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Timing Classification of United States Influenza Epidemics from 1999-2014 and the Association of Epidemic Timing Classification with Influenza-Associated Mortality

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ABSTRACT

Timing Classification of United States Influenza Epidemics from 1999-2014 and the Association of Epidemic Timing Classification with Influenza-Associated Mortality

By Taylor Alexandra Hudalla

Epidemics of influenza occur annually in the United States, causing 3,000- 49,000 deaths, and costing an estimated $16 billion each year. The seasonality of Northern Hemisphere influenza epidemics is well established, but the classification of influenza season timing is not defined. This study attempted to describe three influenza epidemic timing metrics: epidemic start, epidemic peak, and epidemic start to peak interval, for the classification of season timing using United States virologic surveillance data from 1999-2014 (n=13). Epidemic start and epidemic peak were identified and seasons were classified as early, average, or late. Epidemic start to peak interval was identified and seasons were classified as short, average, or long. Using the developed timing metrics, a cross-sectional study of virologic and mortality surveillance data assessed the association of influenza season timing with pneumonia & influenza (P&I) associated mortality through Poisson regression adjusted for predominant influenza A subtype. Among the three timing metrics, epidemic start to peak interval had the strongest association with P&I associated mortality. Short epidemic start to peak interval seasons were associated with a 10% increase in mortality rate compared to average epidemic start to peak interval seasons ($RR_{ShortInterval}$=1.10 95% CI=1.10, 1.11). Long epidemic start to peak interval seasons were associated with a 10% decrease in mortality rate compared average epidemic start to peak interval seasons ($RR_{LongInterval}$=0.90 95% CI=0.90, 0.91). Given the P&I mortality rate during an average epidemic start to peak interval season of 20.1 deaths per 100,000, and the current United States population of 318.9 million, a short epidemic start to peak interval season could indicate 6,400 more deaths. The findings suggest that classification of epidemic start to peak interval is associated with influenza-associated mortality, but as classification requires the influenza season to reach peak incidence, does not allow for early intervention. Further research is needed to identify the mechanism underlying the association of epidemic start to peak interval and P&I associated mortality to provide a method to predict influenza season mortality. A method of early prediction could allow public health and clinical stakeholders to target prevention and intervention efforts.

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BACKGROUND

Influenza is a contagious respiratory illness, resulting from annual epidemics of influenza virus. Each year, influenza causes 3-5 million illnesses worldwide, and an estimated 3,000 - 49,000 deaths in the United States annually (1). Influenza epidemics additionally pose a substantial economic burden with a projected cost of 16 billion each year due to lost productivity and demands on healthcare resources (2, 3). The breadth of clinical and economic impacts due to influenza warrant evaluation of potential predictors of influenza epidemic severity, such as epidemic timing. Although influenza seasonality is well described, there are no defined metrics to classify epidemic timing as early, average, and late, or short, average, and long within the United States.

It is well established that in the Northern Hemisphere, influenza epidemics typically occur from late fall through early spring (4). The influenza epidemic curve follows three phases: exponential growth, period of peak activity, and decline (5). Previous studies have attempted to describe influenza epidemic timing by identifying the epidemic midpoint, the date when 50% of the total number of positive influenza isolates were reported for the season (6). Another characterization of influenza season in previous studies is epidemic peak, the week of maximum weekly incidence (7). Although these characterizations of influenza epidemics attempt to describe timing, none have been applied to recent United States influenza surveillance data, and have not attempted to classify influenza epidemics into early, average, and late seasons, or classify epidemics as short, average, and long seasons.

United States influenza surveillance includes monitoring of influenza illness presentation at outpatient care providers facilitated through the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet). Sentinel healthcare providers report incidence of "influenza-like illness" (ILI), which is defined as fever greater than or equal to 37.8° Celsius with cough and/or sore throat without a known cause (8). Previous studies have used ILINet surveillance data for characterization of influenza epidemics. Data from the ILINet surveillance system was not used in this study due to artifacts from population behavior regarding presentation to healthcare providers (9). ILINet data consistently reflects increases in provider seeking behavior during the winter holiday season, which may introduce bias into measurement of influenza activity (9).

United States influenza surveillance also monitors influenza positive isolates among tested respiratory specimens at public health and clinical laboratories (8). Virologic surveillance provides an indication of influenza activity that is not as sensitive to artifacts of population behavior. Virologic surveillance identifies when percent of influenza positive isolates increases, and when influenza incidence reaches its peak. Considering the traditional epidemic curve of influenza epidemics, as well as the lack of influence of population behavior on virologic surveillance data, this study develops three metrics using laboratory data to describe the influenza season timing: epidemic start, epidemic peak, and epidemic start to peak interval.

An attempt is made to classify United States influenza epidemics between 1999-2014 as early, average, or late seasons using epidemic start and epidemic peak. Duration of influenza epidemics will also be described using the surrogate metric of epidemic start to peak interval. Epidemic start to peak interval provides an indication of how long in weeks influenza infection incidence was increasing before the epidemic reached its peak. Epidemic start to peak interval

of influenza epidemics in this study will be used to classify seasons as short, average, or long. Each metric definition and timing classification guidelines are outlined in Table 1. Given the potential for severe outcomes from influenza infection, this study also aimed to evaluate the association of influenza epidemic timing classification with P&I associated mortality using Poisson regression. Previous studies performed by Zinder, Daniel et al, and Klepser, Michael suggest that early or short influenza seasons have been associated with increased morbidity and mortality (2, 10).

Influenza seasons with early or short epidemic timing could plausibly lead to more mortality due to emergence of antigenically drifted strains that may or may not be more pathogenic, but to which the population immunity is reduced, or protection provided by vaccination is less than optimal, as well as other unknown factors (4, 7, 11, 12). Using timing of influenza epidemics in the United States as a potential indicator of excess mortality could inform prevention and intervention efforts of healthcare, public, and policy stakeholders to reduce the annual disease burden of influenza.

