

# **Heterogeneity in Estimates of the Impact of Influenza on Population**

## **Mortality: A Systematic Review**

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This work was funded by the Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (grant no.: HKS-16-E08), the Research Grants Council of the Hong Kong Special Administrative Region, China (project number T11-705/14N), and the Harvard

Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant number U54 GM088558).

Conflict of interest: BJC has received research funding from Sanofi Pasteur, and consults for Crucell NV. The authors report no other potential conflicts of interest.

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 ( $\geq 65$  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  $\geq 10$  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  $\geq 65$  years or  $\geq 60$  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  $\geq 65$  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  $\mu_t$ , i.e.  $\mu_t - \mu_{0,t}$ ; 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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### **2) Grants and/or financial support**

This work was supported by the Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (grant no.: HKS-16-E08), the Research Grants Council of the Hong Kong Special Administrative Region, China (project number T11-705/14N), and the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant number U54 GM088558).

### **3) Conflict of interest**

BJC has received research funding from Sanofi Pasteur, and consults for Crucell NV. The authors report no other potential conflicts of interest.

## REFERENCES

1. World Health Organization. Influenza (Seasonal).  
<http://www.who.int/mediacentre/factsheets/fs211/en/>. Accessed April 28, 2016.
2. Metersky ML, Masterton RG, Lode H, et al. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. *Int J Infect Dis.* 2012;16(5):e321-331.
3. Lee KH, Gordon A, Foxman B. The role of respiratory viruses in the etiology of bacterial pneumonia: An ecological perspective. *Evol Med Public Health.* 2016;2016(1):95-109.
4. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis.* 2009;9(10):601-610.
5. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis.* 2006;194 Suppl 2:S82-91.
6. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA.* 2003;289(2):179-186.
7. Jhung MA, Swerdlow D, Olsen SJ, et al. Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. *Clin Infect Dis.* 2011;52 Suppl 1:S13-26.

8. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis.* 2012;12(9):687-695.
9. Reichert TA, Sugaya N, Fedson DS, et al. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med.* 2001;344(12):889-896.
10. Baguelin M, Flasche S, Camacho A, et al. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Med.* 2013;10(10):e1001527.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012.
12. Simonsen L, Viboud C. The art of modeling the mortality impact of winter-seasonal pathogens. *J Infect Dis.* 2012;206(5):625-627.
13. Charu V, Simonsen L, Lustig R, et al. Mortality burden of the 2009-10 influenza pandemic in the United States: improving the timeliness of influenza severity estimates using inpatient mortality records. *Influenza Other Respir Viruses.* 2013;7(5):863-871.
14. Molbak K, Widgren K, Jensen KS, et al. Burden of illness of the 2009 pandemic of influenza A (H1N1) in Denmark. *Vaccine.* 2011;29 Suppl 2:B63-69.
15. Cooper BS, Kotirum S, Kulpeng W, et al. Mortality attributable to seasonal influenza A and B infections in Thailand, 2005-2009: a longitudinal study. *Am J Epidemiol.* 2015;181(11):898-907.



16. Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. *J Infect Dis.* 2012;206(12):1862-1871.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.
18. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology* (3rd Edition). 2008; Philadelphia, PA: Lippincott, Williams & Wilkins.
19. Cooper H, Hedges LV, Valentine JC. *The handbook of research synthesis and meta-analysis* (2nd Edition). 2009; New York, NY: Russell Sage Foundation.
20. Collins SD, Lehmann J. Excess deaths from influenza and pneumonia and from important chronic diseases during epidemic periods, 1918-51. *Public Health Monogr.* 1953;10:1-21.
21. Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 influenza pandemic from the GLaMOR project: a modeling study. *PLoS Med.* 2013;10(11):e1001558.
22. Presanis AM, Pebody RG, Paterson BJ, et al. Changes in severity of 2009 pandemic A/H1N1 influenza in England: a Bayesian evidence synthesis. *BMJ.* 2011;343:d5408.
23. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One.* 2015;10(3):e0118369.
24. Shrestha SS, Swerdlow DL, Borse RH, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). *Clin Infect Dis.* 2011;52 Suppl 1:S75-82.

25. Aungkulanon S, Cheng PY, Kusreesakul K, et al. Influenza-associated mortality in Thailand, 2006-2011. *Influenza Other Respir Viruses*. 2015;9(6):298-304.
26. Wong JY, Wu P, Nishiura H, et al. Infection fatality risk of the pandemic A(H1N1)2009 virus in Hong Kong. *Am J Epidemiol*. 2013;177(8):834-840.
27. Wu P, Goldstein E, Ho LM, et al. Excess mortality impact of two epidemics of pandemic influenza A(H1N1pdm09) virus in Hong Kong. *Influenza Other Respir Viruses*. 2014;8(1):1-7.
28. Park M, Wu P, Goldstein E, et al. Influenza-associated excess mortality in South Korea. *Am J Prev Med*. 2016;50(4):e111-119.
29. Chow A, Ma S, Ling AE, et al. Influenza-associated deaths in tropical Singapore. *Emerg Infect Dis*. 2006;12(1):114-121.
30. Wong CM, Chan KP, Hedley AJ, et al. Influenza-associated mortality in Hong Kong. *Clin Infect Dis*. 2004;39(11):1611-1617.
31. Wong CM, Peiris JS, Yang L, et al. Effect of influenza on cardiorespiratory and all-cause mortality in Hong Kong, Singapore and Guangzhou. *Hong Kong Med J*. 2012;18 Suppl 2:8-11.
32. Yang L, Chan KP, Cowling BJ, et al. Excess mortality associated with the 2009 pandemic of influenza A(H1N1) in Hong Kong. *Epidemiol Infect*. 2012;140(9):1542-1550.
33. Yang L, Ma S, Chen PY, et al. Influenza associated mortality in the subtropics and tropics: results from three Asian cities. *Vaccine*. 2011;29(48):8909-8914.

34. Cheng PY, Palekar R, Azziz-Baumgartner E, et al. Burden of influenza-associated deaths in the Americas, 2002-2008. *Influenza Other Respir Viruses*. 2015;9 Suppl 1:13-21.
35. Green HK, Andrews N, Fleming D, et al. Mortality attributable to influenza in England and Wales prior to, during and after the 2009 pandemic. *PLoS One*. 2013;8(12):e79360.
36. Kessaram T, Stanley J, Baker MG. Estimating influenza-associated mortality in New Zealand from 1990 to 2008. *Influenza Other Respir Viruses*. 2015;9(1):14-19.
37. Lopez-Cuadrado T, de Mateo S, Jimenez-Jorge S, et al. Influenza-related mortality in Spain, 1999-2005. *Gac Sanit*. 2012;26(4):325-329.
38. Matias G, Taylor R, Haguenet F, et al. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. *Influenza Other Respir Viruses*. 2014;8(5):507-515.
39. Newall AT, Viboud C, Wood JG. Influenza-attributable mortality in Australians aged more than 50 years: a comparison of different modelling approaches. *Epidemiol Infect*. 2010;138(6):836-842.
40. Newall AT, Wood JG, Macintyre CR. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine*. 2008;26(17):2135-2141.
41. Schanzer DL, Sevenhuysen C, Winchester B, et al. Estimating influenza deaths in Canada, 1992-2009. *PLoS One*. 2013;8(11):e80481.

42. Tempia S, Walaza S, Viboud C, et al. Mortality associated with seasonal and pandemic influenza and respiratory syncytial virus among children <5 years of age in a high HIV prevalence setting--South Africa, 1998-2009. *Clin Infect Dis*. 2014;58(9):1241-1249.
43. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among persons  $\geq 5$  years of age in HIV-prevalent area, South Africa, 1998-2009(1). *Emerg Infect Dis*. 2015;21(4):600-608.
44. Wijngaard CC, Asten L, Koopmans MP, et al. Comparing pandemic to seasonal influenza mortality: moderate impact overall but high mortality in young children. *PLoS One*. 2012;7(2):e31197.
45. Lee VJ, Yap J, Ong JB, et al. Influenza excess mortality from 1950-2000 in tropical Singapore. *PLoS One*. 2009;4(12):e8096.
46. Linhart Y, Shohat T, Bromberg M, et al. Excess mortality from seasonal influenza is negligible below the age of 50 in Israel: implications for vaccine policy. *Infection*. 2011;39(5):399-404.
47. Simonsen L, Clarke MJ, Schonberger LB, et al. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J Infect Dis*. 1998;178(1):53-60.
48. Ohmi K, Marui E. [Estimation of the excess death associated with influenza pandemics and epidemics in Japan after world war II: relation with pandemics and the vaccination system]. *Nihon Koshu Eisei Zasshi*. 2011;58(10):867-878.

49. Tachibana T, Kawaminami K, Minowa M. [Excess mortality from influenza epidemics in Japan, 1980-1994]. *Nihon Koshu Eisei Zasshi*. 1999;46(4):263-274.
50. Takahashi M, Nagai M. [Estimation of excess mortality associated with influenza epidemics specific for sex, age and cause of death in Japan during 1987-2005]. *Nihon Eiseigaku Zasshi*. 2008;63(1):5-19.
51. Takahashi M, Tango T. [Comparative study of new method and the Kawai and Fukutomi methods for estimating excess mortality associated with influenza-epidemics, based upon national vital statistics from 1975 to 1997]. *Nippon Koshu Eisei Zasshi*. 2001;48(10):816-826.
52. Takahashi M, Tango T. [Estimation of excess mortality associated with influenza-epidemics by age and cause specific death in Japan, 1975-1999]. *Nihon Eiseigaku Zasshi*. 2002;57(3):571-584.
53. Zucs P, Buchholz U, Haas W, et al. Influenza associated excess mortality in Germany, 1985-2001. *Emerg Themes Epidemiol*. 2005;2:6.
54. Andreasen V, Simonsen L. The perils of using annual all-cause mortality data to estimate pandemic influenza burden. *Vaccine*. 2011;29 Suppl 2:B49-55.
55. Bonmarin I, Belchior E, Levy-Bruhl D. Impact of influenza vaccination on mortality in the French elderly population during the 2000-2009 period. *Vaccine*. 2015;33(9):1099-1101.
56. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health*. 2000;3(1):32-38.

57. Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. *J Epidemiol Community Health*. 2005;59(7):586-590.
58. Jansen AG, Sanders EA, Hoes AW, et al. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J*. 2007;30(6):1158-1166.
59. Murray CJ, Lopez AD, Chin B, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. *Lancet*. 2006;368(9554):2211-2218.
60. Richard SA, Sugaya N, Simonsen L, et al. A comparative study of the 1918-1920 influenza pandemic in Japan, USA and UK: mortality impact and implications for pandemic planning. *Epidemiol Infect*. 2009;137(8):1062-1072.
61. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respir Viruses*. 2009;3(1):37-49.
62. Mamelund SE, Iversen BG. [Morbidity and mortality in pandemic influenza in Norway]. *Tidsskr Nor Laegeforen*. 2000;120(3):360-363.
63. US Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep*. 2010;59(33):1057-1062.
64. US Centers for Disease Control and Prevention. What you should know and do this flu season if you are 65 years and older.

<http://www.cdc.gov/flu/about/disease/65over.htm>. Accessed April 28, 2016.

65. Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004–2012. *Pediatrics*. 2013;132(5):796-804.
66. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003-2004. 2005;353(24):2559-2567.
67. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999-2010. *Influenza Other Respir Viruses*. 2013;7(1):35-45.
68. Goldstein E, Viboud C, Charu V, et al. Improving the estimation of influenza-related mortality over a seasonal baseline. *Epidemiology*. 2012;23(6):829-838.
69. Lipsitch M, Jha A, Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. *Int J Epidemiol*. 2016;45(6):2060-2074.
70. Brinkhof MW, Spoerri A, Birrer A, et al. Influenza-attributable mortality among the elderly in Switzerland. *Swiss Med Wkly*. 2006;136(19-20):302-309.
71. Carrat F, Valleron AJ. Influenza mortality among the elderly in France, 1980-90: how many deaths may have been avoided through vaccination? *J Epidemiol Community Health*. 1995;49(4):419-425.
72. Dushoff J, Plotkin JB, Viboud C, et al. Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. *Am J Epidemiol*. 2006;163(2):181-187.

73. Foppa IM, Cheng PY, Reynolds SB, et al. Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14. *Vaccine*. 2015;33(26):3003-3009.
74. Foppa IM, Hossain MM. Revised estimates of influenza-associated excess mortality, United States, 1995 through 2005. *Emerg Themes Epidemiol*. 2008;5:26.
75. Lemaitre M, Carrat F, Rey G, et al. Mortality burden of the 2009 A/H1N1 influenza pandemic in France: comparison to seasonal influenza and the A/H3N2 pandemic. *PLoS One*. 2012;7(9):e45051.
76. Schanzer DL, Tam TW, Langley JM, et al. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect*. 2007;135(7):1109-1116.
77. Sprenger MJ, Mulder PG, Beyer WE, et al. Impact of influenza on mortality in relation to age and underlying disease, 1967-1989. *Int J Epidemiol*. 1993;22(2):334-340.
78. Alling DW, Blackwelder WC, Stuart-Harris CH. A study of excess mortality during influenza epidemics in the United States, 1968-1976. *Am J Epidemiol*. 1981;113(1):30-43.
79. Gran JM, Iversen B, Hungnes O, et al. Estimating influenza-related excess mortality and reproduction numbers for seasonal influenza in Norway, 1975-2004. *Epidemiol Infect*. 2010;138(11):1559-1568.
80. Gran JM, Kacelnik O, Grijibovski AM, et al. Counting pandemic deaths: comparing reported numbers of deaths from influenza A(H1N1)pdm09 with estimated excess mortality. *Influenza Other Respir Viruses*. 2013;7(6):1370-1379.



81. Li CK, Choi BC, Wong TW. Influenza-related deaths and hospitalizations in Hong Kong: a subtropical area. *Public Health*. 2006;120(6):517-524.
82. Mann AG, Mangtani P, Russell CA, et al. The impact of targeting all elderly persons in England and Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study. *BMJ Open*. 2013;3(8):e002743.
83. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect*. 1996;116(1):51-63.
84. Quandelacy TM, Viboud C, Charu V, et al. Age- and sex-related risk factors for influenza-associated mortality in the United States between 1997-2007. *Am J Epidemiol*. 2014;179(2):156-167.
85. Tillett HE, Smith JW, Clifford RE. Excess morbidity and mortality associated with influenza in England and Wales. *Lancet*. 1980;1(8172):793-795.
86. Tillett HE, Smith JW, Gooch CD. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol*. 1983;12(3):344-352.
87. Choi K, Thacker SB. Mortality during influenza epidemics in the United States, 1967-1978. *Am J Public Health*. 1982;72(11):1280-1283.
88. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect*. 2007;54(6):530-538.

89. Yu H, Feng L, Viboud CG, et al. Regional variation in mortality impact of the 2009 A(H1N1) influenza pandemic in China. *Influenza Other Respir Viruses*. 2013;7(6):1350-1360.
90. van Asten L, van den Wijngaard C, van Pelt W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. *J Infect Dis*. 2012;206(5):628-639.
91. Muscatello DJ, Newall AT, Dwyer DE, et al. Mortality attributable to seasonal and pandemic influenza, Australia, 2003 to 2009, using a novel time series smoothing approach. *PLoS One*. 2014;8(6):e64734.
92. Nielsen J, Mazick A, Glismann S, et al. Excess mortality related to seasonal influenza and extreme temperatures in Denmark, 1994-2010. *BMC Infect Dis*. 2011;11:350.
93. Ivan A, Freund S, Ionescu T, et al. [Problem of excess mortality in influenza]. *Viata Medicala*. 1969;16(21):1483-1491.
94. Mazick A, Gergonne B, Wuillaume F, et al. Higher all-cause mortality in children during autumn 2009 compared with the three previous years: pooled results from eight European countries. *Euro Surveill*. 2010;15(5):pii=19480.
95. Azziz-Baumgartner E, Cabrera AM, Cheng PY, et al. Incidence of influenza-associated mortality and hospitalizations in Argentina during 2002-2009. *Influenza Other Respir Viruses*. 2013;7(5):710-717.

96. Viboud C, Grais RF, Lafont BA, et al. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. *J Infect Dis.* 2005;192(2):233-248.
97. Kuo HW, Schmid D, Liu YL, et al. Influenza-related excess mortality, Austria 2001 till 2009. *Wien Klin Wochenschr.* 2011;123(19-20):593-598.
98. Ansart S, Pelat C, Boelle PY, et al. Mortality burden of the 1918-1919 influenza pandemic in Europe. *Influenza Other Respir Viruses.* 2009;3(3):99-106.
99. Viboud C, Tam T, Fleming D, et al. 1951 influenza epidemic, England and Wales, Canada, and the United States. *Emerg Infect Dis.* 2006;12(4):661-668.
100. Rizzo C, Bella A, Viboud C, et al. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969-2001. *Emerg Infect Dis.* 2007;13(5):694-699.
101. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no decline associated with increasing vaccination coverage. *Vaccine.* 2006;24(42-43):6468-6475.
102. Charu V, Chowell G, Palacio Mejia LS, et al. Mortality burden of the A/H1N1 pandemic in Mexico: a comparison of deaths and years of life lost to seasonal influenza. *Clin Infect Dis.* 2011;53(10):985-993.
103. Nogueira PJ, Nunes B, Machado A, et al. Early estimates of the excess mortality associated with the 2008-9 influenza season in Portugal. *Euro Surveill.* 2009;14(18):pii=19194.

104. Cohen C, Simonsen L, Kang JW, et al. Elevated influenza-related excess mortality in South African elderly individuals, 1998-2005. *Clin Infect Dis*. 2010;51(12):1362-1369.
105. Simon Mendez L, Lopez-Cuadrado T, Lopez Perea N, et al. [Premature mortality excess related to influenza in Spain during an interpandemic period]. *Rev Esp Salud Publica*. 2012;86(2):153-163.
106. Chowell G, Erkoreka A, Viboud C, et al. Spatial-temporal excess mortality patterns of the 1918-1919 influenza pandemic in Spain. *BMC Infect Dis*. 2014;14:371.
107. Leon-Gomez I, Delgado-Sanz C, Jimenez-Jorge S, et al. [Excess mortality associated with influenza in Spain in winter 2012]. *Gac Sanit*. 2015;29(4):258-265.
108. Nguyen AM, Noymer A. Influenza mortality in the United States, 2009 pandemic: burden, timing and age distribution. *PLoS One*. 2013;8(5):e64198.
109. Housworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957-1966. *Am J Epidemiol*. 1974;100(1):40-48.
110. Lui KJ, Kendal AP. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am J Public Health*. 1987;77(6):712-716.
111. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265-272.

112. Serfling RE, Sherman IL, Houseworth WJ. Excess pneumonia-influenza mortality by age and sex in three major influenza A2 epidemics, United States, 1957-58, 1960 and 1963. *Am J Epidemiol.* 1967;86(2):433-441.
113. Simonsen L, Clarke MJ, Williamson GD, et al. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health.* 1997;87(12):1944-1950.
114. Egger M, Jennings S, Spuhler T, et al. [Mortality in influenza epidemics in Switzerland 1969-1985]. *Schweiz Med Wochenschr.* 1989;119(13-14):434-439.
115. Imaz MS, Eimann M, Poyard E, et al. [Influenza associated excess mortality in Argentina: 1992-2002]. *Rev Chilena Infectol.* 2006;23(4):297-306.
116. Kyncl J, Prochazka B, Goddard NL, et al. A study of excess mortality during influenza epidemics in the Czech Republic, 1982-2000. *Eur J Epidemiol.* 2005;20(4):365-371.
117. Nunes B, Viboud C, Machado A, et al. Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004. *PLoS One.* 2011;6(6):e20661.
118. Stroup DF, Thacker SB, Herndon JL. Application of multiple time series analysis to the estimation of pneumonia and influenza mortality by age 1962-1983. *Stat Med.* 1988;7(10):1045-1059.
119. Viboud C, Simonsen L, Fuentes R, et al. Global mortality impact of the 1957-1959 influenza pandemic. *J Infect Dis.* 2016;213(5):738-745.
120. Lee VJ, Chen MI, Chan SP, et al. Influenza pandemics in Singapore, a tropical, globally connected city. *Emerg Infect Dis.* 2007;13(7):1052-1057.

## **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





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

Characteristics	Number of studies (n=103) <sup>a</sup>	References
<b>Models</b>		
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)
<b>Consider effects of time in regression models with influenza activity proxy</b>		
Yes	51	(6, 13-16, 21, 25-44, 61, 63, 67, 68, 70-80, 82-87, 89-92)
No	3	(81, 88, 93)
<b>Lag between influenza activity and outcome in regression models</b>		
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 <sup>b</sup>	14	(15, 25, 31, 35, 44, 67, 68, 73, 75, 84, 90-93)
<b>Whether respiratory syncytial virus activity was considered in the regression models with influenza activity proxy</b>		
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)
<b>Income level</b>		
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 <sup>c</sup>	4	(8, 21, 94, 119)
<b>Climatic zone</b>		
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 <sup>c</sup>	4	(8, 21, 94, 119)

<sup>a</sup> 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).

