WEB MATERIAL

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

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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^th^ influenza season or calendar year, and pop_i represents the source population of the i^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:

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

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

Web Table 1. Basic Information on Included Articles

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

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

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

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

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

Yang, 2012 (102)	Hong Kong	1998-2009	GLM	Seasonal and 2009 pandemic	LAB %	P&I, R&C, AC	ICD-10	0-19, 20-64, ≥65, 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.

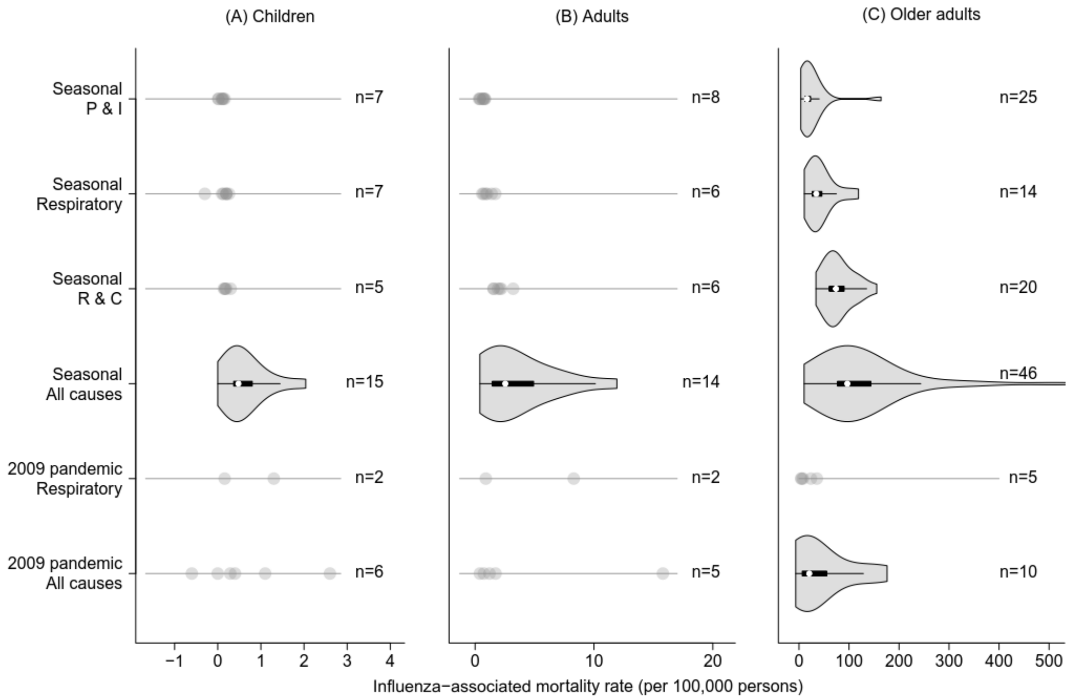
§: GLM, generalized linear model; RD, incidence rate-difference model; Serfling, Serfling-type model; ARIMA, autoregressive integrated moving average model; MA, moving average method; Multiplier, multiplier method; Surv, survival analysis; Regression, regression model without influenza activity proxy;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

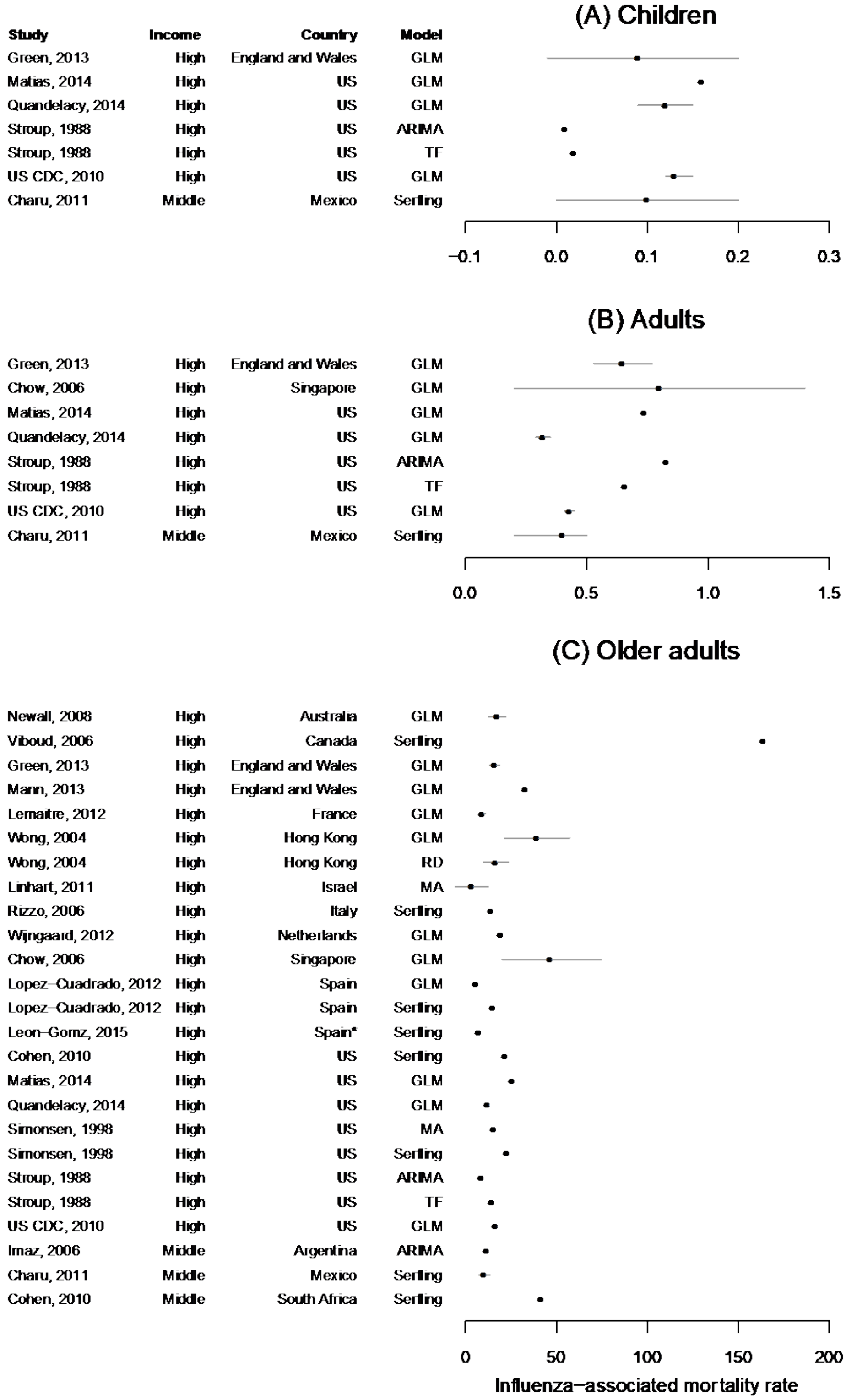
Models without an influenza activity proxy other than multiplier methods and Serfling-type models include Regression, ARIMA, TF, Surv, MA, RD, and RMD.

