Influenza as a proportion of pneumonia mortality: United States, 1959–2007*

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Abstract

Background: Influenza virus is believed to be the etiology of much mortality classified as pneumonia. As causes of death, influenza and pneumonia are typically analyzed together, but sometimes influenza-only analysis is conducted.
Objectives: To quantify influenza's contribution to the combined pneumonia and influenza time series of mortality for the United States, 1959–2007. To determine if influenza mortality data can be meaningfully analyzed separately from pneumonia.
Methods: We extracted population-level mortality data on pneumonia and influenza in the United States. The analysis includes time series plots and calculation of distributions. A key statistic is the proportion of all pneumonia and influenza mortality that is accounted for by influenza, I/(P+I).
Results: Year-to-year, I/(P+I) is highly variable and shows long-term decline. Extreme values of I/(P+I) are associated with extreme P+I death rates and vice-versa, but the ratio I/(P+I) is a weak predictor of P+I mortality overall. Prominence of influenza in the medical news is associated with high I/(P+I).
Conclusions: In population-level studies, influenza and pneumonia should be analyzed as a combined cause of death unless there is a specific, and especial, reason to separate the two causes. The question of influenza's role in combined pneumonia and influenza mortality at the population level is difficult if not impossible to answer by using vital registration data alone.
Keywords: cause of death classification; influenza; methodology; mortality; pneumonia; time series.

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Introduction and overview

Fatal cases of influenza involve secondary pneumonia. However, pneumonia is often reported on the death certificate without mention of influenza. Thus, influenza mortality is usually studied as an amalgam of the two causes[1,2]. The analysis of influenza morbidity is also dogged by the fact that the majority of influenza cases are not laboratory-confirmed[3,4]. The analogous practice in morbidity studies is to look at influenza-like illness (ILI)[5]. The goals of this analysis are (i) to quantify influenza's contribution to the combined pneumonia and influenza time series of mortality for the United States, 1959–2007, using the mortality statistics themselves, and (ii) to determine if influenza mortality data can be meaningfully interpreted separately from pneumonia.

Our interest in this study is the relationship between influenza mortality (coded as such) and pneumonia mortality. Some proportion of pneumonia mortality is due to influenza virus[6], but the present analysis concerns what is recorded on the death certificate. Thus, when we speak of influenza, we mean mortality explicitly coded as influenza, and for pneumonia we mean that coded as pneumonia without mention of influenza.

We analyzed age- and sex-specific mortality for influenza and pneumonia (separately) for the United States, by month, from 1959 to 2007. The overall trend of pneumonia and influenza mortality (combined) exhibits fairly regular long-term tendencies, punctuated by events such as the 1968–69 "Hong Kong" H3N2 pandemic. Yet, we find that the proportion of combined pneu-

monia and influenza mortality that is explicitly coded as influenza is highly variable over time, and exhibits a long-term decline.

Taken at face value, this would suggest high year-to-year variability of influenza mortality (and, thus, of incidence or case fatality or both). However, combined pneumonia and influenza death rates do not show as much variation. To continue the thought experiment of taking the data at face value, it would seem to suggest that other causes of fatal pneumonia become more prominent in years when there is less influenza. That is to say, in years when there is little influenza mortality, the other causes of pneumonia pick up the slack, to fill-out the total pneumonia and influenza (P+I) mortality. Conversely, these causes, such as pneumococcus or respiratory syncytial virus, must become less prominent when influenza mortality is ascendant. This seems to lack biological plausibility. A more parsimonious explanation is that the cause of death classification for explicit influenza changes from year-to-year.

It is important to understand thoroughly the relative trends in influenza and pneumonia mortality because Serfling regression, a technique to estimate excess mortality, takes mortality (or morbidity) data on pneumonia and influenza (usually combined) as its input[7]. On the other hand, a recent study considered influenza mortality, solely (i.e., without pneumonia)[8], and these data have subsequently been used by other investigators[9]. Our results suggest that the variation over time in influenza-only mortality is just as affected, if not more so, by seemingly-random year-to-year reporting changes as by actual changes in influenza-associated mortality. These results strongly

endorse the standard practice of combined analysis of pneumonia and influenza mortality.

