Influenza and the Winter Increase in Mortality in the United States, 1959–1999

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In economically developed countries, mortality increases distinctly during winter. Many causes have been suggested, including light-dark cycles, temperature/weather, and infectious agents. The authors analyzed monthly mortality in the United States during the period 1959–1999 for four major disease classes. The authors isolated the seasonal component of mortality by removing trends and standardizing the time series. They evaluated four properties: coincidence in mortality peaks, autocorrelation structure and autoregressive integrated moving average (ARIMA) models, magnitude, and age distribution. Peak months of mortality for ischemic heart disease, cerebrovascular disease, and diabetes mellitus coincided appropriately with peaks in pneumonia and influenza, and coefficients of autocorrelation and ARIMA models were essentially indistinguishable. The magnitude of the seasonal component was highly correlated with traditional measures of excess mortality and was significantly larger in seasons dominated by influenza A(H2N2) and A(H3N2) viruses than in seasons dominated by A(H1N1) or B viruses. There was an age shift in mortality during and after the 1968/69 pandemic in each disease class, with features specific to influenza A(H3N2). These findings suggest that the cause of the winter increase in US mortality is singular and probably influenza. Weather and other factors may determine the timing and modulate the magnitude of the winter-season increase in mortality, but the primary determinant appears to be the influenza virus.

age distribution; cause of death; influenza; models, statistical; mortality; respiratory tract infections; seasons

Abbreviations: ARIMA, autoregressive integrated moving average; ZLS, *z*-like score.

In developed countries with temperate climates, mortality incidence is highest during the winter months (1, 2). Defined as the number of deaths above the summer trough, the winter increase in mortality is substantial, spanning several months and accounting for 3–18 percent of total annual mortality (1, 3–5). Monthly mortality attributed to respiratory, cardiovascular, and cerebrovascular disease and monthly mortality due to all causes have been noted to have similar patterns (5–11). As early as 1932, Collins noted that excess mortality due to causes other than pneumonia and influenza had the same time distribution and "must in some way be related to the epidemic" (6, p. 2174). Historically, a significant portion of the winter increase in pneumonia and influenza deaths has been attributed to influenza epidemics, and the US Centers for Disease Control and Prevention has used weekly reports of pneumonia and influenza mortality from 122 US cities to help gauge the timing and severity of the impact of annual epidemics (12). In addition, the total impact of influenza epidemics on mortality has traditionally been estimated as the winter increase in mortality due to all causes (excess all-cause mortality) relative to a baseline of usual expected mortality estimated in various ways (13–17).

Other explanations have been offered to explain seasonal variations in mortality. Some investigators have concluded

that the variations are principally the result of a lack of microclimate control (2) and that trends in seasonal mortality in specific disease classes such as cardiovascular disease are associated with improved microclimate control (18, 19). Others have concluded that most of the increase in winter-season mortality results from an inverse relation of mortality with temperature, with only a small fraction being attributable to influenza (20); that mortality increases follow abrupt changes in temperature (21); or that variations in the duration of sunlight affect human immunocompetence (22).

Several years ago, investigators in the United Kingdom demonstrated a close relation between excursions in winter-season mortality and clinical reports of influenza-like illness that was independent of the effect of temperature (23). Others later argued that sizable portions of winter-season excess mortality should be attributed to epidemics of other respiratory pathogens (e.g., respiratory syncytial virus (24, 25)), and recently an attempt was made to include both respiratory syncytial virus and influenza in a model of excess mortality (26).

While excess all-cause mortality is generally accepted as a measure of influenza impact, no study has provided evidence that excess mortality in disease classes other than pneumonia is actually explained by influenza. We asked whether an approach free of ad hoc assumptions might reconcile these varying impressions and possibly provide new insight. To formally evaluate the occurrence and cause of winter excess mortality, we studied mortality patterns for major disease classes in the United States over a period of 40 years. We gave special attention to relations with influenza.

MATERIALS AND METHODS

Data sources: disease and age groups

From tabulations of underlying causes of death in the United States from 1959 through 1999 (unpublished data from National Center for Health Statistics public-use data files), we extracted monthly numbers of deaths due to all causes and deaths attributed to pneumonia, influenza, ischemic heart disease, cerebrovascular disease, diabetes mellitus, and cancer. We chose these disease classes because they constituted a substantial portion of all mortality (~60 percent in 1990), and coding for these disease classes was reasonably consistent throughout the study period. Details on the *International Classification of Diseases* codes used, their limitations, and our adjustments to these limitations are provided in the Appendix. We used US Census data to generate mortality rates that we adjusted to a 30.4-day month and to the age distribution of the 1970 US population, for two age groups: <75 years and ≥75 years. Reports of laboratory-based influenza virus surveillance from the Centers for Disease Control and Prevention were used to determine the influenza virus subtype dominant in circulation for all winter seasons.

Statistical approach

To assess the degree of similarity of seasonal components of mortality over time, we examined four properties in each

disease class over the study period: 1) coincidence in time of peak mortality, 2) time series properties, 3) magnitude, and 4) the age distribution of the seasonal component. We specifically considered differences related to the circulation of different subtypes of influenza viruses and focused on changes associated with the 1968/69 influenza A(H3N2) pandemic.