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

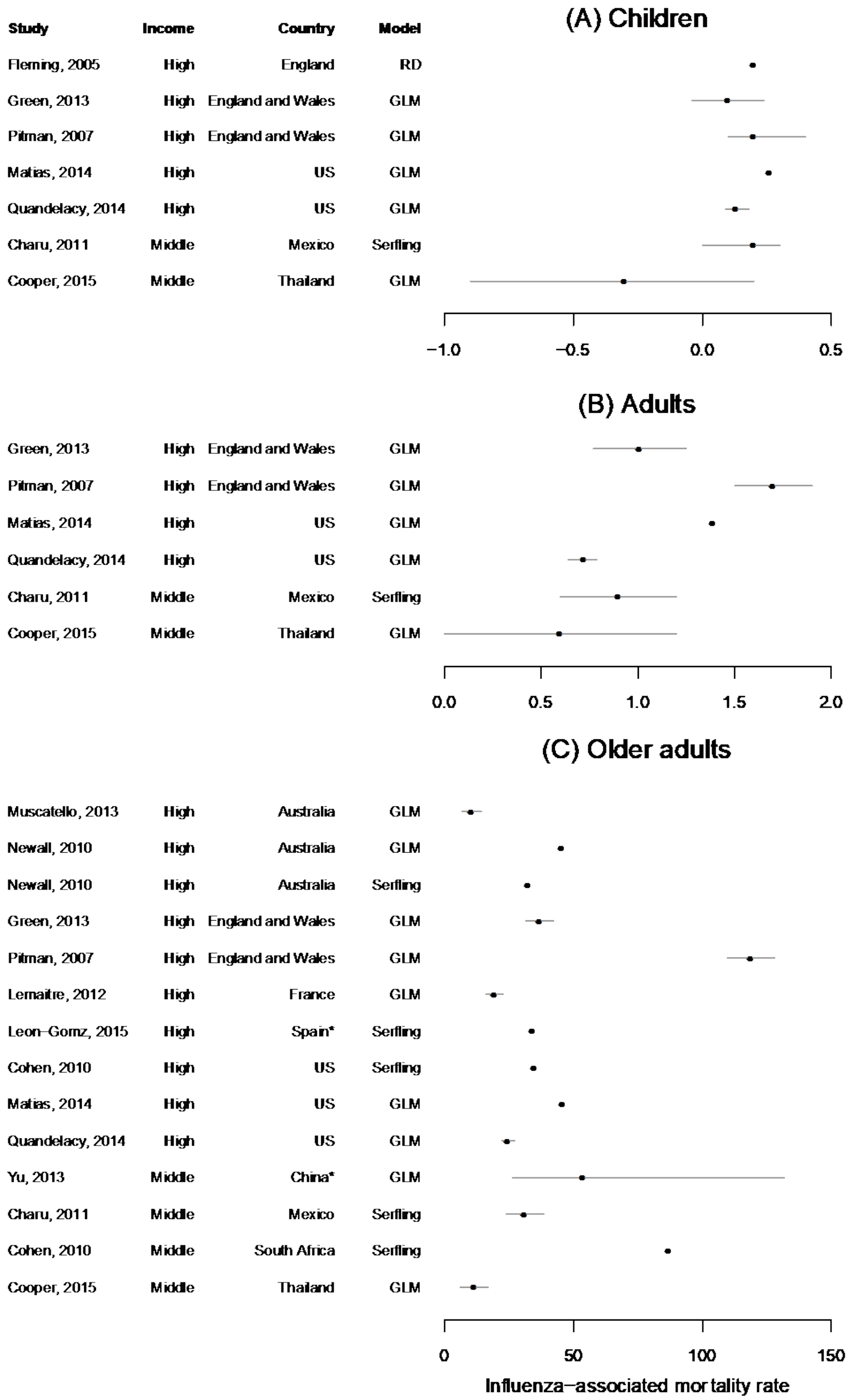
Δ: ICD, the International Classification of Diseases.



