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The Effects of Weather and Climate on the Seasonality of Influenza: What We Know and What We Need to Know

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Abstract

Influenza is one of the most deadly of all airborne and upper-respiratory infections. On average, 22,000 deaths and over 3 million hospitalizations in USA are attributed to influenza each year. The distinct seasonality of influenza suggests a climate connection, but the wide range of methodologies used to explore this connection makes it difficult to elucidate a definitive relationship. Much of what is known about the effects of weather and climate on the seasonality of influenza stems from research conducted by members of the public health and medical communities, with few contributions from other physical and social science fields. Most of these studies are either based on experiments conducted under controlled laboratory conditions or on the broad-scale patterns of morbidity and mortality and their relationship to large-scale climate signals. What remains largely unknown is the suitability of these results for the development of early warning systems and for determining the dynamics of viral transmission on multiple space and time scales.

Introduction

Influenza, commonly referred to as the 'flu', is a respiratory virus that causes significant mortality and morbidity during annual epidemics, and is capable of affecting nearly half of the global population during severe pandemics (e.g., the 1918–1920 'Spanish Flu'; Potter 2001). In temperate climate regions, influenza epidemics display a distinct seasonality, with widespread infection typically occurring during the winter season months: November to March in the Northern Hemisphere and May to September in the Southern Hemisphere (Hope-Simpson 1992).

To date, the leading epidemiological hypothesis for the seasonality of influenza involves the crowding of sick and healthy individuals indoors in response to the winter season decrease in outdoor temperatures. Despite the simplistic and unscientific nature of this hypothesis, it has continued to prevail almost unchallenged for the better part of half a century (Lofgren et al. 2007). There are, however, growing bodies of literature that reveal both biological and physical mechanisms involving the influenza virus and the susceptibility of the host immune system that may be responsible for the seasonality of epidemics. In general, these studies can be divided into two areas: (i) laboratory-based studies on viral etiology and host susceptibility and how they vary under different environmental conditions, and (ii) epidemiological studies relating large-scale morbidity and mortality patterns to various climate signals and atmospheric conditions. The objective of this article is to synthesize the results of these studies in an effort to increase the transparency of what is currently known about the effects of weather and climate on influenza and what aspects of the relationship remain unexplored.

On average, over 22,000 deaths are attributed to influenza each year in USA (Thompson et al. 2009), making it one of the top-10 leading causes of death in the country (Heron et al. 2009). Moreover, the effect of annual influenza epidemics on the health care system is substantial: 3.1 million hospitalized days and 31.4 million outpatient visits (e.g., doctor's office and clinic visits) are attributed to influenza epidemics in the USA each year, with direct medical costs estimated at over $10 billion (Molinari 2007). Statistics on notable epidemics and pandemics worldwide have been reported by medical geographers (e.g., Pyle 1986). The overall burden of influenza, including the threat for a global pandemic, has lead to substantial preventative and mitigation efforts, as well as proposals for early warning systems (Kuhn et al. 2005). A better understanding of how weather and climate contribute to influenza is needed before successful warning systems are established. This will ultimately require close collaboration between biomedical researchers, epidemiologists, health care officials, geographers, and atmospheric scientists.

In this article, the section titled 'Conceptual Framework' describes the conceptual framework used to explore the roles of weather and climate on the seasonality of influenza. The section titled 'Deconstructing the Weather–Climate–Influenza Relationship' provides detailed discussions of what is currently known about these roles as they pertain to the major components and pathways of disease ecology. The section titled 'Macro-Scale Studies of Influenza Mortality' discusses the associations between large-scale climate signals and the geographic spread of influenza. Lastly, the section titled 'Conclusion' provides a summary of the discussions and poses directives for future work.

