ISSN: 3066-9812
Research Article

Journal of Clinical Epidemiology and Public Health

You Can Observe A Lot Just by Watching: A Cautionary Note on Establishing Baseline Influenza Mortality

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Submitted: 04 February 2025 **Accepted:** 11 February 2025 **Published:** 17 January 2025

https://doi.org/10.63620/MKJCEPH.2025.1029

Citation: *Koziol, J. A., & Schnitzer, J. E. (2025). You Can Observe A Lot Just by Watching: A Cautionary Note on Establishing Baseline Influenza Mortality. J of Clini Epi & Public Health, 3(1), 01-07.*

Abstract

Objectives

We compare two statistical models for establishing "baseline" mortality attributable to pneumonia and influenza in the United States during the non-epidemic seasons 2013-14 through 2018-19. We aim to provide robust estimates of the burden of mortality from pneumonia and influenza during non-epidemic years in the United States, and to detail methodology for characterization of baseline mortality.

Methods

We obtained data on United States mortality attributable to pneumonia and influenza for the epidemiological seasons 2013-14 through 2018-19 from the U.S. National Center for Health Statistics Mortality Surveillance System. The data comprise weekly national mortality totals attributable to pneumonia and influenza, separately for adults 18 to 64 years old and adults aged 65 and older. We fit both generalized linear models and generalized linear mixed models to the mortality data; in contrast to the former models, the mixed models explicitly incorporated additional random components associated with intrinsic year to year variability in the mortality patterns. We also invoked a randomization procedure to ascribe uncertainty bounds to the summary descriptions of the mortality experience.

Results

The generalized linear models are analogous to averaging the mortality patterns over the 6 seasons, but failed to provide adequate representations of the annual mortality patterns. The generalized linear mixed models provided superior fits to the observed mortality data, but with a tradeoff of rather large uncertainty bounds on the mortality experience.

Conclusions

Summary estimates of "baseline" mortality attributable to pneumonia and influenza should be accompanied with an assessment of how well these summary measures represent the observed mortality experience, and metrics reflective of the variability inherent in the estimates.

Keywords: Baseline Mortality, Generalized Linear Models, Generalized Linear Mixed Models, Poisson Regression, Bias-variance Tradeoff.

Introduction

Annual influenza outbreaks constitute a major public health concern worldwide. The World Health Organization estimates that there are about one billion cases of seasonal influenza annually, with up to 650,000 respiratory deaths [1]. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that seasonal influenza leads to 9 to 41 million illnesses, 100,000 to 710,000 hospitalizations, and 5,000 to 51,000 deaths annually, between 2010 and 2023 [2]. We have previously compared the disease burden of the influenza A pandemic 2009-10 and

seasonal influenza 2010-19 in the United States, using the CDC metrics of illnesses, medical visits, hospitalizations, and deaths [3]. Among our conclusions, we found that determination of a baseline influenza mortality profile in the United States over the 2010-19 decade was not straightforward. We return to this issue in the current work, with the goal of establishing baseline (non-epidemic) annual respiratory mortality profiles in the United States.

Average mortality profiles are invaluable from a public health perspective. Surveillance systems can utilize them to monitor changes in mortality patterns, thereby identifying unusual spikes or trends that require immediate attention or intervention. Identification of high-risk groups (e.g., the elderly) can prioritize allocation of resources, or shape public health messaging to encourage preventive behavior or vaccination. Mortality rates can inform policy decisions aimed at reduction of influenza transmission and mortality. Average mortality profiles are thus crucial metrics for assessing the disease burden of influenza and steering efforts to mitigate its public health impact.

In the following section, we introduce a statistical framework for establishing baseline mortality attributable to pneumonia and influenza in the United States. We report on the adequacy of these modeling efforts in the results, and conclude with lessons drawn and recommendations arising from our findings.

Methods

We obtained data on United States mortality attributable to influenza and pneumonia from the U.S. National Center for Health Statistics Mortality Surveillance System [4]. These data are weekly mortality totals attributable to influenza and pneumonia for the influenza seasons 2013-14 through 2018-19, separately for adults aged 65 and older, and adults aged 18 through 64. For each epidemiological season, the weekly mortality totals begin with calendar week 40 and continue through calendar week 39 of the subsequent year. We also obtained related population data derived from the U.S. Census Bureau, as our analyses reflect mortality rates and not absolute numbers. All data are freely available to any interested parties [5].