Materials and methods

We obtained data on number of deaths, by cause, from the mortality detail files of the US National Center for Health Statistics (NCHS)[10]. Deaths were stratified by age, sex, month, and underlying cause from the death certificate. We extracted data on deaths from influenza, and from pneumonia without mention of influenza, from January 1959 to December 2007. This period spans four revisions of the International Classification of Diseases (ICD 7–10); the specific ICD codes used for each revision are given in the appendix. To ensure comparability, all data were converted to ICD-10 using the published crossover tables[11,12,13]. Data after 2007 have not yet been released.

One advantage of working with data on death counts is that deaths are well-documented. The US has complete mortality registration, so every death results in a death certificate with a cause. On the other hand, rate data also require population counts from the census, which are subject to higher error rates. Censuses are generally regarded as having small undercounts, and the data are interpolated between decennial censuses, which compounds uncertainties. So while rates are subject to error in both numerator and denominator[14], the data we use are mostly numerator data, where the count error rates are minimal. Conveniently, the ratio of counts and the ratio of death rates are equal, since the population denominators of the rates

cancel out. For example, I/(P+I), the ratio of influenza to combined pneumonia and influenza, is the same whether "I" and "P+I" denote counts or rates. The quantity I/(P+I) plays an important role in our analysis. However, we also analyze some rate data. For this purpose, rates were calculated using the above-described death counts in the numerator, with exposure data (i.e., person-years at risk) for the denominator coming from the Human Mortality Database[15]. Analyses were conducted using AWK[16], Stata v10.1 (College Station, TX, USA), and IDL v8.1 (Boulder, CO, USA).

Results and discussion

Time series of influenza and pneumonia deaths

Figure 1 plots two mortality time series for females: influenza, and pneumonia excluding influenza. Figure 2 presents the same data for males. These figures display two noteworthy patterns. It is strikingly regular over the 49-year span how much the two causes of death follow each other. Both peak in the winter and are in seemingly perfect synchrony. Pneumonia kills far more than influenza: the left axes (pneumonia) range from 800 to 8,000 deaths per month per sex, while the right axes (influenza) range from 1 to 2,500 deaths per month per sex (and the data rarely exceed 1,000).

The second thing to note in figures 1 and 2 is the long-run change in the two causes of death. Pneumonia deaths have moved upward with population growth, with the summer troughs going from about 1,000 deaths per month per sex in the 1960s, to approximately 2,000 deaths per month per sex in the 2000s. Influenza deaths, on the other hand, and despite population

