7-28-2006

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ABSTRACT

Linkages between influenza prevalence and climate (e.g. precipitation, temperatures, El Nino Southern Oscillation ENSO) have been suspected, but definitive evidence remains elusive. This analysis investigated a climatic relationship between influenza mortality (measured by multiple caused pneumonia and influenza deaths) and influenza morbidity (measured by isolates tested for influenza). Influenza-climate linkages were analyzed at multiple spatial scales (e.g. local analysis, and regional analysis) and multiple temporal scales (e.g. annualized mortality counts, and mortality counts based on cumulative percentiles). Influenza mortality and morbidity were found to have significant correlations to seasonal temperatures, precipitation, and ENSO. Influenza-climate associations varied spatially and temporally, and underscore the importance of considering geographic scale in investigative analyses of disease. Evidence for an influenza-climate relationship provides a greater understanding of the enviro-climatic factors that can contribute to an influenza epidemic, and provides an impetus for further studies that incorporate climatic factors in influenza risk modeling.

INDEX WORDS: Influenza, Mortality, Morbidity, Weather, Climate, Precipitation, ENSO, SOI, Georgia State University

INFLUENZA PREVALENCE IN THE US ASSOCIATED WITH CLIMATIC FACTORS, ANALYZED AT MULTIPLE SPATIAL AND TEMPORAL SCALES.

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

In the College of Arts and Sciences

Georgia State University

2006

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Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

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August 2006

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Chapter 1 - INTRODUCTION

History of influenza

Influenza is a virus that has continually afflicted human populations on a global scale for at least the past two millennia (Patterson 1986). Its role in causing minor to severe health problems continues into the modern era, as it, for example, caused an estimated 36,000 deaths annually from 1990-1999 (CDC 2006a). Although deaths and the most severe complications (e.g. pneumonia) resulting from the respiratory virus usually occur only in the elderly population, all demographic populations can be infected by the virus with symptoms of high fever, malaise, dry coughing, diarrhea, and vomiting (CDC 2006a; Cox *et al.* 2000). Although un-immunized children and the elderly (i.e. 65 years of age and older) are particularly susceptible to influenza and influenza like symptoms, healthy adults have also been known to suffer significant mortality during influenza pandemics (global influenza epidemics) (Patterson 1986; Pyle 1979). Although infrequent throughout recorded human history, influenza pandemics can decimate entire region with high rates of mortality. The influenza pandemic of 1918, for example, killed at least 20 million people worldwide (Patterson 1986).

Similar to many infectious diseases contracted through close interaction with domesticated animals (e.g. measles, small pox, tuberculosis), influenza is thought to have been introduced into human populations via domesticated wild birds and animals (Kawaoka *et al.* 1988). Unlike other diseases such as measles however, to which the human body can eventually gain immunity after a single infection, influenza is capable of

rapid genetic mutation, and attempts to counteract human immunological defenses (i.e. previous immunity to influenza does not necessarily lend to immunological resistance to the most current influenza strain in circulation). The ability to mutate in order to overcome survival pressures is crucial to the antigenicity, or the ability to incite an immune response in the human body, that is exhibited by the influenza virus. Influenza is in a continuous state of change in an effort to infect and re-infect a host (Horimoto *et al.* 2005). This dynamic virus requires constant surveillance to identify the most recent virus strain in circulation, which is essential to the development of an effective vaccine for each influenza season (CDC 2006b). Even with the modern advances in medicine and science (e.g. vaccines and medical surveillance), influenza is still a respiratory illness of major public health concern (CDC 2006b).

The introduction of influenza into human populations is thought to have coincided with the domestication of animals (e.g. pigs and ducks) around 5000 B.C., the suspected natural reservoirs of the disease (Patterson 1986; McNeill 1998; Diamond 1999). The first discernable accounts describing influenza-like symptoms date back to 462 B.C. from Hippocrates (Koch 2005), and also a description of the virus in 1173 A.D. (Patterson 1986). North America experienced one of its first influenza epidemics in 1558-1559 which originated from a severe epidemic in England that caused mortality of at least 20% of the total population (McNeill 1998). However, the most severe influenza pandemic in modern history occurred in 1918-1919 and coincided with the proliferation of steam-ship travel following World War I, and caused mortality in excess of 20 million people (Pyle 1986; Patterson 1986). Significant changes in the antigenicity of influenza, either through ‘point’ mutations or recombination of influenza viruses (i.e. antigenic shift) is

thought to have been a key factor in the high mortality of the 1918 pandemic, along with the introduction of the virus into immunologically naïve regions of the world that were aided by technological advances in global transportation (i.e. steam ship travel) (Cliff *et al.*1986; Patterson 1986; Pyle 1986; McNeill 1998; Diamond 1999; Horimoto *et al.* 2005; Taubenberger *et al.* 2006; Kilbourne 2006).

Although influenza occurs throughout the world, it is most severe in temperate regions where it exhibits seasonality with prevalence peaking during the winter (e.g. DEC, JAN, FEB) and declining significantly during summer (Cliff *et al.*1986; Pyle 1986). The winter peak of influenza in temperate climates has been conventionally explained by human behavioral changes, as during this season people congregate indoors more often. Thus, there is a greater likelihood of infection because of increased interaction in confined indoors spaces (Cliff *et al.*1986; Meade *et al.* 2000; Mims *et al.* 2004; Patz *et al.* 2003). However, evidence for increased influenza incidence associated with increased crowding is inconclusive (Meade *et al.* 2000). Nonetheless, because of the winter peak and summer trough of influenza prevalence, temperature or other environmental factors are suspected to be the driving forces of variability in influenza seasons (Cliff *et al.*1986; Pyle 1986), yet little is understood this potential climatic linkage.

Influenza & Climate

Medical climatologists in the early 20th century investigated linkages between weather and health. Mill's (1939) book on medical climatology provides case studies as evidence for an association between temperature and influenza like symptoms or complications arising from influenza infection. For example, pneumonia deaths, which

are commonly used as a proxy for influenza prevalence, were associated with abrupt declines in ambient temperature (Mills 1939:pg 127). Licht's (1969) medical climatology text also furthered the notion of a relationship between weather and disease by proposing that certain atmospheric conditions (e.g. dry air) are ideal for the accumulation of micro-organisms. Associations between climatic conditions and the onset of respiratory diseases, more specifically influenza and pneumonia, are not a novel idea, but have not been examined at regional geographic scale using high-resolution climatic and influenza data.

The linkage between climate (i.e. precipitation, temperature, long-term climatic trends) and influenza is suggested in many texts analyzing influenza incidence. In Patterson's (1986) reconstruction of influenza pandemics and epidemics occurring from 1700-1900, his historical analysis reveals that "…cool, dry air seems to favor the survival of the virus in the environment" (pg 3). In the most recent text solely devoted to medical geography, Meade (2000) briefly discusses the environmental conditions that may play a role in the transmission of the disease. "It has been suggested that in lower humidity, or perhaps in lower ultraviolet radiation, the virus may survive longer in the air between people, and so be able to infect more of them" (Meade *et al.*. 2000: 284). Supporting the theories provided by Meade (2000) and Patterson (1986), a medical microbiology text by Mims (2004) explains that winter influenza peaks in temperate regions occur because, "…during cold weather, people spend more time inside buildings with limited air space, which favors transmission, and perhaps also because of decreased host resistance.". Furthermore, Patz (2003) suggests that climate factors such as humidity may play a role

in the cyclical nature of influenza, along with the behavioral changes that coincide with more severe winters (Patz *et al.* 2003:pg 107).

Although many researchers propose this association between indoor crowding during winter months and influenza prevalence, the evidence of this linkage is weak, at best (Meade and Earickson 2000; Hope-Simpson 1992). Dushoff (2006) conducted an investigation to analyze associations between temperature and influenza mortality in the US, but found only that H3 and B influenza viruses were correlated with excess mortality, rather than weather. However, data were only examined at a single temporal scale (e.g. mortality based on an entire influenza season) rather than monthly or weekly (Dushoff *et al.* 2006). Further, Dushoff *et al.*(2006) found no association between US mortality trends and temperature, both at a national level and at a larger scale analysis of New York city and the surroundings areas of Chicago. Dushoff *et. al* (2006) used aggregated temperature data, taken as a mean temperature for an entire flu season (November through April), which could potentially both deflate any fluctuations of temperature within each influenza season and mask actual temperature-mortality relationships.

A climatic analysis of three major cities in California found that temperature and El Niño Southern Oscillation ENSO phases exhibited significant associations with viral pneumonia hospitalizations, which is often associated with complications from influenza; significant associations were geographically distinct (Ebi *et al.* 2001). The study site in which influenza hospitalizations exhibited an association with ENSO phases was Sacramento, CA, which concomitantly was the only city associated with decreased winter-spring temperatures caused by El Nino events (Ebi *et al.* 2001). Increased

hospitalizations were associated with decreased minimum temperature, but were not associated with fluctuations in precipitation (Ebi *et al.* 2001). ENSO tends to affect regional weather differently throughout the US. A similar climatic analysis in different regions of the US, utilizing mortality data or another measure of morbidity (i.e. national influenza surveillance data), could prove to be fruitful in determining the spatial variation of significant factors affecting influence prevalence.

Similar ENSO linkage findings were identified in Europe. A study examining France's influenza morbidity/mortality as related to climate at a global scale found cold ENSO episodes produced significantly higher mortality than warm ENSO conditions (Viboud *et al.* 2004). Although ENSO phases were incorporated into the analysis, humidity and temperatures observations were not examined for associations with influenza morbidity/mortality by Viboud (2004). Changes in temperature, precipitation, and humidity were the most likely determinants for influenza prevalence, but were not validated as significant factors in the Viboud (2005) study. Weather conditions should first be examined for influenza linkages, rather than the short-term climatic conditions (e.g. ENSO) that determine observable weather. However, the importance of ENSO phases has basis in the typical lag between ENSO measurements (e.g. Southern Oscillation Index SOI) and observed regional and local weather conditions (e.g. temperature, precipitation) (Ahrens 2003), which allows for early disease-prediction

The intriguing, but inconclusive linkage between climate and influenza prevalence suggests that a thorough analysis is required to determine the spatial variability and magnitude of these associations. If climate conditions are a determinant of influenza prevalence, can enviro-climatic factors be used to predict influenza

epidemics? A climatic and geographic analysis of influenza is needed to understand the ecology and etiology of the disease.

Examining Climate Linkages to Influenza Prevalence

This research investigates associations between influenza prevalence and the effects of temperature, precipitation, and short-term climatic trends (e.g. ENSO) at multiple spatial and temporal scales.

Objectives:

- **I.** Identify significant associations between climatic variables (i.e. temp, precipitation, ENSO) and influenza prevalence (i.e. morbidity and mortality) at varying temporal scales (e.g. annual, percentiles).
- **II.** Contrast the associations between influenza prevalence and climate at varying spatial scales (i.e. regional and local scales).
- **III.** Identify significant variable that may hasten or delay the onset of an influenza season (fall to summer).

Hypotheses:

- **I.** Variation in seasonal or monthly temperature and precipitation will significantly affect influenza prevalence at a regional and local scale.
- **II.** Regions where ENSO phases (i.e. El Nino and La Nina) significantly affect temperature, humidity, and precipitation, will also exhibit an association between influenza prevalence and ENSO.
- **III.** Seasonal variations in temperature or precipitation will affect the timing of (i.e. delays or expedites) an influenza season.

Approach:

Multiple spatial scales were examined: 1) Large scale analysis of the New York City, New York (NYC) area utilizing a twenty-two year mortality time-series from Dushoff (2006),

2) Regional and local analysis of influenza related mortality aggregated by regional districts as reported by the US CDC. A second part of the regional analysis utilized isolate data (i.e. a measure of influenza morbidity) provided by the World Health Organization WHO and National Respiratory and Enteric Virus Surveillance System NREVSS Collaborating Laboratories.

Climatic factors (e.g. temperature, precipitation, ENSO) were also analyzed for influenza prevalence at multiple temporal scales: 1) Annualized counts of mortality and morbidity counts aggregated to an influenza season (June- July), 2) Mortality and morbidity counts aggregated to the 15^{th} percentile (i.e. early influenza onset), 50^{th} percentiles, and the 75^{th} percentiles (i.e. late influenza penetration), as performed in Pyle's (1979) analysis of the seasonality of influenza, also examined regionally and locally. Seasonal influenza percentile measures (e.g. 15^{th} percentile) were used to assess the existence of environmental triggering events for the onset of influenza.

Analyzing morbidity and mortality data at multiple spatial and temporal scales provide a better understanding of the relationship between weather and climate toward the prevalence of influenza.

Chapter 2 – THE INFLUENZA VIRUS

2.1 THE NATURE OF THE INFLUENZA VIRUS

Influenza is an airborne contagion, and is easily transmittable as compared to other infectious diseases. The influenza virus is thought to be shed through coughing and sneezing, and then transmitted through droplet inhalation from the air (Mims *et al.* 2004). Currently, there are three known types of influenza viruses (A, B, and C), although type C influenza is not usually associated with significant epidemics and confined to outbreak in young children (Webster *et al.* 1992; Mims *et al.* 2004:pg 227). Furthermore, influenza B and C viruses are confined only to the human host and although epidemics are common as of recent, there has never been a pandemic associated with either (Webster *et al.* 1992; Mims *et al.* 2004). Webster (1992) believes that as opposed to Type A influenza, Type B and C influenza are, "…approaching an evolutionary equilibrium with their human hosts, whereas the A viruses are not (pg 166)".

Type A influenza is the greatest public health concern of all influenza types, the cause for most of the epidemics and all of the human pandemics throughout modern history (Cliff *et al.* 1986; Pyle 1986; Webster *et al.* 1992; Cox *et al.* 2000; Horimoto *et al.* 2005; Mims *et al.* 2004). Variants of the influenza type A viruses are responsible for the influenza pandemic of 1968, 1956, and the most severe influenza pandemic in 1918, with global mortality estimated at 20 million (Pyle 1986). A more liberal mortality estimate of 200 million possibly accounts for the overlooked populations in developing regions of the world (Pyle 1986; Patterson 1986).

The antigenicity, the ability to incite an immune system response, of influenza is determined by the combination of surface proteins, more specifically the glycoproteins

Haemagglutinin (HA) and Neuraminidase (NA) found on the surface of the virus particle (Webster *et al.* 1992; Cox *et al.* 2000; Horimoto *et al.*2005). Because influenza is a single-stranded RNA virus that lacks error-checking mechanism, replication occurs more quickly yet less accurately as compared to the replication found in the DNA viruses, which increases the possibility for numerous mutations in the genetic coding (Webster *et al.* 1992). Although mutations are not the sole reason for drifts in antigenicity, these mutations do allow numerous changes to the configuration of the surface glycoproteins (i.e. antigenic drift and antigenic shift) thereby affecting its ability to invade the host (e.g. humans, ducks, pigs).

2.2 ANTIGENIC DRIFT

Antigenic mutations appear to be a survival mechanism for the influenza virus, an effort by the virus to counteract the human's immune system response to protect itself from antigens (Webster *et al.* 1992). Unfortunately for the human body, even small changes in the HA and NA configuration may render existing human antibodies incapable of coping with a new strain of influenza. These point mutations in the genetic coding, which determine HA and NA configuration are referred to as antigenic drift (Webster *et al.* 1992; Mims *et al.* 2004). Antigenic drift causes only sporadic outbreaks for all types of influenza, since previously infected populations retain the antibodies from past infections that partially counteract virus infection (Mims *et al.* 2004).

The importance in determining the extent of antigenic drift is realized in the development of influenza vaccines. Because of antigenic drift, the antibodies incited by last season's influenza vaccination may be ineffective against a new influenza strain. WHO surveils prevalent influenza types globally to identify which virus strains pose the

greatest epidemic threat, and then develops a vaccine that incites the appropriate antibodies to prevent against influenza infection (Mims *et al.* 2004; Hsieh *et al.* 2005; CDC 2006a). However, since WHO decides the seasonal composition of the vaccine for the entire world, the influenza vaccine may be less effective in certain regions of the world due to the spatial variability of influenza strains (i.e. antigenic drift) (Hsieh *et al.* 2005).

2.3 ANTIGENIC SHIFT

Major changes in the antigenicity of influenza usually occur through viral re-assortment (i.e. antigenic shift), which results in significant increases in morbidity and mortality; the pandemics of 1957 and 1968 are a result of antigenic shift. Antigenic shift occurs through the co-infection of influenza strains within a single host (e.g. humans infected with both avian and human influenza) which replicates into a recombinant influenza strain (Webster *et al.* 1992; Cox *et al.* 2000; Mims *et al.* 2004). Antigenic shifts have only been observed in influenza A type viruses, are far more infrequent than antigenic drift, and are associated with influenza pandemics. A recombinant influenza virus could diffuse through a population unimpeded causing significant morbidity and mortality in immunologically naïve populations (i.e. human populations would have no previous exposure to this novel strain of influenza and therefore would have no antibodies to cope with the virus). Influenza viruses have been known to recombine in aquatic bird species (e.g. ducks), while pigs are thought to act as a “mixing vessel” in the development of pandemic influenza (Webster *et al.* 1992; Horimoto et al. 2005; Kilbourne 2006). The notion of swine as a vessel to recombine influenza strains (i.e. antigenic shifting) was the motive to implement a massive human inoculation program

for the entire US population after an outbreak at a military facility in 1976. However, much to the chagrin of the US government and influenza researchers, the "swine flu epidemic" never emerged (Meade *et al.* 2000)

Because influenza antigenicity is determined by HA and NA, influenza A virus subtypes are classified according to the configuration of these surface glycoproteins. The more abundant HAs on the influenza particle control the binding of the viral envelope to host cells (Webster *et al.* 1992), while the lesser numbered NA are responsible for the release the virus into the cell (Mims *et al.* 2004). The classification of a new influenza virus subtype occurs as new strains exhibit distinct variations in the HA or NA configuration, increasing their antigenicity to humans. The first influenza A subtype refers to the 1918 influenza virus that caused the most severe pandemic in history, denoted as H1N1 by Kilbourne. This notation describes the first HA configuration and the first NA configuration classified for influenza A viruses. Currently there are 16 HA and 9 NA known subtypes, all existing in wild bird populations, more specifically in aquatic birds (Webster *et al.* 1992; Horimoto *et al.* 2005). Although there are 16 HA subtypes possible, only three HA subtypes (H1, H2, H3) have been known to cause pandemics (Webster *et al.* 1992; Kilbourne 2006).

The last genetic shift, or significant changes in either the HA or NA, occurred in 1968 and produced the H3N2 strain (Schulman *et al.* 1969); the 1977 pandemic was thought to have derived from the original 1918 H1N1 pandemic and inadvertently reintroduced into the human population (Horimoto *et al.* 2005). The influenza strain of the 1968 influenza pandemic (Hong Kong, H3N2) differs from the 1957 pandemic (Asian influenza, H2N2) in that it possesses a different HA (HA-3) configuration, but retains the

same NA (NA-2) from the preceding virus. Since much of the population had previous NA-2 immunity during the 1957 pandemic (Asian influenza, H2N2), the 1968 pandemic (Hong Kong influenza, H3N2) was termed a 'smoldering' virus due to the milder mortality rates, as compared to the 1957 pandemic (Pyle 1986; Webster *et al* 1992). Conversely, the 1957 (Asian influenza, H2N2) exhibited a novel HA and NA configuration as compared to the predominant H1N1 virus in circulation prior to 1957, and resulted in significant morbidity and morality worldwide (Pyle 1986).

H3N2 is still one of the predominant influenza strains in circulation, which originated from the 1968 pandemic in Hong Kong. However, the H3N2 and H2N2 is descended from the 1918 H1N1 virus, or the "mother of all pandemics" (i.e. the foundation of all current influenza virus strains in circulation), as termed by Taubenberger (2006) through his molecular pathology studies (Taubenberger *et al.* 2006). The geographic origins of the 1918 influenza pandemic are still debatable. Once commonly known as the Spanish flu, the pandemic is now thought to have originated from central China or even the US (Pyle 1979; Patterson 1986; Webster *et al.* 1992; Cox *et al.* 2000). The more likely candidate however is China, which along with being suspected as the starting point for the 1918 pandemic is also implicated as being the epicenter for all influenza type A viruses (Webster *et al.* 1992). Predating the 1918 pandemic, "…the majority of pandemics of human influenza since about 1850 have originated from China" (pg 171) (Webster *et al.* 1992). Furthermore, Patterson's (1986) historical analysis of influenza found all pandemics from the 1700-1900 as emerging from China or Eurasia (i.e. mainland China and Russia). Unlike the temperate climate of North America and Western Europe, the tropical and subtropical climate of Southern

China experiences influenza prevalence year round with a summer peak (Webster *et al.* 1992; Cox *et al.* 2000). The occurrence of continual influenza prevalence throughout the year, dense human population, and large pig and duck population, point to prime environmental conditions for Southern China and Southeast Asia to act as the epicenter for influenza (Webster *et al.* 1992).

