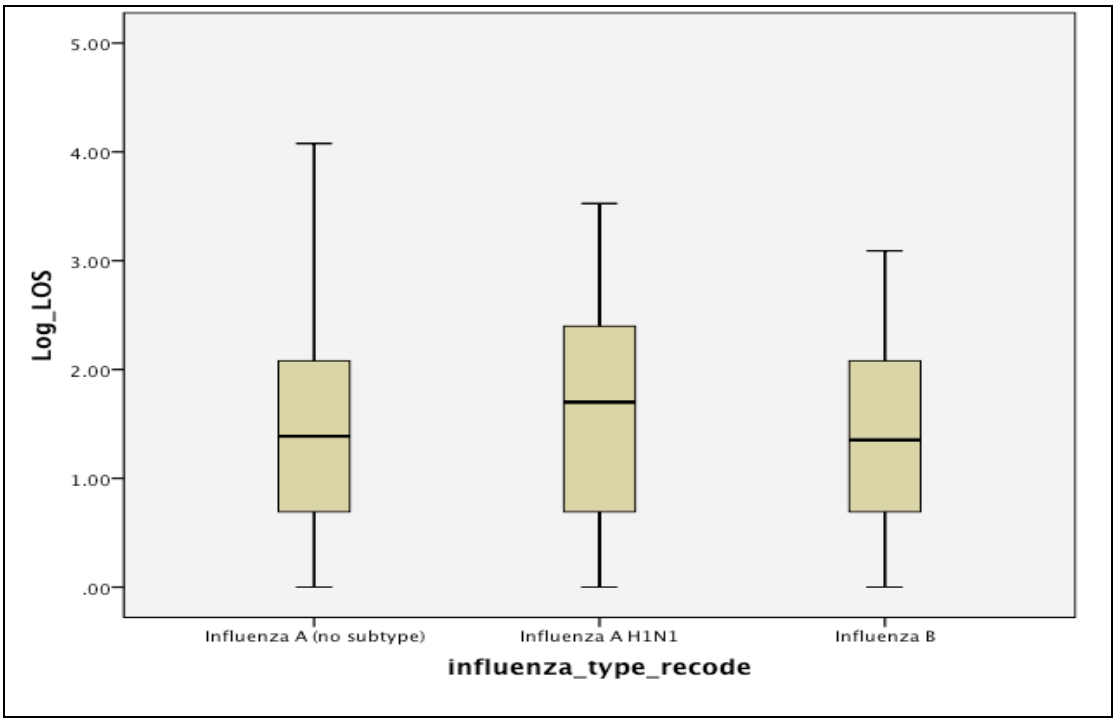

Figure 5: Log-tranformed length of hospital stay by influenza strain type- Clark County, 2010-2011 influenza season

An analysis of covariance (ANCOVA) was utilized to control for other factors that may influence the relationship between length of stay and influenza strain type. The following variables were evaluated: age, gender, race, ethnicity, ICU status, mechanical ventilation status, underlying conditions, antiviral medications, and vaccine status. The following factors were statistically significant in the final adjusted model: ICU status (p= .010), mechanical ventilation (p= 0.33), and underlying conditions (p= .022). As discussed earlier, placement on mechanical ventilation and admission to the ICU extend

the length of hospital stay. Further analyses of the underlying conditions were unable to be performed due to inadequate sample sizes (Table 7).

Underlying conditions

Underlying conditions and co-morbidities were classified based on the admitting diagnoses listed on the admission history and physical examination. The distribution of underlying conditions and co-morbidities, as well as their distribution by age group, for all hospitalizations is shown in Table 7. Among deaths, the following underlying conditions were identified: 3 with a chronic pulmonary disorder, 4 with an immunosuppressive disorder, 1 with diabetes mellitus, 2 with a secondary bacterial infection, 11 with a condition not listed in the SNHD survey (i.e., "other"), 2 with none, and 2 with an unknown condition.

