Impact of Influenza Vaccination on Seasonal Mortality in the US Elderly Population

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Background: Observational studies report that influenza vaccination reduces winter mortality risk from any cause by 50% among the elderly. Influenza vaccination coverage among elderly persons (≥65 years) in the United States increased from between 15% and 20% before 1980 to 65% in 2001. Unexpectedly, estimates of influenza-related mortality in this age group also increased during this period. We tried to reconcile these conflicting findings by adjusting excess mortality estimates for aging and increased circulation of influenza A(H3N2) viruses.

Methods: We used a cyclical regression model to generate seasonal estimates of national influenza-related mortality (excess mortality) among the elderly in both pneumonia and influenza and all-cause deaths for the 33 seasons from 1968 to 2001. We stratified the data by 5-year age group and separated seasons dominated by A(H3N2) viruses from other seasons.

Results: For people aged 65 to 74 years, excess mortality rates in A(H3N2)-dominated seasons fell between 1968 and the early 1980s but remained approximately constant thereafter. For persons 85 years or older, the mortality rate remained flat throughout. Excess mortality in A(H1N1) and B seasons did not change. All-cause excess mortality for persons 65 years or older never exceeded 10% of all winter deaths.

Conclusions: We attribute the decline in influenza-related mortality among people aged 65 to 74 years in the decade after the 1968 pandemic to the acquisition of immunity to the emerging A(H3N2) virus. We could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group. Because fewer than 10% of all winter deaths were attributable to influenza in any season, we conclude that observational studies substantially overestimate vaccination benefit.

Arch Intern Med. 2005;165:265-272

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Financial Disclosure: Dr Blackwelder was an independent consultant to the EMMES Corporation, Rockville, Md, during this study; Dr Taylor was an independent contractor for NIAID.

ACCURATE ASSESSMENT OF the seasonal impact of influenza on mortality is a difficult task. The diagnosis of influenza virus infection is rarely confirmed in the laboratory, and influenza infection is often cleared before onset of the secondary complications that actually cause a patient's death.[1,2] Consequently, influenza-related mortality must be determined indirectly, using statistical models that estimate the winter-seasonal excess of either pneumonia and influenza (P&I) or all-cause mortality above a baseline of expected mortality (**Figure 1**).[3-8] The study of trends in influenza-related mortality over time is further complicated both by substantial season-to-season variation in the number of deaths—0 to 70 000 since 1968[7,8]—and by the fact that mortality is much higher in seasons dominated by influenza A(H3N2) viruses than in seasons dominated by influenza B and A(H1N1) viruses.[5]

Influenza vaccination in the United States has long been recommended for all persons 65 years or older.[9] Vaccination coverage for this age group increased from between 15% and 20% before 1980 to 65% in 2001.[10] However, 3-year moving averages of unadjusted excess P&I mortality rates among people 65 years or older—compiled for the *Healthy People 2000* initiative[11] to track the effect of vaccination on US influenza-related mortality—rose substantially during this period.[12] This was surprising because influenza vaccination is thought to be highly effective at reducing influenza-related mortality.[13-19]

We therefore decided to analyze data on influenza-related mortality for the past 3 decades and to adjust the data for 2 important factors likely to affect the observed trends. First, although influenza mortality risk increases rapidly with age,[6] the moving averages were not adjusted for the substantial increase in average age of the US elderly population that occurred over the past 3 decades.[20] Second, the moving averages did not adjust for the increased frequency with which A(H3N2) viruses dominated influenza seasons in the 1990s. We