- <sup>b</sup> 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.
- <sup>c</sup> 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

<b>Variable</b>	<b>Change in annual excess deaths (per 100,000 persons)</b>	<b>95% CI</b>	<b>P</b>
<b>Age group, years <sup>a</sup></b>			
Children	ref		
Adults	2	-10, 15	0.694
Older adults	57	46, 67	<0.001
<b>Whether the estimate is for seasonal periods or pandemic periods</b>			
Seasonal	ref		
2009 pandemic	-23	-33, -13	<0.001
<b>Cause of death</b>			
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
<b>Statistical modeling technique</b>			
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
<b>Income level <sup>b</sup></b>			
High-income	ref		
Middle-income	3	-14, 19	0.766
<b>Climatic zone</b>			
Temperate	ref		
Tropical or subtropical	5	-7, 18	0.408

Abbreviations: 95% CI, 95% confidence interval.

<sup>a</sup> Only studies reporting the age-specific estimates of influenza-associated mortality rate were included into the analysis.

<sup>b</sup> 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  $i^{\text{th}}$  influenza season or calendar year, and  $pop_i$  represents the source population of the  $i^{\text{th}}$  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:

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

Where  $SE_i$  is the standard error of the  $i^{\text{th}}$  estimate;  $|MR_i|$  represents the absolute value of the influenza-associated mortality rate of the  $i^{\text{th}}$  estimate;  $age_i$  represents the age group of the  $i^{\text{th}}$  estimate, and  $COD_i$  represents the cause of death of the  $i^{\text{th}}$  estimate.

**Web Table 1.** Basic Information of Included Articles.

Reference	Country or region	Study period	Statistical or modeling technique <sup>s</sup>	Whether the estimate is for seasonal periods or pandemic periods, or both	Influenza activity proxy <sup>#</sup>	Cause of death <sup>†</sup>	ICD <sup>A</sup>	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 <sup>d</sup>	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, Africa, 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.

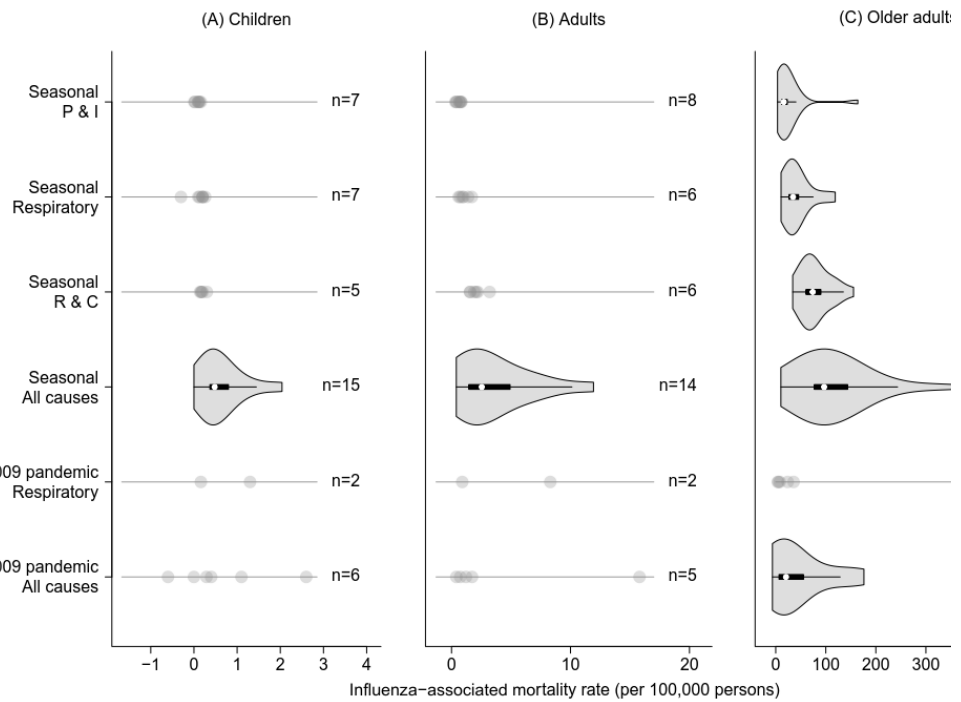
§: GLM, generalized linear model; RD, incidence rate-difference model; Serfling, Serfling-type model; ARIMA, autoregressive integrated moving average model; MA, moving average method; Multiplier, multiplier method; Surv, survival analysis; Regression, regression model without influenza activity proxy; 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.

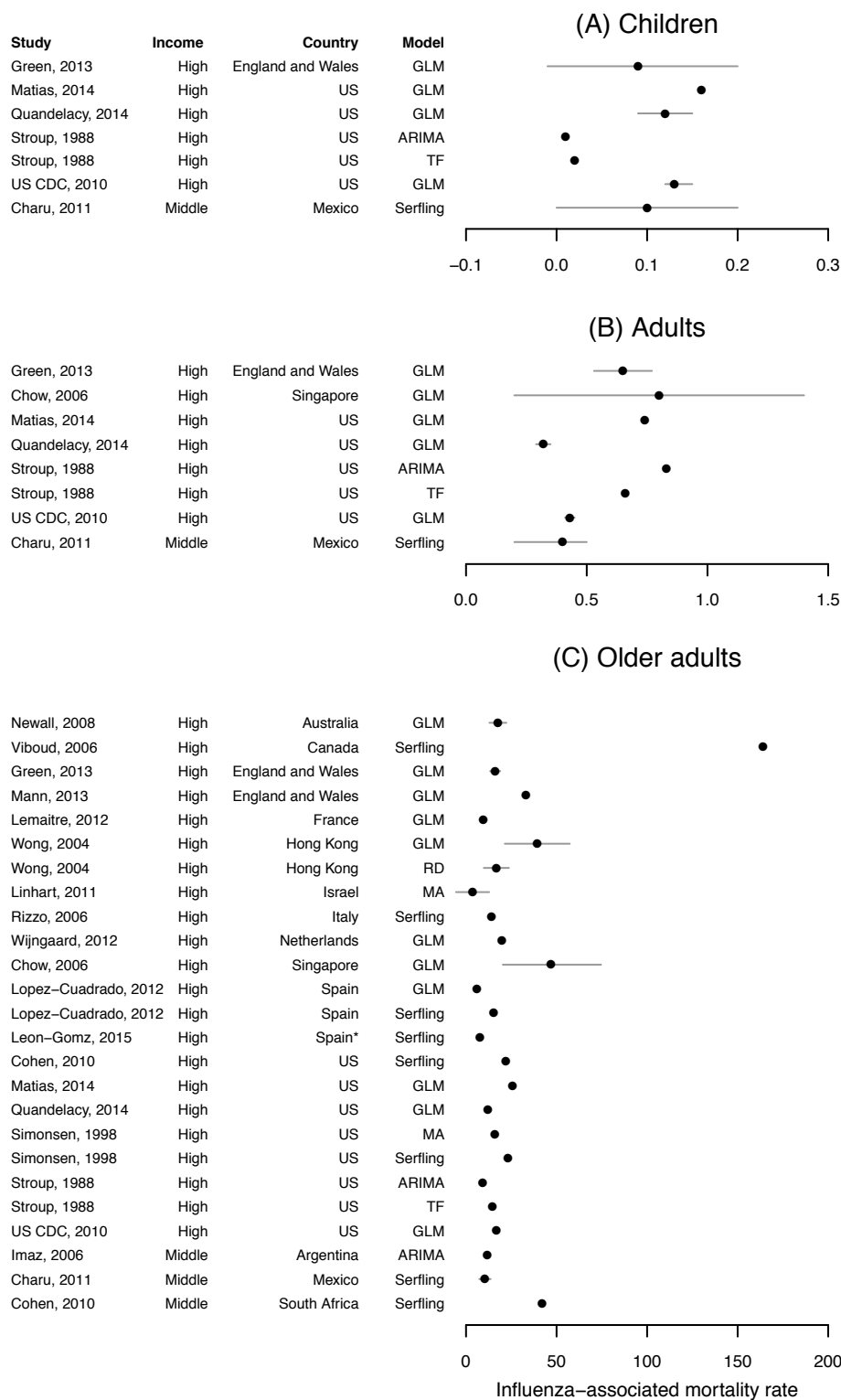
Models without an influenza activity proxy other than multiplier methods and Serfling-type models include Regression, ARIMA, TF, Surv, MA, RD, and RMD.

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

Δ: ICD, the International Classification of Diseases.