2.4 AVIAN INFLUENZA

The emergence of Avian Influenza (AI) in 2003 and into 2006, first erupted in Southeast Asia, spread into the eastern Mediterranean regions (e.g. Turkey), and then into seemingly disconnected regions of the world (e.g. Nigeria) (OIE 2006). The recent cause for concern is the potential development of a new human pandemic derived from the H5N1 (2006) AI virus. The prevalent strain of AI (as of April 2006) is currently not efficient in avian-to-human or human-to-human transmission. The few human cases were transmitted only through direct and close contact with infected chickens or restricted to intra-familial infections (e.g. daughter to mother) (Ungchusak *et al.* 2005; Horimoto *et al.* 2005). According to a recent literature review of influenza viruses by Horimoto *et al.* (2005), direct transmission of AI to humans is rare. Lacking the ability for efficient human-to-human transmission, the H5N1 strains can only cause sporadic illness and death in humans, with significant mortality confined to wild birds. Although uncommon throughout history, it is possible through a genetic re-assortment (i.e. antigenic shift) or other adaptation, that the 2006 H5N1 Asian strain could acquire the capability for efficient human-to-human infection, resulting in the emergence of an influenza pandemic.

The past influenza pandemics of the 20th century are all of avian origin (Horimoto *et al.* 2005), including the 1918 influenza pandemic (Taubenberger *et al.* 2005). Research by Taubenberger (2005) acquired tissue samples from early 20th century and found the genetic coding of the 1918 influenza pandemic was very similar to avian influenza, and made the remarkable conclusion that the 1918 pandemic was not a recombinant virus, which was unlike the 1957 and 1968 pandemics. Although the prevalent influenza strain prior to 1918 cannot be confirmed due to the lack of viable samples, it is probable that the 1918 virus was a novel virus that was an, "…avian like virus that adapted to humans" (pg. 892), according to Taubenberger (2005). In order for the 2006 H5N1 avian influenza virus to become a pandemic, it would also need to adapt to humans and possess a high rate of human-to-human transmission. Taubenberger's (2005) research solidifies the concern of AI developing into a pandemic, because it may be possible for an influenza virus to develop into a pandemic without the rare occurrence of an antigenic shift. However, since the first known H5N1 transmission to humans in 1997, the most recent AI has not adapted to humans to allow efficient human-to-human transmission (WHO 2006).

Avian Influenza (AI) in wild bird populations is not novel, but is ubiquitous in aquatic bird species throughout world, including North America (Webster *et al.* 1992; Horimoto *et al.* 2005). Generally, AI is asymptomatic in aquatic birds, providing evidence of an ecological stasis and implicating them as the natural reservoir to the virus (Webster *et al.* 1992). In aquatic birds (e.g. ducks, geese, swans) AI is shed through feces and is efficiently retained in water (e.g. ponds, marshes), which allows for extensive avian-to-avian transmission through the digestion of contaminated water; this

also poses potential for avian-to-human transmission (Webster *et al.* 1992; Horimoto *et al.* 2005) . There is a distinction between the influenza strains of ducks as compared to other aquatic birds, stressing their unique importance to the ecology of influenza (Webster *et al.* 1992). When AI comes into contact with domesticated bird species (e.g. turkeys and chickens) through mingling with wild birds, there is potential for increased pathogenicity, or the ability to cause disease. A low-pathogenic LPAI strain migrated into live bird markets (i.e. domesticated poultry) and was associated with an outbreak in1997-1998 and two outbreaks from 2001 to 2002 (Spackman *et al.* 2003). Prior to these LPAI outbreaks, AI outbreaks in domesticated poultry in North America also occurred in 1983-1984 (Bean *et al.* 1985; Webster *et al.* 1992). AI is not new to North America, but the current strain (2006) of AI (H5N1) emanating from Southeast Asia could create significant morbidity and mortality in wild and domesticated bird species if introduced into the American continents.

The scientific community and the poultry industry are concerned with LPAI outbreaks because of the possible transformation of these viruses into highly-pathogenic avian influenza HPAI, which could result in a serious public health risk and catastrophic loss for the poultry industry (Suarez *et al.*2003). HPAI, as opposed to LPAI, is rare in wild bird populations, including aquatic bird species and can cause significant morbidity and mortality in bird populations (Webster *et al.* 1992; Spackman *et al.* 2003). HPAI influenza viruses are also transmitted through fecal contaminated water, but are more effectively transmitted in dense flocks through nasal inhalation of infected materials (Horimoto *et al.* 2005). LPAI symptoms can be localized infections or even asymptomatic, while HPAI can cause fatal hemorrhaging in wild animal species (Webster

et al. 1992; Horimoto and Kawaoka 2005). The threat of human infection from AI was emphasized in an outbreak of AI H5N1 denoted (A/Hong Kong/156/97) in 1997. Eighteen people were infected in Southeast Asia, with some patients experiencing severe medical complications (e.g. pneumonia, kidney failure) resulting in six deaths; although human-to-human transmission was limited and found to be inefficient (Horimoto *et al.* 2005). An AI H5N1 outbreak in 2004 resulted in 53 deaths in Southeast Asia (Horimoto *et al.* 2005), with significant human-to-human transmission, and is directly related to the AI influenza in circulation in 2006. Previous outbreaks were mediated through extensive extermination of poultry flocks in Hong Kong and surrounding regions (Tiensin *et al.* 2005; Horimoto *et al.* 2005). Authorities dealing with the most recent H5N1 (2006) outbreak are also utilizing the same extermination measures in an effort to control the disease (WHO 2006). The development of the 2006 Asian AI virus into a pandemic still requires significant changes in antigenicity, either through antigenic shift or antigenic drift. None of the previous H5N1 outbreaks since 1997 underwent these genetic changes (WHO 2006).

There is concern that the 2006 AI viruses currently in the Mediterranean will migrate into North and South America. Although transmigration is a serious possibility, there is a historic geographic distinction of AI viruses between Eurasia and North and South America.(Webster *et al.* 1992). Physical geographic barriers appear to play a role in the distribution of AI “genetic pools” by confining natural bird migration flyways and preventing intermixing (Webster *et al.* 1992). Moreover, the isolation of the American Continents from the Eurasian continent, resulting in only two major bird migration pathways between the Eastern and Western Hemispheres (NGS 2004), may prevent or

hinder the diffusion of the 2006 Asian AI (H5N1) into the North and South American Continents. The degree to which these physical geographic barriers and other enviro-climatic factors play a role in the prevalence of AI is still unknown (Webster *et al.* 1992; Horimoto *et al.* 2005).

2.5 – MEDICAL GEOGRAPHY

Historical Perspective on Medical Geography

An aspect of medical geography attempts to define the geographic distribution of disease, to determine the contributing factors (e.g. environmental, sociological) that play a role in its distribution, and to study disease spatial ecology in terms of medical geography (Johnston *et al.*1994). Complementing epidemiological research, medical geography is concerned with spatial aspects of disease prevalence and the incorporation of the interdependencies of scale in analysis. Medical geographers can examine the spatial relationships between ecology (i.e. environmental factors) and disease (Pyle 1986), and have interests in disease diffusion modeling by lending a geographic perspective to medical and epidemiological research (Cliff *et al.* 1986). Recently, medical geography has found interests beyond disease ecology, focusing efforts on analyzing the spatial disparity in health care coverage, and recognizing the importance of qualitative methods of analysis, which Johnston *et al.* (1994) describes as the geography of health and health care (Meade and Earickson 2000).

A classic example of medical geographic research is John Snow's investigation of cholera in London in 1854. Snow developed a map that portrayed the location and quantity of cholera cases in London, allowing him to further investigate locations where incidence was rampant and where it was nonexistent. Through interviews with other

London doctors, along with graphical evidence from his London cholera map, Snow was able to correctly deduce that cholera originated from a single water well and reported this to the health authorities, who then removed the pump handle; cholera incidence decreased in the area thereafter (Tufte 1998). One of the first and most popular accounts of geographic analysis applied to the study of disease, Snow's work was integral to the development of medical mapping (i.e. medical geography) and epidemiology (Koch 2005).

There has been a recent resurgence in the study of *spatial disease ecology* and the geography of *health and health care* which are both fundamental aspects of medical geography. Recent advancements in Geographic Information Systems GIS along with increased accessibility of databases on the internet has fueled interest in disease diffusion modeling, spatial analysis of disease distributions, the integration of disease data with environmental datasets (e.g. elevation, land cover, precipitation), and the analysis of socioeconomic factors that contribute to disease distributions or disease susceptibility. These applications to GIS all have links to medical geographic research in analyzing the spatiality of disease. Similarly, this research examines the spatial disparity in influenza prevalence analyzed at multiple spatial and temporal scales in order to determine the significant environmental and sociological factors that affect its spatial distribution. GIS data techniques were utilized in this analysis to aggregate data according to spatial and temporal scales, and to develop maps of the study sites. This study built upon previous geographic works related to disease diffusion and more specifically influenza (Pyle 1979; Patterson 1986; Cliff *et al. 1*986; Haggett 2000).

2.6 – DISEASE DIFFUSION AND INFLUENZA

Medical geographers studying disease diffusion adopted techniques that were originally used to model waves of innovation, as put forth by Haagerstand (1968). Haagerstand's (1968) *Innovation Diffusion as a Spatial Process* utilized 'physical barriers' and 'individual resistance' to impede the flow of innovation through space, and used a 'mean information field' to structure this flow of innovation adoption (Johnston *et al.* 1994:pg 132). This diffusion theory is based upon person to person contact (i.e. contagious innovation) and is appropriately applied to 'simple' epidemics such as measles, but viruses such an influenza do not always operate according to such models (Pyle 1986:pg 17). Medical geographers interested in disease diffusion also incorporated ideas from other geographic disciplines (e.g. economic geography) through the realization that Christaller's (1966) central place theory could be useful in explaining hierarchical disease diffusion (e.g. disease diffusing from dense urban centers into the rural/suburban periphery), such as in Pyle's (1969) analysis of cholera epidemics in the US.

Pyle's (1979) *Applied Medical Geography* describes the adaptation of Haagerstand's diffusion model based upon percentiles: the infusion stage (25^{th} percentile), inflection (50th percentile), saturation (75^{th} percentile), and waning (beyond the 75^{th} percentile) (pg. 138). Pyle (1979) also cites the importance of classifying diffusion according to 1) translocation, 2) expansion diffusion (e.g. diffusion occurs until full adoption within the population has taken place), 3) contagious diffusion (infectious disease diffusion), and 4) hierarchical diffusion, which refers to spreading from a larger urban core to subordinate population centers (pg. 137). Pyle's *Applied Medical*

Geography (1979) also emphasizes the contribution of Haggett's *Locational Analysis in Human Geography* (1966) to the field of medical geography through the development of location analysis, which attempts to determine the order of spatial patterns and their linkages (Johnston *et al.* 1994:pg 346). Determining a locational order becomes exceedingly important in predicting the pathways of infectious disease through space. Cliff *et al.* (1986) observed that influenza epidemics initially arise in more populated areas and gradually disperse to surrounding regions (i.e. hierarchical diffusion) (Cliff *et al.* 1986; p. 263). Pyle's (1969:1979) and Cliff *et al.* (1986) reconstruction of the spatial trends of cholera and influenza illustrated the importance of these classic principles of disease diffusion.

In an analysis of the 1918 influenza pandemics, Pyle (1979) used historical mortality data from 50 major cities across the US to define the spatio-temporal distribution of the disease. Utilizing weekly cases of influenza mortality during the 1918 pandemic from Crosby (1977), he confirmed the existence of influenza waves as they spread across the US (Pyle 1979). He also found that when a population was immunologically naïve (i.e. had no previous exposure to the virus) influenza transmission increased geometrically, while a more linear relationship of transmission existed when there was previous exposure to the virus (Pyle 1986:pg 16). The observations of Pyle (1986) support the ideas of virus drift or shift (i.e. increased antigenicity of the influenza virus, or the ability to incite an immune response) put forth by Kilbourne (1973), who proposed that a population introduced to a genetically recombined virus would have little or no immunity, resulting in increased morbidity and mortality.

The Diffusion of Influenza (1986), along with providing more insight into the 1918 pandemic, provides in-depth assessment of influenza diffusion during 1957 and 1968 pandemics. Pyle (1986) emphasizes the importance of scale in the analysis of influenza, noting that utilizing regional and national P&I mortality data rather than local (i.e. city) P&I counts in analysis can potentially mask the presence of an epidemics (Pyle 1986:pg 11). Furthermore, using P&I counts from cities can predict epidemic outbreak because certain cities experience the onset of influenza earlier than the rest of the country (Pyle 1986:pg 14). Focusing surveillance measures on these historically 'sentinel' cites can provide an early warning system for potential influenza epidemics.

Using the same analytical techniques he used for the 1918 influenza pandemic, Pyle (1979) reconstructed influenza epidemics from the 1973-1974 to 1977-1978 influenza seasons, using Pneumonia and Influenza (P&I) as an indicator for virus prevalence. Building upon his adaptation of Haagerstand's model, he included the use of 15^{th} percentile of P&I mortality as a measure to indicate the early onset of virus into the population. Incorporating the use of percentiles allows for the analysis of influenza timing (i.e. peaks and onset of the disease) as compared to other influenza seasons. Through the comparison of percentiles, he found that the late onset of influenza (75^{th} percentile) was associated with the following season's early onset of influenza (15^{th} percentile) in adjacent cities (Pyle 1979:pg 155)

Pyle (1986) also provides a thorough review of several influenza models, including the Serfling model, which was used for several years by the US CDC in predicting influenza epidemics. Seminal to other influenza studies, the Serfling model used influenza related deaths as a measure for influenza prevalence, rather than a ratio of

influenza deaths normalized by total deaths. Serfling's basis for utilizing total counts was based upon issues regarding influenza surveillance reporting (e.g. infrequent reporting and changes in reporting criteria), that tended to understate epidemics in dense urban area and exaggerate epidemics in less population rural regions (i.e. denominators provided by surveillance data were problematic in providing a reasonable measure of influenza prevalence) (Pyle 1986:pg 11). For analyzing trends in influenza, Pyle suggests using a proportional scale of influenza mortality, with denominators being mortality counts taken over several years. This approach is similar to the Serfling method and provides a more accurate measure to determine the existence of an epidemic (e.g. an epidemic is usually defined as a 4.5 percent increase in mortality from the previous week) (Pyle 1986:pg 11).

Cliff *et al.* (1984) and Cliff *et al.* (2000) further developed and refined theories of disease diffusion through their island epidemic studies of measles and influenza. Similar to E.O. Wilson and Robert MacArthur's use of 'islands as laboratories' to reveal the evolutionary and ecological nature of plant and bird species (i.e. island biogeography), Cliff et. al (2000) used 'islands as laboratories' to gain a better understanding of disease dissemination and ecology in a simplified environment. The underlying theme in Cliff *et al.* (2000) is that disease isolation, which prevents immunological immunity from viruses, has drastic consequences for island populations (e.g. significant morbidity and mortality) when isolation is breached as a result advancements in human mobility (e.g. planes, trains, and automobiles). Cliff *et al.* (2000) recognized the importance of specific disease corridors and how they can facilitate infection, either solely through contagious spread or through hierarchical diffusion.

2.7 – INFLUENZA SEASONALITY

Influenza exhibits distinct seasonality, with a higher incidence in winter months and sharp decreases of morbidity and mortality in the summer months in temperature regions of world (Pyle 1986). The magnitude of morbidity and mortality prevalence varies from season-to-season (Pyle 1986). A trans-equatorial swing in influenza occurs, as the Southern Hemisphere experiences increased influenza incidence six months after the Northern Hemisphere (Cliff *et al.*Ord 1986; Hope-Simpson 1992). In tropical regions, influenza occurs continually with summer peaks (Pyle 1979). The year-round prevalence of influenza in tropical climates, more specifically in mainland Southern China and Southeast Asia, has implicated the region to be the epicenter for all influenza outbreaks (Webster *et al.* 1992). Webster (1992) theorized that the region's dense population, the lack of distinct seasonality, and strong interactions with domesticated and wild avian species creates an exceptional atmosphere for influenza to undergo antigenic mutations or even recombinations, and provides great potential for the development of influenza epidemics (or pandemics). The close interaction of dense human populations with wild and domestic birds may play a pivotal role in the development of influenza and AI human epidemics, since most epidemics and all pandemics are associated with the influenza type A virus, which in turn is derived from AI in wild bird species. Greater interaction likely leads to a greater probability of mutation into a more virulent virus.

The exact cause for this winter peak in still unknown, but is thought to be associated with intra-seasonal (i.e. monthly or weekly) temperatures or other climatic factors such as precipitation (Meade and Earickson 2000). Although a connection between temperature and influenza prevalence has been referred to in many texts (Pyle

1979; Cliff *et al.*1986; Hope-Simpson 1992; Parmenter and Yadav 1999; Meade and Earickson 2000), substantial empirical evidence for a temperature-influenza association is still lacking. As mentioned earlier, the basis for a suspected weather-influenza linkage relies on the notion that during low temperatures or heavy snowfall, people will congregate indoors more often. A dense, crowded space allows a higher probability for influenza infection (Meade and Earickson 2000). An alternative theory postulates that certain conditions of the air mass may promote the transmission or increase the survival of the virus, which is shed through coughing or sneezing and could result in a higher incidence of disease transmission. A dry and cold air mass is thought to promote influenza virus survival and dispersion (Mills 1939; Licht 1964; Cliff *et al.*1986; Parmenter and Yadav 1999; Meade and Earickson 2000).

In an attempt to explain apparent simultaneous outbreaks of influenza, Hope-Simpson (1979;1992) proposed that influenza was not transmitted by person-to-person contact as conventional contagious influenza transmission theory dictated. Instead, environmental "triggering events" spurred the onset of influenza in seemingly disconnected regions of the world. Although recent research definitively points to a human-to-human exposure route, and in some cases an animal/avian-to-human exposure route (Horimoto and Kawaoka 2005), parts of Hope-Simpson (1992) hypothesis can still provide insight into the transmission of the virus. The existence of a latent influenza virus and the notion of an environmental event triggering influenza symptoms may help explain the cyclical nature of the disease.

2.8 – DISEASE AND CLIMATE

Research analyzing linkages between climate and disease has increased significantly in recent years, perhaps because of the proliferation of Geographic Information Systems (GIS) and medical surveillance systems, along with publicly available datasets on the internet. There is abundant research about the climatic linkages of water-borne and vector-borne disease because of the known ecological connection between vector/host abundance and environment. For example, climate affects the distribution of vector-borne diseases (i.e.. transmitted by a mosquito) such as malaria and Dengue Fever (Githeko *et al.* 2000; Hopp 2001; Subak 2003; Kolivaris 2004; McCabe and Bunnel 2004). Moreover, the distributions of the host and vector for Lyme disease are dependent upon rainfall because precipitation defines the availability of favorable breeding conditions and the magnitude of ecosystem productivity (Hunter 2003).

Initially analyzed by medical geographers and epidemiologists in their formative stages, linkages between climate and non-vector borne infectious diseases (e.g. cholera) and their impact to human health are reemerging in the scientific literature (Meade and Earickson 2000). Patz *et al.* (2000) provides an extensive list of linkages between weather and disease, and more specifically the effects of weather on many aspects of public health: air pollution, famine, arboviruses (e.g. insect borne viruses), waterborne diseases (e.g. cholera, diarrhea), aeroallergens, are all associated with changes in weather conditions. Certain conditions of the air mass (i.e. the condition of humidity, temperature and pressure of the air that people breathe and interact) may promote the dissemination of allergens (e.g. dry air) to create an outbreak of asthma like symptoms. Thus, associations with climate are reflected in many forms of disease affecting humanity (Glass *et al.* 1992;

Parmenter and Yadav 1999; Patz *et al.* 2000; Hjelle and Glass 2000; Githeko *et al.* 2000; Kolivaris 2003; Patz *et al.* 2003; Bouma 2003; Hunter 2003; Subak 2003; Patz *et al.* 2005; Viboud *et al.* 2004).

Disease modeling that incorporates enviro-climatic factors (e.g. precipitation, vegetation indices) show promise for estimating the onset or magnitude of an epidemic before it occurs. For example, vegetation and climate indices were used to model "trigger events" of Ebola epidemics on the continent of Africa (Pinzon and Wilson 2004), and distinct patterns in rainfall and temperature have been linked to *coccidioidomycosis* incidence, a fever with flu-like symptoms caused by a soil-dwelling fungus (Kolivaris 2003). Incorporating environmental and climatic factors into disease analysis can provide disease endemnicity maps (i.e. portray geographic likelihood of disease), which are useful for predicting disease prevalence (Yabsley *et al.* 2005).