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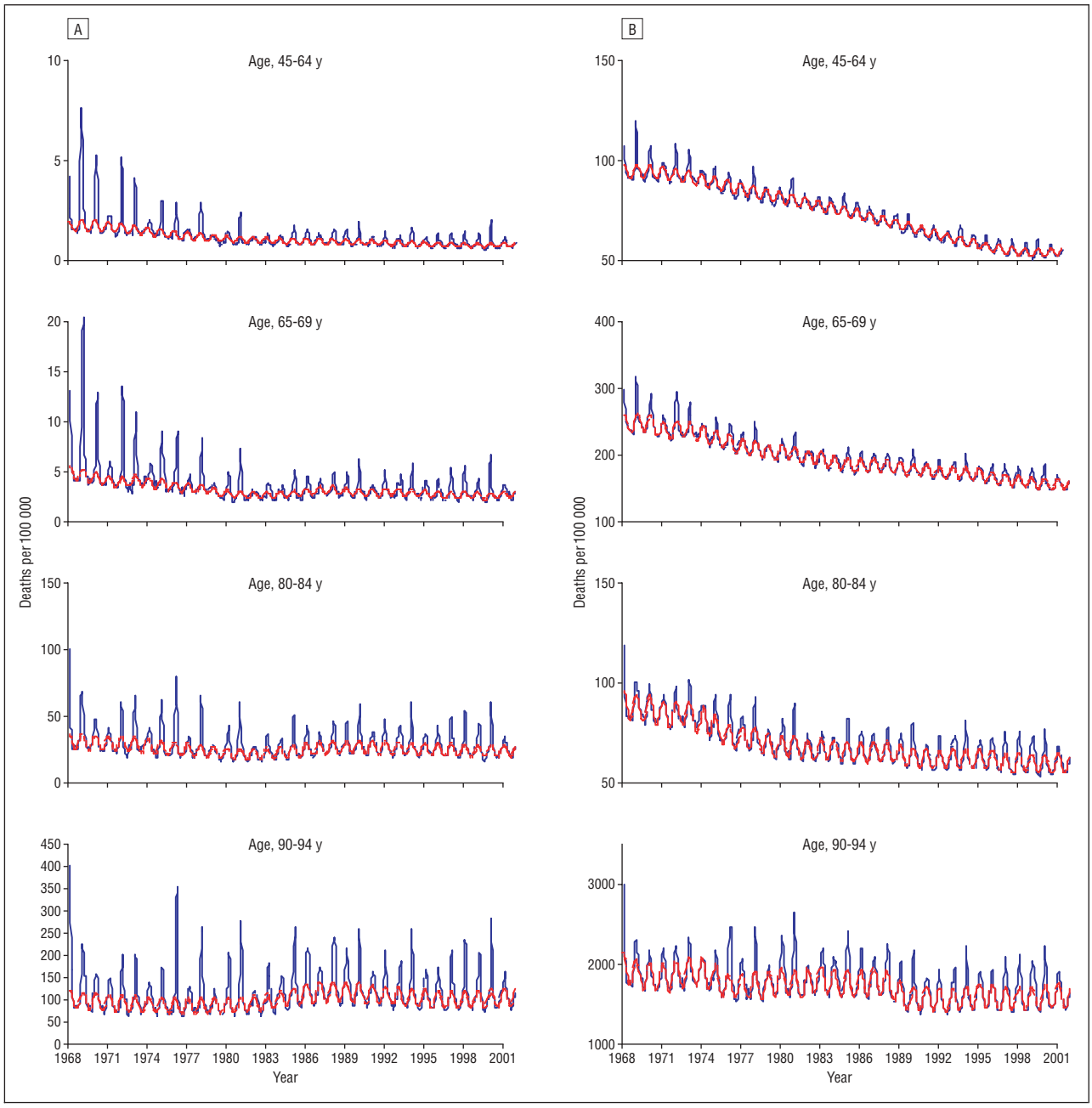

Figure 1. Monthly pneumonia and influenza (A) and all-cause (B) mortality rates are shown in blue for four age groups. The baseline mortality rates determined by our Serfling model are shown in red.

therefore adjusted influenza-related mortality estimates for age and analyzed mortality trends over time for seasons dominated by influenza A(H3N2) viruses separately from those dominated by influenza A(H1N1) or B viruses.

METHODS

DATA SOURCES

Age-Specific Mortality Data

We extracted all deaths with P&I listed as the underlying cause from US national multiple-cause-of-death databases for the years 1968 through 2001.[21-23] For each year, we generated summary data sets of the monthly numbers of influenza, P&I, and all-cause deaths, stratified by 5-year age intervals (65-69, 70-74, 75-79, 80-84, 84-89, 90-94, and ≥95 years). We included a younger age group (45-64 years) to assess the trend in persons with lower vaccination coverage. We adjusted for the conversion from *International Classification of Diseases, Ninth Revision* (*ICD-9*) to *ICD-10* in 1999 by multiplying the reported number of monthly P&I deaths in the 1999-2001 period by the ratio of the mean summer P&I mortality rate (June-September) for the years 1996 through 1998 to the mean summer P&I rate in 1999.