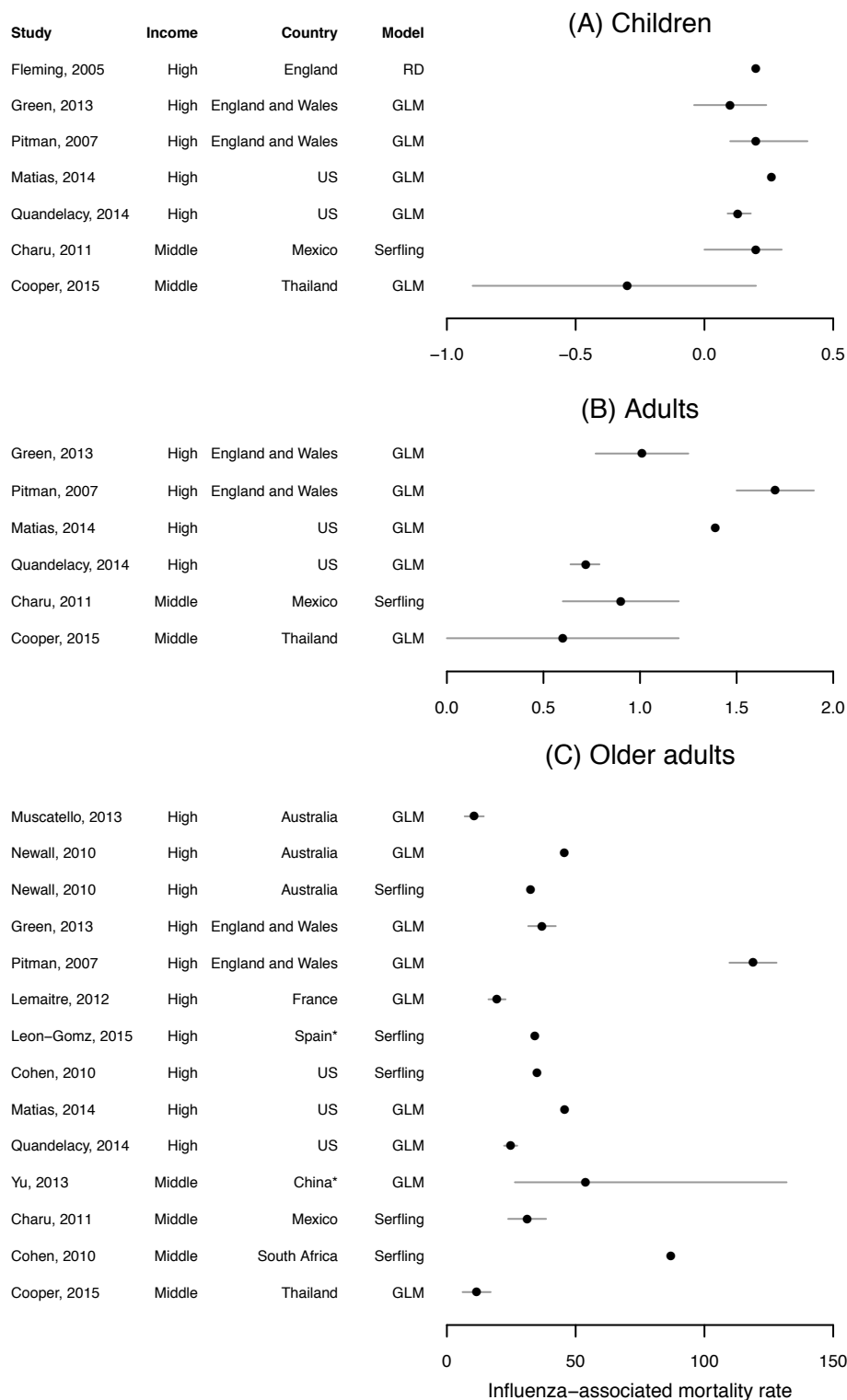


**Web Figure 1.** Estimates of the annual influenza-associated mortality rate by age group and cause of death. Abbreviations: P&I, pneumonia and influenza; R&C, respiratory and cardiovascular diseases. If the number of estimates was less than 5, violin plots were used to show the estimates. If the number of estimates was  $\geq 5$ , dot plots were used. n indicates the number of studies for each category. The white point represents the median, the black box represents the interquartile range and the black line represents the range of the estimates included in that outcome-population category; e.g. 46 estimates of the influenza-associated all-cause mortality burden were extracted for older adults, with a median of 97 per 100,000 persons and an interquartile range between 77 and 144 per 100,000 persons. The width of the violin represents the probability density of the estimates at different values; the wider the violin, 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

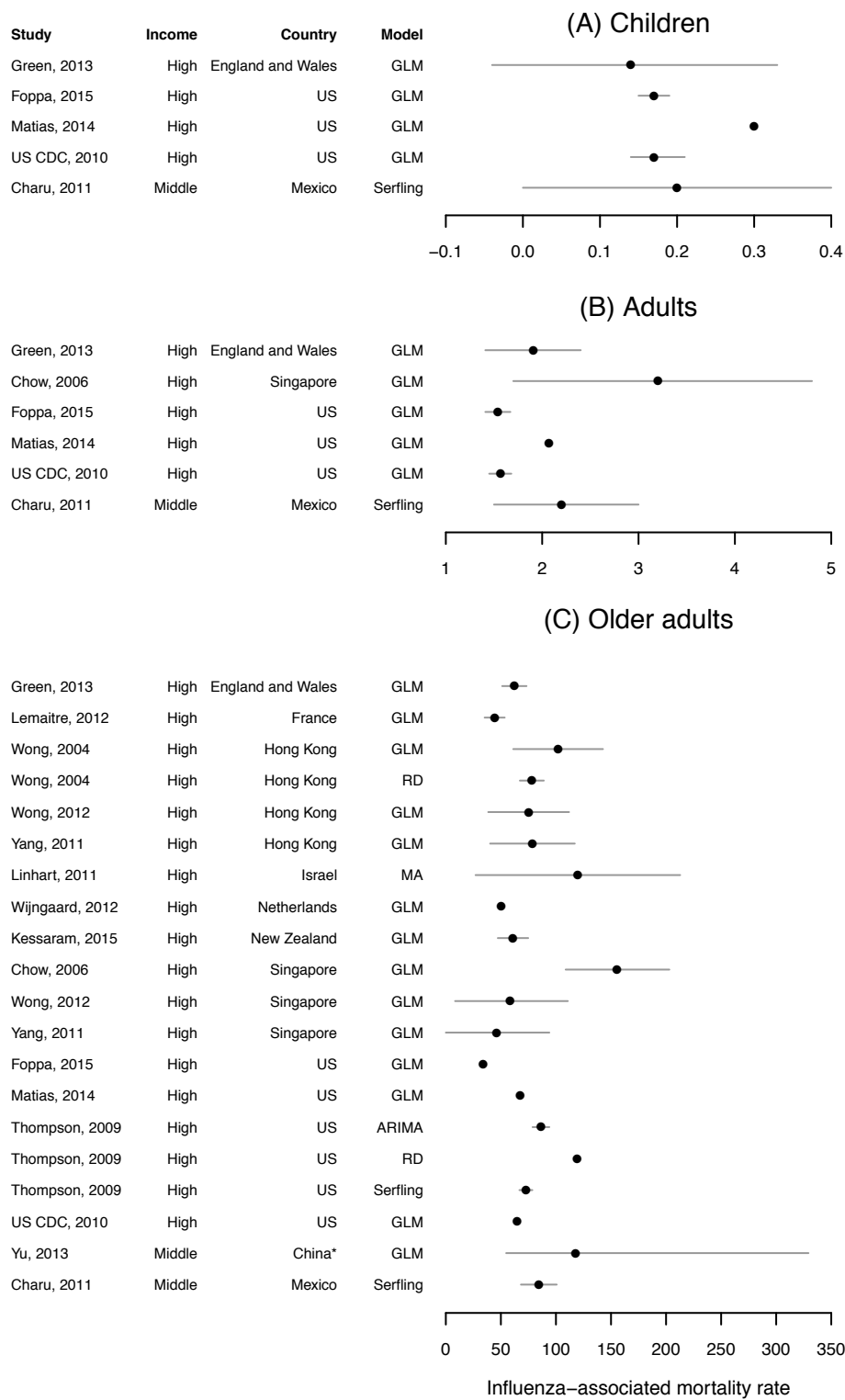
older adults (Cochran's  $Q$  for GLM:  $Q = 285, P < 0.001$ ; Serfling:  $Q = 1658, P < 0.001$ ; other models:  $Q = 13, P < 0.023$ ). Spain\* means 52 provincial capitals in Spain. GLM, generalized linear model; ARIMA, autoregressive integrated moving average model; TF, transfer function; Serfling, 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:  $Q = 93, P <$

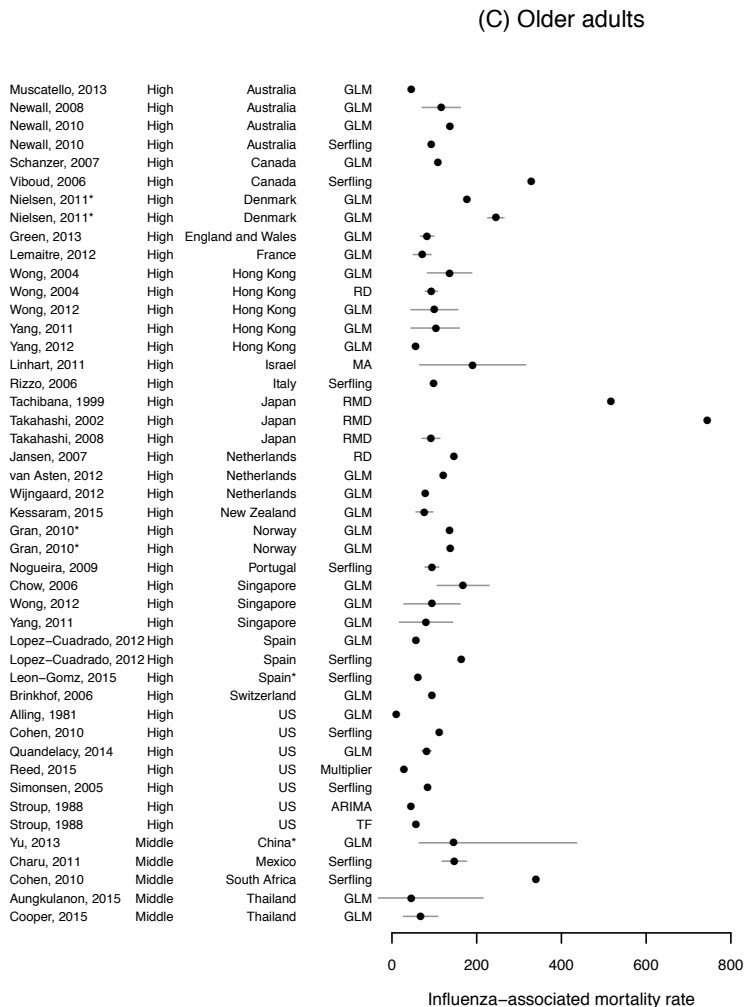
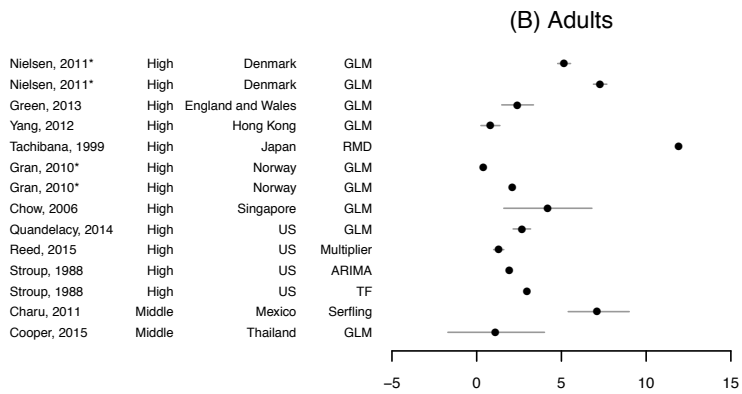
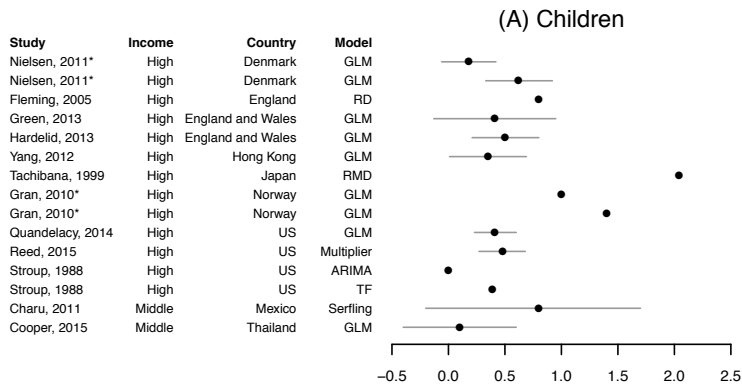
0.001). (C) Estimates for older adults (Cochran's  $Q$  for GLM:  $Q = 558, P < 0.001$ ; Serfling:  $Q = 85, P < 0.001$ ). Spain\* means 52 provincial capitals in Spain. China\* represents 128 sites in China. RD, incidence rate-difference model. GLM, generalized linear model; Serfling, Serfling-type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



