DOI:10.1111/j.1750-2659.2009.00073.x
www.blackwellpublishing.com/influenza

Original Article

Estimates of US influenza-associated deaths made using four different methods

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Accepted 12 January 2009. Published Online 19 February 2009.

Abstract

Background A wide range of methods have been used for estimating influenza-associated deaths in temperate countries. Direct comparisons of estimates produced by using different models with US mortality data have not been published.

Objective Compare estimates of US influenza-associated deaths made by using four models and summarize strengths and weaknesses of each model.

Methods US mortality data from the 1972–1973 through 2002–2003 respiratory seasons and World Health Organization influenza surveillance data were used to estimate influenza-associated respiratory and circulatory deaths. Four models were used: (i) rate-difference (using peri-season or summer-season baselines), (ii) Serfling least squares cyclical regression, (iii) Serfling–Poisson regression, (iv) and autoregressive integrated moving average models.

Results Annual estimates of influenza-associated deaths made using each model were similar and positively correlated, except for estimates from the summer-season rate-difference model, which were consistently higher. From the 1976/1977 through the 2002/2003 seasons the, the Poisson regression models estimated that an annual average of 25 470 [95% confidence interval (CI) 19 781–31 159] influenza-associated respiratory and circulatory deaths [9·9 deaths per 100 000 (95% CI 7·9–11·9)], while peri-season rate-difference models using a 15% threshold estimated an annual average of 22 454 (95% CI 16 189–28 719) deaths [8·6 deaths per 100 000 (95% CI 6·4–10·9)].

Conclusions Estimates of influenza-associated mortality were of similar magnitude. Poisson regression models permit the estimation of deaths associated with influenza A and B, but require robust viral surveillance data. By contrast, simple peri-season rate-difference models may prove useful for estimating mortality in countries with sparse viral surveillance data or complex influenza seasonality.

Keywords Excess mortality, human, Influenza, mortality

Please cite this paper as: Thompson *et al.* (2009) Estimates of US influenza-associated deaths made using four different methods. Influenza and Other Respiratory Viruses 3(1), 37–49.

Introduction

For several decades, the Centers for Disease Control and Prevention (CDC) has made annual estimates of influenza-associated deaths in the US.[1–4] We use the term influenza-associated death herein to refer to a death for which influenza infection was likely a contributor to mortality, but not necessarily the sole reason for the acute illness that led to the death. Estimates of influenza-associated deaths have been used to determine costs and benefits associated with influenza prevention and control strategies (including vaccination) and in preparing for both seasonal epidemics and future pandemics.[5–7]

Influenza infections result in morbidity and mortality nearly every season in the US.[4,8] Mortality associated with influenza varies by age group, by chronic disease status, and by influenza virus type and subtype.[4,9–11] Introductions of a novel efficiently transmitted influenza A virus into the population can result in pandemics, which are often associated with more deaths than annual influenza epidemics. Primarily because the US population of those aged ≥65 years has increased substantially since the last pandemic in 1968–1969, current annual estimates of influenza-associated deaths exceed the annual estimates of deaths associated with that pandemic.[4]

Previous estimates for both pandemic and epidemic influenza-associated deaths have varied, based on outcomes modeled and the specific statistical methods used.[4,9,12,13] Four classes of models have been used by CDC to estimate influenza-associated deaths in the US: (i) rate-difference models,[14–17] (ii) Serfling least squares cyclical regression models which do not incorporate influenza viral surveillance data,[1,2,18] (iii) Serfling–Poisson regression models which do incorporate influenza viral surveillance data,[4,19] and (iv) autoregressive integrated moving average (ARIMA) models which do not use influenza surveillance data.[13,20,21] In this study, we used these four classes of models to estimate underlying respiratory and circulatory deaths that were associated with influenza among persons aged <65 or ≥65 years. Our objectives were to compare estimates made by using each of the models, to assess similarities and differences among the estimates produced by using each model, and to suggest several strengths and weakness of each model. We believe these results will be of interest not only to researchers and health officials in countries that currently use these models, but also to those in countries that are considering methods to estimate the mortality burden of influenza.

Methods

Data and analyses

United States laboratory-based surveillance for influenza viruses was conducted from October through mid-May (calendar week 40 through week 20). During the 1976–1977 through 2002–2003 respiratory seasons, we obtained weekly influenza test results from 50 to 75 World Health Organization (WHO) collaborating virology laboratories in the US. The laboratories provided weekly numbers of total respiratory specimens tested for influenza and the number of positive influenza tests by virus type and subtype.[22]

National mortality data were obtained from the National Center for Health Statistics.[23] Deaths were categorized using the International Classification of Diseases eighth revision (ICD-8), ninth revision (ICD-9) [24] or tenth revision (ICD-10), as appropriate. We modeled underlying respiratory and circulatory deaths (ICD-8 codes 390–519; ICD-9 codes 390–519; ICD-10 codes I00–I99, J00–J99). Underlying respiratory and circulatory deaths provide an estimate of death-associated respiratory infections that is more sensitive than underlying pneumonia and influenza deaths and more specific than all-cause deaths.[4]

We used four types of models to estimate influenza-associated deaths: (i)rate-difference models,[16] (ii) Serfling least squares cyclical regression models,[18] (iii) Serfling–Poisson regression models,[4] and (iv) autoregressive integrated moving average models.[20] Human subject review was not required for this study as only aggregate national data without personal identifiers were used in analyses.

Peri- and summer-season rate-difference models

Incidence rate-difference models have been used frequently to estimate influenza-associated hospitalizations and deaths.[14,16,17,25] We defined five periods for each season: (i) a period when ≥10% of specimens tested were positive for influenza, (ii) a period when ≥15% of specimens were positive, (iii) a peri-season baseline period when <10% of specimens were positive, (iv) a peri-season baseline period when <15% of specimens were positive, and (v) a summer-season baseline period. The summer-season baseline period was defined as the weeks from July through September at the beginning of each season and May and June at the end of each season when there is little influenza activity.

The peri-season excess mortality rates were defined as the difference in the average weekly mortality rates between an influenza period and a peri-season period for a particular season. The summer-season excess mortality rates were defined as the difference in the average weekly rates between an influenza period and a summer-season period.

Weekly excess mortality rates were converted to annual excess numbers of deaths by using the number of weeks that were above an epidemic threshold, and available US census data: annual excess deaths = (excess weekly rate) × (number of epidemic weeks) × (population).