Population Data

We obtained annual population estimates from the US Bureau of the Census by single year of birth for the years 1970 to 2001[20]

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Table 1. Influenza Seasons, Dominant Virus Subtype, Vaccination Coverage, Seasonal Excess All-Cause Mortality, and Vaccine Effectiveness Estimates in Persons 65 Years or Older

Influenza Season	Influenza Vaccination Coverage, %	No. of Excess All-Cause Deaths (Serfling Spline Regression Model[3])	Total US Winter Deaths (December-March)	Excess All-Cause Mortality, % of All Winter Deaths (December-March)	Observational Studies' Estimated Reduction in Total Winter All-Cause Mortality Among Vaccinated Persons,* %
1968-1969†	NA	24 605	435 148	5.7	NA
1969-1970†	NA	9636	425 776	2.3	NA
1970-1971	NA	10 287	422 061	2.4	NA
1971-1972†	NA	20 025	445 898	4.5	NA
1972-1973†	16	10 327	451 754	2.3	NA
1973-1974	17	1766	438 181	0.0	NA
1974-1975†	22	18 201	448 089	4.1	NA
1975-1976†	21	38 198	458 847	8.3	NA
1976-1977	38	3477	439 339	0.8	NA
1977-1978†	23	32 492	472 773	6.9	NA
1978-1979	22	4440	441 712	1.0	NA
1979-1980	19	19 537	481 481	4.1	NA
1980-1981†	20	40 414	503 132	8.0	NA
1981-1982	21	5018	473 208	1.1	NA
1982-1983†	21	14 615	494 356	3.0	27[13]
1983-1984	22	9398	508 960	1.8	NA
1984-1985†	23	39 637	541 551	7.3	NA
1985-1986	24	26 604	542 023	4.9	30[13]
1986-1987	25	10 976	535 051	2.1	NA
1987-1988†	28	30 680	570 079	5.4	NA
1988-1989	31	22 222	556 087	4.0	NA
1989-1990†	37	49 661	577 878	8.6	NA
1990-1991	42	11 353	549 800	2.1	51[15]
1991-1992†	48	32 197	574 245	5.6	54[15]
1992-1993	52	34 881	592 063	5.9	39[15]
1993-1994†	55	47 230	616 435	7.7	41[15]
1994-1995†	58	14 226	604 630	2.4	57[14]
1995-1996	62	25 071	622 295	4.0	68[14]
1996-1997†	63	49 913	641 318	7.8	60[16]
1997-1998†	63‡	59 452	655 252	9.1	39[16]
1998-1999†	63	64 525	666 553	9.7	48[17]
1999-2000†	65	59 332	672 160	8.9	NA
2000-2001	65	14 628	655 506	2.2	NA

Abbreviation: NA, data not available.
*Data from various cohort and case-control studies of North American elderly populations.
†Season dominated by influenza A(H3N2) virus.
‡Vaccine A(H3N2) component was mismatched with circulating viruses.

and calculated the annual number of elderly in each 5-year age group. Because US census population estimates for the years 1960 through 1969 grouped all persons 85 years or older, we estimated the populations in the 5-year age groups older than 85 years by polynomial extrapolation. We calculated monthly mortality rates per 100 000 for each age group and standardized these to 30.4-day months.

Influenza Vaccination Coverage

Vaccination rates in noninstitutionalized elderly people 65 years or older were available from analysis of data collected by the National Health Interview Survey (NHIS).[24,25] For the seasons 1989 through 1998, a database containing estimates of coverage rates for 5-year elderly age groups was provided by James Singleton, MS, and Peng-Jun Lu, PhD, of the Centers for Disease Control and Prevention. Because these estimates were quite similar for all 5-year age groups but with wider confidence limits, we elected to use the coverage rates for all persons 65 years or older as the best estimate for any elderly age group.

Laboratory Surveillance Data to Determine the Dominant Strain

We reviewed annual *Morbidity and Mortality Weekly Report* influenza summaries of viral subtypes that were identified in US laboratories during each influenza season; we considered an influenza subtype to be dominant when it accounted for at least 50% of all isolates that were subtyped in that season.[26] Of the 33 seasons studied, A(H3N2) viruses predominated in 19; the remaining 14 seasons were dominated by A(H1N1) or influenza B viruses (**Table 1**).

STATISTICAL MODEL

To estimate age-specific excess P&I and all-cause mortality for 33 influenza seasons, 1968 through 2001, we applied a Serfling-type regression model to monthly data.[3] We first detrended the time series by dividing by the average summer (June-August) mortality using a spline smooth function. We applied a seasonal regression model to the

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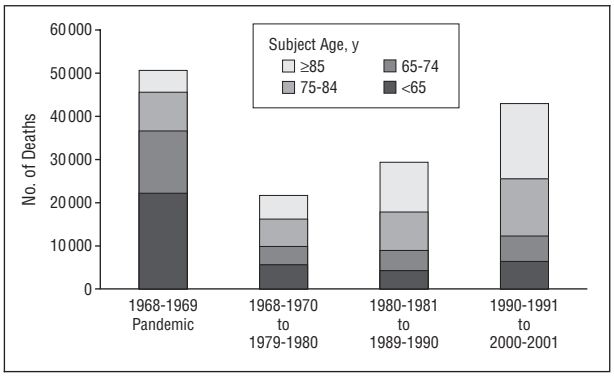