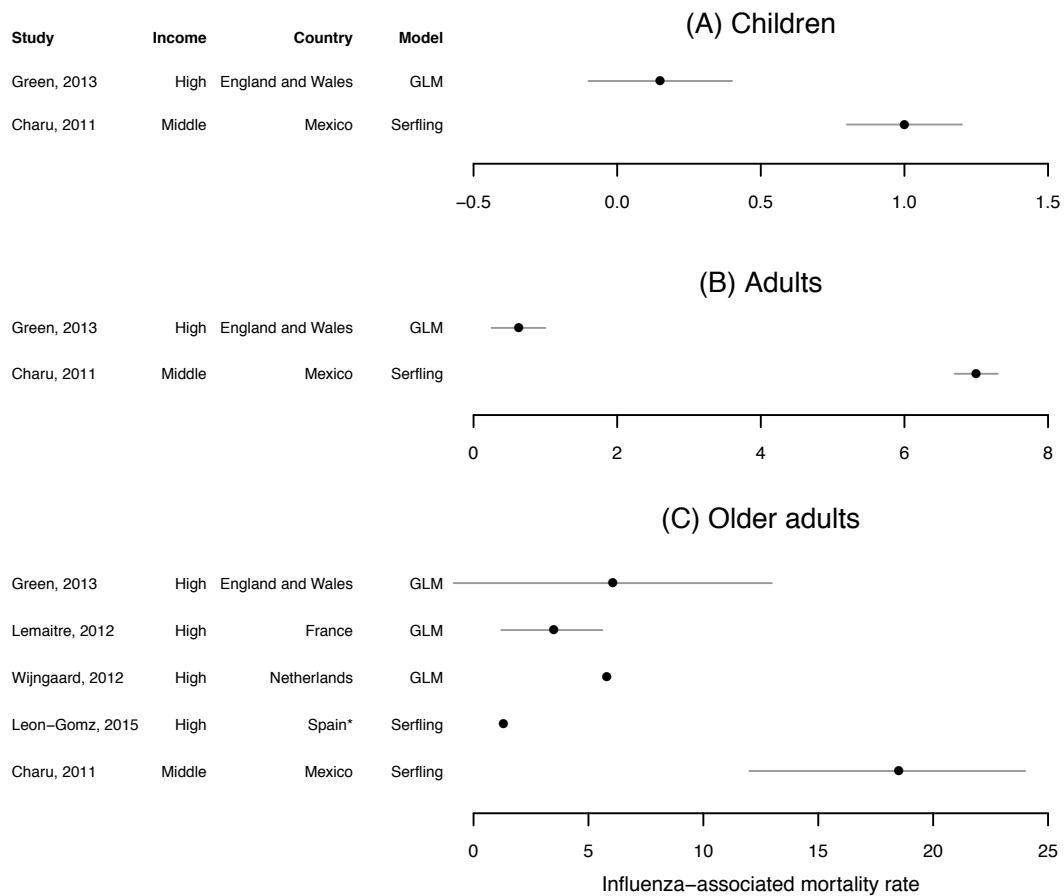


**Web Figure 4.** Annual age-specific influenza-associated excess respiratory and cardiovascular mortality rates in seasonal periods. (A) Estimates for children. (B) Estimates for adults (Cochran’s  $Q$  test for GLM:  $Q = 10$ ,  $P = 0.047$ ). (C) Estimates

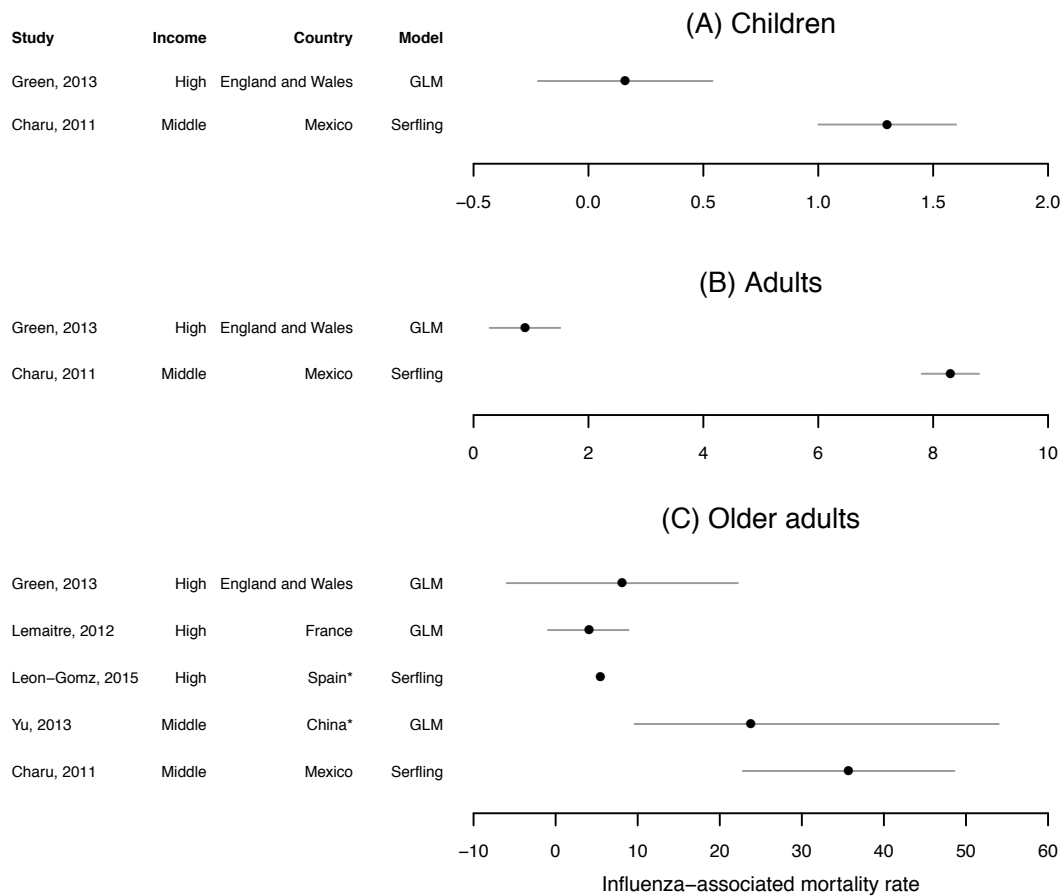
for older adults (Cochran's  $Q$  for GLM:  $Q = 517, P < 0.001$ ). China\* represents 128 sites in China. GLM, generalized linear model; Serfling, Serfling-type model; MA, moving average method; RD, incidence rate-difference model; ARIMA, autoregressive integrated moving average model.



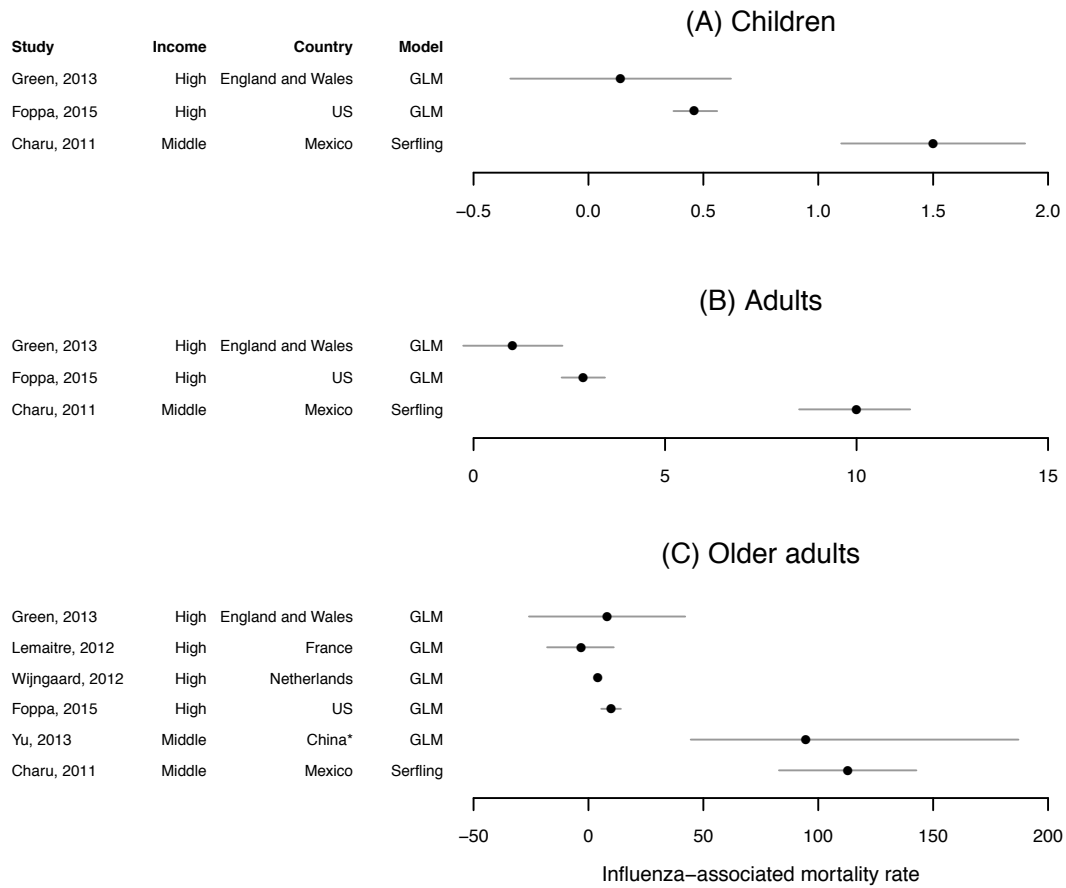
**Web Figure 5.** Annual age-specific influenza-associated excess all-cause mortality rates in seasonal periods. (A) Estimates for children (Cochran's  $Q$  for GLM:  $Q = 29, P < 0.001$ ). (B) Estimates for adults (Cochran's  $Q$  for GLM:  $Q = 521, P < 0.001$ ). (C) Estimates for older adults (Cochran  $Q$  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.



