Heterogeneity in Estimates of the Impact of Influenza on Population Mortality: A Systematic Review

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Running head: Influenza-associated Population Mortality

Abstract

Influenza viruses are associated with substantial global burden of morbidity and mortality every year. Estimates of influenza-associated mortality often vary between studies due to differences in study settings, methods and measurement of outcomes. We reviewed 103 published articles assessing population-based influenza-associated mortality through searching PubMed and Embase, and identified considerable variation in the statistical methods used across studies. In studies using regression models with an influenza activity proxy, four approaches were applied to estimate the influenza-associated mortality. The estimates increased with age and ranged widely from -0.3-1.3 and 0.6-8.3 respiratory deaths per 100,000 population for children and adults to 4-119 respiratory deaths per 100,000 population for older adults. Meta-regression analysis identified that study design features were associated with the observed variation in estimates. The estimates increased with broader cause-of-death classification, and were higher for older adults than for children. The multiplier methods tended to produce lower estimates, while Serfling-type models were associated with higher estimates compared with other methods. No 'average' estimate of excess mortality could reliably be made due to the substantial variability of the estimates partially attributable to methodological differences in the studies. Standardization of methodology in estimation of influenza-associated mortality would permit improved comparisons in the future.

Key words: epidemiology, excess mortality, influenza, systematic review

It has been estimated that, globally, human seasonal influenza virus infections result in 250,000 to 500,000 annual deaths, approximately 0.5% to 1% of all deaths every year (1). The mortality impact of influenza is greatest at the extremes of age, i.e. young children and older adults. Influenza-associated deaths can occur following primary viral pneumonia (2), or more frequently secondary bacterial pneumonia (3), or exacerbation of co-existing underlying medical conditions such as cardiovascular diseases (4). However, influenza is not often listed as an underlying cause of death (5, 6). This is possibly due to the temporal delay between influenza virus infections and secondary consequences, such as bacterial pneumonia or myocardial infarction, or lack of access to laboratory testing (7). Therefore, studies of influenza-associated mortality often examine broader consequences of influenza epidemics on various causes of death, not limited to deaths recorded as "influenza".

It is well understood that the impact of influenza on mortality varies across geographic locations and populations, because of differences in population structure, access to and quality of medical care, and the prevalence of underlying medical conditions (8) . The mortality impact can also vary over time within geographic locations, because of evolution in circulating viruses, changes in host immunity following prior epidemics or vaccination strategies (8). Thus, there can be no single 'true' representative estimate of the mortality impact of influenza that applies in all places and all times. However, there may be a typical range within which the estimates of annual mortality impact in a particular location are likely to fall.

It is important to assess the mortality impact of influenza, as a key component of the overall burden of disease associated with influenza, to support planning and resource allocation. Variation in the mortality impact among different segments of the population can inform vaccination programs and other public health measures. In addition to understanding the impact of influenza on mortality, having a baseline measure of typical mortality can allow assessment of the impact of specific interventions on mortality (9), as part of economic evaluations of potential consequences of new control strategies (10).

Many studies, using various methods, have now been conducted to estimate the impact of influenza on population mortality. The objectives of our review were to identify published population-based studies of the impact of influenza virus infections on mortality in defined populations, to describe and compare the methodological approaches used, to report the estimates of influenza-associated mortality, and to examine the influence of methodological factors on reported estimates.

METHODS

Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11) to conduct this review. Relevant studies were retrieved from Medline (PubMed) and Embase on 22 March 2016. We searched

for published journal articles using the following searching terms #1 AND #2 AND #3 in 'All fields':

#1: mortality OR deaths OR burden

#2: influenza OR flu

#3: excess OR attributable OR influenza-associated OR influenza-related OR influenza-attributed OR influenza-attributable OR "associated with influenza" OR "attributable to influenza" OR "attributed to influenza" OR "related to influenza" OR flu-associated OR flu-related OR "associated with flu" OR "attributable to flu" OR "attributed to flu" OR "related to flu"

No language restriction was applied to retrieved articles. Additional relevant studies were manually retrieved from the references of papers identified from the two databases.

Two authors (L.L. and H.B.) independently screened all titles identified in the literature search. Abstracts and full texts of all potentially eligible articles were retrieved and reviewed for final inclusion. Disagreement in study selection between the two authors was resolved by a third author (J.Y.W.).

Eligible articles were those reporting population-based estimates of influenza-associated mortality from the following four causes of death: 1) pneumonia and influenza; 2) respiratory diseases; 3) respiratory and cardiovascular diseases; 4) and all causes. These causes are most commonly used in mortality studies of influenza. They represent a gradient of specificity, with pneumonia and influenza being the most specific, while the other three groups should

incrementally capture a greater fraction of the full impact of influenza (12, 13). Studies were excluded if: 1) the full-text was not available; 2) the estimates reported were not at country- or region-level; 3) no annual influenza-associated excess mortality rates could be derived; 4) only laboratory-confirmed influenza deaths were reported; 5) influenza-associated excess mortality was only estimated for a specific risk population, such as pregnant women or those with underlying medical conditions; 6) the study could not be repeated by another published study; or 7) the study reported a subset of complete data published elsewhere. Reviews, book chapters, conference abstracts/summaries, commentaries, and letters were also excluded.

Data extraction

All data were extracted into a standardized form by two authors independently (L.L. and H.B.). The primary data extracted included technical details of the methods used for estimation of influenza-associated mortality, and country-level estimates of the annual average influenza-associated mortality rate in all ages, by age group and by selected cause of death, during a defined study period. If a study reported separate estimates for each year included in their study, we calculated an average estimate across the years studied. The extracted data were not limited to positive estimates since relatively wide 95% confidence intervals have been reported for certain age groups such as children and young adults (14-16). Technical details included the analytic approaches used, how covariates, including temperature, humidity, respiratory syncytial virus activity and other covariates, were controlled for, which influenza activity proxy was used, and

how the influenza-associated mortality was derived from the model. We extracted the estimates for children (0-14 years), adults (15-64 years) and older adults (≥65 years). Reported age-specific annual estimates of the influenza-associated mortality rate were classified as the closest group to these three pre-defined age groups if the reported age group did not match exactly. Methodological details were retrieved from the cited references if the selected study itself did not provide sufficient information. Statistical methods used by different studies to estimate influenza-associated mortality were classified as multiplier methods, regression models with an influenza activity proxy, Serfling-type models (in this review, we defined Serfling-type models as regression models with Fourier terms but without an influenza activity proxy) and other models without an influenza activity proxy. Details of how data were treated and how each of the methods was applied are provided in Web Appendix 1.

Statistical analysis

We constructed forest plots to examine the age-specific estimates of influenza-associated mortality rates across different causes of death. In addition, data were plotted within categories of the measured outcome and population. If $\geqslant$10 estimates were reported for a particular outcome-population category they were plotted using violin plots. These plots are an extension of box plots and histograms that have the advantage of indicating the probability density of each reported or recalculated estimate, as well as their common numerical characteristics including median and interquartile range. If there were <10 estimates in an outcome-population category, then only the annual influenza-

associated mortality rate from each included study was plotted. For studies that did not report the standard error of an estimate, we imputed the standard error using a linear regression (Web Appendix 1). Statistical heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic (17).

When heterogeneity is high, as recommended (18), we used a meta-regression to identify factors associated with variations in the age-specific estimates of influenza-associated mortality rate instead of computing a single summary estimate. In these models, the outcome was the age-specific estimate from each study, while the explanatory variables were study design features, including age group, whether the estimate was made for seasonal periods or pandemic periods, cause of death, statistical modeling technique employed, income level and climatic zone of the study country or region. The R^2 statistic was used to indicate the proportion of heterogeneity explained by the covariates examined (19). We included in the meta-regression estimates for the 2009 A(H1N1) pandemic because there were a large number of studies available for the 2009 pandemic with large sample sizes. However, studies for the 1918, 1957 and 1968 pandemics were excluded from the meta-regression because of the relative paucity of studies for these pandemics and their smaller sample sizes. The potentially large variation in the estimates from these earlier pandemics may obscure the relationships between influenza-associated mortality estimates and selected independent variables. All analyses were performed using R software version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified 103 articles which met the inclusion criteria (Figure 1). Details of the studies included in this review are presented in Web Table 1. The majority of studies were published within the past 10 years (Figure 2). The first article identified was a study by Collins and Lehmann in the 1950s reporting influenza-associated excess deaths from a range of diseases including chronic diseases (20). The included studies reported estimates from 39 countries or regions covering North and South America, Europe, Southern Africa, East and Southeast Asia, and Oceania. Two studies estimated the global mortality associated with the 2009 pandemic (8, 21), and one study assessed the global mortality impact of the 1957 pandemic.

Large variation in estimates was observed among studies. The annual crude influenza-associated all-cause mortality rate for all ages, subdivided by period ranged from: 0 to 178 per 100,000 persons in seasonal periods; 100 to 2230 per 100,000 persons in the 1918 pandemic periods; 23 to 123 per 100,000 persons in the 1957 pandemic periods; 12 to 88 per 100,000 persons in the 1968 pandemic periods; and -1 to 25 per 100,000 persons in the 2009 pandemic periods. By comparison, the age-standardized rate ranged from 3 to 81 per 100,000 persons in seasonal periods, and from -1 to 31 per 100,000 persons in the 2009 pandemic periods. Three studies reported negative point estimates of influenza-associated mortality for children (14-16).

Various age group categorizations were used. We reclassified the reported age-specific estimates into three age groups. Reported estimates for 0-14, 1-14, 5-14, 0-17, 0-18, 0-19 or 0.5-19 years were grouped for "children", 15-64, 15-59, 18-59, 20-59, 18-64, 19-64 or 20-64 years for "adults", and ⩾65 years or ⩾60 years for "older adults". Mean estimates of the influenza-associated mortality increased with age. The estimate number of respiratory deaths per 100,000 population was from -0.3-1.3 for children, 0.6-8.3 for adults, and 4-119 for older adults ≥65 years. The influenza-associated mortality rates in older adults were generally higher than those in children and adults, and the median estimate of seasonal influenza mortality burden for older adults increased when a broader cause of death outcome was applied (Web Figures 1-9). Age-standardized influenza-associated all-cause mortality rates were similar or higher in middle-income countries than in high-income countries (Web Figure 10).

Statistical modeling techniques

Four studies (8, 22-24) used the multiplier methods to estimate the influenza-associated mortality. These included multiplying the estimated number of symptomatic infections by the estimated ratio of hospitalizations to infections and the estimated ratio of deaths to hospitalizations. A brief technical description of how these approaches were implemented is listed in Web Table 2.

Fifty-four studies using regression models with an influenza activity proxy were identified (Table 1). Among them, 21 used polynomial and trigonometric functions of time to control for temporal trends and seasonality in mortality, respectively. The majority of the general linear models assumed that mortality followed a normal distribution with an identity link, or a Poisson distribution with a log link. Temperature, humidity (absolute humidity (16, 25-28) or relative humidity (15, 29-33)), and respiratory syncytial virus activity (6, 13, 16, 26, 27, 30, 31, 34-44) were the covariates most commonly included in the regression models. More than ten different influenza activity proxies were used in the reviewed studies. The most commonly used influenza activity proxy (33.3%) was the proportion of sentinel samples positive for influenza (Web Figure 11). Thirty-four studies using general linear models assumed no time lag between influenza activity and population mortality (Table 1). Details of the studies using regression models with an influenza activity proxy are shown in Web Appendix 2.

Thirty-five studies provided estimates of the influenza-associated excess mortality from models without an influenza activity proxy (Table 1). Of these, 28 used Serfling-type models. Most studies (15/28) using Serfling-type models assumed that the mortality followed a normal distribution with an identity link, and used a linear or quadratic function of time, and a trigonometric function of time to control for the trend and seasonality of mortality. Details of studies using Serfling-type models were shown in Web Appendix 2.

Four studies applied moving average methods (20, 45-47), 6 used relative mortality distribution models (48-53), and 10 applied incidence rate-difference models (30, 54-62).

Most of the included studies reported estimates of high-income countries, while only one study (59) provided the 1918-1920 pandemic influenza mortality in a low-income country (Sri Lanka). Eighty-one studies gave the estimates of temperate countries/regions, while 25 studies reported estimates of tropical or subtropical countries/regions.

Derivation of influenza-associated mortality

The majority of studies using Serfling-type models estimated the excess mortality by subtracting the baseline mortality from the observed mortality when the observed mortality was greater than the upper limit of the baseline mortality 95% confidence interval.

Four approaches were applied in the studies using regression models with an influenza activity proxy to estimate the excess mortality: 1) the observed mortality minus the predicted baseline mortality estimated from the fitted regression model in which influenza activity was assumed to be zero $\mu_{0,t}$; 2.1) subtraction of $\mu_{0,t}$ from the predicted mortality estimated from a model that fitted the observed influenza activity μ_t, i.e. μ_t - $\mu_{0,t}$; 2.2) same as method 2.1, but the estimate of excess mortality for a particular year would be set to zero if the annual number of excess deaths for that year was negative; and 2.3)

same as method 2.1, but the estimate of excess mortality at a particular time *t* would be set to zero if a negative excess mortality was obtained at time *t*.