Serfling least squares cyclical regression model

A previously published Serfling least squares cyclical regression model was used to estimate annual numbers of influenza-associated deaths.[18] In this model

$$Y_i = \beta_0 + \beta_1(t_i) + \beta_2(t_i^2) + \beta_3[\sin(2t_i\pi/52)] + \beta_4[\cos(2t_i\pi/52)] + e_i,$$

where Y_i represented the number of deaths in a particular week i, β_0 represented the intercept, β_1 represented a coefficient for the linear time trend, β_2 represented a coefficient for the quadratic time trend, β_3 and β_4 represented coefficients associated with seasonal fluctuations in deaths, and e_i represented the error term. Epidemic thresholds were defined for the first 5 years of data for each age-group based primarily on visual inspection of the data. These thresholds were based on the 1978/1979 influenza season, when influenza A(H1N1) viruses predominated and other evidence suggested that few deaths were attributable to influenza.[18,26] For subsequent seasons, annual baselines were forecasted using the prior 5-year non-epidemic data.

Serfling–Poisson regression model

Poisson regression models which incorporated weekly influenza circulation data were used to estimate influenza-associated deaths by age group.[4,27,28] The models included coefficients similar to those described for the least squares regression models as well as additional terms corresponding to the circulation of influenza A(H3N2), A(H1N1), and B viruses.[4] The three terms represented the percentages of specimens testing positive by subtype during a particular week. The age-specific population size was used as an offset term. Weekly estimates of the US population by age group were obtained from the US Census Bureau.[29]

In each Poisson regression model,

$$Y_i = \alpha \exp\{\beta_0 + \beta_1[t_i] + \beta_2[t_i^2] + \beta_3[t_i^3] + \beta_4[\sin(2t_i\pi/52)] + \beta_5[\cos(2t_i\pi/52)] + \beta_6[\mathrm{A(H1)}_i] + \beta_7[\mathrm{A(H3)}_i] + \beta_8[\mathrm{B}_i]\},$$

where, Y_i represented the number of deaths at week i, α was the population offset, β_0 represented the intercept, β_1 through β_3 represented coefficients associated with secular trends, β_4 and β_5 represented coefficients associated with seasonal changes in deaths, and β_6–β_8 represented coefficients associated with the percentages of specimens testing positive for each influenza virus type and sub-type during a given week. We did not have data for respiratory syncytial virus (RSV) before 1990 so an RSV term was not included in the model. Previous estimates of influenza-associated deaths have suggested that the total estimates of influenza-associated deaths are not significantly influenced by the inclusion of a RSV term.[30] However, it is possible that if we made age-specific estimates for young children that the inclusion of RSV in the model could lead to significant differences in death estimates.

Predicted values for the full model for a given week were estimated and then predicted values for models that excluded one viral term were subtracted to estimate influenza-associated deaths associated with that viral type/subtype. The weekly influenza-associated deaths were summed for each viral term across the influenza season.

Autoregressive integrated moving average (ARIMA) models

Previously published methods developed by Choi and Thacker [13,20,31,32] were used to estimate influenza-associated deaths. For each age group, a Fourier equation was used to estimate baseline, non-influenza deaths during the influenza epidemic weeks of 1972–1973 and 1973–1974; epidemic weeks were defined as two or more consecutive weeks when mortality was greater than two standard deviations (SD) above the mean. Influenza-related excess deaths were defined as the difference between actual deaths and estimated non-influenza deaths. During epidemic weeks, total deaths were replaced with estimates of non-influenza deaths. Following Box-Jenkins procedures,[33] we removed seasonal patterns from the data by taking the difference in weekly deaths one year apart (e.g., deaths week 40 in 1974–deaths week 40 in 1973). We used the actual deaths during non-epidemic weeks and the Fourier-estimated non-influenza deaths to build the model to estimate deaths for the next 52 weeks. Influenza epidemic weeks were defined as two or more consecutive weeks when actual mortality was greater than the upper bound of a 95% confidence interval (CI) around the non-influenza deaths. We replaced actual deaths for epidemic weeks with estimated non-influenza deaths, and repeated the process for each subsequent season, re-estimating the coefficients from the ARIMA equation. Goodness-of-fit was tested by using the Ljung modification of the Box-Pierce Q statistic.[39]

Comparisons of annual numbers of influenza-associated deaths by age group

We compared the annual numbers of deaths for each model by age group using Wilcoxon signed-rank tests with a Bonferroni adjustment for multiple comparisons; an adjusted P-value of <0·05 was considered statistically significant.

Results

Estimates of influenza-associated deaths using rate-difference models with a 15% threshold

Among persons aged <65 years, the average annual excess death rate using the peri-season baseline was 0·15 (95% CI 0·11–1·8) deaths per 100 000 person-weeks and ranged from 0 to 0·42 deaths per 100 000 person-weeks (Appendix S1). The annual average summer-season excess rate was 0·27 deaths per 100 000 person-weeks (95% CI 0·22–0·31). Among persons aged ≥65 years, excess mortality rates were substantially higher. Using the peri-season baseline, there were 8·00 (95% CI 6·16–9·84) deaths per 100 000 person-weeks with substantial variation by seasons (0–18·5 deaths per 100 000 person-weeks). The average annual excess rate using the summer-season baseline was 15·1 deaths per 100 000 person-weeks (95% CI 12·9–17·3).

The annual average number of epidemic weeks (when >15% of specimens tested were positive for influenza) was 7·4 (range 0–15 weeks) (Table 1). Among persons aged <65 years, the estimated number of influenza-associated deaths for the peri-season model ranged from 0 to 6574 deaths with an annual average of 2507 deaths. Similarly, using the summer-season model, the number of deaths ranged from 0 to 9264 deaths with an annual average of 4509 deaths. Among those aged ≥65 years, the estimated number of influenza-associated deaths for the peri-season model ranged from 0 to 51 122 deaths with an annual average of 19 954 deaths. Using the summer-season model, the number of deaths ranged from 0 to 74 821 deaths with an annual average of 36 430 deaths. Eighty-nine percent of all deaths occurred among persons aged 65 and older. Among all persons, the peri-season model estimated an annual average of 22 454 (95% CI 16 189–28 179) influenza-associated deaths.

Table 1. Incidence rate-difference model annual estimates for underlying respiratory and circulatory deaths using a 15% threshold* .