Because precipitation and temperature are sometimes dependent upon long-term climatic cycles in particular regions of the world, global climate indices have also been found to affect disease incidence. Short-term climatic episodes produced by the El Nino Southern Oscillation (ENSO) were found to affect malaria in Madagascar because of the above-average winter temperatures produced during an El Nino year (Bouma 2003). A review of the human health effects of climate change discussed the ecological linkage of Cholera outbreaks in Bangladesh spawned by the eruption of disease-causing plankton during particular ENSO episodes (Patz *et al.* 2005). ENSO episodes were also responsible for the sporadic occurrence of hantavirus and plague outbreaks in the Four Corners region of the southwestern United States because of the heavy precipitation associated with these periods (Parmenter *et al.* 1999; Hjelle *et al.* 2000).

Hantavirus epidemics in the Four Corners region of the Southwestern US are an exceptional example of how climate, and more specifically short-term trends in climate (e.g. ENSO), can affect disease incidence. More importantly, it provides a case-study that exemplifies the importance of considering scale and regional climatology in determining disease incidence. The precipitation of the arid Four Corners region of the US is significantly dependent upon the warm phases (i.e. El Nino) of ENSO. More specifically a strong El Nino event, which usually occurs only once or twice every decade, can bring dramatic precipitation into the Four Corners Region (Redmond and Koch 1991). During these wet conditions in the arid Southwest, plant productivity and seed dispersal is at its peak, initiating a cascade of events that can result in a hantavirus epidemic. The *trophic cascade* theory as postulated by Parmenter (1999) originally describes plague outbreaks as a result of increased vegetation productivity (e.g. pinon pine nuts) that subsequently caused dramatic increases in mice fecundity because of the increased carrying capacity of the environment. Deer mice are the host to the vector (i.e. flea) for plague. With an abundance of the host vector (i.e. deer mice) plague incidence increased dramatically because fleas were also mobile and abundant due to the increased population of their host species (i.e. mice) (Parmenter and Yadav 1999). Similar to plague, Hantavirus incidence is directly influenced by the population of the host species, the deer mice. Hantavirus is shed through deer mice feces and is lethal to humans through the aerosolization of infected feces, causing severe hemorrhagic fever (Yates *et al.*2002). Along with Plague, Hantavirus incidence is defined by the influence of ENSO on the region's precipitation, and is also subject to Parmenter's (1999) trophic cascade theory. Hantavirus outbreaks are confined spatially (e.g. Southwest Four Corners region

of the US) and are influenced by climatic episodes measured at a global scale (e.g. ENSO) but outbreaks are produced by specific weather patterns (e.g. precipitation) that only exist regionally. The development of a Hantavirus epidemic underscores the importance of considering scale both climatologically and ecologically when analyzing disease incidence.

Studies analyzing linkages between climate and disease, by epidemiologists and geographers, portray the intense interconnectivity that exists between disease, ecology, and weather. The methodologies developed from the recent scientific focus of vector-borne disease need to be applied to other infectious (i.e. non-vector borne) diseases that are potentially affected by weather and climate variability. Infectious disease such as tuberculosis, Ebola virus, Marburg virus, and influenza deserve more attention to determine if associations between weather and climate exist.

2.9 – INFLUENZA RELATED TO WEATHER AND CLIMATE

Medical climatologists from the early 20th century provided early explanations for a link between climate and health and more specifically proposed that certain qualities of the air mass affected the onset of respiratory illness (Licht 1964; Mills 1939). More recently, bio-meteorologists have studied the effects of solar radiation (e.g. sunlight, ultraviolet light), and weather and climate on human health. However, other than human illness associated with temperature extremes (e.g. anomalies of high temperature associated with elderly deaths) there is still little evidence for linkages between health and weather (Meade and Earickson 2000). Weather, as opposed to climate, refers to the immediate combination of precipitation, temperature, and humidity experienced, while

climate refers to long-term (e.g. yearly, inter-decadal) and short-term (e.g. weeks, months) weather conditions (Ahrens 2003).

Biometeorologists have observed the effects of acclimatization, or lack there of, in the human body. In order to cope with abrupt changes in the environment, the human body can compensate through physiological (e.g. sweating and shivering) or behavioral changes (Meade and Earickson 2000). A recent study examining the onset of *'common cold'* symptoms (which are similar to influenza symptoms but less severe in nature) chilled the feet of human test subjects for a twenty minute period, and found a significant correlation between the delayed onset (e.g. four to five days) of *'common cold'* symptoms and those persons who were chilled (i.e. feet immersed in cold water for twenty minutes), as compared to the control group (Johnson *et al.* 2005). Results for the Johnson *et al.* (2005) study also suggest that, "... there is a sub population in the general population who are more susceptible to developing common cold symptoms each year" (pg 5). An explanation for the delayed onset of the *'common cold'* as proposed by Johnson *et al.* (2005) was the increased susceptibility of the human immune system because of the physiological reaction of vasoconstriction of blood vessels in the upper respiratory region of the body (i.e. opening of the blood vessels in the nose and throat may cause increased susceptibility to infection) in response to acute chilling. Either the test cases acquired the *'common cold'* during the five days following the acute chilling because of compromised immunological immunity, or the acute chilling was a triggering event that spawned the onset of *'common cold'* like symptoms. The Johnson (2005) study provides a controlled scenario of acute chilling that can easily occur in the natural environment (e.g. acute chilling caused by abrupt rainfall or snowfall in the winter), and

may provide evidence suggesting the existence of an environmental triggering event for influenza or the common cold, as proposed by Hope-Simpson (1992).

There have been a few recent studies analyzing potential climatic triggering events for influenza. Analyses have looked at influenza at a national level (e.g. France), and at a local scale (e.g. hospitalizations in three California cities). Viboud *et al.* (2004) examined influenza epidemics for France utilizing the conventionally used P&I mortality counts from a twenty-six year time-series. Influenza at a national level (France) was analyzed for an association with ENSO phases as defined by a Multivariate ENSO Index (MEI) measured at a global scale (Viboud *et al.* 2004). Viboud (2004) averaged MEI over a four month period (September to December) against P&I deaths, and found a significant association between cold ENSO phases and increased morbidity mortality. The regional effects of ENSO are different around the world, and during cold ENSO phases (i.e. La Nina) Europe experiences decreased temperatures and higher humidity during the winter months (Viboud *et al.* 2004). Although P&I mortality was measured at a national scale, the size of France is roughly the size of Texas. Therefore, associations between weather and climate and influenza P&I mortality counts at a national scale would be less appropriate in the US due to the large climate variability, while in France national reporting of influenza would be more appropriate due to the relatively similar climate throughout the country. Nonetheless, ENSO phases as a determinant to influenza prevalence has been statistically proven, but consideration of scale is needed. Although ENSO is a global phenomenon, it creates local and regional variations in weather and climate.

Analyzing influenza in two different climatic regions in California, Ebi *et al.* (2001) utilized viral pneumonia related hospitalizations as a measure for disease prevalence. Three study sites represented the major metropolitan areas of California: Sacramento, San Francisco, and Los Angeles, CA. Ebi (2001) undertook a large scale temporal analysis by examining aggregated hospitalization data (e.g. four days) as compared to weather conditions seven days earlier. ENSO measurements were incorporated into the analysis by using theSouthern Oscillation Index (SOI) values, rather than MEI values used in Viboud's (2004) study. SOI is a global climate measurement for ENSO, which is the difference between mean sea-level pressure from Darwin, Australia and Tahiti (Ahrens 2003). Associations between weather (e.g. precipitation and temperature) and climate (e.g. ENSO and Sea Surface Temperature) and influenza prevalence were found in only one of the three study sites, exhibiting the importance of considering regional and local climate for analytical purposes. Warm ENSO phases were associated with increased viral pneumonia hospitalizations in Sacramento, CA. Not surprisingly, the inland Sacramento was also the only city with weather conditions that exhibited consistent association with ENSO phases. Sacramento experiences warmer autumn seasons (November – January) along with cooler winter and early spring temperatures (January – April) during a Warm ENSO period (i.e. El Nino). Generally in Sacramento, as minimum temperatures decreased viral pneumonia hospitalization increased, however associations were not as consistent during cold ENSO events (i.e. La Nina); precipitation was found not to be a factor in influenza prevalence (Ebi *et al.* 2001). Furthermore, association between minimum temperature and viral pneumonia hospitalizations were significant in San Francisco, but only during normal and El Nino

periods; there was no association with ENSO (i.e. influenza-climate association in San Francisco were complex and not straight-forward). The study by Ebi *et al.* (2001) again underscores the important of considering scale in the analysis of influenza and more generally in disease incidence, and the efficacy of utilizing disease data at varying temporal aggregations (i.e. temporal scales). The analysis of Ebi *et al.* (2001) provides other proxies (e.g. viral pneumonia hospitalizations) that can be used for estimating influenza prevalence in other regional studies.

The most recent US study relating influenza incidence to climatic factors was performed by Dushoff *et al.* (2006). Attempting to utilize measures other than just strictly P&I to define influenza prevalence, P&I mortality counts in conjunction with "multiple cause" mortality counts were used in their analysis, in hopes to counteract any disease misclassification in the surveillance data. A twenty-two year dataset time-series from the US CDC National Centers for Health Statistics was used (Dushoff *et al.* 2006). Dushoff *et al.* (2006) used excess mortality as defined by a total number of deaths above a monthly average, for two regions in the US: 1) NYC region (e.g. sixteen counties surrounding NYC) and 2) state-wide mortality from Illinois and Indiana. As opposed to other influenza studies utilizing monthly mortality counts, Dushoff *et al.* (2006) used an annualized approach aggregated to a single influenza season, resulting in one mortality count per season. Temperature data was taken from a single reporting station for each study site (Newark International Airport and O'Hare International Airport), with the coldest temperature value averaged from November to April. Dushoff *et al.* (2006) found no significant association between temperature and influenza related mortality. However, they provided our study with an exceptional dataset. The datasets from the Dushoff *et al.*

(2006) was used in our analysis, but further incorporated temperature, precipitation, and SOI measurements. Our analysis aggregated the Dushoff (2006) multiple caused P&I dataset according to annualized cumulative counts, in order to identify seasonal percentiles, similar to the analytical methods used by Pyle (1979;1986).

Chapter 3 – ANALYZING INFLUENZA PREVALENCE IN THE US

Many aspects of influenza are still unknown: the apparent disappearance of influenza in the summer months, the variability of influenza prevalence among flu seasons, the sporadic occurrences of spring influenza infection, apparent outbreaks in isolated regions of the world, the timing of the influenza season, and the effects of weather and climate to influenza prevalence (Hope-Simpson 1979, 1992; Pyle 1986; Cliff *et al.* 1986; Meade and Earickson 2000; Cox and Subbaro 2000; Horimoto and Kawaoka 2005). Our research investigates the existence of significant associations between influenza mortality/morbidity and environmental climatic conditions (e.g. temperature, precipitation, humidity, El Nino Southern Oscillation (ENSO) analyzed across varying temporal scales (e.g. monthly, yearly) and spatial scales (e.g. county, state, regional, national).

Influenza-climate relationships were compared at different spatial scales by the examination of local versus regional relationships. The South Atlantic and the Northeast region were chosen as our study sites because of their close proximity to each other and their latitudinal differences (i.e. the regions exhibit seasonal differences in weather and climate) (Ahrens 2003). Influenza-climate relationships were also compared at varying temporal scales to determine if relationships differed. Specifically, comparing annualized influenza counts to cumulative percentiles representative of the epidemic curve (e.g. 15^{th} percentile – early onset of disease, 75^{th} percentile late penetration of the disease) (Pyle 1979; Pyle 1986). The idea of varying correlations according to spatial scale is predicated by the idea that influenza case data aggregated to regions may include cities containing both high and low influenza incidence, confounding the identification of

climate-influenza relationships. Utilizing the annualized cumulative aggregations of the 15^{th} percentile (i.e. early onset) and the 50^{th} percentile (i.e. the average peaking), the timing of influenza (i.e. expedited or lagged peaks in influenza during a season) was examined for dependencies to climatic factors (e.g. temperature, precipitation, ENSO) (Pyle 1979; Pyle 1986). This research builds upon the knowledge of the spatial and temporal trends of influenza developed by geographers (e.g. Cliff, Haggett, Pyle) by providing insight into the climatic factors that may lead to increased influenza prevalence.

Identifying significant associations between influenza and weather conditions may have implications for the etiology of influenza. A seasonal climatic association may imply a period of latency for influenza (i.e. infection could occur in the summer but remain latent until certain environmental conditions are met), similar to the theory postulated by Hope-Simpson (1992). Influenza-climate relationships may confirm conventional theories of influenza transmission, such as the idea that certain climatic conditions (e.g. cold or wet weather) cause behavioral changes in humans, which thereby increase influenza incidence through increased human-to-human contact (Cliff *et al.* 1986; Webster *et al.* 1992; Cliff *et al.* 2000; Meade and Earickson 2000). Nevertheless, there is much speculation about the effects of observable temperature and precipitation on influenza prevalence, but with no definitive evidence for US mortality. *Our geographic study analyzed influenza prevalence associated with climatic conditions at varying temporal and spatial scales in an attempt to clarify any suspected linkages.*

3.1 STUDY SITE

Our study examined influenza prevalence in NYC at a local scale, and also analyzed morbidity and mortality data from the Northeast US and the South Atlantic region. The northeastern United States is a more densely populated region than the South Atlantic region. Theoretically, a higher population density in the Northeast may lend to an increased influenza related mortality count as compared to the South Atlantic states (Cliff *et al.*1986). Increased influenza related mortality counts according to regions, however, should not affect our analysis because we are comparing regional versus local (i.e. cities contained within the same region) influenza-climate relationships. According to the US Census 2000, more populous states of the Northeast such as New York and New Jersey have a higher percentage of persons aged 65 years of age and older as compared to the South Atlantic (Census Bureau 2006). On the other hand, the South Atlantic region encompasses the state of Florida, which possesses the highest percentage of persons 65 years of age and over, according to the 2000 Census (Census Bureau 2006). Although particular demographic trends may affect associations between mortality and climate, because of the vulnerability of the 65+ age group to influenza-related morbidity, the fairly consistent age distribution throughout these regions should not be a confounding factor in Northeast US. The lower proportion of the elderly in the South Atlantic states may be compensated for in a regional analysis of the South Atlantic because of the inclusion of Florida, and remains an appropriate study region for our analysis.

The extreme Northeastern states are classified as humid continental with a moist climate and severe winters (Ahrens 2003). However, the most densely populated regions

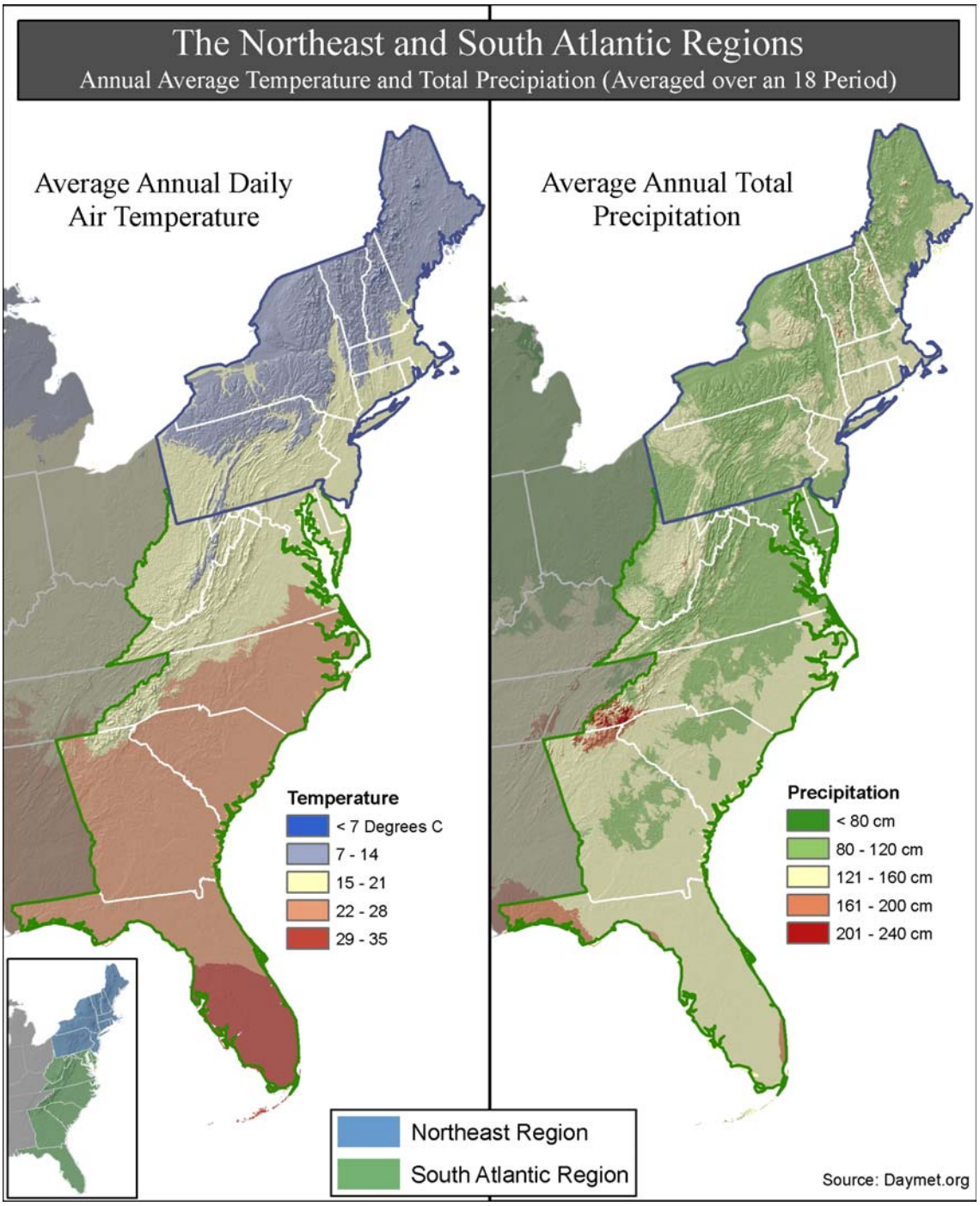
(e.g. New York City) are on the margin of being defined as a humid subtropical climate with hot humid summers and mild winters according to the Köppen classification (Ahrens 2003). The South Atlantic US primarily falls in this latter climate classification, with hot summers and mild winters The inclusion of FL in the South Atlantic regions may produce unexpected results when attempting to derive a 'regional' measure of average temperature and precipitation. In general, the northeast region is defined by a more similar climate, while in the South Atlantic region contains greater climatic variability. Comparing the South Atlantic and the Northeast, observed precipitation appear to be similar, however average temperatures are considerably lower in the Northeast US (Figure 1). A more homogenous region with respect to climate may affect regional climate associations to influenza prevalence.

3.2 DATA

NYC Mortality Data

For a large scale analysis of NYC we utilized a dataset provided by Dushoff *et al.* (2006). Dushoff *et al.* (2006) obtained the monthly mortality data time-series (1979 – 2001) from the US CDC National Center for Health Statistics (NCHS) for New York City, NY (NYC). The Dushoff *et al.* (2006) dataset was only used in this analysis for the large scale analysis of NYC influenza prevalence. The dataset consisted of P&I mortality counts resulting from 'multiple' causes, in an attempt to compensate for potential errors in mortality reporting to the CDC (Dushoff *et al.* 2006). P&I multiple cause mortality was reported according to age, and was further aggregated in this analysis to produce three subpopulations: 1) *children* aged 0 – 14 years of age, 2) *adults* aged 15 to 64 years of age, and 3) *elderly* aged 65 years of age and older. Dushoff *et al.*(2006) compiled the

multiple caused P&I mortality dataset from sixteen counties surrounding NYC (Figure 2). Previous studies have used historic P&I mortality to assess the magnitude and diffusion of influenza during epidemics and pandemics (Pyle 1986; Cliff *et al.* 1986; Cliff *et al.* 2000; Viboud *et al.* 2004; Dushoff *et al.* 2006) and to predict influenza related mortality (Choi *et al.* 1981). Furthermore, Pyle (1979) used P&I mortality to retrace the diffusion of influenza in the US during the 1918 pandemic. P&I multiple cause mortality counts were annualized from the months of July to June. The 15^{th}, 50^{th}, and 75^{th} percentiles were calculated from annualized cumulative P&I multiple cause mortality counts.