Meta-regression analysis

The results of the Cochran *Q* test indicated the presence of heterogeneity in the age-specific estimates (children: $Q = 425$, $P < 0.001$; adults: $Q = 6502$, $P < 0.001$; older adults: $Q = 16449$, $P < 0.001$), and the I^2 statistic indicated that 100% of variance in the estimates was attributable to study heterogeneity rather than chance. The potential factors explored in the meta-regression analysis – age group, seasonal versus pandemic, cause of death used, income level and climatic zone of the study country/region, and the statistical modeling technique employed – explained 57.3% heterogeneity of the estimates. It suggested that estimates of influenza-associated mortality derived from the multiplier methods were generally smaller than those estimated from other models while estimates from the Serfling-type models were generally higher than those estimated from other models (Table 2). Within the estimates from each category of statistical method, the heterogeneity was also observed (regression models with influenza activity proxy: $Q = 34163$, $P < 0.001$; Serfling-type models: $Q = 7602$, $P < 0.001$; other models: $Q = 4142$, $P < 0.001$). The estimates were higher during seasonal influenza periods compared with the 2009 pandemic period, and higher for older adults. Estimates of the influenza-associated mortality were also increased when the model adopted a broader cause of death. The estimates in middle-income and tropical or subtropical countries/regions were higher than that in high-income

and temperate countries/regions, respectively, but the difference was not statistically significant.

DISCUSSION

We reviewed 103 published studies of influenza-associated mortality and observed substantial variation among the methods used. Estimates of influenza-associated mortality varied considerably across studies, with the annual age-standardized all-cause excess mortality rates ranging from 3 to 81 per 100,000 persons in seasonal periods and from -1 to 31 per 100,000 persons in the 2009 pandemic periods (Web Figure 2). No 'average' estimate of excess mortality could reliably be made due to the substantial heterogeneity of the estimates, and a more comprehensive modeling approach would be needed to extrapolate annual estimates of global mortality taking into account the variability between locations and years. The meta-regression indicated that modeling techniques were an important predictor of mortality estimates.

Consistent with previous studies (16, 28, 63), our review identified that the influenza-associated mortality burden was highest in older adults. This finding supports policies that recommend vaccination for the elderly, who are generally at a higher risk of serious complications from influenza (64). Influenza was reported to be associated with 0.1 laboratory-confirmed pediatric deaths per 100,000 persons annually in the US in 2004-2012 (65), which was generally less than the annual average influenza-associated all-cause mortality rate (0.7 per 100,000 persons) estimated for children in high-

income temperate countries/regions in our study. The observed difference between the laboratory-confirmed influenza deaths and the estimates of all-cause mortality from statistical models could be due to a substantial number of clinically undocumented deaths which were actually associated with influenza virus infection. However the laboratory-confirmed influenza deaths in children were very close to the influenza-associated pediatric mortality estimated from multiple models (Web Figure 2). This might be explained by the observation that fatal influenza virus infections in children were likely to have respiratory presentations and most of these deaths were more likely to be confirmed and reported (66). Negative estimates of the influenza-associated mortality with relatively wide 95% confidence intervals were observed for children in some studies (14-16). This may be attributable to the difficulty in differentiating seasonal excesses in childhood mortality, which is generally low. Therefore, greater uncertainty in influenza-associated mortality estimates for children would be expected in milder influenza seasons.

On average, the estimated influenza-associated all-cause excess deaths were higher than the cause-specific estimates. However, compared with cause-specific estimates, greater variation was observed in all-cause excess mortality estimates. Influenza virus infection may only marginally contribute to all-cause mortality but is more specifically associated with deaths caused by respiratory diseases or pneumonia (12, 67). The use of specific conditions to measure influenza-associated mortality may substantially underestimate

the population-level impact of influenza (67). The impact of influenza on causes of death not included in this review deserves further investigation to establish potential associations between influenza and other diseases (16, 30, 68). Conversely, conditions clearly not associated with influenza would be eligible for use as negative controls in cohort studies (69). We therefore suggest that future studies report estimates of influenza-associated mortality for a broader range of outcomes to provide a more comprehensive picture of the burden of influenza on mortality.

The meta-regression analysis suggested that the estimates of mortality burden vary by study design. Most of the included studies used time-series data in regression models to estimate the excess mortality associated with influenza; i.e. the excess mortality estimated from the observed mortality or the predicted mortality with and without incorporating influenza virus activities. In contrast, fewer studies applied multiplier methods using cross-sectional data to quantify the mortality burden. The multiplier method seemed to be associated with smaller estimates of influenza mortality burden compared to those from other methods. Further studies may be needed to investigate the possible impact of the methods on estimation of the disease burden.

In our study, estimates of the influenza-associated excess mortality were generally higher from the models that did not include a proxy of influenza virus activity (Table 2). Such studies often estimated influenza-associated mortality as the difference between the observed population mortality and a

baseline mortality that was mainly derived from time periods without apparent influenza virus activity. However the excess deaths estimated during influenza seasons might have also resulted from other underlying causes such as low temperature or co-circulating pathogens (16, 61). In addition, estimation of the baseline mortality solely dependent on data collected in inter-seasonal periods may not fully capture patterns in the baseline mortality, leading to a potential bias in estimates of excess mortality.

In models with an influenza activity proxy, the influenza-associated excess mortality was estimated as either: Method 1) subtraction of the predicted mortality Y with the influenza proxy X set to zero from the predicted mortality under the fitted model, i.e. $E(Y|X) - E(Y|X=0)$ (6, 13, 15, 16, 25-28, 34, 36, 37, 39-43, 61, 63, 70-77); or Method 2) subtraction of the predicted baseline mortality from the observed mortality, i.e. $Y - E(Y|X=0)$ (29-33, 68, 78-87). Estimates from Method 1 should represent the specific contribution from influenza, without residual errors in Y. In contrast, estimates from Method 2 would have the same point estimate but potentially greater uncertainty or variability owing to the persistence of residual errors in Y.

Some studies used zeros to replace negative estimates of the weekly excess mortality. Replacing negative estimates (i.e. reduced mortality) with zero has been justified by the biological argument that influenza epidemics should increase but not reduce mortality, although this depends to some extent on the cause of death examined. Some studies identified particular causes of

death such as unintentional injuries or bone fracture as negative controls (16, 30, 68). Influenza-associated mortality under these causes would be expected to have point estimates close to zero, with uncertainty intervals generally overlapping zero. This is a useful approach. However, if negative estimates are replaced with zeros it is not possible to confirm a null association of influenza with a control outcome, or potentially a positive association of influenza with other outcomes, because a positive association was already assumed when replacing negative values. In some studies, similar manipulations were made on annual estimates of the negative annual influenza-associated excess mortality (35, 44, 67), and this might lead to some overestimation of the average excess mortality.

Some studies used identity link or log link functions in the generalized linear regression models. The identity link function might be preferred for theoretical reasons if one assumes an additive effect of influenza virus activity and mortality; i.e. the number of excess deaths is assumed to be directly proportional to the number of infections rather than the logarithm of the number of infections (68). This approach presupposes that the influenza proxy should preferably be a direct correlate of the incidence of infection, an assumption that is rarely stated. For models that estimated excess mortality by subtracting baseline mortality (assuming influenza activity equals zero) from predicted mortality, the log link function may be less appropriate because it assumes a multiplicative effect of influenza and other covariates on mortality (16). A theoretical examination of the methodology used in excess

mortality studies would be valuable. Although we observed no major differences between mortality estimates using the two link functions, simulations may identify the conditions under which large discrepancies could arise (26).

There are several limitations to this study. First, we used three predefined age groups for an easier comparison in age-specific excess estimates from different studies. Sometimes the incomplete matching of the age classification reported in the included studies might have obscured the differences in the estimates between age groups. Second, standard errors were not provided for all estimates and we estimated these for some studies using a regression model (Web Appendix 1). Differences between true and estimated standard errors may have influenced the results of the meta-regression. Third, although we classified studies by four broad causes of deaths, the exact diagnostic codes used varied across studies. Fourth, we did not examine the influence of predominant virus(es) in the study period because they were not usually reported in the included studies. This is likely to be an important source of variation in mortality estimates, as mortality is typically higher in years when A(H3N2) predominates (6, 16, 68). Further studies may be needed to assess the temporal variation of the influenza-associated mortality and the potential influence of different predominant strains on the disease burden. Fifth, the age-standardized annual estimate of influenza-associated mortality was based on the individual estimates extracted from the selected studies and may have been calculated from influenza seasons of varying lengths. Finally, in the

meta-regression we included multiple estimates from the same study without accounting for potential clustering.

Conclusions

Methodological differences may account for much of the variation seen among reported estimates of influenza-associated mortality. Standardization of the methodology used for estimation would allow a more valid comparison of the estimates.

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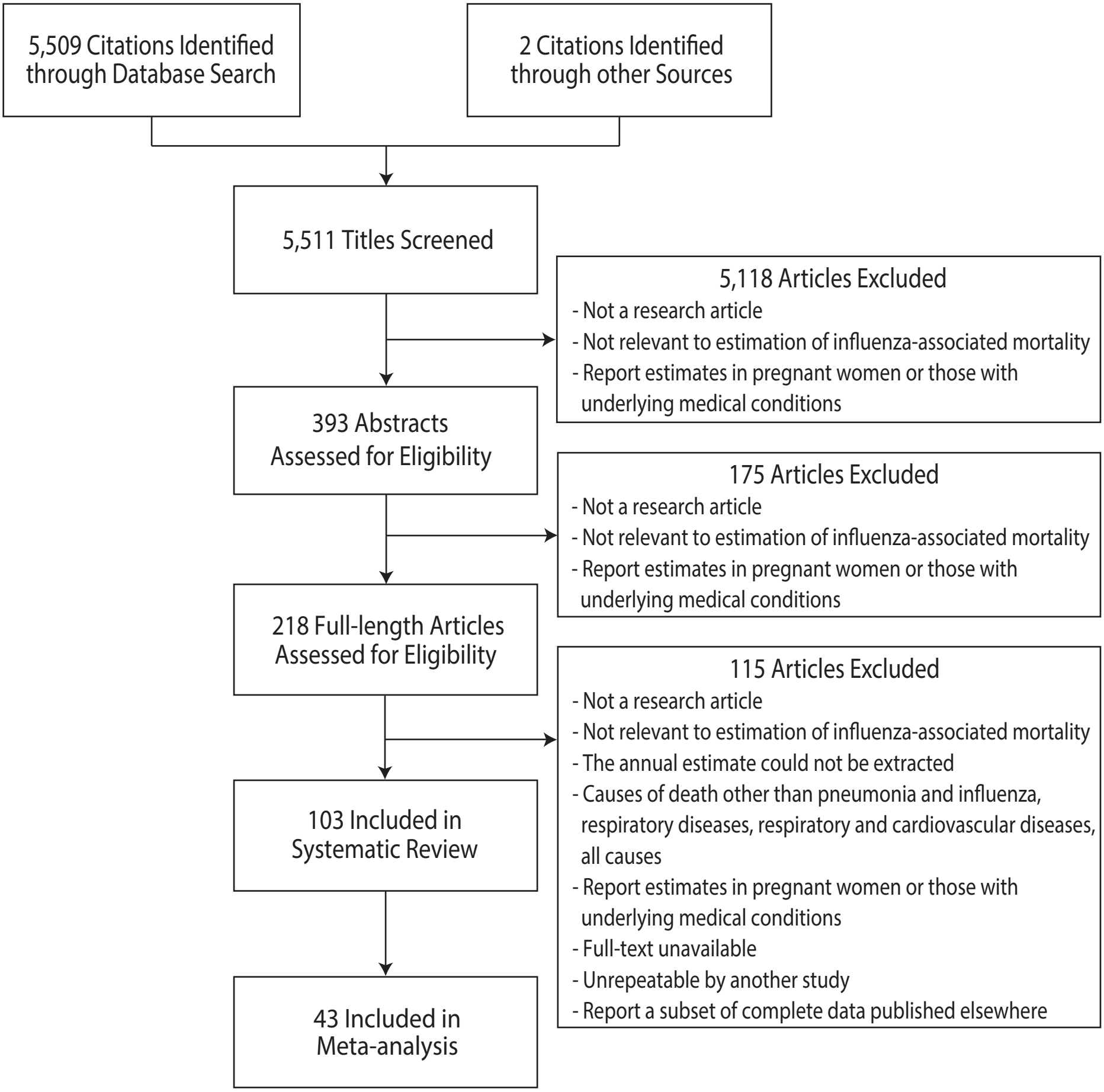
FIGURE LEGENDS

Figure 1. Flow chart for selection of studies.

Figure 2. Annual numbers of publications of studies on the influenza-associated mortality as of 22 March 2016.