Table 7: Underlying conditions and co-morbidities for severe influenza-associated hospitalizations and deaths by age group- Clark County, 2010-2011 influenza season

Underlying conditions	Totals	Underlying conditions by age group (years)					
	N= 158 (%)	< 5	5-49	50-59	60-69	70-79	≥ 80
Asthma	12 (7.6)	2	7	2	0	1	0
Bacterial infection	4 (2.5)	2	1	1	0	0	0
Cardiac disease	17 (10.8)	1	2	2	4	4	4
Chronic pulmonary disorder	19 (12.0)	2	3	1	3	7	3
Diabetes	12 (7.6)	0	3	3	3	3	0
Immunosuppressed	18 (11.4)	0	10	3	4	0	1
Pregnancy	3 (1.9)	0	3	0	0	0	0
Recently post partum	1 (0.6)	0	1	0	0	0	0
Renal disease	3 (1.9)	0	1	1	0	1	0
None	28 (17.7)	16	10	2	0	0	0
Other	38 (24.1)	16	10	5	2	3	2
Unknown	3 (1.9)	2	1	0	0	0	0

Antiviral medications

Whether or not antiviral medications were started, the type, and the start date relative to admission date were analyzed. Of the total number of patients started on antiviral therapy (n= 114, 72.2%), all but one of them was started on oseltamavir phosphate, also known by the brand name, Tamiflu (Genentech, USA). Forty-four (27.8%) severe influenza-associated hospitalizations and deaths did not receive antiviral therapy. The majority of patients were initiated on antiviral therapy after admission (n= 110) with a mean start of 1.68 days, SD= 3.788. Four patients were started on antiviral therapy prior to admission, and these numbers are represented as negative integers to indicate a start date prior to admission, M= -1.25, SD= 0.500. These were calculated and

reported separately to decrease their influence on the mean when looking at the total population of patients who received antiviral medications (n= 114) (Table 8).

Table 8: Antiviral start date for severe influenza-associated hospitalizations and deaths calculated by total population, after, and before admission- Clark County, 2010-2011 influenza season

Antiviral start date (days between admission and antiviral start date)*	Antiviral start date (days)	Antiviral start after admission (days)	Antiviral start before admission (days)
Totals	n= 114	n= 110	n= 4
Minimum	-2	0	-2
Maximum	24	24	-1
Mean	1.58	1.68	-1.25
Median	0	1	-1
Mode	0	0	-1
Standard deviation	3.760	3.788	.500

Discussion

This research study describes the epidemiology of severe influenza-associated hospitalizations and deaths in Clark County, Nevada, for the 2010-2011 influenza season. During this study period, there were 133 reported cases of severe influenza-associated hospitalizations resulting in discharge, 20 reported cases of severe influenza-associated hospitalization resulting in death, and 5 influenza-associated deaths occurring outside of the hospital setting (total study population N= 158). In comparison to males, a disproportionate number of females (68%) died as a result of severe influenza-associated complications. There are several factors that may have contributed

to this, such as small sample size (n= 25 deaths), and an undetermined combination of underlying conditions or co-morbidities among females in the study population that may not have been present among males in the study population. The greatest proportion of deaths occurred in the 5-49 age group (n= 7, 28%), and the lowest proportion of deaths occurred in the < 5 years and the 70-79 years age groups (n= 2, 8% for both). Once again, the small sample size may account for the fact that more deaths were not observed among the older age groups (≥ 65 years), as would be expected according to national and historic trends (Thompson *et al.*, 2010).

There are several limitations to consider when interpreting the findings from this secondary analysis of the 2010-2011 severe influenza-associated hospitalizations and deaths surveillance data collected by the SNHD. First and foremost, it should be noted that the purpose of this project was for surveillance. The data collection process was developed with this in mind; therefore, some limitations are a direct reflection of this and should be considered while analyzing these results, especially with regard to our hypotheses. The hypotheses were developed during the data collection period and not in advance, as a research study would proceed. The data collected are representative of routine public health practice and not formulated with these hypotheses in mind; therefore, the analysis of these results is considered to be secondary.

The peak number of reported cases occurred in the week ending in February 19, 2011 (week 7). Over half of the study population were tested using influenza rapid antigen diagnostic tests (n= 86, 54.4%). Influenza A (no subtype) was the most commonly identified strain among the study population (n= 94, 59.4%), followed by

influenza A (H1N1) (n= 36, 22.8%), influenza B (n= 27, 17.1%), and, lastly, influenza A (H3) (n= 1, 0.6%).

