Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States

William W. Thompson, PhD
David K. Shay, MD, MPH
Eric Weintraub, MPH
Lynnette Brammer, MPH
Nancy Cox, PhD
Larry J. Anderson, MD
Keiji Fukuda, MD, MPH

Context Influenza and respiratory syncytial virus (RSV) cause substantial morbidity and mortality. Statistical methods used to estimate deaths in the United States attributable to influenza have not accounted for RSV circulation.

Objective To develop a statistical model using national mortality and viral surveillance data to estimate annual influenza- and RSV-associated deaths in the United States, by age group, virus, and influenza type and subtype.

Design, Setting, and Population Age-specific Poisson regression models using national viral surveillance data for the 1976-1977 through 1998-1999 seasons were used to estimate influenza-associated deaths. Influenza- and RSV-associated deaths were simultaneously estimated for the 1990-1991 through 1998-1999 seasons.

Main Outcome Measures Attributable deaths for 3 categories: underlying pneumonia and influenza, underlying respiratory and circulatory, and all causes.

Results Annual estimates of influenza-associated deaths increased significantly between the 1976-1977 and 1998-1999 seasons for all 3 death categories ($P<.001$ for each category). For the 1990-1991 through 1998-1999 seasons, the greatest mean numbers of deaths were associated with influenza A(H3N2) viruses, followed by RSV, influenza B, and influenza A(H1N1). Influenza viruses and RSV, respectively, were associated with annual means (SD) of 8097 (3084) and 2707 (196) underlying pneumonia and influenza deaths, 36155 (11055) and 11321 (668) underlying respiratory and circulatory deaths, and 51203 (15081) and 17358 (1086) all-cause deaths. For underlying respiratory and circulatory deaths, 90% of influenza- and 78% of RSV-associated deaths occurred among persons aged 65 years or older. Influenza was associated with more deaths than RSV in all age groups except for children younger than 1 year. On average, influenza was associated with 3 times as many deaths as RSV.

Conclusions Mortality associated with both influenza and RSV circulation disproportionately affects elderly persons. Influenza deaths have increased substantially in the last 2 decades, in part because of aging of the population, underscoring the need for better prevention measures, including more effective vaccines and vaccination programs for elderly persons.

JAMA. 2003;289:179-186 www.jama.com

INFLUENZA INFECTIONS RESULT IN substantial morbidity and mortality nearly every year[1,2] and estimates of this burden have played a pivotal role in formulating influenza vaccination policy in the United States.[3] However, numbers of deaths attributable to influenza are difficult to estimate directly because influenza infections typically are not confirmed virologically or specified on hospital discharge forms or death certificates. In addition, many influenza-associated deaths occur from secondary complications when influenza viruses are no longer detectable.[4,5] Nonetheless, wintertime influenza epidemics have been shown to be associated with increased hospitalizations and mortality for many diagnoses, including congestive heart failure, chronic obstructive pulmonary disease, pneumonia, and bacterial superinfections.[6-9]

Respiratory syncytial virus (RSV) epidemics often overlap with influenza epidemics,[8,10] and RSV infections have been associated with substantial morbidity and mortality in young children and more recently in older adults.[10-14] Like influenza, RSV infections can precipitate both cardiac and pulmonary complications.[15-17] Respiratory syncytial virus infections are rarely diagnosed in

For editorial comment see p 227.

Author Affiliations: Influenza Branch (Drs Thompson, Cox, and Fukuda, and Mr Weintraub and Ms Brammer) and Respiratory and Enteric Viruses Branch (Drs Shay and Anderson), Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga. Drs Thompson and Shay, and Mr Weintraub are now with the Immunization Safety Branch, Epidemiology and Surveillance Division, National Immunization Program.
Corresponding Author and Reprints: William W. Thompson, PhD, Immunization Safety Branch, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS E61, Atlanta, GA 30333 (e-mail: wct2@cdc.gov).

adults, in part because available rapid antigen-detection tests are insensitive in adults and few tests for RSV are requested for this age group by medical practitioners.[16,18] It is likely that some deaths previously attributed to influenza are actually associated with RSV infection.[13,14,19]

In this study, we provide age-specific estimates of deaths attributable to influenza, by virus type and subtype, and to RSV using Poisson regression models that incorporates national respiratory viral surveillance data. Recent deliberations of the Advisory Committee on Immunization Practices (ACIP) regarding influenza vaccination recommendations[3] guided our choice of age groups for these analyses.

METHODS

Definition of Respiratory Season

Influenza and RSV typically circulate during winter months and across calendar years. Therefore, we defined each annual respiratory season as the period from July 1 through June 30 of the following year.

National Viral Surveillance Data

In the United States, laboratory-based surveillance for influenza viruses is conducted from October through mid-May (calendar week 40 through week 20). For the influenza virus surveillance periods from the 1976-1977 through 1998-1999 seasons, we obtained numbers of influenza virus isolates reported weekly by 50 to 75 World Health Organization collaborating virology laboratories in the United States to the Influenza Branch of the Centers for Disease Control and Prevention (CDC). The collaborating laboratories provided weekly numbers of total respiratory specimens tested for influenza and positive-influenza isolates by virus type and subtype[20] (TABLE 1).