A common scale for mortality, the *z*-like score

To directly compare seasonal mortality attributed to different diseases, it was necessary to remove long-term trends from the mortality time series and to account for differences in variation. We characterized the underlying trend using the moving average of mortality for the 13-month periods centered on each month, and we removed that trend by subtracting the moving average from the observed or adjusted mortality for each disease class and month. We chose a 13-month moving average centered on the month of interest because this period would be unaffected by preceding or following epidemics. A moving average functions as a crude low-frequency-pass filter, capturing the effects of variation with a frequency lower than the reciprocal of the averaging interval—in this case, trends longer than 1 year (27). For this reason, it was important that we taper the rectangular window for the moving average to protect against the introduction of filter artifacts. We used a Hamming data window for this purpose (28). In this procedure, each mortality value included in the moving average was multiplied by a coefficient, and the sum was divided by the sum of the coefficients. The window coefficients are shown in the Appendix. By taking the difference between the observed or age-adjusted mortality and the windowed moving average associated with that observation, we removed long-term trends and isolated the within-year portion of the observed mortality. We standardized the variation in the within-year portion of the observed mortality by dividing this difference by the standard deviation of this difference over all study years. The result was a time series for each disease class that had a mean value of zero and a standard deviation of 1. The form of this calculation was similar to that for the *z* score in basic statistics (29). Therefore, we called this process "*z*-like scaling" and called the result the *z*-like score (ZLS). We transformed mortality data into ZLS curves for each disease class and all-cause mortality.

The ZLS could be interpreted as the difference between the observed mortality and a "natural" baseline, the trend estimated from the data for the 6 months preceding and following each data point. This is analogous to the traditional process that has been used to estimate excess mortality, in which a baseline of normal or usual seasonal mortality particular to each time, place, and disease class is subtracted from observed mortality. Serfling-type models of excess mortality utilize a polynomial in time and a single sinusoid together with the data from a number of years to estimate a baseline (14, 16). We determined the extent to which the ZLS measured excess mortality by comparing the sum of ZLS values that were positive during the winter months with

seasonal excess mortality estimates for pneumonia and influenza generated by a Serfling-type regression model (30).

Coincidence in the time of peak mortality

We identified the peak month in each season in the ZLS curve for each disease class and compared that month with the month of the peak in pneumonia and influenza deaths. We summarized the offsets (lead/lag) in peak occurrence for each disease class relative to pneumonia and influenza over the 40-year period.

Statistical (time series) properties of the seasonal component

Mortality patterns for individual disease classes might appear to be similar if each has underlying stochastic processes with similar statistical properties, and if special alignment conditions are present. To examine this possibility, we calculated the coefficients of the autocorrelation and partial autocorrelation functions for all time lags—that is, all shifts in time of each series relative to itself. We also fitted an autoregressive integrated moving average (ARIMA) model to each disease ZLS curve (31). The ARIMA model coefficients for the ZLS curves for each disease class were compared with all others. In addition, the ARIMA model was subtracted from each ZLS curve, and the residuals were compared (32).

Magnitude of the seasonal component of mortality

We determined the positive area under the ZLS curve (designated ZLS_{pa}) for pneumonia and influenza for each season and correlated this quantity with excess mortality determined using a Serfling model. During the winter seasons of the 1990s, annual mean numbers of deaths were greatest for influenza A(H3N2) viruses, intermediate for influenza B viruses, and lowest for influenza A(H1N1) viruses (26). This same order has been used as the basis for an index of severity for seasonal mortality spanning 22 seasons (17). Accordingly, we tabulated ZLS_{pa} values separately by dominant influenza virus subtype. For winter seasons from 1959/60 to 1980/81, the dominant subtype was selected on the basis of a primary analysis of excess mortality (33, table A.1.13; 34). For seasons after 1976, the dominant subtype was that named as responsible for more than 50 percent of typed influenza isolates in the relevant *Morbidity and Mortality Weekly Report* articles on influenza surveillance for that season. An exception was the 1985/86 season, when an influenza B virus was isolated from the majority of samples. However, most isolates taken from elderly persons were A(H3N2) viruses, and most of the influenza-related mortality occurred in this group (35). Since our analysis focused on mortality, the 1985/86 season was classified as A(H3N2)-dominant.

Age distribution of the seasonal component

The age distribution of excess pneumonia and influenza mortality changed dramatically during the 1968/69 pandemic and during the first decade of A(H3N2) circulation (36). We characterized the age distribution of the seasonal component of mortality by determining ZLS_{pa} values for age-standardized mortality for pneumonia and influenza, ischemic heart disease, cerebrovascular disease, diabetes, and all causes for two age groups: <75 years and ≥75 years. We converted each ZLS_{pa} value to an excess mortality estimate by multiplying the seasonal ZLS_{pa} by the standard deviation of the difference between monthly mortality and the 13-month Hamming-windowed moving average computed over the study period. We then calculated the proportion of mortality that occurred among persons under 75 years of age for each season and disease class.

RESULTS

Plots of the numbers of deaths reported monthly for each disease class revealed distinct annual cycles (figure 1). The midwinter peaks for pneumonia and influenza, ischemic heart disease, cerebrovascular disease, and diabetes varied in size and differed widely in terms of both mean value and seasonal variation. Cancer mortality showed little monthly variation, and we did not include this disease class in further analyses. Figure 2 shows the age-adjusted ZLS curves for the four disease classes, as well as the numbers of deaths attributed to influenza (by death certificate), for the 40-year period. The shift-and-scale operation that produced the *z*-like scores converted the distinct mortality curves for each disease class shown in figure 1 into essentially the same ZLS curve.

