

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

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Abstract

Throughout the duration of any influenza season, influenza strains have the ability to evolve through mutation causing alterations in virulence. These changes may result in severe illness or death among susceptible populations; therefore, it is important to closely monitor influenza-associated hospitalizations and deaths. The University of Nevada, Las Vegas in collaboration with the Southern Nevada Health District analyzed data from the hospitalized influenza morbidity and mortality surveillance project for Clark County for the 2010-2011 influenza season. Among the study population (N= 158): the influenza strain type was found to be significantly associated with deaths (n= 25), vaccination status was not found to be significantly associated with death among hospitalized patients, and transformed data showed no statistically significant difference in the mean length of hospital stay based on the influenza strain type. These results will help inform public health agencies of the impact of influenza-associated hospitalizations and deaths, and inform the design of future surveillance systems.

Key words influenza, morbidity, mortality, hospitalized

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 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 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.

National and state level surveillance programs are useful in determining the health and economic burden associated with influenza circulation and helping to prepare for future pandemics (Thompson, Comanor, & Shay, 2006). 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 et al., 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 et al., 2010). 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.

Since the 2009 H1N1 pandemic, and with these surveillance functions in mind, the Southern Nevada Health District (SNHD), Office of Epidemiology (OOE) has conducted a severe hospitalized influenza morbidity and mortality surveillance program to

describe the epidemiology of influenza in Clark County, Nevada, which includes the city of Las Vegas and the 38 million tourists that visit annually (Las Vegas Convention and Visitors Authority [LVCVA], 2011). The SNHD severe influenza-associated hospitalizations and deaths surveillance project most closely resembles the viral, morbidity, and mortality surveillance components of the Centers for Disease Control and Prevention (CDC) national influenza surveillance program (CDC, 2010). In this study, a secondary analysis was conducted of these surveillance data to examine severe influenza-associated hospitalizations and deaths, and to address the following research questions. Among severe influenza-associated hospitalizations: 1) Will the strain of influenza be associated with death? 2) Will vaccination status be associated with death? and 3) Will there be a difference in the length of hospital stay based on the influenza type?

Methods

Study Population and Inclusion Criteria

The study population consists of all residents of Clark County, Nevada who were hospitalized for \geq 24 hours or expired between October 1, 2010 and May 31, 2011, and met both the clinical case definition and the laboratory criteria for diagnosis described below.

Clinical case definition and laboratory criteria for diagnosis:

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, 2011b). The viral subtype for influenza A viruses is unable to be identified by rapid diagnostic testing. However, the advantage to using rapid diagnostic testing is that results are processed in 10 to 15 minutes (CDC, 2011b). 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, Michaud, Deslandes, & Frost, 2003; CDC, 2011b). To optimize effectiveness, initiation of antiviral medication is recommended within 48 hours of the onset of flu-like symptoms (CDC, 2011c); 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 *r*RT-PCR requires approximately 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 bronchioalveolar lavage sputum (CDC, 2011b).

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 the SNHD jurisdiction (i.e., Clark County). Although cases among tourists are reported by their home state for statistical purposes, the SNHD is responsible for providing public health services to tourists when they are visiting Clark County.

SNHD Data Collection Process

As part of routine public health practice, the SNHD conducts seasonal influenza surveillance through passive and active methods. Laboratory-confirmed influenza is a reportable condition in Nevada; health care providers (HCPs) and clinical laboratories must report all cases to the designated health authority.

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. Cases with commonly listed complications of influenza illness as the COD or as contributing factors were further investigated to elicit influenza-related infection or involvement.

The SNHD Disease Investigation and Intervention Specialist staff members studied each report of influenza to determine if it met the case definition for severe-hospitalized influenza morbidity or mortality. Compatible cases were investigated further according to a standard protocol to collect demographic and disease information.

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 depict the distribution of severe influenza-associated hospitalizations and deaths, and an analytical approach was utilized to identify associations between the various predictor variables of interest (i.e., age, gender, race, ethnicity, ICU status, mechanical ventilation status, underlying conditions, antiviral medications, and vaccination status) and death among the study population.

Data Analysis

The variables collected were operationalized and the following statistical methods and software were employed: Chi-Square and ANOVA statistical methods, Microsoft® Excel, and PASW, SPSS® software versions 18 and 19. Population-based hospitalization and mortality rates were calculated using the 2010 U.S. Census Bureau statistics for Clark County, Nevada (US Census Bureau, 2011).

Human Subjects

Institutional Review Board (IRB) approval was obtained for this research study from the UNLV IRB. The data collection process was completed by the SNHD in accordance with mandates set forth by the Nevada Administrative Code for the purposes of routine public health practice. The data were de-identified of all personal patient identifiers, and permission was obtained from the SNHD 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 during the study period. The first reported case occurred in the week ending October 2, 2010 (CDC 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.

Mortality and hospitalization rates

During the study period, a total of 25 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 (US Census Bureau, 2011). Severe influenza-associated hospitalizations and deaths were further categorized by age group, and by mortality and hospitalization rates by age group (Table 1). Females accounted for 68% of deaths, even though the overall study population was normally distributed with regards to gender. 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.