5,509 Citations Identified through Database Search
2 Citations Identified through other Sources
5,511 Titles Screened
5,118 Articles Excluded
- Not a research article
- Not relevant to estimation of influenza-associated mortality
- Report estimates in pregnant women or those with underlying medical conditions
393 Abstracts Assessed for Eligibility
175 Articles Excluded
- Not a research article
- Not relevant to estimation of influenza-associated mortality
- Report estimates in pregnant women or those with underlying medical conditions
218 Full-length Articles Assessed for Eligibility
115 Articles Excluded
- Not a research article
- Not relevant to estimation of influenza-associated mortality
- The annual estimate could not be extracted
- Causes of death other than pneumonia and influenza, respiratory diseases, respiratory and cardiovascular diseases, all causes
- Report estimates in pregnant women or those with underlying medical conditions
- Full-text unavailable
- Unrepeatable by another study
- Report a subset of complete data published elsewhere
103 Included in Systematic Review
43 Included in Meta-analysis

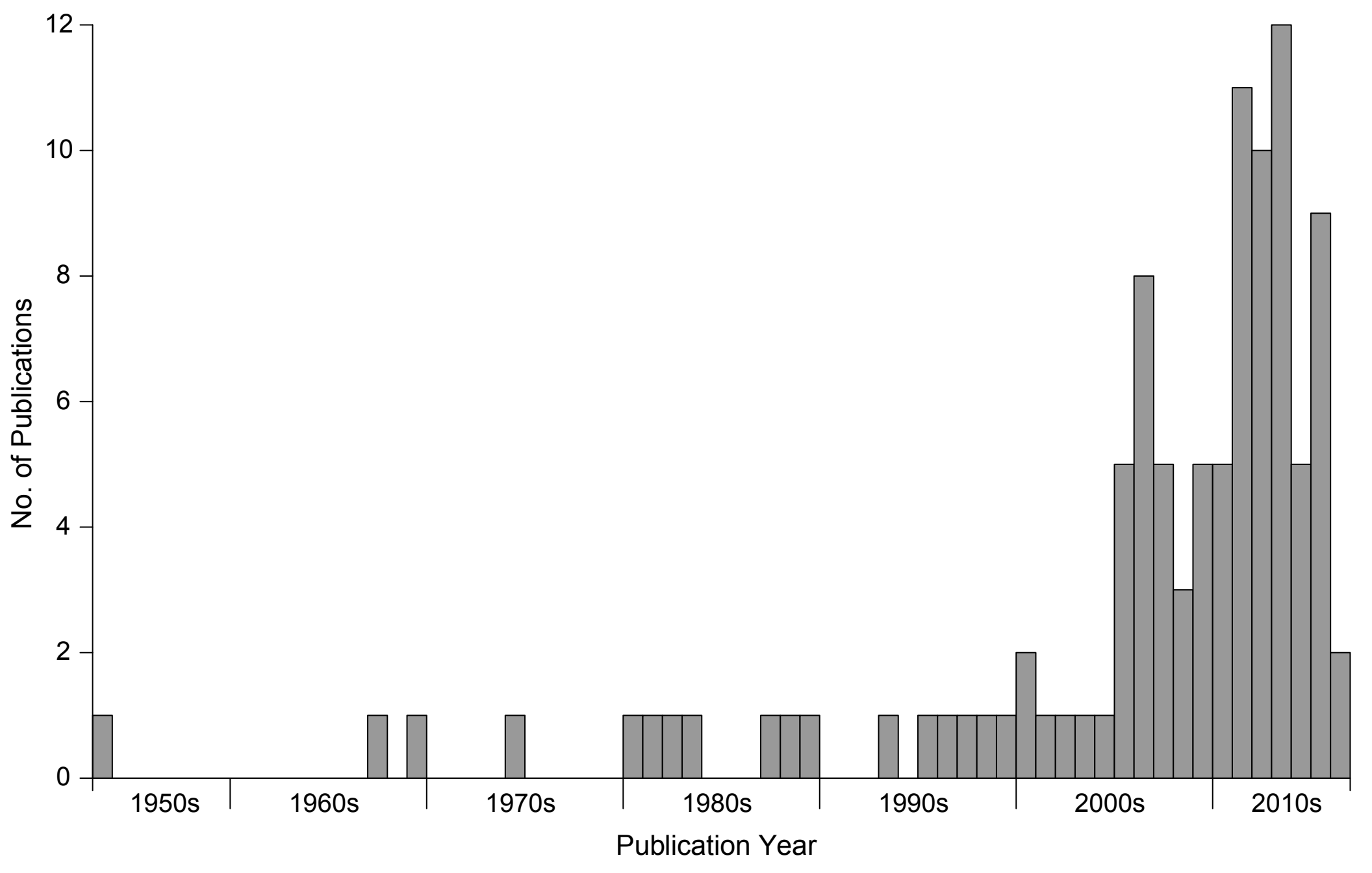

12
10
8
6
4
2
0
No. of Publications
1950s
1960s
1970s
1980s
1990s
2000s
2010s
Publication Year

Table 1. Characteristics of the Statistical Methods Applied in the Selected Studies to Estimate Influenza-associated Excess Mortality.

Characteristics	Number of studies (n=103) [a]	References
Models		
Multiplier methods	4	(8, 22-24)
Regression models with an influenza activity proxy	54	(6, 13-16, 21, 25-44, 61, 63, 67, 68, 70-93)
Serfling-type models	28	(34, 37, 39, 47, 53, 60, 61, 87, 94-113)
Other models	28	(20, 30, 45-62, 87, 114-120)
Consider effects of time in regression models with influenza activity proxy		
Yes	51	(6, 13-16, 21, 25-44, 61, 63, 67, 68, 70-80, 82-87, 89-92)
No	3	(81, 88, 93)
Lag between influenza activity and outcome in regression models		
0 week/month/year	35	(6, 13, 14, 21, 29, 31-34, 36-43, 61, 63, 70-72, 74, 76-79, 81-83, 85-89)
1 week	6	(16, 26-28, 30, 80)
Others [b]	14	(15, 25, 31, 35, 44, 67, 68, 73, 75, 84, 90-93)
Whether respiratory syncytial virus activity was considered in the regression models with influenza activity proxy		
Yes	18	(6, 13, 16, 26, 27, 30, 31, 34-44)
No	38	(6, 14, 15, 21, 25, 28, 29, 31-33, 61, 63, 67, 68, 70-93)
Income level		
Low-income	1	(59)
Middle-income	16	(15, 21, 25, 34, 42, 43, 59, 89, 93, 95, 98, 102, 104, 115-117)
High-income	89	(6, 13, 14, 16, 20-24, 26-41, 44-63, 67, 68, 70-88, 90-92, 96-101, 103-114, 118, 120)
Others [c]	4	(8, 21, 94, 119)
Climatic zone		
Temperate	81	(6, 13, 14, 20-24, 28, 34-41, 44, 47-63, 67, 68, 70-80, 82-93, 95-99, 103-118)
Tropical or sub-tropical	25	(15, 16, 21, 25-27, 29-34, 42, 43, 45, 46, 54, 59, 81, 98, 100-102, 104, 120)
Others [c]	4	(8, 21, 94, 119)

[a] We only included statistical methods used in the main analysis of each study into our analysis. Multiple statistical methods or models might have been used in one study to estimate the influenza-associated mortality, and therefore were counted separately in our data analysis. Similarly, some studies could also report estimates for more than one country. So these studies would be counted more than once in the table, leading to the subtotal in each category different from the total number of studies (n=103).

[b] Refers to studies applying a lag of 2 weeks, multiple lags, a moving average of influenza activity proxy in week 0 through week -2 with equal weights or in week -1 through week -2 with unequal weights, and those without indication of the lag.

[c] Refers to studies reporting a combined estimate for multiple countries.

Table 2. Results of the Meta-regression Analysis to Identify Variables that Influence Influenza-associated Mortality Estimates

Variable	Change in annual excess deaths (per 100,000 persons)	95% CI	*P*
Age group, years [a]			
Children	ref		
Adults	2	-10, 15	0.694
Older adults	57	46, 67	<0.001
Whether the estimate is for seasonal periods or pandemic periods			
Seasonal	ref		
2009 pandemic	-23	-33, -13	<0.001
Cause of death			
Pneumonia and influenza	ref		
Respiratory diseases	11	-2, 25	0.105
Respiratory and cardiovascular diseases	29	16, 42	<0.001
All causes	43	32, 54	<0.001
Statistical modeling technique			
Multiplier methods	ref		
Regression models with influenza activity proxy	30	-5, 65	0.096
Serfling-type models	40	3, 77	0.033
Other models	30	-6, 67	0.101
Income level [b]			
High-income	ref		
Middle-income	3	-14, 19	0.766
Climatic zone			
Temperate	ref		
Tropical or subtropical	5	-7, 18	0.408

Abbreviations: 95% CI, 95% confidence interval.

[a] Only studies reporting the age-specific estimates of influenza-associated mortality rate were included into the analysis.

[b] Income level in the middle year of the study period reported by the World Bank was used to classify the income level of a country. If no national income data was available for a specific year, the closest year to the study period with national income reported by the World Bank was used for the analysis.

WEB MATERIAL

Heterogeneity in Estimates of the Impact of Influenza on Population Mortality: A Systematic Review

Li Li, Jessica Y. Wong, Peng Wu, Helen S. Bond, Eric H. Y. Lau, Sheena G. Sullivan, and Benjamin J. Cowling

Web Appendix 1. Derivation of the mortality estimates

For studies reporting estimates of the influenza-associated mortality rate for each influenza season or calendar year, we calculated the average estimates directly. For studies that provided the number of influenza-associated deaths for each influenza season or calendar year, we first searched for an estimate of the source population, then we calculated the influenza-associated mortality rate as:

$$\left(\sum_i \frac{ED_i}{pop_i} \right) / N_T$$

where ED_i represents the number of influenza-associated deaths of the ith influenza season or calendar year, and pop_i represents the source population of the ith influenza season or calendar year, N_T represents the number of influenza seasons or years. When the data by age group were available, we calculated the age-standardized influenza-associated mortality rate using the WHO world standard population (1) as the reference. For studies which did not provide a standard error for the estimate, we imputed the standard error using the following regression model:

$$\log(SE_i) = |MR_i| + age_i + COD_i \qquad (1)$$

Where SE_i is the standard error of the ith estimate; $|MR_i|$ represents the absolute value of the influenza-associated mortality rate of the ith estimate; age_i represents the age group of the ith estimate, and COD_i represents the cause of death of the ith estimate.

Web Table 1. Basic Information of Included Articles.

Reference	Country or region	Study period	Statistical or modeling technique§	Whether the estimate is for seasonal periods or pandemic periods, or both	Influenza activity proxy#	Cause of death¶	ICDΔ	Age group (years)
Alling, 1981 (2)	US	1968-1976	GLM	Seasonal and 1968 pandemic	The number of acute respiratory deaths	AC	-	≥65, all ages
Andreasen, 2011 (3)	Denmark, Norway, Sweden, Italy, Netherlands, Spain, Sweden, US	1918-1920	RD	1918 pandemic	N	AC	-	1-14, all ages
Ansart, 2009 (4)	Finland, England and Wales, Scotland, Denmark, Norway, France, Switzerland, Germany, Sweden, Netherlands, Spain, Portugal, Bulgaria	1918-1919	Serfling	1918 pandemic	N	AC	-	All ages
Aungkulanon, 2015 (5)	Thailand	2006-2011	GLM	Seasonal and 2009 pandemic	LAB %	P&I, Res, AC	ICD-10	≥65, all ages
Azziz-Baumgartner, 2013 (6)	Argentina	2002-2009	Serfling	Seasonal and 2009 pandemic	N	P&I, R&C	ICD-10	All ages
Bonmarin, 2015 (7)	France	2000-2009	RD	Seasonal	N	AC	-	≥65
Brinkhof, 2006 (8)	Switzerland	1969-1999	GLM	Seasonal and 1968 pandemic	Influenza mortality rate	AC	ICD-8, ICD-10	≥60
Carrat, 1995 (9)	France	1980-1990	GLM	Seasonal	Influenza mortality rate	AC	ICD-9	Others
Charu, 2011 (10)	Mexico	2000-2010	Serfling	Seasonal and 2009 pandemic	N	P&I, Res, R&C, AC	ICD-10	5-19, 20-59, ≥60, all ages
Charu, 2013 (11)	US	2003-2009	GLM	Seasonal and 2009 pandemic	LAB %	P&I, Res, R&C	-	All ages
Cheng, 2015 (12)	Argentina, Chile, Mexico, Paraguay, Uruguay, US	2002-2009	Serfling, GLM	Seasonal	LAB %	Res, R&C	ICD-10	All ages
Choi, 1982 (13)	US	1968-1979	ARIMA, Serfling, GLM	Seasonal and 1968 pandemic	The number of acute respiratory deaths	P&I, AC	ICD-8	All ages
Chow, 2006 (14)	Singapore	1996-2003	GLM	Seasonal	LAB %	P&I, R&C, AC	ICD-9	20-64, ≥65, all ages
Chowell, 2014 (15)	Spain	1918-1919	Serfling	1918 pandemic	N	Res, AC	-	All ages
Cohen, 2010 (16)	South Africa, US	1998-2005	Serfling	Seasonal	N	P&I, Res, AC	ICD-9, ICD-10	≥65