In order to characterize the pneumonia and influenza mortality patterns over the epidemiological seasons 2013-14 through 2018-19, we initially investigated generalized linear models (GLMs). GLMs constitute extensions of linear regression models to settings in which a nonlinear relationship exists. In particular, the response (dependent variable) can have a distribution other than normal (e.g., Poisson), with parameters including a mean □□□a coefficient vector b defines a linear combination Xb of the predictors X; and, a link function f defines the model as f (□□□Xb . Generalized linear models have been widely studied in the statistics literature, so we will not review them here in any detail, and refer the interested reader to resources with more comprehensive treatments [6-8]. But we here highlight input parameters we used to fit GLMs to the mortality data in Matlab v2018a.

Our model specification, in Wilkinson notation, is simply

Mortality ~ Week

where Mortality is a 312x1 vector of weekly pneumonia and influenza mortality from the 6 seasons encompassing 2013-14 through 2018-19, and Week (also 312x1) is a categorical variable, taking the values 1 through 52 for each season (a fixed effect, in regression parlance) [9]. We specify the distribution of the response variable (mortality) as Poisson, link function as log, and include an Offset variable log (population at risk).

The mortality counts should be somewhat proportional to the size of the population at risk, and the inclusion of this offset together with a log link function causes the model to satisfy this theoretical constraint. Essentially, with the inclusion of the offsets, we are analyzing rates as derived from the counts. We fit separate GLMs to the mortality data from individuals 18 to 64 and individuals 65 and older – separate Mortality vectors and offsets for these two cohorts, other parameters remaining the same.

We found that the GLMs did not provide suitable representations for the mortality patterns: although the GLMs provided average representations of the mortality patterns over the 2013 through 2019 experience, the averages failed to model accurately the season-to-season variability in mortality, as well as differences in phases (e.g., times of peak mortality) across the seasons. We therefore formulated generalized linear mixed models (GLMMs), which explicitly incorporated random components into the GLM formulations, in particular, random effects for the weekly fixed effects. The models therefore took on the following form:

Mortality ~ Week + (Week | Season).

In this formulation, we have included random effects terms represented by (Week | Season): for each week, there is a fixed effect estimate, but we are also allowing random variation in these coefficients from season to season. In other words, Week is also a random factor within the grouping variable Season. Model specification is similar to the GLMs, but with additional arguments: we selected the covariance pattern, that is, the pattern of the covariance matrix of the random effects, as diagonal (diagonal entries not necessarily equal, and off-diagonal entries set to 0), and the method of estimating model parameters as REMPL (restricted maximum pseudo likelihood).

Differences in Akaike's information criterion (AIC) indicated that, formally, the GLMMs provided much improved fits to the observed mortality patterns compared with the corresponding GLMs; the graphs of the observed versus fitted models, as well as examination of the residuals (observed – fitted), corroborate the improvement in fits with the GLMMs. We do not wish to rely solely on statistical arguments here, but in keeping with our theme that you can observe a lot just by watching, the visual evidence in the plots of fits and residuals should be persuasive.

It is not straightforward to predict responses of a generalized linear mixed model if a grouping variable (here, season) has levels that are not in the original data. To overcome this difficulty, we instead rely on a randomization procedure to incorporate the random effects attributable to seasons into a prediction region. Separately for both age cohorts (18 to 64 and 65+), we generated n=1500 random responses from the fitted GLMM models, that is, 1500 randomly generated versions of the observed Mortality 312x1 vectors.

We then took the 9000 seasons' randomly generated responses (1500 randomly generated responses x 6 years per random response), and determined the 95% central regions from these responses. Importantly, these 95% randomization intervals incorporate the random effects variability representative of season to season variability in the mortality patterns as well as the variability due to parameter estimation uncertainty (fixed effects).

Results

As mentioned in the Methods, we acquired data on weekly mortality from pneumonia and influenza in the United States between the years 2013-14 and 2018-19, separately for individuals aged 18 to 64 years and those 65 years and older. Through appropriate modeling, we attempted to find consistent and consonant patterns in these pre-pandemic mortality data. Explicit details of the modeling schemes are given in the Methods.

Our simple initial approach to modeling mortality utilized generalized linear model (GLMs) with fixed effects representing the weeks. In Figure 1A we depict the observed data for the 18 to 64-year olds along with the corresponding GLM fit; the similar figure for the 65-year olds and older is given in Figure 2A. The GLM fits are deterministic, and essentially represent weighted averages of the observed mortality curves, with slight trends reflecting increasing sample sizes (numbers of individuals at risk) from 2012 through 2019. Neither GLM fit passes the eye test: in particular, mortality peaks are consistently underestimated, and temporal shifts in phases are largely missed. In Figures 1B and 2B we plot the residuals (observed - fitted) for the GLMs: clearly, the magnitudes of the residuals are indicative of inadequate fits.