Weekly RSV data were obtained from the National Respiratory and Enteric Virus Surveillance System for the 1990-1991 through 1998-1999 seasons. During this period, 63 to 72 clinical and public health laboratories in 44 states reported to CDC weekly numbers of specimens tested for RSV by antigen-detection and viral-isolation methods and numbers of positive results.[21] We used the results of both antigen-detection and isolation tests to determine the circulation pattern of RSV. The weekly percentages of specimens that tested positive for both influenza and RSV were used in estimating the association of virus circulation with weekly deaths in the United States (Table 1).

Mortality Data and Outcomes

National mortality data were obtained from the National Center for Health Statistics (NCHS).[22] Deaths were categorized using the *International Classification of Diseases, Ninth Revision (ICD-9)* codes for NCHS mortality data obtained from 1976 through 1998.[23]

Table 1. Annual Respiratory Virus Surveillance Data for the 1976-1977 Through 1998-1999 Seasons

	No. of Influenza Specimens					No. of RSV Specimens	
Season	Specimens Tested	A(H1N1) Positive Isolates	A(H3N2) Positive Isolates	B Positive Isolates	Total Positive Isolates	Specimens Tested	Total Positive Tests
1976-1977	17 600	3	212	633	848	NA	NA
1977-1978	18 727	311	1617	5	1933	NA	NA
1978-1979	13 275	1140	1	21	1162	NA	NA
1979-1980	15 195	20	17	1298	1335	NA	NA
1980-1981	16 128	315	1125	1	1441	NA	NA
1981-1982	14 804	143	0	461	604	NA	NA
1982-1983	16 929	165	1263	160	1588	NA	NA
1983-1984	16 111	1059	79	937	2075	NA	NA
1984-1985	15 355	2	1977	53	2032	NA	NA
1985-1986	20 234	2	554	1789	2345	NA	NA
1986-1987	22 056	2206	5	11	2222	NA	NA
1987-1988	26 258	167	1776	354	2297	NA	NA
1988-1989	29 357	2234	359	2530	5123	NA	NA
1989-1990	29 956	46	3342	13	3401	NA	NA
1990-1991	32 420	179	271	2732	3182	67 374	11 449
1991-1992	38 557	1055	4854	47	5956	100 867	18 586
1992-1993	36 233	132	1126	3081	4339	98 203	14 335
1993-1994	35 597	22	4193	35	4250	104 028	18 047
1994-1995	38 705	62	2819	1005	3886	107 528	17 445
1995-1996	37 612	2357	1650	716	4723	111 318	19 745
1996-1997	39 183	0	5047	1449	6496	117 814	17 370
1997-1998	46 413	14	7838	53	7905	133 648	19 589
1998-1999	52 505	50	6732	2286	9068	128 621	18 418
Mean (SD)	27 360 (11 551)	508 (779)	2037 (2277)	855 (998)	3400 (2290)	107 711 (19 374)	17 220 (2685)

Abbreviations: NA, not applicable (reporting period began in 1990-1991); RSV, respiratory syncytial virus.

The *International Classification of Diseases, 10th Revision (ICD-10)* was used for classifying NCHS mortality data obtained for 1999.[24] Analyses were based on the underlying cause-of-death because it represents the disease or injury that initiated the chain of morbid events that led directly to the death.[25] The change from *ICD-9* to *ICD-10* in January 1999 resulted in a 30% decrease in the number of coded underlying pneumonia deaths.[26] Therefore, all analyses of underlying pneumonia and influenza deaths were carried out using data collected through the 1997-1998 season, which limited the analyses to *ICD-9* coded deaths.

The 3 death categories modeled were underlying pneumonia and influenza deaths (*ICD-9* codes 480-487), underlying respiratory and circulatory deaths (*ICD-9* codes 390-519 and *ICD-10* codes I00-I99, J00-J99), and all-cause deaths (all *ICD* codes). Underlying pneumonia and influenza deaths exclude some deaths, such as those related to exacerbations of underlying cardiac and pulmonary conditions, which are associated with both influenza and RSV infections.[6,18] Influenza-associated all-cause death estimates have been previously used to represent the full spectrum of deaths associated with influenza infections.[1,2] However, these estimates include deaths such as those caused by fires and motor vehicle crashes, which are not directly associated with respiratory viral infections. Therefore, we also modeled a third category of deaths, underlying respiratory and circulatory deaths (which includes pneumonia and influenza deaths), to provide an estimate of deaths that was more directly associated with viral respiratory infections. These estimates would be expected to be more sensitive than estimates using underlying pneumonia and influenza deaths and more specific than estimates using all-cause deaths.

