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Retrospective Epidemiologic Analysis of Influenza Pandemics in Arkansas, A

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A Retrospective Epidemiologic Analysis of Influenza Pandemics in Arkansas

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Abstract

This study compares influenza mortality in Arkansas during the pandemics of: 1918 (aka Spanish flu), 1957, 1968, and 2009 (H1N1, aka Swine flu). Death certificate and U.S. census data were gathered and analyzed for statistical differences in mortalities based on sex, age, and geographic regions of Arkansas for each pandemic. The geographic regions were defined by the five Public Health Units classified by the Arkansas Department of Health. Regional mortalities were also analyzed across all pandemics to investigate how the different pandemics affected each individual region. Chi-square analyses for each pandemic showed only the 1918 pandemic had statistical differences between male and female mortalities ($p<0.005$). All pandemics showed differences in mortalities across age groups. Cross-region analyses found statistical differences in mortalities for all pandemics except 1968 ($p>0.5$). Data showed urban regions sustained higher proportional mortalities than rural regions. Over time, the four pandemics resulted in decreased flu mortalities throughout the state. Regional mortality rates suggest areas for increased public health efforts during future influenza outbreaks in Arkansas, and more efficient distribution of resources may reduce mortality rates of future pandemics.

Introduction

Influenza A virus affects people year-round but increased incidence of infection occurs during "flu season," which lasts from November to April in the northern hemisphere (Reichert et al. 2004). During a typical year, on average, influenza hospitalizes around 200,000 and kills nearly 36,000 people in the U.S. (Doshi 2008). Most of the hospitalizations and mortalities occur among young children and elderly adults (Simonsen et al. 1998). Influenza is spread through aerosols and attacks the ciliated epithelial linings of the host respiratory tract. Once infected, the virus causes necrosis and sloughing of airway cells that are infected (Bouvier and Palese 2008). The loss of these epithelial cells destroys the mucociliary escalator in our airway which normally helps reduce bronchial infections. This escalator transports microbes and other inhaled particles from the lower respiratory tract to the pharynx to then be coughed out or swallowed. With this escalator disabled, microbes are able to secondarily infect the lower respiratory tract, often leading to pneumonia. Most of the hospitalizations and mortalities related to influenza are due to the secondary pneumonia that shortly follows the primary viral infection (Korteweg and Gu 2008, Morens et al. 2008, Serfling 1963). The incubation period for influenza is 1-4 days and most infected patients feel a rapid onset of malaise, coupled with fever, myalgia, and coughing. Some influenza infections can be asymptomatic, but the vast majority present with the same common symptoms. These symptoms may last for seven days or more with a convalescence period of up to two weeks (Eccles 2005, Edler et al. 2011).

Influenza is a virus in the family *Orthomyxoviridae* and includes three strains: influenza A, B, and C (Neumann et al. 1999). All three viruses infect humans, although C is uncommon and mild. The prevalence of A and B make this virus extremely widespread and one of the largest health problems worldwide. Influenza is an enveloped RNA virus with seven or eight segmented strands of RNA, each containing one or two genes, for a total of ten or eleven genes, depending on the type (A & B=8 segments, 11 genes; C=7 segments, 10 genes). These genes code for proteins essential for replication and successful release of virions from infected cells (Bouvier and Palese 2008, König et al. 2009). The viral envelope consists of viral glycoproteins as well as portions of host cell membrane, which allow it to efficiently enter new host cells (Korteweg and Gu 2008).

Influenza originates as a zoonotic infection in bird and mammal species in the wild, which may then infect a human (if that particular strain has the ability to infect humans) (Hulse-Post et al. 2005). Not all influenza viruses infect humans due to the variability of its two major surface antigens of influenza, hemagglutinin (HA) and neuraminidase (NA) (Korteweg and Gu 2008, Potter 2001). There are

sixteen known subtypes of HA, but only subtypes 1-3 are known to infect humans (Reid et al. 1999). The HA antigen is involved in the process of inserting the viral genome into the target cell. One HA protein chain is responsible for the viral attachment to a host cell while the other initiates permeation of the endosome (Wilson et al. 1981). Once the virus has entered the host cell, a channel is formed between the virus envelope and endosome membrane to allow the release of viral-bound RNA segments into the cytoplasm for replication via viral RNA polymerase (König et al. 2009).