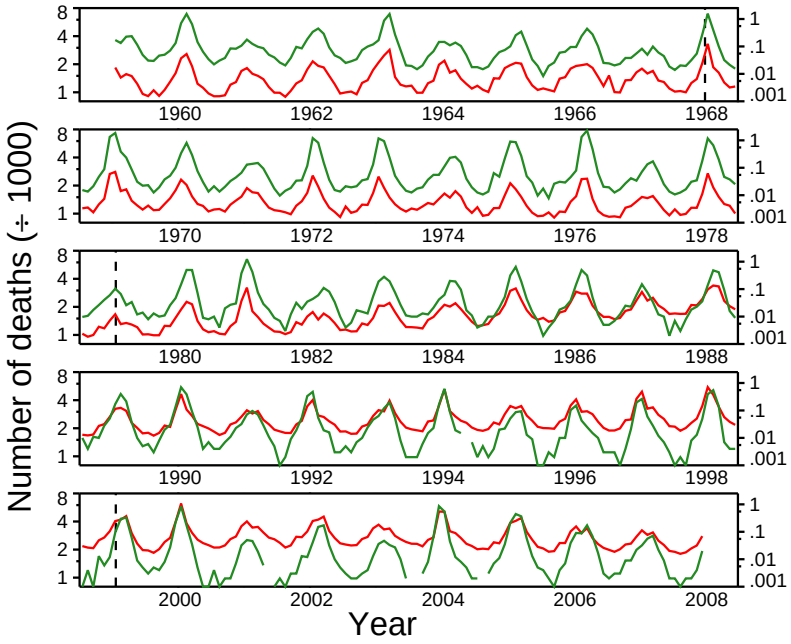

Figure 1: Females. Time series graph of pneumonia deaths (red), left scale, and influenza deaths (green), right scale. Vertical axes are logarithmic. Dashed lines denote changes in ICD revisions, although the data are ICD-adjusted. Gaps in the green data series correspond to months with no influenza deaths.

growth, have become rarer, with the summer troughs going from about 10 or more deaths per month per sex in the 1960s to under 5 deaths per month per sex in the 2000s. Starting in the 1990s, some months did not experience a single influenza death for either sex. Advances in influenza surveillance have lead to the knowledge that summertime outbreaks of influenza-like illness (ILI) are only rarely caused by the influenza virus[17]. Evidently, this knowledge has influenced death recording practices. What is more, winter peaks in a number of recent years have not exceeded 100 deaths per month

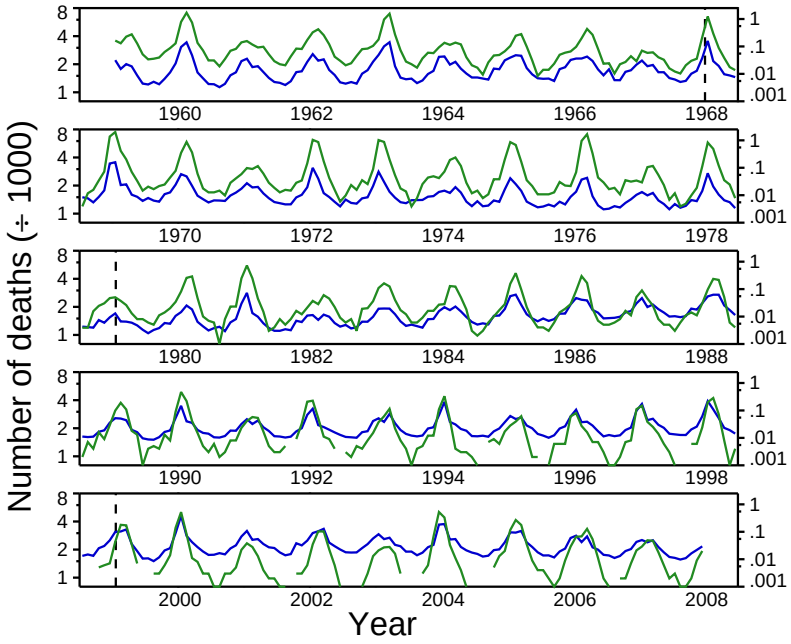

Figure 2: Males. Time series graph of pneumonia deaths (blue), left scale, and influenza deaths (green), right scale. Vertical axes are logarithmic. Dashed lines denote changes in ICD revisions, although the data are ICD-adjusted. Gaps in the green data series correspond to months with no influenza deaths.

per sex, whereas in the 1960s there was only one winter (1966–67) during which influenza deaths failed to exceed 100 per month per sex.

Influenza as a proportion of influenza and pneumonia, I/(P+I)

The changes documented in figures 1 and 2 are seen more starkly in figure 3, which plots influenza as a proportion of all pneumonia and influenza (P+I) mortality, over time. This illustrates the long-term diminishing use of influenza as a cause of death. In the 1960s and 1970s it was not unusual, in the peak month of the flu season, to see at least one-quarter of all P+I