(Figure 1. Average Temperature and Precipitation of the Northeast and South Atlantic)

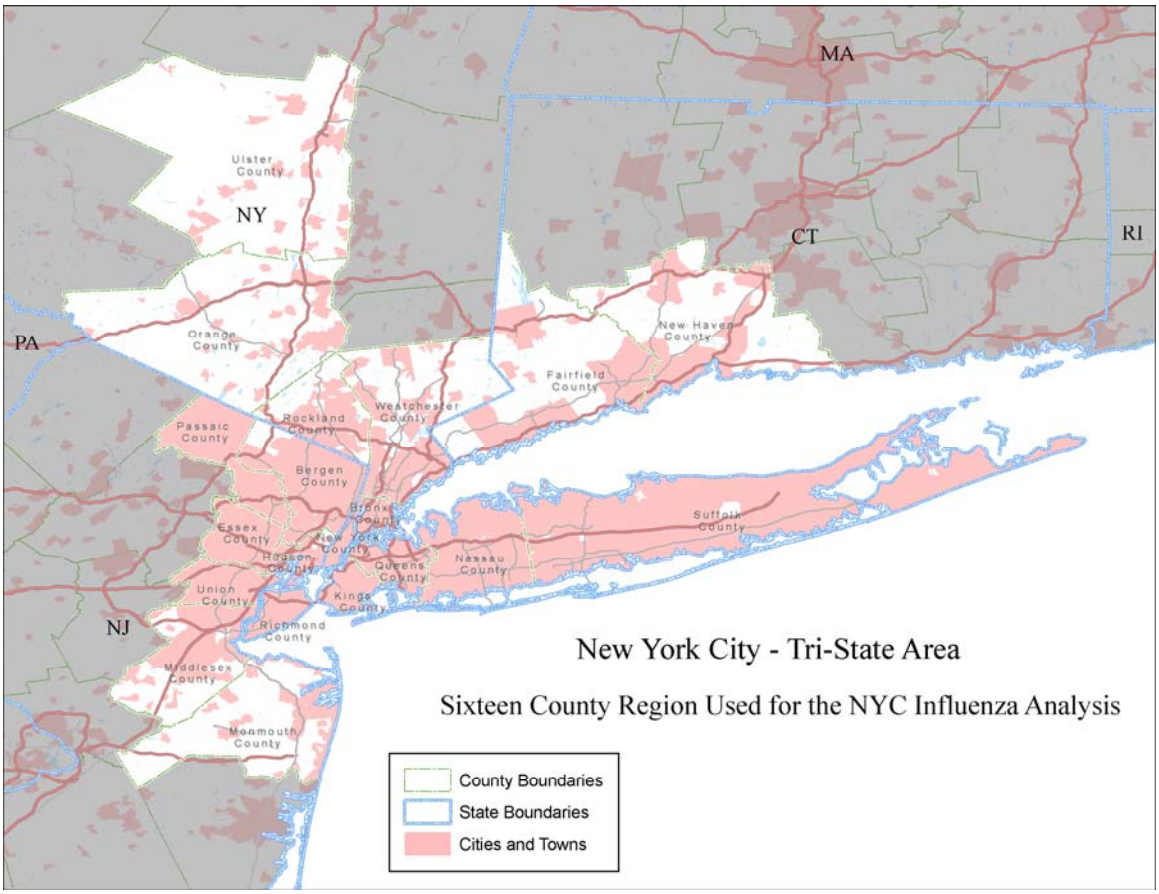
Regional Mortality Data

For the regional analysis of influenza, P&I mortality counts, provided by the CDC's Morbidity and Mortality Weekly Report (MMWR), were used for a dataset spanning ten influenza seasons (1996-2005). Weekly mortality counts related to P&I deaths are compiled by the Centers for Disease Control and Prevention from a network of 122 cities across the US and are disseminated to the public through the MMWR (MMWR 1996-2006). Weekly mortality counts were annualized and aggregated according to an influenza season spanning the months of July to June.

Regional Morbidity Data

Surveillance data extracted from the WHO/NREVSS influenza surveillance system was used as a proxy for influenza morbidity. The WHO/NREVSS dataset contained tallies of positive influenza isolates according to type (e.g. A, B) and subtype (e.g. H3N2, H1N1) for an eight year time span (1997- 2005). According to the CDC flu activity webpage (http://www.cdc.gov/flu/weekly/fluactivity.htm), laboratories voluntary submit isolate results (e.g. isolates specific to testing HIN1 and H3N2 influenza) to the CDC and are reported on a voluntary weekly basis, and are aggregated regionally. A second surveillance dataset provided by the U.S. Influenza Sentinel Physicians Surveillance Network directed and provided by the CDC was also available for our analysis, but because the database reports influenza like illness (ILI) rather than positively tested influenza isolate, we chose not to incorporate this dataset. Using reported ILI cases as proxies for influenza related morbidity becomes potentially problematic in that influenza like symptoms are very similar to symptoms of the 'common cold'. The WHO/NVRESS dataset was the best measure of influenza

morbidity available with an appropriate time-span that was valid for a temporal analysis. THE WHO/NREVSS isolate is a more accurate reflection of actual influenza prevalence than other morbidity datasets. Isolate data was annualized according to influenza type and subtype.

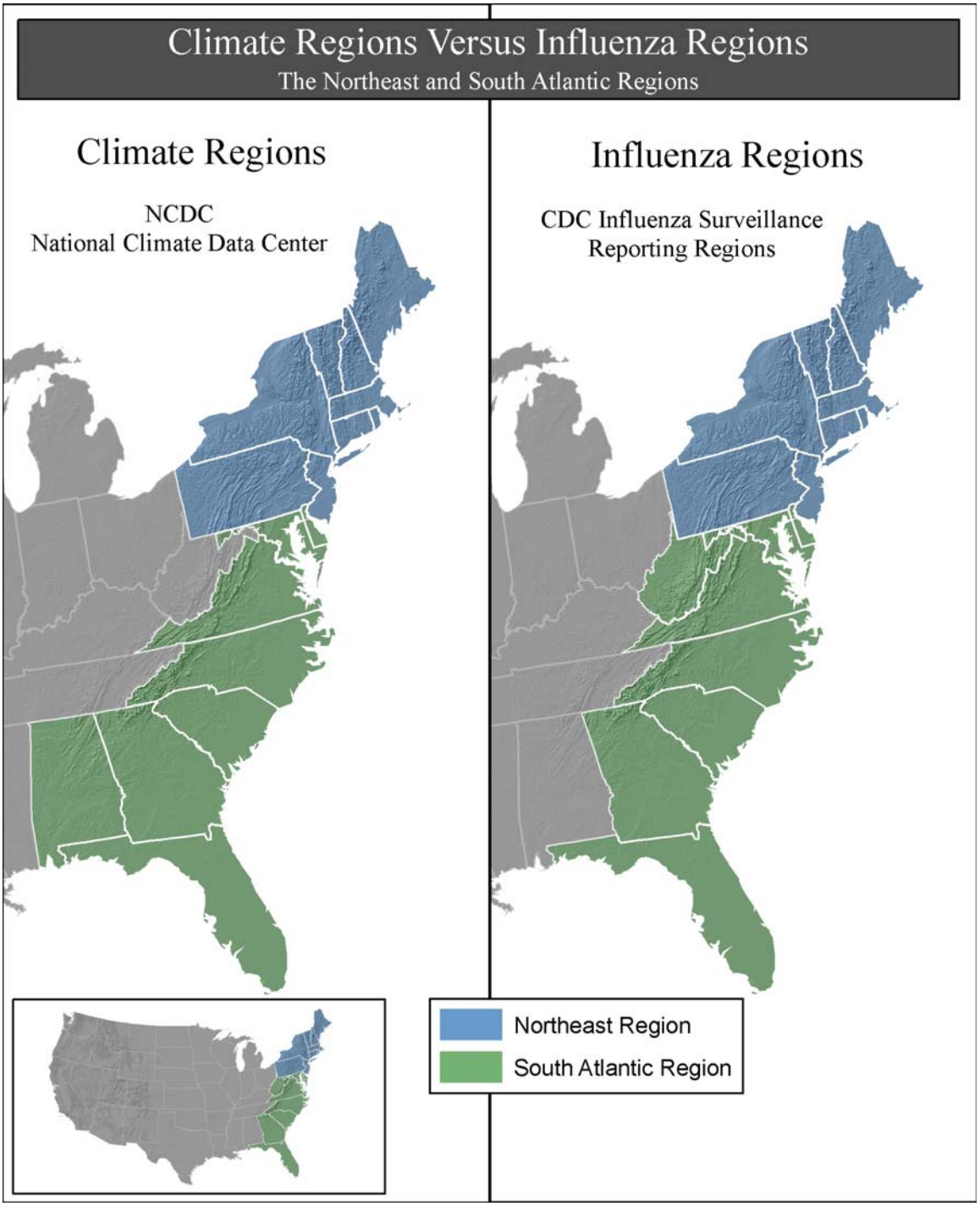


(Figure 2. Sixteen County Region Used to Compile the NYC Mortality Dataset)

Climate Data

Regional climate data was provided by NOAA's National Climatic Data Center (NCDC), which produced precipitation measurement and average temperatures. The NCDC also provided temperature and precipitation data for NYC, Boston, Ma (Blue Hill, MA weather observation), and Baltimore, MD (Washington, DC weather observations).

Precipitation and temperature data for Philadelphia, PA was provided by the Pennsylvania State Climatologist Office and NCDC. Philadelphia, PA weather was measured according Pennsylvania's region 3 observations. Precipitation and weather observations for the Tampa Bay, FL were provided by the Florida Climate Center and NCDC. Weather data was aggregated according to seasons (e.g. winter, spring) and in some cases precipitation and temperature observations were extracted according to certain months. There was some disparity between the CDC influenza reporting regions and the NCDC climate regions (Figure 3), however a regional measure of precipitation and temperature from the NCDC is still appropriate for this comparative analysis because the regions retain a similar climate. The global climate measurement for ENSO was based on the Southern Oscillation Index SOI, which is a measure in the differences between mean sea-level pressure from Darwin, Australia and Tahiti (Ahrens 2003). Historical monthly SOI values were obtained from the Australian Government Bureau of Meteorology.



(Figure 3. Differences in Climate and Influenza Reporting Regions)

3.3 METHODS AND MATERIALS

Objective I & II – Influenza & Climate According to Scale

This section will be separated according to the type of analysis: 1) NYC local analysis of P&I multiple cause *mortality* according to climate at *several temporal scales*, 2) Analysis of MMWR P&I *mortality* according to climate at *two spatial scales*, in regions of Northeast and South Atlantic US, 3) Analysis of influenza related *regional morbidity*, as measured by WHO/NVRESS influenza isolate data.

Local Influenza Analysis of NYC -Annualized Method

For the large scale multi-temporal analysis of NYC, we used a twenty-two year time series (1979-1995) of P&I multiple cause mortality counts from Dushoff (2006). P&I multiple cause mortality counts were compiled from death certificates that made any mention of influenza or pneumonia, the time-series attempts to compensate for any reporting changes made in 1999 to the CDC influenza surveillance system (Dushoff *et al.* 2006). Comparing the two P&I datasets, the annualized *P&I as underlying cause of death* dataset exhibits a significant drop in P&I cases reported after 1999 (Figure 4), while the counts of the *P&I from multiple cause*s dataset appear to be more consistent with the data trend of the previous years (Figure 5). P&I mortality from multiple causes, as provided by Dushoff (2006), was used in our multi-temporal scale analysis of NYC because it is a more accurate portrayal of influenza prevalence throughout the entire twenty-two year time-series. P&I multiple caused mortality data were further broken down into age group of children (0-14), adult (15-64) and the elderly (greater than 65 years of age). The first temporal analysis of annualized (July – June) deaths attempts to account for the winter peaking of influenza, and results in a single P&I measure for each

influenza season. The annualized P&I multiple cause mortality counts were then analyzed to determine if seasonal precipitation and temperature along with ENSO phases were a determinant for increased influenza incidence. Because the primary concern of this study is to determine if influenza mortality varies according to weather, P&I counts were used rather than the conventional measures of excess mortality or a normalized mortality. Furthermore, mortality counts rather than mortality percentages were utilized in the analysis, since mortality percentages tend to mask epidemics (Pyle 1986).

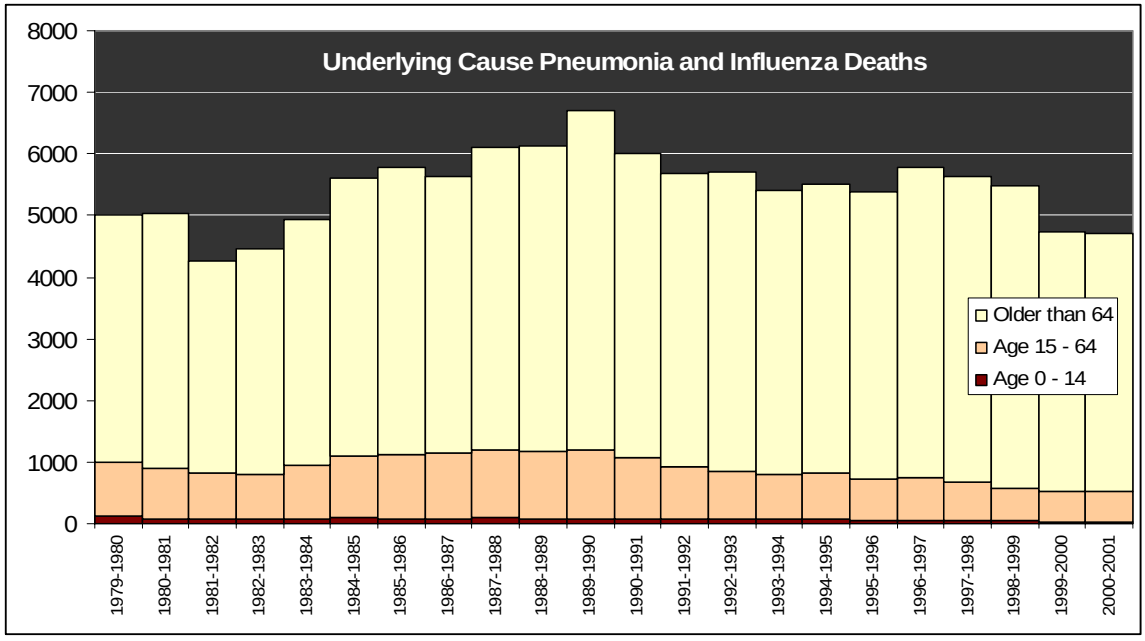


Figure (4). NYC - Underlying Cause of P&I Deaths

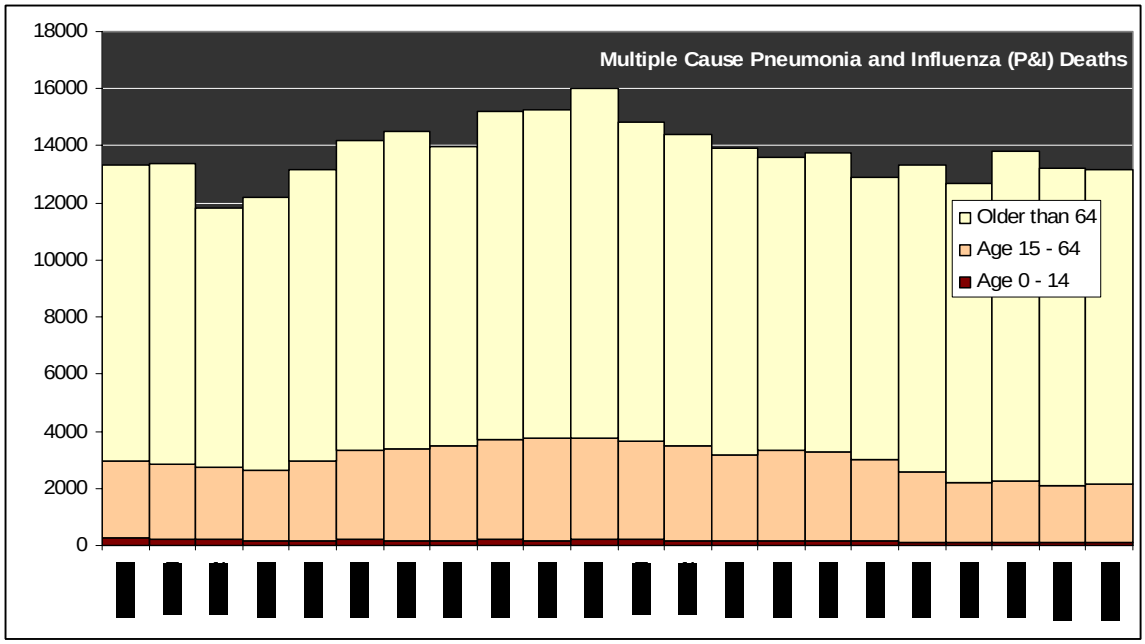


Figure (5). NYC - Multiple Caused P&I Deaths

Percentile Method

To further determine the effect of environmental factors on influenza prevalence, the data was aggregated according to the 1) early onset of influenza (i.e. 15th percentile), 2) the statistical mean of influenza (i.e. 50th percentile), and 3) the late penetration of influenza (i.e. 75th percentile). Using this percentiles method allows for the comparison of influenza seasons, and was utilized in Pyle's (1986) influenza study. The seasonal nature of influenza is variable in magnitude every year (Pyle 1979; Pyle 1986; Cliff *et al.*1986; Cliff *et al.*2000; Haggett 2000). Furthermore, the different progressions of the epidemic curve (e.g. early onset, late penetration) may also exhibit different patterns for each demographic population (e.g. children, adults, elderly). For NYC, the early onset of influenza (15th percentile) for two seasons in particular, 1991-1992 and 1992-1993, exhibits a relatively low mortality count (Figure 6). However, by the time the 75th percentile of cases was reached for the 1991-1992 and 1992-1993 seasons, mortality

counts attained a level that was comparable to the trends of the late 1980's and early 1990's (Figure 6). The comparison of cumulative percentiles allows us to examine relationships between influenza and climate throughout the progression of an influenza season, in hopes to unmask significant associations in the dataset. The Dushoff *et al.* (2006) influenza dataset and the NCDC climate data were also normally distribution and allowed the use of the robust parametric correlation coefficient of Pearson's product to test for associations between climate and influenza (Figure 7) (Rogerson 2001).