Statistical Analyses

For the influenza model, we developed an age-specific Poisson regression model that used weekly influenza circulation data. Deaths were stratified into the following 5 age groups: younger than 1 year, 1 to 4 years, 5 to 49 years, 50 to 64 years, and 65 years or older. Influenza-associated deaths were estimated for influenza A(H1N1), A(H3N2), and B viruses. The viral circulation terms represented percentages of specimens testing positive for each of the 3 influenza virus types and subtypes during a particular week. Estimates of the weekly age-specific population size were used to account for changes in population trends over time. The US population estimates by age group were obtained from the US Census Bureau.[27]

For the influenza and RSV model, we used a model identical to the influenza model except it included an additional coefficient for RSV viral circulation. The full model was written as follows:

$$Y = \alpha \exp\{\beta_0 + \beta_1[t] + \beta_2[t^2] + \beta_3[\sin(2\pi/52)] + \beta_4[\cos(2\pi/52)] + \beta_5[A(H1N1)] + \beta_6[A(H3N2)] + \beta_7[B] + \beta_8[RSV]\}$$

where Y represents the number of deaths during a particular week for a specific age group, α is the offset term and is equal to the log of the age-specific population size, β_0 represents the intercept, β_1 accounts for the linear time trend, β_2 accounts for nonlinear time trends, β_3 and β_4 account for seasonal changes in deaths, and β_5 through β_8 represent coefficients associated with the percentage of specimens testing positive for a given week.

We fit the influenza model to national influenza surveillance data available from the 1976-1977 through 1998-1999 seasons. The influenza and RSV model was fit to data available from the 1990-1991 through 1998-1999 seasons, when both weekly influenza and RSV data were available (PROC GENMOD, SAS, version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

Annual Influenza and RSV Laboratory Surveillance

National influenza and RSV surveillance data are summarized in Table 1. Influenza isolate data were available for the 1976-1977 through 1998-1999 seasons. A mean of 27 360 specimens (range, 13 275-52 505) was tested for influenza viruses during each of the influenza surveillance periods (October through May). During weeks that testing for influenza occurred, an average of 12% of specimens tested positive for influenza. Influenza A(H1N1), A(H3N2), and B viruses, respectively, comprised 15%, 60%, and 25% of the positive influenza isolates. From the 1990-1991 through 1997-1998 season, the annual mean number of specimens tested for RSV was 107 711 (range, 67 374-133 648) with an average of 17 220 specimens (16%) testing positive each season for RSV.

Annual US Deaths by Underlying Diagnosis

From the 1976-1977 through 1998-1999 seasons, there was an annual mean of 69 140 (range, 47 133-90 895) underlying pneumonia and influenza deaths, 1 135 724 (range, 1 069 560-1 203 728) underlying respiratory and circulatory deaths, and 2 126 740 (range, 1 879 039-2 407 494) all-cause deaths. The numbers of deaths in each of these categories increased linearly during this period. From the 1976-1977 through 1997-1998 seasons, underlying pneumonia and influenza deaths increased by 83%, substantially more than underlying respiratory and circulatory deaths or all-cause deaths (11% and 28%, respectively). From the 1990-1991 through 1998-1999 seasons, there was an annual mean of 82 239 (range, 74 872-90 895) underlying pneumonia and influenza deaths, 1 158 964 (range, 1 098 086-1 203 728) underlying respiratory and circulatory deaths, and 2 277 268 (range, 2 135 976-2 407 494) all-cause deaths.

Annual Influenza-Associated Deaths From the 1976-1977 Through 1998-1999 Seasons Using the Influenza Model

The mean annual estimates of underlying pneumonia and influenza deaths, underlying respiratory and circulatory deaths, and all-cause deaths associated with influenza were 5977, 25 420, and 34 470 (TABLE 2). Each of these 3 estimates increased significantly during the study period ($P<.001$ for trend for all 3 death categories).

Annual Influenza- and RSV-Associated Deaths From the 1990-1991 Through 1998-1999 Seasons Using the Influenza and RSV Model

For underlying pneumonia and influenza deaths, we estimated an annual mean of 8097 (SD, 3084; range, 3515-13 033) influenza-associated deaths, representing 9.8% (8097/82 239) of these deaths (TABLE 3). Influenza A(H1N1), A(H3N2), and B viruses were associated with annual means of 381 (SD, 617; range, 0-1742), 6613 (SD, 3928; range, 944-12 941), and 1103 (SD, 1030; range, 53-2619) deaths, respectively. Respiratory syncytial virus was associated with an annual mean of 2707 (SD, 196; range 2336-2880) deaths or 3.3% (2707/82 239) of all such deaths. The year-to-year variation in influenza-associated deaths was higher than the year-to-year variation in RSV-associated deaths.

For underlying respiratory and circulatory deaths, we estimated an annual mean of 36 155 (SD, 11 055; range, 17 056-51 296) influenza-associated deaths, representing 3.1% (36 155/1 158 964) of these deaths. Influenza A(H1N1), A(H3N2), and B viruses were associated with annual means of 1960 (SD, 3372; range, 0-10 080), 28 940 (SD, 14 848; range, 4435-50 855), and 5255 (SD, 4513; range, 253-12 067) deaths, respectively. Respiratory syncytial virus was associated with an annual mean of 11 321 (SD, 668; range, 10 047-12 385) deaths or 1.0% (11 321/1 158 964) of all such deaths.