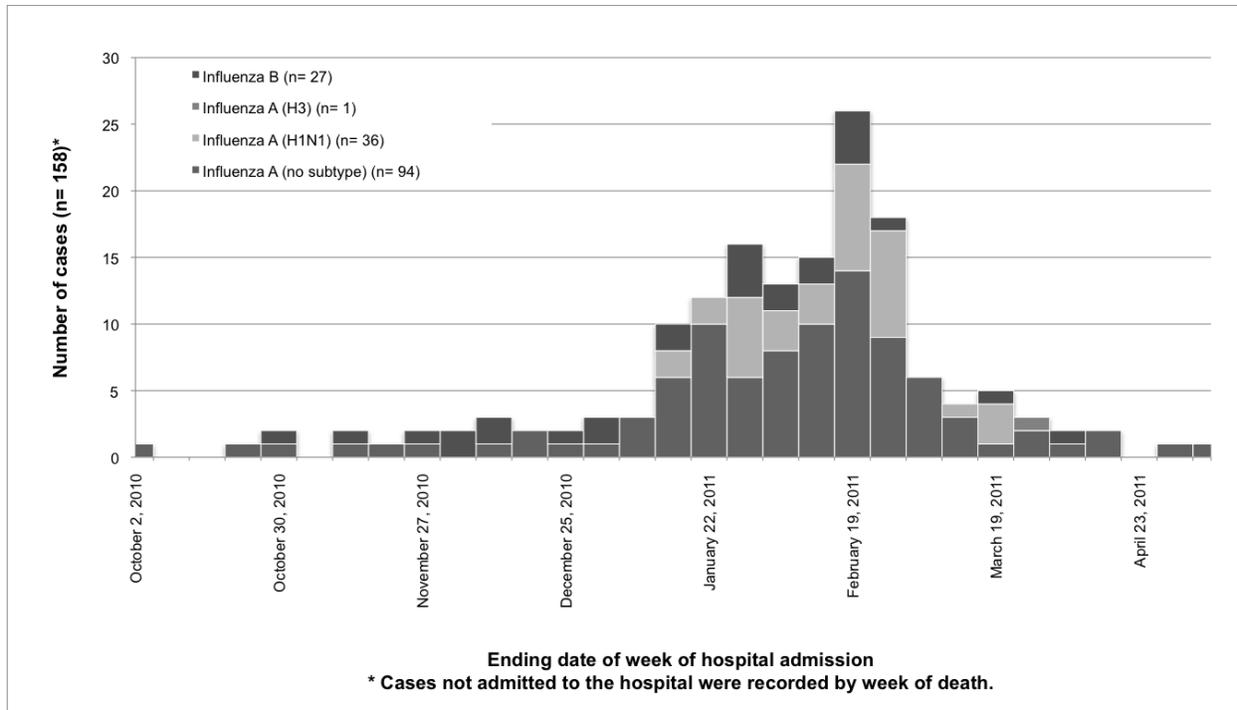


Figure 1. Number of cases by ending date of week of hospital admission by strain type- Clark County, 2010-2011 influenza season.

Table 1. Severe influenza-associated hospitalizations and deaths by age group- Clark County, 2010-2011 influenza season.

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 (32.0)	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)	NA	74 (48.4)	NA
Males	8 (32)	NA	79 (51.6)	NA

*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 2). Overall, the hospitalization rates in Clark County are significantly lower than those of the nation.

Table 2. 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)	43.8
5- 17 years	2.6 (n= 9)	8.5
18-49 years	4.4 (n= 40)	10.7
50-64 years	8.5 (n= 29)	21.7
≥ 65 years	16.3 (n= 36)	62.5

*Includes deaths that were admitted to the hospital (n= 20).

†FluSurv-NET surveillance data for the 2010-2011 influenza season (CDC, 2011a).

According to the CDC (2011a), 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, 2011a). In Clark County, of the 25 reported deaths, there were 3 deaths under the age of 18 for this same time period. These rates were comparable to the national numbers, but due to the small sample size we are unable to make any further inferences regarding influenza-related pediatric deaths in Clark County.

Influenza vaccination status

Vaccination status was obtained on 132 of the 158 subjects (83.5%). Individuals who received the influenza vaccine prior to 2010, during, or after their hospitalization were categorized as not having received 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%). 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 vaccination status. Chi-square analysis was run between vaccination status and death (excluding those that were classified as unknown), and vaccination 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)

Influenza strain type

The largest proportion of test results were reported as influenza rapid tests (n= 86, 54.4%), followed by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) (n= 67, 42.4%), both rapid test and rRT-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 Southern Nevada Public Health Laboratory (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%).

Influenza strain was significantly associated with deaths, G= 16.2, p= 0.001. 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 1. Results show the week ending on February 19, 2011 (week 7) to be the peak of influenza-associated hospitalizations and deaths in Clark County with 26 cases reported. According to the CDC summary of the 2010-2011 influenza season, national influenza activity peaked in early February as well (CDC, 2011a).