Once the virus has replicated inside the host cell, proteins and genomic segments are packaged and sent to the host cell plasma membrane. The new virus buds off the host cell, with neuraminidase (NA) being crucial for the separation of newly formed virions from the host cell. There are nine known types of NA, although human infection typically only occurs with N1 and N2 (Reid et al. 1999). At the terminus of the NA protein are the active sites that bind to polysaccharides on the cellular surface and clip them to release the virus (König et al. 2009, Lentz et al. 1987). Once the virions are cleaved from the host human cell, they are free to infect other cells within the body or they may be expelled from the host to infect another person. These two surface proteins are crucial to the successful entry and release of the virus, and they are ever-changing as well.

Influenza is constantly undergoing minor changes in the genome, resulting in antigenic drift (Figure 1). These drifts are random errors in replication of the viral RNA inside the host cell that lead to small changes in the HA and NA antigens (König et al. 2009). They can help the virus evade the host immune system and enter host cells more quickly because the virus is slightly different than previous viruses. The slight differences create a virus that is not easily recognized by the host immune system, giving the virus more time to spread throughout the body. Antigenic drifts occur in all types of influenza viruses and are a major key to the persistence of this virus from year-to-year (Treanor 2004). Each year, lab researchers and technicians from the Centers for Disease Control (CDC) and World Health Organization (WHO) speculate on the most probable antigenic drifts for that year's influenza. This prediction ultimately dictates the formulation of the influenza vaccine.

Influenza A can also undergo antigenic shift (Figure 1), which is a major genetic change resulting in a new HA or NA antigen. This type of change is