Figure 2. Mean seasonal number of all-cause excess deaths by age group during the 1968-1969 pandemic and the following 3 decades.

detrended series, Yt, excluding values for the period December to April:

$$Yt = a + b\cos(2\pi t/12) + c\sin(2\pi t/12) + e_t,$$

where t is the index for month of death (1-408), and e_t is the error term.

We identified influenza epidemic periods by applying this procedure to mortality rates specifically attributed to influenza (*ICD-9* code 487) for all ages. We then defined the "epidemic months" for each season as those winter months for which influenza deaths exceeded the upper 95% confidence limit of that predicted by the model. Next, we applied the model to P&I and all-cause mortality rates for each age group. Monthly excess mortality rates were calculated as the observed minus predicted mortality rate for all "epidemic months." Seasonal excess mortality was estimated as the sum of monthly excess mortality after back-adjusting for the true month length and time trend.

We achieved an excellent fit for all age groups (Figure 1). All model terms included were statistically significant ($P<.001$), but additional terms were not ($P>.05$). The number of epidemic months identified by the model decreased from a mean of 4.4 to 3.2 months per season over the 3 decades ($P<.01$).

ADJUSTING MORTALITY DATA FOR AGING

For each 5-year age group, we standardized the seasonal numbers of excess deaths to the age distribution of the US population in 1970. We then summed the standardized 5-year age group excess deaths for each combined age group (≥65, 65-74, 75-84, and ≥85 years) and divided these numbers by the 1970 population of that combined age group to generate age-adjusted excess mortality rates.

RESULTS

UNADJUSTED NUMBERS OF SEASONAL EXCESS DEATHS, 1968 TO 2001

Excess all-cause mortality was only a small portion of the approximately 500 000 deaths that occur annually among the elderly during winter months, never exceeding 10% (Table 1). The annual unadjusted number of excess all-cause deaths for all ages, averaged by decade, nearly doubled over the 3 decades studied, from about 21 000 in the 1970s to about 39 000 in the 1990s (**Figure 2**). The proportions of these influenza-related deaths that occurred among different age groups also changed substantially during this time; for example, people 85 years or older accounted for 24% of all influenza-related deaths in the 1970s, but this group accounted for 44% in the 1990s.

TRENDS IN AGE-ADJUSTED EXCESS MORTALITY RATES, 1968 TO 2001

Trends Among All Persons 65 Years or Older

Adjusting excess mortality rates for age and analyzing only A(H3N2) seasons substantially reduced the increases observed in unadjusted rates (**Figure 3**). However, the decreases in excess P&I deaths during the 19 A(H3N2)-dominated seasons occurred before 1980, after which the mortality rates remained flat. Overall, the average P&I mortality rates for A(H3N2)-dominated seasons was 2.8 times greater than that of the 14 seasons dominated by A(H1N1) and influenza B viruses, which displayed no identifiable trend over the entire study period.

Trends in Mortality Among Various Elderly Age Groups

The weak trends we observed in excess P&I mortality among all elderly people for the entire study period masked important age group and temporal differences in excess mortality patterns. Among persons aged 65 to 74 years, excess P&I mortality rates fell by 69% ($P<.01$) in the 12 years following the 1968 pandemic but leveled off thereafter; similar results obtained for all-cause excess mortality. A similar pattern was observed for persons aged 45 to 64 years, an age group with lower vaccination coverage. In contrast, among persons 85 years or older, excess P&I mortality rates remained virtually unchanged, while excess all-cause mortality rates tended to increase over time (**Figure 4**). The trends for persons aged 75 to 84 years were intermediate (data not shown). For seasons dominated by influenza A(H1N1) and/or B viruses, excess P&I and all-cause mortality rates for all age groups remained constant or increased marginally over the study period (Figure 4).