Length of stay

Length of hospital stay ranged from 1 to 59 days. The length of stay distribution for influenza-associated hospitalizations and deaths (n= 153) was non-normal (Shapiro-Wilks= 0.645, df 152, $p < 0.0001$), 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 (Table 3). 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 prior to log transformation (Table 3).

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 (n= 152) from further analyses. The non-parametric equivalent of an ANOVA (Kruskal-Wallis) was employed to investigate whether 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, $p = 0.347$. 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 of 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, $F = 0.893$, $p = 0.412$, indicating that there was no statistically significant difference in the mean length of stay based on influenza strain type.

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 vaccination status. The following factors were statistically significant in the final adjusted model: ICU status ($p = 0.010$), mechanical ventilation ($p = 0.033$), and underlying conditions ($p = 0.022$). Further analyses of the underlying conditions were not performed due to inadequate sample sizes.

Table 3. 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)	Influenza B (n=24)	Influenza A (no subtype) (n=94)	Influenza A (H1N1) (n=34)	Influenza A (H3) (n=1)	Total (n=153)
Minimum	1	1	1	1	1
Maximum	22	59	34	1	59
Median	4	4	5.50	1	4
Mode	2	2	2	1	2
Mean	5.46	7.96	8.59	1	7.70
Standard Deviation	4.836	11.273	8.560	NA	9.943

Discussion

This research study describes the epidemiology of severe influenza-associated hospitalizations and

deaths in Clark County, Nevada, for the 2010-2011 influenza season. Results showed that the number of deaths identified in this study were lower in

comparison to what is expected according to national numbers reported by a subset of states to the CDC. In comparison to males, a disproportionate number of females (68%) died as a result of severe influenza-associated complications. Factors that may have contributed to this include small sample size and an undetermined combination of underlying conditions or co-morbidities among females in the study population. The greatest proportion of deaths occurred in the 5-49 age group ($n=7$), and the lowest proportion of deaths occurred in the <5 years and the 70-79 years age groups ($n=2$, for both). 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).

The data showed 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%.

However, our study is limited by the laboratory testing ordered and performed on the study population. The majority of these tests were rapid antigen results; which are only able to differentiate between influenza A and influenza B viruses (CDC, 2011b). Therefore, an unknown proportion of influenza A isolates (no subtype) could 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% and range in specificity from 90% to 95%; this translates to considerable variation in the positive and negative predictive values of the tests as the prevalence of disease fluctuates throughout the season (CDC, 2011b). Because of these concerns, it is difficult to report the analysis of the influenza A (no subtype) data with external validity.

Comparison of vaccination status with death among the study population demonstrated that there was no statistically significant association between vaccination status and death. These results should be interpreted cautiously due to the small sample size

and the fact that vaccination status was only obtained on 11 of the 25 deaths, which renders these results inconclusive. The vaccination status classification "unknown" includes subjects who were unable to be confirmed through any of the methods described below.

Vaccination status was the most difficult variable to collect because people have multiple sources throughout their community from which to obtain influenza vaccination. The SNHD registers patient vaccination information with the online statewide Nevada vaccination registry: WebIZ. However, there is not one central source for immunization records, which made it difficult to find the vaccination status of people who received their influenza vaccination from sources other than the SNHD. Vaccination status was also limited by recall bias and death, further making it difficult to confirm. If the vaccination history was unknown, attempts were made to obtain vaccination records from multiple sources including hospital and provider patient records, and immunization registries.

Lastly, 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 vaccination status and influenza-associated hospitalizations. In the future, more detailed data collection in regards to the vaccination status may resolve these limitations.

There was no statistically significant difference in the mean length of stay based on the influenza strain type. This could be due to *i*) a relatively small sample size and unequal sample sizes once the study population was divided further by influenza strain types, and *ii*) lack of 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. In addition, 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 logistical factors that could extend the length of hospital stay (e.g., availability of outpatient beds), many of which were unable to be accounted for in this study.

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.

Multiple underlying conditions and co-morbidities were not analyzed in this study. If the patient did not have one of the conditions listed on the 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. 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 should attempt to obtain this information in order to be able to further analyze these relationships.

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. Foremost, it should be noted that the purpose of this project was for surveillance. The data collected are representative of routine public health practice and the data collection process is reflective of this; therefore, the analysis of these results is considered to be secondary and is subject to the limitations specific to secondary analyses.

While our sample size for this study was small (N=158), the information gathered is still 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 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.

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 SNHD, 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 38 million people who visit Las Vegas as a popular tourism destination each year (LVCVA, 2011; US Census Bureau, 2011). To protect the population of any city, this requires surveillance of circulating strains, monitoring the population closely for unusual influenza activity, and monitoring severe influenza-associated hospitalizations and deaths for potential changes in virulence. Changes in the influenza virus would most likely result in hospitalization or death, and because of this, projects such as this one are essential to monitoring, maintaining, and improving public health.

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