The units of ZLS were the number of standard deviations by which the mortality for that month differed from the time-local average. Each standard deviation unit corresponded (in units of deaths/100,000 persons) to 2.994 for all-cause mortality, 1.094 for ischemic heart disease, 0.335 for cerebrovascular disease, 0.077 for diabetes, and 0.587 for pneumonia and influenza. The sum of positive ZLS values for each season, ZLS_{pa}, for deaths attributed to pneumonia and influenza correlated well with Serfling model estimates of excess pneumonia and influenza mortality, an accepted measure of influenza activity (figure 3; $r^2 = 0.90$). The sinusoidal baseline assumed for the Serfling model varied as the logarithm of the average mortality for that season, whereas the Hamming-windowed moving average (the ZLS baseline) tracked the peak size much more closely (figure 4).

Coincidence in the time of peak mortality

The peak months in the ZLS curve for pneumonia and influenza coincided with those for ischemic heart disease 34 of 40 times, for cerebrovascular disease 33 of 40 times, and for diabetes 34 of 40 times. When misaligned, the pneumonia and influenza peak always occurred 1 month later than the peak in other disease mortality.

Statistical (time series) properties of the seasonal component

We computed the partial autocorrelation coefficients for the ZLS curves for each disease class for all time lags. For a
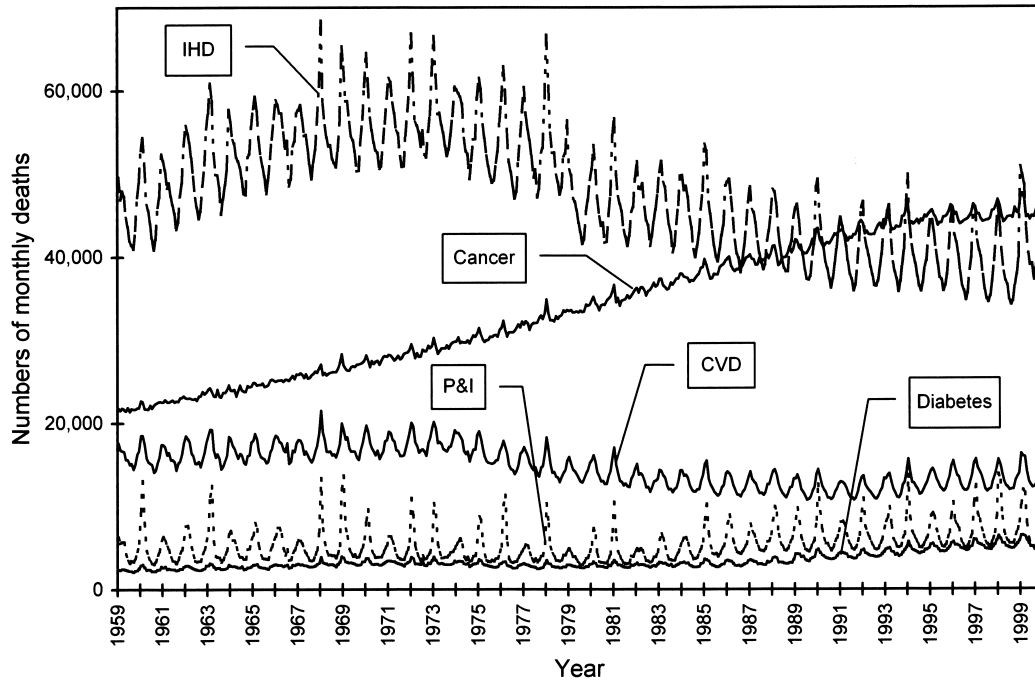
FIGURE 1. Monthly numbers of deaths attributed to five classes of disease in the United States during the period 1959–1999. Numbers of deaths for the individual disease classes differed greatly, and deaths in all classes except cancer showed regular increases during the winter season. IHD, ischemic heart disease; P&I, pneumonia and influenza; CVD, cerebrovascular disease.

lag of one time unit, the values estimated for all partial autocorrelation coefficients lay within the 95 percent confidence intervals estimated for the coefficients for every disease class. This was also true for lags greater than 1 for all disease classes except pneumonia and influenza (data not presented). The fits for ARIMA models of the ZLS curves for all disease classes were good, with small residuals that were symmetrically distributed about zero. Correlations of the residuals for all ARIMA models were null for all time lags, except for lag 0, where all disease classes and all-cause mortality were significantly correlated (data not presented). The 95 percent confidence intervals for ARIMA model coefficients overlapped for all disease classes except pneumonia and influenza. The coefficients for pneumonia and influenza lay only slightly outside of the mutual band. We observed that at each seasonal peak in figure 2, the pneumonia and influenza value was almost always the largest. These peak excursions were analytical outliers. When the ZLS series were each subjected to a standard process of outlier removal (37), we observed the following for all disease classes and for all-cause mortality: 1) the autocorrelation functions became approximately sinusoidal; 2) the partial autocorrelation coefficients became indistinguishable and took on values approximating zero for all lags greater than 2; 3) the fit of the ARIMA models improved to excellent—that is, residuals remained symmetric about zero and were reduced a log order in

magnitude; and 4) both ARIMA coefficients became nearly identical. Essentially one model emerged. It seems reasonable to conclude that the process underlying the seasonal component of mortality attributed to these disease classes was the same (38).