LITERATURE REVIEW

Biology of Influenza Virus

Influenza Virus Genome and Replication

Influenza is a virus of the Orthomyxoviridae family (13). There are 3 different strains of influenza: A, B and C, although only A and B cause clinical illness in humans. Influenza A virus is found in both humans and animals, such as pigs, horses, and nondomestic waterfowl. Influenza B virus is solely carried in humans (13). The genome of influenza virus is composed of 8 single stranded RNA segments, which code for 11 proteins. The RNA genome is susceptible to both antigenic drift and antigenic shift, processes which yield a constantly evolving influenza phylogenic tree. Antigenic drift occurs frequently through the accumulation of small point changes in nucleotides resulting in similar, but slightly different proteins. Both influenza A and influenza B viruses are susceptible to antigenic drift. Only influenza A virus can undergo the rare event of antigenic shift. Antigenic shift occurs when one or more of the RNA segments in an influenza A virus re-assort, or the virus directly adapts to infect a new host. The occurrence of antigenic shift yields changes in antigenic properties to which global populations are naïve (13).

Influenza Virus Proteins

Within the influenza RNA genome, two important surface proteins, hemagglutinin (HA) and neuraminidase (NA), are responsible for infection and pathogenesis. There are 18 HA subtypes and 11 NA subtypes recognized within animal and human species. HA facilitates the infection of host cells, by binding to epithelial cells in the upper respiratory tract, and allowing entry into the host. The binding site for HA is highly conserved and consistent among circulating strains. The highly conserved specificity of the HA epithelial binding site determines which species are

susceptible to infection. NA mechanizes the release of newly synthesized influenza virions in the host, by cleaving the host cell membrane upon replication (13). Influenza A subtypes are classified according to their HA and NA subtypes.

Clinical Manifestation of Influenza Virus

Influenza Infection Symptoms

Influenza is a contagious virus to which all individuals are susceptible. Attack rates of the virus have been described as 10-30% throughout all regions globally (14). The virus is transmitted through respiratory secretions, often as a result of coughing, sneezing, and talking, but transmission occurs through direct and indirect contact as well. Once infected, there is an incubation period of 1-4 days, at which time clinical symptoms can manifest (14). Influenza illness is an infection solely of the respiratory tract with an acute onset (13). There is a spectrum of clinical symptoms when infected, but typically include fever, cough, chills, and muscle aches (13). These symptoms are consistent with other respiratory viruses that circulate throughout the population, although influenza is often differentiated from other respiratory illnesses in that rhinorrhea is not common. The symptoms of influenza illness often self-resolve, but can be palliated through use of over-the-counter remedies, alleviating some burden for care on the healthcare system (2).

Influenza Illness Diagnosis

Influenza virus infection appears clinically similar to other respiratory illnesses. Thus, diagnosis cannot be made through symptom presentation alone (14). The exception to a formal clinical diagnosis is during an epidemic situation. Influenza virus is difficult to grow in a laboratory setting, but isolation and culture from nasopharyngeal washings remains the gold standard for

diagnosis (13). Other laboratory methods of identification of influenza virus include reverse transcription polymerase chain reaction (RT-PCR), rapid immunofluorescence, and enzyme-linked immunosorbent assays (13). Specimens positive for influenza can be tested further for identification of influenza A subtypes and influenza B lineages.

Influenza Hospitalization

When infected with influenza virus, individuals usually can self-resolve the illness within 3-5 days. In some demographic groups, influenza illness has a higher risk of hospitalization (14, 15). Previous studies have estimated that an average of 200,000 individuals are hospitalized each year (2). Very young, old, and immunocompromised populations may develop pneumonia, which may require further medical care. Most hospitalizations occur in those older than 65 years of age (2). This increase in hospitalizations among older adults can be attributed to the increasing percentage of the population in older age groups, and the increased prevalence in underlying conditions that decrease host response in older individuals (2). Adults requiring hospitalization due to influenza virus infection typically have an underlying co-morbidities including metabolic disease, cardiovascular disease, or obesity (15).

Influenza Death

Thousands of deaths are associated with influenza infection each year in the United States (1). Measuring mortality due to influenza is difficult, as a formal clinical diagnosis of influenza virus infection requires laboratory confirmation, and often influenza is not the documented cause of death on mortality records. Influenza is highly correlated with deaths from pneumonia and influenza, providing a conservative estimate of mortality associated with influenza infection (16). Deaths attributed to pneumonia and influenza are classified by the *International*

Classification of Diseases, tenth revision (ICD-10) codes J09-18. These ICD-10 codes account for deaths that include both laboratory and clinical diagnosis of influenza or pneumonia (17).

Epidemiology of Influenza Virus

Age Distribution

Incidence of influenza infection is higher in infants and children compared to adults. Those that are infected are more likely to be hospitalized if they are extremely young or old (14). School-aged children, those 5-17 years of age, are potential drivers of influenza epidemics as they are among the first to become infected among all strains of influenza (6). School-aged children provide an avenue of exposure to others which are susceptible, such as infant siblings or elderly family (14). The proportion of those above age 65 years in the United States is also growing, a population at risk of increased morbidity and mortality from influenza. Although the population gains immune memory with age, the ability for the immune system to rapidly mount is hindered for those greater than 65 years (2).