CORRELATING TRENDS IN VACCINATION COVERAGE WITH EXCESS MORTALITY, 1980 TO 2001

To assess changes in excess mortality rates during the period of increasing coverage, we fit linear regression models for the logarithm (base 10) of excess mortality rate on year, age, and age-year interaction for the seasons 1980 through 2001, which encompassed 12 A(H3N2) seasons (**Table 2**). We used the age range 65 through 94 years in 5-year age groups and fit separate models for P&I and all-cause mortality. We found no evidence for differences among 5-year age groups in trends over time for either P&I ($P>.99$) or all-cause ($P=.80$) excess mortality rates. Furthermore, we found no evidence of any nonzero trend during the period, either for P&I ($P=.40$) or all-cause ($P=.30$) mortality. We could only approximate *P* values and confidence intervals from these models because residuals were not normally distributed, but these findings were confirmed by regression using ranks

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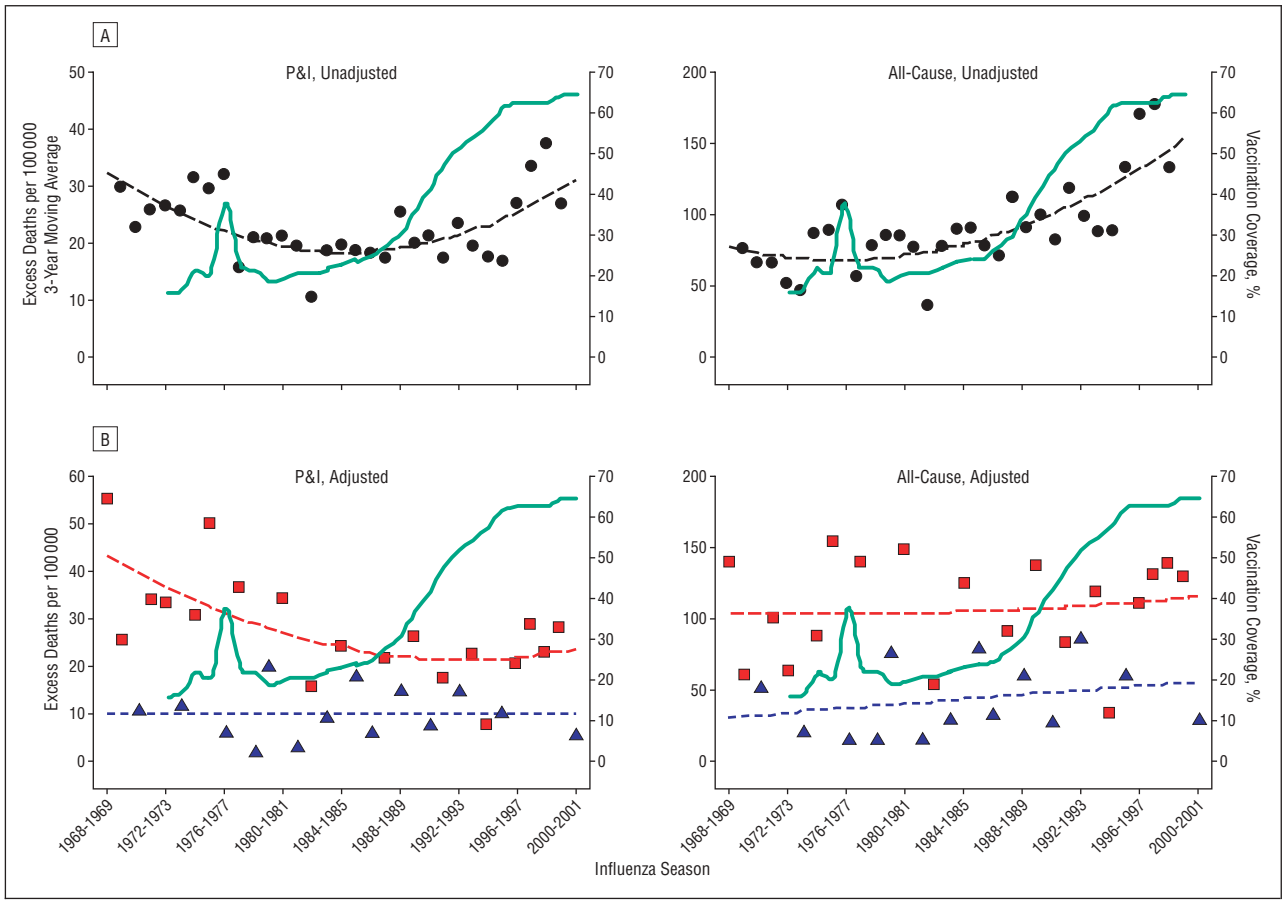