Season	Epi weeks	Age < 65 years				Age >65 years				Total	
		Annual excess numbers		Annual excess rates		Annual excess numbers		Annual excess rates		Annual excess numbers	
		Peri**	Summer***	Peri**	Summer***	Peri**	Summer***	Peri**	Summer***	Peri	Summer
1976	3	0	844	0·0	0·4	0	5749	0·0	24·2	0	6593
1977	5	4169	6107	2·1	3·1	18 658	29 272	77·3	121·2	22 827	35 379
1978	4	985	2228	0·5	1·1	3337	10 002	13·5	40·4	4322	12 230
1979	4	1275	2616	0·6	1·3	7896	17 461	31·2	68·9	9171	20 077
1980	3	2072	3170	1·0	1·6	14 334	21 753	55·4	84·1	16 406	24 923
1981	0	0	0	0·0	0·0	0	0	0·0	0·0	0	0
1982	6	1038	2714	0·5	1·3	7591	20 122	28·0	74·2	8629	22 836
1983	12	1080	4788	0·5	2·3	8197	33 704	29·6	121·6	9277	38 492
1984	9	3311	6360	1·6	3·1	29 960	50 028	106·0	176·9	33 271	56 388
1985	7	2022	4147	1·0	2·0	16 454	33 590	57·0	116·4	18 476	37 737
1986	8	2664	4789	1·3	2·3	17 107	32 709	58·3	111·4	19 771	37 498
1987	3	502	1488	0·2	0·7	5285	13 886	17·6	46·3	5787	15 374
1988	11	2511	5059	1·2	2·3	19 314	41 823	63·2	136·9	21 825	46 882
1989	7	1429	3897	0·7	1·8	17 743	36 461	57·1	117·3	19 172	40 358
1990	5	963	2361	0·4	1·1	5575	17 393	17·6	55·0	6538	19 754
1991	8	3269	5080	1·5	2·3	25 555	42 434	79·8	132·4	28 824	47 514
1992	8	2440	4767	1·1	2·1	20 442	40 631	62·7	124·7	22 882	45 398
1993	7	4193	5647	1·8	2·5	35 972	51 450	109·0	155·9	40 165	57 097
1994	7	1457	3319	0·6	1·4	14 795	31 670	44·2	94·6	16 252	34 989
1995	7	2631	4565	1·1	2·0	16 434	34 265	48·6	101·3	19 065	38 830
1996	10	3522	6201	1·5	2·6	35 806	61 385	104·7	179·5	39 328	67 586
1997	9	4498	6593	1·9	2·8	45 431	66 220	131·5	191·6	49 929	72 813
1998	11	3945	6777	1·6	2·8	43 398	70 799	124·4	203·0	47 343	77 576
1999	12	6574	9264	2·7	3·8	51 122	74 821	145·7	213·2	57 696	84 085
2000	10	3486	5924	1·4	2·4	21 171	43 358	59·9	122·7	24 657	49 282
2001	15	5050	7665	2·0	3·0	41 801	67 143	117·7	189·1	46 851	74 808
2002	10	2614	5384	1·0	2·1	15 374	35 482	43·2	99·6	17 988	40 866
Average during the 1976/77 through the 2002/03 seasons	7·4	2507	4509	1·2	2·1	19 954	36 430	64·7	119·3	22 461	40 939

*The 15% threshold represent weeks in which the number of positive influenza isolates exceeded 15% of the total specimen tested.
**The Peri-season model estimates are calculated by multiplying the peri-season rates in Appendix S1 times the number of epiweeks times the population divided by 100 000.
***The summer-season model estimates are calculated by multiplying the summer-season rates in Appendix S1 times the number of epiweeks times the population divided by 100 000.

Estimates of influenza-associated deaths using rate-difference models with a 10% threshold

As expected, estimates of numbers and rates of influenza-associated deaths were higher with this model than the model using a 15% threshold (Appendices S2 and S3). The annual average number of epidemic weeks (when >10% of specimens tested positive for influenza) was 11·8 (range 2–20 weeks). For persons aged <65 years, the estimated number of influenza-associated deaths for the peri-season model ranged from 0 to 7084 deaths with an annual average of 3819 deaths. Using the summer-season model, the number of deaths ranged from 436 to 10 069 deaths with an annual average of 6574 deaths. For persons aged ≥65 years, the estimated number of influenza-associated deaths for the peri-season model ranged from 0 to 57 844 deaths with an annual average of 29 971 deaths. Using the summer-season model, the number of deaths ranged from 4072 to 93 789 deaths with an annual average of 52 795 deaths.

Estimates of influenza-associated deaths using Serfling least squares regression models

Among persons aged <65 or ≥65 years, the average annual number of epidemic weeks estimated during the 1976–1977 through 2002–2003 seasons was 3·6 and 9·7, respectively

Table 2. Linear regression model annual estimates using underlying respiratory and circulatory deaths*

Season	Age < 65 years				Age ≥ 65 years					Total			
	Epi weeks	Annual excess numbers	L 95% CI	U 95% CI	Annual excess rate**	Epi weeks	Annual excess numbers	L 95% CI	U 95% CI	Annual excess rate**	Annual excess numbers	L 95% CI	U 95% CI
1972	9	5206	2212	8200	2·7	6	12 174	5763	18 585	56·9	17 380	7975	26 785
1973	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1974	2	836	175	1497	0·4	7	12 140	4693	19 587	54·1	12 976	4868	21 084
1975	0	0	0	0	0·0	8	22 543	14 047	31 039	98·0	22 543	14 047	31 039
1976	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1977	7	5299	2904	7695	2·7	9	30 387	20 485	40 289	125·9	35 687	23 389	47 984
1978	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1979	0	0	0	0	0·0	7	14 494	7673	21 314	57·3	14 494	7673	21 314
1980	7	4035	2233	5837	2·0	11	34 726	25 292	44 159	134·2	38 761	27 525	49 996
1981	0	0	0	0	0·0	7	7758	1947	13 568	29·3	7758	1947	13 568
1982	0	0	0	0	0·0	6	8600	3373	13 827	31·8	8600	3373	13 827
1983	2	743	267	1220	0·4	2	3467	1707	5226	12·5	4210	1975	6446
1984	7	2595	1044	4147	1·2	9	21 908	13 843	29 972	77·6	24 503	14 887	34 119
1985	2	742	300	1185	0·4	12	20 426	8798	32 055	70·9	21 169	9097	33 240
1986	2	530	126	934	0·2	7	10 974	5117	16 831	37·4	11 504	5243	17 765
1987	0	0	0	0	0·0	16	26 857	15 518	38 197	89·8	26 857	15 518	38 197
1988	0	0	0	0	0·0	4	3446	848	6043	11·3	3446	848	6043
1989	5	2495	1503	3487	1·1	9	27 016	20 426	33 606	87·2	29 510	21 928	37 093
1990	2	642	254	1030	0·3	18	20 881	7632	34 130	66·3	21 523	7887	35 160
1991	5	2085	1101	3069	0·9	20	36 658	21 855	51 461	114·5	38 743	22 956	54 530
1992	3	885	283	1487	0·4	21	35 302	20 132	50 472	108·6	36 187	20 415	51 959
1993	4	2026	1266	2785	0·9	8	30 908	24 860	36 956	93·8	32 934	26 126	39 742
1994	0	0	0	0	0·0	8	10 569	4259	16 879	31·7	10 569	4259	16 879
1995	3	1449	872	2027	0·6	6	13 408	8805	18 011	39·7	14 857	9677	20 037
1996	4	1542	755	2329	0·7	9	26 841	19 702	33 980	78·5	28 383	20 457	36 309
1997	8	2604	1130	4077	1·1	11	33 901	26 058	41 744	98·2	36 504	27 188	45 821
1998	7	2290	983	3597	0·9	15	41 106	29 934	52 279	117·9	43 396	30 917	55 875
1999	8	4157	2698	5616	1·7	10	37 805	31 379	44 230	107·6	41 962	34 077	49 847
2000	15	4303	1475	7131	1·7	28	34 195	15 010	53 380	96·6	38 498	16 485	60 511
2001	5	1403	438	2368	0·6	8	12 712	6665	18 760	35·7	14 116	7103	21 128
2002	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
Average during the 1976/77 through the 2002/03 seasons	3·6	1475	855	2095	0·7	9·7	20 161	14 907	25 415	65·0	21 636	15 914	27 358

*Model estimates are based on the linear regression model used in Simonsen *et al.* (1997).
**Deaths per 100 000 person years.