Conceptual Framework

The role of weather and climate in disease ecology and epidemiology may be illustrated in a variety of ways and with varying levels of complexity. The most comprehensive conceptual models include environmental, social, economic, and health care system conditions and the direct and indirect effects they have on human health (e.g., Figure 8.1 of the Fourth Assessment Report of the Intergovernmental Panel on Climate Change; Confalonieri et al. 2007). While the complexity of the climate–health problem is recognized, the full scope of these conditions is beyond the goal of this article. As a means of emphasizing the weather and climate components of influenza, a diagrammatical construct adopted from the field of epidemiology – the Triangle of Disease (Figure 1) – is utilized as a framework from which the components of disease can be identified and the pathways between them explored in the context of weather and climate (Timmerick 2002). The vertices of the triangle represent the major epidemiological components of influenza (i.e., host, virus, aerosol/droplet) while the arms of the triangle represent the dynamic processes, conditions, and pathways that facilitate and maintain the cycle of disease (i.e., transmission, susceptibility, virulence). It is important to note that the exact components and pathways of the triangle often vary depending on its use or the nature of the health conditions being studied (Comrie 2007). For the purposes of this article, the form of the triangle shown in Figure 1 is used to isolate the individual components of the atmosphere–influenza relationship, synthesize the available information, data, and research results, as well as pose new questions that invite multidisciplinary collaboration among experts in atmospheric science and disease.

Deconstructing the Weather–Climate–Influenza Relationship

To assess what is currently known about the links between weather, climate, and influenza, an attempt was made to identify all studies in the published literature that addressed

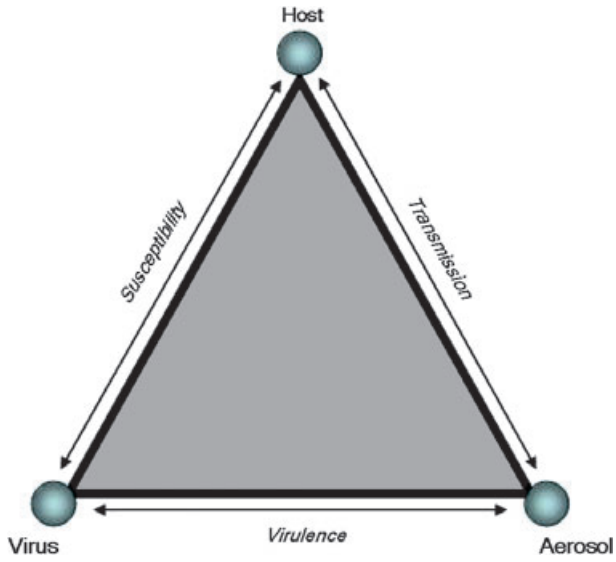

Fig. 1. The Epidemiologic Triangle of Disease for influenza.

these relationships. Two online databases were utilized: Medline and the Science Citation Index. In addition to search terms directly related to influenza (see Brankston et al. 2007), atmospheric search terms such as 'temperature', 'precipitation', 'humidity', 'wind', 'circulation', 'radiation', 'weather', 'climate', and 'climate change' were also used to identify studies that addressed the weather–climate–influenza relationships. Although no restrictions were placed on publication date, the vast majority of articles found were published after 2003. The earliest relevant articles were published in the 1960s.

EFFECTS OF WEATHER AND CLIMATE ON VIRAL TRANSMISSION

The transmission of influenza involves the shedding of respiratory particles (i.e., droplets or aerosols) by an infected host into the ambient environment, generally through coughing and sneezing. A typical cough or sneeze can produce tens of thousands of individual respiratory particles, ranging in size from one-tenth of a micrometer (μm) to 100 μm in diameter (Hall 2007).