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 ⩾10, we used violin plots to show the estimates. If the number of estimates was <10, the estimate from each study was indicated with dots. 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 all 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.

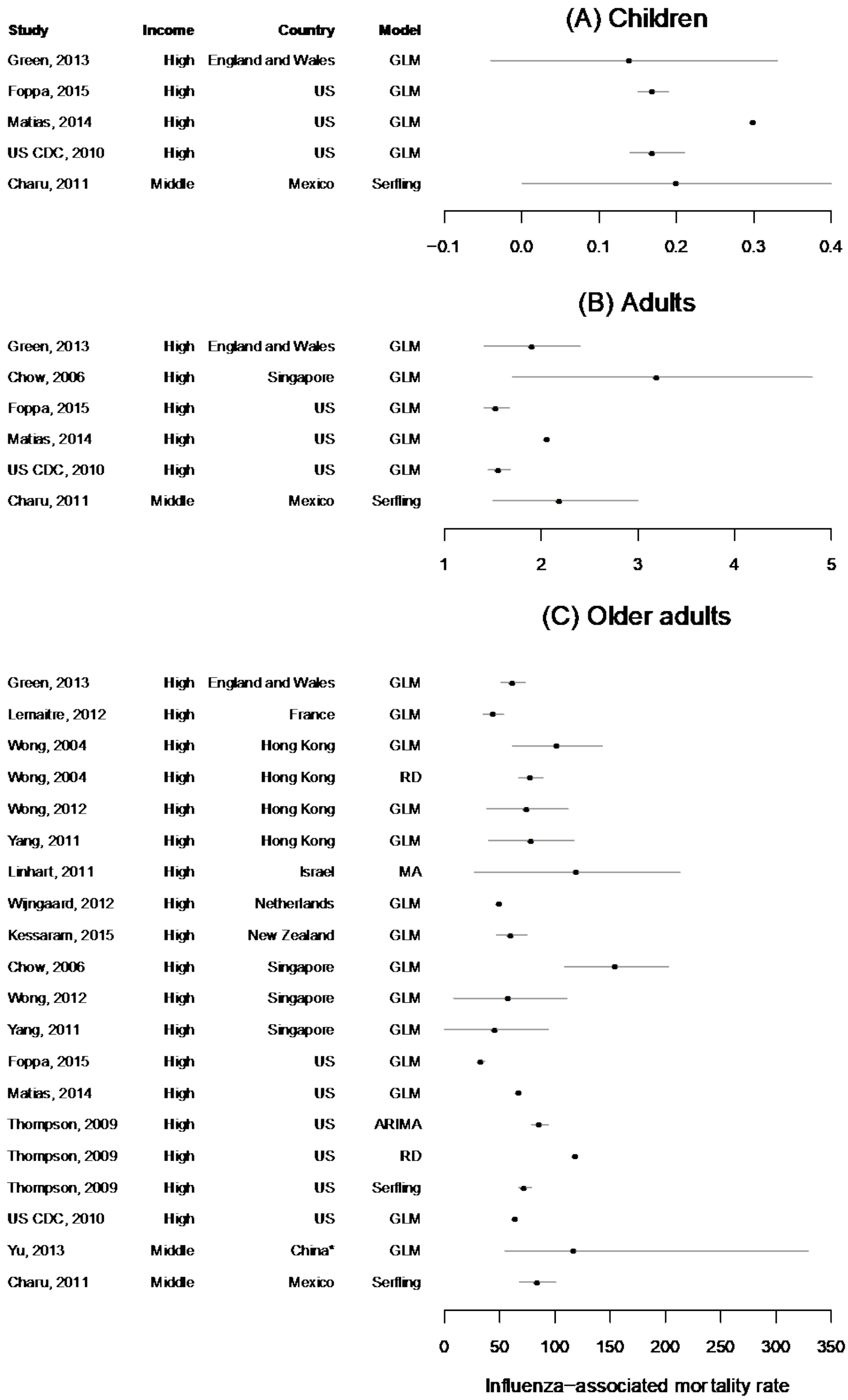


Web Figure 2. Annual age-specific influenza-associated excess pneumonia and influenza mortality rates in seasonal periods. (A) Estimates for children. (B) Estimates for adults (Cochran's Q for GLM: Q = 71, P < 0.001). (C) Estimates for older adults (Cochran's Q for GLM: $Q = 285$, $P < 0.001$; Serfling: $Q = 1658$, $P < 0.001$; 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.