(Table 2). Among persons aged ≥65 years during the 2000/2001 season, the model estimated 28 epidemic weeks, which represented an outlier. Among persons aged <65 or ≥65 years, the model estimated annual averages of 1475 (95% CI 855–2095) and 20 161 (95% CI 14 907–25 415) influenza-associated deaths, respectively. The average annual rates of influenza-associated deaths among those aged <65 or ≥65 years were 0·7 (range 0–2·7) and 65·0 (range 0–134·2) per 100 000 person-weeks, respectively. The total number of influenza-associated deaths annually was 21 636 (95% CI 15 914–27 358). More than 90% of influenza-associated pneumonia and influenza deaths occurred among persons aged ≥65 years.

Estimates of influenza-associated deaths using Serfling Poisson regression models

Among persons aged <65 years, the models estimated an annual average of 2680 (95% CI 2188–3171) deaths annually (Table 3). The annual rates of influenza-associated deaths ranged from 0·29 to 2·06 deaths per 100 000 person years. Among persons aged ≥65 years, the models estimated an annual average of 22 790 (95% CI 17 565–28 033), and

Table 3. Poisson regression model annual estimates using underlying respiratory and circulatory deaths*

Season	Age < 65 years				Age ≥ 65 years				Total			
	Annual excess numbers	L 95% CI	U 95% CI	Annual excess rate**	Annual excess numbers	L 95% CI	U 95% CI	Annual excess rate**	Annual excess numbers	L 95% CI	U 95% CI	Annual excess rate**
1976	1549	1474	1628	0·79	10 889	10,686	11 095	45·9	12 438	12 221	12 659	5·7
1977	3618	3502	3738	1·84	21 370	21 085	21 658	88·5	24 988	24 680	25 300	11·3
1978	1504	1430	1582	0·76	3318	3207	3433	13·4	4822	4688	4960	2·2
1979	906	849	967	0·45	9107	8922	9296	35·9	10 013	9819	10 211	4·4
1980	2914	2810	3022	1·45	17 979	17 718	18 244	69·5	20 893	20 612	21 178	9·2
1981	584	539	633	0·29	4702	4570	4838	17·7	5286	5145	5430	2·3
1982	3375	3263	3491	1·64	23 881	23 580	24 186	88·0	27 256	26 934	27 582	11·7
1983	1822	1740	1908	0·88	11 706	11 496	11 920	42·2	13 528	13 302	13 758	5·8
1984	4294	4167	4424	2·06	33 448	33 091	33 808	118·3	37 742	37 363	38 125	15·9
1985	1638	1561	1719	0·78	16 139	15 892	16 390	55·9	17 777	17 518	18 040	7·4
1986	1303	1234	1376	0·61	3429	3316	3546	11·7	4732	4599	4869	2·0
1987	2328	2235	2425	1·08	19 598	19 326	19 874	65·3	21 926	21 638	22 218	9·0
1988	2049	1962	2140	0·95	15 272	15 032	15 516	50·0	17 321	17 065	17 581	7·0
1989	3299	3188	3414	1·51	29 005	28 673	29 341	93·3	32 304	31 954	32 658	12·9
1990	1232	1165	1303	0·56	13 888	13 659	14 121	43·9	15 120	14 881	15 363	6·0
1991	3632	3516	3752	1·63	31 073	30 729	31 420	97·0	34 705	34 342	35 072	13·6
1992	2110	2022	2202	0·93	23 022	22 727	23 321	70·6	25 132	24 823	25 445	9·7
1993	3297	3186	3411	1·45	31 452	31 106	31 802	95·3	34 749	34 386	35 116	13·3
1994	2481	2385	2581	1·07	25 000	24 692	25 312	74·7	27 481	27 158	27 808	10·4
1995	2531	2434	2632	1·09	20 564	20 285	20 847	60·8	23 095	22 799	23 395	8·6
1996	3948	3827	4073	1·67	41 220	40 824	41 620	120·5	45 168	44 753	45 586	16·7
1997	4429	4300	4561	1·85	43 824	43 416	44 236	126·8	48 253	47 824	48 685	17·6
1998	3763	3645	3885	1·55	38 884	38 499	39 272	111·5	42 647	42 244	43 054	15·4
1999	4678	4546	4814	1·91	44 818	44 405	45 235	127·7	49 496	49 062	49,934	17·7
2000	1608	1531	1689	0·65	12 013	11 800	12 230	34·0	13 621	13 394	13 852	4·8
2001	5187	5048	5330	2·06	51 390	50 948	51 836	144·7	56 577	56 113	57 045	19·7
2002	2269	2178	2364	0·89	18 351	18 087	18 618	51·5	20 620	20 340	20 903	7·1
Average during 1976/77 through the 2002/03 seasons	2680	2188	3171	1·20	22 790	17 565	28 016	72·4	25 470	19 781	31 159	9·90

*The Poisson regression model is based on the methods described in Thompson *et al.* (2003).
**Deaths per 100 000 person years.

annual rates of influenza-associated deaths ranged from 11·7 to 144·7 deaths per 100 000 person years. The average annual total number of influenza-associated deaths estimated from this model was 25 470 (95% CI 19 781–31 159). Eighty-nine percent of the estimated deaths occurred among persons aged ≥65 years.

Age-specific annual estimates for the Poisson regression model were made by influenza virus type and subtype (Table 4). Among persons aged <65 years, the models estimated annual averages of 345 (range 0–1462), 2027 (range 0–4743), and 307 (range 0–825) influenza-associated deaths for A(H1), A(H3) and B viruses, respectively. Among persons aged ≥65 years, the models estimated annual averages of 887 (range 0–3241), 17 797 (range 0–45 339), and 4107 (4–10 342) influenza-associated deaths for A(H1), A(H3) and B viruses, respectively.