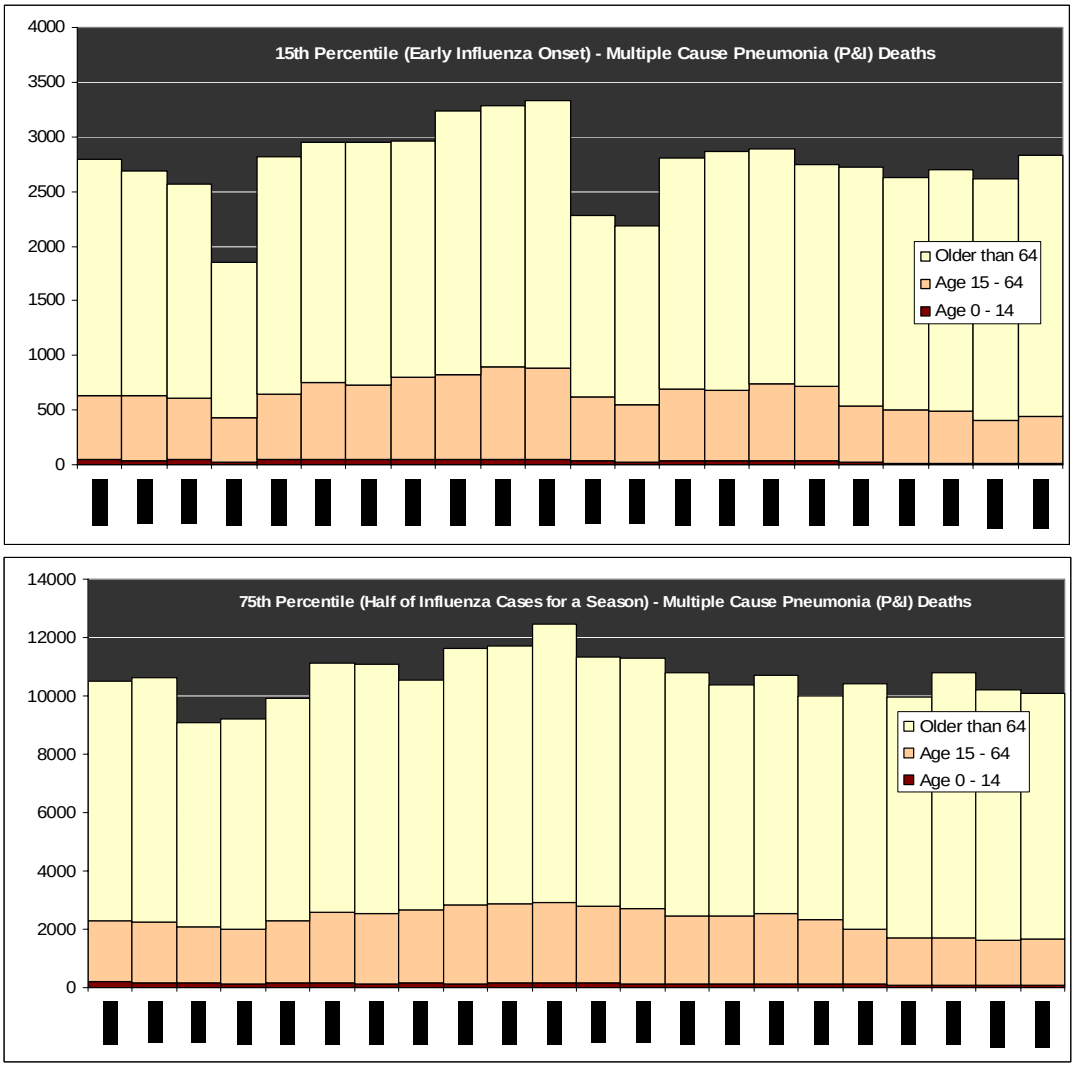


Figure (6) NYC - 15th, 50th, 75th Percentiles

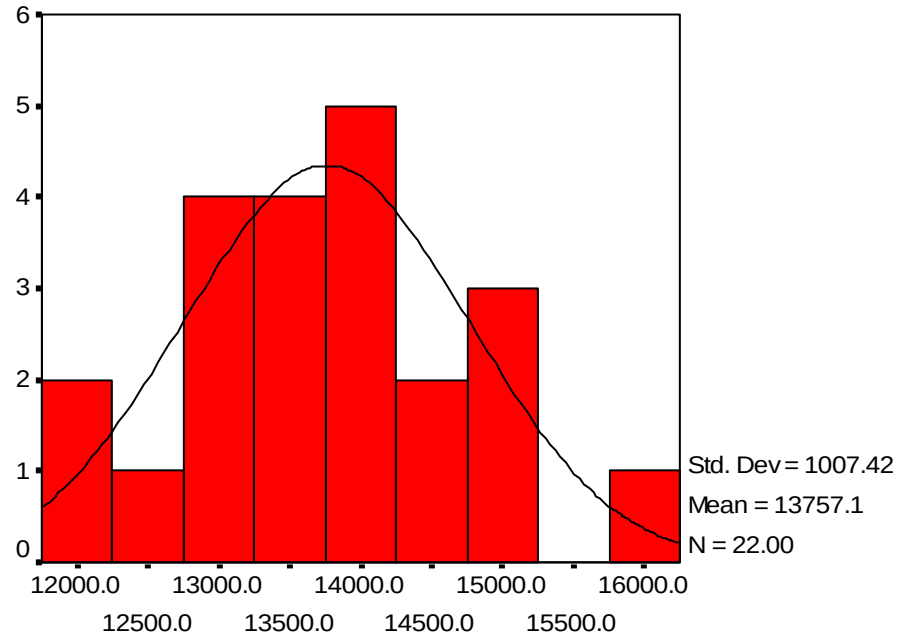


Figure (7) NYC – P&I Multiple Cause Mortality Histograms

For the large scale analysis of NYC, a local isolate dataset containing the predominant influenza strains was not readily available for our twenty-two year time space. Therefore, the effects of climate on a particular influenza strain (e.g. H3N2,

H1N1, influenza B) could not be determined for NYC. The dataset provided by Dushoff (2006) may have a drawback as being used as a proxy for influenza prevalence in NYC because the Dushoff (2006) dataset contains mortality for pneumonia and influenza, perhaps overestimating actual influenza prevalence. However, P&I based proxies have been used in numerous studies to analyze and even predict influenza epidemics (Pyle 1979; Pyle 1986; Cliff *et al.*1986; Haggett 2000; Meade and Earickson 2000; Cliff *et al.* 2000; Thompson *et al.* 2003). The P&I multiple cause mortality dataset is an effective proxy for influenza prevalence and was used exclusively throughout our analysis of NYC.

Regional Influenza Analysis (Southeast and Northeast US)

P&I Mortality (MMWR)

The regional analysis of influenza was limited by the availability of mortality and morbidity data, and although the length of the time-series was not comparable to the large scale analysis undertaken for NYC, the P&I mortality counts provided by the MMWR was adequate for a regional comparison of influenza prevalence. Our study of P&I deaths examined the regions of the South Atlantic (Georgia, Florida, Maryland, North Carolina, South Carolina, Virginia) as compared to the combined mortality of New England (Connecticut, Massachusetts, and Rhode Islands) and the Mid-Atlantic (New York, New Jersey, Pennsylvania) (Figure 8). The New England and Mid-Atlantic mortality counts were aggregated to add consistency to our regional climate dataset and will be referred to as the *Northeas*t P&I dataset for our analysis. Although the dataset spans an eleven year period from (1996-2005), only nine influenza seasons were adequate for our study. Two P&I annual counts were omitted because mortality counts

were not complete for the specified influenza season (i.e. July-June). To examine climatic relationships, an annualized approach was undertaken that resulted in a single mortality count for each influenza season, which was analyzed against regional precipitation, temperature, and ENSO. Aggregated weekly P&I morbidity according to an influenza season (i.e. annualized data) was similar to the approach taken by (Dushoff *et al.* 2006).

To compare regional influenza-climate association to local influenza-climate associations, MMWR P&I mortality counts for two cities within the South Atlantic region and two cities within the Northeast region were analyzed according to climate. The inclusion criteria for each of the cities were based on data availability (i.e. cities that reported significant seasonal influenza mortality throughout the ten-year time period). The cities from the Northeast region were Boston, MA and Philadelphia, PA, and Baltimore, MD and Tampa, FL from the South Atlantic region. Tampa, FL was included in the analysis to investigate influenza prevalence in a city with a large subpopulation of adults 65 years of age and older. For the local influenza analysis, weather data from nearby airports or other weather stations representative of each locale were used. Similar to the large-scale analysis of NYC, mortality counts rather than mortality percentages were utilized, since mortality percentages tend to mask epidemics (Pyle 1986).

Influenza Morbidity Data (WHO/NVRESS)

As a second proxy for influenza prevalence we used influenza-related morbidity, defined by tallies of positive isolates tested for influenza, from a surveillance database provided by the US CDC and maintained by WHO/NREVSS. The data was extracted from the WHO/NREVSS influenza surveillance system, which compiles regional isolate

data on a weekly basis ((NREVSS) 1997-2006). The dataset is an accurate portrayal of the prevalent influenza strains in circulation throughout the US, and provides counts of influenza types and subtypes (e.g. H1N1, H3N2, type B). Isolate data has been used at a national level to analyze influenza morbidity in the US and France (Thompson *et al.* 2003; Viboud *et al.* 2004; Dushoff *et al.* 2006). For this study, each influenza type (e.g. B) and subtype (e.g. H1N1) were analyzed separately for associations to specific seasonal climatic variables (e.g. summer temperature, spring precipitation, ENSO).

To avoid the use of nonlinear modeling when analyzing influenza (e.g. Pyle's 1986 harmonic wave analysis), an annualized approach (i.e. data aggregated annually from July to June) was used for the isolate data, similar to the annualized regional and local analyses of P&I mortality data. Because of the large variation in the reporting of total counts of positive influenza isolates per season, a normalized count of influenza isolate was developed. Annualized isolate counts for specific influenza types and subtypes were normalized by the total number of isolates testing positive for that season. This normalization technique allows the comparison of the predominant strains of influenza isolates types (e.g. H3N2, H1N1) within an influenza season and across the entire data time-series. Pyle (1986) described a technique for influenza P&I data that normalized values by a data "trend" (i.e. normalize data by the summation of isolate counts several weeks prior to and after a particular time period). Although this dataset is not of mortality counts, our similar technique of dividing annualized isolate count by the *trend* in reporting provides a more representative measure of influenza prevalence. A different technique was used for the annualized tally of *all isolates* testing positive for influenza, which was normalized by the total number of isolates submitted for testing

annually. Because of the small dataset (n = 8), the non-parametric Spearman's rho correlation coefficient was used for determining significant correlations.

To compare regional influenza morbidity, two isolate datasets were used. The South Atlantic (i.e. Southeast US) and the Northeast US each had a distinct representative isolate dataset (Figure 9 and Figure 10). Similar to the Northeast Mortality data, the Northeast US dataset was created through the combination of the *New England* and *Mid-Atlantic* isolate counts, as extracted from the CDC's influenza surveillance website, which is maintained by the WHO and NREVSS collaborating laboratories (CDC 2006b)). Tallies of influenza isolate were grouped according to: influenza *B*, Influenza-*A- H3N2*, combined influenza A-H1N1/H2N2, influenza A –Unknown subtype, and count of total isolates tested positive.

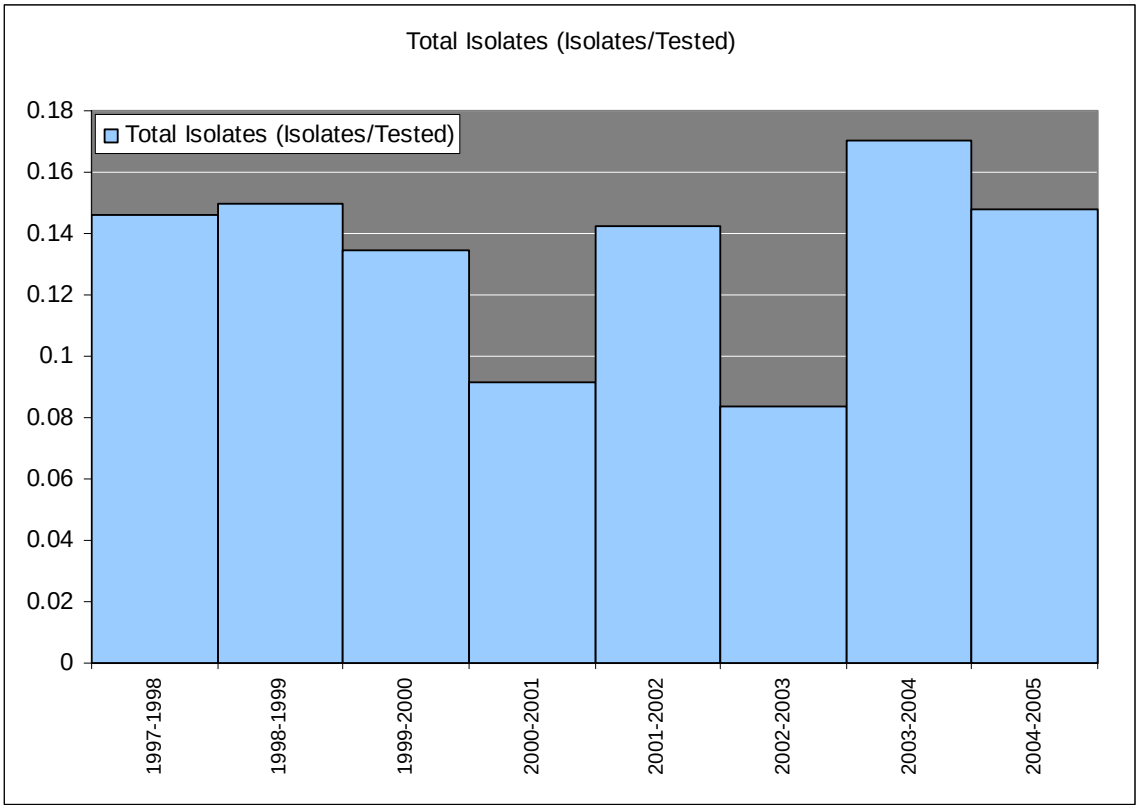


Figure (9) – Northeast US Total Isolates Tested Positive for Influenza

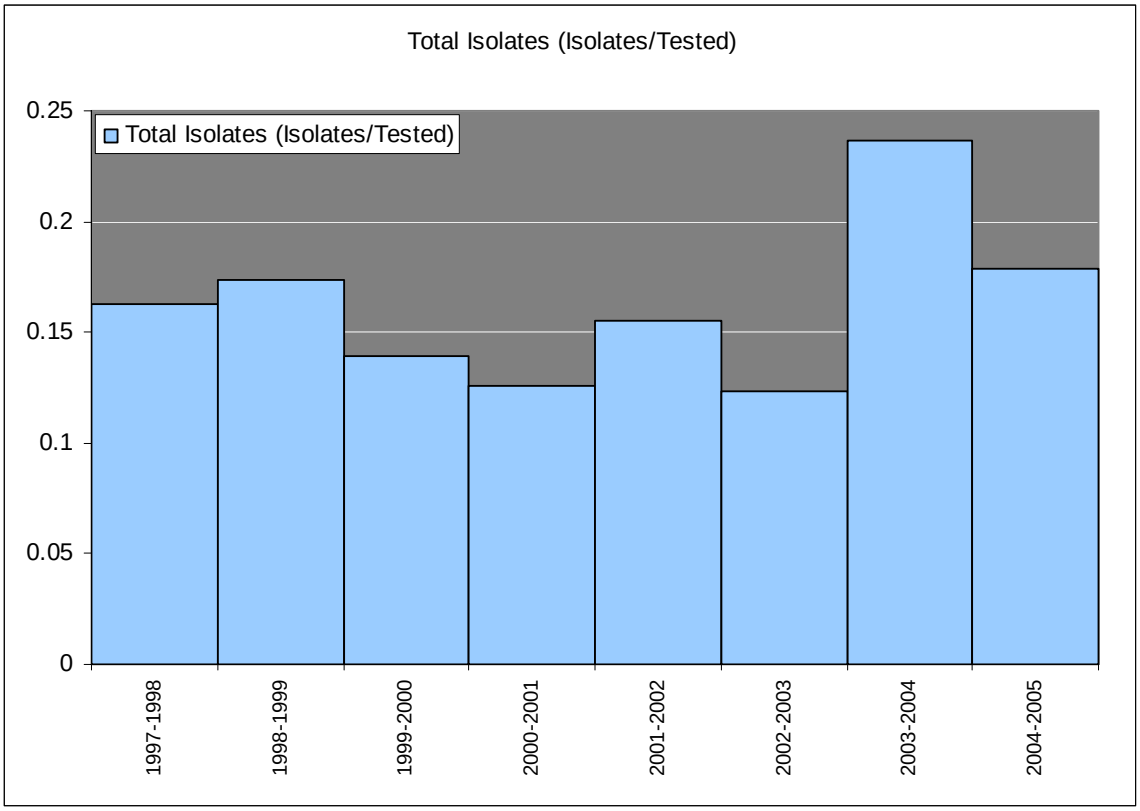


Figure (10) – South Atlantic US Total Isolates Tested Positive for Influenza

Objective III – Timing of Influenza According to Climatic Factors

To determine the effects of climate to the timing of influenza seasons in NYC, we determined the months in which the 15th percentile (i.e. early onset of influenza) and the peaking (i.e. highest recorded monthly influenza P&I mortality count) were reached for each influenza season. Once the timing of early onset and peaking was determined, those resulting months were then assigned values according to their sequence in the influenza season (July – June) (e.g. July was assigned one, March was assigned nine). These monthly values, which represent the timing of influenza, were then analyzed according to climatic factors (e.g. temperature, precipitation, and ENSO). Because of the small sample size and the utilization of ranked data, the non-parametric test of *Spearman's Rho*

was used rather than the typical parametric test used in the other large-scale analysis of NYC.

Climatic Analysis

In addition to association with influenza, each study site (e.g. city, region) was examined for a precipitation and temperature responses to the ENSO. Monthly SOI values were used as a measure for ENSO and were obtained from Australia's Bureau of Meteorology (Meteorology 2009). Monthly SOI values were examined individually and aggregated according to seasons (e.g. winter months were Jan, Feb, Mar). As significant associations with influenza, temperature, or precipitation were determined during sequential or near-sequential months, SOI values were aggregated and averaged accordingly, in an attempt to define a more representative measure of SOI. Customized averaged SOI values were then reexamined for specific associations to influenza, precipitation, and temperature to determine their statistical significance. Even if influenza and ENSO associations were found not to exist within a study site, a climatic analysis was undertaken to determine the effect of ENSO on regional and local weather (e.g. temperature and precipitation).

3.4 RESULTS

Objective I - (Multi-Temporal Analysis of NYC)

NYC - Annualized Counts

The annualized *P&I multiple cause* counts were found to have a significant relationship with climate but varied according to demographic sub-populations (e.g. children, elderly). Annualized mortality count for the *total population*, which was a compilation of counts from all sub-population groups, was found to have a significant

positive correlation with summer precipitation (June, July, and August). However, according to subpopulation only the *adults* (i.e. 15 – 64 years of age) exhibited a positive correlation to summer precipitation (Table 1). As summer precipitation increased, P&I mortality also increased in adults. Utilizing *total population*, rather than characterizing the P&I mortality according to subpopulations (e.g. children, adults), may not provide as accurate portrayal of influenza-climate relationships.

Fluctuations in winter temperatures were also associated with P&I multiple cause mortality in children (i.e. 0 – 14 years of age) (Table 1). More specifically, winter temperatures from the previous year were found to be highly correlated (i.e. significant at the 0.01 level of a 2-tailed test) with a negative relationship to children's mortality. Winter temperatures that occurred during the influenza season were also correlated, but with less significance (Table 1). As winter temperature decreased, either before or during the influenza season, influenza mortality increased for children. Temperature did not a produce any significant associations with either the *elderly*, *adults*, nor for the *total population*. Characterizing influenza-climate associations according to subpopulations provides a more in-depth analysis of the influenza dataset.

Table 1. **Annualized (July – June) P&I Multiple Cause Mortality Correlations for NYC.**

		Precipitation (Summer JJA)	Temperature (Winter DJF - Lag)	Temperature (Winter DJF - Current)
P&I Mortality (Age 0 -14)	Pearson Correlation	.120	-.614(**)	-.480(*)
	Sig. (2-tailed)	.595	.002	.024
	N	22	22	22
P&I Mortality (Age 15 - 64)	Pearson Correlation	.432(*)	-.356	-.337
	Sig. (2-tailed)	.045	.104	.125
	N	22	22	22
P&I Mortality (Age GE 65)	Pearson Correlation	.414	.351	.281
	Sig. (2-tailed)	.056	.109	.205
	N	22	22	22
All Ages	Pearson Correlation	.511(*)	.038	.005
	Sig. (2-tailed)	.015	.866	.983
	N	22	22	22

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

NYC - Percentile P&I Counts

The results of the percentile based temporal analysis of NYC supports these previous findings from the annualized analysis, but also revealed interesting relationships between the progression of influenza according to climate. Each sub-population (e.g. children, adults, elderly) was examined according to percentiles (i.e. 15^{th}, 50^{th}, 75th) which are representative of the phases of influenza diffusion according to the cumulative epidemic curve (Cliff *et al.*1986; Cliff *et al.* 2000; Haggett 2000; Pyle 1986). Analyzing the P&I multiple cause mortality counts according to the *Total Population,* the late progression (i.e. 75^{th} percentiles) and the peaking stage (i.e. 50^{th} percentile) exhibited significant positive correlations with summer precipitation, which was similar to results of annualized mortality counts (Table 2). The early onset of influenza (i.e. 15^{th} percentile) exhibited no association with summer precipitation, but did maintain a

positive correlation with fall precipitation (Table 1). For the early onset of influenza (i.e. 15th percentile) in NYC, as fall precipitation (September, October, and November) increased, mortality counts for the *total population* also increased.

Table 2. **All Ages - Percentile (15th, 50th, and 75th) P&I Multiple Cause Mortality Correlations for NYC.**

All Ages		Precipitation (Summer JJA)	Precipitation (Fall SON)	Precipitation (Winter DJF – Current)
15th Percentile	Pearson Correlation	.078	.499(*)	-.118
	Sig. (2-tailed)	.730	.018	.600
	N	22	22	22
50th Percentile	Pearson Correlation	.499(*)	.219	-.488(*)
	Sig. (2-tailed)	.018	.327	.021
	N	22	22	22
75th Percentile	Pearson Correlation	.493(*)	.243	-.465(*)
	Sig. (2-tailed)	.020	.276	.029
	N	22	22	22
100th Percentile	Pearson Correlation	.511(*)	.292	-.403
	Sig. (2-tailed)	.015	.188	.063
	N	22	22	22

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Analyzing each subpopulation (e.g. children, adults, and elderly), each group produced different associations to climate. Increased P&I mortality in children was associated the colder temperatures from the previous winter (Table 3). This correlation was significant throughout all stages (i.e. 15th, 50th, and 75th percentiles) of disease progression. Furthermore, children's mortality exhibited significant associations with the inclusive winter's temperatures (i.e. winter temperatures that occurred during the influenza season). For example in children, increased mortality that occurred late in the influenza season (i.e. the 75th percentile in March) was associated with colder winter temperature occurring within the influenza season (e.g. DEC, JAN, FEB) (Table 3). A consistent association between temperature and influenza mortality throughout all phases of disease penetration was only found in the children (Aged 0-14) subpopulation.