There are three primary modes of viral transmission involving the shedding of respiratory particles: droplet, contact, and airborne (Brankston et al. 2007). Both the droplet and contact modes involve large respiratory particles (>100 μm) that are too heavy to remain suspended in the air. Droplet transmission occurs when these particles are expelled directly onto another person, usually within 1 m of the infected host and focused near the eyes, nose, and mouth. Contact transmission involves physical contact with respiratory particles that have settled on surfaces. Subsequent contact with the nose or mouth can result in inhalation of viral particles. Unlike droplet or contact transmission, airborne transmission involves smaller respiratory particles (i.e., aerosols < 10 μm). Their smaller size allows them to remain suspended in the air and makes them more likely to be respired (i.e., pass into the lower respiratory tract) (Tellier 2006). Viral particles that pass into the lungs are likely to cause other airway infections, such as pneumonia, which are often closely associated with influenza infection.

There has been much debate as to which mode of transmission is most significant with respect to the epidemiology of influenza. For example, Lemieux et al. (2007) found that respiratory particles are most likely to settle in the upper respiratory tract, implicating droplet and contact modes (i.e., large particles) as the primary means of transmission. This is further supported by Brankston et al. (2007) who suggested that most viral infections occur over short distances through physical or direct contact. However, a later study by Lowen et al. (2008) on guinea pigs found that the relative role of contact and airborne transmission may be sensitive to changes in ambient temperature. Therefore, the dominant mode of transmission likely varies according to environmental conditions (Hall 2007). Earlier work by Schulman (1967) on virus transmission between mice corroborates this statement. While no study was found that quantified the size distribution of respiratory particles expelled during a typical cough or sneeze, it may be safe to assume that both small and large droplets, as defined above, are expelled simultaneously. If this is the case, then smaller respiratory particles may disperse and affect susceptible populations across a broader geographical area (i.e., airborne mode), while larger particles may settle directly onto an individual or other surface in a more confined environment (i.e., contact or droplet mode) (Hall 2007). Over the course of a full seasonal epidemic, it is likely that all three modes of transmission contribute to infection across varying space and time scales (Weber and Stilianakis 2008).

Until now, research on the environmental effects of influenza transmission has focused primarily on ambient humidity and temperature in laboratory-controlled settings. The ambient humidity is important in the transmission of influenza because it can affect the size of the respiratory particle (Weber and Stilianakis 2008). When the air is dry, large drops partially evaporate, creating smaller, lighter drops that are more likely to remain airborne for extended periods of time. Based on studies of aerosol dynamics, a typical respiratory particle exposed to an ambient relative humidity of 80% can remain airborne for up to 1 h. When the relative humidity is decreased to 20%, the same particle is able to remain airborne for more than 24 h (Weber and Stilianakis 2008). Dispersion studies of atmospheric particulate matter between 0.1 and 0.3 μm, which is comparable in size to the smallest respiratory particles, have revealed that such particles can in fact remain airborne for many days (Hammond et al. 1989). Therefore, even large particles expelled through coughing and sneezing may shrink to a size that favors long-range transport when the air is sufficiently dry.

Viral transmission may also be sensitive to ambient temperature. Lowen et al. (2008) found that increasing the ambient temperature of guinea pig cages during transmission experiments appeared to prevent airborne transmission but not contact transmission. To simulate airborne transmission conditions, both inoculated and recipient guinea pigs were placed in separate cages in a chamber held at a temperature of 30 °C. After a week of exposure, no recipient guinea pigs were infected. However, when placed in the same cage to simulate contact transmission conditions at 30 °C, between 75% and 100% of the recipient guinea pigs became infected. Moreover, these results were insensitive to changes in ambient relative humidity.

When considering the combined effects of ambient humidity and temperature on influenza transmission, it appears as though airborne transmission is more sensitive to changes in these variables than contact and droplet modes. As temperature and humidity fluctuate with the seasons in temperate climates, and as influenza epidemics exhibit a distinct seasonality in these areas, it is believed that the airborne route is the dominant mode of transmission in temperate regions (Lowen et al. 2008). The relative lack of seasonality in influenza prevalence in tropical regions, as well as less variability in temper-

ature and humidity, suggests that contact and droplet modes are dominant there. Further, the primary source for sporadic and isolated outbreaks that sometimes occur in temperate regions during the summer may be contact and droplet transmissions operating in optimal microclimate conditions.