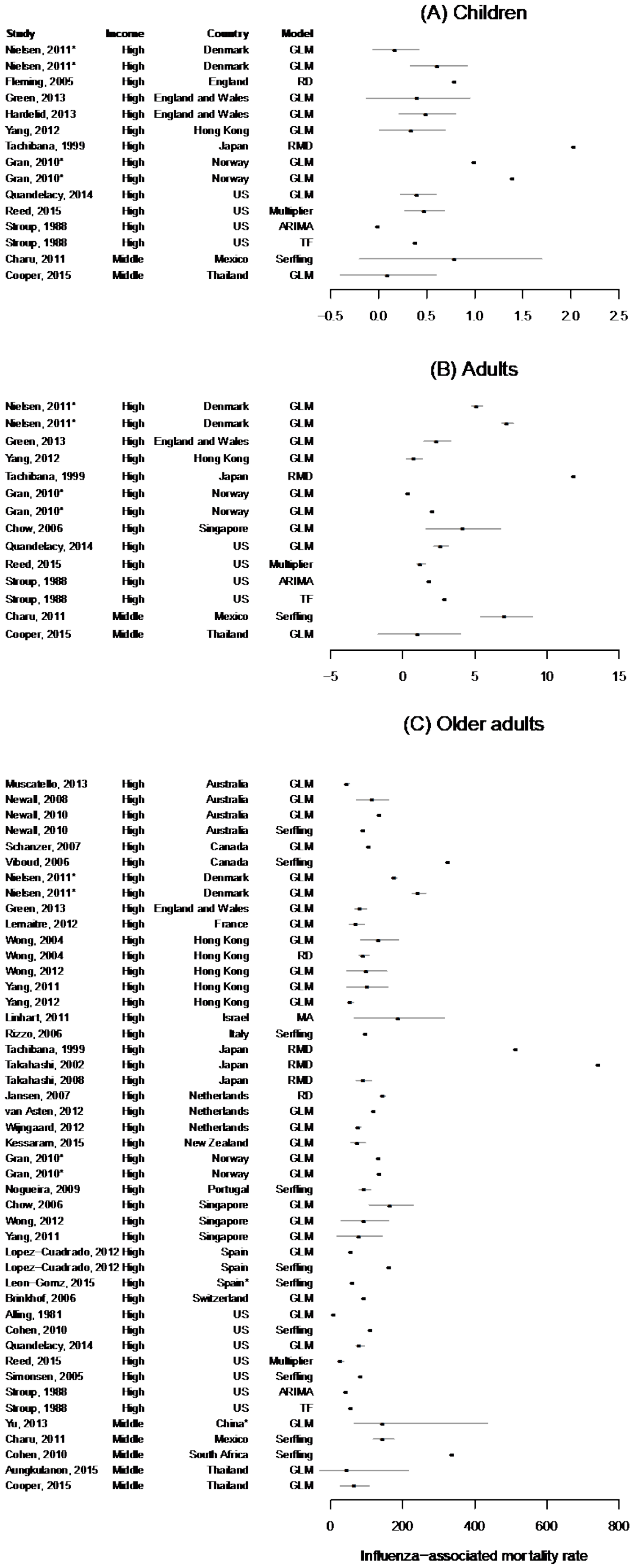
Web Figure 3. Annual age-specific influenza-associated excess respiratory mortality rates in seasonal periods. (A) Estimates for children (Cochran's Q for GLM: Q = 6, P = 0.209). (B) Estimates for adults (Cochran's Q for GLM: Q = 93, P <

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.