Figure 3. Seasonal excess pneumonia and influenza (P&I) and all-cause mortality rates in persons 65 years or older from 1968 through 2001. A, In the unadjusted findings, the black circles show the 3-year moving averages of the excess mortality rates, and the green line shows influenza vaccination coverage. B, Adjusting for age and controlling for dominant influenza virus subtypes modified the excess P&I and all-cause mortality rates; here, red squares indicate mortality rates for individual seasons dominated by influenza A(H3N2) viruses. Seasons dominated by influenza A(H1N1) and/or B viruses are shown as triangles.

of excess rates instead of logs. Approximate 95% confidence intervals for the overall trends in excess mortality rates from 1980 to 2001 have lower bounds at –35% (P&I) and –18% (all cause), narrowly excluding the 35% to 40% decrease that would be expected for either outcome based on the 50-percentage-point increase in vaccination coverage. These estimates were heavily influenced by the relatively high 1980-1981 excess mortality estimates: deleting data for that season resulted in increasing trends in excess mortality rates for both P&I and all-cause mortality (data not shown).

COMMENT

Influenza vaccination has been reported by several measures to be highly effective among elderly people. A clinical trial among the elderly found that the vaccine was about 60% efficacious in reducing culture-confirmed influenzalike illness.[27] Although mortality as an outcome has never been studied in clinical trials, it is widely believed that vaccine efficacy in preventing mortality is higher, perhaps 70% to 80%.[9] In addition to such efficacy estimates, multiple observational studies have provided measures of vaccine effectiveness by measuring changes in nonspecific outcomes such as hospitalization or death from any cause. A meta-analysis of 20 such case-control and cohort studies concluded that vaccination reduces the total number of winter deaths from any cause among people 65 years or older living in community settings by an astonishing 50%.[19]

In our study, however, we examined influenza-related deaths in the entire US elderly population by estimating seasonal numbers of excess all-cause deaths. These estimates, which provide the best available national estimates of the fraction of all winter deaths that are specifically attributable to influenza,[5,28] show that the observational studies must overstate the mortality benefits of the vaccine. For the 33 seasons studied, influenza-related mortality (excess all-cause mortality) was always less than 10% of the total number of winter deaths among the elderly (Table 1). This period included the 1968 pandemic and the severe 1997-1998 season[29] during which the mismatched vaccine formulation provided little protection[30]; for both of these seasons, the estimated influenza-related mortality was probably very close to what would have occurred had no vaccine been available. We conclude, therefore, that there are not enough influenza-related deaths to support the conclusion that vaccination can reduce total winter mortality among the US elderly population by as much as half.

Nonetheless, estimates of vaccine efficacy available from clinical trials suggest that increased influenza vac-

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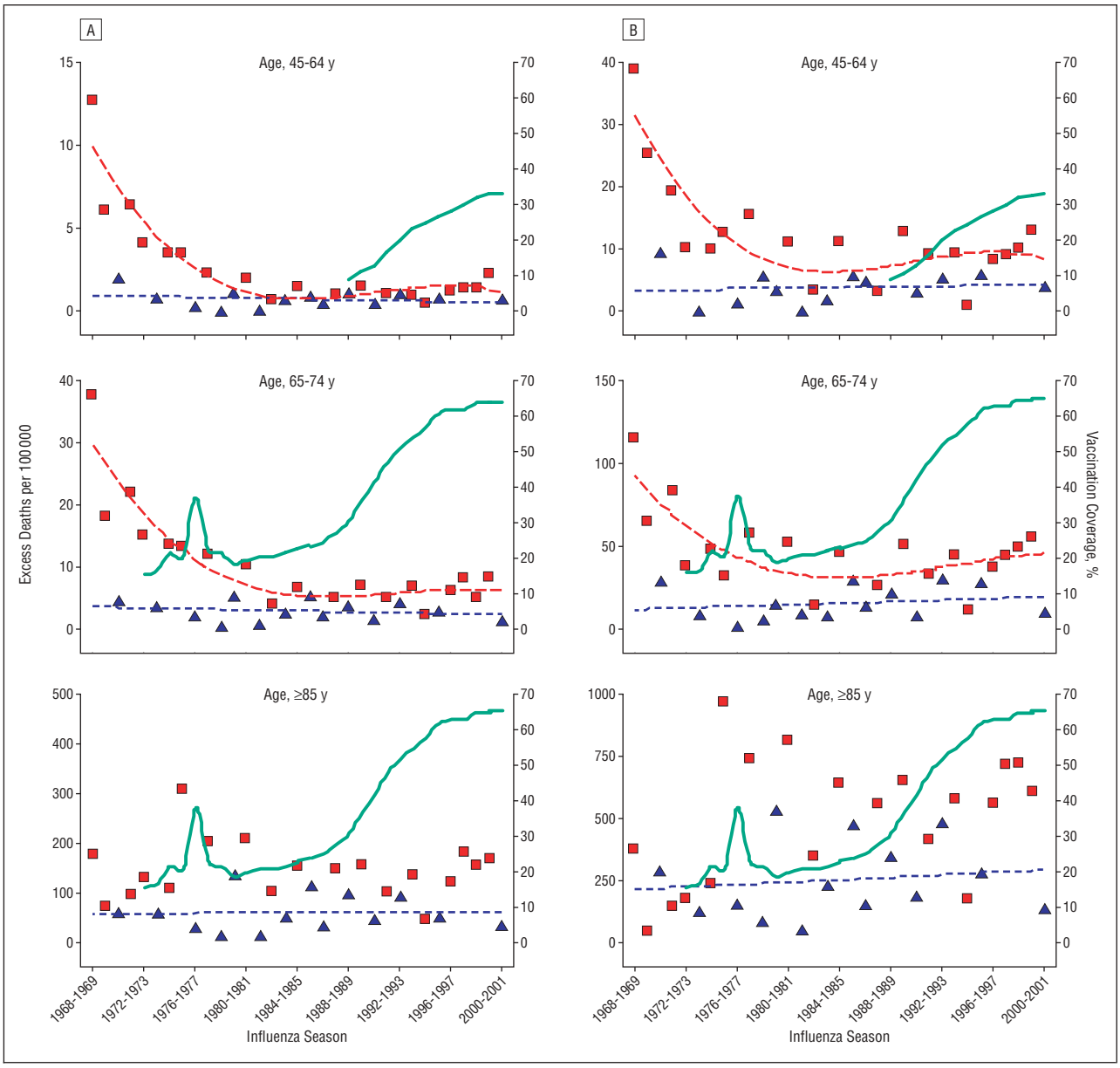