The role of weather and climate on influenza transmission may also extend to regions where the disease is endemic. The epicenter for most avian influenza strains and variants is in the Eastern Hemisphere, mainly Southeast Asia and China (Pyle 1986; Shortridge 1997). Climate conditions in this part of the world have been linked to the migratory patterns of aquatic bird species (e.g., duck, goose, swan), which are a major reservoir for the virus (Gilbert et al. 2008). Their breeding and wintering patterns, however, extend northward into central Asia and much of Europe. Current projections of global climate change indicate that these regions will experience greater warming than lower latitude regions, which will likely affect the migration cycle of birds that help carry the virus (Gilbert et al. 2008). Within the epicenter regions of Southeast Asia and China, rainfall patterns connected with climate variability (e.g., the Asian Monsoon) and unmanaged agricultural practices (e.g., backyard duck farms, live markets) may widen the areas of possible contact (and transmission) between domestic water fowl and wild bird species (Henning et al. 2009). Changes in solar output and activity, as indicated by sunspot frequency, may also hold some predictive power in terms of forecasting global-scale pandemics (Hope-Simpson 1978). As the migratory patterns of most bird species are sensitive to changes in solar output and the resulting magnetism on earth, analyzing sunspot activity may provide an indicator of changing interspecies transmission cycles on a global scale. Recent work by Yeung (2006), who considered up to 15 global pandemics beginning in the 18th century, offers support for this theory.

EFFECTS OF WEATHER AND CLIMATE ON HOST SUSCEPTIBILITY

At the core of the debate over the causal mechanisms responsible for the seasonality of many infectious diseases is the role of population immunity and overall susceptibility to infection. One of the pioneers in this area of study was Edgar Hope-Simpson (Cannell et al. 2008). His proposed theory on viral transmission of infectious disease can be summarized as follows: the seasonal, epidemic influenza virus will tend to propagate through the environment via a series of transmissions from a small number of highly infectious but generally symptomless hosts who briefly become contagious as a result of a 'seasonal stimulus' (Hope-Simpson 1992). Hope-Simpson identified the seasonal stimulus as a deficiency in vitamin D levels because of seasonal reductions in exposure to ultra-violet (UV) radiation. Low levels of vitamin D have been shown to impair the body's antimicrobial peptide system, which is responsible for regulating the immune response (Cannell et al. 2006, 2008).

A corollary to the seasonal stimulus argument is the concept of photoperiod, which relates to seasonal oscillations in dark-light cycles in the middle and high latitudes (Dowell 2001). Seasonal changes in length of day can interfere with an individual's circadian rhythm, which is regulated largely by the release of the hormone melatonin. This interference can weaken the immune system and increase the risk of infection. Changes in photoperiod and sunlight exposure have been used to explain the observed latitudinal migration of influenza activity during the winter season (Cannell et al. 2008). On a global scale, the appearance and subsequent diffusion of influenza occurs along latitudinal belts, which coincide with changes in photoperiod and sunlight exposure because of changes in solar elevation, day length, and solar insolation. Cannell et al. (2008) also raise the possi-

bility that the lack of a decline in influenza mortality among the elderly may be due at least partially to the fact that the elderly are advised to limit exposure to the sun.