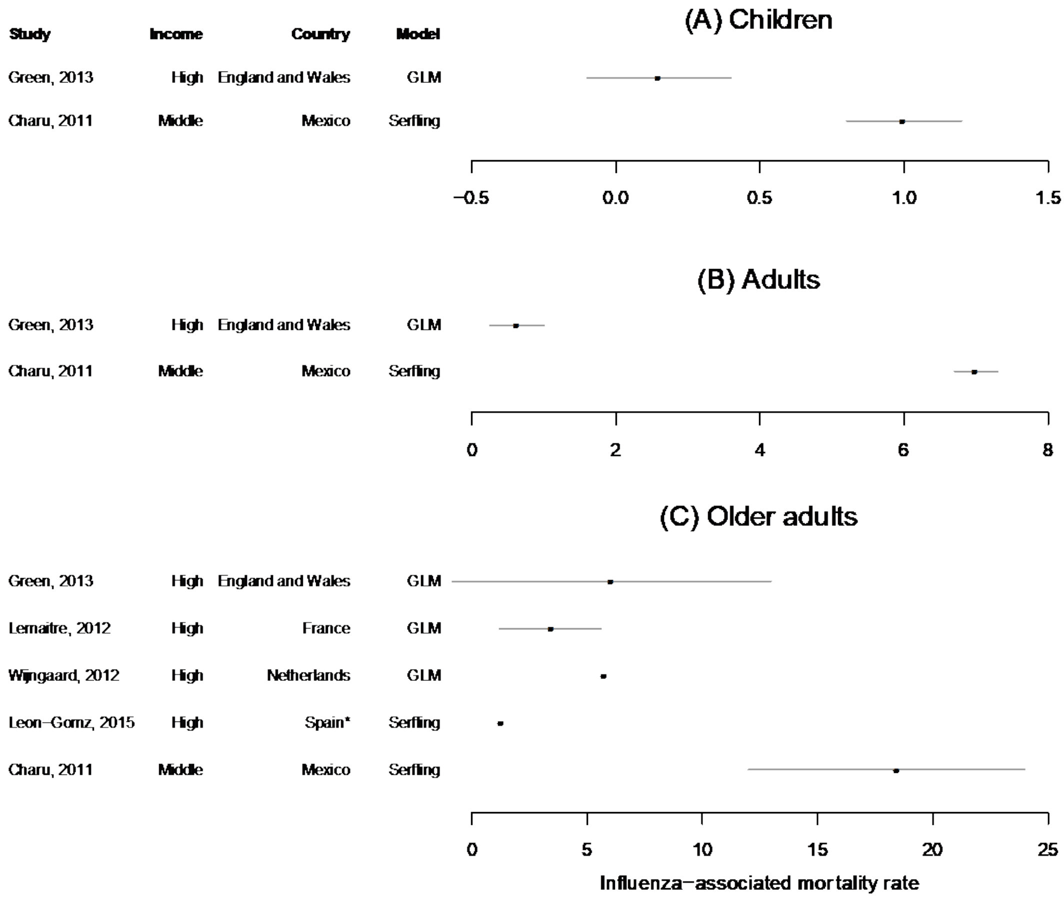


Web Figure 4. Annual age-specific influenza-associated excess respiratory and cardiovascular mortality rates in seasonal periods. (A) Estimates for children. (B) Estimates for adults (Cochran's Q test for GLM: $Q = 10$, $P = 0.047$).

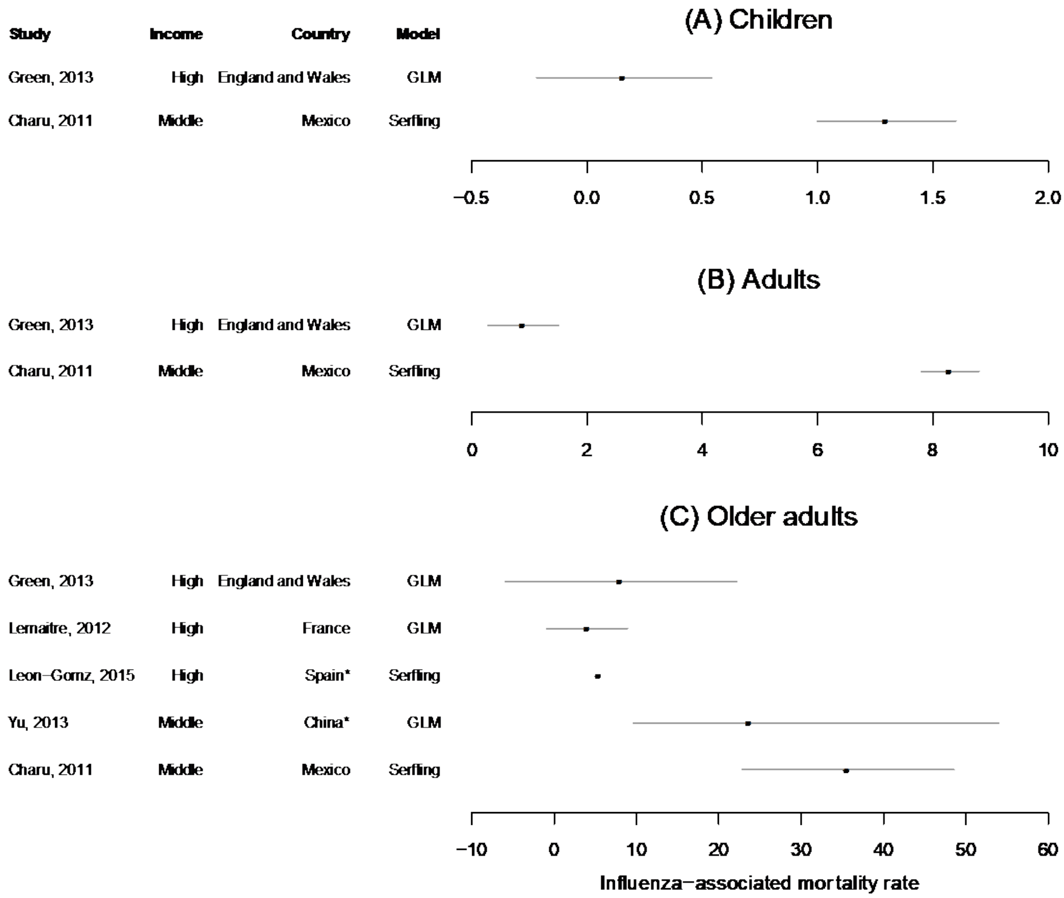
(C) Estimates for older adults (Cochran's *Q* for GLM: $Q = 517$, $P < 0.001$). China* represents 128 sites in China. GLM, generalized linear model; Serfling, Serfling-type model; MA, moving average method; RD, incidence rate-difference model; ARIMA, autoregressive integrated moving average model.