**Magnitude of the seasonal component of mortality**

The tallest peaks in the ZLS curves for all disease classes studied occurred during the influenza A(H3N2) pandemic season, 1968/69, and in the most severe epidemic seasons (figure 2). Both ZLS_{pa} and the peak amplitude of the ZLS curves were almost always lower in years dominated by influenza A(H1N1) and B viruses and higher in seasons dominated by influenza A(H2N2) or A(H3N2) virus. While the range of excess mortality found in seasons dominated by A(H3N2) viruses strongly overlapped the range found in seasons dominated by A(H2N2) viruses, the combined ranges were quite separate from the ranges of excess mortality found in seasons dominated by A(H1N1) and B viruses. Therefore, we found it useful to label the 40 study seasons as dominated either by the category A(H3N2) and A(H2N2) viruses or the category A(H1N1) and B viruses (figure 5). This categorization correctly sorted 36 of the 40 winter seasons as having high or low excess mortality, with no additional information.
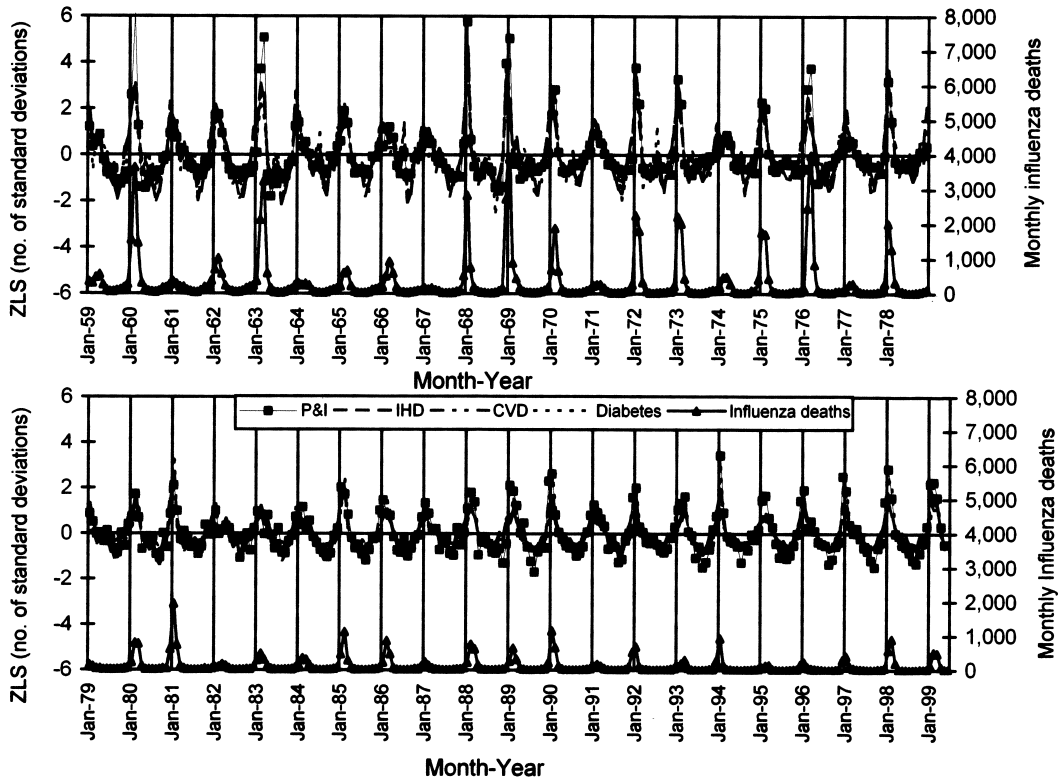
FIGURE 2. Monthly *z*-like score (ZLS) curves for pneumonia and influenza (P&I), ischemic heart disease (IHD), cerebrovascular disease (CVD), and diabetes mellitus in the United States, 1959–1999. The curves very nearly superimpose for all years. The upper panel covers the months January 1959 through December 1978, and the lower panel covers the months January 1979 through July 1999. The units on the *y*-axes of both panels are standard deviations. The peak ZLS values for P&I mortality (solid squares) were more positive than those of other disease classes during seasons with pandemic influenza (1968/69) and severe influenza epidemics. The monthly numbers of deaths attributed to influenza by death certificates (solid triangles) are plotted against the right-hand scale of each panel.