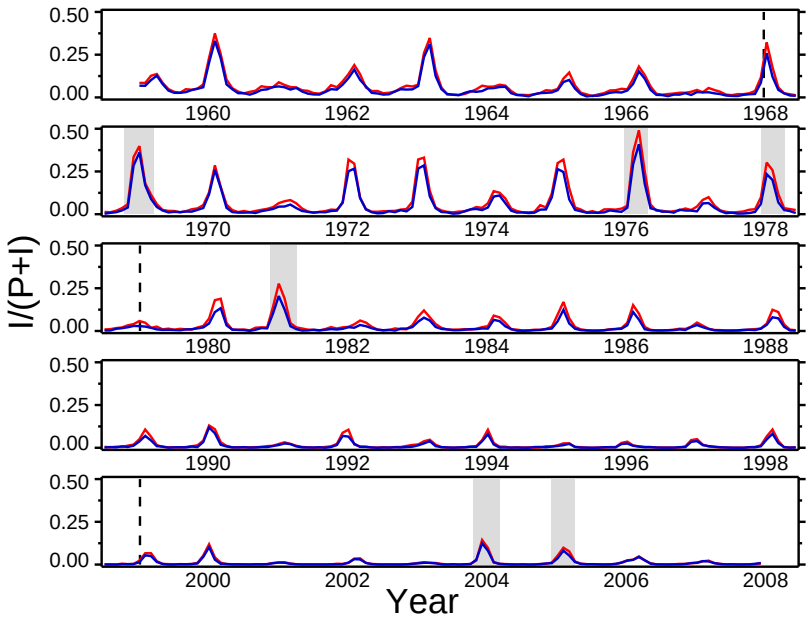

Figure 3: Time series graph of influenza as a proportion of total pneumonia and influenza mortality, all ages. Red, females; blue, males. Dashed lines denote changes in ICD revisions, although the data are ICD-adjusted. Shaded regions are discussed in detail in the text.

deaths attributed to influenza. There has been a steady decline in this pattern, starting in the 1980s. More recently, influenza typically accounts for less than 10% of all P+I deaths. The 1980–81 flu season was the last in which influenza deaths exceeded 25% of all P+I deaths in a given month.

Certain years are noteworthy in figure 3. The 1968–69 flu season (the "Hong Kong" flu pandemic of H3N2[18]) recorded the highest influenza proportion of the 1960s. Over the 49-year span, the highest flu season on record for I/(P+I) was 1975–76, coincident with the "swine flu" scare[19]. Specifically, from January to March 1976, the age-standardized death rate (ASDR, per 100,000) for P+I for males increased 112%, to 84.3 from 39.8, while

I/(P+I) increased a whopping 966%, to 40.9% from 3.8% (females showed a parallel trend: the ASDR increased 150% and I/(P+I) increased 896%). The height of the swine flu scare in March 1976 witnessed high P+I death rates, but not as high as the peak of the H3N2 pandemic in January 1969, when the male ASDR was 100.7. Moreover, age standardization dulls the comparison somewhat: for both sexes, at every age below age 85, the Hong Kong pandemic saw higher P+I death rates than the swine flu. The 1976 outbreak (i.e., the winter of 1975–76) had a pattern more like seasonal flu, explaining the crossover at age 85, relative to the 1968–69 pandemic.

The 1977–78 flu season, in which there was reemergence of "Russian" H1N1 influenza A virus[20], shows much higher I/(P+I) than either of the surrounding seasons, although P+I mortality was indeed somewhat elevated (figures 1 and 2). After 2000, influenza was more seldom used, with the two highest peaks being the 2003–04 and 2004–05 flu seasons, corresponding, respectively, to an influenza vaccine shortage[21] (discussed more below) and H5N1 "bird flu"[22]. The use of influenza on death certificates seems to reflect its presence in the medical news. The 2009 final mortality data are not released, but data for 2009–10 (viz., after the H1N1 pandemic that began in April 2009) will be able to test this hypothesis further. Note that although the sexes are almost perfectly overlapping in figure 3, during the winter peaks of P+I mortality, females are consistently slightly higher than males for the concurrently-peaking I/(P+I) proportion.