After analysis of the data obtained from the 2010-2011 influenza-associated morbidity and mortality surveillance project conducted by the SNHD, our first null hypothesis, which stated that among severe influenza-associated hospitalizations, the influenza strain type would not show an association with deaths, was rejected. The data displayed a statistically significant difference among severe influenza-associated deaths by strain type. The proportion of deaths (n= 8) among patients diagnosed with influenza B was 29.6%, which was similar to the proportion of deaths (n= 11) among patients diagnosed with influenza A (H1N1) at 30.6%. In comparison, the proportion of deaths among patients diagnosed with influenza A (no subtype) was much less at 6.4%.

Our study is limited by the laboratory testing ordered and performed on the study population. The majority of these tests were rapid antigen results (54.4%). Rapid tests are only able to differentiate between influenza A and influenza B viruses (CDC, 2011); therefore, an unknown proportion of the influenza A (no subtype) may be any undetermined influenza A subtype. Not being able to differentiate between the influenza A subtypes is a significant limitation to our study because there are differences in virulence between the influenza A virus subtypes. Historically, this is supported by higher rates of hospitalizations and deaths during influenza seasons in which influenza (H3) viruses predominate (Thompson, et al., 2010). Influenza rapid tests range in sensitivity from 50% to 70% (CDC, 2011); this translates to the tests accurately detecting influenza in individuals who truly have the flu (true positives) approximately 50-70% of

the time. Because of these concerns, it is difficult to report the analysis of the influenza A (no subtype) data with external validity.

Vaccine status and history was the most difficult variable to collect because people have multiple vaccine sources throughout their community from which to obtain influenza vaccination. Flu shots are available through HCPs, the SNHD, and various vaccine clinics and pharmacies throughout Clark County. The SNHD registers patient vaccine information with the online statewide Nevada vaccine registry: WebIZ. However, not all of the sources listed above comply with the request by the NSHD to record immunization records in the WebIZ database, which made it difficult to find the vaccine status of people who received their influenza vaccination from sources other than the SNHD. Vaccine status was also limited by recall bias, further making it difficult to confirm.

If the vaccine history was not documented in the hospital admission history and physical examination, attempts were made to contact the registered nurse caring for the patient to obtain this information while the subject was still hospitalized. Occasionally, the nurse was able to obtain this information from elsewhere within the chart, from a family member, or from the patients themselves. If, after these attempts, the vaccine history was still unobtainable, the patient name and date of birth were queried in WebIZ for documentation of their vaccine history registered there. Influenza vaccines are only approved and administered to individuals older than 6 months of age (Fiore *et al.*, 2010); therefore, only these subjects were explored for in the WebIZ database, and rarely were they registered. Occasionally, the demographic face sheet

listed a primary care physician (PCP) for the patient. If present, the PCP was contacted for vaccine records. This was common practice in the case of expired individuals. If all of these previously described methods failed, the family or the patient was contacted as a last resort; however, in the event of a death, the family was never contacted out of respect for their loss.

The second null hypothesis stated that vaccine status would not be associated with death among the study population. There was no statistically significant association between vaccine status and death; therefore, we failed to reject this null hypothesis. These results should be interpreted cautiously due to the small sample size and the fact that vaccine status was only obtained on 11 of the 25 deaths (44%); the majority of deaths had an unknown vaccine status (n= 14), which renders these results inconclusive. The vaccine status classification "unknown" includes subjects who were unable to be confirmed through any of the methods described above.

Lastly, another limitation regarding vaccine status is that children in the study population were assessed to determine if they had received the influenza vaccine and the date of administration. Children receiving the influenza vaccine for the first time, regardless of whether it is the inactivated form (injection) or the live attenuated form (intranasal), are recommended to receive two doses given at least 4 weeks apart (CDC, 2011). This information was not obtained in the data collection process and it is not clear if an affirmative answer indicates a complete influenza vaccine series. The type of influenza vaccine (inactivated or live attenuated) administered was also not differentiated. It is difficult to ascertain if or how these omissions may have affected

the analysis, but it may be a confounding factor in any associations between vaccine status and influenza-associated hospitalizations. Although lack of vaccination was not positively associated with deaths, it is still essential for public health officials to stress the importance of yearly influenza vaccination to prevent influenza infection and its related complications.