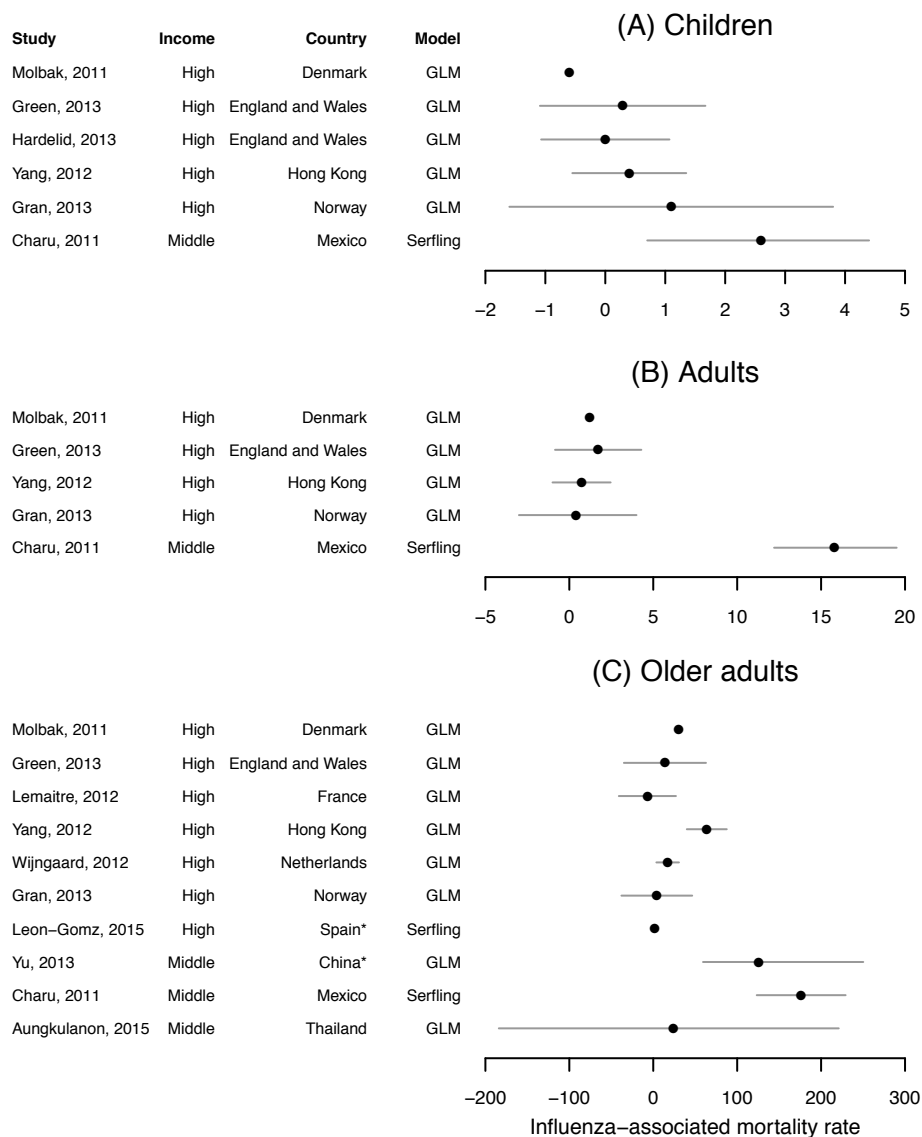
**Web Figure 6.** Annual age-specific influenza-associated excess pneumonia and influenza mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults. Spain\* means 52 provincial capitals in Spain. Serfling, Serfling-type model; GLM,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

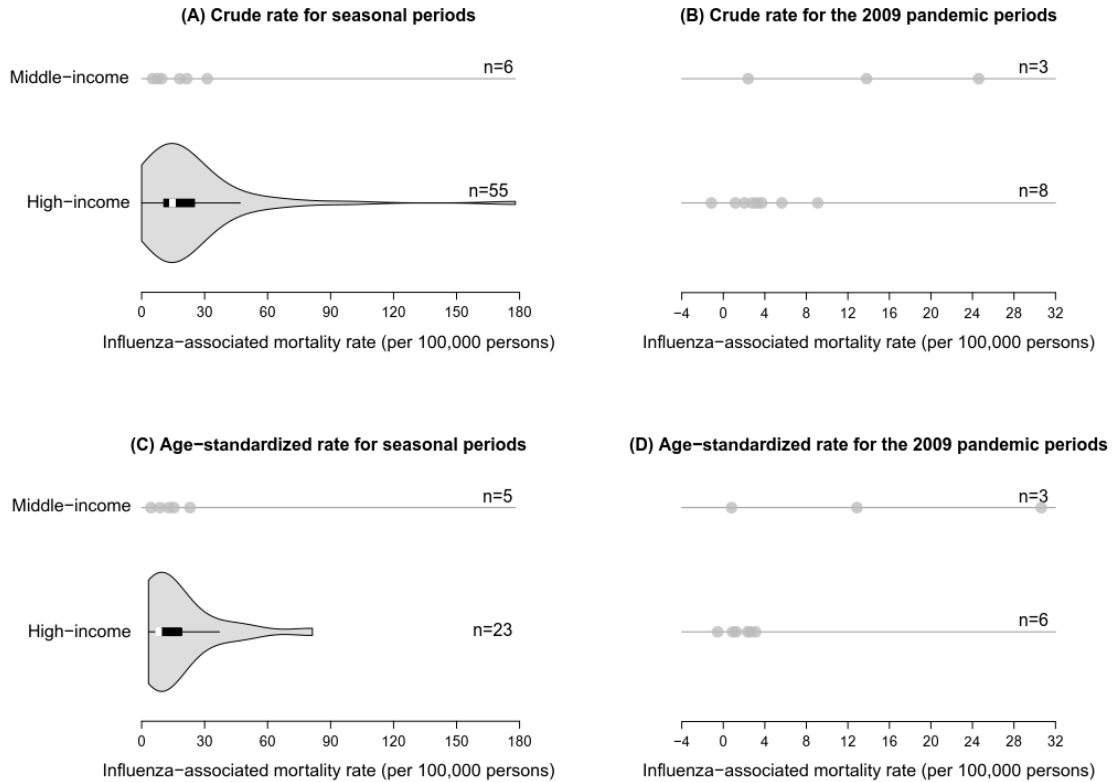


**Web Figure 8.** Annual age-specific influenza-associated excess respiratory and cardiovascular mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults (Cochran's  $Q$  for GLM:  $Q = 9, P = 0.061$ ). China\* represents 128 sites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