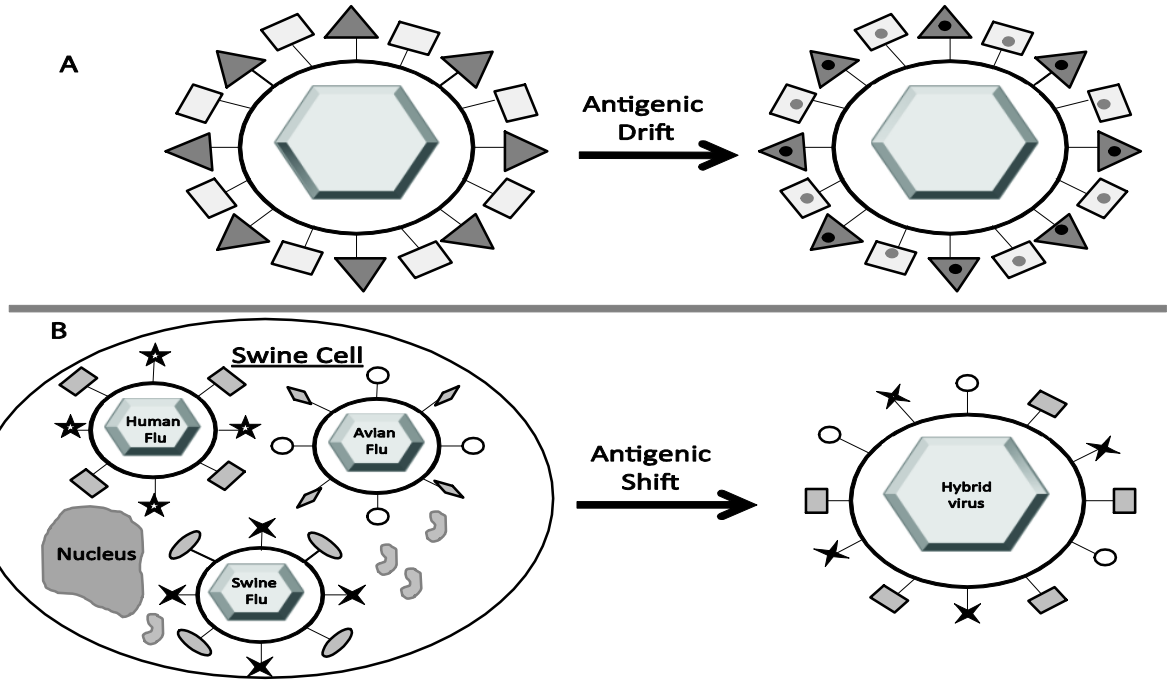

Figure 1. A: Minor mutations to influenza antigens as a result of antigenic drift. B: Co-, or super-infection of a swine cell leading to a novel, hybrid virus from genetic reassortment during antigenic shift.

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the result of a genetic reassortment or an adaptive mutation (Hampson 2002). Genetic reassortment happens when single-stranded RNA (*ss*RNA) from two or more separate viruses end up in the same virion. For example, pig cells can be infected with human, avian, and swine influenza at the same time, creating a superinfection. Multiple gene segments from different viruses can combine during replication to form a new virus (Taubenberger et al. 1997). Adaptive mutation occurs when a novel virus slowly adjusts and becomes transmissible from an animal host to a human (Mehle and Doudna 2009). Both of these shifts result in a novel strain of influenza that is completely unfamiliar to the human population. As such, these new viruses can be extremely pathogenic and are what have caused the historic pandemics of the last century (Hampson 2002). An influenza pandemic is defined as the rapid spread of a new influenza virus against which the human population has little or no immunity (Morens et al. 2009). Pandemics have the potential to rapidly infect humans worldwide with enormous numbers of illnesses and deaths. However, sometimes a new strain of influenza actually kills fewer people than the typical seasonal flu.

Throughout the past century, there have been four influenza pandemics: 1918, 1957, 1968, and 2009. The 1918 pandemic, also known as the Spanish flu, was caused by the H1N1 virus and killed an estimated 50 million to 100 million people worldwide. In the United States, roughly 28% of the population was affected and 500,000 to 675,000 people died (Taubenberger 2006). This pandemic is famous for the sheer number of people affected and the unusually high mortalities seen in young adults (15 – 44 years of age) and the middle-aged (45 – 64 years of age). 99% of the excess deaths from this pandemic were in people under the age of 65. Persons between 15 and 35 had the highest observed death rates, and there were also high mortalities seen in pregnant women (Simonsen et al. 1998). Historians compare the Spanish flu pandemic on the same scale as the bubonic plague that killed millions across Europe in the 14th century.

The pandemics in 1957 and 1968 showed more typical mortality trends, primarily affecting young children and the elderly populations. The 1957 pandemic was caused by the H2N2 virus (Asian flu) and later shifted into the H3N2 virus (Hong Kong flu), which caused the 1968 pandemic. The 1957 pandemic killed 69,800 Americans while the 1968 pandemic killed 33,800 (Henderson et al. 2009, Schulman and Kilbourne 1969). The pandemic in 2009 was caused by a new H1N1 virus, known as 2009 H1N1 in order to differentiate it from the H1N1 virus of the 1918 Spanish flu. This virus is thought to have originated in Mexico and contained RNA segments from human, avian, and swine influenza viruses. Due to the same H and N make-up, this pandemic scared the scientific community because it was believed to have the same virulent potential towards young adults and middle-aged individuals that was seen in the 1918 pandemic. In the end, the mid-range estimated number of deaths attributed to 2009 H1N1 in the U.S. was 12,270, which was lower than the average number of seasonal flu mortalities (Morens et al. 2010).

Due to the large media attention drawn from the 2009 H1N1, the other influenza pandemics received increased attention as well. There have been a number of studies that have compared and contrasted the influenza pandemics on a national scale. However, there are few studies that look at the pandemics in local and state-level details, especially regarding the Spanish Flu.