Vaccination

Vaccination is the primary method of preventing influenza virus infection. Health recommendations from the Centers for Disease Control and Prevention (CDC) include vaccination of those greater than 6 months of age (2). Due to antigenic shift and drift of the viral genome, re-composition, and re-administration of vaccines is required annually. Vaccines available include both inactivated and live attenuated combinations of three or four strains of influenza A and B. The strains included in the Northern Hemisphere vaccine result from the recommendation of organizations monitoring influenza virus circulation, including the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and Pan American

Health Organization (PAHO). Upon administration of the influenza vaccine, the immune system develops antibodies, including those to the highly conserved HA protein responsible for host cell infection, among others (14). The strength of the host immune response is dependent on how genetically distant the infecting influenza virus is from influenza viruses the host was previously exposed to through vaccination and influenza infection (12). Vaccination may offer protection from influenza virus infection, but may also reduce the course of clinical illness and mortality upon infection (2).

Seasonality of Influenza Epidemics in the United States

Timing

The antigenic variation of influenza virus is responsible for the occurrence of annual epidemics and rare pandemic events throughout the world. All regions globally experience epidemics, and within the Northern Hemisphere, influenza season is typically seen from November through March (14). The cold temperature and decreased humidity occurring in the winter months could contribute to the influenza epidemic seasonality experienced in the Northern Hemisphere, as the virus remains more stable in those environmental conditions. Another suggestion explaining the winter seasonality is the crowding that occurs in winter months which promotes transmission (14). Influenza epidemics follow a traditional epidemic curve: exponential growth, period of peak activity, and decline (5). Although timing of influenza is unpredictable, epidemics typically peak in January and February (2). Previous studies have identified that the mean epidemic duration for influenza in the United States is 12.5 weeks (18).

Circulation of Strains

In the United States, 5- 20% of the population contracts influenza virus in a given year (13). Due to circulation of multiple influenza strains during a single epidemic, a single locality can experience more than one wave of epidemic illness. Multiple studies have evaluated the varying pathogenicity of influenza A subtypes and influenza B lineages. Among influenza subtypes, the H3N2 strain of influenza A has been described to cause more severe illness (12, 18). The evolution of emerging influenza strains depends upon population host immunity, the mobility of the host population, the degree of antigenic shift or antigenic drift, among other unknown factors (12). Previous studies have identified that influenza strains emerging early in a season are typically mutant viruses (12). Although vaccines are selected through virologic monitoring, seasonal influenza strains may drift, and yield an ineffective vaccine match.

Domestic Influenza Surveillance

History of CDC Surveillance

Influenza activity in the Northern Hemisphere can be measured through several surveillance systems managed by the CDC (8). These systems include monitoring of syndromic influenza illness, influenza virus virologic testing, influenza-related hospitalizations, and influenza-associated mortality. The surveillance systems detect increases in influenza activity at different points in annual influenza epidemics. Influenza illness is the first indication of an influenza epidemic, reflected in school and work absenteeism, as well as increased visits to healthcare providers for influenza-like illness. Virologic monitoring then detects rises in influenza positive specimens, as more respiratory specimens are tested at public health and clinical laboratories. As influenza illness increases, influenza-related hospitalizations are reported. Mortality associated with influenza is the last marker of influenza activity (14). Each surveillance system

provides a picture of influenza activity in the United States and can produce an influenza epidemic curve (8).

U.S. Outpatient Influenza-like Illness Surveillance Network (ILINET)

United States monitoring of influenza illness is facilitated by the U.S Outpatient Influenza-like Illness Surveillance Network (ILINet). The network includes over 2,900 outpatient healthcare providers throughout the country. Providers include those treating pediatric, internal medicine, emergency medicine, obstetric, and student health populations. Providers report weekly the total number of patients seen with ILI and the total number of patients seen, to allow for a calculation of the percent ILI throughout the United States. Reports are aggregated and percent ILI is reported at both a national and Health and Human Services level on CDC's FluView Interactive (8). Percent ILI reported is weighted on the state population and compared to a national epidemic threshold baseline calculated each year. The national endemic level is based upon the mean percent ILI during non-influenza weeks for the previous 3 seasons. A non-influenza week is considered a period when two or more consecutive weeks account for less than 2% of the season's total number of influenza positive specimens (8).

WHO/NREVSS Collaborating Laboratories (WHO/NREVSS)

CDC works with partners including the United States collaborating World Health Organization (WHO) laboratories and National Respiratory and Enteric Virus Surveillance System (NREVSS) to continuously monitor virologic influenza activity throughout the United States (8). Laboratories participating in the WHO/NREVSS virologic surveillance system include both public health laboratories and clinical laboratories. Both laboratory types report the total number of specimens tested and number of isolates positive for influenza. Public health laboratories

additionally report subtyping of influenza A virus, and may report lineage results of influenza B viruses. Clinical laboratories do not routinely report subtype and lineage of samples. Virologic results are aggregated weekly and reported on CDC's FluView Interactive (8). The virologic surveillance system also includes collection of specimens from public health laboratories for testing at the CDC to determine antiviral resistance patterns, confirm novel influenza strains, and to assist in vaccine strain selection (8).

National Center for Health Statistics

Mortality associated with influenza is monitored by the National Center for Health Statistics (NCHS) (17). Causes of mortality are collected nationally from death certificate data managed by vital statistics offices within each state. Deaths attributed to influenza are monitored along with deaths attributed to pneumonia to provide an indication of excess mortality during influenza season. *International Classification of Diseases,* tenth revision (ICD-10) cause of death codes J09-18 are used to identify which deaths are associated with influenza and pneumonia. CDC reports the percent of deaths attributed to pneumonia and influenza weekly (8, 17).

MATERIALS AND METHODS

Dataset

Determination of influenza epidemic timing metrics: epidemic start, epidemic peak, and epidemic start to peak interval were derived from United States influenza surveillance data from 1999-2014. The dataset used for analysis was a compilation of two Centers for Disease Control established surveillance data sources: United States World Health Organization Collaborating Laboratories and National Respiratory and Enteric Virus Surveillance System Laboratories (WHO/NREVSS) and vital statistics from the National Center for Health Statistics (NCHS) (8, 17). These datasets are available to the public for download and use. No IRB approval was needed for this study, as data are presented at a national aggregate level, and contain no human subject research or personally identifiable information, thus they are considered non-research.