One of the competing explanations for the seasonality of viral infectious disease was proposed by researchers at Cardiff University's Common Cold Centre in the UK and involves cooling of the nasal passageway (Eccles 2002). On a physiologic scale, the breathing of cold, dry air can slow mucociliary clearance of the nasal passage. Under normal conditions, the cilia in the nasal passage act to filter out pathogens and other aerosols from the upper respiratory tract. Experiments on the cilia of laboratory animals and humans indicate that exposure to cold air dramatically reduces mucus velocity (Baetjer 1967). This hypothesis has been used as a mechanism to explain the often observed rise in acute upper respiratory infections following a cold-air outbreak (Assaad and Reid 1971; Eccles 2002). In this case, a symptomless, subclinical infection may become clinical if the infected individual is exposed to cold air. The subsequent rise in clinical infections among a large population may then reveal itself, from a public health perspective, as an infectious outbreak. Although Eccles (2002) presents some compelling evidence for the nasal cooling hypothesis, it remains largely untested in the natural environment and among large populations. A more recent study by Johnson and Eccles (2005) found that chilling of the feet in cold water leads to vascoconstriction of the upper respiratory system, which may increase susceptibility if exposed to viral particles.

The susceptibility of an individual to influenza infection may also be mediated by exposure to other pathogens. In this case, modification of the host immune response to a given infection predisposes the individual to infection from other pathogens (Fisman 2007). For example, recent work by Wong et al. (2009) in Hong Kong found that those infected with influenza were at greater risk for developing chronic obstructive pulmonary disease during periods of poor air quality. This was particularly the case for major pulmonary irritants, such as ozone. Prior expose to atmospheric pollutants can adversely affect mucociliary action in a manner similar to that experienced while breathing cold, dry air as described earlier.

In addition to the innate immunity of healthy individuals, the host response to infection with respect to viral shedding has been shown to be sensitive to changes in ambient temperature. In their experimental studies involving viral transmission between guinea pigs, Lowen et al. (2007) found that infected hosts exposed to lower ambient temperatures shed significantly higher quantities of viral particles than those exposed to higher temperatures. Moreover, the period of peak shedding was extended by as many as 2 days when infection occurred at 5 °C compared with 20 °C. The abrupt rise in clinical infections typically associated with large-scale influenza outbreaks during the winter season may be at least partially related to the increased efficiency and duration of viral transmitters when the air is cold. Oddly, the efficiency and duration of viral shedding does not appear to be related to the degree of impairment of the host immune system because of cold stress (Lowen et al. 2007). This suggests that the environmental impacts on viral shedding may be acting at the level of the virus itself.

EFFECTS OF WEATHER AND CLIMATE ON VIRULENCE

In addition to factors such as transmission cycles and host susceptibility, the ability of the influenza virus to cause infection (i.e., virulence) is also important in the context of disease ecology and the seasonality of infection. Viral strains with a history of high infectivity, such as the H5N1 avian influenza, may indeed override any innate or adaptive

immunity (i.e., vaccination) regardless of environmental conditions. Virulence of the circulating viral strain, which often varies from year to year, has been used to explain why many influenza epidemics end rather abruptly, although there may be a large number of susceptible hosts.

There is evidence that the degree of infectivity of a circulating viral strain may be controlled at least partially by environmental factors. Recent work suggests that the survival of a virus is determined primarily by the characteristics of its outer casing, or envelope, which is composed of lipid compounds. Polozov et al. (2008) suggest that the lipid envelope encasing the virus remains intact longer when the air is sufficiently cold and dry. As the aerosolized viral particle enters the upper respiratory tract, the envelope melts, exposing the virus to healthy host cells. In addition, air pollution can have adverse effects on the RNA sequence of the virus. Weber and Stilianakis (2008) discuss this option, along with other forms of potential environmental inactivation of influenza virus. Interestingly, there remains a paucity of work on virus inactivation because of environmental factors. One possibility is prolonged exposure to UV radiation under clear sky conditions. Germicidal UV radiation produced by UV lamps has been shown to be highly effective at inactivating viruses on contaminated surfaces (Hall 2007). The effect to which this process occurs in the ambient environment is still unknown and warrants further investigation, particularly in light of the 'seasonal stimulus' hypotheses put forth by Hope-Simpson.