$$ZLS_{pa} = 0.461 \times \text{Serfling} + 2345.2$$
$$R^2 = 0.904$$
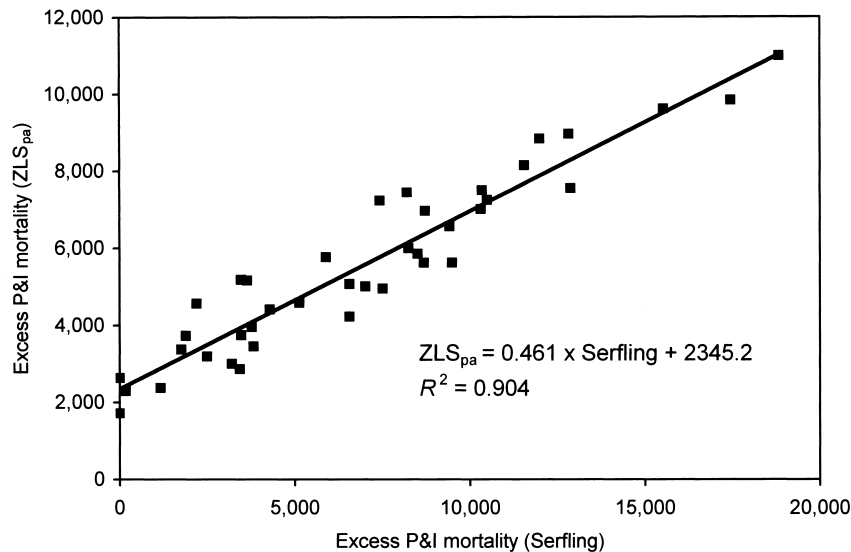
FIGURE 3. Correlation between excess pneumonia and influenza (P&I) mortality (number of deaths per 100,000 population) for each season estimated using a Serfling-type model and an estimate obtained using the *z*-like score (ZLS) method, United States, 1959–1999. ZLS$_{pa}$, ZLS-positive area.
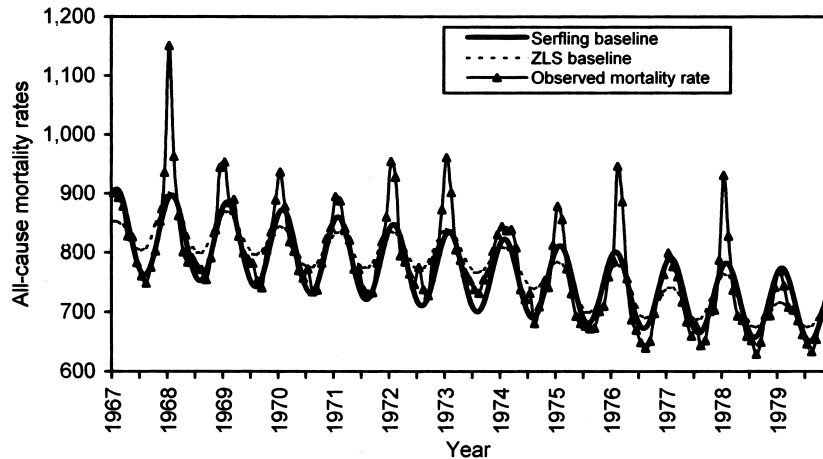
FIGURE 4. Monthly rates of all-cause mortality (number of deaths per 100,000 age-specific population) for the US population aged ≥75 years for the period 1967–1979. The Serfling model baseline was the overall best fit to the data from all nonwinter months, and it assumed a sinusoidal shape. The z-like score (ZLS) baseline was computed as the Hamming window-weighted average of the mortality for the 13-month period centered on each monthly data point.

Age distribution of the seasonal component

In pandemic years, the age distribution of excess mortality is known to shift toward younger age groups, and it remains shifted for several years thereafter (36). Figure 6 shows that for both Serfling estimates (top panel) and ZLS_{pa} (bottom panel), there were similar increases in the proportion of excess pneumonia and influenza mortality that occurred in the younger age group (<75 years) during the 1968/69 pandemic year. The magnitude of the age shift decreased steadily until 1975/76, after which time the age shift appeared to be independent of the circulating influenza virus type, although it continued to move toward older age groups.
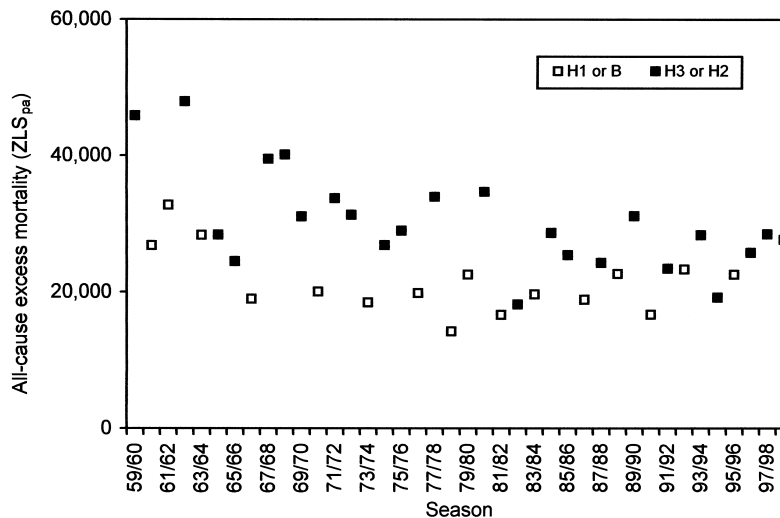
FIGURE 5. Excess all-cause mortality estimated using the z-like score (ZLS) method, United States, 1959–1999. Mortality data were adjusted to the age distribution of the US population in 1970. Influenza A(H2N2) viruses circulated prior to the 1968/69 season. A(H1N1) viruses circulated only after 1977. Excess mortality estimates for most years that were dominated by either A(H3N2) or A(H2N2) viruses (labeled "H3 or H2") were much greater than those for seasons dominated by either A(H1N1) or B viruses (labeled "H1 or B"). This distinction was less useful after 1978, when A(H3N2), A(H1N1), and B viruses began to co-circulate. Estimates of excess mortality in years dominated by influenza A(H3N2) virus were approximately constant, except for the 1968/69 pandemic year. ZLS_{pa}, ZLS-positive area.
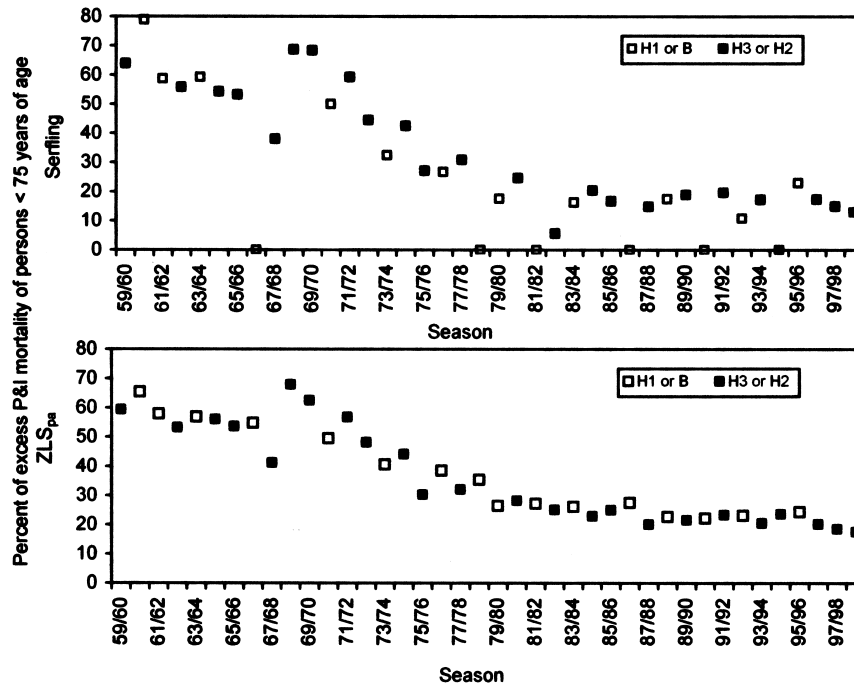
FIGURE 6. Proportion of seasonal excess pneumonia and influenza (P&I) mortality that occurred among persons under 75 years of age as estimated using a Serfling-type model (top panel) and the *z*-like score (ZLS) method (bottom panel), United States, 1959–1999. Mortality data were not adjusted for changes in the age distribution of the population. The shift toward younger ages in the distribution of deaths associated with the A(H3N2) pandemic is evident in both panels. ZLS_{pa}, ZLS-positive area.