For all-cause deaths, we estimated an annual mean of 51 203 (SD, 15 081; range, 25 570-71 416) influenza-associated deaths, representing 2.2% (51 203/2 277 268) of these deaths. Influenza A(H1N1), A(H3N2), and B viruses were associated with annual means of 2836 (SD, 4909; range, 0-14 727), 40 017 (SD, 20 656; range, 6033-70 701), and 8349 (SD, 7105; range, 404-19 030) deaths, respectively. Respiratory syncytial virus was associated with an annual mean of 17 358 (SD, 1086; range, 15 464-19 262) deaths or 0.8% (17 358/2 277 268) of all such deaths. Influenza-associated deaths again showed higher year-to-year variability than did RSV-associated deaths.

Table 2. Estimated Annual Influenza-Associated Deaths for the 1976-1977 Through 1998-1999 Seasons Using the Influenza Model

		No. of Deaths		
Season	Predominant Influenza Type and Subtype	Underlying Pneumonia and Influenza	Underlying Respiratory and Circulatory	All-Cause
1976-1977	B/A(H3N2)	2265	13 294	16 263
1977-1978	A(H3N2)/A(H1N1)	4449	26 829	32 172
1978-1979	A(H1N1)	1008	4692	7608
1979-1980	B	2359	10 605	13 832
1980-1981	A(H3N2)/A(H1N1)	4068	22 338	27 729
1981-1982	B-A(H1N1)	1260	5524	7612
1982-1983	A(H3N2)	5743	29 106	36 701
1983-1984	A(H1N1)/B	3437	14 051	19 923
1984-1985	A(H3N2)	8644	40 457	50 789
1985-1986	B/A(H3N2)	4649	18 923	24 994
1986-1987	A(H1N1)	1257	4650	8144
1987-1988	A(H3N2)	5307	23 376	30 755
1988-1989	B/A(H1N1)	5149	18 115	26 408
1989-1990	A(H3N2)	8254	34 602	45 493
1990-1991	B	4448	16 036	22 732
1991-1992	A(H3N2)/A(H1N1)	9449	37 159	50 563
1992-1993	B/A(H3N2)	7366	26 816	37 729
1993-1994	A(H3N2)	9717	37 367	50 729
1994-1995	A(H3N2)/B	7791	29 476	40 950
1995-1996	A(H1N1)/A(H3N2)	6560	24 562	36 280
1996-1997	A(H3N2)/B	13 674	48 726	68 328
1997-1998	A(H3N2)	14 628	52 148	72 399
1998-1999*	A(H3N2)/B	NA	45 817	64 684
Mean (SD)		5977 (3727)	25 420 (13 898)	34 470 (18 988)

Abbreviation: NA, not applicable.
*Pneumonia and influenza estimates are based on the 1976-1977 through 1997-1998 seasons.

Age-Specific Annual Influenza- and RSV-Associated Deaths From the 1990-1991 Through 1998-1999 Seasons Using the Influenza and RSV Model

In children younger than 1 year, RSV was associated with annual means of 124 underlying pneumonia and influenza deaths, 211 underlying respiratory and circulatory deaths, and 214 all-cause deaths (TABLE 4). In this age group, influenza viruses were associated with annual means of 13 underlying pneumonia and influenza deaths, 26 underlying respiratory and circulatory deaths, and 88 all-cause deaths. There were more influenza-associated deaths relative to RSV-associated deaths among children aged 1 to 4 years for all 3 death categories.

Among underlying pneumonia and influenza deaths, 90% (7326/8097) of influenza-associated deaths and 88% (2388/2707) of RSV-associated deaths occurred among persons aged 65 years or older. For underlying respiratory and circulatory deaths, 90% (32 651/36 155) of influenza-associated deaths and 78% (8811/11 321) of RSV-associated deaths occurred among persons aged 65 years or older. For all-cause deaths, 43 979 and 9812 all-cause deaths were attributable to influenza and RSV, respectively.

Age-Specific Mortality Rates

Annual mean influenza-associated mortality rates for underlying pneumonia and influenza deaths, underlying respiratory and circulatory deaths, and all-cause deaths were 3.1, 13.8, and 19.6 per 100 000 person-years, respectively (TABLE 5). Similarly, annual mean RSV-associated mortality rates for these death categories were 1.0, 4.3, and 6.6 per 100 000 person-years, respectively. The relative risks (RRs) and 95% confidence intervals (CIs) comparing influenza mortality rates with RSV mortality rates for the 3 death categories were 3.0 (95% CI, 2.9-3.1), 3.2 (95% CI, 3.1-3.3), and 2.9 (95% CI, 2.9-3.0), respectively.