Collins, 1953 (17)	US*	1918-1951	MA	Seasonal and 1918 pandemic	N	P&I, AC	-	All ages
Cooper, 2015 (18)	Thailand	2005-2009	GLM	Seasonal	LAB % × ILI %	Res, AC	ICD-10	0-18, 18-59, ≥60, all ages
Dawood, 2012 (19)	Africa, Americas, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific	2009-2010	Multiplier	2009 pandemic	N	Res, R&C	-	All ages
Dushoff, 2006 (20)	US	1979-2001	GLM	Seasonal	LAB %	P&I, R&C, AC	ICD-9, ICD-10	All ages
Egger, 1989 (21)	Switzerland	1970-1985	ARIMA	Seasonal	NA	AC	-	All ages
Fleming, 2000 (22)	England and Wales	1989-1999	RD	Seasonal	N	AC	-	All ages
Fleming, 2005 (23)	England	1989-2000	RD	Seasonal	N	Res, AC	ICD-9	0-14, all ages
Foppa, 2008 (24)	US	1995-2005	GLM	Seasonal	The number of influenza-certified deaths	AC	ICD-9, ICD-10	All ages
Foppa, 2015 (25)	US	2005-2014	GLM	Seasonal and 2009 pandemic	Others	R&C	ICD-10	0.5-19, 20-64, ≥65, all ages
Goldstein, 2012 (26)	US	1997-2007	GLM	Seasonal	LAB % × ILI %	P&I, Res, AC	ICD-9, ICD-10	All ages
Gran, 2010 (27)	Norway	1975-2004	GLM	Seasonal	ILI number	AC	-	0-14, 15-64, ≥65, all ages
Gran, 2013 (28)	Norway	1998-2011	GLM	Seasonal and 2009 pandemic	ILI number	P&I, AC	ICD-10	0-14, 15-64, ≥65, all ages
Green, 2013 (29)	England and Wales	2006-2012	GLM	Seasonal and 2009 pandemic	LAB % × ILI %	P&I, Res, R&C, AC	ICD-10	0-14, 15-64, ≥65
Hardelid, 2013 (30)	England and Wales	1999-2010	GLM	Seasonal and 2009 pandemic	LAB number	AC	-	0-14, all ages
Housworth, 1974 (31)	US	1957-1966	Serfling	Seasonal and 1957 pandemic	N	Res, AC	-	All ages
Imaz 2006 (32)	Argentina	1992-2002	ARIMA	Seasonal	NA	P&I, AC	-	≥65, all ages
Ivan 1969 (33)	Moldova	1957-1967	GLM	Seasonal and 1957 pandemic	Unclear	AC	-	All ages
Jansen, 2007 (34)	Netherlands	1997-2003	RD	Seasonal	N	AC	ICD-9	≥65
Kessaram, 2015 (35)	New Zealand	1990-2008	GLM	Seasonal	LAB number	R&C, AC	ICD-9, ICD-10	≥65, all ages
Kuo, 2011 (36)	Austria	2001-2009	Serfling	Seasonal	N	AC	-	All ages
Kyncl, 2005 (37)	Czech Republic	1982-2000	Surv	Seasonal	N	AC	ICD-9	All ages
Lee, 2007 (38)	Singapore	1918, 1957, 1968-1970	Regression	1918, 1957, 1968 pandemic	N	AC	-	All ages
Lee, 2009 (39)	Singapore	1972-2000	MA	Seasonal	N	AC	-	All ages

Lemaitre, 2012 (40)	France	1997-2010	GLM	Seasonal and 2009 pandemic	ILI %	P&I, Res, R&C, AC	ICD8, ICD-9, ICD-10	≥65, all ages
Leon-Gomez, 2015 (41)	Spain*	2006-2012	Serfling	Seasonal and 2009 pandemic	N	P&I, Res, AC	ICD-10	≥65, all ages
Li, 2006 (42)	Hong Kong	1999-2000	GLM	Seasonal	LAB %	P&I, R&C	ICD-9	All ages
Linhart, 2011 (43)	Israel	1999-2005	MA	Seasonal	N	P&I, R&C, AC	ICD-10	≥65, all ages
Lopez-Cuadrado, 2012 (44)	Spain	1999-2005	Serfling, GLM	Seasonal	LAB number	P&I, AC	ICD-10	≥65, all ages
Lui, 1987 (45)	US	1973-1985	Serfling	Seasonal	N	P&I, AC	ICD-8, ICD-9	All ages
Mamelund, 2000 (46)	Norway	1918-1919, 1957-1958, 1969-1970, 1977-1978	RD	Seasonal and 1918, 1957, 1968 pandemic	N	AC	-	All ages
Mann, 2013 (47)	England and Wales	1975-2005	GLM	Seasonal	Others	P&I	ICD-8, ICD-9, ICD-10	≥65
Matias, 2014 (48)	US	1997-2009	GLM	Seasonal	LAB %	P&I, Res, R&C	ICD-9, ICD-10	0-17, 18-64, ≥65, all ages
Mazick, 2010 (49)	Europe*	2009	Serfling	2009 pandemic	N	AC	-	5-14
Molbak, 2011 (50)	Denmark	2009	GLM	2009 pandemic	ILI %	AC	-	0-14, 15-64, ≥65, all ages
Murray, 2006 (51)	Argentina, Venezuela, Australia, Austria, Belgium, Canada, Chile, Denmark, England, Finland, France, Germany, India, Italy, Japan, Netherlands, New Zealand, Norway, Philippines, Portugal, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Uruguay, US	1918-1920	RD	1918 pandemic	N	AC	-	All ages
Muscatello, 2014 (52)	Australia	2003-2009	GLM	Seasonal and 2009 pandemic	LAB number	Res, R&C, AC	ICD-10	≥65, all ages
Newall, 2008 (53)	Australia	1997-2004	GLM	Seasonal	LAB number	P&I, AC	ICD-10	≥65
Newall, 2010 (54)	Australia	1997-2004	GLM, Serfling	Seasonal	LAB number	Res, AC	ICD-10	≥65
Nguyen, 2013 (55)	US	2009-2010	Serfling	Seasonal and 2009 pandemic	N	P&I	ICD-7, ICD-8, ICD-9, ICD-10	0-14, 15-64, ≥65, all ages
Nicholson, 1996 (56)	England and Wales	1975-1990	TwoR	Seasonal	Unclear	AC	-	All ages
Nielsen, 2011 (57)	Denmark	1994-2010	GLM	Seasonal and 2009 pandemic	Others	AC	-	0-14, 15-64, ≥65, all ages

Nogueira, 2009 (58)	Portugal	2008-2009	Serfling	Seasonal	N	AC	-	≥65, all ages
Nunes, 2011 (59)	Portugal	1980-2004	ARIMA	Seasonal	N	P&I, Res, AC	ICD-9, ICD-10	Others
Ohmi, 2011 (60)	Japan	1952-2006	RMD	Seasonal	N	AC	-	All ages
Park, 2016 (61)	South Korea	2003-2013	GLM	Seasonal and 2009 pandemic	LAB % × ILI %	P&I, Res, AC	ICD-10	0-14, 15-64, ≥65, all ages
Pitman, 2007 (62)	England and Wales	1996-2004	GLM	Seasonal	LAB number	Res	ICD-9, ICD-10	0-14, 15-64, ≥65, all ages
Presanis, 2011 (63)	England	2009-2010	Multiplier	2009 pandemic	N	AC	-	All ages
Quandelacy, 2014 (64)	US	1997-2007	GLM	Seasonal	LAB % × ILI %	P&I, Res, AC	ICD-9, ICD-10	0-17, 15-64, ≥65, all ages
Reed, 2015 (65)	US	2010-2013	Multiplier	Seasonal	N	AC	-	0-18, 19-64, ≥65, all ages
Richard, 2009 (66)	Japan, UK, US	1918-1920	Serfling, RD	1918 pandemic	N	P&I, AC	-	All ages
Rizzo, 2006 (67)	Italy	1970-2001	Serfling	Seasonal	N	P&I, AC	ICD-8, ICD-9	≥65
Rizzo, 2007 (68)	Italy[d]	1970-2001	Serfling	Seasonal	N	P&I, AC	ICD-8, ICD-9	Others
Schanzer, 2007 (69)	Canada	1990-1999	GLM	Seasonal	The number of influenza-certified deaths	P&I, AC	ICD-9	≥65, all ages
Schanzer, 2013 (70)	Canada	1992-2009	GLM	Seasonal	Others	AC	ICD-9, ICD-10	All ages
Serfling, 1967 (71)	US	1957-1958	Serfling	1957 pandemic	N	P&I	-	5-14, all ages
Shrestha, 2011 (72)	US	2009-2010	Multiplier	2009 pandemic	N	AC	-	0-17, 18-64, ≥65, all ages
Simonsen, 1997 (73)	US	1972-1992	Serfling	Seasonal	N	P&I, AC	ICD-8, ICD-9	All ages
Simonsen, 1998 (74)	US	1968-1995	MA, Serfling	Seasonal and 1968 pandemic	N	P&I	ICD-8, ICD-9	All ages
Simonsen, 2005 (75)	US	1968-2001	Serfling	Seasonal and 1968 pandemic	N	AC	ICD-9, ICD-10	≥65, all ages
Simonsen, 2013 (76)	Africa, Eastern Mediterranean, Europe, Africas, Southeast Asia, Western Pacific, Mexico, US, China, France	2009	GLM	2009 pandemic	LAB number	Res, R&C, AC	ICD-10	≥65
Simon Mendez, 2012 (77)	Spain	1980-2008	Serfling	Seasonal	N	P&I	ICD-9, ICD-10	≥65, all ages
Sprenger, 1993 (78)	Netherlands	1967-1989	GLM	Seasonal and 1968 pandemic	Influenza mortality rate	AC	ICD-9	≥60, all ages
Stroup, 1988 (79)	US	1968-1983	ARIMA, TF	Seasonal and 1968 pandemic	N	P&I, AC	-	0-14, 15-64, ≥65, all ages

Tachibana, 1999 (80)	Japan	1980-1994	RMD	Seasonal	N	AC	ICD-9	0-14, 15-64, ≥65, all ages
Takahashi, 2001 (81)	Japan	1975-1997	RMD	Seasonal	N	AC	ICD-8, ICD-9	All ages
Takahashi, 2002 (82)	Japan	1975-1999	RMD	Seasonal	N	AC	ICD-8, ICD-9, ICD-10	≥65, all ages
Takahashi, 2008 (83)	Japan	1987-2005	RMD	Seasonal	N	AC	ICD-9, ICD-10	≥65, all ages
Tempia, 2014 (84)	South Africa	1998-2009	GLM	Seasonal and 2009 pandemic	LAB %	P&I, Res	ICD-10	Others
Tempia, 2015 (85)	South Africa	1998-2009	GLM	Seasonal and 2009 pandemic	LAB %	P&I, Res, AC	ICD-10	5-19, 20-64, ≥65
Thompson, 2003 (86)	US	1976-1999	GLM	Seasonal	LAB %	P&I, AC	ICD-9, ICD-10	All ages
Thompson, 2009 (87)	US	1976-2003	RD, Serfling, GLM, ARIMA	Seasonal	LAB %	R&C	ICD-8, ICD-9, ICD-10	≥65, all ages
Tillett, 1980 (88)	England and Wales	1975-1979	GLM	Seasonal	Others	AC	-	All ages
Tillett, 1983 (89)	England and Wales	1968-1978	GLM	Seasonal and 1968 pandemic	Others	Res	ICD-8	All ages
US CDC, 2010 (90)	US	1976-2007	GLM	Seasonal	LAB %	P&I, R&C	ICD-8, ICD-9, ICD-10	0-19, 20-64, ≥65, all ages
van Asten, 2012 (91)	Netherlands	1999-2007	GLM	Seasonal	LAB number	AC	-	≥65
Wijngaard, 2012 (92, 93)	Netherlands	1999-2010	GLM	Seasonal and 2009 pandemic	ILI %	P&I, R&C, AC	ICD-10	≥65, all ages
Viboud, 2005 (94)	US, Canada, England and Wales, France, Japan, Australia	1967-1970	Serfling	Seasonal and 1968 pandemic	N	P&I, AC	-	All ages
Viboud, 2006 (67)	Canada, England and Wales	1951, 1957-1958	Serfling	Seasonal and 1957 pandemic	N	P&I, AC	ICD-6, ICD-7, ICD-8, ICD-9, ICD-10	All ages
Viboud, 2016 (95)	World	1957-1959	Regression	1957 pandemic	N	P&I, Res, R&C	ICD-7	≥65, all ages
Wong, 2004 (96)	Hong Kong	1996-1999	RD, GLM	Seasonal	LAB %	P&I, R&C, AC	ICD-9	≥65, all ages
Wong, 2012 (97)	Hong Kong, Singapore	2006-2008	GLM	Seasonal	LAB %	P&I, R&C, AC	-	≥65, all ages
Wong, 2013 (98)	Hong Kong	2009	DLM, GLM	2009 pandemic	Incidence rate of influenza, LAB % × ILI %, ILI %, LAB %	AC	ICD-10	0-14, 15-59, ≥60, all ages
Wu, 2012 (99)	Hong Kong	1998-2009	GLM	Seasonal and 2009 pandemic	LAB % × ILI %	P&I, Res, AC	ICD-9, ICD-10	0-14, 15-64, ≥65, all ages
Wu, 2014 (100)	Hong Kong	2009-2011	GLM	Seasonal and 2009 pandemic	LAB % × ILI %	Res, AC	ICD-9, ICD-10	≥65
Yang, 2011 (101)	Hong Kong, Singapore	2004-2006	GLM	Seasonal	LAB %	P&I, R&C, AC	ICD-10, ICD-9	≥65, all ages
Yang, 2012 (102)	Hong Kong	1998-2009	GLM	Seasonal and 2009	LAB %	P&I, R&C, AC	ICD-10	0-19, 20-64, ≥65,

				pandemic				all ages
Yu, 2013 (103)	China*	2004-2010	GLM	Seasonal and 2009 pandemic	LAB %	Res, R&CAC	ICD-10	≥65, all ages
Zucs, 2005 (104)	Germany	1985-2001	Serfling, RMD	Seasonal	N	AC	-	All ages

US* represents 35 large US cities for the periods of 1918-1934 and 56 large US cities for the periods of 1935-1951. Spain* means 52 provincial capitals in Spain. Europe* is 8 European Countries including Belgium, Denmark, Greece, Hesse (region of Germany), Malta, the Netherlands, Sweden and Switzerland. Italy* means Northern, Central and Southern Italy. China* represents 128 sites in China.