Lastly, the curve in figure 3 follows a (half-wave rectified) sinusoidal pattern. While it makes sense that the proportion of P+I deaths attributed to influenza is very low in the summer, this graph could in theory follow more

Peak month, I/(P+I)	Peak month, P+I Age-Standardized Death Rate							
	Males				Females			
	Dec	Jan	Feb	Mar	Dec	Jan	Feb	Mar
December	1	2	0	0	1	0	0	0
January	0	14	0	0	0	14	0	0
February	0	4	13	0	0	5	11	1
March	0	1	4	8	0	4	8	4
April	0	2	0	0	0	1	0	0

Table 1: Cross-tabulation of peak months for I/(P+I) and P+I ASDR, 49 winters, 1958–59 to 2006–07. The first winter starts in January 1959 due to data availability; all others run November–April, inclusive. Peaks of I/(P+I) almost always co-occur or lag the peak P+I death rate. Please refer to text for discussion.

of a square wave pattern: during the flu season, some constant proportion is flu, and during the summer a much lower (or zero) proportion is flu. Instead, the use of influenza as a cause of death seems to build along with the number of deaths from P+I, as well as decline with it.

Intra-season timing of I/(P+I)

To examine further the idea that I/(P+I) builds during the flu season, table 1 compares the intra-season timing of peaks of I/(P+I), as shown in figure 3, and the timing of the peak P+I ASDR. The cross-tabulation shows that the two quantities peak concurrently (i.e., on the diagonal), or with I/(P+I) lagging the P+I ASDR. Only three times in 49 flu seasons does I/(P+I) lead the P+I ASDR (once in the female series, and twice for males), each time by one month. On the other hand, I/(P+I) lags the ASDR in 11 seasons for males and 18 seasons for females. For two seasons for males and one for females, I/(P+I) peaks in April, lagging the ASDR by three months. The only

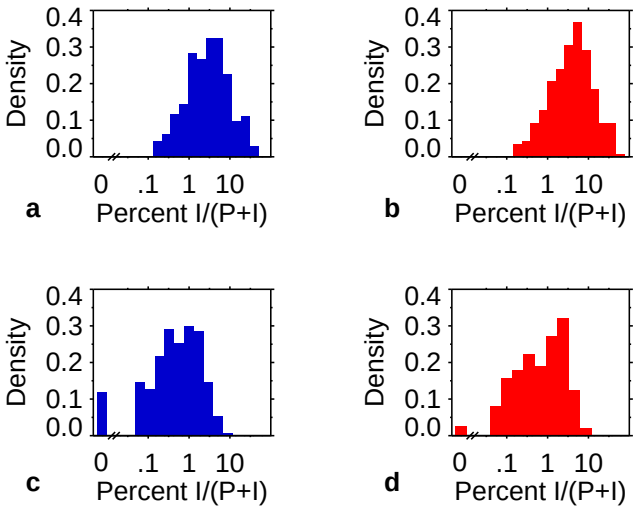

Figure 4: Histograms of influenza as a proportion of all pneumonia and influenza mortality, I/(P+I), by month (log transformed). Panel (a) is winter males, (b) is winter females, (c) is summer males, (d) is summer females. Pseudoseasons as defined in the text.

occurrence of December in table 1 is 2003, evidently an unusual flu season. Not only was influenza prominent in the medical news due to the vaccine shortage, but P+I death rates peaked unusually early (since January peaks are the most common, the practical significance of the December peak may be modest).

Distributions of I/(P+I)

Figure 4 gives the monthly distribution of I/(P+I), using log scale as a normalizing transform[23]. Panels a and b (top row) are winter (November through April), and panels c and d (bottom) are summer (May through October); panels a and c (left column, blue) are males, and b and d are females (right,

red). These six-month pseudoseasons approximate the circulation of influenza virus better than any other half-year periods[24]. A standard formula for bin width[25] was used in calculating the histograms. Even after the transform, the winter distributions are more mesokurtic than those of the summer. There are 19 months for males and 5 for females, all in the summer, for which there are zero recorded influenza deaths.