Estimates of influenza-associated deaths using ARIMA models

Using a two-SD threshold and data for persons aged <65 years, the average annual number of epidemic weeks from the 1976/1977 through 2002/2003 seasons was 1·6 (range 0–7 weeks), and the average annual number of influenza-associated deaths was 809 (95% CI 292–1326) (Table 5). Among persons aged ≥65 years, the average annual number of epidemic weeks was 9·0 and the average annual number of influenza-associated deaths were 24 856 (95% CI 19 576–30 136). Using these models, more than

Table 4. Poisson regression model annual estimates by virus type and subtype using underlying respiratory and circulatory deaths*

		A(H1) viruses			A(H3) viruses			B viruses			All influenza		
Age group	**Season**	**Annual excess number**	**L 95% CI**	**U 95% CI**	**Annual excess number**	**L 95% CI**	**U 95% CI**	**Annual excess number**	**L 95% CI**	**U 95% CI**	**Annual excess number**	**L 95% CI**	**U 95% CI**
<65 years	1976	5	2	12	1103	1040	1170	441	402	484	1549	1474	1628
	1977	290	258	325	3323	3212	3438	5	2	12	3618	3502	3738
	1978	1462	1389	1539	2	1	8	40	29	55	1504	1430	1582
	1979	25	17	37	56	43	73	825	771	883	906	849	967
	1980	382	346	422	2532	2435	2633	0	0	0	2914	2810	3022
	1981	199	173	229	0	0	0	385	348	425	584	539	633
	1982	250	221	283	2937	2833	3045	188	163	217	3375	3263	3491
	1983	924	866	986	228	200	260	670	621	723	1822	1740	1908
	1984	3	1	9	4237	4111	4367	54	41	71	4294	4167	4424
	1985	1	0	7	977	918	1040	660	612	712	1638	1561	1719
	1986	1283	1215	1355	14	8	24	6	3	13	1303	1234	1376
	1987	103	85	125	2058	1971	2149	167	143	194	2328	2235	2425
	1988	949	891	1011	435	396	478	665	616	718	2049	1962	2140
	1989	25	17	37	3268	3158	3382	6	3	13	3299	3188	3414
	1990	116	97	139	438	399	481	678	629	731	1232	1165	1303
	1991	369	333	409	3243	3133	3357	20	13	31	3632	3516	3752
	1992	65	51	83	1356	1286	1430	689	639	742	2110	2022	2202
	1993	9	5	17	3276	3166	3390	12	7	21	3297	3186	3411
	1994	28	19	41	2207	2117	2301	246	217	279	2481	2385	2581
	1995	760	708	816	1513	1439	1591	258	228	291	2531	2434	2632
	1996	0	0	0	3525	3411	3643	423	385	465	3948	3827	4073
	1997	4	2	11	4404	4276	4536	21	14	32	4429	4300	4561
	1998	16	10	26	3426	3313	3543	321	288	358	3763	3645	3885
	1999	153	131	179	4506	4376	4640	19	12	30	4678	4546	4814
	2000	985	925	1048	74	59	93	549	505	597	1608	1531	1689
	2001	45	34	60	4743	4610	4880	399	362	440	5187	5048	5330
	2002	873	817	933	858	802	917	538	494	585	2269	2178	2364
	Average 1976/1977–2002/2003	345	169	521	2027	1388	2667	307	198	416	2680	2188	3171
≥65 years	1976	8	4	16	6609	6452	6770	4272	4146	4402	10 889	10 686	11 095
	1977	570	525	619	20 759	20 479	21 043	41	30	56	21 370	21 085	21 658
	1978	2916	2812	3024	10	5	19	392	355	433	3318	3207	3433
	1978	51	39	67	377	341	417	8679	8498	8864	9107	8922	9296
	1980	824	770	882	17 151	16 896	17 410	4	2	11	17 979	17 718	18 244
	1981	435	396	478	0	0	0	4267	4141	4397	4702	4570	4838
	1982	569	524	618	21 196	20 913	21 483	2116	2028	2208	23 881	23 580	24 186
	1983	2173	2084	2266	1674	1596	1756	7859	7687	8035	11 706	11 496	11 920
	1984	6	3	13	32 775	32 422	33 132	667	618	720	33 448	33 091	33 808
	1985	4	2	11	7729	7559	7903	8406	8228	8588	16 139	15 892	16 390
	1986	3241	3131	3355	110	91	133	78	62	97	3429	3316	3546
	1987	273	242	307	17 105	16 851	17 363	2220	2130	2314	19 598	19 326	19 874
	1988	2591	2493	2693	3675	3558	3796	9006	8822	9194	15 272	15 032	15 516
	1989	66	52	84	28 821	28 490	29 156	118	99	141	29 005	28 673	29 341
	1990	324	291	361	3862	3742	3986	9702	9511	9897	13 888	13 659	14 121
	1991	1084	1021	1150	29 683	29 347	30 023	306	274	342	31 073	30 729	31 420
	1992	191	166	220	12 489	12 272	12 710	10 342	10 145	10 543	23 022	22 727	23 321
	1993	28	19	41	31 209	30 865	31 557	215	188	246	31 452	31 106	31 802
	1994	89	72	110	21 130	20 847	21 417	3781	3662	3903	25 000	24 692	25 312
	1995	2319	2227	2415	14 353	14 120	14 590	3892	3772	4016	20 564	20 285	20 847
	1996	0	0	0	34 692	34 329	35 059	6528	6372	6688	41 220	40 824	41 620
	1997	12	7	21	43 484	43 077	43 895	328	294	365	43 824	43 416	44 236
	1998	45	34	60	33 707	33 349	34 069	5132	4993	5274	38 884	38 499	39 272
	1999	462	422	506	44 039	43 630	44 452	317	284	354	44 818	44 405	45 235
	2000	2975	2870	3084	714	664	768	8324	8147	8505	12 013	11 800	12 230

Table 4. Continued

Age group	Season	A(H1) viruses Annual excess number	L 95% CI	U 95% CI	A(H3) viruses Annual excess number	L 95% CI	U 95% CI	B viruses Annual excess number	L 95% CI	U 95% CI	All influenza Annual excess number	L 95% CI	U 95% CI
≥65 years	2001	134	113	159	45 339	44 924	45 758	5917	5768	6070	51 390	50 948	51 836
	2002	2559	2462	2660	7818	7647	7993	7974	7801	8151	18 351	18 087	18 618
	Average 1976⁄1977–2002⁄2003	887	440	1334	17 797	11 833	23 760	4107	2660	5554	22 790	17 565	28 016

*The Poisson regression model is based on the methods described in Thompson *et al.* (2003).

96% of all influenza-associated deaths occurred among persons aged 65 and older (See Appendix S4 for ARIMA model estimates using a one standard deviation threshold).