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

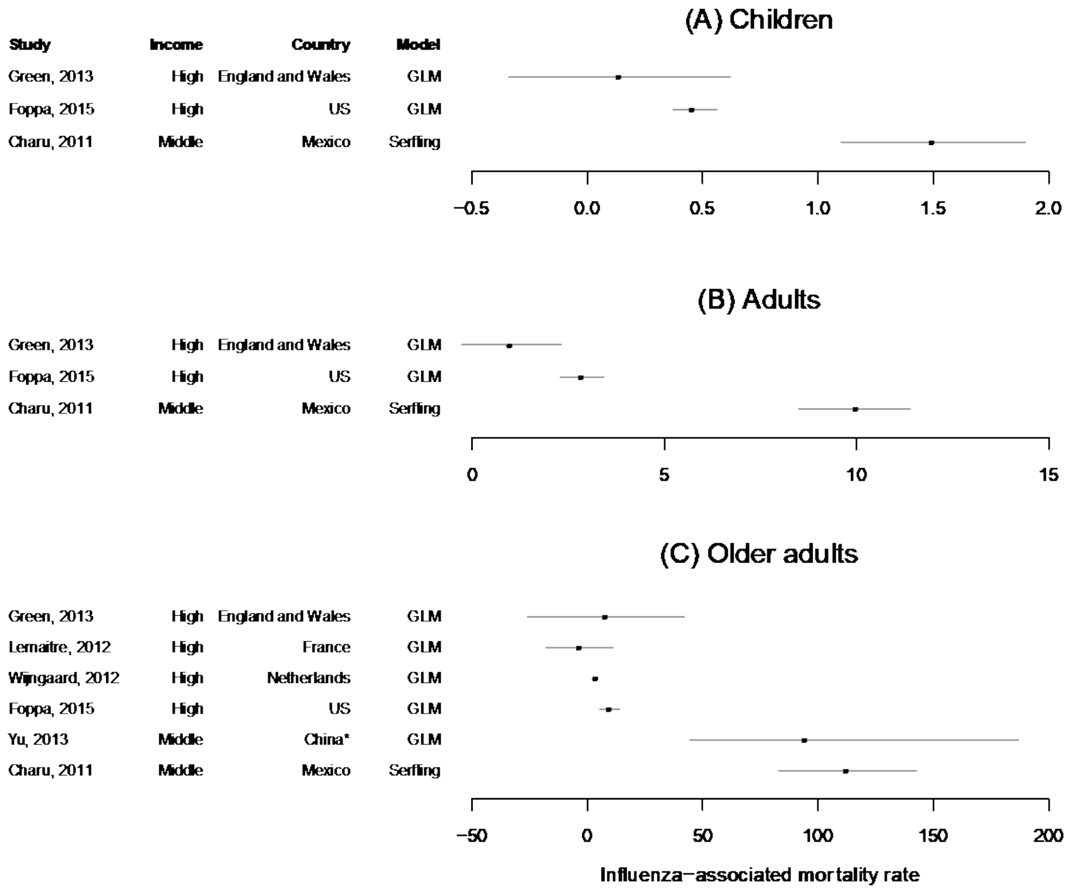
Web Figure 5. Annual age-specific influenza-associated excess all-cause mortality rates in seasonal periods. (A) Estimates for children (Cochran's Q for GLM: $Q = 29$, $P < 0.001$). (B) Estimates for adults (Cochran's Q for GLM: $Q = 521$, $P < 0.001$). (C) Estimates for older adults (Cochran Q for GLM: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