Weekly reports from WHO/NREVSS collaborating laboratories are publicly available at CDC FluView Interactive (8). Mortality data are publicly available from NCHS at CDC Wonder (17). Both data sources report at both a national and a regional level according to the ten regional boundaries defined by Health and Human Services each week (8). This study used data reported at the national level for analysis. All influenza surveillance systems established by CDC report according to Morbidity and Mortality Weekly Report weeks (MMWR), starting on Sunday and ending on Saturday. Values for MMWR weeks range from 1-53 according to the week of the epidemiologic year and are used to report week of disease incidence (19). Emergence and circulation of pandemic influenza A subtype, H1N1pdm09, was reported during the 2008-2009 and 2009-2010 influenza seasons. As this study aimed to evaluate non-pandemic influenza seasons in the United States, data from the 2008-2009 and 2009-2010 seasons were omitted.

This study used data collected through the WHO/NREVSS for assessment of influenza season timing metrics; epidemic start, epidemic peak, and epidemic start to peak interval. Virologic surveillance data are collected from 110 United States World Health Organization (WHO) Collaborating Laboratories and 240 National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories throughout the United States. All states, as well as some city and county public health laboratories, participate as WHO collaborating laboratories, while hospital and university laboratories participate as NREVSS clinical reporters. All laboratories report the total number of respiratory specimens tested and the number positive by virus type. Public health laboratories additionally report influenza A subtype (H1N1, H1N1pdm09 or H3N2) and may report influenza B lineage (Victoria or Yamagata) of influenza positive specimens. Testing methods and triaging of specimens vary by laboratory type.

Deaths due to pneumonia and influenza (P&I) were used for analysis as deaths due to influenza are highly correlated with deaths from P&I, thus providing a conservative estimate and proxy of mortality associated with influenza infection (16). Surveillance for P&I associated deaths use mortality data collected by the NCHS (17). Cause of death is collected from death certificate data from vital statistics offices within all 50 states. Data are aggregated by week of death and are continuously updated as more recent death certificate data is received (17). Cause of death is classified by *International Classification of Diseases,* tenth revision (ICD-10). P&I associated fatalities are defined as deaths classified by ICD-10 codes J09-18. These ICD-10 codes account for deaths that include both laboratory and clinical diagnosis of pneumonia or influenza (17). Each influenza season starts in MMWR week 40 and ends in MMWR week 39. P&I associated fatalities were aggregated from MMWR week 40 through MMWR week 39 to provide a total mortality count for each influenza season in this study.

Epidemic Timing Classification

Influenza epidemics in the United States can be described by a traditional epidemic curve (5). This study developed three timing metrics: epidemic start, epidemic peak, and epidemic start to peak interval to attempt to classify timing of influenza seasons. Epidemic start was defined as the MMWR week in which the percentage of respiratory specimens positive for influenza among public health and clinical laboratories exceeded or equaled the threshold of 10.0%. Epidemic peak was defined as the MMWR week in which the percentage of respiratory specimens positive for influenza reached the maximum value for the season. Epidemic start to peak interval was defined as the number of MMWR weeks between the epidemic start and the epidemic peak for each season. WHO/NREVSS surveillance data was used for identification of all three timing metrics among the study sample.

Classification of early, average, and late season timing for epidemic start was completed by grouping the thirteen United States influenza seasons in tertiles depending on the MMWR week identified as the epidemic start. Influenza seasons were classified as average epidemic start seasons if the percent of specimens positive for influenza exceeded or equaled 10% during MMWR weeks 51 and 52. Influenza seasons were classified as early epidemic start seasons if the percent of specimens positive for influenza exceeded or equaled 10% before MMWR week 51. Influenza seasons were classified as late epidemic start seasons if the percent of specimens positive for influenza exceeded or equaled 10% after MMWR week 52.

Classification of early, average, and late season timing for epidemic peak was completed by grouping the thirteen United States influenza seasons in tertiles depending on the MMWR week identified as the epidemic peak. Influenza seasons were classified as average epidemic peak

seasons if the maximum percent of specimens positive for influenza occurred during MMWR week 4 through 6. Influenza seasons were classified as early epidemic peak seasons if the maximum percent of specimens positive for influenza occurred prior to MMWR week 4. Influenza seasons were classified as late epidemic peak seasons if the maximum percent of specimens positive for influenza occurred after MMWR week 6.

Classification of short, average, and long season timing for epidemic start to peak interval was completed by grouping the thirteen United States influenza seasons in tertiles depending on the value for epidemic start to peak interval. Influenza seasons were classified as average epidemic start to peak interval seasons if the number of weeks from epidemic start to epidemic peak was 6 or 7. Influenza seasons were classified as short epidemic start to peak interval seasons if the number of weeks from epidemic start to epidemic peak was less than 6. Influenza seasons were classified as long epidemic start to peak interval seasons if the number of weeks from epidemic start to epidemic peak was greater than 7. Epidemic start, epidemic peak, and epidemic start to peak interval metric definitions and classification guidelines are outlined in Table 1. The results of epidemic start, epidemic peak, and epidemic start to peak interval classification for the United States influenza seasons in this study are illustrated in Table 2.

Influenza A Subtype Variable Description

Prior studies have identified that predominant subtype of influenza A virus circulating is associated with influenza-associated mortality (5, 8). The predominant influenza A viral subtype circulating during each influenza epidemic was classified by comparing the number of influenza A subtyped viruses reported each year, and identifying the most abundant virus reported. In the

United States, the influenza A virus subtypes circulating during the period of this study include H3N2, H1N1, and H1N1pdm09.