The last null hypothesis stated that among severe influenza-associated hospitalizations and deaths, the type of influenza strain would not have an effect on the average patient length of hospital stay. Length of hospital stay ranged from 1 to 59 days. The median length of stay for influenza A (H1N1) was 5.5 days, which was longer than both influenza A (no subtype) and influenza B, which both had a median length of stay of 4 days. However, the length of stay data were highly skewed and leptokurtic due to several extreme outliers, and the majority of patients (70.4%) having been hospitalized for ≤ 7 days. The five patient deaths that occurred outside of the hospital setting were excluded from the ANOVA to avoid the influence of a zero value, and the lone patient with laboratory confirmed influenza A (H3N2) was excluded as well to remove the effects of a small sample size. With these samples removed, the length of stay data were log transformed due to the non-normal distribution, as discussed earlier. An ANOVA was performed, and the results were non-significant, $p = .412$, indicating that there was no statistically significant difference in the mean length of stay based on the influenza strain type; therefore, we failed to reject this last hypothesis. This could be due to several reasons. For one, we had a relatively small sample size and unequal sample sizes once the study population was divided further by influenza strain types.

Secondly, we did not have data reflecting the further characterization of the patients with laboratory-confirmed influenza A (no subtype). As a result, we do not know what proportions of these patients were infected with influenza A (H3) or (H1) viruses, or possibly an unknown influenza A subtype. Lastly, we do not have detailed data regarding underlying conditions with which to draw further conclusions (e.g., the presence of multiple underlying conditions, or what "other" conditions may include). There are many factors that could extend a patients' length of hospital stay, many of which were unable to be accounted for in this analysis.

In the ANCOVA analysis, several factors were analyzed and only ICU status, placement on mechanical ventilation, and underlying conditions were statistically significant. The fact that admission to the ICU and placement on a mechanical ventilator extend length of stay was an expected finding, as both of these variables indicate a higher acuity of illness. Further analyses of the underlying conditions were unable to be performed due to inadequate sample sizes.

Specifically in regards to the data collection process, and as mentioned above, the fact that multiple underlying conditions and co-morbidities were unable to be analyzed is a limitation. If the patient did not have one of the conditions listed on the SharePoint survey, a review of their medications was performed to determine if a medical condition existed that was not listed as an admitting diagnosis. Patients with multiple underlying conditions and co-morbidities were limited to the classification of just one. As indicated earlier, it is known that specific underlying conditions (e.g., asthma) and co-morbidities (e.g., COPD) can be exacerbated by influenza infection.

Chronic health conditions can commonly occur in association with each other (e.g., diabetes and heart disease often occur in conjunction with one another), and this information would have been helpful in determining which combination of diseases contributed to severe influenza-associated deaths among our study population. Future surveillance projects may obtain this information in order to be able to further analyze these data.

The fact that close to one third of the study population did not receive antiviral medications may have been due to several reasons. For one, the recommended dosing time period of antiviral medications is within 48 hours after the onset of flu-like symptoms. Limited efficacy has been shown with the administration of antiviral medications outside of this window (www.cdc.gov/flu); therefore, antivirals may not have been initiated on patients who presented to the hospital > 48 hours after the onset of their symptoms. Also, antiviral medications may not have been started on patients who expired outside of the hospital setting or shortly after admission.

While our sample size for this analysis was small (N= 158), and this affects the external validity of our findings as well as our ability to perform further statistical analyses with any confidence, this information will still be beneficial for future comparisons of severe influenza-associated hospitalizations and deaths surveillance data conducted in Clark County. It is expected that data obtained from the 2010-2011 severe influenza-associated hospitalizations and deaths surveillance project will help guide subsequent influenza surveillance projects and will provide an important database of information from which to compare future trends in the epidemiology of influenza

specific to Clark County, Nevada. Surveillance systems are vital to public health efforts to protect the population, and influenza surveillance is especially vital because the virus is capable of changing its viral composition within a single flu season. According to the CDC (2010), surveillance measures provide: demographic data to identify emerging trends in infection rates to guide public health interventions tailored to subsets of the population; viral surveillance to identify circulating strains, which is the basis for the development of yearly vaccines; and morbidity and mortality data from which national response systems are dependent upon to assess epidemic threshold indicators. Since the 2009 H1N1 pandemic, and with these functions in mind, the SNHD, OOE has conducted its severe hospitalized influenza morbidity and mortality surveillance program to describe the epidemiology of influenza in Clark County, Nevada.