#: Lab % refers to the proportion of laboratory samples testing positive for influenza. Lab number represents the number of laboratory samples testing positive for influenza. ILI % is the proportion of ambulatory consultations for influenza-like illness. ILI number refers to the number of ambulatory consultations for influenza-like illness. Others (influenza activity proxy) include Lab % × normalized number of outpatient visits due to ILI, number of laboratory-confirmed influenza A infections, a variation of ILI % (i.e. a product of ILI % of a specific influenza season and a normal distribution whose mean and standard derivation are the same as the ILI % over the same influenza season), mixed proxies used for different types of influenza viruses (i.e. influenza A: a combination of laboratory positive tests and the number of hospital admissions with laboratory-confirmation of influenza; influenza B: Lab %), and rate of clinical 'epidemic influenza'. N means no influenza activity proxy used in the model. Others (age group) include <1, 1-4, <5, ≥75 years, and standardized rates for 0-14, 15-44, 45-64, ≥65 years.

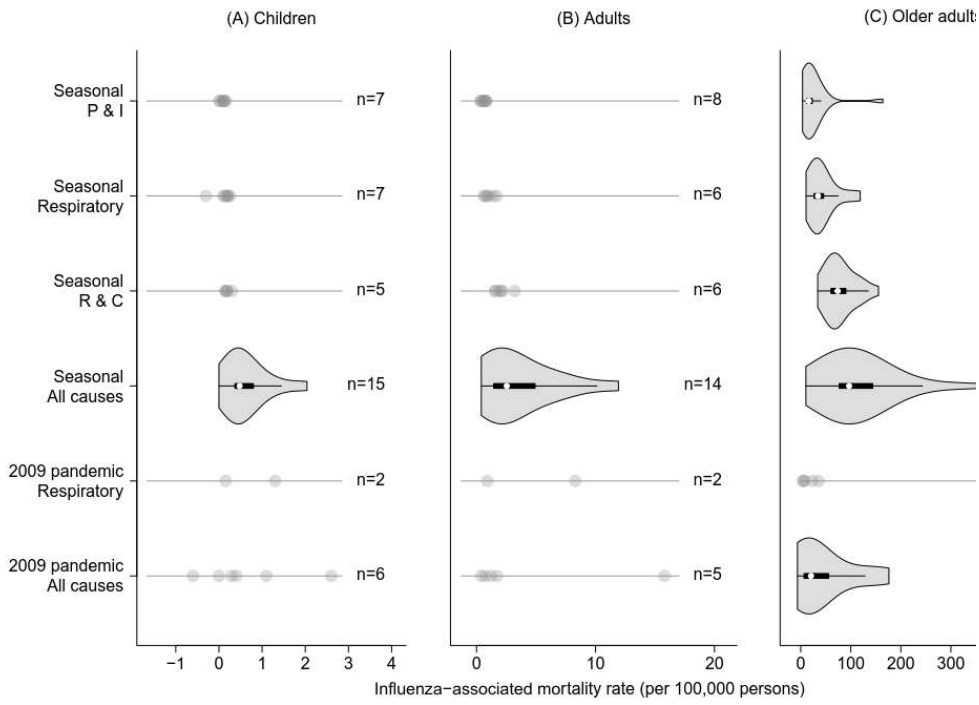
§: GLM, generalized linear model; RD, incidence rate-difference model; Serfling, Serfling-type model; ARIMA, autoregressive integrated moving average model; MA, moving average method; Multiplier, multiplier method; Surv, survival analysis; Regression, regression model without influenza activity proxy; TwoR, primary and secondary regression models to estimate the influenza-associated mortality with the predicted outcome of the primary regression as the dependent variable of the secondary regression; TF, transfer function; DLM, dynamic linear model; RMD, relative mortality distribution model.

Regression models with an influenza activity include DLM, GLM, and TwoR.

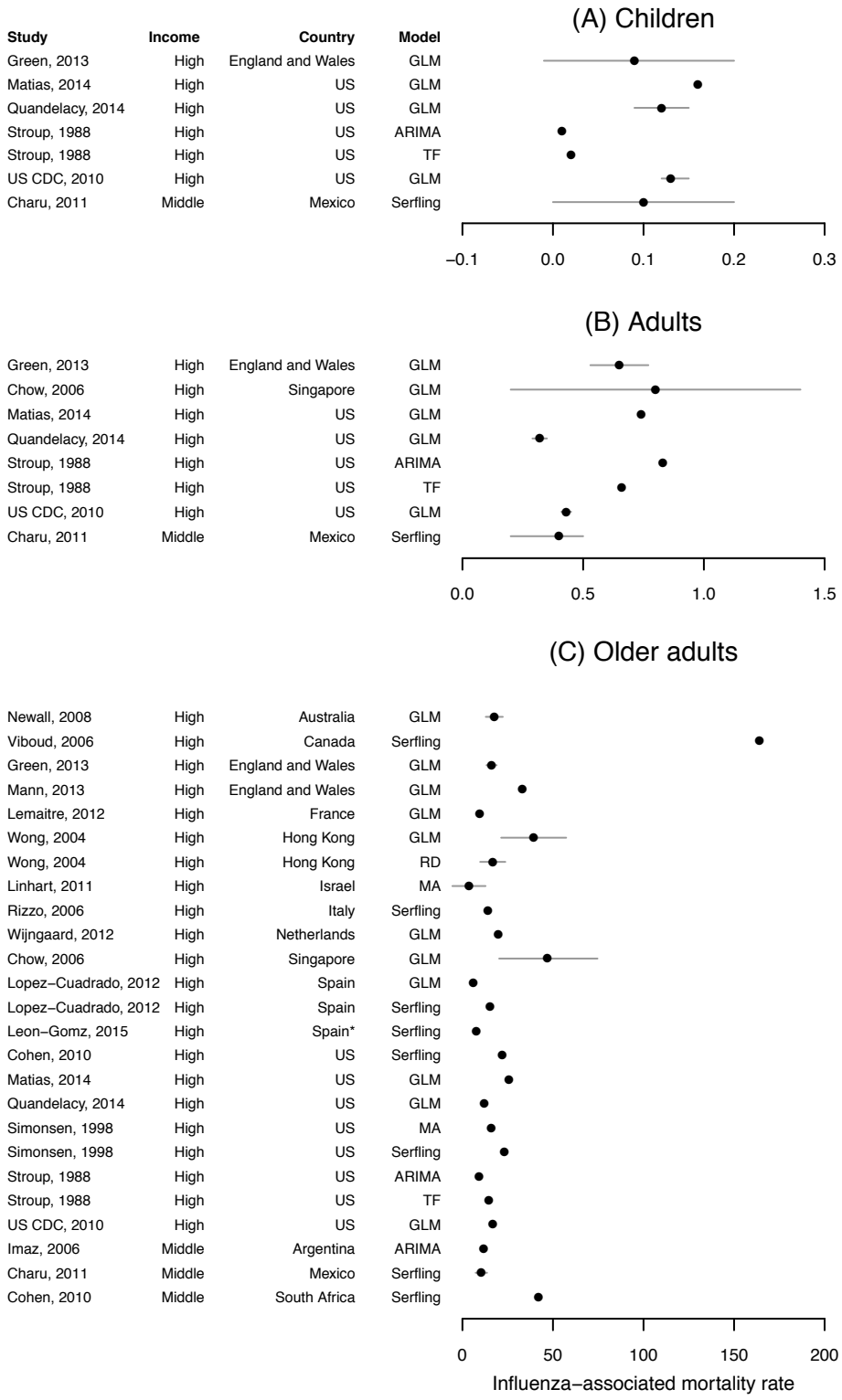
Models without an influenza activity proxy other than multiplier methods and Serfling-type models include Regression, ARIMA, TF, Surv, MA, RD, and RMD.

¶: P&I, pneumonia and influenza; Res, respiratory diseases; R&C, respiratory and cardiovascular diseases; AC, all causes.

Δ: ICD, the International Classification of Diseases.

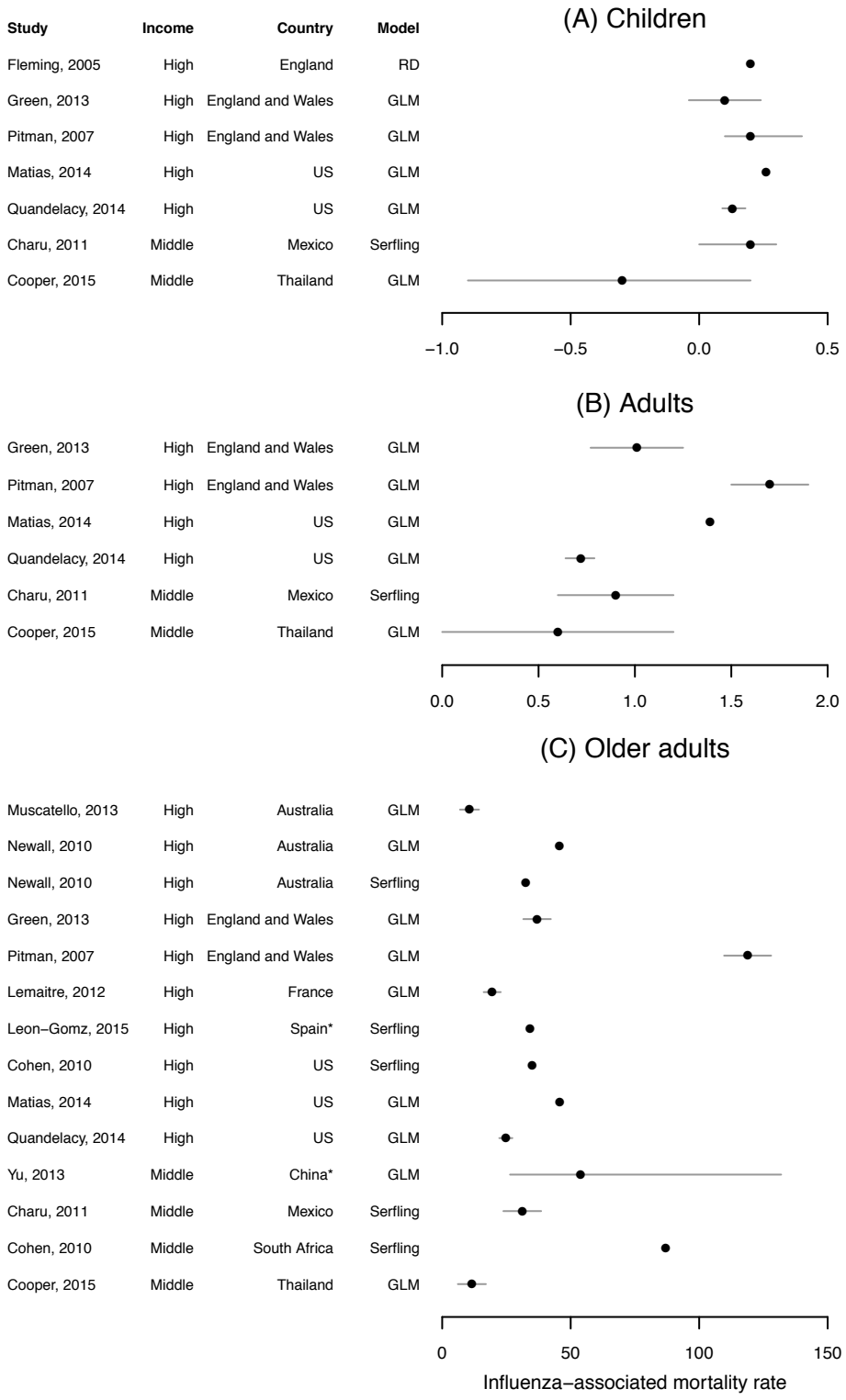


Web Figure 1. Estimates of the annual influenza-associated mortality ra
age group and cause of death. Abbreviations: P&I, pneumonia and influe
respiratory and cardiovascular diseases. If the number of estimates was
used violin plots to show the estimates. If the number of estimates was <
estimate from each study was indicated with dots. n indicates the numbe
studies for each category. The white point represents the median, the bla
represents the interquartile range and the black line represents the rang
the estimates included in that outcome-population category; e.g. 46 estin
the influenza-associated all-cause mortality burden were extracted for o
adults, with a median of 97 per 100,000 persons and an interquartile ran
between 77 and 144 per 100,000 persons. The width of the violin repres
the probability density of the estimates at different values; the wider the
the more variable the estimated mortality rates.