We then examined generalized linear mixed effects models (GLMMs), in which we added random effects representing the year to year variability in the weeks to the GLM models. Thereafter, we found much improved fits to the 18 to 64-year-old data (Figure 3), as well as to the 65 and older data (Figure 4). In particular, the GLMM fits are remarkably congruent with the observed data, with the residuals from the GLMMs well over 10-fold smaller than from the GLMs (cf. Figures 3B and 4B vs. 1B and 2B respectively).

A "baseline" or "typical" mortality curve characterizing the 2013-14 through 2018-19 experience would be represented by the GLM models (Figures 1A and 2A): by their nature these are indeed summary curves, but fail to capture the nuances in the mortality patterns. With the inherent season to season variability in peaks and valleys as well as phase differences, we instead chose to invoke a randomization procedure that incorporates week to week and season to season components of variability to characterize this mortality experience. Figures 5 (18 to 64-year olds) and 6 (65 and older) show the randomization 95% bounds derived from the GLMMs, along with the observed mortality data. The randomization bounds are quite wide, though this should not be surprising given the magnitudes of the season to season changes in mortality patterns.

Discussion

Let us recast Yogi Berra's dictum as, you can learn a lot by observing. Averaging mortality from pneumonia and influenza over several recognized non-epidemic years is per se an inadequate representation of the observed experience, since the years are far from homogeneous (in terms of both amplitude and phase). In non-epidemic years, these differences are random and not predictable, and are best captured in mixed models that explicitly incorporate these sources of random variation. At play here is a basic dictum of Statistics 101, namely, statistical estimates should be accompanied with measures of the uncertainty intrinsic to the estimates.

Although our focus has been on aspects of modeling the mortality profiles, the huge disparity in pneumonia and influenza mortality between adults 18 to 64 years old and the elderly aged 65 and older has not escaped our notice. Our graphs, through different mortality (y-axis) scales, deemphasize this disparity, but we would be remiss in failing to recognize that pneumonia and influenza mortality during these non-epidemic seasons impacts the elderly disproportionately. We have commented on this disparity previously, as well as, the stark contrast with the age-specific mortality rates observed in the United States during the 1918-19 influenza epidemic [10, 11]. Clearly, mitigating the mortality risk from pneumonia and influenza among the elderly is a vital public health imperative.

We remark that our models are not very parsimonious, as we are treating the individual weeks as both fixed and random effects in the GLMM framework. We explicitly chose our models to reflect the observed data very closely, so that subsequent emphasis could be placed on intrinsic season to season variability. This variability is incorporated in Figures 5 and 6, where our uncertainty bounds from a randomization-based approach explicitly incorporate contributions from both fixed and random effects. The bounds are rather wide, as the underlying epidemiological seasons do vary greatly in both phase and amplitude. At play here is the bias-variance tradeoff [12]. one might term our GLMMs as complex and sophisticated, achieving high accuracy (low bias) at the cost of high variance.

We emphasize that with data from other or additional years, these profiles will likely be altered, perhaps dramatically. In this regard, we have chosen a window of 6 non-epidemic seasons for our analyses, as there is no consensus concerning optimal window size for establishing baseline mortality.

An early ingenious approach to modeling non-epidemic level weekly mortality data for pneumonia and influenza was introduced by Serfling [13]. This approach entailed linear regression, with the number of weekly cases regressed on a linear trend and trigonometric terms (sines and cosines) describing seasonal changes, thereby determining "a standard curve of expected seasonal mortality". The method is not at all computationally intensive, as the orthogonality of the regressors greatly simplifies the least squares fitting [14].

And, the mathematical fact that the trigonometric functions suitably normalized constitute a complete orthonormal system over any closed finite interval ensures that any resulting Fourier series expansion can be made sufficiently accurate with enough terms. Nevertheless, with the ready availability of modern computing resources, Serfling's model is not commonly implemented as originally formulated, but extensions to the generalized linear

model setting with Poisson regression are straightforward [15]. As such, the method remains popular to this day [16, 17]. We remark that, although the trigonometric functions are complete, any derived Fourier series expansion may well involve higher order terms, for which practical interpretation might remain elusive [18].