The goal of our study was to analyze the effects of the four influenza pandemics in the state of Arkansas. We anticipated a decrease in overall mortality rates as the pandemics approach the present day due to the improvements in medical technology, vaccinations, and better healthcare in general. The mortalities in each pandemic were classified by: sex, age, and geographic region, and analyzed for statistical differences. Male and female mortality rates from the 1918 pandemic vary from nation to nation. However, data have shown that males exhibited higher mortality rates than females in the U.S (Noymer and Garenne 2000). We hypothesized that significant differences would be seen in male/female mortalities in Arkansas as well. National data also shows that more deaths from influenza are typically seen in the young and elderly populations ($\leq$14 and 65+ respectively) (Simonsen et al. 1998). The exceptions are the 1918 and 2009 H1N1 pandemics, which killed larger proportions of young adults (15-44 years old) and middle-aged (45-64 years old) individuals than observed in the 1957 and 1968 pandemics (Potter 2001). We hypothesized that the deaths observed in Arkansas in the aforementioned age groups followed these national trends. The geographic regions were based on the five local health units established by the Arkansas Department of Health: Northwest, Northeast, Southwest, Southeast, and Central. We determined if the urban or rural areas of the state exhibited greater mortalities due to influenza. We hypothesized that more influenza-related deaths were recorded in the rural areas within each pandemic occurrence due to

decreased access to medical treatment. Individual geographic regions were also analyzed across the four pandemics to evaluate mortalities over time.

Methods

The data for this study were collected from death certificates at the Arkansas Department of Health-Health Statistics in Little Rock. The death certificates were available in the form of microfiche for the first three pandemics and data from the most recent pandemic required retrieval via electronic query (Statistical Analysis Software). Once certificates with an influenza cause of death were found, certificate number, age, sex, date of death, county of death, and primary and secondary causes of death were recorded. Census data were also collected to establish population numbers during the pandemics. These population numbers were used to derive the expected number of deaths for each category (sex, age, and geographic region). The data were collected from the US Census Bureau (American FactFinder) from the years closest to the pandemics (1920, 1960, 1970, and 2010). Once the state populations were recorded, death rates were calculated for each pandemic by dividing the total number of influenza deaths by the state population. These death rates were used to establish the expected numbers of deaths for each sex, region, and age range for the individual pandemics and were used in chi-square test of goodness of fit analyses. The expected numbers were calculated by multiplying the death rate for that pandemic by the number of people in the given sex, region, or age range. After all expected numbers were calculated, chi-square tests for goodness of fit were performed using the observed numbers recorded from the death certificates to determine significant differences. An alpha level of 0.05 was used for significance.

The collection of death records was deemed exempt from IRB protocols due to non-living subjects. Approval from the Arkansas Department of Health's Scientific Review Board was attained prior to collecting death records. Death certificate data collection and publication without identifiers is lawfully permitted by Arkansas Statute 20-18-305, Section 4D.

Results

Observed deaths from each pandemic were tested for significant differences in sex, age, and regions. Deaths in individual regions were also tested across all pandemics for statistical differences. The 1918 pandemic showed the only significant difference between sexes in which females exhibited higher mortalities than males (X^2_1=4.76, n=4412, p<0.005), with all other pandemics not statistically significant (Table 1). Significant differences in age groups were seen in all pandemics (Table 2). The 15-44 years of age group had the highest observed deaths in the 1918 pandemic. The 65+ group had the highest observed deaths during the 1957 and 1968 pandemics while the 2009 pandemic recorded the highest deaths in the 45-64 years of age range. When regions were compared within the individual pandemics, all pandemics showed significant regional differences in mortalities with the 1968 pandemic being the lone exception (X^2_4=3.09, n=138, p>0.5) (Table 3). The central region recorded the most deaths in the 1918 and 2009 pandemics (Figure 2). The 1957 and 1968 pandemics had the highest deaths in the northwest and northeast regions, respectively. Individual regions, when compared across the four pandemics, showed significant differences as well (Table 3). Due to the large number of mortalities in the 1918 pandemic, individual regions were analyzed again with the 1918 data excluded for a

TABLE 1. Observed Arkansas influenza mortality totals and expected vs. observed mortalities by sex.