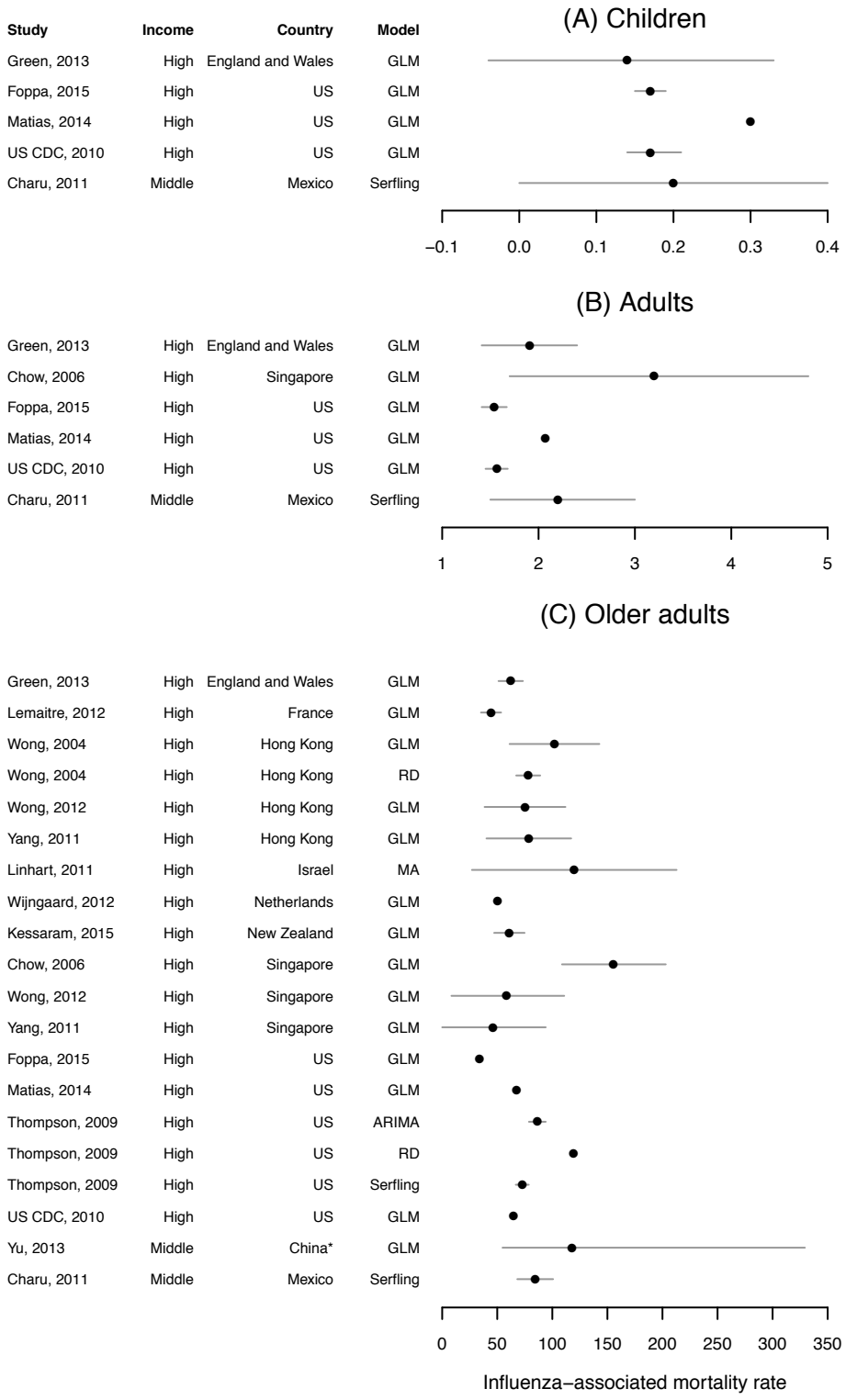
Web Figure 2. Annual age-specific influenza-associated excess pneumonia and influenza mortality rates in seasonal periods. (A) Estimates for children. (B) Estimates for adults (Cochran's Q for GLM: $Q = 71$, $P < 0.001$). (C) Estimates for

older adults (Cochran's Q for GLM: $Q = 285$, $P < 0.001$; Serfling: $Q = 1658$, $P < 0.001$; other models: $Q = 13$, $P < 0.023$). Spain* means 52 provincial capitals in Spain. GLM, generalized linear model; ARIMA, autoregressive integrated moving average model; TF, transfer function; Serfling, Serfling-type model; MA, moving average method; RD, incidence rate-difference model.



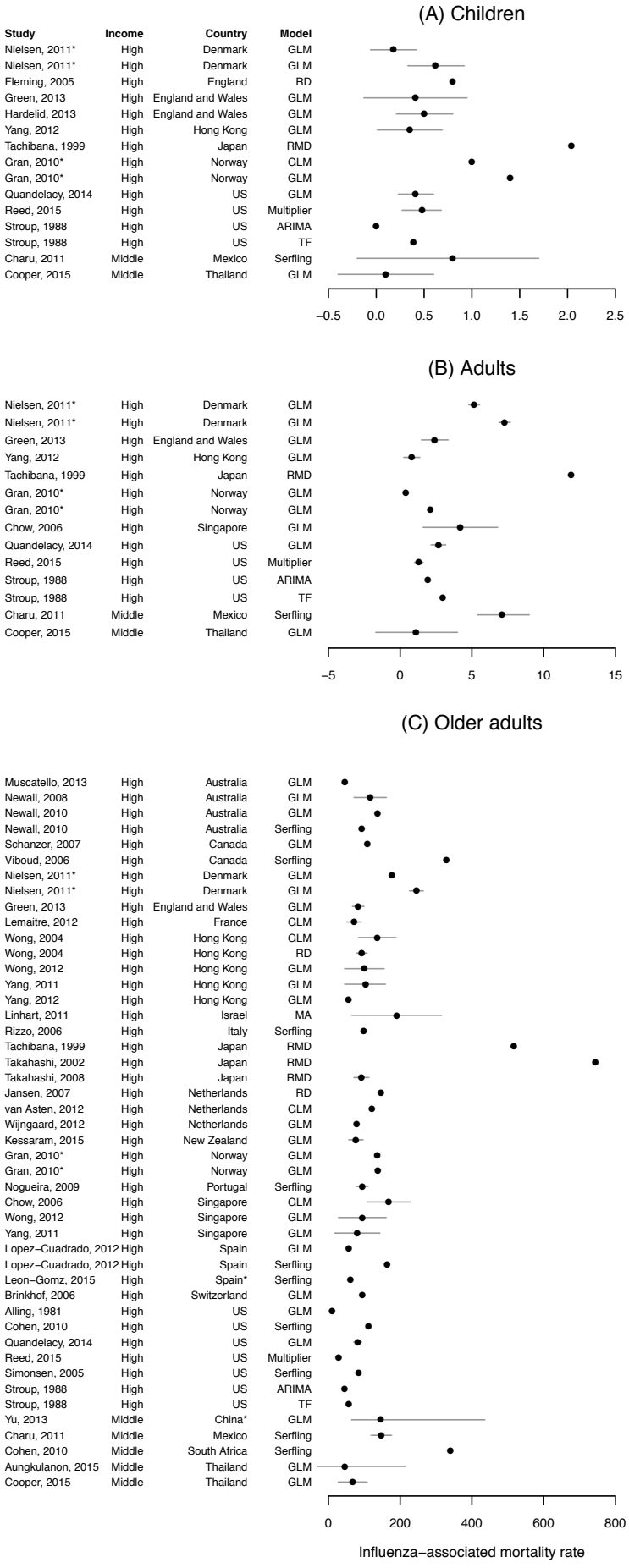
Web Figure 3. Annual age-specific influenza-associated excess respiratory mortality rates in seasonal periods. (A) Estimates for children (Cochran's Q for GLM: $Q = 6$, $P = 0.209$). (B) Estimates for adults (Cochran's Q for GLM: $Q = 93$, $P <$

0.001). (C) Estimates for older adults (Cochran's Q for GLM: $Q = 558$, $P < 0.001$; Serfling: $Q = 85$, $P < 0.001$). Spain* means 52 provincial capitals in Spain. China* represents 128 sites in China. RD, incidence rate-difference model. GLM, generalized linear model; Serfling, Serfling-type model.

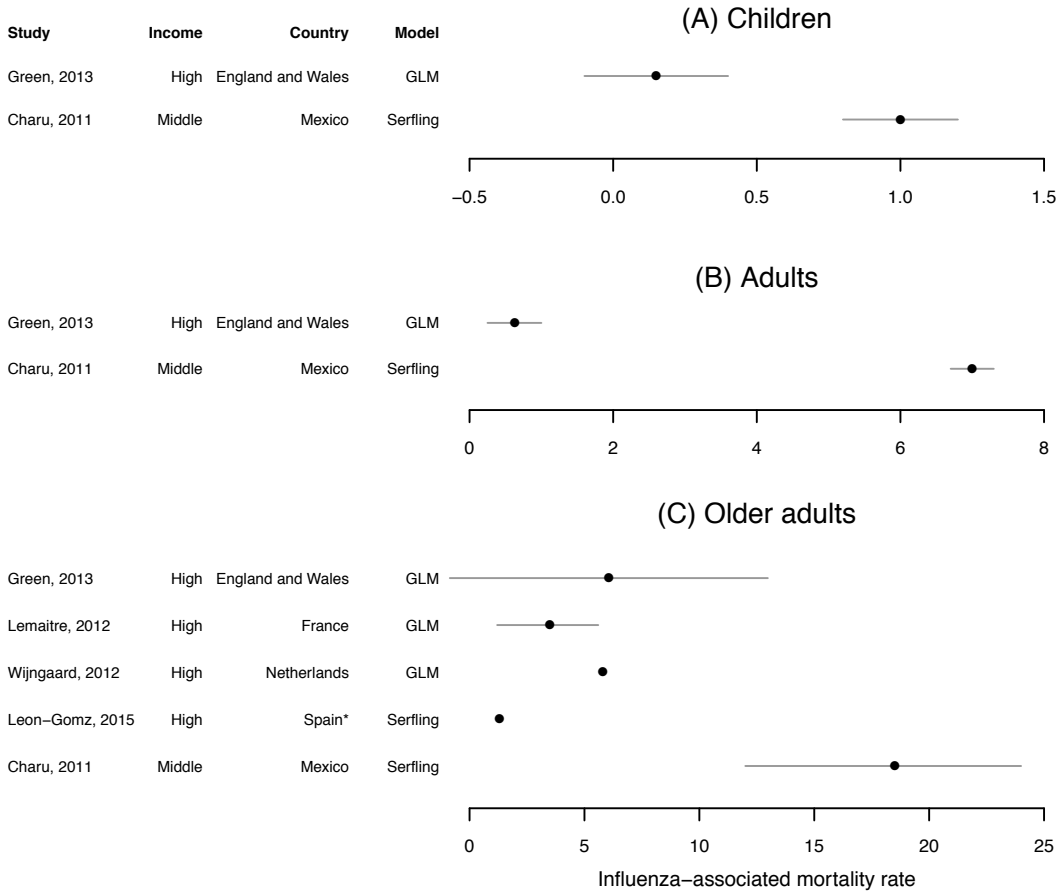


Web Figure 4. Annual age-specific influenza-associated excess respiratory and cardiovascular mortality rates in seasonal periods. (A) Estimates for children. (B) Estimates for adults (Cochran's Q test for GLM: $Q = 10$, $P = 0.047$). (C) Estimates

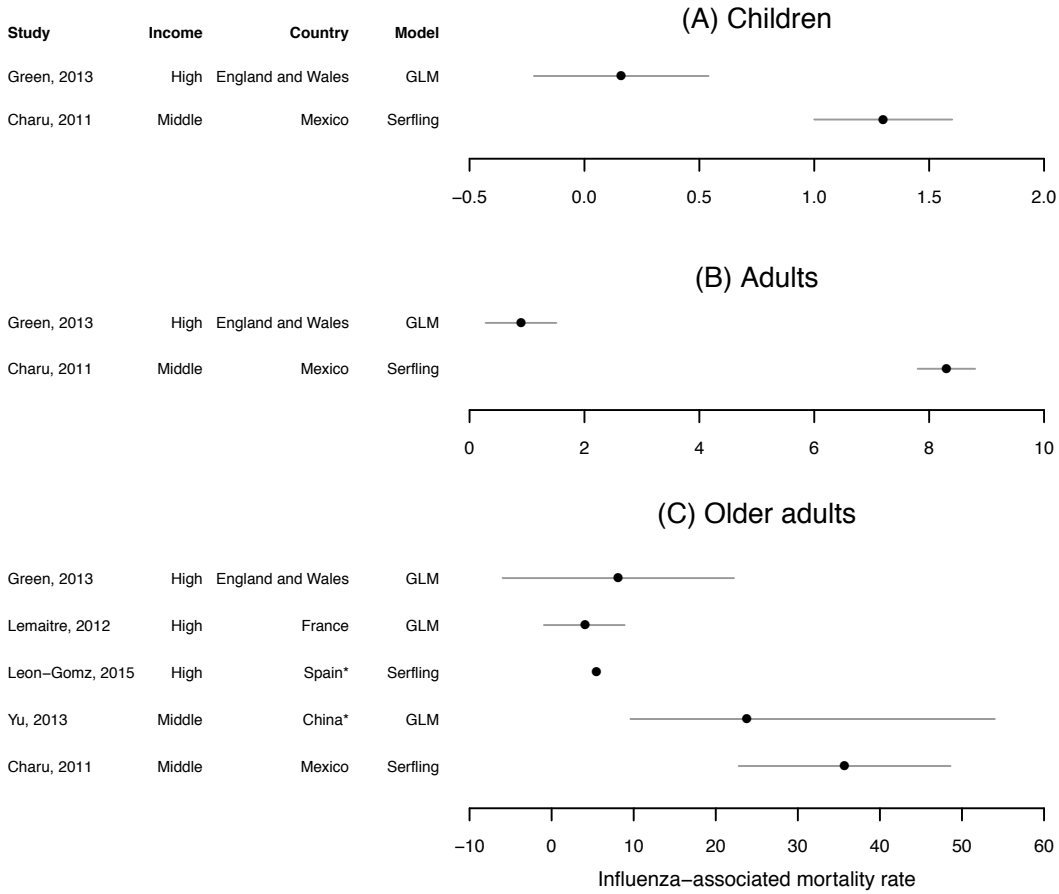
for older adults (Cochran's Q for GLM: $Q = 517$, $P < 0.001$). China* represents 128 sites in China. GLM, generalized linear model; Serfling, Serfling-type model; MA, moving average method; RD, incidence rate-difference model; ARIMA, autoregressive integrated moving average model.