Comparisons of annual estimates of influenza-associated deaths by age and model type

Annual estimates of influenza-associated deaths for each model by season are summarized in Table 6. Correlations between annual estimates by model type were all at least moderately correlated ($r > 0{\cdot}53$) and statistically significant (Table 7). The lowest correlations were seen for comparisons with the Serfling linear regression model.

Estimates from each model were compared using the Wilcoxon signed-rank tests with a Bonferroni adjustment for multiple comparisons. For models that used viral surveillance data, these comparisons were limited to the 1976–1977 through the 2002–2003 seasons when viral surveillance data were available. For persons aged <65 years, the summer-season 10% rate-difference estimates were significantly higher than all other estimates. (See Appendix S5a for annual estimates) Summer-season 15% estimates were significantly lower than the summer-season 10% estimates and higher than the linear, Poisson, and ARIMA estimates. The peri-season 10% estimates were significantly higher than the linear and ARIMA estimates. The ARIMA model estimates were significantly lower than estimates from all other models, except for the linear regression estimates.

For persons aged ≥65 years, the summer-season 10% rate-difference estimates were significantly higher than all other model estimates with the exception of the summer-season 15% model. (See Appendix S5b for annual estimates).

Discussion

Annual estimates of influenza-associated deaths have been used to describe the relative severity of inter-pandemic and pandemic influenza seasons. Numbers and rates of influenza-associated deaths also have been used in economic analyses to assess the costs and benefits of public health interventions. Specifically, estimates of influenza-associated deaths have been influential in analyses of the cost-effectiveness of possible expansions of US influenza vaccination recommendations.[34,35] Thus, estimates of influenza-associated deaths on a national level have been directly relevant to US influenza control policies.

The four excess death models used by CDC over the past four decades to make estimates of influenza-associated deaths produced a similar picture of the burden of influenza-associated mortality during our 31-year study period. While there is no gold standard currently available for assessing the performance of the different models, with the exception of estimates made by using the summer-season 10% rate-difference model, the models produced mortality estimates that were similar in absolute magnitude and similar across 31 influenza seasons.

While most models yielded similar excess death estimates, each model has several strengths and weaknesses. Rate-difference models have been used for many years because they are straightforward and can be used with less than five seasons of baseline data. Rate-difference models may be used in countries with more than a single peak in influenza activity each season. These models are easy to implement, they do not require the manual definition of epidemic thresholds, and they allow other factors (e.g., the circulation of RSV) to be incorporated into models, if viral data for other pathogens are available. However the many advantages of rate-difference models must be balanced against their weaknesses. While peri-season rate-difference models produce estimates of US influenza-associated deaths that are comparable with those produced by using other methods, the summer-season rate-difference models consistently produce estimates of mortality that appear inflated when compared with those obtained from other models. Rate-difference models usually cannot be used to estimate influenza type- and subtype-specific mortality, because circulation of influenza types and subtypes overlap, and overlapping viral data is difficult to incorporate in these simple models. Finally, seasonal factors other than influenza circulation are difficult

Table 5. Autoregressive integrated moving average (ARIMA) model annual estimates using two SD threshold using underlying respiratory and circulatory deaths*

	Age < 65 years				**Age ≥ 65 years**					**Total**			
Season	**Epi weeks**	**Annual excess numbers**	**L 95% CI**	**U 95% CI**	**Annual excess rate**	**Epi weeks**	**Annual excess numbers**	**L 95% CI**	**U 95% CI**	**Annual excess rate**	**Annual excess numbers**	**L 95% CI**	**U 95% CI**
1972	4	690	NA**	NA**	0·4	4	3698	NA**	NA**	17·3	4388	NA**	NA**
1973	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1974	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1975	2	1043	113	1974	0·5	6	17 879	7744	28 015	77·7	18 922	7857	29 989
1976	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1977	7	4702	1887	7517	2·4	8	25 246	13 064	37 426	104·6	29 948	14 951	44 943
1978	0	0	0	0	0·0	0	0	0	0	0·0	0	0	0
1979	0	0	0	0	0·0	7	18 582	8958	28 205	73·5	18 582	8958	28 205
1980	6	3715	1562	5869	1·8	11	37 319	22 498	52 139	144·2	41 034	24 060	58 008
1981	2	892	172	1611	0·4	4	6376	1184	11 566	24·1	7268	1356	13 177
1982	0	0	0	0	0·0	10	19 732	6892	32 573	72·9	19 732	6892	32 573
1983	0	0	0	0	0·0	9	16 424	5109	27 739	59·4	16 424	5109	27 739
1984	6	3109	932	5285	1·5	12	37 535	22 663	52 407	133·0	40 644	23 595	57 692
1985	0	0	0	0	0·0	12	27 305	12 768	41 841	94·8	27 305	12 768	41 841
1986	0	0	0	0	0·0	10	18 252	6350	30 155	62·2	18 252	6350	30 155
1987	0	0	0	0	0·0	14	37 528	21 097	53 960	125·4	37 528	21 097	53 960
1988	0	0	0	0	0·0	11	22 967	10 398	35 537	75·4	22 967	10 398	35 537
1989	4	1846	617	3076	0·8	11	35 694	23 200	48 187	115·1	37 540	23 817	51 263
1990	0	0	0	0	0·0	5	10 038	4431	15 645	31·9	10 038	4431	15 645
1991	0	0	0	0	0·0	9	20 883	10 877	30 889	65·2	20 883	10 877	30 889
1992	3	1191	285	2097	0·5	13	36 381	22 082	50 681	112·0	37 572	22 367	52 778
1993	4	2058	884	3232	0·9	10	39 624	28 657	50 592	120·3	41 682	29 541	53 824
1994	0	0	0	0	0·0	10	23 065	12 971	33 158	69·1	23 065	12 971	33 158
1995	2	802	231	1373	0·3	10	22 406	12 379	32 433	66·3	23 208	12 610	33 806
1996	2	645	80	1210	0·3	14	36 951	23 016	50 887	108·1	37 596	23 096	52 097
1997	0	0	0	0	0·0	12	42 928	31 084	54 772	124·3	42 928	31 084	54 772
1998	2	617	50	1185	0·3	15	49 097	34 518	63 677	140·9	49 714	34 568	64 862
1999	4	2268	1157	3378	0·9	9	39 915	31 257	48 573	113·6	42 183	32 414	51 951
2000	0	0	0	0	0·0	6	17 967	10 329	25 604	50·7	17 967	10 329	25 604
2001	0	0	0	0	0·0	8	22 256	14 569	29 944	62·5	22 256	14 569	29 944
2002	0	0	0	0	0·0	3	6646	3717	9574	18·6	6646	3717	9574
Average 1976/1977–2002/2003	1·6	809	292	1326	0·4	9·0	24 856	19 576	30 136	80·3	25 665	20 148	31 182

*The ARIMA models are based on the methods described in Choi & Thacker (1982).
**Excess death confidence intervals could not be estimated.

to control for and therefore the results could be biased by such factors temperature and humidity.