We conclude with a salient cautionary note: Although we have limited our presentation to mortality attributable to pneumonia and influenza, our arguments obtain mutatis mutandis to all-cause mortality. Reports assessing excess all-cause mortality need to consider how baseline all-cause mortality is estimated, and whether the variability in the baseline estimation procedure is accounted for.

Figure Legends

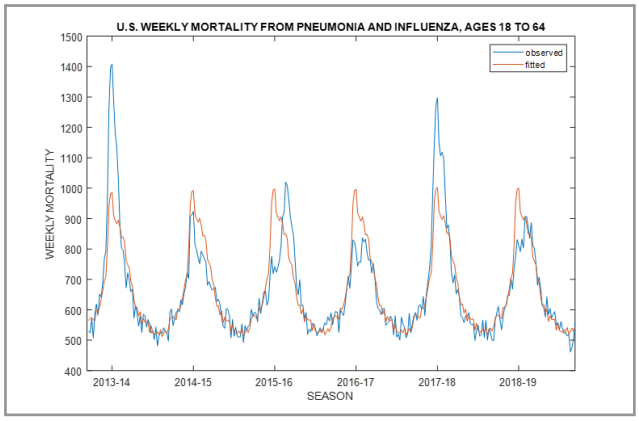
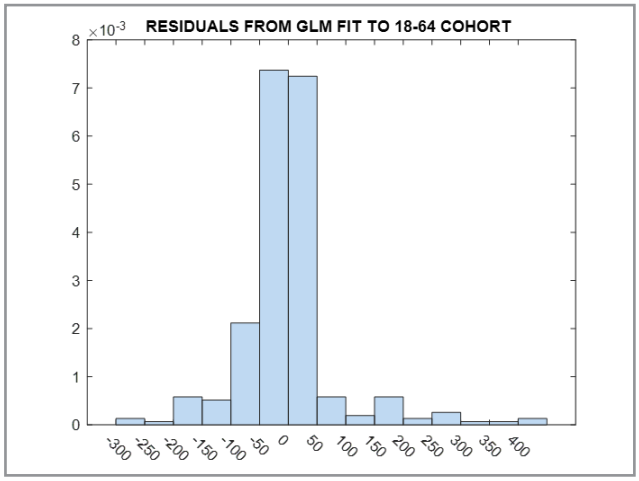


Figure 1: A. Weekly mortality from pneumonia and influenza among individuals aged 18 to 64 years in the United States in the 6 epidemiological seasons 2013-14 through 2018-19, along with the fitted data from a generalized linear model. See Methods for details.



B. Histogram of residuals (observed - fitted) from the data and generalized linear model depicted in Figure 1A. The histogram uses probability density function scaling: The area of each bar is the relative number of observations, and the sum of the bar areas is equal to 1.

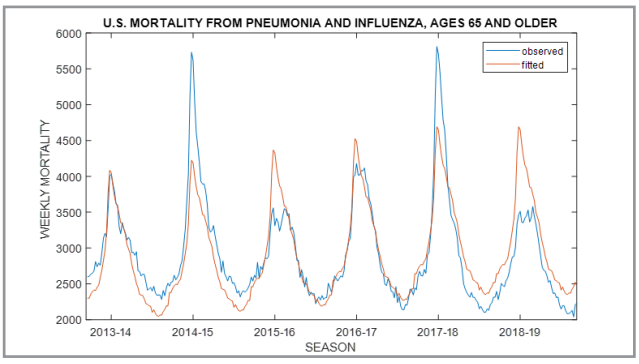
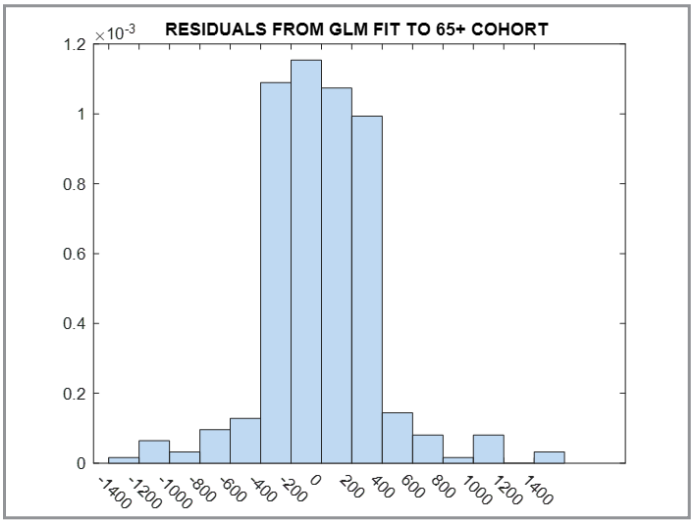


Figure 2: A. Weekly mortality from pneumonia and influenza among individuals aged 65 years and older in the United States in the 6 epidemiological seasons 2013-14 through 2018-19, along with the fitted data from a generalized linear model. See Methods for details.