(A) Children
Study Income Country Model
Nielsen, 2011* High Denmark GLM
Nielsen, 2011* High Denmark GLM
Fleming, 2005 High England RD
Green, 2013 High England and Wales GLM
Hardelid, 2013 High England and Wales GLM
Yang, 2012 High Hong Kong GLM
Tachibana, 1999 High Japan RMD
Gran, 2010* High Norway GLM
Gran, 2010* High Norway GLM
Quandelacy, 2014 High US GLM
Reed, 2015 High US Multiplier
Stroup, 1988 High US ARIMA
Stroup, 1988 High US TF
Charu, 2011 Middle Mexico Serfling
Cooper, 2015 Middle Thailand GLM
−0.5 0.0 0.5 1.0 1.5 2.0 2.5
(B) Adults
Nielsen, 2011* High Denmark GLM
Nielsen, 2011* High Denmark GLM
Green, 2013 High England and Wales GLM
Yang, 2012 High Hong Kong GLM
Tachibana, 1999 High Japan RMD
Gran, 2010* High Norway GLM
Gran, 2010* High Norway GLM
Chow, 2006 High Singapore GLM
Quandelacy, 2014 High US GLM
Reed, 2015 High US Multiplier
Stroup, 1988 High US ARIMA
Stroup, 1988 High US TF
Charu, 2011 Middle Mexico Serfling
Cooper, 2015 Middle Thailand GLM
−5 0 5 10 15
(C) Older adults
Muscatello, 2013 High Australia GLM
Newall, 2008 High Australia GLM
Newall, 2010 High Australia GLM
Newall, 2010 High Australia Serfling
Schanzer, 2007 High Canada GLM
Viboud, 2006 High Canada Serfling
Nielsen, 2011* High Denmark GLM
Nielsen, 2011* High Denmark GLM
Green, 2013 High England and Wales GLM
Lemaitre, 2012 High France GLM
Wong, 2004 High Hong Kong GLM
Wong, 2004 High Hong Kong RD
Wong, 2012 High Hong Kong GLM
Yang, 2011 High Hong Kong GLM
Yang, 2012 High Hong Kong GLM
Linhart, 2011 High Israel MA
Rizzo, 2006 High Italy Serfling
Tachibana, 1999 High Japan RMD
Takahashi, 2002 High Japan RMD
Takahashi, 2008 High Japan RMD
Jansen, 2007 High Netherlands RD
van Asten, 2012 High Netherlands GLM
Wijngaard, 2012 High Netherlands GLM
Kessaram, 2015 High New Zealand GLM
Gran, 2010* High Norway GLM
Gran, 2010* High Norway GLM
Nogueira, 2009 High Portugal Serfling
Chow, 2006 High Singapore GLM
Wong, 2012 High Singapore GLM
Yang, 2011 High Singapore GLM
Lopez−Cuadrado, 2012 High Spain GLM
Lopez−Cuadrado, 2012 High Spain Serfling
Leon−Gomz, 2015 High Spain* Serfling
Brinkhof, 2006 High Switzerland GLM
Alling, 1981 High US GLM
Cohen, 2010 High US Serfling
Quandelacy, 2014 High US GLM
Reed, 2015 High US Multiplier
Simonsen, 2005 High US Serfling
Stroup, 1988 High US ARIMA
Stroup, 1988 High US TF
Yu, 2013 Middle China* GLM
Charu, 2011 Middle Mexico Serfling
Cohen, 2010 Middle South Africa Serfling
Aungkulanon, 2015 Middle Thailand GLM
Cooper, 2015 Middle Thailand GLM
0 200 400 600 800
Influenza−associated mortality rate

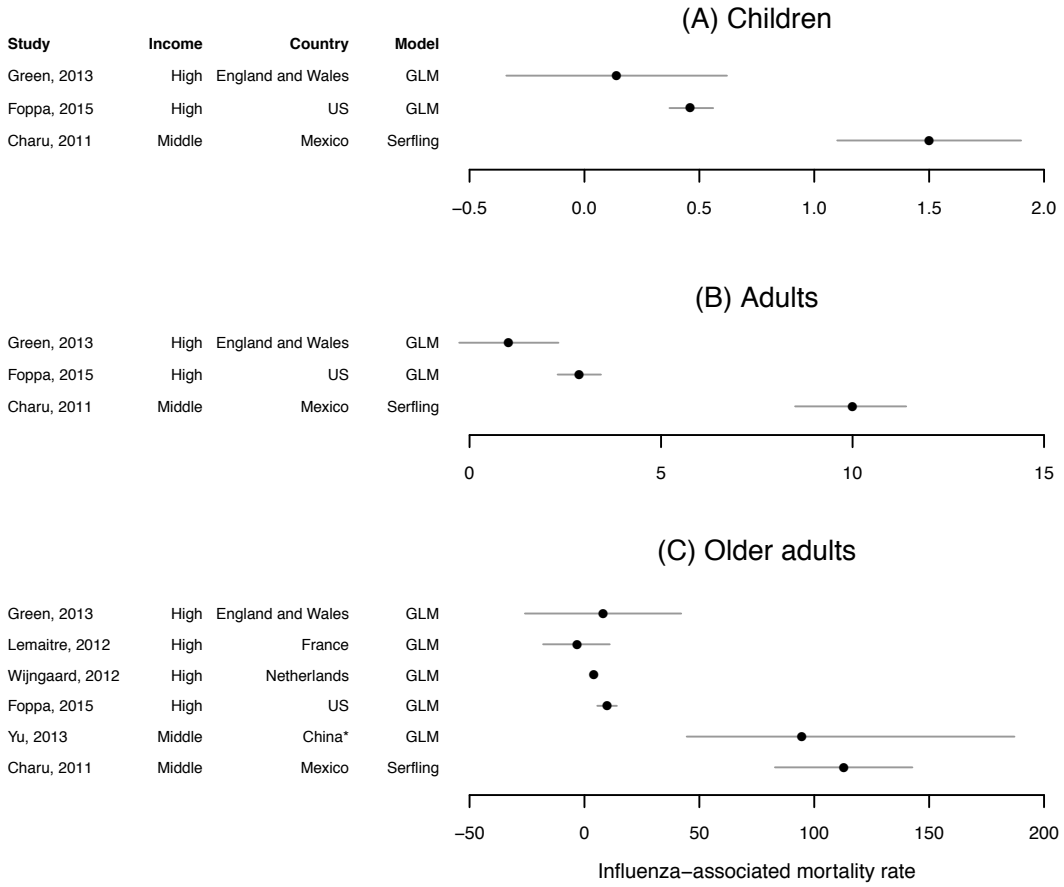
Web Figure 5. Annual age-specific influenza-associated excess all-cause mortality rates in seasonal periods. (A) Estimates for children (Cochran's *Q* for GLM: $Q = 29$, $P < 0.001$). (B) Estimates for adults (Cochran's *Q* for GLM: $Q = 521$, $P < 0.001$). (C) Estimates for older adults (Cochran *Q* for GLM: $Q = 1383$, $P < 0.001$; Serfling: $Q = 64$, $P < 0.001$; other models: $Q = 140$, $P < 0.001$). Nielsen, 2011* means there are two estimates derived from models using two different influenza activity proxies. Gran, 2010* means there are two estimates for the periods of 1975-1998 and the periods of 1998-2004, respectively. Spain* means 52 provincial capitals in Spain. China* represents 128 sites in China. RD, incidence rate-difference model; GLM, generalized linear model; Multiplier, multiplier method; ARIMA, autoregressive integrated moving average model; TF, transfer function; RMD, relative mortality distribution model; Serfling, Serfling-type model; MA, moving average method.



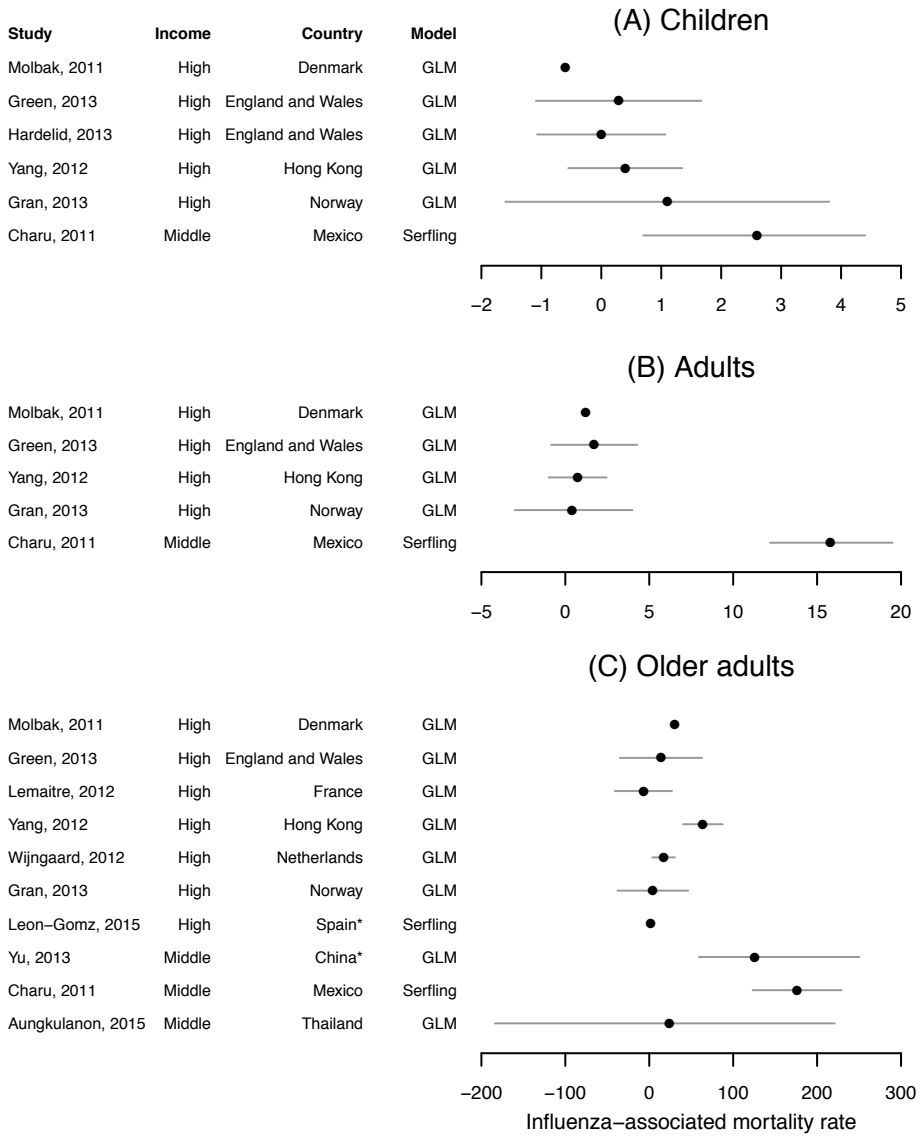
Web Figure 6. Annual age-specific influenza-associated excess pneumonia and influenza mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults. Spain* means 52 provincial capitals in Spain. Serfling, Serfling-type model; GLM, generalized linear model.