The histograms quantify the variation in figure 3. The bins in the right-hand tail of the winter distribution correspond to I/(P+I) of about 10% and greater. This underscores how uncommon it is — even in the winter — to have months in which influenza deaths are a large proportion of all P+I mortality. The modal proportion for the winter months is around 5%, which, given the tendency to focus on the peaks, is lower than one might suppose from figure 3. The distributions of the summer months have their modes lower: about 1% of all P+I deaths. The summer distribution is platykurtic, and note that the left-hand tail corresponds to truly negligible values, of 0.1% and lower. Apart from the greater number of months in which no influenza deaths were recorded (19 male versus 5 female), the sexes do not have markedly different patterns. For the winter histograms, the female one is slightly more peaked. This relates to the fact, as remarked about figure 3, that on a within-season basis females have slightly but consistently higher peaks of I/(P+I).

Relationship between I/(P+I) and P+I mortality rates

Figure 5 presents scatterplots showing the variation between the intensity of the flu season (measured by the P+I death rate), and the propensity for

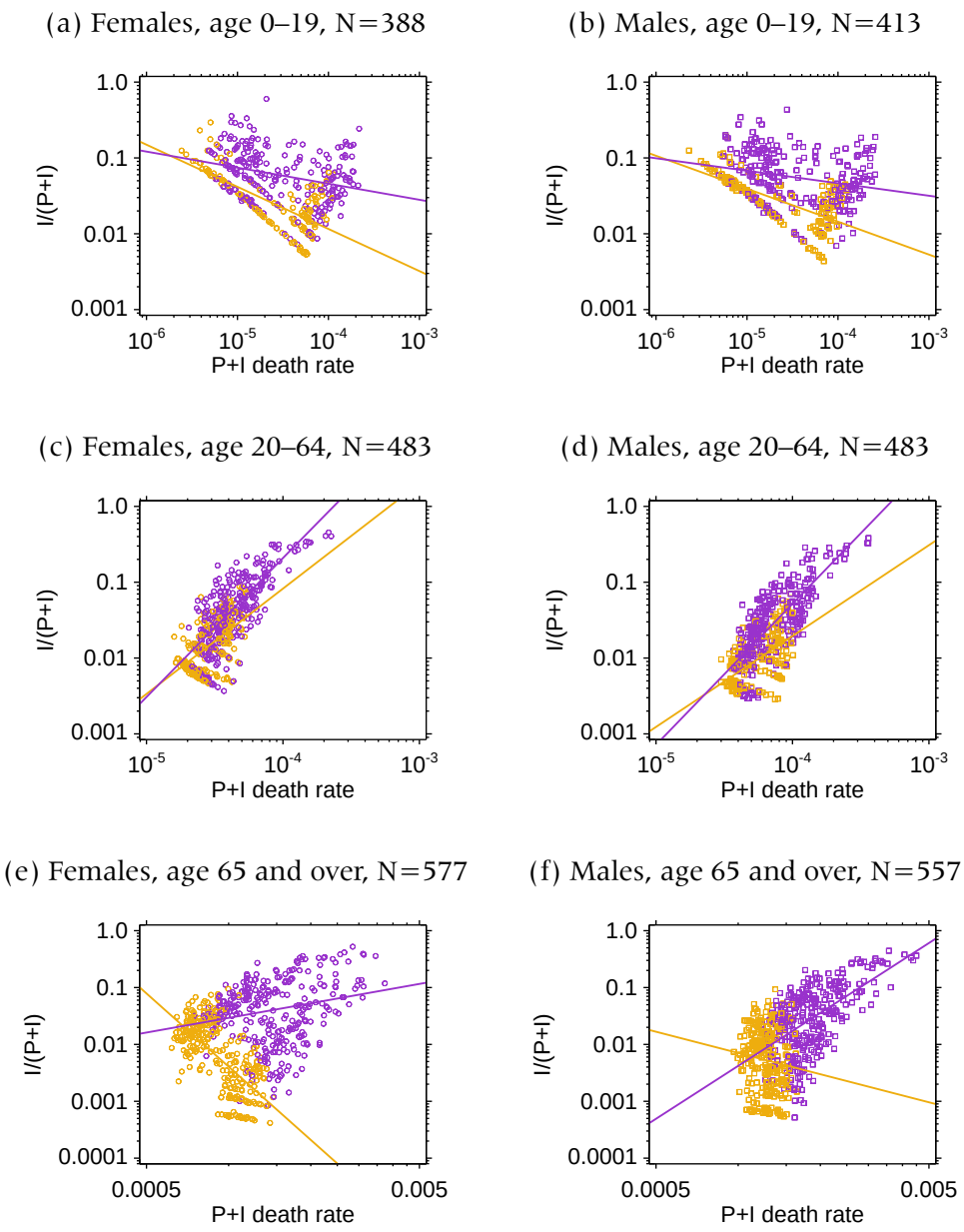

Figure 5: Scatterplots of I/(P+I) vs. P+I death rate, age 0–19 (a,b), age 20–64 (c,d), and 65 and older (e,f). Females, left panels (circles); males, right panels (squares). Each plotting symbol represents one month, 1959–2007. Summers are gold; winters are purple. Ordinary least-squares regression lines are also shown for each pseudoseason; all slopes differ significantly from zero ($p < 0.0005$) except panel (f), summer ($p = 0.076$), but the two lines in panel (f) are statistically different from each other ($p < 0.0005$). Months plotted in random sequence to avoid systematic summer or winter overlap.

influenza to be used explicitly as the cause of death (measured by I/(P+I) mortality). The graphs plot monthly data for both males (right panels) and females (left panels). Three age groups are shown: 0–19 (panels a,b), 20–64 (panels c,d), and 65 and older (panels e,f). Over time, crude death rates, including those for specific causes, have increased through population aging. Thus we disaggregate by age to provide a better comparison[26]. Summer and winter pseudoseasons are plotted in gold and purple, respectively, along with their corresponding regression lines. The plots are log-log, or scale-invariant[27,28].