Table 3**. Children -Percentile (15th, 50th, and 75th) P&I Multiple Cause Mortality Correlations for NYC.**

		Temperature (Winter DJF – Lag)	Temperature (Winter DJF – Current)
15th Percentile	Pearson Correlation	-.578(**)	-
	Sig. (2-tailed)	.005	-
	N	22	-
50th Percentile	Pearson Correlation	-.575(**)	-.419
	Sig. (2-tailed)	.005	.052
	N	22	22
75th Percentile	Pearson Correlation	-.599(**)	-.450(*)
	Sig. (2-tailed)	.003	.036
	N	22	22
100th Percentile	Pearson Correlation	-.614(**)	-.480(*)
	Sig. (2-tailed)	.002	.024
	N	22	22

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Initially, other temperature-influenza associations were identified in the early penetration of influenza (i.e. 15th percentile) for adults. Statistical results explained that as fall (i.e. September, October, November) temperatures decreased, there was an associated increase in the first 15% of a season (i.e. 15th percentile). Further examination of the data revealed that the 15th percentile of mortality was reached in September, therefore due to timing only temperature from the single month of September rather than the entire fall season can be logically associated with influenza prevalence. September temperatures were analyzed singularly, and revealed a significant association with influenza throughout all phases of influenza penetration in *Adults* (Table 4). September temperatures also exhibited a negative correlation to *annualized* P&I mortality counts for the *Adult* subpopulation (Table 4), which is consistent with the finding from other subpopulations. Both September and fall temperatures affected influenza prevalence differently throughout the progression of the virus (i.e. 15th, 50th, and 75th percentile) in the *Adult* population.

A*dult* mortality was found to be positively associated with summer (i.e. June, July, August) precipitation. This precipitation relationship was found in every phase of influenza penetration, except for initial onset (i.e. 15th percentile) of virus. For example, as summer precipitation increased, *Adult* mortality during the late seasonal penetration of the virus (i.e. 75th percentiles) also increased. These precipitation relationships are consistent with the results of the *annualized influenza* counts aggregated to the *adult* subpopulation.

Table 4. **Adults (Age 15–64) - Percentile (15th, 50th, and 75th) P&I Multiple Cause Mortality Correlations.**

All Ages		Precipitation (Summer JJA)	Temperature (Fall SON)	Temperature (September)
15th Percentile	Pearson Correlation	.286	-.435(*)	-.400
	Sig. (2-tailed)	.197	.043	.065
	N	22	22	22
50th Percentile	Pearson Correlation	.459(*)	-.290	-.506(*)
	Sig. (2-tailed)	.032	.191	.016
	N	22	22	22
75th Percentile	Pearson Correlation	.449(*)	-.309	-.513(*)
	Sig. (2-tailed)	.036	.161	.015
	N	22	22	22
100th Percentile	Pearson Correlation	.432(*)	-.286	-.510(*)
	Sig. (2-tailed)	.045	.197	.015
	N	22	22	22

* Correlation is significant at the 0.05 level (2-tailed).

Within the elderly population (i.e. greater than or equal to 65 years of age) there were no significant temperature-influenza relationships found throughout any phases of disease penetration (i.e.15th, 50th, and 75th percentile). Supporting these results, the annualized approach also exhibited no significant temperature relationships in the elderly. Analysis according to percentiles, however, identified significant association between winter precipitation and September precipitation in the elderly. Initially, fall (September, October, November) precipitation was found to be significant, but further analysis

revealed that only precipitation from the September could logically affect the 15th percentile, which according to our results consistently occurred on or before September throughout the entire time-series. Analyzing precipitation only from September exhibited a significant correlation with *Elderly* P&I mortality early in the influenza season (i.e. up until the 15th percentile of mortality was reached for a particular season).

Table 5

Elderly (Age Greater than or equal to 65) - Percentile (15th, 50th, and 75th) P&I Multiple Cause Mortality Correlations for NYC.

		Precipitation (September)	Precipitation (Winter DJF – Current)
15th Percentile	Pearson Correlation	.483(*)	-.073
	Sig. (2-tailed)	.023	.748
	N	22	22
50th Percentile	Pearson Correlation	.322	-.468(*)
	Sig. (2-tailed)	.144	.028
	N	22	22
75th Percentile	Pearson Correlation	.349	-.464(*)
	Sig. (2-tailed)	.111	.029
	N	22	22
100th Percentile	Pearson Correlation	.382	-.397
	Sig. (2-tailed)	.079	.068
	N	22	22

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

P&I Mortality in NYC also exhibited significant association with short-term trends in climatic (e.g. ENSO), however only in certain subpopulations. For the early onset of influenza (i.e. 15th percentile) in the elderly subpopulation, averaged fall SOI values (September, October, November, December) were found to be by highly correlated (i.e. significant at the .01 level) with P&I mortality counts (Table 5). Moreover, in the *total population* within the 15th percentile (i.e. early onset), there was also a highly significant correlation to a similar measure of fall SOI (AUG, SEP, OCT) (Table 5). Through our climatic analysis of the NYC we found that fall SOI (AUG, SEP,

OCT) was associated with fall precipitation (SEP, OCT, NOV) (Table 6). This supports the results from the *annualized* approach, that P&I mortality was associated with September rainfall.

Table 6
NYC - Early Onset (15th Percentile) in the Elderly and Total Population - P&I Multiple Cause Mortality

		SOI (AUG, SEP, OCT)	SOI (SEP, OCT, NOV, DEC)
Age GE 65 (15th Percentile)	Pearson Correlation	.387	.629(**)
	Sig. (2-tailed)	.075	.002
	N	22	22
Total Population (15th Percentile)	Pearson Correlation	.568(**)	.497(*)
	Sig. (2-tailed)	.006	.019
	N	22	22

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 7
NYC - Averaged SOI (AUG, SEP, OCT) Associated with Fall Precipitation

		SOI (AUG, SEP, OCT)
Precipitation Fall	Pearson Correlation	.460(*)
	Sig. (2-tailed)	.031
	N	22

* Correlation is significant at the 0.05 level (2-tailed).

The multi-temporal analyses showed consistency in the 'direction' of climatic relationships. For example, influenza-precipitation relationships were always found to be positive and usually occurred in summer and fall months. As precipitation in NYC increased, the influenza-related mortality also increased. Moreover, influenza-temperature relationships were always negative in nature, and only occurred in the fall and winter months. As temperature in NYC became colder, influenza morality increased in both the Children and Adult subpopulations. P&I mortality was also associated with

global climate indices (e.g. ENSO), which produced local weather conditions in NYC that affected influenza prevalence. These results underscore the importance of taking into account temporal scale in medical geography and epidemiological studies of disease, along with characterizing subpopulations. Examining influenza at different temporal time-scales can potentially unmask enviro-climatic associations.

Objective II - Regional Spatial Analysis

Regional analysis of influenza prevalence examined both annualized mortality (i.e. P&I deaths counts) and morbidity (i.e. positive testing influenza isolate counts) for the Northeast US and the South Atlantic States. The results of these analyses are divided into sections according to region, and the source of the data (e.g. morbidity and mortality). Climatic analysis was conducted for each geographic region and inclusive cities to determine the dependencies of influenza on climate in regard to changes in scale.

Mortality (P&I) – South Atlantic

There were no significant correlations between regional influenza mortality (i.e. P&I counts) in the South Atlantic region and any of the climatic factors analyzed. Although not associated with P&I mortality, our analysis of ENSO-weather associations found a significant correlation between winter (current) precipitation and SOI averaged over the preceding spring months of March, April and May (MAM) (i.e. one-year lagged spring SOI values) (Table 8). Spring SOI exhibits potential for predicting the severity of winters (e.g. rain and snow) in the South Atlantic regions of the US, and any associated diseases. Furthermore, within the nine year time period, SOI averaged over the months

of JAN, FEB, and MAR (JFM SOI) were associated with fall temperatures, although narrowly significant.

Table 8
South Atlantic ENSO Association to Precipitation and Temperature.

			Precipitation Winter	Temperature Fall
Spearman's rho	SOI MAR, APR, MAY	Correlation Coefficient	-.750(*)	-.467
		Sig. (2-tailed)	.020	.205
		N	9	9
	SOI JAN, FEB, MAR	Correlation Coefficient	-.483	-.667(*)
		Sig. (2-tailed)	.187	.050
		N	9	9

* Correlation is significant at the 0.05 level (2-tailed).

Although a South Atlantic US regional association between influenza and climate did not exist, which was similar to the result found in Tampa, FL, one of the cities in the region exhibited significant correlations. P&I mortality in Baltimore, MD was associated with spring precipitation (March, April, May) occurring within the influenza season (Table 9). Along with a seasonal precipitation association, P&I mortality was also highly correlated with SOI values averaged over the summer and fall months of June, July, August, September, and October (i.e. Summer and Fall) (SF SOI). SF SOI was found to be highly correlated (i.e. significant at the 0.01 level (2-tailed test) to spring precipitation (Table 10, Figure 11). The significant SF SOI values associated with influenza occurred during the influenza season rather than preceding the influenza season. Because of the significant lag period, SF SOI rather than spring precipitation may be a more effective measure to predict influenza mortality in Baltimore, MD.

Table 9

Baltimore, MD – P&I Mortality Associated to Climate.

Spearman's Rho		Precipitation (Spring MAM)	SOI – Summer/Fall (JJASO)
Influenza P&I	Correlation Coefficient	-.750(*)	.817(**)
	Sig. (2-tailed)	.020	.007
	N	9	9

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

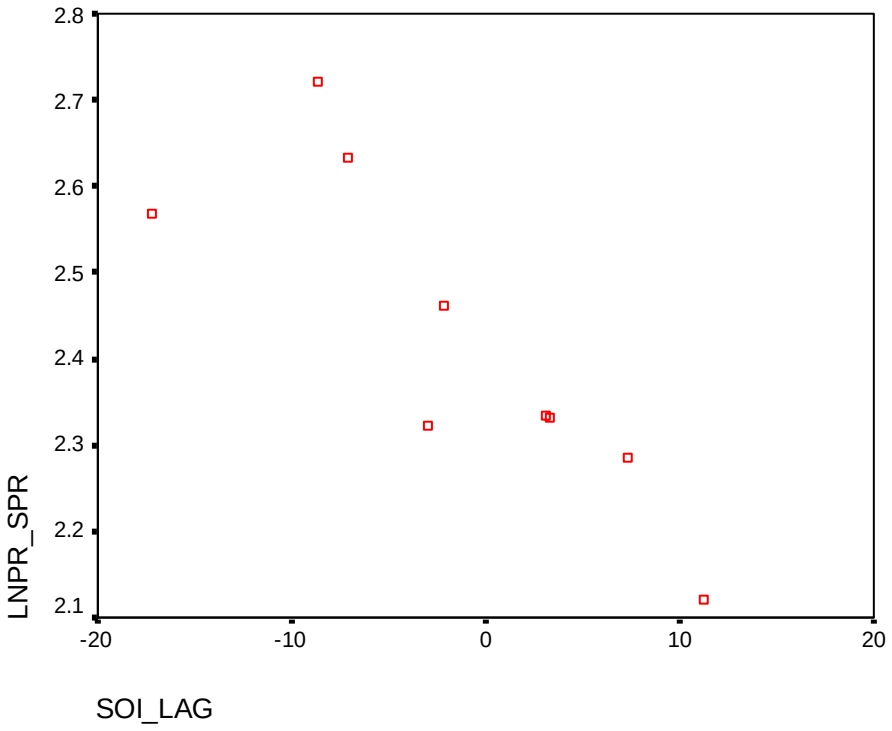
Table 10

Baltimore, MD – Spring Precipitation Associated with SOI Lagged 1 year.

Spearman's Rho		SF SOI (Lagged 1 year)
Spring Precipitation (Natural Log)	Correlation Coefficient	-.850(**)
	Sig. (2-tailed)	.004
	N	9

** Correlation is significant at the 0.01 level (2-tailed).

Figure 11. Baltimore Spring Precipitation versus SOI (JJASO) Lagged by One Year



Mortality (P&I) – Northeast

Climate exhibited significant correlations to annualized P&I mortality in the Northeast region of the United States (i.e. combined P&I mortality from the Mid-Atlantic and New England regions). Winter temperatures preceding an influenza season (i.e. lagged winter temperatures) exhibited a negative association to annualized P&I mortality (Table 11). A decrease in winter temperatures was correlated with increased influenza deaths. For a more detailed analysis of P&I morality in the Northeast, two cities in the region were analyzed for local relationships to climate. P&I mortality in Boston, MA exhibited no direct association with seasonal precipitation and temperature fluctuations. However, Boston's annualized P&I death counts did exhibit a significant correlation to one-year lagged SOI values averaged over the months of January, February, March and April (Table 12).

Philadelphia, PA, the second city analyzed in the Northeast region, did demonstrate a relationship between P&I mortality and winter precipitation preceding the influenza season (Table 13; Figure 12). There was no statistical relationship between P&I and SOI, but Philadelphia's spring precipitation was found to be significantly correlated to SOI values averaged over the autumn months of August, September, and October within the nine year time period. Unfortunately for predictive purposes, spring precipitation in not a determinant of influenza mortality and Philadelphia, thus precluding the use of SOI as factor for estimating influenza prevalence.

Table 11

Northeast Region – P&I Mortality Associated With Winter Temperature

Spearman's rho		Temperature Winter
P&I Mortality	Correlation Coefficient	-.795(*)
	Sig. (2-tailed)	.010
	N	9

* Correlation is significant at the 0.05 level (2-tailed).

Table 12

Boston, MA – P&I Mortality Associated with One Year Lagged Avergage SOI (Jan, Feb, Mar, Apr)

			SOI (Jan, Feb, Mar, Apr)
Spearman's rho	P&I Mortality	Correlation Coefficient	-.700(*)
		Sig. (2-tailed)	.036
		N	9
	P&I Mortality (Natural Log)	Correlation Coefficient	-.700(*)
		Sig. (2-tailed)	.036
		N	9

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 13

Philadelphia, PA – P&I Mortality Associated with Previous Winter's Precipitation (Jan, Feb, Mar, Apr)

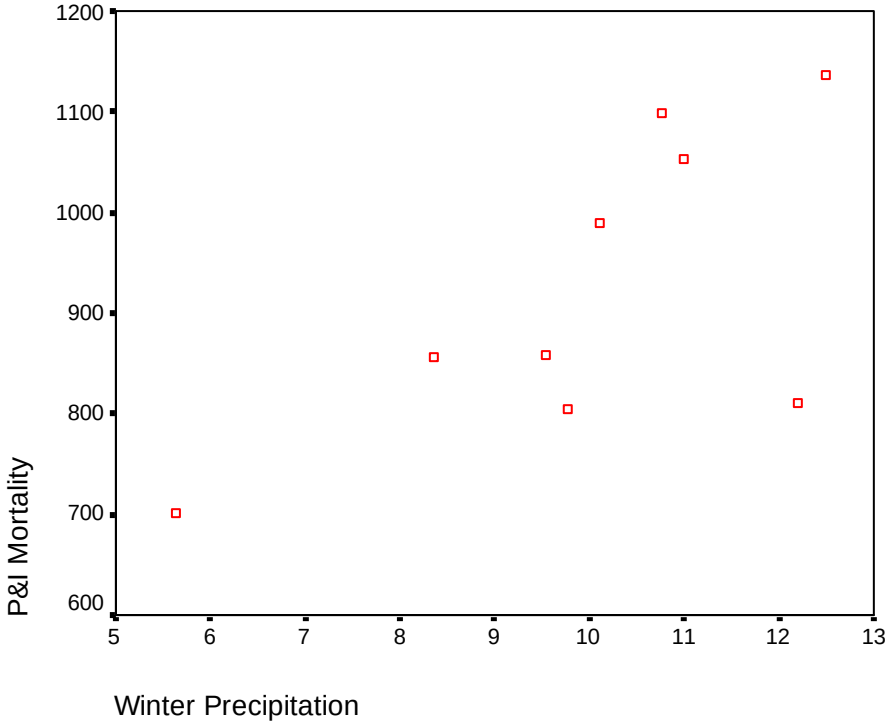
			Winter Precipitation	SOI (Aug, Sep, Oct)
Kendall's tau_b	P&I Mortality	Correlation Coefficient	.556(*)	.278
		Sig. (2-tailed)	.037	.297
		N	9	9
	P&I Mortality (Natural Log)	Correlation Coefficient	.556(*)	.278
		Sig. (2-tailed)	.037	.297
		N	9	9
	Spring Precipitation	Correlation Coefficient	-.222	.611(*)
		Sig. (2-tailed)	.404	.022
		N	9	9
Spearman's rho	Spring Precipitation	Correlation Coefficient	-.250	.733(*)
		Sig. (2-tailed)	.516	.025
		N	9	9

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Figure 12

Philadelphia, PA – Scatter Plot –P&I Mortality VS Winter Precipitation (DEC, Jan, Feb)



Morbidity (Isolate Data)

Northeast Morbidity

Influenza morbidity, as represented by isolate data counts, exhibited significant relationships to climatic variables. An annualized tally of *all isolates* in the Northeast US produced an association to summer precipitation (Table 14). As summer precipitation increased in the Northeast, annualized influenza morbidity also increased (i.e. a wet summer in the Northeast US was associated with an increased number of influenza isolates testing positive). Interestingly, the annualized total of H1N1 influenza A was also associated with summer precipitation but in the opposite direction (i.e. a negative correlation), the only climatic association for this virus subtype (Table 14).

Influenza type B and the combined influenza A subtypes (H3N2 and H2N2), both exhibited associations to spring temperature, and winter and spring precipitation (Table

14). All associations for temperature and precipitation were observed before the influenza season (i.e. lagged climatic variables). However, the directions of the correlations were not consistent between the influenza types and subtypes. Accordingly, low spring temperatures and lower precipitation are associated with an increase in Type B influenza prevalence. Furthermore, increased spring precipitation tends to also increase influenza Type B prevalence. The opposite conditions are associated with an increase in H3N2 prevalence. For the isolate counts of *unknown* influenza A subtype, an irregular positive correlation with spring temperature was significant. *A regional relationship between positive tested influenza isolates and climatic factors in the Northeast US are directionally inconsistent (i.e. exhibited both positive and negative correlations) across the examination of all influenza types and subtypes. However, the results of our regional isolate analysis in the Northeast US may exhibit the complex nature of specific influenza strains in human populations, and the variation of a specific isolate response to certain climatic conditions.*

Table 14.
Northeast US – Influenza Isolates associated with Climate

	Spearman's rho	Temperature Spring	Precipitation Winter	Precipitation Spring	Precipitation Summer
All Isolates (Normalized)	Correlation Coefficient	.405	.619	-.214	.738(*)
	Sig. (2-tailed)	.320	.102	.610	.037
	N	8	8	8	8
H1N1 (Normalized)	Correlation Coefficient	-.381	-.500	.310	-.738(*)
	Sig. (2-tailed)	.352	.207	.456	.037
	N	8	8	8	8
H3N2 (Normalized)	Correlation Coefficient	.881(**)	.738(*)	-.762(*)	-.143
	Sig. (2-tailed)	.004	.037	.028	.736
	N	8	8	8	8
Type B (Normalized)	Correlation Coefficient	-.881(**)	-.738(*)	.762(*)	.143
	Sig. (2-tailed)	.004	.037	.028	.736
	N	8	8	8	8
Type A – Unknown Subtype (Normalized)	Correlation Coefficient	.762(*)	.690	-.643	.119
	Sig. (2-tailed)	.028	.058	.086	.779
	N	8	8	8	8

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

South Atlantic Morbidity

Linkages exist between climate and influenza isolates in the South Atlantic region, and are not as confounding as the results produced from climatic analysis of morbidity in the Northeast US. Although the number of *total isolates* were not associated with any direct effects of temperature and precipitation, there was a significant association to SOI averaged over the months of JAN, FEB, MAR, APR (i.e. JFMA SOI) (Table 15). Interestingly, JFMA SOI was not directly associated with any seasonal precipitation or temperature. However, through the mortality analysis of the Southeast it was found that a very similar measure of ENSO, JFM SOI, was narrowly significant to

fall temperatures. Type B influenza, Type A-(H3N2/H2N2), and Type A (unknown) influenza exhibited no significant association to climate (Table 15).