Pandemic	Total Deaths	Expected Deaths		Observed Deaths		*P value*
		Male	*Female*	*Male*	*Female*	
1918-1919	4412	2254.2	2157.9	2182*	2230*	p<0.05*
1957-1958	199	97.9	101.1	106	93	p<0.5
1968-1969	138	66.9	71.1	72	66	p>0.25
2009-2010	51	25	26	24	27	p>0.75

** Designates significance*

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TABLE 2. Observed Arkansas pandemic influenza deaths by age groups.

Pandemic	≤14	15-44	45-64	65+	*P value*
1918-1919	1120	2675	377	176	p<0.001*
1957-1958	22	14	39	124	p<0.001*
1968-1969	15	6	24	93	p<0.001*
2009-2010	6	8	29	8	p<0.001*

** Designates significance*

TABLE 3. Observed deaths by geographic region and percentage of total deaths in Arkansas.

Pandemic	NW	NE	SE	SW	Central	*P value (w/in pandemic)*
1918-1919	997 (22.6)	949 (21.5)	646 (14.6)	636 (14.4)	1184 (26.8)	p<0.001*
1957-1958	49 (24.6)	29 (14.6)	40 (20.1)	46 (23.1)	47 (23.6)	p<0.005*
1968-1969	27 (19.6)	34 (24.6)	28 (20.3)	23 (16.7)	26 (18.8)	p>0.5
2009-2010	6 (11.8)	15 (10.9)	3 (2.2)	3 (2.2)	24 (47.1)	p<0.001*
P value (across all pandemics)	p<0.005*	p<0.001*	p<0.001*	p<0.001*	p<0.001*	
P value (1918 excluded)	p<0.05*	p<0.05*	p>0.25	p>0.1	P<0.05*	

** Designates significance*
Values in ( ) are percentage of total mortalities across the state

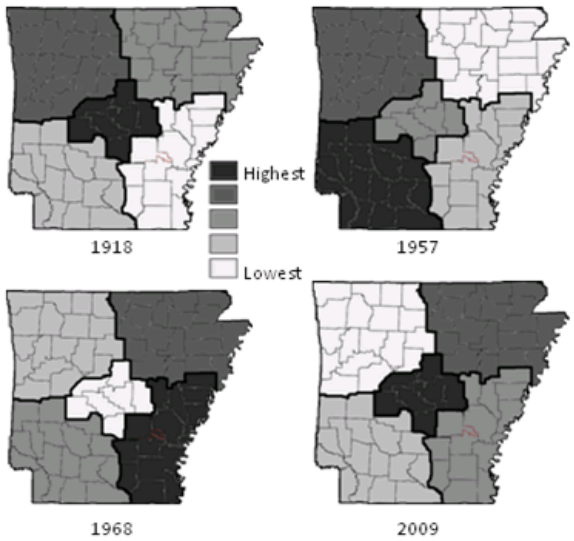

Figure 2. Regional percentage of influenza mortalities across pandemics. The percentages of total deaths from each pandemic were calculated for each region and ranked from lowest to highest percentage. Note the high mortalities in central region for the two H1N1 pandemics – 1918 and 2009.

more accurate look at the most recent three pandemics. The Northwest, Northeast, and Central regions showed significant differences across the pandemics after the exclusions. Deaths occurring in each region decreased with each consecutive pandemic, which was expected.

Discussion

National data show that male mortality rates were higher than female rates in the 1918 pandemic, and most seasonal influenza pandemics affect disproportionate numbers of young children and the elderly (Noymer and Garenne 2000, Simonsen et al. 1998). These were the first two questions tested in order to see if Arkansas held consistent with the national trends. Analyses of mortalities by sex revealed that only the 1918 pandemic had significant differences in mortalities; specifically, that more females died than males. This does not follow national data, and it is suggested that the sex mortality difference was due to the high mortality rates that were

seen in pregnant females during the pandemic (Carlson et al. 2009). More recent pandemics were not found to have higher mortalities in pregnant females, possibly due to better access to and an increase in quality healthcare.