Figure 7 shows the proportion of excess mortality (estimated as ZLS_{pa}) that was found in the population under 75 years of age for all causes and the four disease classes. These calculations used mortality data that were age-standardized to the 1970 US population. In the 1968/69 pandemic, the distribution of excess deaths for every disease class shifted toward the younger age group. In the decade that followed, the age distribution shifted back toward prepandemic levels and later to larger fractions in the older age group. The change was greatest for pneumonia and influenza mortality.

DISCUSSION

Summary of our findings

We studied monthly US mortality due to four major diseases and to all causes for the period 1959–1999. We sought to determine whether and to what degree the number and identity of the causes of seasonal winter increases might be specified. We chose a simple method, calculation of the ZLS, to remove long-term trends and to standardize variation in plots of disease-attributed mortality over time. The ZLS values for the seasonal components of mortality attributed to four disease classes were highly similar over a 40-year period. This statistical tool required few assumptions, was simple to use, and was easily applied to situations with a

wide range of complexity in the underlying trend of mortality.

Our work follows an earlier study which found that only a common set of factors, most likely acute respiratory diseases, could explain the high concordance in monthly mortality across four disease classes in four Western European countries over an 8-year period (5). In our study, we considered four disease classes (pneumonia and influenza, ischemic heart disease, cerebrovascular disease, and diabetes) that accounted for 60–70 percent of annual all-cause mortality and approximately 80 percent of excess all-cause mortality during winter seasons. We examined four basic properties of the ZLS curves for mortality attributed to these diseases. Altogether, we believe our findings are compatible with the hypothesis that the cause of winter-season excess mortality is singular and is most likely to be influenza.

Interpretation of the evidence

Property #1. We observed strong but not complete coincidence in the peak mortality for each disease class. In approximately 85 percent of comparisons, the monthly peaks for ischemic heart disease, cerebrovascular disease, and diabetes coincided with the peak for pneumonia and influenza. In seasons in which peak months were discordant, mortality for both classes of vascular disease and diabetes
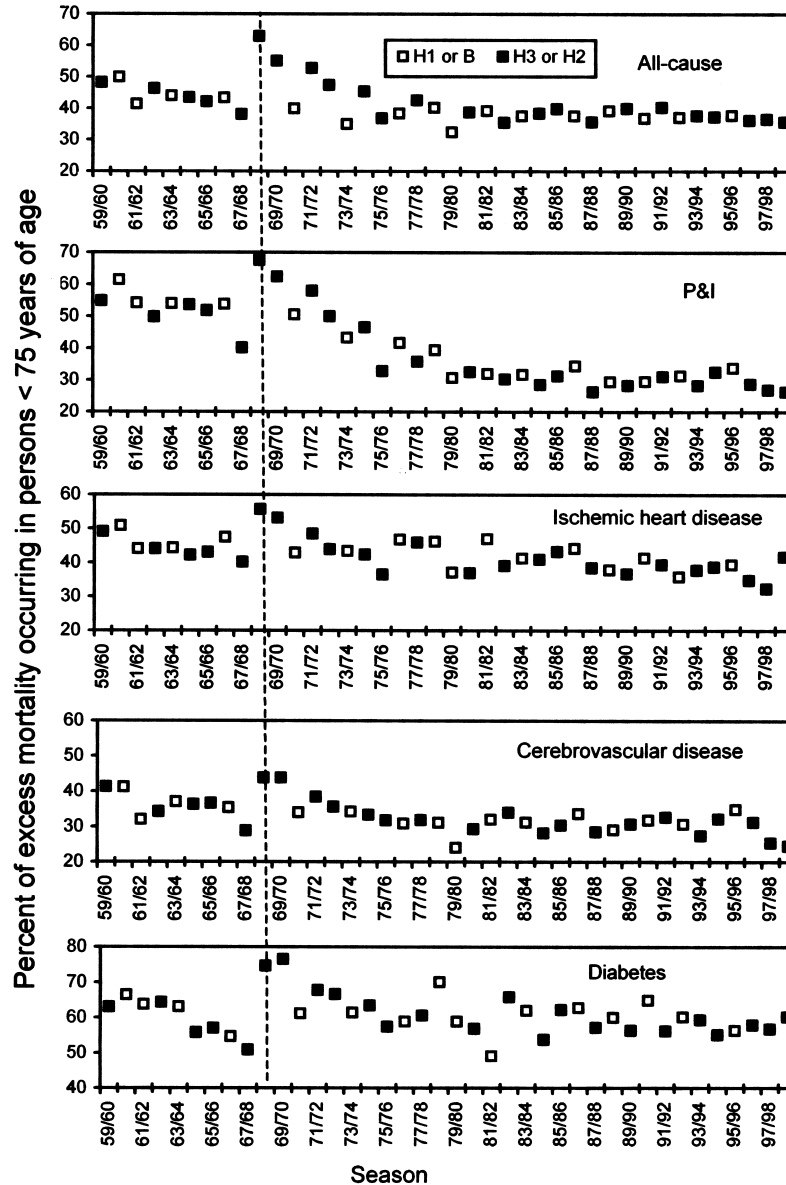
FIGURE 7. Proportion of excess mortality that occurred among persons under 75 years of age for all causes and for four classes of disease as estimated using the z-like score method, United States, 1959–1999. The mortality estimates were standardized to the US population in 1970. The fraction of excess deaths increased among persons under 75 years of age during the influenza A(H3N2) pandemic of 1968/69, and the increase was evident in all disease classes. During the years following the pandemic, the proportion of total excess mortality in this age group decreased for all disease classes (especially pneumonia and influenza (P&I)), and it remained relatively constant after 1980. The 1968/69 pandemic is marked by a vertical dashed line.