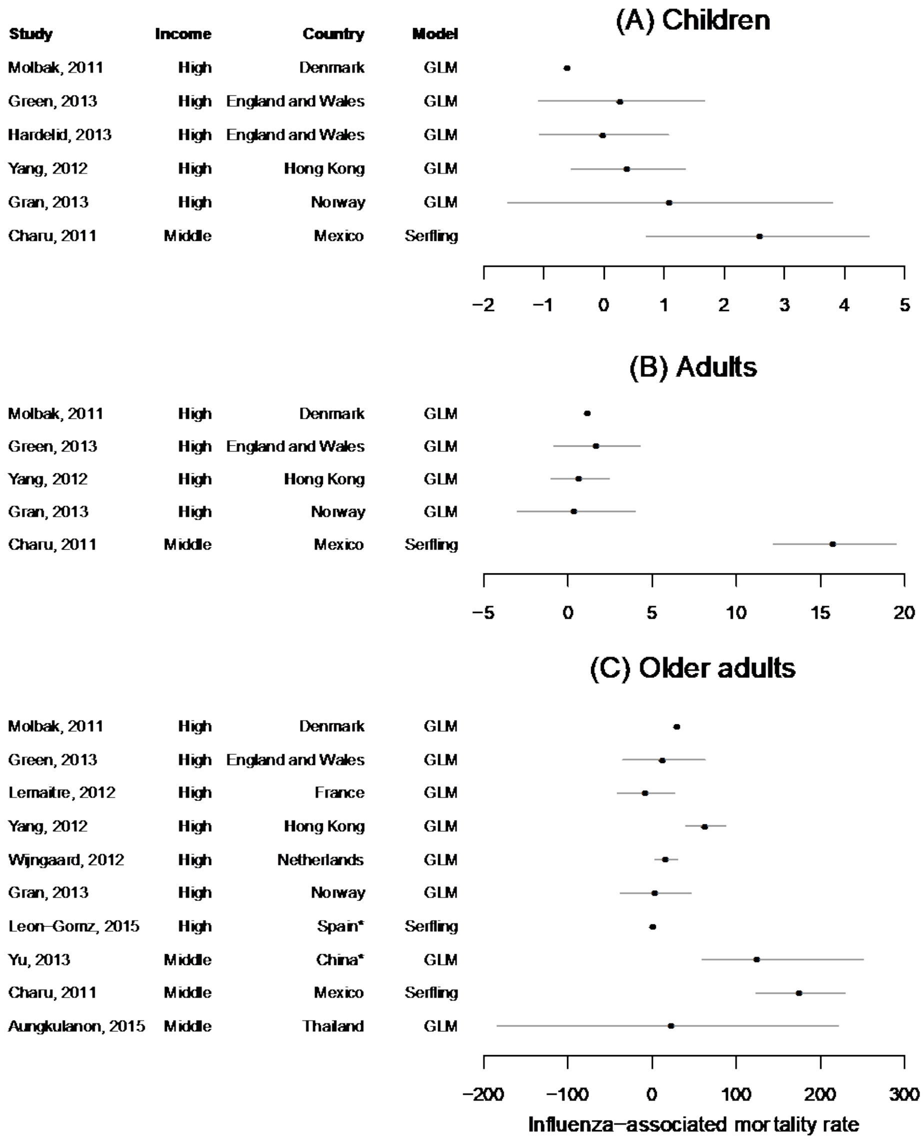
Web Figure 6. Annual age-specific influenza-associated excess pneumonia and influenza mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults. Spain* means 52 provincial capitals in Spain. Serfling, Serfling-type model; GLM, generalized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



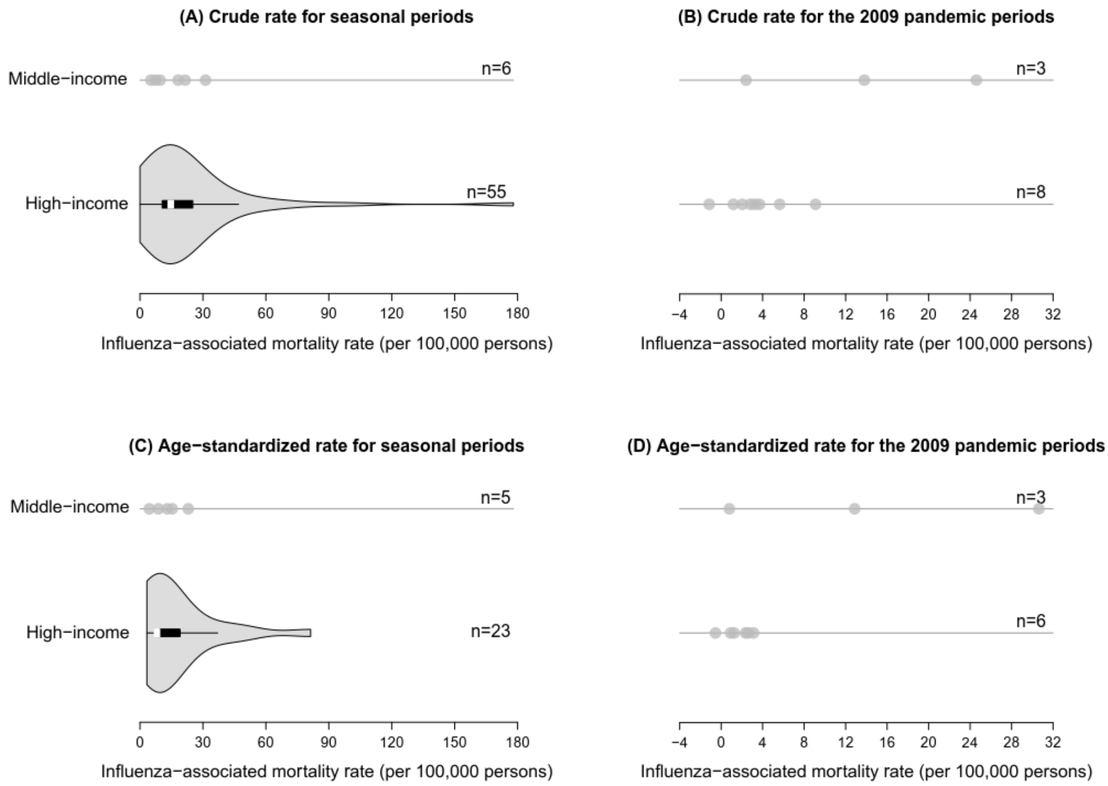
Web Figure 7. Annual age-specific influenza-associated excess respiratory mortality rates in the 2009 pandemic periods. (A) Estimates for children. (B) Estimates for adults. (C) Estimates for older adults. Spain* means 52 provincial capitals in Spain. China* represents 128 sites in China. Serfling, Serfling-type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