The one-way variation in figure 5 is worth noting. Specifically, as age increases, the P+I death rate shows less total variation: the 0–19 year-old data span about 2 logs on the horizontal axis (panels a,b), the 20–64 year-old data span about one log (panels c,d), and the 65 and older data are nested within one log (panels e,f). On the other hand, for I/(P+I), the oldest age group shows the most variation, spanning about three logs on the vertical axis of panels e and f, while the other two age groups span about two logs.

One feature of figure 5 is the hard boundary with a somewhat striped appearance, seen on the lower left of each panel. This is an artifact of integer constraints on the number of deaths per month. The 0–19 age group has many months with 1, 2, or 3 influenza deaths, which makes the stripes particularly apparent in panels a and b. The time span is 588 months, but months in which I/(P+I)=0 cannot be plotted on log scale. Thus, the number of points plotted in each figure is less than 588 (the numbers are given in the panel captions).

The bivariate analysis in figure 5 reveals important relationships. The 0–19 age group (panels a,b), as noted earlier, represents the fewest number of deaths and also exhibits much variation. This contributes to the overlapping of the summer (gold) and winter (purple) data, making it difficult to discern a clear differentiation between the two pseudoseasons. The regression lines for winter and summer, interestingly, are negative. In other words, as the P+I death rate increases, the proportion flu decreases. Causality could run the other way; this is discussed below.

The 20–64 age group (panels c,d), on the other hand, demonstrates the opposite bivariate relationship, with positive slopes of both the summer and winter regression lines. As the P+I death rate increases, so does the proportion flu. Perhaps not surprisingly, the winter slope is steeper than that of the summer. While a clear distinction between the summer and winter data is lacking here as well, the differentiation is more apparent than in the younger group.