A strength of the Serfling least squares regression model is that it provides estimates of influenza-associated deaths without the need for influenza virus surveillance data, at least when these models are used in temperate areas in which the seasonality of influenza has been documented. While this may be a strength for countries that are not collecting consistent influenza virus surveillance data, the lack of such data may mean that the model's underlying assumption that essentially all excess winter mortality is associated with influenza circulation may be unreasonable. These models also are simple when compared with other regression models. Particular weaknesses of the least squares regression model are the requirement to visually examine data to define initial baseline periods and the use of arbitrary statistical thresholds (e.g., z-score cut-points) to define influenza-associated deaths.

The Serfling–Poisson regression models produce estimate of numbers and rates of deaths by influenza type and subtype, an advantage for countries like the US that have many years of robust influenza virus surveillance data.

Table 6. Summary of average annual numbers of influenza-associated deaths by model type

Season	Peri-10%	Sum-10%	Peri-15%	Sum-15%	Linear	Poisson	ARIMA 2 SD
1972	NA*	NA*	NA*	NA*	17 380	NA*	4388
1973	NA*	NA*	NA*	NA*	0	NA*	0
1974	NA*	NA*	NA*	NA*	12 976	NA*	0
1975	NA*	NA*	NA*	NA*	22 543	NA*	18 922
1976	0	16 610	0	6593	0	12 438	0
1977	37 785	56 323	22 827	35 379	35 687	24 988	29 948
1978	8565	23 353	4322	12 230	0	4822	0
1979	25 971	45 929	9171	20 077	14 494	10 013	18 582
1980	47 663	64 942	16 406	24 923	38 761	20 893	41 034
1981	0	4508	0	0	7758	5286	7268
1982	22 027	47 513	8629	22 836	8600	27 256	19 732
1983	9552	48 383	9277	38 492	4210	13 528	16 424
1984	36 389	66 081	33 271	56 388	24 503	37 742	40 644
1985	23 274	49 339	18 476	37 737	21 169	17 777	27 305
1986	19 771	37 498	19 771	37 498	11 504	4732	18 252
1987	23 767	47 605	5787	15 374	26 857	21 926	37 528
1988	26 386	56 341	21 825	46 882	3446	17 321	22 967
1989	57 268	81 590	19 172	40 358	29 510	32 304	37 540
1990	20 090	46 889	6538	19 754	21 523	15 120	10 038
1991	36 345	59 542	28 824	47 514	38 743	34 705	20 883
1992	40 293	74 836	22 882	45 398	36 187	25 132	37 572
1993	50 242	71 382	40 165	57 097	32 934	34 749	41 682
1994	35 325	62 601	16 252	34 989	10 569	27 481	23 065
1995	32 455	68 758	19 065	38 830	14 857	23 095	23 208
1996	64 791	103 858	39 328	67 586	28 383	45 168	37 596
1997	61 335	87 824	49 929	72 813	36 504	48 253	42 928
1998	58 638	89 915	47 343	77 576	43 396	42 647	49 714
1999	63 111	91 602	57 696	84 085	41 962	49 496	42 183
2000	30 311	57 805	24 657	49 282	38 498	13 621	17 967
2001	55 023	87 343	46 851	74 808	14 116	56 577	22 256
2002	25 957	54 606	17 988	40 866	0	20 620	6646
Average during the 1976/77 through the 2002/03 seasons	33 790	59 369	22 461	40 939	21 636	25 470	25 665
SD during the 1976/77 through the 2002/03 seasons	18 778	23 279	15 839	22 054	14 462	14 377	13 943

ARIMA, autoregressive integrated moving average; SD, standard deviation.
*Excess death numbers and rates could not be estimated due to lack of viral surveillance data.

Table 7. Correlations between annual estimates of influenza-associated deaths*

	Peri-10%	Sum-10%	Peri-15%	Sum-15%	Linear	Poisson	ARIMA
Peri-10%	1·00						
Sum-10%	0·95	1·00					
Peri-15%	0·86	0·84	1·00				
Sum-15%	0·83	0·88	0·97	1·00			
Linear	0·72	0·63	0·62	0·54	1·00		
Poisson	0·86	0·86	0·86	0·83	0·54	1·00	
ARIMA 2SD	0·82	0·78	0·69	0·65	0·79	0·68	1·00

ARIMA, autoregressive integrated moving average; SD, standard deviation.
*All correlations were statistically significant.

Other strengths of Poisson models include the ability to account for changes in population size over time and the ability to incorporate other variables, such as the circulation of other pathogens (e.g., RSV) or climatic variables such as temperature. Disadvantages of Poisson models as used by CDC include requirements for consistent, robust weekly viral surveillance data and for at least 5 years of mortality data before stable estimates of the effects of all three currently circulating influenza types and subtypes can be made. Nonetheless, when the necessary data are available the ability of these models to provide weekly estimates of type- and subtype-specific deaths represent a step forward in efforts to better understand the burden of influenza on mortality. Another disadvantage of this method is that it makes an assumption that a linear relationship exists between the percentage of specimens testing positive for influenza and the log of the mortality rate. This assumption is difficult to test. However, it is logical to assume that increasing intensity of influenza circulation does lead to increases in influenza-associated deaths.

The ARIMA method is a dynamic forecasting method that uses the relationship between past data to forecast future values. A strength of this method for estimating influenza-associated deaths is that virologic data and manually setting baselines are not required. Another advantage is that as more data are collected the model can be updated and re-validated (i.e., the coefficients changed) to improve model fit and accuracy. Autoregressive integrated moving average methods have several disadvantages when compared with more commonly used models. They can be complicated to implement successfully, provide relatively few advantages over the more simple linear regression models, and suffer from some of the same weaknesses as these models, including defining influenza seasons solely by the use of statistical thresholds.

Centers for Disease Control and Prevention's most recent published estimates of influenza-associated deaths for the 1990–1991 through 1998–1999 seasons made use of Poisson regression models. The annual average number of underlying respiratory and circulatory deaths associated with influenza during those nine seasons was 36 155 deaths.[4] An annual estimate for a longer period (the 1976/1977 season through the 1998/1999 season) of 25 420 deaths was also made by using the Poisson regression model.[4] The mortality estimates made in this study for 1976–1977 to 2002–2003 were similar to these previous estimates. The annual average for the 1990–1991 through 1998–1999 seasons was 32 928. The average annual estimate for the 1993–1994 through the 2002–2003 seasons, the last decade of the study period, was 36 171 deaths.