peaked 1 month earlier. Given that deaths due to cardiovascular and cerebrovascular disease are often immediate, whereas those attributed to pneumonia and influenza are often delayed (21), the degree of coincidence observed was close to what would be expected if a single factor were responsible for excess mortality in all of these disease classes.

Property #2. Throughout the 40-year study period, the ZLS curves for the four disease classes could be superimposed. Detailed mathematical representations (ARIMA models) of these time series were essentially indistinguishable (data not presented). Therefore, with high likelihood, the process underlying the seasonal component of mortality for these disease classes was the same. Furthermore, equivalent information about the seasonal component of mortality for all disease classes could be acquired from mortality data for any one of them. These findings reinforce the view that the cause of seasonal excess mortality is singular and is either one factor or a group of tightly coupled factors.

Property #3. We observed a strong correlation between the magnitude of the seasonal component of mortality and both the severity and the dominant influenza subtype of each influenza epidemic. The magnitudes of the positive areas under the ZLS curves (ZLS_{pa}) were highly correlated with Serfling-type estimates of the severity of influenza epidemics (figure 3). Moreover, for seasons dominated by influenza A(H2N2) or A(H3N2) viruses, the range of ZLS_{pa} values determined for all-cause mortality was much greater than the range for seasons dominated by A(H1N1) or B viruses (figure 5). This was true for all disease classes (data not shown). These findings imply that the singular cause of winter-season excess mortality must include and be tightly coupled with influenza.

Property #4. A shift in age distribution to younger ages in pandemic seasons and the years following them is another unique characteristic of influenza-attributable deaths (36). In a recent analysis (39), we showed that in the United States, excess pneumonia and influenza and all-cause mortality increased in the first year of the influenza A(H3N2) pandemic (1968/69) and declined over the decade after the pandemic. This pattern was seen in years dominated by influenza A(H3N2) virus and only for persons under 75 years of age (39). In the present study, we demonstrated that the age distribution of the seasonal component of mortality (ZLS_{pa}) exhibited a pandemic shift to younger ages in 1968/69 and a postpandemic drift to older ages in A(H3N2)-dominated seasons that was similar for pneumonia and influenza, ischemic heart disease, cerebrovascular disease, and diabetes (figure 7).

Thus, two independent properties of excess mortality in all of the studied diseases—range of magnitude and the age distribution—were found to be uniquely determined by influenza. We believe this further increases the likelihood that the singular cause of excess winter seasonal mortality is, in fact, influenza.

Several studies have suggested that respiratory pathogens other than influenza viruses, especially respiratory syncytial virus, contribute to the winter increase in mortality (5, 24, 25). Investigators at the Centers for Disease Control and Prevention recently introduced a model that separately estimates mortality attributable to influenza and respiratory syncytial virus infections directly from respiratory virus surveillance reports (26). Their estimates of numbers of deaths related to respiratory syncytial virus were surprisingly constant from year to year, exhibiting less than 10 percent of the variability estimated for influenza-related deaths. An earlier report from the United Kingdom also demonstrated that the numbers and time periods of respiratory syncytial virus isolation were much more constant than were those for influenza viruses (24). To the extent that periods of activity for respiratory syncytial virus and other infectious agents might overlap those for influenza, ZLS_{pa} estimates might include a portion of the mortality due to other such seasonal agents in addition to that due to influenza. However, the portion of mortality that is similar year-to-year should be substantially removed by the Hamming-windowed moving average and therefore subtracted out in the ZLS. Moreover, we know that the contributions of respiratory syncytial virus to the within-year variable component cannot be large, because the impact of respiratory syncytial virus on mortality would not exhibit either the pandemic age shift or the association with dominant influenza subtype demonstrated in ZLS_{pa} estimates. Therefore, the bulk of the contribution that agents like respiratory syncytial virus make to the winter increase in mortality must lie beneath the ZLS baseline.