Determining the environmental effects of virus infectivity requires a more complete understanding of how the virus exists in the ambient environment. Even today, there is still much debate as to lifecycle of the virus, particularly in the period between seasonal epidemics. Does the virus simply decay once temperatures and humidity levels rise to a critical point? Does the virus enter a dormant state between epidemics, only to be reactivated under a combination of biological and environmental triggers? Tracing the evolution of viral particles during and between epidemics using environmental modeling and atmospheric dispersion models may help solve this enigma. Recent work suggests that the influenza virus may in fact migrate from the tropics to temperate regions in both hemispheres during the winter (Alonso et al. 2007). In their study, Alonso et al. (2007) found that the incidence of influenza mortality in Brazil exhibited a latitudinal shift from the northern, tropical regions in summer (November) to the southern, temperate regions of the country in winter (May). They suggest a strong environmental component to this pattern, as it flows against the expected population-driven diffusion pattern (i.e., south to north).

Macro-Scale Studies of Influenza Mortality

Much of what is known about the effects of weather and climate on influenza prevalence results from studies examining monthly or annual morbidity and mortality for large geographical areas and their relationship to large-scale climate indices. In particular, the strongest relationships identified between large-scale climate patterns and influenza are associated with the El Nino-Southern Oscillation (ENSO), which is a coupled ocean-atmosphere circulation phenomenon representing the dominant mode of climate variability over the Pacific Ocean (Allan et al. 1996). The effects of ENSO are global in scale and tend to persist for extended periods of time (2–7 years on an average). This leads to extended precipitation and temperature anomalies across various regions, which can force changes in disease transmission cycles, vector density, population susceptibility, and virulence. Diseases such as malaria, cholera, dengue, rift valley fever, and Australian

encephalitis show strong dependence on temperature and precipitation patterns associated with ENSO and are well-documented (Kovats et al. 2003). Similar studies addressing the regional to global spread of influenza have been published within the last decade and are now being tested for implementation in early warning systems (Kuhn et al. 2005).

One of the first published studies on the effects of ENSO with respect to respiratory illness was performed by Ebi et al. (2001) for viral pneumonia hospitalizations among females in three California cities. Over a 16-year period, they found up to a 40% increase in hospitalizations for every 5 °F decrease in temperature in Los Angeles and San Francisco, irrespective of season or ENSO phase. Only in Sacramento did they find a statistically significant increase in hospitalizations during the warm ENSO phase (El Nino), which is associated with cooler temperatures and slightly higher precipitation in northern California (Null 2009).

More recent studies examining the effect of ENSO on influenza have been performed for the USA and France. Flahault et al. (2004) found that cold ENSO phases (La Nina) the previous autumn lead to more severe epidemics in both countries. In the USA, the number of excess deaths because of pneumonia and influenza rose 70% during the ten cold ENSO periods identified from 1971 to 1997. A similar study by the same research group (Viboud et al. 2004) developed a suite of linear regression models to explain influenza morbidity patterns in France. The base model, which considered only viral subtype, explained about 25% of the model variance. When a climate covariate, based largely on ENSO phase, was added to the base model, the explained variance increased to 61%. A more recent study of influenza in Japan revealed that ENSO phase only affected the timing of peak infection with no discernable relationship between ENSO and the severity of infection (Zaraket et al. 2008). These studies suggest that environmental conditions may be an important determinant of the large-scale mortality impact of a given influenza epidemic.

In general, the associations between influenza morbidity/mortality and large-scale climate patterns identified in these studies support the assertion that climate 'signals' at global and continental scales are important to the epidemiology of influenza. On a global scale, the dispersion of viral particles from endemic regions such as Southeast Asia may be connected with ENSO-induced circulation patterns over the northern Pacific Ocean. On a more local scale, the timing and duration of certain weather patterns associated with ENSO may affect population immunity. A study for northern Spain concluded that abrupt changes in regional circulation patterns, and therefore changes in temperature and humidity, coincided with the epidemic rise in excess influenza diagnoses (Fdez. de Arróyabe Hernáez 2004). In a study of weekly influenza mortality in Scotland, Assaad and Reid (1971) showed that over 40% of all annual influenza deaths occurred during the coldest week of the year. Dushoff et al. (2006), however, postulated that the effect of temperature on winter season mortality likely occurs on shorter time scales. Individuals who died as a result of exposure to cold temperatures would not have been likely to live much longer if not exposed; therefore, excess mortality would not reflect the true role of temperature on winter season mortality. As influenza was in most cases still recorded as the primary cause of death on the official certificate, it is likely that they were already infected with the virus prior to exposure to cold weather. As a result, susceptible populations, such as the elderly or those with weakened immune systems, should receive warning when an exceptionally cold-air mass is forecasted over their location.