Annual mean influenza-associated mortality rates for underlying pneumonia and influenza deaths in persons younger than 1 year, 1 to 4 years, 5 to 49 years, 50 to 64 years, and 65 years or older were 0.3, 0.2, 0.2, 1.3, and 22.1 deaths per 100 000 person-years, respectively. The RSV-associated mortality rates for underlying pneumonia and influenza deaths in persons younger than 1 year, 1 to 4 years, 5 to 49 years, 50 to 64 years, and 65 years or older were 3.1, 0.1, <0.1, 0.5, and 7.2 deaths per 100 000 person-years, respectively. For children younger than 1 year, the RR for RSV vs influenza mortality rates was 9.5 (95% CI, 5.4-16.9) for underlying pneumonia and influenza deaths and 8.1 (95% CI, 5.4-12.2) for underlying respiratory and circulatory deaths. For all-cause deaths, the RR among this age group was substantially lower (RR, 2.4; 95% CI, 1.9-3.1).

Age-Specific Mortality Rates Among Persons 65 Years or Older

Periseason influenza rate-difference models[10] were fit to the 1976-1977 through the 1998-1999 seasons and revealed substantial differences in relative influenza-attributable mortality rates among elderly persons. Persons aged 85 years or older were 32 times more likely to die of an influenza-associated underlying pneumonia and influenza death compared with persons aged 65 to 69 years (RR, 32.1; 95% CI, 31.3-32.9). Persons aged 85 years or older were 16 times more likely to die of an influenza-associated all-cause death compared with persons aged 65 to 69 years (RR, 14.8; 95% CI, 14.6-14.9). However, there were no statistically significant increases in any of the 5-year age-specific mortality rates from the 1976-1977 through the 1998-1999 seasons (*P*>.05 for all).

The number of persons aged 65 years or older increased substantially between the 1976-1977 and 1998-1999 seasons.[27] During the 1990s, the growth rate for the number of persons aged 50 to 64 years also increased substantially relative to the period from 1976 through 1990.[27]

COMMENT

Morbidity and mortality associated with seasonal epidemics of influenza in the United States have provided the impetus for public health policies and strategies to control influenza infections, particularly among specific target groups.[3] Mortality associated with in-

Table 3. Estimated Annual Influenza- and Respiratory Syncytial Virus–Associated Deaths for the 1990-1991 Through 1998-1999 Seasons Using the Influenza and RSV Model

Season	No. of Influenza Deaths				No. of Total RSV Deaths
	A(H1N1)	A(H3N2)	B	Total	
Underlying Pneumonia and Influenza Deaths					
1990-1991	226	944	2345	3515	2472
1991-1992	845	7904	73	8822	2858
1992-1993	142	3227	2619	5988	2336
1993-1994	20	8530	53	8603	2820
1994-1995	65	5710	995	6770	2781
1995-1996	1742	3816	964	6522	2880
1996-1997	0	9831	1691	11 522	2729
1997-1998	10	12 941	82	13 033	2778
1998-1999*	NA	NA	NA	NA	NA
Mean (SD)	381 (617)	6613 (3928)	1103 (1030)	8097 (3084)	2707 (196)
Underlying Respiratory and Circulatory Deaths					
1990-1991	1386	4435	11 235	17 056	11 156
1991-1992	4594	33 927	357	38 878	11 795
1992-1993	822	14 465	12 067	27 354	10 047
1993-1994	118	35 763	253	36 134	11 479
1994-1995	389	24 475	4473	29 337	11 797
1995-1996	10 080	16 895	4639	31 614	12 385
1996-1997	0	40 131	7803	47 934	11 105
1997-1998	47	50 855	394	51 296	10 806
1998-1999	203	39 514	6076	45 793	11 322
Mean (SD)	1960 (3372)	28 940 (14 848)	5255 (4513)	36 155 (11 055)	11 321 (668)
All-Cause Deaths					
1990-1991	1988	6033	17 549	25 570	16 947
1991-1992	6518	45 928	566	53 012	17 825
1992-1993	1190	19 892	19 030	40 112	15 464
1993-1994	173	48 923	404	49 500	17 581
1994-1995	572	33 767	7129	41 468	18 312
1995-1996	14 727	23 605	7509	45 841	19 262
1996-1997	0	55 937	12 609	68 546	17 100
1997-1998	66	70 701	649	71 416	16 461
1998-1999	293	55 367	9698	65 358	17 273
Mean (SD)	2836 (4909)	40 017 (20 656)	8349 (7105)	51 203 (15 081)	17 358 (1086)

Abbreviations: NA, not applicable; RSV, respiratory syncytial virus.
*Pneumonia and influenza estimates are based on the 1990-1991 through 1997-1998 seasons.