While the estimates of numbers and rates of influenza-associated deaths were similar and highly correlated across models, the estimates of the numbers of epidemic weeks were less highly correlated. The beginning and end of the epidemic periods (i.e., the tails) are typically associated with small differences between expected mortality and observed mortality. Therefore, differences in epidemic weeks lead to smaller differences than might be expected in the estimated annual number of influenza-associated deaths. Understanding why differences in estimates of epidemic weeks are found using various models is an area for future research.

In summary, each of the four models we used to estimate annual influenza-associated mortality produced similar estimates, with the exception of summer baseline rate-difference and the ARIMA models. Several factors must be considered when seeking to make the most efficient and reliable estimates of influenza-associated deaths. Depending on the availability of consistent and robust surveillance data, the length of the period for which mortality estimates are being made, and the general seasonality of influenza circulation in area of the world being studied, different models might be selected for primary use. We suggest that as countries or areas that have not previously made estimates of influenza-associated mortality begin this process, that it is reasonable to compare estimates made by using several different methods to see how similar the results are, and how they vary over time. Poisson models seem well-suited for use in countries with robust viral surveillance data. In countries where viral surveillance data are limited and where the seasonality of influenza is more complex, rate-difference models represent a reasonable starting point for making estimates of influenza-associated mortality. An important area for additional research is how to apply statistical models to estimate influenza-associated mortality in those subtropical and tropical countries that include the majority of the world's population.

Acknowledgement

We wish to thank Ericka Sinclair, Erin Murray, and Alicia Budd for assistance in organizing the WHO influenza isolate data.

Financial Support

The work presented in this manuscript was funded solely by the US Centers for Disease Control and Prevention. The findings and conclusions in this study are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflict of interest

We declare that we have no conflict of interest.

References

1 Serfling RE. Methods for current statistical analysis of excess pneumonia-influenza deaths. Public Health Rep 1963; 78:494–505.
2 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; 77:712–716.
3 Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. J Infect Dis 2000; 181:831–837.
4 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289:179–186.
5 Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg Infect Dis 1999; 5:659–671.
6 Nichol KL. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. Vaccine 2003; 21:1769–1775.
7 Bridges CB, Harper SA, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2003; 52(RR-8):1–34.
8 Thompson WW, Shay DK, Weintraub E *et al.* Influenza-associated hospitalizations in the United States. JAMA 2004; 292:1333–1340.
9 Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. J Infect Dis 1998; 178:53–60.
10 Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. Ann Intern Med 1999; 130:397–403.
11 Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998; 158:1769–1776.
12 Noble GR. Epidemiogical and clinical aspects of influenza; in Bears AS (ed): Basic and Applied Influenza Research. Boca Raton, FL: CRC Press, 1982, 11–50.
13 Choi K, Thacker SB. Mortality during influenza epidemics in the United States, 1967–1978. Am J Public Health 1982; 72:1280–1283.
14 Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 1980; 112:798–811.
15 Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implications for prevention. Arch Intern Med 1982; 142:85–89.
16 Izurieta HS, Thompson WW, Kramarz P *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000; 342:232–239.
17 O'Brien MA, Uyeki TM, Shay DK, *et al.* Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. Pediatrics 2004; 113(3 Pt 1):585–593.
18 Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health 1997; 87:1944–1950.
19 Neuzil KM, Maynard C, Griffin MR, Heagerty P. Winter respiratory viruses and health care use: a population-based study in the northwest United States. Clin Infect Dis 2003; 37:201–207.
20 Choi K, Thacker SB. An evaluation of influenza mortality surveillance, 1962–1979 I. Time series forecasts of expected pneumonia and influenza deaths. Am J Epidemiol 1981; 113:215–226.
21 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; 7:1045–1059.
22 Brammer TL, Izurieta HS, Fukuda K *et al.* Surveillance for influenza–United States, 1994–95, 1995–96, and 1996–97 seasons. Morb Mortal Wkly Rep CDC Surveill Summ 2000; 49:13–28.
23 Vital Statistics Mortality Data, Multiple Cause Detail, 1972–2004. Public Use Data Tapes Contents and Documentation Package. Hyattsville, MD: National Center for Health Statistics, 2004.
24 World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, based on recommendations of the Ninth Revision Conference, 1975. Geneva: World Health Organization, 1977.
25 Mullooly JP, Bridges CB, Thompson WW *et al.* Influenza- and RSV-associated hospitalizations among adults. Vaccine 2007; 25:846–855.
26 Simonsen L, Clarke MJ, Stroup DF, Williamson GD, Arden NH, Cox NJ. A method for timely assessment of influenza-associated mortality in the United States. Epidemiology 1997; 8:390–395.
27 Thompson WW, Weintraub E, Shay DK, Brammer L, Cox NJ, Fukuda K. Influenza-attributable hospitalizations in the United States; in Osterhaus A, Cox NJ (eds): Options for the Control of Influenza V. Hampson: Elsevier Science, 2003.
28 Thompson WW, Shay DK, Weintraub E, Brammer L, Cox NJ, Fukuda K. Influenza-attributable deaths among the elderly in the United States; in Osterhaus A, Cox NJ (eds): Options for the Control of Influenza V. Hampson: Elsevier Science, 2003.
29 US Bureau of the Census. Intercensal Estimates of the Population by Age, Sex, and Race: 1970-2000. Washington DC: US Bureau of the Census, 2005.
30 Thompson WW, Shay DK, Weintraub E *et al.* In Reply to Letters. JAMA 2003; 289:2500–2502.
31 Choi K, Thacker SB. From the centers for disease control. Improved accuracy and specificity of forecasting deaths attributed to pneumonia and influenza. J Infect Dis 1981; 144:606–608.
32 Choi K, Thacker SB. An evaluation of influenza mortality surveillance, 1962–1979. II. Percentage of pneumonia and influenza deaths as an indicator of influenza activity. Am J Epidemiol 1981; 113:227–235.
33 Box G, Jenkins GM. Time-Series Analysis; Forecasting and Control. San Francisco: Holden-Day, 1970.
34 Meltzer MI, Neuzil KM, Griffin MR, Fukuda K. An economic analysis of annual influenza vaccination of children. Vaccine 2005; 23:1004–1014.
35 Prosser LA, Bridges CB, Uyeki TM *et al.* Health benefits, risks, and cost-effectiveness of influenza vaccination of children. Emerg Infect Dis 2006; 12:1548–1558.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Excess mortality rates per 100 000 person weeks by year, age, and baseline for 15% threshold*.

Appendix S2. Excess mortality rates per 100 000 person weeks by year, age, and baseline for 10% threshold*.

Appendix S3. Rate-difference model estimates for underlying respiratory and circulatory deaths using a 10% threshold*.

Appendix S4. ARIMA model annual estimates using a one standard deviation threshold using underlying respiratory and circulatory deaths.

Appendix S5a. Summary of average annual numbers of influenza-associated deaths for <65 by model type.

Appendix S5b. Summary of average annual numbers of influenza-associated deaths for ≥65 by model type.

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