There is also a body of evidence suggesting that, when considering the effect of large-scale climate signals, the space–time distribution of influenza epidemics must be examined on regional scales. For example, Greene et al. (2006), in a study covering the contiguous

United States, used aggregated mortality data separated by climate division and found significant regional differences in both the magnitude and timing of peak infection that seemed to suggest a coherent space–time pattern of diffusion. Interestingly, the regional-scale diffusion of annual influenza epidemics could not be fully explained by demographics, transportation routes, or other adaptive or preventative measures. Therefore, Greene et al. (2006) suggested that environmental factors, such as climate, may be just as important as the traditionally-cited social and behavioral factors to the spread of infection. The regional diffusion of influenza was also examined by Choi et al. (2006) for the state of California under different ENSO phases. They found that mortality rates were as much as three times greater during cold ENSO phases (La Nina), but this trend was not uniform across the state. A novel suggestion by Choi et al. (2006) with regard to ENSO and infectious disease is that the anomalous weather patterns associated with ENSO (i.e., variability in rainfall and temperature patterns) place a large burden on the health sector, making it difficult to adequately prepare for and respond to emerging epidemics.

An important consideration when evaluating the regional to continental scale patterns of influenza mortality is the random genetic mutations (i.e., antigenic drift) and re-assortment of viral genes (i.e., antigenic shift) that characterize the evolution of influenza viruses (Earn et al. 2002; Thacker 1986). Antigenic shifts and drifts can severely affect the virulence of the circulating pathogen and can lead to lost immunity and vaccine mismatches. Large shifts and drifts can result in much larger influenza outbreaks (as well as pandemics), which may mask or obscure a perceived relationship with prevailing weather and climate conditions.

Conclusion

Despite the increasing amount of research and knowledge on the seasonality of influenza (Table 1), the seemingly simple question of why epidemics in temperate regions occur in the wintertime continues to remain elusive. Indeed, there are a number of characteristics regarding influenza prevalence that are still not fully understood in the context of prevailing weather and climate conditions: (i) the timing, or onset of an influenza epidemic; (ii)

Table 1. Epidemiologic components of influenza and sensitivity to weather and climate.

Component	Relationship quantified?	Strength of climate relationship	Scale(s) of climate relationship	Key atmospheric variable(s)
Climate → Pathogen (pathogencity)		Weak	Micro	Temperature Humidity Radiation Air Quality
Climate → Particle (aerosol dynamics)	✔	Important	Micro	Temperature Humidity
Climate → Host (susceptibility)		Important	Regional to local	Temperature Radiation Air Quality
Pathogen → Particle Host → Particle (transmission)	✔	Moderate	Global to regional	Temperature Humidity Wind/Stability

the severity of a given epidemic; (iii) the spatial distribution, or spread of influenza infection; (iv) the variability in timing and severity among individual epidemics; and (v) the apparent disappearance of influenza during the summer season, with only occasional isolated occurrences. Moreover, it is unclear why certain viral strains, such as the currently circulating novel H1N1, seem to emerge out of phase with the more common seasonal avian strains, such as H3N2 (Dowell and Ho 2004).