B. Histogram of residuals (observed - fitted) from the data and generalized linear model depicted in Figure 2A. The histogram uses probability density function scaling: The area of each bar is the relative number of observations, and the sum of the bar areas is equal to 1.

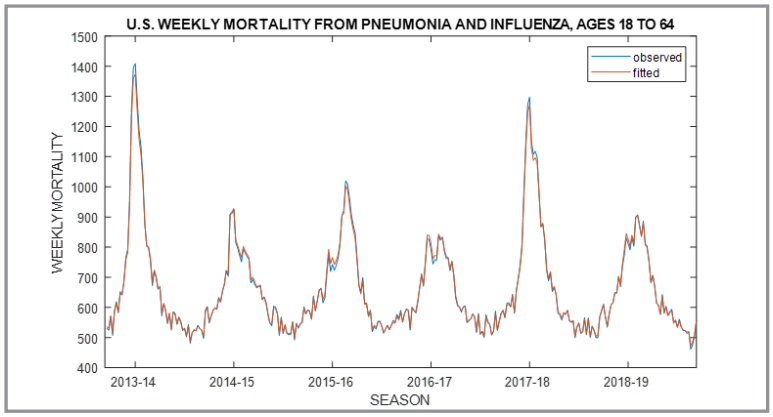
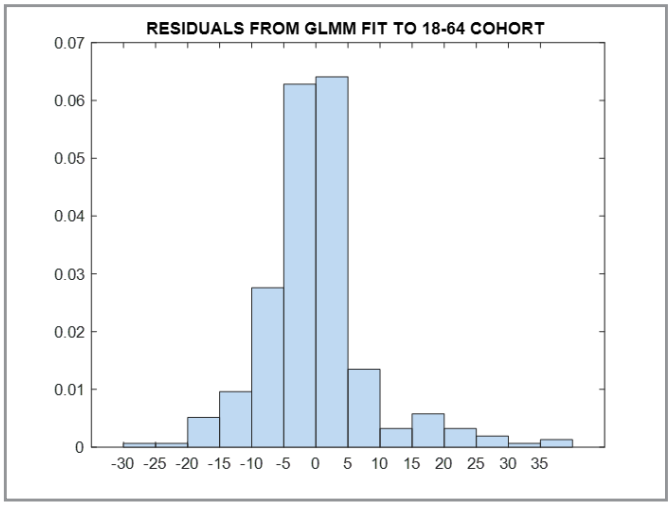


Figure 3: A. Weekly mortality from pneumonia and influenza among individuals aged 18 to 64 years in the United States in the 6 epidemiological seasons 2013-14 through 2018-19, along with the fitted data from a generalized linear mixed model. See Methods for details.



B. Histogram of residuals (observed - fitted) from the data and generalized linear model depicted in Figure 3A. The histogram uses probability density function scaling: The area of each bar is the relative number of observations, and the sum of the bar areas is equal to 1.