Several investigators have proposed that temperature, humidity, or some combination of environmental factors is primarily responsible for the winter increase in mortality and that influenza and other respiratory pathogens take opportunistic advantage of these seasonal changes (2, 18–20). We suggest that there is evidence to the contrary. Over the 40-year study period, approximately 90 percent of deaths were related to disease. Of these, 17–26 percent were attributed to cancer, and these deaths demonstrated little seasonal variation. Other diseases constituting 3–5 percent of disease-related deaths also demonstrated minimal seasonal variation. All of these diseases with little or no seasonal variation in mortality were conditions with considerable morbidity due to either the diseases themselves or their treatment.

Consider the hypothesis that the seasonal variation in disease is principally driven by temperature changes. Clearly, this putative driver/cause is nonspecific in action. If, then, disease classes that contributed 20–30 percent of disease-attributed mortality exhibited low/no winter-season increase, such disease classes must have been specifically excluded from the effects of this nonspecific driver/cause. This is a contradiction in terms. We believe it is unlikely that temperature and other environmental factors are primary factors in the winter-season increase in mortality. However, they may act as accessory or modulating variables. For example, combinations of temperature and humidity might determine the timing of influenza epidemics. Within the range of excess mortality typical of each influenza virus subtype, such factors could also modify the magnitude of the epidemics. Nonetheless, since the circulating influenza subtype is the primary determinant of the range of magnitude of winter excess in mortality for all disease classes (figure 5), environmental factors can, at most, only modulate the severity of epidemics.

Influenza epidemics have been associated with excess cardiovascular disease mortality (6), cases of pulmonary embolism and acute myocardial infarction (7), and increased prevalence of symptoms of respiratory infection in acute myocardial infarction patients (8, 10). Influenza vaccination has been associated with large reductions in the risks of primary cardiac arrest (40), recurrent myocardial infarction (41), cardiac disease (42), and stroke (42, 43). Markers of inflammation, particularly C-reactive protein, have been associated with an increased incidence of first cardiovascular events in asymptomatic women (44) and mortality in the elderly (45). We believe it is reasonable to suggest that an inflammatory process, possibly triggered by influenza virus infection, could be responsible for a significant portion of the mortality currently assigned to these broadly defined disease classes. If an inflammatory reaction to influenza virus infection does play a role in these deaths, the eventual control of excess mortality might require specific treatment(s) in addition to current control measures that are based on the use of influenza vaccines and antiviral agents.

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APPENDIX

Disease classification

Codes for the disease classes studied from the three different revisions of the *International Classification of Diseases* (ICD) falling within the study period (1959–1999) are given in appendix table 1. We used underlying cause of death to determine disease class in this study. The well-known bias in attributing underlying cause of death to

APPENDIX TABLE 1. Data codes used for specific classes of disease in three revisions of the *International Classification of Diseases*

Disease class	ICD* code(s)		
	ICD-7 (1958–1967)	ICD-8 (1968–1978)	ICD-9 (1979–1999)
Ischemic heart disease	420	410–414	410–414
Cerebrovascular disease	330–334	430–438	430–438
Diabetes mellitus	260	250	250
Cancer	140–205	140–209	140–209
Pneumonia	490–493	480–486	480–486
Influenza	480–483	470–474	487

* ICD[-7, -8, -9], *International Classification of Diseases*, Seventh, Eighth, or Ninth Revision.

chronic conditions could have obscured the contribution to mortality of more acute causes such as pneumonia. This issue has been raised often, but its resolution would be unlikely to alter the results presented here, because pneumonia constituted, at most, 10 percent of total annual mortality and never more than 15 percent of total excess mortality. Furthermore, a preliminary analysis of complete US mortality data for 3 years in the early 1990s found that only about 3 percent of deaths listing ischemic heart disease as the underlying cause listed pneumonia as one of the secondary causes (our unpublished data). However, to directly address this problem, future investigators should consider multiple causes of death.

Because the ICD was revised twice during our study period, we restricted our study to disease classes for which coding remained highly similar throughout the study period. For example, we elected not to include chronic respiratory disease (1.6 percent of US mortality in 1970 and 4.7 percent in 1997) because of multiple changes in both codes and coding practices during the study period. A difficulty remaining, however, was the marked change in the codes/coding for chronic forms of ischemic heart disease in the Ninth Revision of the ICD (ICD-9). The shift of substantial numbers of what were called ischemic heart disease deaths in the Seventh and Eighth revisions to the catchall category "Cardiovascular disease, unspecified" (ICD-9 code 429.2) made data on this type of mortality essentially unavailable after 1978 (46). However, the seasonal variation in mortality coded as 429.2 was similar to that for ischemic heart disease, as coded. Therefore, the results for ischemic heart disease shown in figure 7 would probably be unchanged for a disease class that included deaths coded as 429.2.

Hamming window coefficients

Hamming window coefficients or weights are given by the equation

$$w(n) = 0.54 - 0.46 \cos(2\pi n/(N-1)), 0 \leq n \leq (N-1),$$

where $N = 13$ in our usage. We used the values 0.080, 0.142, 0.310, 0.540, 0.770, 0.938, 1.000, 0.938, 0.770, 0.540, 0.310, 0.142, and 0.080.