Table 4. Estimated Annual Age-Specific Influenza- and Respiratory Syncytial Virus–Associated Deaths for the 1990-1991 Through 1998-1999 Seasons

Age Group, y	No. of Influenza Deaths: A(H1N1)	A(H3N2)	B	Total	No. of Total RSV Deaths
Underlying Pneumonia and Influenza Deaths*					
<1	1	12	0	13	124
1-4	7	11	7	25	13
5-49	39	178	55	272	0
50-64	37	322	102	461	182
≥65	298	6089	939	7326	2388
Total	**382**	**6612**	**1103**	**8097**	**2707**
Underlying Respiratory and Circulatory Deaths					
<1	4	15	7	26	211
1-4	7	42	17	66	24
5-49	168	484	137	789	641
50-64	196	2121	306	2623	1634
≥65	1585	26 278	4788	32 651	8811
Total	**1960**	**28 940**	**5255**	**36 155**	**11 321**
All-Cause Deaths					
<1	0	3	85	88	214
1-4	34	103	38	175	132
5-49	501	1685	383	2569	4464
50-64	348	3360	684	4392	2736
≥65	1954	34 866	7159	43 979	9812
Total	**2837**	**40 017**	**8349**	**51 203**	**17 358**

Abbreviation: RSV, respiratory syncytial virus.
*Pneumonia and influenza estimates are based on the 1990-1991 through 1997-1998 seasons.

Table 5. Estimated Annual Influenza- and Respiratory Syncytial Virus–Associated Mortality Rates per 100 000 Person-Years for the 1990-1991 Through 1998-1999 Seasons

Age Group, y	Mortality Rate per 100 000 Person-Years: Influenza	RSV
Underlying Pneumonia and Influenza Deaths*		
<1	0.3	3.1
1-4	0.2	0.1
5-49	0.2	<.01
50-64	1.3	0.5
≥65	22.1	7.2
Total	3.1	1.0
Underlying Respiratory and Circulatory Deaths		
<1	0.6	5.3
1-4	0.4	0.2
5-49	0.5	0.4
50-64	7.5	4.7
≥65	98.3	26.5
Total	13.8	4.3
All-Cause Deaths		
<1	2.2	5.4
1-4	1.1	0.9
5-49	1.5	2.6
50-64	12.5	7.8
≥65	132.5	29.6
Total	19.6	6.6

Abbreviation: RSV, respiratory syncytial virus.
*Pneumonia and influenza estimates are based on the 1990-1991 through 1997-1998 seasons.

fluenza can vary dramatically by season and models developed to assess influenza-associated mortality date back to 1847.[28] These approaches have been feasible because well-defined peaks in deaths occur in association with influenza outbreaks in temperate countries. In the recent past, the CDC has used a linear regression model, applied to either complete national mortality data or more immediately available mortality surveillance data from 122 cities, to estimate annual deaths associated with influenza.[1,2] The influenza and RSV model presented in this study will be used to provide future estimates of influenza-associated mortality in the United States, because the model permits estimates of influenza subtype-specific mortality and also simultaneously estimates RSV-associated mortality.

Our results indicate that US influenza-associated deaths have increased substantially from the 1976-1977 through 1998-1999 seasons. We believe this is explained in part by the aging of the US population. Between 1976 and 1999, the number of persons aged 85 years or older doubled in the United States.[29] We found that persons in this age group were 16 times more likely to die of an influenza-associated all-cause death than persons aged 65 to 69 years during a period in which all-cause age-specific death rates have remained stable. Other studies have also shown that influenza-attributable mortality rates increased rapidly with age among persons aged 65 years or older.[30-32] For example, Nordin et al[32] found that persons aged 75 years or older were 3 to 9 times more likely to die from influenza infections than persons aged 65 to 74 years. Another important factor contributing to the increase in influenza-associated deaths during the 1990s was the predominance of influenza A(H3N2) viruses, the most virulent of the recently circulating influenza viruses. Influenza A(H3N2) viruses were 1 of the predominant strains in 8 of 9 seasons we analyzed during the 1990s.

The influenza and RSV model confirmed that influenza A(H3N2) viruses were associated with the highest attributable mortality rates, followed by RSV, influenza B, and influenza A(H1N1) viruses. The annual effect of RSV on mortality was relatively stable, although the numbers of deaths associated with influenza viruses varied substantially, depending on the predominant circulating virus type or subtype. In this study, RSV was the most common viral cause of death in children younger than 5 years, particularly in children younger than 1 year. However, RSV-associated mortality rates were higher in elderly persons and substantially more RSV-associated deaths occurred among elderly persons than among young children.

Determining the most appropriate death category for characterizing the burden of influenza on mortality is difficult. Pneumonia and influenza deaths are highly correlated with the circulation of influenza, and these estimates are useful for monitoring year-to-year trends and variability in the severity of influenza seasons. However, this death category underestimates the total burden of influenza because many deaths are caused by other secondary complications of influenza (eg, congestive heart failure).[7] Traditionally, all-cause deaths have been used to estimate the total burden of influenza on mortality.[1,2] However, this death category is also not ideal because it includes deaths that are not causally linked with respiratory viral infections. Therefore, we analyzed underlying respiratory and circulatory deaths to provide a more specific estimate of the total burden of influenza and RSV on mortality. Our estimate of annual mean influenza-associated underlying respiratory and circulatory deaths was 36 155 (29% lower than the annual mean all-cause estimate).