The most revealing climatic association to influenza was within the H1N1 influenza A subtype. Contrary to other associations, summer precipitation was found to have a negative association with H1N1, while summer temperature exhibited a positive relationship. As summer temperatures increased in the South Atlantic states, H1N1 prevalence also increased. Similarly, increased H1N1 prevalence was associated with decreased precipitation. *The patterns of climatic associations differ regionally (i.e. Northeast influenza prevalence is significantly different than South Atlantic influenza prevalence with respect to climate)* (Figure 13). *Furthermore, there is significant variation in the prevalence of each type and subtypes throughout the time-series, including influenza A-H1N1* (Figure 14). *Climatic factors were found to be statistically significant determinant of influenza morbidity analyzed at a regional scale, but results could be confounding.*

Table 15

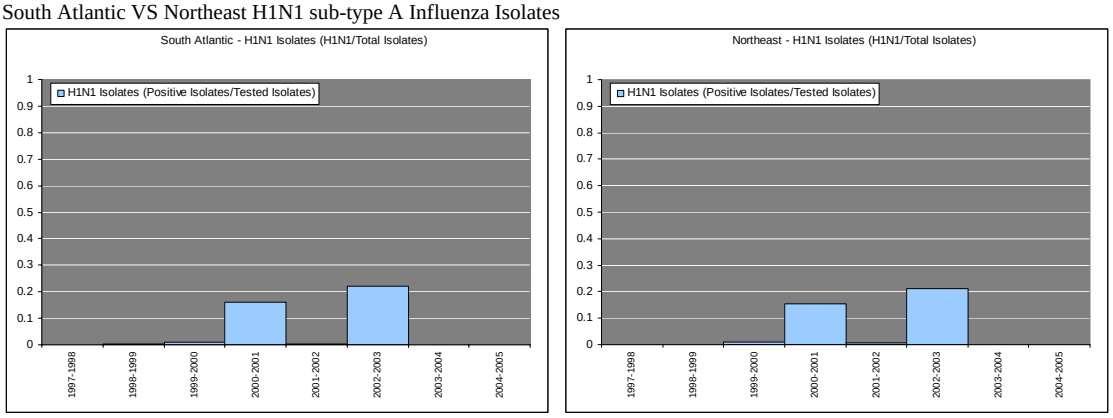
South Atlantic US – Influenza Isolates associated with Climate

	Spearman's rho	Temperature Summer	Precipitation Summer	SOI JFMA
Total Isolates (Normalized)	Correlation Coefficient	-.361	.595	-.762*
	Sig. (2-tailed)	.379	.120	.028
	N	8	8	8
Type B (Normalized)	Correlation Coefficient	.361	-.357	-.095
	Sig. (2-tailed)	.379	.385	.823
	N	8	8	8
H1N1 (Normalized)	Correlation Coefficient	.735(*)	-.762(*)	.548
	Sig. (2-tailed)	.038	.028	.160
	N	8	8	8
H3N2 (Normalized)	Correlation Coefficient	-.241	.690	.000
	Sig. (2-tailed)	.565	.058	1.000
	N	8	8	8
Unknown (Normalized)	Correlation Coefficient	-.590	.476	-.143
	Sig. (2-tailed)	.123	.233	.736
	N	8	8	8

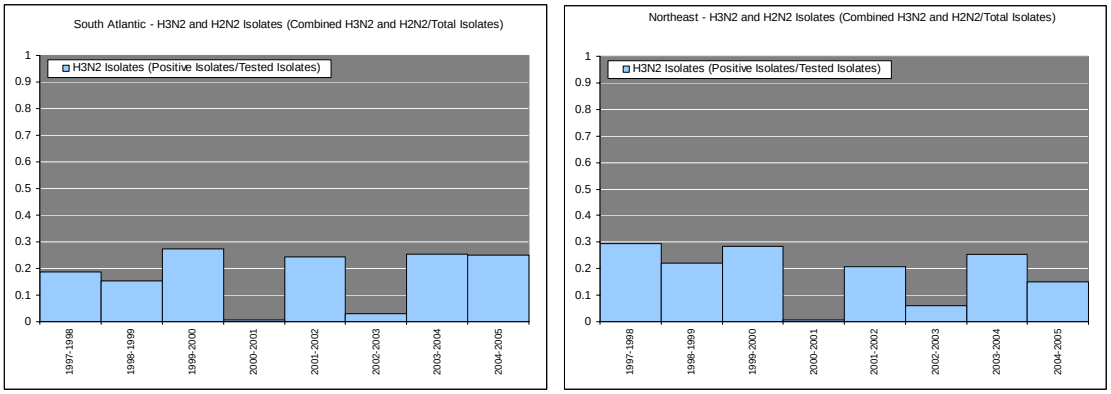
** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

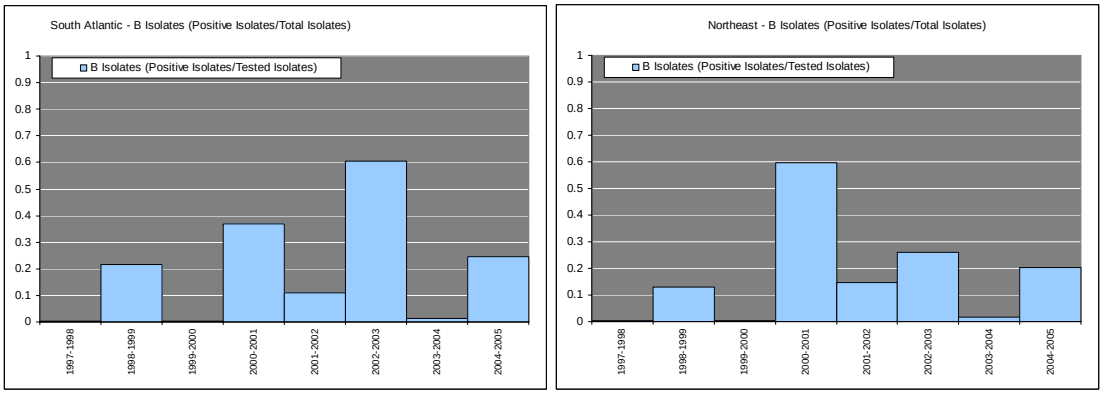
South Atlantic VS Northeast H1N1 sub-type A Influenza Isolates



South Atlantic VS Northeast H3N2/H2N2 sub-type A Influenza Isolates



South Atlantic VS Northeast B Type Influenza Isolates



South Atlantic VS Northeast Unknown (non-typed) Isolates

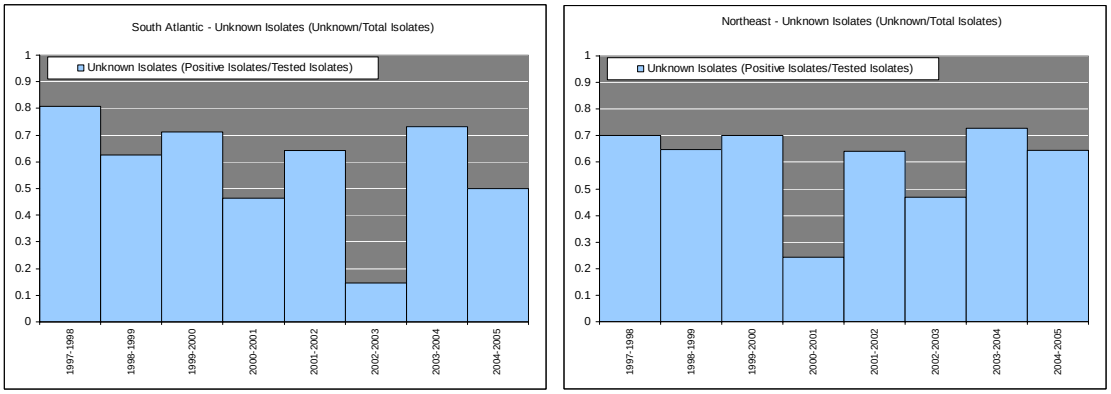


Figure 13 - Influenza Isolates According to the Northeast and South Atlantic

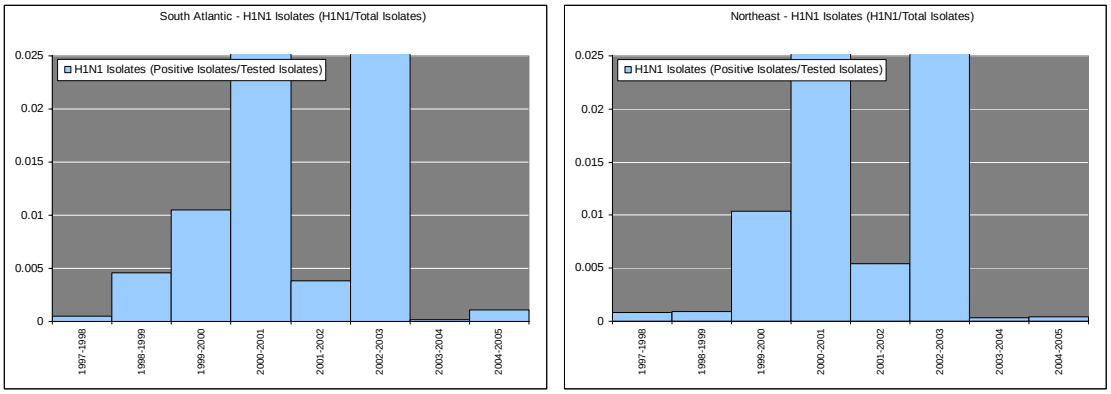


Figure 14 - South Atlantic VS Northeast H1N1 sub-type A Influenza Isolates

Objective III – Timing of Influenza Season

Analyzing the timing of monthly peaks of influenza (i.e. months with the largest monthly mortality counts) and the timing of the onset of influenza (i.e. the month when the 15th percentile was reached) in NYC, we found one significant climatic association, spring precipitation, which only occurred within in the elderly subpopulation and. There was a negative association with spring precipitation (spring precipitation preceding the influenza season) and the peaking of influenza in the elderly (Table 15). As spring precipitation increased, the peak of influenza was hastened in the elderly population (i.e. the peaking of influenza occurred in December or January rather than in March, when spring precipitation preceding the influenza season was increased).

Table 16
NYC – Climate's Affect on the Timing of Influenza Mortality

			Precipitation (Spring – MAM)
Spearman's rho	15th Percentile	Correlation Coefficient	-.031
		Sig. (2-tailed)	.890
		N	22
	Peak (Children)	Correlation Coefficient	-.101
		Sig. (2-tailed)	.655
		N	22
	Peak (Adults)	Correlation Coefficient	-.366
		Sig. (2-tailed)	.094
		N	22
	Peak (Elderly)	Correlation Coefficient	-.432(*)
		Sig. (2-tailed)	.045
		N	22
	Peak (Total Population)	Correlation Coefficient	-.395
		Sig. (2-tailed)	.069
		N	22

* Correlation is significant at the 0.05 level (2-tailed).

3.5 DISCUSSION

Large-Scale Annualized Analysis (NYC)

The approach of using annualized counts of multiple cause P&I deaths as a proxy for influenza prevalence, although the simplest measure used in all of our analyses, may be the most useful and straightforward for predicting the magnitude of influenza from year-to-year. There is a known usefulness in modeling weekly or monthly influenza counts (Cliff *et al.* 1986; Pyle 1986; Thompson *et al.* 2003), but if temperature observations a year beforehand can predict an influenza season with above average mortality (e.g. epidemic), an annualized approach can provide significant benefits to public health. The usefulness of the annualized approach to influenza starts with

partitioning monthly or seasonal data appropriately. Partitioning monthly influenza mortality into a 'season' that incorporates any possible aberrations in the peaking of influenza is an essential first step. For example, aggregating monthly influenza counts starting in July and continuing until next year's June, divides the time-series according to the usual troughs of influenza mortality and captures any variable peaking of influenza in either the winter or the spring.

Utilizing annualized mortality and morbidity counts is an appropriate technique to determine climatic relationships, but characterizing influenza dataset according to population was also integral to this analysis. The dissimilarity in climatic associations according to subpopulation (e.g. children, adults, and the elderly) leads to the conclusion that utilizing an all encompassing category of *total population* is inappropriate, and may obfuscate significant relationships. Lower winter temperature were associated with an increases in annualized P&I mortality, but only in those aged zero to 14 years of age (i.e. children). Further supporting the incorporation of subpopulation data into future predictive modeling of influenza, only *adult* P&I mortality was associated with above-average summer precipitation. As summer precipitation in NYC increased, *adult* P&I mortality also increased. Previous research by Dushoff *et al.* (2006) found no associated between annualized excess mortality deaths and temperature. Dushoff *et al.* (2006), however, appear not to have utilized demographic subpopulation in their analysis, even though "various combination of monthly mean temperatures" were used in their analysis (Dushoff *et al.* 2006:pg 184). Dushoff *et al.* (2006) only incorporate temperature data from November to April, while this analysis found temperature observations from the previous winter as highly significant to the following year's influenza prevalence.

Dushoff *et al.* (2006) calculated excess mortality of influenza for their analysis, while this analysis incorporated raw P&I multiple cause mortality counts because of the primary concern with determining co-variation of influenza according to fluctuations in climate. Examining only a *total population,* rather than subpopulations of P&I mortality from multiple causes can potentially conceal statistical climatic relationships to influenza.

These annualized results portray the higher susceptibility of children to influenza related mortality with regards to climatic variables. Infants and young children do not usually possess the appropriate antibodies to cope with influenza, unless they are appropriately vaccinated (Mims *et al.* 2004). The young are developing their immune system and are prone to several diseases, including influenza (Mims *et al.* 2004). Johnson and Eccles (2005) described increased susceptibility to the 'common cold' according to acute chilling of the body, and proposed that because of physiological responses of the human body the respiratory tract is more prone to infection. Supporting the notion that cooler weather affects respiratory illness, early in the 20th century medical climatologists also found that body chilling is the primary factor for the onset of the "common cold", while this research seems to have been forgotten, it is insightful for the results of this analysis that increased cold may make the body more susceptible to infection (Mills 1939:pg 127). The research by Johnson and Eccles (2005) and the case studies provided by Mills (1939) may support the findings of this analysis, that cooler winter temperatures can increase influenza mortality. Temperature linkages to influenza have also been explained by the increased likelihood of indoor interaction (i.e. increased exposure to the virus in a confined airspace) when ambient temperatures are uncomfortably cold, forcing people indoors (Cliff *et al.*1986; Cliff *et al.* 2000; Meade and

Earickson 2000). This finding, that decreased temperatures result in increased influenza mortality, also supports the latter mentioned theories of influenza transmission.

The relationship between temperature and influenza related mortality found only in children may infer that colder temperatures only affect the transmission of 'new' influenza viruses rather than viruses already in circulation, since most children have not yet been exposed to many influenza viruses, except through vaccination. For this research, isolate data detailing the prevalent strain of influenza was only available at a regional and national level, and most likely would not reflect the prevalent strain in NYC. More research is needed to determine the prevalent strain of influenza affecting children, which can only be done through increased surveillance measures (e.g. reporting specific influenza strains isolate reports according to children and other sub-populations), and to determine if increased mortality in children is caused by the emergence of a particular influenza strain (e.g. type B influenza, type A H3N2 influenza) according to climatic factors. Although there is a recent movement to collect this demographic information during isolate testing, it is not available over an extended mortality time-series dataset (CDC 2006b).

The results of the local (i.e. NYC) analysis of influenza are probably the most accurate portrayal of climate affecting influenza prevalence, although several regional associations were statistically significant. Even though this study only incorporated one set of precipitation and temperature observations for NYC (i.e. a single representative sample), as compared to 'average' regional (e.g. Northeast US) observations, which can be misleading due to the non-uniformity of temperature within a region, the local analysis provides a much accurate portrayal of observable climate. The NYC P&I multiple cause

time-series data set were also twice as long as the regional datasets (i.e. 22 years), and along with the normal distribution of both the dependent and independent data sets, allowed use of the more robust Pearson's product parametric correlation technique. The NYC region incorporated in this study is one most populous metropolitan statistical areas in the US (Gibson 1998), and attains all the proposed population densities that are required to sustain an influenza epidemic or exhibit statically predictive patterns (Cliff *et al.* 1986; Cliff *et al.* 2000; Haggett 2000). However, because NYC is an exception rather than common place in terms of population in the US, the demographic environment may create 'idealized' conditions for influenza transmission, exhibiting transmission trends unlike those found in other regions of the US.

Large Scale Percentile Analysis (NYC)

The approach of using cumulative percentiles for each influenza seasons allows the identification of influenza waves of transmission according to the early onset (e.g. 15^{th} percentiles), the peaking or average mean (e.g. 50^{th} percentile), and the late penetration (e.g. 75^{th} percentile) of influenza into human populations (Pyle 1979; Pyle 1986). These percentiles are then analyzed for associations to seasonal climatic factors. The most definitive association found through this analysis was the dependency children's influenza mortality to the previous winter's temperature, which was highly significant (i.e. significant at the .01 level for a two-tailed test) throughout all stages of influenza penetration, and is supported through the results of the annualized approach to influenza analysis. There was not another relationship between influenza and climate that exhibited such a trend with such high significance in all or our analysis. Not only was one-year lagged temperature significant, the correlation was strong throughout all

percentiles (i.e. transmission phases) in children. It is apparent through this analysis that the waves (i.e. percentiles) of influenza penetration exhibit different dependencies to climatic variables. For example in the elderly subpopulation, increased mortality during the early onset (i.e. 15^{th} percentiles) was found to be associated only with September precipitation, while during the late penetration of influenza winter precipitation appeared to be the only climatic determinant. In general, the elderly population was *less* affected by weather and climate interactions, in regards to influenza, as compared to *adults* and *children.* The elderly were only affected by precipitation rather than weather and climate, the most reasonable relationship was an association between early fall precipitation (i.e. SEP, OCT). Influenza P&I increased as precipitation increased. However, a significant anomalous negative association with precipitation was identified, which occurred only during the 50^{th} and 75^{th} percentiles. These results may be a reflection of an elderly population that has been exposed to numerous influenza viruses throughout life, possessing a distinguished repertoire of antibodies, but with a waning immune systems (i.e. a significant proportion of P&I deaths in the most populous category of our analysis may be attributed to other illnesses other than influenza).

In NYC, increased precipitation during the summer or fall months would provoke people to congregate indoors for recreation (e.g. movie theatres, shopping malls, gymnasiums), which the contained (i.e. indoor) environment could promote increased person-to-person influenza transmission. From experience, people are more deterred from outdoor activity by rain, rather than cooler temperatures. Increased winter precipitation was not a factor for influenza probably because NYC winters are already generally cold enough to force people indoors (i.e. increased winter precipitation would

not change human behavioral patterns as much as increased summer precipitation). Meade (2000) states that along with making the human body more susceptible to infection, certain climatic conditions would force people indoors thereby increased influenza infection. The results of this analysis specifically implicate summer precipitation as cause for increased influenza mortality in NYC. In NYC, cooler temperatures may provide a more efficient air mass for the transfer influenza virus particles (Meade and Earickson 2000), since generally cooler temperatures are associated with less humidity (Ahrens 2003). Moreover, medical climatologists proposed that a dry air mass could promote the transmission of airborne virus particles (Licht 1964; Mills 1939).

The climatic associations identified in this analysis infer a lag period between influenza infection and the onset of symptoms. For example, cooler temperatures from the previous winter were correlated to increased influenza mortality a year later. Although we provide no definitive microbiological evidence for a latent influenza virus, the results of this analysis certainly suggest that climatic conditions can affect the transmission of influenza virus several months before the associated mortality. A percentile-based approach along with the incorporation of subpopulation data can provide surprising insight into the nature of the influenza virus, by identifying early or late influenza trends that are specific to age.

Regional Mortality and Morbidity

Regional associations of MMWR's P&I mortality to climate did not exist in the South Atlantic (i.e. Southeast US), which may be due to the inclusion of states such as Florida in the region. This may have confounded aggregated influenza counts because of

the warmer climate and the differences in influenza seasonality. In tropical climates, influenza does not maintain a winter peak of influenza prevalence, rather a summer peaking of P&I mortality (Pyle 1979; Pyle 1986; Cliff *et al.*1986; Hope-Simpson 1992; Cliff *et al.* 2000; Meade and Earickson 2000). Examining Tampa, FL P&I data, which also produced no significant climatic correlations, influenza peaking exhibited less winter seasonality with sporadic peaking in spring, summer, and fall (Figure 16). As compared to the Northeast region, the South Atlantic region spans several more degrees latitude, resulting in more salient climatic differences throughout the region. A 'regional' measure of climate temperature and precipitation averages may be less representative of the actual climate experienced in any of the region, which may confound any associations to influenza prevalence.