The age group 65 and older (panels e,f) not only represents the most deaths, but, of all the age groups, has the most interesting bivariate relationship. The summer (gold) and winter (purple) data show a salient differentiation here, clearly occupying different regions. What is more, the slopes of the summer and winter regression lines have different signs. In the winter, as the P+I death rate increases, the proportion flu does too. In the summer, there is a negative relationship between P+I death rate and I/(P+I). In the end of the pseudosummer (e.g., October), P+I death rates begin to increase but I/(P+I) stays low, which creates a negative relationship over-

all. For males, in the summer there is large spread of I/(P+I) over a narrow range of rates, and hence no strong relationship.

The most important point from the scatterplots, especially panels e and f, is that the highest P+I death rates are predictive of the highest I/(P+I) proportion (or vice-versa); this only applies to a handful of months, however. Beyond that, there is a poor relationship between I/(P+I) despite the fact that, as seen in figures 1 and 2, the cycles follow each other so well. Indeed, the goodness of fit of panels e and f of figure 5 as measured by the R^2 is quite poor in the winter for females ($R^2 = 0.045$) and is higher for males but hardly overwhelming ($R^2 = 0.32$). This is seen not only in the scatterplots but by reconsideration of figure 3, where there are huge year-to-year swings in I/(P+I). These drastic changes may be compared to figures 1 and 2, which over short time spans are good approximations to the rate changes, since the populations at risk in the rate denominators change relatively slowly.

Conclusion

As a cause of death, influenza is highly variable from year-to-year. Influenza and pneumonia are typically combined in mortality analysis, although this has been challenged[8]. We analyzed disaggregated influenza and pneumonia data to quantify their relationship and to determine the best practice. Serfling regression, for example, takes as its inputs the data considered herein to produce estimates of excess mortality[7]. Detailed knowledge of the inputs can help interpretation of the outputs and models[29].

Since about 1980, influenza has been much less frequently used on the death certificate. Years in which influenza is the medical news are exceptions to this trend, with the 1975–76 "swine flu" scare on record as the highest proportion I/(P+I). Even during a regular flu season, the proportion I/(P+I) builds during the winter. Of course, that could only go to show that as influenza viral circulation grows each winter, so does its impact on mortality. This is probably part of what is happening, but it does not explain the tremendous variation from year-to-year in the proportional use of influenza, in the face of more-or-less similar overall P+I mortality. As the flu season builds, so does short-term medical awareness of influenza, and this is reflected by I/(P+I). It may be that explicitly-coded influenza deaths are the result of greater laboratory confirmation, but that just begs the question of whether there is increased testing in years when influenza is making medical news. For example, 1975–76 was the swine flu scare but not an actual outbreak: pneumonia deaths at their peak were similar to the winter of 1974–75.

Figures 1 and 2 show that influenza and pneumonia mortality co-move, but figures 3 and 5 show that, overall, influenza mortality is a poor predictor of P+I mortality. Epidemic phenomena are often assumed to be power-law processes, but our results show that the influenza and pneumonia relationship is a poor fit to scale-invariance, reinforcing the notion that influenza alone should not be used as a stand-in for P+I mortality. The simplest interpretation of our results is that influenza is not a cause-of-death classification to be trusted. Barring an especial reason, influenza mortality should never

be analyzed as a stand-alone cause, but instead should be combined with pneumonia.

Our analysis both supports and contradicts a recent finding, that "recorded influenza" mortality is in decline[8]. It is supportive in the sense that it's replicative: we show that influenza deaths have indeed undergone secular decline in the period 1959–2007, despite population growth. However, this is overwhelmingly driven by a reduction in the propensity for influenza (as opposed to pneumonia) to be used as the underlying cause of death. Using vital statistics data alone is not sufficient to address the question of influenza's relative importance in P+I mortality. Large-scale autopsy studies, though expensive, would be the gold standard[30].

Appendix: ICD codes for influenza and pneumonia

	Cause of death	
Years	Influenza	Pneumonia†
1959–1967 (ICD 7)	480–483	490–493
1968–1978 (ICD 8)	470–474	480–486
1979–1998 (ICD 9)	487	480–486
1999–2007 (ICD 10)	J10–J11	J12–J18

† excluding influenza

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