Figure 4. Age-adjusted estimates of seasonal excess pneumonia and influenza (A) and all-cause (B) mortality rates among persons 45 to 64, 65 to 74, and 85 years or older. Red squares indicate seasons dominated by influenza A(H3N2) viruses; blue triangles, seasons dominated by influenza A(H1N1) and/or B viruses. The green line shows influenza vaccination coverage rates.

Table 2. Trends in Excess Mortality Rates Among US Elderly People for 19 Influenza A(H3N2)-Dominated Seasons*

		P&I Excess Mortality			All-Cause Excess Mortality		
Time Period	Age Group, y	Annual Change, %	Total Change, %	*P* Value	Annual Change, %	Total Change, %	*P* Value
1968-1980 (8 A/H3N2 seasons)	65-74	−6	−69	.02	−5	−53	.12
	75-84	0	0	.99	+10	+110	.047
	≥85	+9.2	+100	.20	+64	+706	.03
1980-2001 (12 A/H3N2 seasons)	65-94	−0.6	−12	.40	+1	+21	.3

Abbreviation: P&I, pneumonia and influenza.
*The 1980-1981 season was included in both intervals.

cination coverage should have substantially reduced influenza-related mortality as measured by excess mortality estimates. If vaccination reduces influenza-related mortality by 70% to 80%, then the 50-percentage-point increase in vaccination coverage among the elderly after 1980 should have reduced both excess P&I and excess all-cause mortality by about 35% to 40%. We found no evidence to indicate that such a reduction had occurred

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in excess P&I or excess all-cause mortality in any elderly age group (Table 2). But because of the large seasonal variability in excess mortality estimates typical for influenza epidemics, the confidence limits on the slope were wide and only narrowly excluded the expected decline.

Our findings indicate that the mortality benefits of influenza vaccination may be substantially less than previously thought but for different reasons among different age groups. The sharp decline in influenza-related deaths among people aged 65 to 74 years in the years immediately after A(H3N2) viruses emerged in the 1968 pandemic was most likely due to the acquisition of natural immunity to these viruses. Because of this strong natural immunization effect, by 1980, relatively few deaths in this age group (about 5000 per year) were left to prevent. We found a similar pattern in influenza-related mortality rates among persons aged 45 to 64 years (Figure 4), an age group with substantially lower vaccine coverage. Together with the flat excess mortality rates after 1980, this suggests that influenza vaccination of persons aged 45 to 74 years provided little or no mortality benefit beyond natural immunization acquired during the first decade of emergence of the A(H3N2) virus. It is important to note, however, that if high vaccination coverage had been achieved during the 1968 pandemic and the following decade, many of the approximately 130 000 influenza-related deaths that occurred in this period among people aged 45 to 74 years might have been prevented.