Baltimore, MD, which was in the northern most frontier of the South Atlantic region did, however, exhibit significant association between influenza and climate and local weather conditions and to the global climate phenomenon ENSO. In Baltimore, SOI averaged over several summer and fall months was found to be associated with the following spring's precipitation which was in turn associated with influenza P&I mortality. SF SOI was found to be more highly correlated (significant at the 0.01 level of a 2-tailed test) with P&I mortality than spring precipitation. According to this study's statistical results, a summer-fall *La Nina* ENSO cold phase (i.e. positive SF SOI) for Baltimore resulted in decreased precipitation during the following spring. The decreased precipitation then resulted in greater P&I mortality (i.e. negative correlation coefficient). However, a negative relationship between influenza prevalence and precipitation was an uncommon result from the rest of our analyses. For Baltimore, which is a coastal city

that may be more influenced by sea surface temperatures, decreased precipitation during the spring months might have different effects on human behavior patterns as compared to the usual summer or winter climatic associations. Several theories of influenza transmission have been proposed that certain conditions of the air mass could be predisposed to more efficient viral transmission, such as in dry air (Licht 1964; Mills 1939; Meade and Earickson 2000). Less precipitation may be an indicator of drier air, which may be associated with less spring humidity in Baltimore, MD, but further analysis is needed.

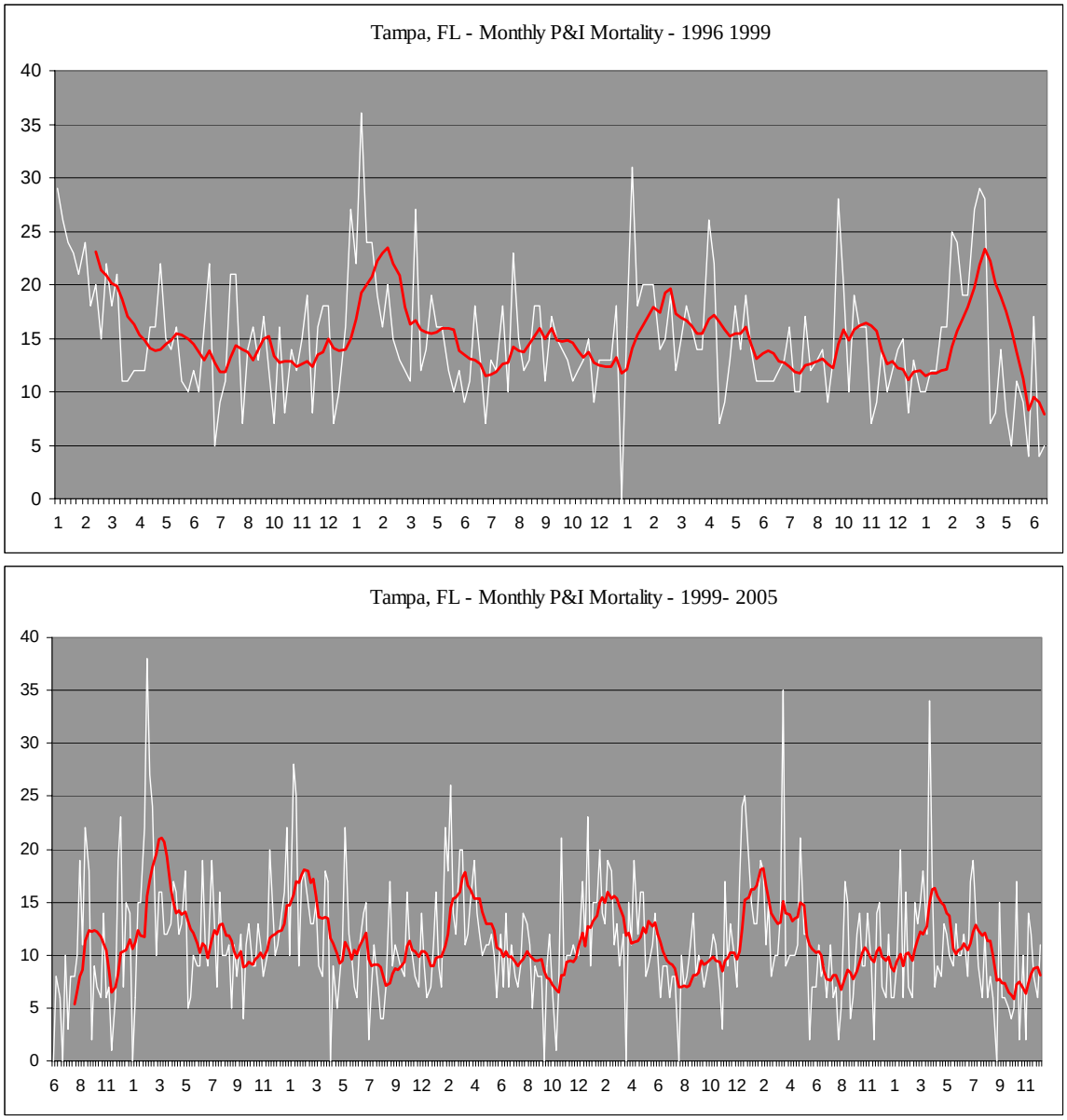


Figure 15 – Tampa, FL P&I Mortality Time Series – 1996 - 2005

The Northeast region influenza dataset, which was the combination of Mid-Atlantic and New England P&I counts from the MMWR, exhibited a strong negative relationship to winter temperature from the previous year (i.e. one-year lagged winter precipitation). Lowered temperature resulting in increased influenza mortality coincides with these results for increased *children* mortality in NYC, and supports theories that increased exposure to the influenza virus in confined spaces results in higher influenza

prevalence (Cliff *et al.*1986; Pyle 1986; Cliff *et al.* 2000; Haggett 2000; Meade and Earickson 2000) Unfortunately, P&I data from the MMWR cannot be further analyzed according to specific subpopulations, which might have corroborated our previous results that colder temperatures have an affect on influenza related mortality in children. As compared to the South Atlantic region, the Northeast region is more populated, is at higher latitude, and generally experiences more severe winter because of the closer vicinity to the artic regions (Ahrens 2003), which may affect influenza prevalence because of the increased tendency of significant seasonal and annual weather fluctuations. Taken as a whole, the northeast region contains less inclusive climatic variability than the South Atlantic, making a 'regional' measure of average temperature and observed precipitation more representative of the actual climate experienced throughout the area. Boston, MA was the only other city in the Northeast region to exhibit P&I associations to climate, with relationships neither to seasonal precipitation nor temperature, but only to winter-spring SOI. However, JFMA SOI was not correlated with any specific weather patterns, but may have other effects on Boston that were not analyzed, such as humidity or an abundance of extraordinary temperatures.

Regional isolate data, compiled from the WHO NREVSS collaborating laboratories (1997-2005), exhibited significant associations to climate. In both the Northeast and South Atlantic regions, H3N2 and influenza B virus and their variants were the most predominant throughout the time series spanning from 1997 – 2005, while H1N1 transmission was sporadic but significant (13). Influenza A-H3N2, which is derived from the influenza pandemic of 1968, (Taubenberger and Morens 2006; Webster *et al.* 1992), exhibited associations to both temperature and precipitation in our analysis.

In the Northeast region, A H3N2 and temperature positive association was found to be highly significant (e.g. significant at the .01 level of a two-tailed test) and very strong (e.g. Spearmans's rho - .881). An unusual positive correlation was produced, but since this relationship was during the spring months, this increased incidence may be explained by something other than increased familiarity within confined spaces.

Conditions of the air mass associated with warmer spring temperatures may promote virus transmission (i.e. less spring precipitation results in drier air) (Licht 1964; Mims *et al.* 2004), or spring temperatures affect how people congregate in Baltimore. In the South Atlantic, neither H3N2 nor influenza B exhibited any association with climate. However, increased H1N1 prevalence was found to be associated with a hotter and drier summer, which could be explained by changes to human behavior. As increased summer temperatures in the South Atlantic increased to a point of discomfort, people may tend to congregate in public air-conditioned indoor space (e.g. shopping malls, movie theatres), which would then increased the probability of viral transmission through the air. Further analyzing this relationship according to subpopulation could reveal more insight into why this association occurs for each particular virus strain. Increased influenza B incidence was associated with the opposite climatic conditions.

Most intriguing in the Northeast region was the inverse relationship exhibited between influenza B and H3N2. As H3N2 became the predominant strain, influenza B was displaced to the bottom of the hierarchy. This may reflect the ability of influenza strains to subdue other virus competitors (i.e. the predominant strain of influenza may prevent coinfection of influenza viruses) (Webster *et al.* 1992; Horimoto and Kawaoka 2005; Hsieh *et al.* 2005; Taubenberger *et al.* 2005; Taubenberger and Morens 2006).

However, this highly significant and very strong inverse relationship of influenza B and influenza A H3N2 may serve to confound our results of a climatic relationship with the isolate data. The rise of specific influenza strain to predominance may in fact not be associated with climate, but rather may stem from a microbiological mechanism of influenza. This analysis was confined to data availability of the isolate dataset, which was analyzed only at a regional level. A more detailed local analysis of isolate data, such as performed for NYC for multiple cause P&I mortality data, may provide more definitive evidence for a climatological linkage.

Table 17.

Northeast – Inverse Relationship Between Influenza A H3N2 and Influenza B

			Influenza B
Spearman's rho	**Influenza A H3N2**	Correlation Coefficient	-1.000(**)
		Sig. (2-tailed)	.000
		N	8

** Correlation is significant at the 0.01 level (2-tailed).

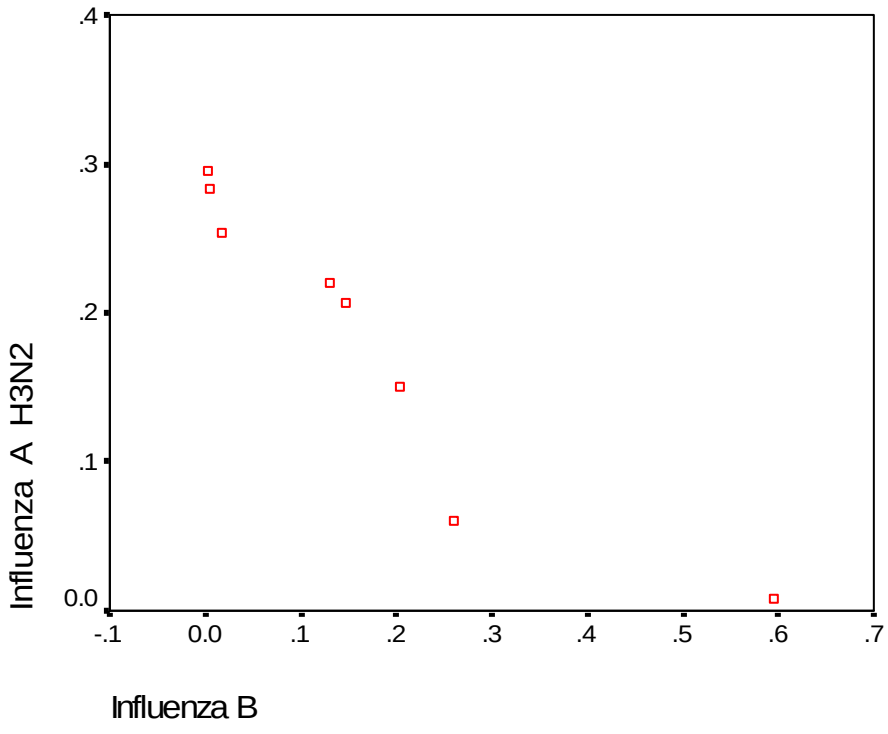


Figure 16 – Scatterplot Diagram of Influenza A H3N2 and Influenza B

Implications of Influenza Linkages to Climate

Public Health

Determining the climatic variables associated with influenza epidemics and other diseases are of great significance to public health, especially for disease control and prevention. Discovering the significance of environmental variables reveals the etiology, or origins, of a disease, and leads to a more accurate portrayal of disease distribution. For example, determining the risk of vector-borne diseases is dependent upon the distribution of the host and vector, which are influenced by ecological factors. Although not a vector-borne disease, the prevalence of influenza was found to be associated with climatic factors such as precipitation, temperature, and phases of ENSO. Other climatic variables such as low humidity have also been proposed to effect influenza transmission by providing a more suitable environment to virus infection (Cliff *et al.*1986; Meade and Earickson 2000), and should be incorporated in further analysis.

The identification of climatic variables that play a role in determining the onset or magnitude of an influenza epidemic allows for increased preparedness for public health officials. Specifically, by establishing the existence of climatic associations to influenza, these factors can now be used in future analysis to develop models that predict influenza prevalence months and up to a year before hand. For example, mortality in children was found to be associated with colder temperatures from the previous winter. Furthermore, distinct weather conditions, could justify an increase in vaccine production, reducing the likelihood of influenza vaccine shortage in an epidemic year. Although vaccines are tailored to each flu season (Hsieh *et al.* 2005), thereby reducing the efficacy of vaccine stockpiling, the incorporation of environmental variables to predict vaccine demand

could still be fruitful since winter conditions (i.e. precipitation and temperature) in many parts of US are accurately predicted according to summer-fall ENSO conditions (Redmond and Koch 1991) Adequate vaccine production along with effective vaccine distribution could decrease both mortality and morbidity related to influenza.

Analytical

Analysis according to spatial and temporal scale was significant in determining climatic relationship to influenza. Regional versus local associations were decidedly different within both areas of study (e.g. South Atlantic and Northeast) when examining the CDC's MMWR Mortality and Morbidity data (i.e. isolate data). For example, in the South Atlantic, when analyzing data regionally there were no significant associations, but examining Baltimore, which is included in the South Atlantic region, several relationships between mortality and climate were identified. To accurately assess influenza-climate relationships, analyzing influenza locally or within regions that constitute similar climates (e.g. Northeast US) is most effective. Incorporating ENSO trends into local analysis, or within appropriately defined regions, is important because *El Niños* and *La Niñas* affect local weather differently throughout the US (Ahrens 2003).

Partitioning cumulative annualized mortality counts according to the phases of the epidemic curve (e.g. early onset, late penetration) reveals statistical relationships that are not apparent when examining just annualized counts. For example, temperature associations may only exist during the early onset of influenza (i.e. 15^{th} percentile). The multi-temporal analysis approach used for influenza can be applied to any disease dataset and could be used to clarify seemingly ambiguous associations. Furthermore, relationships between disease and external factors (e.g. climatic, environmental,

sociological, and physiological) can potentially be unmasked by the use of multi-scale temporal analysis. Identifying the demographic characteristics of the sample population is also important. By characterizing populations according to age (e.g. children, adults, the elderly), susceptible populations can be identified. Analyzing subpopulation according to a multi-temporal analysis (e.g. cumulative 15^{th} percentiles, cumulative 75 percentiles) can further reveal disease associations. For example, early fall temperatures (e.g. September) were only significantly associated with the early onset of influenza (i.e. 15^{th} percentile) in the elderly population. *The results of this study underscore the importance of taking into consideration spatial scale, temporal scale, and characterizing the sample population (i.e. demographic analysis) when analyzing influenza, or any disease.*

Ecological

A climatic association with influenza prevalence several months before the onset of influenza related symptoms or death (i.e. a lagged associated between influenza and climate), may suggest specific patterns to the transmission of influenza. Hope-Simpson (1992) proposed that influenza was a latent virus, which erupted according to specific environmental triggering events, such as changes in photo-period (i.e. changes in daylight hours) or temperatures. The results from our analysis support pieces of this theory. Delayed climatic associations between influenza prevalence were exhibited throughout all facets of the multi-scale and multi-temporal examination, which may suggest a latent influenza virus. However, to prove the existence of a latent virus a more active influenza surveillance approach would need to be implemented, which unfortunately would be costly in resources and in funding. Currently, influenza surveillance data is passive,

meaning that data are not actively supplied. Furthermore, surveillance isolate data is voluntary and is collected as patients' exhibit influenza like symptoms and physician's request confirmation of influenza virus infection (i.e. influenza isolate counts) (CDC 2006b). Therefore, passive influenza surveillance data does not capture influenza prevalence throughout the usual 'troughs' (e.g. summer months) of influenza prevalence because there are few influenza like symptoms reported during these periods resulting in only a few isolates being tested. However, even if active influenza surveillance was implemented, it is not guaranteed that a latent influenza would be identified because many viruses have been known to 'hide' in the human body, only to emerge when certain conditions (e.g. metabolic processes, physiological processes) in the human body are attained (Mims *et al.* 2004).

A lagged climatic association to influenza morbidity or mortality, such as with summer temperature, may suggest that virus infection occurs in the summer months, with influenza related complications (e.g. coughing, sneezing) arising later in the influenza season when certain weather conditions are met (e.g. acute chilling of the body). The identification of an environmental triggering event, such as proposed by Hope-Simpson (1992), could be invaluable for public health officials, since this could provide an early warning for a pending influenza epidemic. According to the results of this analysis, the existence of an environmental triggering event for influenza is promising, since spring precipitation was found to affect the timing of influenza peaking (i.e. the highest monthly incidence of influenza) in the elderly population. As precipitation increased, the peaking of influenza P&I mortality was hastened for the elderly.

Influenza A-H3N2 and H1N1 are two of the predominant influenza subtypes that are in circulation throughout the US. The H3N2 influenza A subtypes have their genetic origin from the 1968 H3N2 pandemic(Horimoto *et al.* 2005), but preceding this mid 20th century pandemic, all these viruses are descendent from the H1N1 1918 influenza pandemic (Taubenberger *et al.* 2006), which killed at least 20 million people worldwide (Patterson 1986; Kilbourne 2006). Furthermore, according to recent research, the 1918 H1N1 virus is derived from an avian influenza that adapted to humans (Taubenberger *et al.* 2005). Therefore, two of the major influenza strains in circulations derive from an avian influenza virus. Most likely, all influenza A type viruses are of avian origin (Horimoto *et al.* 2005). The natural reservoir for influenza is suspected to be aquatic birds (ducks, geese) because they commonly exhibit no ill effects to low pathogenic AI (Webster *et al.* 1992; Horimoto *et al.* 2005). Ducks and other aquatic birds tend to congregate into flocks in the late fall and winter (Sibley 2001), creating dense populations that are optimal for efficient influenza transmission. The flocking instincts of aquatic bird are probably driven by temperature changes (Sibley 2001). Because of their likely avian origin in ducks and other shorebird, the winter seasonal nature of influenza in humans may be a relic of AI in bird species. A dense population is required to sustain a reoccurring influenza epidemic in humans (Cliff *et al.*1986; Cliff *et al.* 2000), which may have linkages to the dense population of flocking aquatic birds in the winter. The flocking instinct may also explain the winter seasonality of peaking in humans. The influenza virus may have originally adapted to disease shedding (i.e. transmitting disease through coughing, sneezing, excrement) during the colder months when bird populations are dense.

Influenza B virus, the third major influenza strain in circulation, is not found in avian species, only in humans, yet exhibits winter seasonality (Webster *et al.* 1992; Horimoto and Kawaoka 2005). Influenza B did not exhibit any association to climate in the South Atlantic. Climatic associations to influenza in the Northeast are inconclusive because of highly significant negative association between influenza A H3N2 and influenza B, which could be confounding any climatic associations. The lack of definitive climatic association toward influenza B, may suggest that the strain possesses distinct climatic dependencies from influenza A viruses. On the other hand, influenza A viruses exhibited associations to climate, including H1N1 which was not correlated with any other influenza type (e.g. influenza B), providing conservative evidence to climatic associations. *Nonetheless, significant climatic associations several months preceding the usual peaking of influenza suggests that enviro-climatic conditions play an important role in determining the magnitude of influenza prevalence according to influenza A viruses. The identification of a latent virus may provide a better understanding in the etiology of the influenza virus.*

3.6 CONCLUSIONS

Seasonal fluctuations in precipitation and temperature were associated with influenza morbidity (i.e. influenza isolate data) and mortality (i.e. P&I mortality). Seasonal ENSO phases (i.e. averaged SOI values) were significantly associated with influenza prevalence, but were also associated with local and regional climate that in turn affected influenza morbidity and mortality. Characterizing the sample population (e.g. adult, children) was useful in determining significant climate association. Similarly, the

consideration of scale in the analytical processes revealed previously undefined associations at smaller scales (i.e. local analysis revealed climatic relationships that were masked at a regional scale). Utilizing varying temporal scales (e.g. percentiles corresponding to the distinct phases of disease diffusion) were useful in determining different associations according to the phases of influenza penetration. Specific influenza types and subtypes (e.g. influenza B, H3N2-A, H1N1-A) exhibited distinct climatic relationships, and a lag time of several months between climatic associations and the usual influenza peaking (e.g. winter), was common throughout the results of this analysis. A climate-influenza lag time can be useful for future disease modeling, by providing a significant amount of time for public health preparedness plans (e.g. vaccination programs, medical supply, and distribution).

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