Analysis Plan

All compilation, cleaning, and analysis of United States surveillance data used in this study was performed using SAS 9.4 (Cary, NC). United State influenza seasons from 1999-2014 were evaluated to determine MMWR weeks for epidemic start and epidemic peak. Epidemic start to peak interval for each season was then derived using the previously identified epidemic start and epidemic peak. Seasons were classified as early, average, or late for epidemic start and epidemic peak. Seasons were classified as short, average, or long for epidemic start to peak interval. Maximum percent positive, predominant influenza A subtype, total number of P&I associated fatalities, and P&I associated mortality rate per 100,000 for each season were then characterized by mean (continuous variables) and frequency (categorical variables). Agreement of influenza season timing classification based on the timing metrics of epidemic start and epidemic peak was evaluated by assessing correlation using a Pearson's Correlation test. The potential association of influenza season timing and P&I associated mortality was evaluated through a cross-sectional study of United States influenza surveillance data from 1999-2014. Crude Poisson regression was initially used to evaluate the association between the three individual timing metrics and P&I associated mortality. An adjusted Poisson regression analysis accounting for predominant influenza A subtype circulating was also used to evaluate the association between the three individual timing metrics and P&I associated mortality.

RESULTS

Evaluation of virologic surveillance data to determine epidemic start among the study sample found that the MMWR weeks in which the percent of specimens testing positive for influenza exceeded or equaled 10% ranged from week 42 through week 5. The mean MMWR week was 50 and the mode MMWR week was 51. Upon classification, 5 seasons were identified as early epidemic starts, 4 seasons were identified as average epidemic starts, and 4 seasons were identified as late epidemic starts. Selected surveillance characteristics of influenza epidemics included in the study are shown in Table 3. Both early and late epidemic start seasons had a higher mean maximum percent positive compared to average epidemic start seasons, with a 6.8 percentage point increase and a 3.3 percentage point increase respectively. Both early and late epidemic start seasons were similar to average epidemic start seasons in mean number of P&I deaths and mean P&I mortality rate.

Evaluation of WHO/NREVESS data to determine epidemic peak among the study sample found that the MMWR weeks in which the maximum percent of specimens positive for influenza ranged from week 48 through week 11. The mean MMWR week was 4, and the mode was MMWR week 5 and 6. Upon classification, 4 seasons were identified as early epidemic peaks, 5 seasons were identified as average epidemic peaks, and 4 seasons were identified as late epidemic peaks. Table 3 illustrates selected surveillance characteristics of the influenza epidemics included in the study. Both early and late epidemic peak seasons had a higher mean maximum percent positive compared to average epidemic peak seasons, with a 7.7 percentage point increase and a 1.5 percentage point increase respectively. Late epidemic peak seasons were similar to average epidemic peak seasons in mean number of P&I deaths, while early epidemic peak seasons had a 3.54% increase in mean number of P&I deaths compared to

average epidemic peak seasons. Both early and late epidemic peak seasons were similar to average epidemic peak seasons in mean P&I mortality rate.

Evaluation of virologic surveillance data to determine the epidemic start to peak interval among the study sample found that the number of weeks between the epidemic start and epidemic peak ranged from 4 weeks to 11 weeks. The mean and mode number of weeks between epidemic start and epidemic peak was 7. Upon classification, 3 seasons were identified as having short epidemic start to peak intervals, 7 seasons were identified as having average epidemic start to peak intervals, and 3 seasons were identified as having long epidemic start to peak intervals. Selected surveillance characteristics of the influenza epidemics included in the study are shown in Table 3. Both short and long epidemic start to peak interval seasons had a lower mean maximum percent positive compared to average epidemic start to peak interval seasons, with a 0.5 percentage point decrease and a 4.6 percentage point decrease respectively. Short epidemic start to peak interval seasons were similar to average epidemic start to peak interval seasons in mean number of P&I deaths, while long epidemic start to peak interval seasons had an 8.26% decrease in mean number of P&I deaths compared to average epidemic start to peak interval seasons. Short epidemic start to peak interval seasons were similar to average epidemic start to peak interval seasons in mean P&I mortality rate, while long epidemic start to peak interval seasons had a 9.95% decrease in mean P&I mortality rate compared to average epidemic start to peak interval seasons.

The study sample was evaluated for agreement in epidemic start and epidemic peak timing classification. Ten of the thirteen seasons (76.9%) had agreement in timing classification of early, average, or late by both epidemic start and epidemic peak definitions. A Pearson's

Correlation test demonstrated strong correlation of epidemic start classification with epidemic peak classification at a correlation value of 0.83. Classification of epidemic start to peak interval was not independently correlated with classification of epidemic start or classification of epidemic peak at correlation values of 0.00 and 0.43 respectively.

The three epidemic timing metrics of epidemic start, epidemic peak, and epidemic start to peak interval were individually evaluated with an unadjusted Poisson regression model for association with P&I associated mortality. Crude rate ratios across all epidemic timing metrics found weak associations of epidemic timing classification with P&I associated mortality. Epidemic start timing demonstrated a statistically significant decreased rate of P&I associated mortality for early and late epidemic start seasons compared to average epidemic start seasons ($RR_{EarlyStart}$=0.98 95% CI=0.97, 0.98) ($RR_{LateStart}$=0.97 95% CI= 0.97, 0.97). Epidemic peak timing demonstrated a statistically significant 2% increase in P&I associated mortality rate for early epidemic peak seasons compared to average epidemic peak seasons ($RR_{EarlyPeak}$=1.02 95% CI= 1.01, 1.02). Late epidemic peak seasons demonstrated a statistically significant 4% decrease in P&I associated mortality rate compared to average epidemic peak seasons ($RR_{LatePeak}$=0.96 95% CI=0.95, 0.96). Epidemic start to peak interval timing demonstrated a statistically significant 2% increase in P&I associated mortality rate for short epidemic start to peak intervals seasons compared to average epidemic start to peak interval seasons ($RR_{ShortInterval}$=1.02 95% CI=1.00, 1.02). Long epidemic start to peak interval seasons demonstrated a statistically significant 10% decrease in P&I mortality rate compared to average epidemic start to peak interval seasons ($RR_{LongInterval}$=0.90 95% CI=0.90, 0.91).