Age group comparisons showed that all age groups were significantly different within each pandemic. The 1918 pandemic recorded the largest number of deaths in young adults, the most deaths in middle-aged individuals occurred during the 2009 pandemic, both of which are consonant with national data. Arkansas totals for the 1957 and 1968 pandemics also followed national trends (Simonsen et al. 1998). These pandemics showed the highest number of deaths in the 65+ age group, which follows the typical seasonal flu mortality distribution.

Why then, were the two pandemics caused by the H1N1 virus different than the other pandemics and typical flu season data? The H1N1 virus was extremely virulent during the 1918 pandemic, and it is believed that the vigorous immune response is why the young adult population was so greatly affected (Kobasa et al. 2004). Young adulthood is when the immune system is at its strongest for most individuals (Taubenberger 2006). Thus, the body produces a strong reaction to any infecting microbe in order to clear it efficiently. The immune reaction consisted of the flu's common symptoms, but greatly amplified and on a quicker timeline. It is believed that the rapid onset of illness increased the likelihood for further complications and infections, such as bacterial pneumonia (Morens et al. 2008). The high immune reactivity to the H1N1 virus suggests that the immune response affected healthy individuals in a severely negative way (Kobasa et al. 2004). Some of those infected also developed severe pulmonary edema, possibly leading to pulmonary hemorrhage (Morens et al. 2008).

Cytokine storm, a hyperactive immune response to virulent microbes in the respiratory tract, can lead to the destruction of lung tissues and possibly bacteremia or viremia through pulmonary hemorrhages. Bacteria in the bloodstream can cause septic shock and ultimately lead to organ dysfunction (Ziegler et al. 1991). It is possible that the hyperactive response to viremia from the highly virulent influenza virus may have resulted in the same bodily dysfunction.

Why were the same devastating effects not seen during the 2009 H1N1 Swine Flu pandemic? The viruses have the same H & N designation, but, thankfully, the mortalities were lower than seen in the 1918 pandemic. There are many factors that may correlate with reduced mortalities in 2009. The quality of life and available nutritional resources in 2009 when compared with the World War I era of 1918 may have played a factor in reduced mortalities, especially in rural Arkansas. The 2009 virus was an H1N1 strain, but it was not the exact same virus as the H1N1 from 1918 (Edler et al. 2011). The minor mutations that differentiate the two viruses might have led to a less lethal virus. The possibility of an upcoming pandemic also caught the eye of the media, which led to increased hygiene reminders. Businesses and schools placed hand sanitizers throughout buildings and promoted hand-washing and proper coughing into the elbow to help eliminate the spread of influenza. An H1N1 vaccine was well-publicized and administered across the nation, which may have decreased mortality rates. Also, due to the awareness of a possible pandemic, it is probable that people were more inclined to seek medical attention more quickly than in previous years. In the 1957 and 1968 pandemics, there were 3-4 times more deaths in the 65+ group than the next closest group. Furthermore, the 65+ population had about half the population of the next lowest group. This means that the 65+ group saw the most deaths from the smallest population. These two pandemics more closely represented the typical flu season mortalities and support why it is crucial for the elderly population, and their care-givers, to take all necessary precautions during flu season.

Regional analyses for each pandemic gave significant differences in all pandemics with the exception of the 1968 pandemic. Regarding the significant pandemics, various regions made up the major differences across the three significantly different pandemics. This shows that each pandemic affected the state differently. There were more deaths in the central region than expected in the 1918 pandemic, while the northwest and southwest regions had resulted in increased mortalities during the 1957 pandemic. The 2009 pandemic had higher than expected deaths in the central region, as well as lower than the calculated expected value in the northwest region. Upon recording the mortalities for the urbanized central region, it was clear that the original hypothesis stating that rural regions would experience higher mortality rates was incorrect. Influenza is dispersed via aerosol droplets and requires the close proximity of people to effectively transfer the virus (Taubenberger 2006). Therefore, an urban area containing high population density will provide easy transmission from one person to the next. This was overlooked at the beginning of the study, where the

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proximity to healthcare was focused upon.