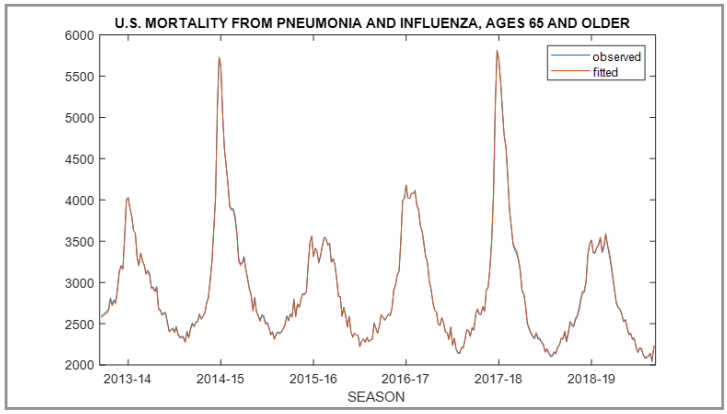
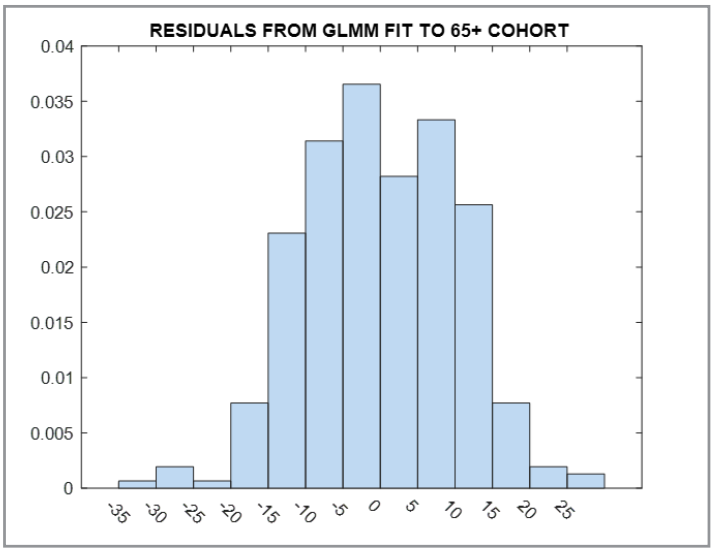


Figure 4: A. Weekly mortality from pneumonia and influenza among individuals aged 65 years and older in the United States in the 6 epidemiological seasons 2013-14 through 2018-19, along with the fitted data from a generalized linear mixed model. See Methods for details.



B. Histogram of residuals (observed - fitted) from the data and generalized linear mixed model depicted in Figure 4A. The histogram uses probability density function scaling: The area of each bar is the relative number of observations, and the sum of the bar areas is equal to 1.

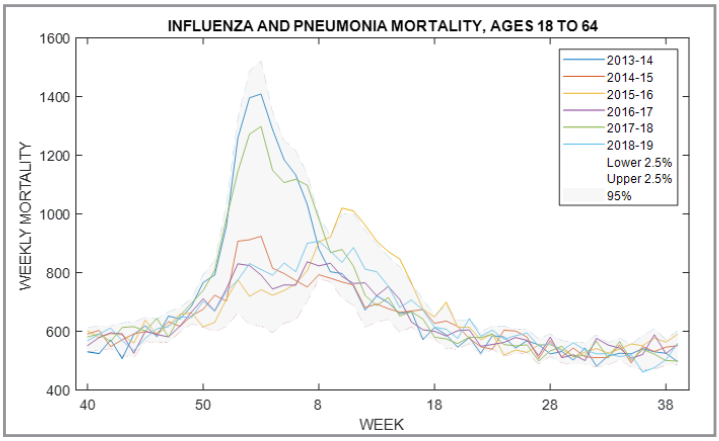


Figure 5: Weekly mortality from pneumonia and influenza among individuals aged 18 to 64 years in the United States, separately for each epidemiological season. Also depicted is a 95% randomization interval derived from the generalized linear mixed model fit to the 6 seasons, accounting for variability in the estimates of both fixed and random effects in the model. See Methods for further details.

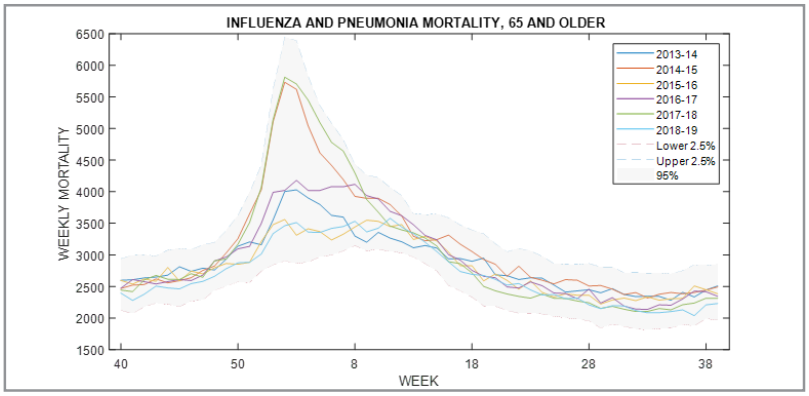


Figure 6: Weekly mortality from pneumonia and influenza among individuals aged 65 years and older in the United States, separately for each epidemiological season. Also depicted is a 95% randomization interval derived from the generalized linear mixed model fit to the 6 seasons, accounting for variability in the estimates of both fixed and random effects in the model. See Methods for further details.

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