Current national surveillance systems are only capable of capturing a limited picture of influenza activity each season. It is vital for smaller public health agencies, such as the Southern Nevada Health District, to conduct surveillance on severe-influenza hospitalizations and deaths. The SNHD is responsible for the public health of approximately 1.95 million people, roughly 72% of Nevada's population, as well as the estimated 35+ million people who visit Las Vegas as a popular tourism destination each year (www.quickfacts.census.gov; www.lvcva.com). To protect the population of any large city, this requires surveillance of circulating strains, monitoring the population closely for unusual influenza activity, and monitoring severe influenza-associated hospitalizations and deaths for any potential changes in virulence. Changes in the influenza virus would most likely result in hospitalization or death, and because of this,

projects such as the SNHD severe influenza-associated hospitalizations and mortality surveillance are essential to monitoring, maintaining, and improving public health.

Appendix A: Data dictionary

Data Dictionary: Severe Influenza Hospitalized Case Surveillance
Southern Nevada Health District (SNHD) 2010-2011 Influenza Season

Variable	Field Type	Description of variable
SNHD_uid	Integer	An anonymous patient accession number created by SNHD to identify patients: 1-158
Sex	Char (1)	The sex of the patient: F= female M= male
Age	Integer	The age of the patient in years at time of admission or time of death if death occurred outside of hospital: 0-90. Those 90 and above will be categorized as 90.
age_group	Integer	The age of the patents in years at time of admission or time of death if death occurred outside the hospital grouped in the following categories: 0-80. 0= 0-4 years 1= 5-49 years 2= 50-59 years 3= 60-69 years 4= 70-79 years 5= 80 years and up
race_ethnicity	Char (1)	Indicates race/ethnicity of each patient: W= White B= Black A= Asian/Pacific Islander N= Native American/Alaska Native H= Hispanic NH= Non-Hispanic O= Other
occupation	Char (1)	The occupation of the patient as listed on the demographic face sheet of the medical record: A= Health care worker B= Daycare worker/client C= Disabled D= Elementary School Student E= Middle School Student F= High School Student G= College/University Student H= Retired I= Unemployed J= Other
hospitalized	Integer	Indicates if the patient was hospitalized > 24 hours: 0= no 1= yes

admit_week	Integer	The corresponding year and week the date of admission coincides with according to the CDC MMWR calendar: 2010(01-52) – 2011(01-52)
hospital_name	Char (1)	Indicates the admitting hospital: A= Boulder City B= Centennial Hills C= Desert Springs D= Mesa View E= Mike O'Callaghan F= Mountain View G= North Vista H= Southern Hills I= Spring Valley J= St. Rose Siena K= St. Rose De Lima L= St. Rose San Martin M= Summerlin N= Sunrise P= UMC Q= VA O= Other
icu	Integer	Indicates if the patient was admitted to the ICU during hospitalization: 0= no 1= yes
vent	Integer	Indicates if the patient was ventilated during hospitalization: 0= no 1= yes
discharge_week	Integer	The corresponding year and week the date of discharge coincides with according to the CDC MMWR calendar: 2010(01-52) – 2011(01-52)
length_of_stay	Integer	The period of time from admission to discharge recorded in days: 0-90
transfer	Integer	Indicates if the patient was transferred to another facility: 0= no 1= yes
transfer_name	Char (1)	Indicates the transfer facility: A= Boulder City B= Centennial Hills C= Desert Springs D= Mesa View E= Mike O'Callaghan F= Mountain View G= North Vista H= Southern Hills