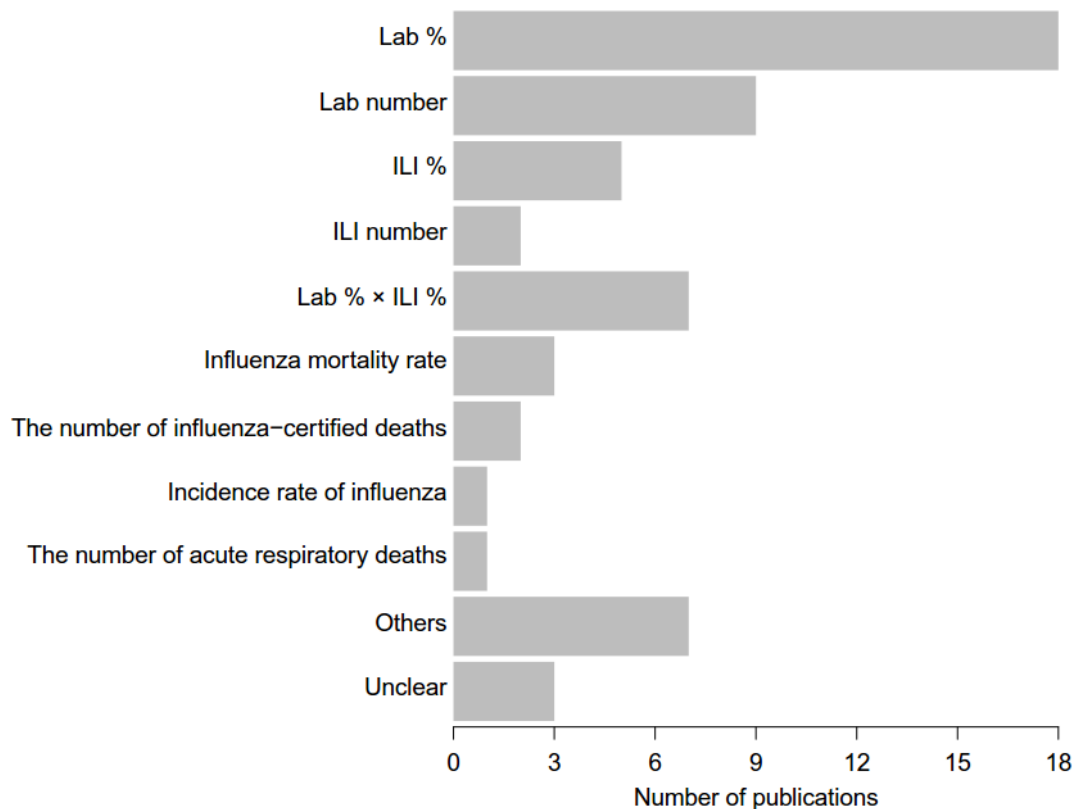




**Web Figure 10.** Annual crude and age-standardized all-cause influenza-associated excess mortality rates by income level. A violin plot was used when the number of estimates is equal to or larger than ten; the original estimate was plotted when there were less than ten estimates reported. (A) Annual 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)	$Num_D = sAR \times sCFR \times RMM \times Num_{pop}$ <p><i>sAR</i>: the percentage of population who developed a symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1  <i>sCFR</i>: the percentage of individuals with symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1 who died  <i>RMM</i>: risk-group-specific respiratory mortality multiplier  <i>Num<sub>pop</sub></i>: population size  <i>Num<sub>D</sub></i>: number of deaths attributable to influenza</p>
Presanis 2011 (63)	$Num_{Inf} = C_{Inf pop} \times Num_{pop}$ $Num_S = C_{S Inf} \times Num_{Inf}$ $Num_H = C_{H S} \times Num_S$ $Num_D = C_{D H} \times Num_H$ <p><i>Num<sub>pop</sub></i>: population size  <i>C<sub>Inf pop</sub></i>: infection attack rate  <i>Num<sub>Inf</sub></i>: number of infections  <i>C<sub>S Inf</sub></i>: proportion of symptomatic infections  <i>Num<sub>S</sub></i>: number of symptomatic infections  <i>C<sub>H S</sub></i>: symptomatic case hospitalization ratio  <i>Num<sub>H</sub></i>: number of hospitalizations  <i>C<sub>D H</sub></i>: deaths to hospitalizations ratio  <i>Num<sub>D</sub></i>: number of deaths attributable to influenza</p>
Reed 2015 (65)	$Rate_M = Rate_H \times Multiplier_U \times Ratio_{DH}$ $Num_D = Rate_M \times Num_{pop}$ <p><i>Rate<sub>H</sub></i>: influenza hospitalization rates  <i>Multiplier<sub>U</sub></i>: the multiplier for under-detection  <i>C<sub>D H</sub></i>: deaths to hospitalizations ratio  <i>Rate<sub>M</sub></i>: influenza mortality rates  <i>Num<sub>pop</sub></i>: population size  <i>Num<sub>D</sub></i>: number of deaths attributable to influenza</p>
Shrestha 2011 (72)	$Num_H = \frac{Rate_{H_M} \times Num_{pop_M}}{100,000}$ $Num_D = Num_H \times Multiplier_R \times C_{D H}$ <p><i>Rate<sub>H</sub></i>: median influenza hospitalization rates  <i>Rate<sub>H_M</sub></i>: <i>Rate<sub>H</sub></i> from Emerging Infections Program (EIP) sites categorized as having mid-range level of hospitalizations  <i>Num<sub>H</sub></i>: median number of hospitalizations  <i>Multiplier<sub>R</sub></i>: the multiplier for under-reporting  <i>C<sub>D H</sub></i>: deaths to hospitalizations ratio  <i>Num<sub>D</sub></i>: median number of deaths attributable to influenza  <i>Num<sub>pop_M</sub></i>: population of the state categorized as having “mid” level of influenza activity</p>



**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  $\mu_t$ .  $D$  is the distribution of  $Y_t$ .  $g(\cdot)$  represents the link function of  $\mu_t$ .  $flu_{it}$  is the  $i$ th 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:

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

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

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

respectively where  $\pi$  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.

## References

1. Ahmad O, Boschi-Pinto C, Lopez A, et al. Age standardization of rates: a new WHO standard. <http://www.who.int/healthinfo/paper31.pdf>. Accessed April 28, 2016.
2. Alling DW, Blackwelder WC, Stuart-Harris CH. A study of excess mortality during influenza epidemics in the United States, 1968-1976. *Am J Epidemiol*. 1981;113(1):30-43.
3. Andreasen V, Simonsen L. The perils of using annual all-cause mortality data to estimate pandemic influenza burden. *Vaccine*. 2011;29 Suppl 2:B49-55.
4. Ansart S, Pelat C, Boelle PY, et al. Mortality burden of the 1918-1919 influenza pandemic in Europe. *Influenza Other Respir Viruses*. 2009;3(3):99-106.
5. Aungkulanon S, Cheng PY, Kusreesakul K, et al. Influenza-associated mortality in Thailand, 2006-2011. *Influenza Other Respir Viruses*. 2015;9(6):298-304.
6. Azziz-Baumgartner E, Cabrera AM, Cheng PY, et al. Incidence of influenza-associated mortality and hospitalizations in Argentina during 2002-2009. *Influenza Other Respir Viruses*. 2013;7(5):710-717.
7. Bonmarin I, Belchior E, Levy-Bruhl D. Impact of influenza vaccination on mortality in the French elderly population during the 2000-2009 period. *Vaccine*. 2015;33(9):1099-1101.
8. Brinkhof MW, Spoerri A, Birrer A, et al. Influenza-attributable mortality among the elderly in Switzerland. *Swiss Med Wkly*. 2006;136(19-20):302-309.
9. Carrat F, Valleron AJ. Influenza mortality among the elderly in France, 1980-90: how many deaths may have been avoided through vaccination? *J Epidemiol Community Health*. 1995;49(4):419-425.

10. Charu V, Chowell G, Palacio Mejia LS, et al. Mortality burden of the A/H1N1 pandemic in Mexico: a comparison of deaths and years of life lost to seasonal influenza. *Clin Infect Dis*. 2011;53(10):985-993.
11. Charu V, Simonsen L, Lustig R, et al. Mortality burden of the 2009-10 influenza pandemic in the United States: improving the timeliness of influenza severity estimates using inpatient mortality records. *Influenza Other Respir Viruses*. 2013;7(5):863-871.
12. Cheng PY, Palekar R, Azziz-Baumgartner E, et al. Burden of influenza-associated deaths in the Americas, 2002-2008. *Influenza Other Respir Viruses*. 2015;9 Suppl 1:13-21.
13. Choi K, Thacker SB. Mortality during influenza epidemics in the United States, 1967-1978. *Am J Public Health*. 1982;72(11):1280-1283.
14. Chow A, Ma S, Ling AE, et al. Influenza-associated deaths in tropical Singapore. *Emerg Infect Dis*. 2006;12(1):114-121.
15. Chowell G, Erkoreka A, Viboud C, et al. Spatial-temporal excess mortality patterns of the 1918-1919 influenza pandemic in Spain. *BMC Infect Dis*. 2014;14:371.
16. Cohen C, Simonsen L, Kang JW, et al. Elevated influenza-related excess mortality in South African elderly individuals, 1998-2005. *Clin Infect Dis*. 2010;51(12):1362-1369.
17. Collins SD, Lehmann J. Excess deaths from influenza and pneumonia and from important chronic diseases during epidemic periods, 1918-51. *Public Health Monogr*. 1953;10:1-21.
18. Cooper BS, Kotirum S, Kulpeng W, et al. Mortality attributable to seasonal influenza A and B infections in Thailand, 2005-2009: a longitudinal study. *Am J Epidemiol*. 2015;181(11):898-907.



19. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis*. 2012;12(9):687-695.
20. Dushoff J, Plotkin JB, Viboud C, et al. Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. *Am J Epidemiol*. 2006;163(2):181-187.
21. Egger M, Jennings S, Spuhler T, et al. [Mortality in influenza epidemics in Switzerland 1969-1985]. *Schweiz Med Wochenschr*. 1989;119(13-14):434-439.
22. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health*. 2000;3(1):32-38.
23. Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. *J Epidemiol Community Health*. 2005;59(7):586-590.
24. Foppa IM, Hossain MM. Revised estimates of influenza-associated excess mortality, United States, 1995 through 2005. *Emerg Themes Epidemiol*. 2008;5:26.
25. Foppa IM, Cheng PY, Reynolds SB, et al. Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14. *Vaccine*. 2015;33(26):3003-3009.
26. Goldstein E, Viboud C, Charu V, et al. Improving the estimation of influenza-related mortality over a seasonal baseline. *Epidemiology*. 2012;23(6):829-838.
27. Gran JM, Iversen B, Hungnes O, et al. Estimating influenza-related excess mortality and reproduction numbers for seasonal influenza in Norway, 1975-2004. *Epidemiol Infect*. 2010;138(11):1559-1568.

28. Gran JM, Kacelnik O, Grijbovski AM, et al. Counting pandemic deaths: comparing reported numbers of deaths from influenza A(H1N1)pdm09 with estimated excess mortality. *Influenza Other Respir Viruses*. 2013;7(6):1370-1379.
29. Green HK, Andrews N, Fleming D, et al. Mortality attributable to influenza in England and Wales prior to, during and after the 2009 pandemic. *PLoS One*. 2013;8(12):e79360.
30. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999-2010. *Influenza Other Respir Viruses*. 2013;7(1):35-45.
31. Housworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957-1966. *Am J Epidemiol*. 1974;100(1):40-48.
32. Imaz MS, Eimann M, Poyard E, et al. [Influenza associated excess mortality in Argentina: 1992-2002]. *Rev Chilena Infectol*. 2006;23(4):297-306.
33. Ivan A, Freund S, Ionescu T, et al. [Problem of excess mortality in influenza]. *Viata Medicala*. 1969;16(21):1483-1491.
34. Jansen AG, Sanders EA, Hoes AW, et al. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J*. 2007;30(6):1158-1166.
35. Kessaram T, Stanley J, Baker MG. Estimating influenza-associated mortality in New Zealand from 1990 to 2008. *Influenza Other Respir Viruses*. 2015;9(1):14-19.
36. Kuo HW, Schmid D, Liu YL, et al. Influenza-related excess mortality, Austria 2001 till 2009. *Wien Klin Wochenschr*. 2011;123(19-20):593-598.
37. Kyncl J, Prochazka B, Goddard NL, et al. A study of excess mortality during influenza epidemics in the Czech Republic, 1982-2000. *Eur J Epidemiol*. 2005;20(4):365-371.