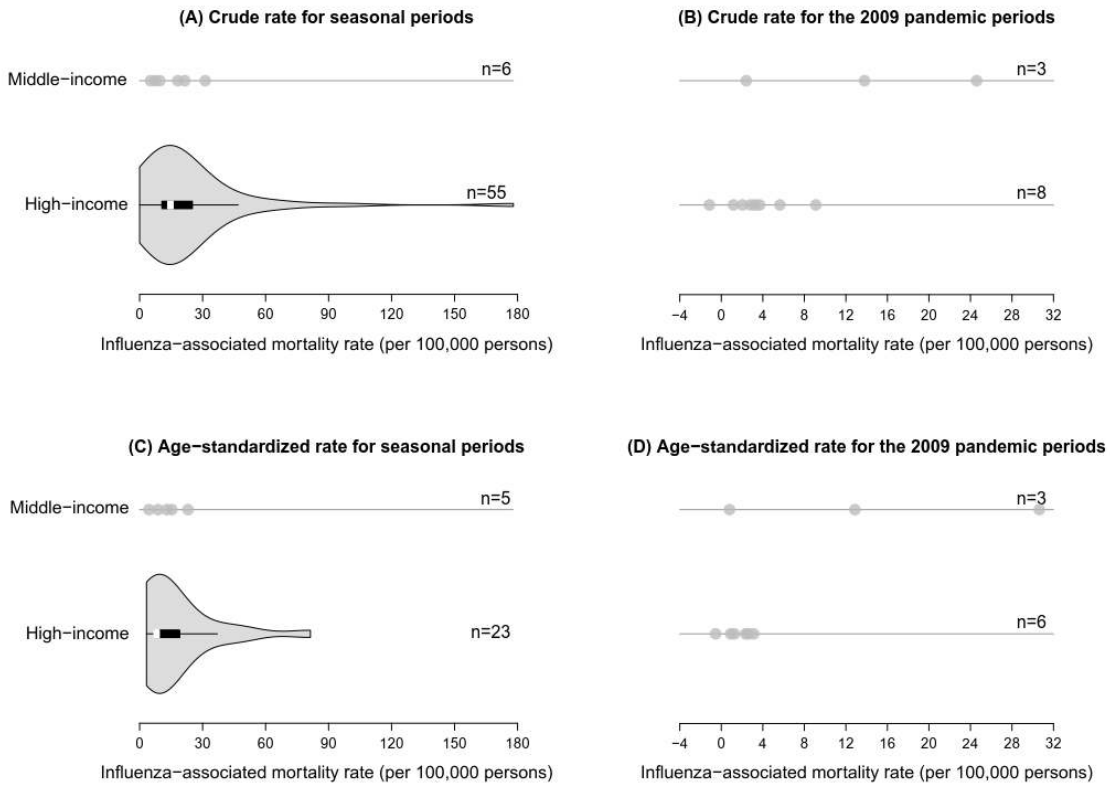
Web Figure 7. Annual age-specific influenza-associated excess respiratory mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults. Spain* means 52 provincial capitals in Spain. China* represents 128 sites in China. Serfling, Serfling-type model; GLM, generalized linear model.



Web Figure 8. Annual age-specific influenza-associated excess respiratory and cardiovascular mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults (Cochran's Q for GLM: $Q = 9$, $P = 0.061$). China* represents 128 sites in China. Serfling, Serfling-type model; GLM, generalized linear model.



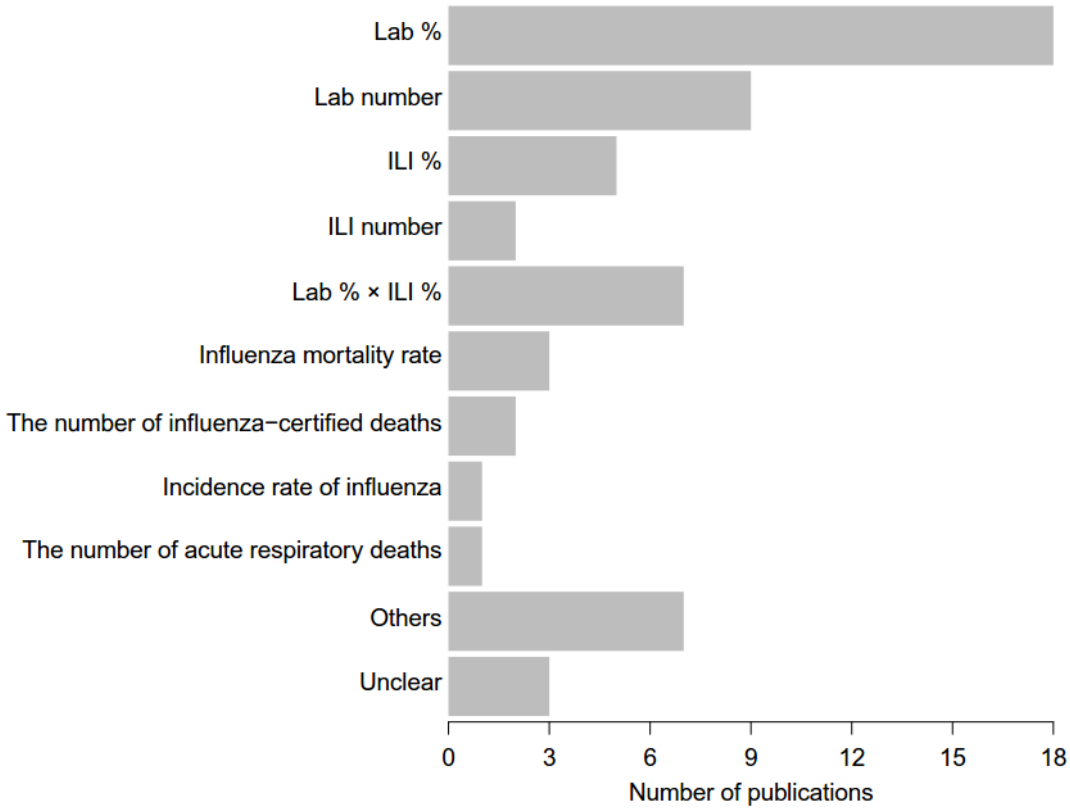
Web Figure 9. Annual age-specific influenza-associated excess all-cause mortality rates in the 2009 pandemic periods. (A) Estimates for children (Cochran's Q for GLM: $Q = 6$, $P = 0.227$). (B) Estimates for adults. (C) Estimates for older adults (Cochran's Q for GLM: $Q = 20$, $P = 0.005$). Europe* is 8 European Countries including Belgium, Denmark, Greece, Hesse (region of Germany), Malta, the Netherlands, Sweden and Switzerland. Spain* means 52 provincial capitals in Spain. China* represents 128 sites in China. Serfling, Serfling-type model; GLM, generalized linear model.



Web Figure 10. Annual crude and age-standardized all–cause influenza-associated excess mortality rates by income level. A violin plot was used when the number of estimates is equal to or larger than ten; the original estimate was plotted when there were less than ten estimates reported. (A) Annual crude influenza-associated all-cause excess mortality rates for seasonal periods. (B) Annual crude influenza-associated all-cause excess mortality rates for the 2009 pandemic periods. (C) Annual age-standardized influenza associated all-cause excess mortality rates for seasonal periods. (D) Annual age-standardized influenza associated all-cause excess mortality rates for the 2009 pandemic period.

Web Table 2. Description of the Multiplier Methods Used in the Included Studies.

Reference	Description
Dawood 2012 (19)	$Num_D = sAR \times sCFR \times RMM \times Num_{pop}$ *sAR*: the percentage of population who developed a symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1 *sCFR*: the percentage of individuals with symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1 who died *RMM*: risk-group-specific respiratory mortality multiplier Num_{pop}: population size Num_D: number of deaths attributable to influenza
Presanis 2011 (63)	$Num_{Inf} = C_{Inf\|pop} \times Num_{pop}$ $Num_S = C_{S\|Inf} \times Num_{Inf}$ $Num_H = C_{H\|S} \times Num_S$ $Num_D = C_{D\|H} \times Num_H$ Num_{pop}: population size $C_{Inf\|pop}$: infection attack rate Num_{Inf}: number of infections $C_{S\|Inf}$: proportion of symptomatic infections Num_S: number of symptomatic infections $C_{H\|S}$: symptomatic case hospitalization ratio Num_H: number of hospitalizations $C_{D\|H}$: deaths to hospitalizations ratio Num_D: number of deaths attributable to influenza
Reed 2015 (65)	$Rate_M = Rate_H \times Multiplier_U \times Ratio_{DH}$ $Num_D = Rate_M \times Num_{pop}$ $Rate_H$: influenza hospitalization rates $Multiplier_U$: the multiplier for under-detection $C_{D\|H}$: deaths to hospitalizations ratio $Rate_M$: influenza mortality rates Num_{pop}: population size Num_D: number of deaths attributable to influenza
Shrestha 2011 (72)	$Num_H = \frac{Rate_{H\_M} \times Num_{pop\_M}}{100{,}000}$ $Num_D = Num_H \times Multiplier_R \times C_{D\|H}$ $Rate_H$: median influenza hospitalization rates $Rate_{H\_M}$: $Rate_H$ from Emerging Infections Program (EIP) sites categorized as having mid-range level of hospitalizations Num_H: median number of hospitalizations $Multiplier_R$: the multiplier for under-reporting $C_{D\|H}$: deaths to hospitalizations ratio Num_D: median number of deaths attributable to influenza Num_{pop_M}: population of the state categorized as having ‘‘mid’’ level of influenza activity



Web Figure 11. Frequency of usage of different influenza activity proxies in the regression models for estimation of influenza-associated excess mortality in the selected studies. Some studies used more than one proxy, so totals exceed 54. Lab % refers to the proportion of laboratory samples testing positive for influenza. Lab number represents the number of laboratory samples testing positive for influenza. ILI % is the proportion of ambulatory consultations for influenza-like illness (ILI). ILI number refers to the number of ambulatory consultations for influenza-like illness. Others include Lab % × normalized number of outpatient visits due to ILI, number of laboratory-confirmed influenza A infections, a variation of ILI % (i.e. a product of ILI % of a specific influenza season and a random number following a normal distribution, the mean and standard derivation of which are the same as the ILI % over the same influenza season), mixed proxies used for different types of influenza viruses (i.e. influenza A: a combination of laboratory positive tests and the number of hospital admissions with laboratory-confirmation of influenza; influenza B: Lab %), and rate of clinical influenza.

Web Appendix 2. Statistical models used in the included studies (except for the multiplier method)

2.1 Regression models with an influenza activity proxy

Studies applying generalized linear models (GLM) (including generalized additive models) incorporated an influenza activity proxy into the model and adopted various ways to control for seasonality. Other relevant covariates could also be included in the model. The basic formula of GLM is:

$$Y_t \sim D(\mu_t)$$
$$g(\mu_t) = \beta_0 + \sum_{i=1}^{m} \beta_i flu_{it} + f(t) + \sum_{j=1}^{k} q_j(z_{jt}) \quad (3)$$

Where Y_t represents the number of deaths or the death rate at time t with a mean of μ_t. D is the distribution of Y_t. $g(\cdot)$ represents the link function of μ_t. flu_{it} is the ith influenza activity proxy at time t; m is the number of proxies; f is the function of the time variable t; z_{jt} represents observed time-varying variables such as temperature and humidity at time t; k is the number of time-varying covariates; q_j is a function of those variables.

Studies used various methods to control for unmeasured confounding. For example, some studies (29, 30, 61, 99-101) used a spline function of time, while Dushoff et al. (20) and Yang et al. (102) detrended data before fitting models. Twenty-one out of 54 studies used a polynomial function of time to control for trends in mortality, and sine and cosine functions of time to control for the seasonality of mortality. Among studies using regression models with an influenza activity proxy, only three studies applied Bayesian statistics (18, 24, 25) to estimate the mortality burden due to influenza. Eight

studies (50, 54, 69, 70, 84, 85, 92, 98) used a Poisson distribution with an identity link, while seven studies applied a negative binomial distribution among which four studies (5, 14, 25, 53) used an identity link function and three (12, 47, 103) applied a log link function. To deal with autocorrelation in time series modeling, Wijngaard et al. (92) used a generalized estimating equation (GEE), some studies (18, 26, 61, 64, 99-101) assumed the error followed an autoregressive (AR) process and one study (9) assumed the error followed an ARIMA process.

Nicholson (56) used two regression models to estimate influenza-associated mortality, with the predicted outcome of the first regression model as the dependent variable of a second regression model.

2.2 Serfling-type models

In this review, we defined Serfling-type models as regression models with Fourier terms but without an influenza activity proxy. The basic Serfling-type model can be expressed as follows:

$$Y_t \sim D(\mu_t)$$

$$g(\mu_t) = \beta_0 + \sum_{i=1}^{m} \beta_i t^i + \sum_{j=1}^{k} \left(\beta_{1j} \sin(\frac{2\pi jt}{T}) + \beta_{2j} \cos(\frac{2\pi jt}{T}) \right)$$

Where Y_t represents the number of deaths or the death rate at time t with a mean of μ_t. D is the distribution of Y_t. $g(\cdot)$ represents the link function of μ_t. m is the order of polynomial components included in the model. β_i is the coefficient for polynomial i. The right hand side of the equation is used to model the seasonal pattern of mortality. β_{1j} and β_{2j} are the coefficients for $\sin(\frac{2\pi jt}{T})$ and $\cos(\frac{2\pi jt}{T})$,

respectively where π is the mathematical constant. k is an integer that is smaller than or equal to $T/2$, but in the studies reviewed was commonly set to 1 or 2. T represents the number of time units within a time-series cycle.

2.3 Other methods

Some studies used non-Serfling regression to estimate the influenza-associated mortality without incorporating influenza activity data into the model. To estimate the deaths attributable to influenza irrespective of the epidemic period, Kyncl et al. (37) applied a survival analysis method treating data as left censored and incorporating age group into the model. Six studies (13, 21, 32, 59, 79, 87) used an autoregressive integrated moving average (ARIMA) model for the estimation of baseline mortality. One study (79) used a transfer function taking age group into account to estimate excess mortality.

Other estimation techniques used in the selected studies included the moving average method, the relative mortality distribution model, and the incidence rate-difference method.

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