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



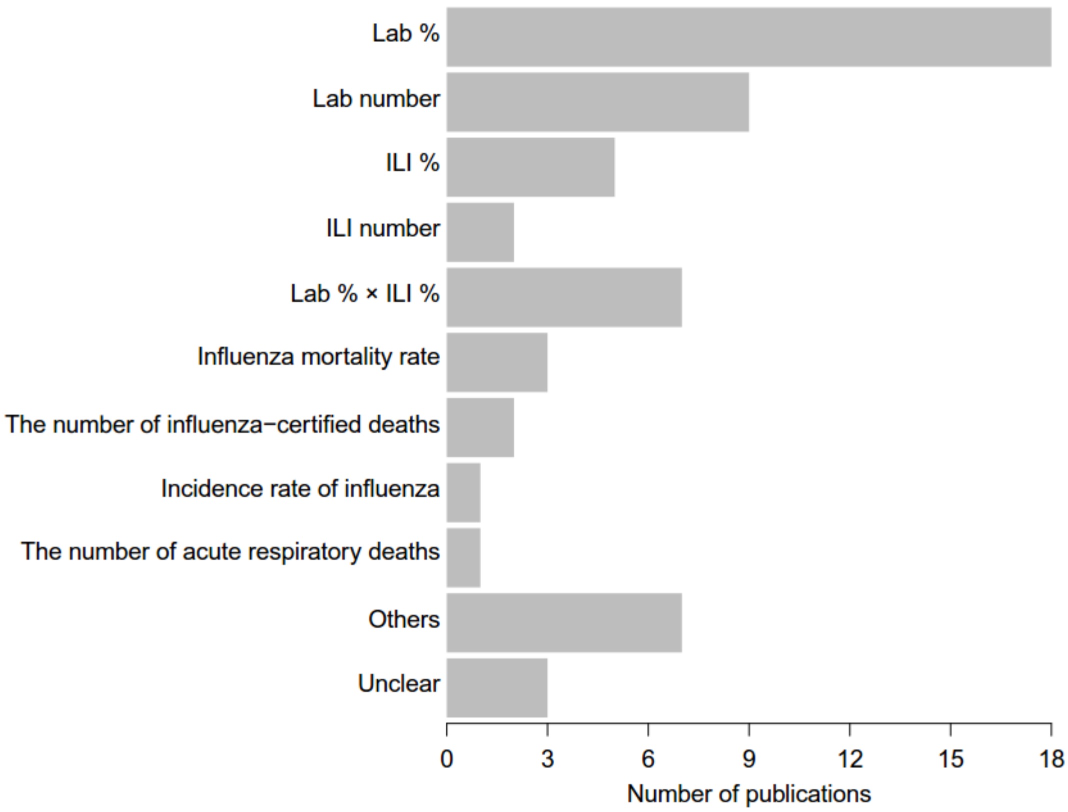
Web Figure 9. Annual age-specific influenza-associated excess all-cause mortality rates in the 2009 pandemic periods. (A) Estimates for children (Cochran's *Q* for GLM: Q = 6, P = 0.227). (B) Estimates for adults. (C) Estimates for older adults (Cochran's *Q* for GLM: Q = 20, P = 0.005). Europe* is 8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



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

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

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



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

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

2.1 Regression models with an influenza activity proxy

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

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

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

Studies used various methods to control for unmeasured confounding. For example, some studies (29, 30, 61, 99-101) used a spline function of time, while Dushoff et al. (20) and Yang et al. (102) detrended data before fitting models. Twenty-one out of 54 studies used a polynomial function of time to control for trends in mortality, and sine and cosine functions of time to control for the seasonality of mortality. Among studies using regression models with an influenza activity proxy, only three studies applied Bayesian statistics (18, 24, 25) to estimate the mortality burden due to influenza. Eight studies (50, 54, 69, 70, 84, 85, 92, 98) used a Poisson distribution with an identity link, while seven studies applied a negative binomial distribution among which four studies (5, 14, 25, 53) used an identity link function and three (12, 47, 103) applied a log link function. To deal with autocorrelation in time series modeling, Wijngaard et al. (92) used a generalized estimating equation (GEE), some studies (18, 26, 61, 64, 99-101) assumed the error followed an autoregressive (AR) process and one study (9) assumed the error followed an ARIMA process.

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

2.2 Serfling-type models

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

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

where Y_t represents the number of deaths or the death rate at time t with a mean of μ_t. D is the distribution of Y_t. $g(\cdot)$ represents the link function of μ_t. m is the order of polynomial components included in the model. β_i is the coefficient for polynomial *i*. The right hand side of the equation is used to model the seasonal pattern of mortality. β_{1j} and β_{2j} are the coefficients for $\sin(\frac{2\pi jt}{T})$ and $\cos(\frac{2\pi jt}{T})$, respectively where π is the mathematical constant. *k* is an integer that is smaller than or equal to *T*/2, but in the studies reviewed was commonly set to 1 or 2. *T* represents the number of time units within a time-series cycle.

2.3 Other methods

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

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

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