38. Lee VJ, Chen MI, Chan SP, et al. Influenza pandemics in Singapore, a tropical, globally connected city. *Emerg Infect Dis.* 2007;13(7):1052-1057.
39. Lee VJ, Yap J, Ong JB, et al. Influenza excess mortality from 1950-2000 in tropical Singapore. *PLoS One.* 2009;4(12):e8096.
40. Lemaitre M, Carrat F, Rey G, et al. Mortality burden of the 2009 A/H1N1 influenza pandemic in France: comparison to seasonal influenza and the A/H3N2 pandemic. *PLoS One.* 2012;7(9):e45051.
41. Leon-Gomez I, Delgado-Sanz C, Jimenez-Jorge S, et al. [Excess mortality associated with influenza in Spain in winter 2012]. *Gac Sanit.* 2015;29(4):258-265.
42. Li CK, Choi BC, Wong TW. Influenza-related deaths and hospitalizations in Hong Kong: a subtropical area. *Public Health.* 2006;120(6):517-524.
43. Linhart Y, Shohat T, Bromberg M, et al. Excess mortality from seasonal influenza is negligible below the age of 50 in Israel: implications for vaccine policy. *Infection.* 2011;39(5):399-404.
44. Lopez-Cuadrado T, de Mateo S, Jimenez-Jorge S, et al. Influenza-related mortality in Spain, 1999-2005. *Gac Sanit.* 2012;26(4):325-329.
45. Lui KJ, Kendal AP. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am J Public Health.* 1987;77(6):712-716.
46. Mamelund SE, Iversen BG. [Morbidity and mortality in pandemic influenza in Norway]. *Tidsskr Nor Laegeforen.* 2000;120(3):360-363.
47. Mann AG, Mangtani P, Russell CA, et al. The impact of targeting all elderly persons in England and Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study. *BMJ Open.* 2013;3(8):e002743.
48. Matias G, Taylor R, Haguinet F, et al. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or

- subtype, age, cause of death, and risk status. *Influenza Other Respir Viruses*. 2014;8(5):507-515.
49. Mazick A, Gergonne B, Wuillaume F, et al. Higher all-cause mortality in children during autumn 2009 compared with the three previous years: pooled results from eight European countries. *Euro Surveill*. 2010;15(5):pii=19480.
  50. Molbak K, Widgren K, Jensen KS, et al. Burden of illness of the 2009 pandemic of influenza A (H1N1) in Denmark. *Vaccine*. 2011;29 Suppl 2:B63-69.
  51. Murray CJ, Lopez AD, Chin B, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. *Lancet*. 2006;368(9554):2211-2218.
  52. Muscatello DJ, Newall AT, Dwyer DE, et al. Mortality attributable to seasonal and pandemic influenza, Australia, 2003 to 2009, using a novel time series smoothing approach. *PLoS One*. 2014;8(6):e64734.
  53. Newall AT, Wood JG, Macintyre CR. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine*. 2008;26(17):2135-2141.
  54. Newall AT, Viboud C, Wood JG. Influenza-attributable mortality in Australians aged more than 50 years: a comparison of different modelling approaches. *Epidemiol Infect*. 2010;138(6):836-842.
  55. Nguyen AM, Noymer A. Influenza mortality in the United States, 2009 pandemic: burden, timing and age distribution. *PLoS One*. 2013;8(5):e64198.
  56. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect*. 1996;116(1):51-63.

57. Nielsen J, Mazick A, Glismann S, et al. Excess mortality related to seasonal influenza and extreme temperatures in Denmark, 1994-2010. *BMC Infect Dis.* 2011;11:350.
58. Nogueira PJ, Nunes B, Machado A, et al. Early estimates of the excess mortality associated with the 2008-9 influenza season in Portugal. *Euro Surveill.* 2009;14(18):pii=19194.
59. Nunes B, Viboud C, Machado A, et al. Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004. *PLoS One.* 2011;6(6):e20661.
60. Ohmi K, Marui E. [Estimation of the excess death associated with influenza pandemics and epidemics in Japan after world war II: relation with pandemics and the vaccination system]. *Nihon Koshu Eisei Zasshi.* 2011;58(10):867-878.
61. Park M, Wu P, Goldstein E, et al. Influenza-associated excess mortality in South Korea. *Am J Prev Med.* 2016;50(4):e111-119.
62. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect.* 2007;54(6):530-538.
63. Presanis AM, Pebody RG, Paterson BJ, et al. Changes in severity of 2009 pandemic A/H1N1 influenza in England: a Bayesian evidence synthesis. *BMJ.* 2011;343:d5408.
64. Quandelacy TM, Viboud C, Charu V, et al. Age- and sex-related risk factors for influenza-associated mortality in the United States between 1997-2007. *Am J Epidemiol.* 2014;179(2):156-167.
65. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One.* 2015;10(3):e0118369.

66. Richard SA, Sugaya N, Simonsen L, et al. A comparative study of the 1918-1920 influenza pandemic in Japan, USA and UK: mortality impact and implications for pandemic planning. *Epidemiol Infect.* 2009;137(8):1062-1072.
67. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no decline associated with increasing vaccination coverage. *Vaccine.* 2006;24(42-43):6468-6475.
68. Rizzo C, Bella A, Viboud C, et al. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969-2001. *Emerg Infect Dis.* 2007;13(5):694-699.
69. Schanzer DL, Tam TW, Langley JM, et al. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect.* 2007;135(7):1109-1116.
70. Schanzer DL, Sevenhuysen C, Winchester B, et al. Estimating influenza deaths in Canada, 1992-2009. *PLoS One.* 2013;8(11):e80481.
71. Serfling RE, Sherman IL, Houseworth WJ. Excess pneumonia-influenza mortality by age and sex in three major influenza A2 epidemics, United States, 1957-58, 1960 and 1963. *Am J Epidemiol.* 1967;86(2):433-441.
72. Shrestha SS, Swerdlow DL, Borse RH, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). *Clin Infect Dis.* 2011;52 Suppl 1:S75-82.
73. Simonsen L, Clarke MJ, Williamson GD, et al. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health.* 1997;87(12):1944-1950.
74. Simonsen L, Clarke MJ, Schonberger LB, et al. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J Infect Dis.* 1998;178(1):53-60.

75. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265-272.
76. Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 influenza pandemic from the GLaMOR project: a modeling study. *PLoS Med*. 2013;10(11):e1001558.
77. Simon Mendez L, Lopez-Cuadrado T, Lopez Perea N, et al. [Premature mortality excess related to influenza in Spain during an interpandemic period]. *Rev Esp Salud Publica*. 2012;86(2):153-163.
78. Sprenger MJ, Mulder PG, Beyer WE, et al. Impact of influenza on mortality in relation to age and underlying disease, 1967-1989. *Int J Epidemiol*. 1993;22(2):334-340.
79. Stroup DF, Thacker SB, Herndon JL. Application of multiple time series analysis to the estimation of pneumonia and influenza mortality by age 1962-1983. *Stat Med*. 1988;7(10):1045-1059.
80. Tachibana T, Kawaminami K, Minowa M. [Excess mortality from influenza epidemics in Japan, 1980-1994]. *Nihon Koshu Eisei Zasshi*. 1999;46(4):263-274.
81. Takahashi M, Tango T. [Comparative study of new method and the Kawai and Fukutomi methods for estimating excess mortality associated with influenza-epidemics, based upon national vital statistics from 1975 to 1997]. *Nippon koshu eisei zasshi*. 2001;48(10):816-826.
82. Takahashi M, Tango T. [Estimation of excess mortality associated with influenza-epidemics by age and cause specific death in Japan, 1975-1999]. *Nihon Eiseigaku Zasshi*. 2002;57(3):571-584.

83. Takahashi M, Nagai M. [Estimation of excess mortality associated with influenza epidemics specific for sex, age and cause of death in Japan during 1987-2005]. *Nihon Eiseigaku Zasshi*. 2008;63(1):5-19.
84. Tempia S, Walaza S, Viboud C, et al. Mortality associated with seasonal and pandemic influenza and respiratory syncytial virus among children <5 years of age in a high HIV prevalence setting--South Africa, 1998-2009. *Clin Infect Dis*. 2014;58(9):1241-1249.
85. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among persons  $\geq 5$  years of age in HIV-prevalent area, South Africa, 1998-2009(1). *Emerg Infect Dis*. 2015;21(4):600-608.
86. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179-186.
87. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respir Viruses*. 2009;3(1):37-49.
88. Tillett HE, Smith JW, Clifford RE. Excess morbidity and mortality associated with influenza in England and Wales. *Lancet*. 1980;1(8172):793-795.
89. Tillett HE, Smith JW, Gooch CD. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol*. 1983;12(3):344-352.
90. US Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep*. 2010;59(33):1057-1062.
91. van Asten L, van den Wijngaard C, van Pelt W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus,



- influenza B, norovirus, and parainfluenza in elderly persons. *J Infect Dis.* 2012;206(5):628-639.
92. Wijngaard CC, Asten L, Koopmans MP, et al. Comparing pandemic to seasonal influenza mortality: moderate impact overall but high mortality in young children. *PLoS One.* 2012;7(2):e31197.
93. Wielders CC, van Lier EA, van 't Klooster TM, et al. The burden of 2009 pandemic influenza A(H1N1) in the Netherlands. *Eur J Public Health.* 2012;22(1):150-157.
94. Viboud C, Grais RF, Lafont BA, et al. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. *J Infect Dis.* 2005;192(2):233-248.
95. Viboud C, Simonsen L, Fuentes R, et al. Global mortality impact of the 1957–1959 influenza pandemic. *J Infect Dis.* 2016;213(5):738-745.
96. Wong CM, Chan KP, Hedley AJ, et al. Influenza-associated mortality in Hong Kong. *Clin Infect Dis.* 2004;39(11):1611-1617.
97. Wong CM, Peiris JS, Yang L, et al. Effect of influenza on cardiorespiratory and all-cause mortality in Hong Kong, Singapore and Guangzhou. *Hong Kong Med J.* 2012;18 Suppl 2:8-11.
98. Wong JY, Wu P, Nishiura H, et al. Infection fatality risk of the pandemic A(H1N1)2009 virus in Hong Kong. *Am J Epidemiol.* 2013;177(8):834-840.
99. Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. *J Infect Dis.* 2012;206(12):1862-1871.
100. Wu P, Goldstein E, Ho LM, et al. Excess mortality impact of two epidemics of pandemic influenza A(H1N1pdm09) virus in Hong Kong. *Influenza Other Respir Viruses.* 2014;8(1):1-7.

101. Yang L, Ma S, Chen PY, et al. Influenza associated mortality in the subtropics and tropics: results from three Asian cities. *Vaccine*. 2011;29(48):8909-8914.
102. Yang L, Chan KP, Cowling BJ, et al. Excess mortality associated with the 2009 pandemic of influenza A(H1N1) in Hong Kong. *Epidemiol Infect*. 2012;140(9):1542-1550.
103. Yu H, Feng L, Viboud CG, et al. Regional variation in mortality impact of the 2009 A(H1N1) influenza pandemic in China. *Influenza Other Respir Viruses*. 2013;7(6):1350-1360.
104. Zucs P, Buchholz U, Haas W, et al. Influenza associated excess mortality in Germany, 1985-2001. *Emerg Themes Epidemiol*. 2005;2:6.