Previous studies on influenza have identified and described the association of predominant influenza A subtype circulating with deaths due to influenza. Poisson regression adjusted for predominant influenza A subtype was used to independently evaluate the three epidemic timing metrics for association with P&I associated mortality. Early epidemic start seasons had a statistically significant 3% increase in P&I associated mortality rate compared to average epidemic start seasons ($RR_{EarlyStart}$ =1.03 95% CI=1.03, 1.04). Late epidemic start seasons had a statistically significant 2% decrease in P&I associated mortality rate compared to average epidemic start seasons ($RR_{LateStart}$=0.98 95% CI=0.98, 0.99). Early epidemic peak seasons had a statistically significant 10% increase in P&I associated mortality rate compared to average epidemic peak seasons ($RR_{EarlyPeak}$=1.10 95% CI=1.09, 1.11). Late epidemic peak seasons had a statistically significant 2% decrease in P&I associated mortality rate compared to average epidemic peak seasons ($RR_{LatePeak}$=0.98 95% CI=0.98, 0.99). Epidemic start to peak interval demonstrated the strongest effect measures for both short epidemic start to peak interval seasons and long epidemic start to peak interval seasons. Short epidemic start to peak interval seasons had a statistically significant 10% increase in P&I associated mortality rate compared to average epidemic start to peak interval seasons ($RR_{ShortInterval}$=1.10 95% CI=1.10, 1.11). Long epidemic start to peak interval seasons had a statistically significant 10% decrease in P&I associated mortality rate compared to average epidemic start to peak interval seasons ($RR_{LongInterval}$ =0.90 95% CI=0.90, 0.91).

DISCUSSION

The mean and mode MMWR week for epidemic start among the study sample was week 50 and 51. Those MMWR weeks correspond to dates in mid to late-December, supporting the timing of influenza season start previously described in literature (5). Seasons in which the influenza epidemic started prior to mid-December were classified as early, while seasons in which the influenza epidemic started after January were classified as late. The mean and mode MMWR week for epidemic peak among the study sample was week 5 and 6. Those MMWR weeks correspond to dates in late-January and mid-February, supporting the timing of influenza season peak previously described in literature (2). Seasons in which the influenza epidemic peaked prior to late-January were classified as early, while seasons in which the influenza epidemic peaked after late-February were classified as late (2).

The results of epidemic start and epidemic peak timing classification provided a picture of influenza epidemics in the United States. The strong Pearson's correlation between epidemic start classification and epidemic peak classification suggest that United States influenza seasons demonstrate a consistency in interval from start of an epidemic to the peak of an epidemic. The timing classification results add support to the observation that the United States influenza seasons from 1999-2014 can be appropriately described by a traditional epidemic curve (5). Thus, early epidemic starts should be correlated with early epidemic peaks, with similar agreements for both average timed epidemics and late timed epidemics.

Epidemic start to peak interval provides an indication of how long in weeks influenza infection incidence was increasing before the epidemic reached its peak. The number of weeks from epidemic start to epidemic peak for each season in the study sample was identified. The mean

and mode number of weeks identified for epidemic start to peak interval was 7. Considering the entire duration of influenza epidemics is described as 13 weeks in previous studies, the value for epidemic start to peak interval found in this study could serve as a surrogate variable for epidemic duration (18). Thus, influenza seasons in which the epidemic start to peak interval is less than 5 weeks were classified as short, while influenza seasons in which the epidemic start to peak interval is greater than 7 weeks were classified as long. There was no correlation of epidemic start to peak interval classification with either epidemic start classification or epidemic peak classification. The lack of correlation would be expected, as the length of an influenza epidemic is not dependent on whether influenza seasons start early, average, or late, or whether influenza seasons peak early, average, or late (5).

The developed timing classifications for epidemic start, epidemic peak, and epidemic start to peak interval were used to evaluate the potential association between epidemic timing classification and P&I associated mortality through an adjusted Poisson regression model. The results of the adjusted Poisson regression model supported the proposed hypothesis that early or short influenza seasons were associated with increased mortality. Although epidemic start and epidemic peak illustrated an effect on mortality rate, neither had a strong association for both early and late season classification compared to average season classification. Epidemic start to peak interval demonstrated a stronger association with P&I associated mortality for both short epidemic start to peak interval seasons and long epidemic start to peak interval seasons compared to average epidemic start to peak interval seasons.

Epidemic start classification had a weak association with P&I associated mortality. Early epidemic start seasons had a rate ratio of 1.03 compared to average epidemic start seasons.

Late epidemic start seasons had a rate ratio 0.98 compared to average epidemic start seasons. Compared to the most recent average epidemic start season in this study, 2006-2007, an influenza season which started early would indicate a 3% increase in mortality rate yielding 1,658 more deaths, and an influenza season which started late would indicate a 2% decrease in mortality rate yielding 1,014 fewer deaths. These increases and decreases in mortality associated with early epidemic start seasons and late epidemic start seasons respectively, are small in comparison to the 53,414 deaths recorded the 2006-2007 season. This suggests that epidemic start timing classification may not be a valuable indicator of influenza-associated mortality.