The greatest differences in observed versus expected values for each region occurred during the 1918 pandemic. It is possible that the large differences are due to the modes of transportation available and occupations during the time period. Much of Arkansas was covered by farmland with miles between inhabitants, reducing spread of influenza A virus due to low numbers of personal interactions. This also helps explain why the central region exhibited higher mortalities from influenza than the neighboring regions. Little Rock and the surrounding communities lead to a high population density in the region. The higher population density multiplies the chances of spreading the influenza virus to numerous individuals, which may increase the likelihood of higher mortalities in the region.

During the most recent pandemics, transportation abilities have decreased the amount of time needed to get from one place to another and subsequently increased the number of interactions across the entire state. The more efficient modes of transportation also increase contacts with non-Arkansas residents. Increased numbers of highways, railways, and airports throughout time bring more opportunities and people to harbor and transfer the virus. Cold and flu season also occurs in the same months as holiday travels across the U.S. An increased number of people, from both in-state and out-of-state, travel through airports, gas stations, and eateries throughout Arkansas and may spread infectious diseases. This likely accounts for the decrease in differences among observed and expected deaths across the state regions, especially in the 1968 pandemic that was not significant.

The significant differences in deaths between the regions during the 2009 pandemic may likely be due to the virulence of the virus. Like the pandemic in 1918, the H1N1 virus was the culprit of the most recent pandemic. This virus was shown to be extremely lethal in 1918 and recorded the most deaths in the central region during both pandemics. The specific nature of the virus and its need for person-to-person transmission may explain why similar results are seen across the regions of the two pandemics.

All individual regions analyzed across the pandemics showed a significant difference in mortalities when the 1918 pandemic was included. When only the most recent three pandemics were analyzed; the Northwest, Northeast, and Central regions showed significant differences. The changes seen in these regions over time are harder to interpret because there are many factors that may contribute to the illness. Influenza, as an upper respiratory tract infection, is influenced by the integrity of the host's respiratory system. Any airborne pollutants and or damage to the respiratory system may help promote infection, especially secondary infection. During the 1918 pandemic, there were many coinfection with tuberculosis and influenza. 150 out of every 100,000 people died from tuberculosis in 1918, compared to 3.6 per 100,000 people in 2010 (CDC 2011, Noymer and Garenne 2000). This serious lung infection severely compromised the patient and made surviving pandemic influenza extremely difficult. The high incidence of tuberculosis in males across the U.S. is proposed to be a major contributing factor to the higher male influenza mortality rate (Noymer and Garenne 2000). Eighty-five Arkansas death certificates from the 1918 pandemic listed tuberculosis as a primary or contributing cause of death. After the advent of antibiotics, tuberculosis decreased in incidence and was not a major factor during the most recent three pandemics (Noymer and Garenne 2000).

However, since the 1918 pandemic there has been a rise in cigarette smoking and air pollutants. Cigarette smoking peaked in the late 1940s for males and the 1960s for females. Inhaled cigarette smoke has been shown to have many effects on the lungs that may lead to more frequent upper and lower respiratory infections (Giovino 2002). An influenza infection will compound the problem and may prove fatal in a compromised patient who is a heavy smoker. The individuals who smoked during, or prior to the influenza pandemics in 1957 and 1968, possibly had higher mortality rates. Air pollution from the increased number of factories, automobiles, and coal-fired power plants may have also contributed to the influenza mortalities.

Arkansas typically ranks high among states for air quality and has consistently met all federal air quality standards for pollutants (Vandevender 2006). The state opened three coal-fired power plants between the 1968 and 2009 pandemics. A fourth plant opened in 2010, which is after the most recent pandemic. The plants are located in the northwest, southern central, and northeast regions and were opened in 1978, 1980, and 1983, respectively. These plants produce large volumes of CO_2 and release sulfur dioxide, carbon monoxide, nitric oxides, and other particulate matter. The areas that are most affected by these plants are the downwind communities. It is unclear, and was not within the scope of this study, how these coal-fired power plants influence respiratory illnesses in the surrounding communities, but it is plausible to have some effect. Increased gases and particulates in the air

may lead to inflammation and promote respiratory illnesses that will compound an influenza infection. This compounding may lead to increased respiratory illness deaths in those areas. Also, urban areas, such as Little Rock, have increased CO_2 emissions due to the large number of automobiles in the city. Carbon particulates released from the automobile exhaust might influence respiratory illnesses as proposed with the power plants. Despite the increase in air pollutants across the state, positive advancements in healthcare may have reduced influenza mortality rates.