		I= Spring Valley J= St. Rose Siena K= St. Rose De Lima L= St. Rose San Martin M= Summerlin N= Sunrise O=Other P= UMC Q= VA R= Harmon Rehab S= Kindred Sahara T= Kindred Desert Springs U= Hospice
death	Integer	Indicates if the patient expired: 0= no 1= yes
death_week	Integer	The corresponding year and week the date of death coincides with according to the CDC MMWR calendar: 2010 (01-52) – 2011 (01-52)
length_of_stay	Integer	For hospitalized patients only. Indicates the number of days from admission to discharge or death: 1-99
underlying_conditions	Integer	Indicates the underlying conditions or co-morbidities for each case: 1= Asthma 2= Chronic Pulmonary Disorder 3= Cardiac Disease 4= Immunosuppressed (e.g. Cancer, HIV) 5= Diabetes 6= Renal disease 7= Bacterial infection 8= Neuromuscular disorder 9= Pregnancy 10= Recently post partum 11= Other 12= None 13= Unknown
antiviral	Integer	Indicates if the patient received antiviral medication: 0= no 1= yes
antiviral_name	Char (1)	Indicates which antiviral medication the patient received: T= Oseltamavir Z= Zanamivir
antiviral_start	Integer	Indicates number of days between laboratory confirmation date and start of antiviral medication. Negative numbers indicate that the antiviral was started prior to hospitalization.

lab_confirm	Integer	Indicates positive laboratory confirmation of any type: 0= no 1= yes
week_lab_confirm	Integer	The corresponding year and week the date of laboratory confirmation coincides with according to the CDC MMWR calendar: 2010(01-52) – 2011(01-52)
lab_name	Char (1)	Indicates the location of laboratory testing: A= Southern Nevada Public Health Laboratory (SNPHL) B= Nevada State Public Health Laboratory (NSPHL) C= Centers for Disease Control and Prevention (CDC) D= Quest E= LabCorp F= Primex G= CPL H= Hospital laboratory I= Focus J= Nichols K= Out-of-state laboratory L= Other Nevada laboratory
influenza_type	Integer	Indicates the type of influenza detected through diagnostic testing: 1= Influenza A (no subtype) 2= Influenza A H1N1 3= Influenza A H3 4= Influenza B
vaccine_status_2010	Char (1)	Indicates if the patient has been vaccinated for influenza: 0= No 1= Yes 2= Unknown 3= Not recently or prior to 2010, or in 2011 (after hospitalization)

Appendix B: List of Abbreviations

AHDRA	Aggregate Hospitalization and Death Reporting Activity
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention
CHF	Congestive heart failure
COD	Cause of death
COPD	Chronic obstructive pulmonary disease
DIIS	Disease Investigation and Intervention Specialist
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
EIP	Emerging Infections Program
FDA	Food and Drug Administration
HCP	Health care providers
H	Hemagglutinin
ICU	Intensive care unit
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, 9th edition, Clinical Modification
ILI	Influenza-like illness
ILINet	U.S. Outpatient Influenza-like Illness Surveillance Network
IRB	Institutional Review Board
MMWR	Mortality and Morbidity Weekly Report
N	Neuraminidase
NAC	Nevada Administrative Code
NHDS	National Hospital Discharge Survey
NREVSS	National Respiratory and Enteric Virus Surveillance System
OOE	Office of Epidemiology
PASW	Predictive Analytics SoftWare
PCP	Primary care physician
RNA	Ribonucleic acid
*r*RT-PCR	Real-time reverse-transcription polymerase chain reaction
SNHD	Southern Nevada Health District
SNPHL	Southern Nevada Public Health Laboratory
SPSS	Statistical Package for Social Sciences
UNLV	University of Nevada, Las Vegas
WHO	World Health Organization

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VITA

Graduate College
University of Nevada, Las Vegas

Kindra Maureen St. Jacques

Degrees:

Bachelor of Science in Nursing, 2000
University of Michigan

Research Experience/Internship:

Primary data collector for the 2010-2011 severe influenza-associated morbidity and mortality surveillance project for the Southern Nevada Health District

Thesis Title: Analysis of the Morbidity and Mortality of Severe Influenza Infection in Clark County, Nevada for the 2010-2011 Influenza Season

Thesis Examination Committee:

Chairperson, Patricia Cruz, Ph.D.
Committee member, Timothy Bungum, Ph.D.
Committee member, Sheniz Moonie, Ph.D.
Committee member, Brian Labus, MPH
Graduate Faculty Representative, Eduardo Robleto, Ph.D.