Epidemic peak classification also demonstrated a weak association with P&I associated mortality. Early epidemic peak seasons had a rate ratio of 1.10 compared to average epidemic peak seasons. Late epidemic peak seasons had a rate ratio 0.98 compared to average epidemic peak seasons. Compared to the most recent average epidemic peak season in this study, 2010-2011, an influenza season which peaked early would indicate a 10% increase in mortality rate yielding 5,442 more deaths, and an influenza season which peaked late would indicate a 2% decrease in mortality rate yielding 200 fewer deaths. Although early epidemic peak classification was associated with a large increase in mortality, late epidemic peak classification was associated with a small decrease in mortality compared to the 54,402 deaths recorded for the 2010-2011 season. This suggests that epidemic peak timing classification may not be a valuable indicator of influenza-associated mortality.

Epidemic start to peak interval classification demonstrated the strongest association with P&I associated mortality. Short epidemic start to peak interval seasons had a rate ratio of 1.10

compared to average epidemic start to peak interval seasons. Long epidemic start to peak interval seasons had a rate ratio of 0.90 compared to average epidemic start to peak interval seasons. Compared to the most recent average epidemic start to peak interval season in this study, 2012-2013, a short influenza season would indicate a 10% increase in mortality rate yielding 5,768 more deaths, and a long influenza season would indicate a 10% decrease in mortality rate yielding 5,789 fewer deaths. These increases and decreases in mortality associated with short influenza seasons and long influenza seasons respectively, are large in comparison to the 57,799 deaths recorded for the 2012-2013 season. This suggests that epidemic start to peak interval timing classification may be a valuable indicator of influenza-associated mortality.

The findings from this study demonstrate that influenza seasons which deviate from the average epidemic start to peak interval value, identified as 6-7 weeks, indicate whether there will be excess or fewer P&I associated deaths for the season. Epidemic start to peak interval classification may indicate the magnitude of mortality for the season, but by the time influenza seasons can be classified as short, average, or long according to the epidemic start to peak interval guidelines developed in this study, the time for intervention has passed. Further studies should evaluate the underlying mechanisms of this association between epidemic start to peak interval classification and P&I associated mortality to identify an earlier predictor of influenza-associated mortality.

STRENGTHS AND LIMITATIONS

The association of epidemic start, epidemic peak, and epidemic start to peak interval with P&I associated mortality rate was evaluated using surveillance data compiled from two Centers for Disease Control reporting systems. These systems, WHO/NREVSS Collaborating Laboratories, and National Center for Health Statistics, each continue to evolve to improve timeliness and accuracy in monitoring of influenza activity. Although internally validated, the data received by these systems are susceptible to a lack of standardized methods of collection, and variability in reporting volumes from laboratories (8). This variability could introduce bias when comparing total number of influenza isolates identified among seasons. Considering percent of specimens testing positive was used to determine epidemic start and epidemic peak, this study would not be biased by increased testing frequency of reporting laboratories. The exposure variables of epidemic start, epidemic peak, and epidemic start to peak interval were additionally identified using virologic surveillance data, which is not as sensitive to population behavior, unlike ILI incidence data used in previous studies.

The outcome of mortality due to influenza is difficult to measure, as *International Classification of Diseases* code standards have changed. Frequency of laboratory confirmation of influenza infection is also increasing, which could impact the potential for influenza diagnoses to be included within death certificate data (16, 17). This study used P&I associated mortality as a proxy for deaths due to influenza, as is strongly correlated with influenza-associated mortality (16). The use of P&I associated mortality is not as sensitive to the influence of laboratory confirmation on cause of death reporting.

A limitation of this study was the absence of additional literature on classifying the timing of influenza seasons. The results of this study could not be compared to the findings of previous studies. Additionally, this study was limited by incomplete surveillance data including both virologic results and P&I associated mortality data needed for Poisson regression. This limited the sample size to 13 seasons. Increasing the size of the sample would have an impact on the classification guidelines for early, average, and late seasons for epidemic start and epidemic peak timing. A larger sample size would also provide more data to determine the epidemic start to peak interval classification guidelines for short, average, and long seasons.

FUTURE DIRECTIONS

The reasons for the association between epidemic start to peak interval classification and P&I associated mortality are unclear. Continued research is needed to evaluate factors mechanizing this association. Understanding the mechanism facilitating the increased mortality indicated by short influenza seasons could potentially identify an earlier predictor of excess mortality. If the magnitude of mortality due to influenza could be predicted, this insight could inform public health stakeholders to tailor prevention efforts through targeted vaccine campaigns and encourage increased utilization of antivirals by clinical stakeholders.

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TABLES

Table 1. Influenza Timing Metrics for this Cross-Sectional Study

Metric	Definition	Classification Guidelines
Epidemic Start:	MMWR week when percent of specimens positive for influenza exceeds or equals the epidemic threshold of 10% for the season	Early: occurs prior to MMWR week 48 Average: occurs during MMWR week 49-52 Late: occurs after MMWR week 52
Epidemic Peak:	MMWR week when percent of specimens positive for influenza reaches the maximum value for the season	Early: occurs prior to MMWR week 52 Average: occurs during MMWR week 53-6 Late: occurs after MMWR week 6
Epidemic Start to Peak Interval:	Number of weeks between the epidemic start MMWR week and the epidemic peak MMWR week for the season	Short: length of 5 weeks or less Average: length of 6-7 weeks Long: length of 8 weeks or more

Table 2. Epidemic Start, Epidemic Peak, and Epidemic Start to Peak Interval Classification of United States Influenza Seasons from 1999-2014

Season	Epidemic Start[1] MMWR Week	Start Timing Classification	Epidemic Peak[2] MMWR Week	Peak Timing Classification	Epidemic Start to Peak Interval[3] in Weeks	Start to Peak Interval Classification
1999-00	47	Early	51	Early	5	Short
2000-01	51	Average	4	Average	6	Average
2001-02	2	Late	8	Late	7	Average
2002-03	3	Late	6	Average	4	Short
2003-04	42	Early	48	Early	7	Average
2004-05	51	Average	5	Average	7	Average
2005-06	51	Average	9	Late	11	Long
2006-07	51	Average	6	Average	8	Long
2007-08	2	Late	7	Late	6	Average
2010-11	47	Early	5	Average	11	Long
2011-12	5	Late	11	Late	7	Average
2012-13	46	Early	52	Early	7	Average
2013-14	48	Early	52	Early	5	Short