Unlike among the younger elderly, influenza-related mortality among the very elderly did not increase markedly during or immediately after the 1968-1969 pandemic, probably because of persistent immunity acquired through exposure to influenza A(H3) viruses that circulated before 1892.[31] This mortality-sparing effect would have waned after a decade, however, because few people who were born before 1892 would still be living. Our finding that influenza-related mortality among the very elderly did not decline after 1980 might be explained by this group's failure to respond vigorously to the vaccine. This possibility is supported by an immunologic study that found that antibody responses following influenza vaccination decline sharply after age 65 years[32] and a clinical trial involving subjects 60 years or older that found that the efficacy of influenza vaccine in preventing influenza illness was lower in people older than 70 years.[27]

Our methods have limitations. First, the Serfling model we used yielded epidemic periods that became shorter over time, possibly owing to a decline in the use of the influenza-specific *ICD* code on death certificates. However, the excess mortality estimates did not change appreciably when we substituted a fixed 4-month epidemic period of December-March (data not shown).

Second, we considered the possibility of a confounding age cohort effect. If, for example, elderly people in the 1990s tended to be more frail than their age peers of the 1980s, the observed trends in influenza-related mortality could mask a true benefit of the vaccine. To address this possibility, we considered trends in summer mortality as an indicator of time trends in noninfluenza deaths. We found that for all elderly age groups, summer all-cause mortality rates remained constant or declined after 1980 (Figure 1), which suggests that the current elderly population is no more frail than the elderly population of earlier years; adjusting for changing summer mortality rates would therefore not reverse the observed trends.

Third, although our estimates are not subject to selection bias because they are based on national data that include all deaths, our excess all-cause mortality estimates for individual seasons lack precision because the winter-seasonal fraction of all winter deaths is small. Therefore, to test the robustness of our findings, we are now extending our excess mortality studies to other countries with different time patterns of mortality and influenza vaccination coverage.

Our results, based on analysis of national vital statistics, are simply not consistent with the very large mortality benefits reported in observational studies. We suggest that this disconnect may be in part explained by a *hypothesis of disparity in vaccination:* Very ill elderly people, whose fragile health would make them highly likely to die over the coming winter months, are less likely to be vaccinated during the autumn vaccination period.

There are indications that such a systematic bias exists in observational studies. A study in Manitoba found that most influenza-related deaths occurred in a small subset of undervaccinated elderly people who had been hospitalized during the fall,[33] while a recent study confirmed that elderly US Medicare enrollees hospitalized during the fall vaccination season often failed to receive influenza vaccine.[34] Moreover, a recent United Kingdom cohort study that specifically addressed this potential bias found that although vaccinated elderly were less likely to die during winter months than the unvaccinated, this difference obtained both before and after the influenza period.[35] This strongly suggests that some or all of the reduction in all-cause mortality in other observational studies was not attributable to vaccination but rather to underlying differences between vaccinated and unvaccinated cohorts.

A recent Dutch cohort study found a 24% reduction in annual mortality risk associated with revaccination of elderly people[36]; the authors further estimated that vaccination prevents 1 death for every 302 elderly people vaccinated—a result that implies that influenza is a leading cause of death among the elderly. Although this study found a nonsignificant difference of 10% in summer mortality rates among vaccinated and nonvaccinated elderly subjects, the authors did not adequately address the possibility of a bias by studying the peri-influenza period, as was done so well in the recent United Kingdom study.[35]

Our results have obvious implications for influenza vaccination policy. For the 2004-2005 season, we face a severe influenza vaccine shortage that will likely result in lower coverage among the elderly, and the effect of this shortfall on mortality is a matter of great interest.[37] The present findings, and those of at least 1 other study,[35] indicate that the shortage will have little impact, perhaps owing to disparities in vaccination rates[33,34] and possibly vaccine failure due to immune senescence.[38] Other cohort studies suggest that the shortage will have a tre-

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mendous impact on mortality among the elderly.[13-19,36] Either way, this vast disconnect between conclusions from different studies must be sorted out.

Accepted for Publication: December 2, 2004.
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Funding/Support: This study was funded by Unmet Needs grant NVPO-01-N55 from the National Vaccine Program Office, Washington, DC.
Acknowledgment: We thank James Singleton, MS, and Peng-Jun Lu, PhD, for providing unpublished data on vaccination coverage; Thomas Dunn, PhD, for providing copies of the US Vital Statistics database; Jonathan Dushoff, PhD, for help with data extraction; and David S. Fedson, MD, for helpful discussions and editing of earlier versions of this article.

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