There are a number of possible reasons why these characteristics remain poorly understood. First, the methodological approaches used to study the seasonality of influenza vary widely. These range from simple correlation of meteorological variables with continental-scale morbidity and mortality to laboratory-based research on viral etiology and host physiology under varying temperature and humidity conditions. Any attempt to integrate the results of these studies must consider the use and interpretation of meteorological variables in laboratory versus natural settings. For instance, it is not clear whether the relationships observed between influenza transmission and temperature in a laboratory cage or chamber could be used to understand transmission cycles on regional or hemispheric scales. Simulating a natural setting is difficult to achieve in a laboratory or other closed space and offers little insight into the dispersion characteristics of respiratory particles on broad time and space scales (Weber and Stilianakis 2008). Other methodological considerations, such as the space–time attributes of health data and the use of population demographics, further complicate the overall picture of influenza seasonality.

Secondly, the influence of influenza on the winter season increase in mortality observed in many temperate regions remains unclear (Davis et al. 2004). Some studies suggest that influenza is the primary determinant of winter mortality, as the virus takes opportunistic advantage of seasonal changes in environmental conditions (Reichert et al. 2004). Other studies suggest that the primary determinant of winter mortality may be stresses and complications arising from influenza, such as thrombotic disease (Donaldson and Keatinge 2002). Improvements in our understanding of cold season mortality and the causes and mechanisms responsible for them likely begin with influenza.

Thirdly, any direct effect that weather and climate patterns might have on influenza activity is likely compounded by a variety of indirect effects related to human behavior, contact with major viral reservoirs (e.g., aquatic bird species), and their migratory and reproductive patterns. In this sense, the virus may take advantage of seasonal changes in ecological factors related to infection. In addition, while indoor crowding in the wintertime remains a popular hypothesis for the seasonality of influenza, there is no empirical evidence to support or refute the claim that individuals spend more time indoors in the winter than at other times of the year (Fisman 2007). Some suggest that differences between heating and air conditioning units may play an important role in the dispersion and activation of viral particles in confined environments (Lofgren et al. 2007). If this is the case, changes in outdoor temperatures, perhaps coupled with changes in cloud cover, humidity, and wind, may force changes in the use of indoor ventilation and thermal units that alter the likelihood of infection. This proposal warrants further investigation.

Lastly, there remains much debate as to how the influenza virus is transmitted to susceptible populations. Ambient weather conditions may have a direct influence on airborne and droplet transmissions, while large-scale climate patterns may indirectly establish environmental conditions that facilitate airborne transmission over broad geographic areas. Micro-scale dispersion of large respiratory particles may contribute to isolated transmission in confined areas, while widespread outbreaks may be driven more by long-range dispersion and transport of smaller particles. These and many of the other hypotheses presented

in this article are difficult to examine with most historical health datasets (Comrie 2007). Future studies may benefit from data obtained through medical surveillance networks with sufficiently high spatial and temporal resolution (e.g., hourly or daily data at the zip code or county level).

Establishing causal, or mechanistic, links between atmospheric conditions and influenza activity at multiple space–time scales can help shed light on the internal dynamics of the virus and how it may respond to changes in these conditions over time. This is of particular importance from the perspective of climate change, as there is growing concern that shifts in the seasonal component of various weather and climate patterns will lead to shifts in the timing, spread, and severity of infectious diseases (Confalonieri et al. 2007). The emerging research addressing climate change and infectious disease is being performed largely by members of the health and medical communities, with few contributions from climate scientists. The multifaceted and complex nature of infectious diseases, as demonstrated here with regards to influenza, should create rich opportunities for cross-disciplinary collaboration.

Short Biography

Christopher Fuhrmann is a Research Climatologist with the NOAA-Southeast Regional Climate Center and doctoral candidate in Geography at the University of North Carolina at Chapel Hill. His research interests are in synoptic climatology, weather and society, climate and human health, winter weather, and climate variability and change. He earned a BA in Geography with highest honors from the University of North Carolina at Chapel Hill and a MS in Geography from the University of Georgia.

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