[1] Epidemic start classified by MMWR week when percent positive for influenza exceeds or equals 10% for the season

[2] Epidemic peak classified by MMWR week when percent positive for influenza reaches the maximum value for the season

[3] Epidemic start to peak interval classified by number of weeks between epidemic start and epidemic peak for the season

Table 3. Selected Surveillance Characteristics of United States Influenza Seasons from 1999-2014

			Maximum Percent Positive	Dominant Influenza A Subtype			Number of Deaths[4]	Mortality Rate[5]
				H3N2	H1N1	H1N1pdm09		
All Influenza Seasons		(n=13)	29.8 (4.5)	9 (69.2%)	3 (23.1%)	1 (7.7%)	58,869.3 (5,350.3)	19.7 (2.5)
Epidemic Start[1]	Early Start	(n=5)	32.0 (4.7)	4 (80.0%)	0 (0.0%)	1 (20.0%)	59,539.8 (5,744.2)	19.7 (3.0)
	Late Start	(n=4)	28.5 (3.3)	3 (75.0%)	1 (25.0%)	0 (0.0%)	58,033.5 (7,012.0)	19.5 (3.1)
	Average Start	(n=4)	25.2 (2.7)	2 (50.0%)	2 (50.0%)	0 (0.0%)	58,867.0 (4,433.7)	20.0 (1.9)
Epidemic Peak[2]	Early Peak	(n=4)	33.7 (3.3)	3 (75.0%)	0 (0.0%)	1 (25.0%)	60,824.3 (5,744.2)	20.3 (3.1)
	Late Peak	(n=4)	27.5 (4.5)	0 (0.0%)	0 (0.0%)	4 (100.0%)	57,071.3 (6,747.9)	19.0 (2.9)
	Average Peak	(n=5)	26.0 (1.9)	2 (40.0%)	3 (60.0%)	0 (0.0%)	58,743.8 (4,472.8)	19.9 (2.1)
Epidemic Start to Peak Interval[3]	Short Interval	(n=3)	29.5 (2.7)	1 (33.4%)	1 (33.4%)	1 (33.4%)	60,314.7 (5,796.8)	20.5 (3.2)
	Long Interval	(n=3)	25.4 (2.8)	2 (66.7%)	1 (33.4%)	0 (0.0%)	54,971.0 (1,906.3)	18.1 (0.9)
	Average Interval	(n=7)	30.0 (5.3)	6 (85.7%)	1 (14.4%)	0 (0.0%)	59,920.6 (5,908.1)	20.1 (2.7)

Note: Some percentages do not add up to 100% because of rounding. Continuous variables presented as mean (SD) and categorical variables as frequency (%)

[1] Epidemic start classified by MMWR week when percent positive for influenza exceeds or equals 10% for the season

[2] Epidemic peak classified by MMWR week when percent positive for influenza reaches the maximum value for the season

[3] Epidemic start to peak interval classified by number of weeks between epidemic start and epidemic peak for the season

[4] P&I associated mortality identified by ICD-10 codes (J09-18)

[5] P&I associated mortality rate per 100,000 population

Table 4. Crude Poisson Regression of Epidemic Timing Metrics with P&I Associated Mortality of United States Influenza Seasons from 1999-2014[1]

Epidemic Timing Metrics	Univariable Analysis[2]	95% CI[3]
Epidemic Start Timing[4]		
Average Start	1.00	Ref
Early Start	0.98	0.97, 0.98
Late Start	0.97	0.97, 0.97
Epidemic Peak Timing[5]		
Average Peak	1.00	Ref
Early Peak	1.02	1.01, 1.02
Late Peak	0.96	0.95, 0.96
Epidemic Start to Peak Interval Timing[6]		
Average Interval	1.00	Ref
Short Interval	1.02	1.00, 1.02
Long Interval	0.90	0.90, 0.91

[1] P&I associated mortality identified by ICD-10 codes (J09-18)
[2] Unadjusted Poisson regression rate ratio
[3] Abbreviation for confidence interval
[4] Epidemic start classified by MMWR week when percent positive for influenza exceeds or equals 10% for the season
[5] Epidemic peak classified by MMWR week when percent positive for influenza reaches the maximum value for the season
[6] Epidemic start to peak interval classified by number of weeks between epidemic start and epidemic peak for the season

Table 5. Adjusted Poisson Regression of Epidemic Timing Metrics with P&I Associated Mortality of United States Influenza Seasons from 1999-2014[1]

Epidemic Timing Metrics	Multivariable Analysis[2]	95% CI[3]
Epidemic Start Timing[4]		
Average Start	1.00	Ref
Early Start	1.03	1.03, 1.04
Late Start	0.98	0.98, 0.99
Epidemic Peak Timing[5]		
Average Peak	1.00	Ref
Early Peak	1.10	1.09, 1.11
Late Peak	0.98	0.98, 0.99
Epidemic Start to Peak Interval Timing[6]		
Average Interval	1.00	Ref
Short Interval	1.10	1.10, 1.11
Long Interval	0.90	0.90, 0.91

[1] P&I associated mortality identified by ICD-10 codes (J09-18)
[2] Adjusted Poisson regression rate ratio
[3] Abbreviation for confidence interval
[4] Epidemic start classified by MMWR week when percent positive for influenza exceeds or equals 10% for the season
[5] Epidemic peak classified by MMWR week when percent positive for influenza reaches the maximum value for the season
[6] Epidemic start to peak interval classified by number of weeks between epidemic start and epidemic peak for the season