The Poisson regression models used to estimate influenza- and RSV-associated deaths were more complex compared with previous influenza models, but the models also provided more specific estimates, including independent estimates of deaths associated with influenza and RSV. The model we used in this study is capable of incorporating additional factors that could not be included in the previous CDC model, such as temperature, that might independently influence winter season mortality. Therefore, we believe this new model represents a step forward in current efforts to better understand the burden of viral respiratory infections on mortality.

We applied the new model to age groups relevant to policy deliberations by ACIP regarding influenza-vaccination recommendations for persons younger than 5 years and persons 50 to 64 years.[3] Currently, ACIP recommends annual influenza vaccination for all persons aged 65 years or older. Because most influenza-associated deaths occur in persons aged 65 years or older, understanding age-specific effects within this age group is also of considerable interest. As a first step, we fit simple periseason rate difference models among those aged 65 years or older by 5-year age intervals and demonstrated increases with age in influenza-associated mortality. Future research will focus attention on ACIP discussions regarding age-specific vaccination policy.

We believe the results of this study have important policy implications. Deaths associated with viral respiratory infections have increased substantially during the past decade and it appears that they will continue to increase as the population continues to age. Increased numbers of patients with serious respiratory infections may further stress hospital systems that are already struggling to cope with wintertime surges in patient visits during influenza seasons. For example, during the 1997-1998 season, a severe influenza outbreak in Los Angeles County resulted in a dramatic increase in hospitalizations and the need to divert patients to other facilities. This problem may have been less severe if more bed capacity had been available.[33]

Vaccinating elderly persons will continue to be the primary strategy for preventing influenza-associated deaths. Studies directly comparing outcomes in vaccinated vs unvaccinated groups have shown that the currently available trivalent inactivated influenza vaccine is approximately 68% effective in preventing deaths from complications of influenza infections.[34-36] However, the effectiveness of influenza vaccines in preventing deaths among elderly persons with associated chronic conditions is significantly lower,[7,35] underscoring the need for influenza vaccines that are more immunogenic in elderly persons.[37,38] Recent studies have also raised the question of whether vaccinating young children against influenza may decrease transmission rates and thus decrease influenza-associated morbidity and mortality among elderly persons,[39,40] but the effectiveness of this approach remains uncertain.

Although the importance of RSV among young children is well recognized,[41,42] we found that more than 78% of RSV-associated underlying respiratory and circulatory deaths occured among persons aged 65 years or older. This finding highlights the need for an effective RSV vaccine in both young children and elderly persons.[12,16,18,43] A number of candidate RSV vaccines are being developed including vaccines based on cold-adapted live attenuated RSV strains[44,45] and subunit vaccines intended for use in RSV nonnaive populations.[46] Effective and safe vaccines for use among persons aged 65 years or older are needed to decrease deaths associated with RSV infection.

Author Contributions: *Study concept and design:* Thompson, Shay, Weintraub, Cox, Fukuda.
Acquisition of data: Thompson, Shay, Weintraub, Brammer.
Analysis and interpretation of data: Thompson, Shay, Weintraub, Brammer, Cox, Anderson, Fukuda.
Drafting of the manuscript: Thompson, Shay, Fukuda.
Critical revision of the manuscript for important intellectual content: Thompson, Shay, Weintraub, Brammer, Cox, Anderson, Fukuda.
Statistical expertise: Thompson, Weintraub.
Obtained funding: Cox.
Administrative, technical, or material support: Thompson, Shay, Cox.
Study supervision: Anderson, Fukuda

Funding/Support: This work was funded directly by the US Centers for Disease Control and Prevention.
Acknowledgment: We thank Lee Schmeltz, Sara Lowther, MPH, and Thomas Török, MD, for providing viral surveillance data; Ericka Sinclair, MS, Erin Murray, MSPH, and Alicia Postema, MPH, for assistance in organizing the World Health Organization influenza isolate data.

REFERENCES

1. Simonsen L, Clarke MJ, Williamson GD, et al. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health.* 1997;87:1944-1950.
2. Simonsen L, Clarke MJ, Schonberger LB, et al. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J Infect Dis.* 1998;178:53-60.
3. Bridges CB, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2002;51(RR-3):1-31.
4. Bisno AL, Griffin JP, Van Epps KA, et al. Pneumonia and Hong Kong influenza: a prospective study of the 1968-1969 epidemic. *Am J Med Sci.* 1971;261:251-263.
5. Douglas RG Jr. Influenza: the disease and its complications. *Hosp Pract.* 1976;11:43-50.
6. 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.
7. 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.
8. Griffin MR, Coffey CS, Neuzil KM, et al. Winter viruses: influenza- and respiratory syncytial virus-related morbidity in chronic lung disease. *Arch Intern Med.* 2002;162:1229-1236.
9. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. *Am Rev Respir Dis.* 1987;136:550-555.
10. 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.
11. Anderson LJ, Parker RA, Strikas RL. Association between respiratory syncytial virus outbreaks and lower respiratory tract deaths of infants and young children. *J Infect Dis.* 1990;161:640-646.