As the pandemics approach present day, the number of mortalities and, consequently, the mortality rates associated with each decrease. This is a positive aspect when analyzing the pandemics because it suggests healthcare and increased knowledge throughout the general public may have helped decrease the number of deaths due to influenza. A major healthcare development that came out after the first pandemic was antibiotics. Antibiotics were first used in the 1940s and greatly reduced the number of influenza deaths by combating any secondary bacterial respiratory infection. Most of the influenza-related deaths are not due to the virus itself, but the secondary bacterial infections that occur simultaneously, or soon after the primary viral infection (Morens et al. 2008). With the advent of antibiotics, major contributing factors to influenza mortalities, like pneumonia and tuberculosis, were manageable. These antibiotics decreased the likelihood of developing a fatal secondary bacterial infection during the most recent three influenza pandemics.

Other factors that have helped to decrease influenza mortalities are the flu vaccine and antivirals. The flu vaccine was developed in the 1940s, but it was not widely distributed until the 1960s. Although the vaccine was available during the 1968 pandemic, it was not administered to a large percentage of people. Vaccination coverage has continued to increase since its approval. In 2008, two-thirds of Americans 65+ received the vaccine compared to just 30% in 1989. Lowest vaccination coverage is seen in 18-49 year olds with 3.4% in 1989 and 20% in 2008 (CDC 2008a). The continual increase in coverage has provided herd immunity for those who did not receive the vaccine, thus further decreasing the number of illnesses. The first antiviral for influenza, amantadine, was approved for use in 1966. Since then, there have been three other antivirals created; rimantadine, approved in 1993, zanamivir, and oseltamivir, both approved in 1999 (Monto et al. 1999, Moscona 2005). These antivirals are the only medication given to directly halt the influenza infection, but resistance has been shown to amantadine and rimantadine in the last decade (Moscona 2005). The CDC also released data showing influenza A resistance to oseltamivir (CDC 2008b). Thus, questions have been posed about the effectiveness of the antivirals that are prescribed, especially once symptoms are already present.

To be most effective, antivirals need to be administered 30-36 hours after onset of illness, but earlier is better (Monto et al. 1999). However, most individuals wait at least a full day after onset before going to see the doctor. This puts many patients past the 30-36 hour mark and reduces the effectiveness of the drugs, and they may not achieve effective pharmacological concentration in the bloodstream before the body naturally begins to clear the infection. The late administration of antivirals is believed to increase rates of resistance (Moscona 2005). Although the effectiveness of both the vaccine and antivirals has been questioned, it is likely that the two most recent pandemics would have shown higher mortalities had they not been distributed and administered.

Conclusions

By looking at the influenza pandemics in Arkansas, one can observe the results of medical research and technology over the last century. Influenza mortality rates have continuously decreased across the pandemics. Although the regions were affected differently across the four pandemics, it is clear that the urban areas contained the highest mortalities. Efforts to promote good hygiene and vaccination, especially for those who are immunodeficient, should be strongly emphasized in those areas. Increasing bacterial resistance to antibiotics has been well documented in the last 60 years, and now there is increasing resistance to antivirals. Both of these classes of medicine have helped reduce influenza mortalities, but they are now becoming less effective. It is crucial that proper planning is made to best prepare for any possible future pandemics. Appropriate readiness will reduce the numbers of those infected with influenza and, consequently, the number of mortalities it causes. Influenza is a virus that will remain ever-watched and the avian flu (H5N1) in Asia may serve as a reminder that a future influenza pandemic is very possible. Further state- and region-specific studies such as this may help increase knowledge surrounding influenza transmission in the area and generate necessary future preparations.

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