12. Han LL, Alexander JP, Anderson LJ. Respiratory syncytial virus pneumonia among the elderly: an assessment of disease burden. *J Infect Dis.* 1999;179:25-30.
13. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect.* 1996;116:51-63.
14. Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet.* 2001;358:1410-1416.
15. Falsey AR, McCann RM, Hall WJ, et al. Acute respiratory tract infection in daycare centers for older persons. *J Am Geriatr Soc.* 1995;43:30-36.
16. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev.* 2000;13:371-384.
17. Dowell SF, Anderson LJ, Gary HE Jr, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. *J Infect Dis.* 1996;174:456-462.
18. Walsh EE, Falsey AR, Hennessey PA. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. *Am J Respir Crit Care Med.* 1999;160:791-795.
19. Fleming DM, Cross KW. Respiratory syncytial virus or influenza? *Lancet.* 1993;342:1507-1510.
20. Brammer TL, Izurieta HS, Fukuda K, et al. Surveillance for influenza—United States, 1994-95, 1995-96, and 1996-97 seasons. *MMWR Morb Mortal Wkly Rep.* 2000;49:13-28.
21. Centers for Disease Control and Prevention. Update: respiratory syncytial virus activity—United States, 1999-2000 season. *MMWR Morb Mortal Wkly Rep.* 2000;49:1091-1093.
22. *Vital Statistics Mortality Data, Multiple Cause Detail, 1972-1999* [package insert]. Hyattsville, Md: National Center for Health Statistics; 1999.
23. 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, Switzerland: World Health Organization; 1977.
24. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on Recommendations of the Tenth Revision Conference, 1992.* Geneva, Switzerland: World Health Organization; 1992.
25. Hetzel AM. *History and Organization of the Vital Statistics System.* Hyattsville, Md: National Center for Health Statistics; 1997.
26. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between *ICD-9* and *ICD-10*: preliminary estimates. *Natl Vital Stat Rep.* 2001;49(2):1-32.
27. US Bureau of the Census. *Intercensal Estimates of the Population by Age, Sex, and Race.* Washington, DC: US Bureau of the Census; 1990.
28. Farr W. *Vital Statistics: A Memorial Volume of Selections From the Reports and Writing With a Biographical Sketch.* London, England: Office of the Sanitary Institute, HSMO; 1885.
29. Centers for Disease Control and Prevention. *Health, United States, 1999: With Health and Aging Chartbooks.* Washington, DC: US Dept of Health and Human Services; 1999. DHHS publication (PHS) 99-1232.
30. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet.* 2001;357:1008-1011.
31. Barker WH, Borisute H, Cox C. A study of the impact of influenza on the functional status of frail older people. *Arch Intern Med.* 1998;158:645-650.
32. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis.* 2001;184:665-670.
33. Glaser CA, Gilliam S, Thompson WW, et al. Medical care capacity for influenza outbreaks, Los Angeles. *Emerg Infect Dis.* 2002;8:569-574.
34. Nichol KL, Margolis KL, Wouremna J, von Sternberg T. Effectiveness of influenza vaccine in the elderly. *Gerontology.* 1996;42:274-279.
35. Nichol KL, Margolis KL, Wuorenma J, von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med.* 1994;331:778-784.
36. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med.* 1995;123:518-527.
37. Katz JM, Lu X, Todd CW, Newman MJ. A nonionic block co-polymer adjuvant (CRL1005) enhances the immunogenicity and protective efficacy of inactivated influenza vaccine in young and aged mice. *Vaccine.* 2000;18:2177-2187.
38. Treanor JJ, Mattison HR, Dumyati G, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. *Ann Intern Med.* 1992;117:625-633.
39. Reichert TA, Sugaya N, Fedson DS, et al. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med.* 2001;344:889-896.
40. Longini IM, Halloran ME, Nizam A, et al. Estimation of the efficacy of live, attenuated influenza vaccine from a two-year, multi-center vaccine trial: implications for influenza epidemic control. *Vaccine.* 2000;18:1902-1909.
41. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA.* 1999;282:1440-1446.
42. Shay DK, Holman RC, Roosevelt GE, et al. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. *J Infect Dis.* 2001;183:16-22.
43. Falsey AR, Walsh EE, Looney RJ, et al. Comparison of respiratory syncytial virus humoral immunity and response to infection in young and elderly adults. *J Med Virol.* 1999;59:221-226.
44. Wright PF, Karron RA, Belshe RB, et al. Evaluation of a live, cold-passaged, temperature-sensitive, respiratory syncytial virus vaccine candidate in infancy. *J Infect Dis.* 2000;182:1331-1342.
45. Teng MN, Whitehead SS, Bermingham A, et al. Recombinant respiratory syncytial virus that does not express the NS1 or M2-2 protein is highly attenuated and immunogenic in chimpanzees. *J Virol.* 2000;74:9317-9321.
46. Falsey AR, Walsh EE. Safety and immunogenicity of a respiratory syncytial virus subunit vaccine (PFP-2) in ambulatory adults over age 60. *Vaccine.* 1996;14:1214-1218.

