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Benefits of influenza vaccination on influenza-related mortality among elderly in the US: an unexpected finding

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Abstract. Although elderly influenza vaccination coverage increased from ~15% to ~65% during 1980–1999 in the US, estimates of influenza-related mortality also increased during this period. We examined these apparently conflicting findings by adjusting mortality estimates for aging within the elderly and the incidence of influenza A (H3N2) virus circulation. Using national mortality statistics for 1968 through 1999, we generated age-specific monthly rates for pneumonia and influenza (P&I) and all-cause mortality for persons ≥65 years of age. We estimated influenza-related mortality as the winter excess in mortality over a Serfling model baseline. After adjusting for age and considering only A (H3N2)-dominated seasons, we found that excess mortality declined sharply among younger elderly (65–74 years) during 1968–1980, but remained level after 1980. Among the most elderly (85+ years), excess mortality rates were essentially unchanged over the entire study period. In conclusion, the increase in elderly influenza vaccination coverage in the US after 1980 was not accompanied by a decline in influenza-related mortality. We hypothesize that disparity in vaccination rates among frail elderly, combined with reduced responsiveness to vaccination with age, may account for these findings. © 2004 Elsevier B.V. All rights reserved.

Keywords: Influenza; Mortality; Mathematical models; Influenza vaccination

1. Background

The burden of influenza has traditionally been measured indirectly as the seasonal increase in winter mortality above an expected baseline level of mortality [1]. Season-to-season variation in the estimated burden of influenza on mortality is substantial, ranging from zero to ~70,000 deaths in the most severe seasons during the 1990s [2]; and in recent years, more than 90% of these influenza-related deaths occurred among those aged 65 years and older, and mostly during seasons dominated by A (H3N2) viruses [3–5].

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To document the progress of influenza control, the Centers for Disease Control and Prevention (CDC) tracked the 3-year moving average of crude excess pneumonia and influenza (P&I) mortality rates among persons ≥65 years of age [6]. Unexpectedly, this index revealed increasing influenza-related mortality rates after 1980, despite a substantial, contemporaneous increase in elderly vaccination rates from 15% to 65% during the 1980s and 1990s.

In this study, we addressed this apparent paradox in mortality trends by adjusting the seasonal estimates for (1) aging within the elderly population and (2) limiting the analysis to seasons dominated by influenza A (H3N2) viruses, to control for increasing domination of these virulent viruses during the 1990s.

2. Methods

From complete mortality data for the United States from 1968 through 1999, we extracted deaths attributed to influenza (I) and pneumonia and influenza (P&I) as the underlying cause of death and generated summary data sets of monthly numbers of influenza, P&I and all-cause deaths by 5 year age groups (65–69, 70–74, . . ., and 95+).

We used a modified version of the classical cyclical regression Serfling-type model [1] to generate a sinusoidal baseline of "expected" winter mortality. We applied the model to age-specific, monthly mortality rates, and introduced multiple polynomial terms to track secular trends during the 31 year study period. Further, we identified "epidemic winter months" of excess mortality by first applying the Serfling model to influenza deaths (ICD9 code 487). The Serfling model was then applied to P&I and all-cause mortality rates, and seasonal excess mortality was estimated by summing the difference between observed rates and the model baseline for all "epidemic winter months."

Each influenza season was characterized by the dominant influenza virus subtype that accounted for at least 50% of all typed isolates in the CDC surveillance reports. To adjust for changing patterns in influenza A (H3N2) circulation, trend analyses of excess mortality patterns were limited to seasons dominated by A (H3N2).

Table 1
Comparison of seasonal, excess mortality estimates, for all ages, by our modified Serfling model and a new CDC model [2]

Influenza season and dominant virus subtype	Our Serfling model number total excess deaths, all ages	CDC new model number total excess deaths, all ages [2]
Individual seasons		
1968–1969 A ((H3N2) Pandemic)	35,700	NA*
1997–1998 A (H3N2)	69,300	72,400
1998–1999 A (H3N2)	74,700	64,700
Mean estimate by decade		
1970/1971 to 1979/1980	17,500	NA*
1980/1981 to 1989/1990	30,200	27,900
1990/1991 to 1998/1999	43,100	49,400
1976–1999 Mean [±S.D.]	32,600 [±20,700]	34,500 [±19,000]

* The new CDC model approach does not permit estimates for seasons before 1976.

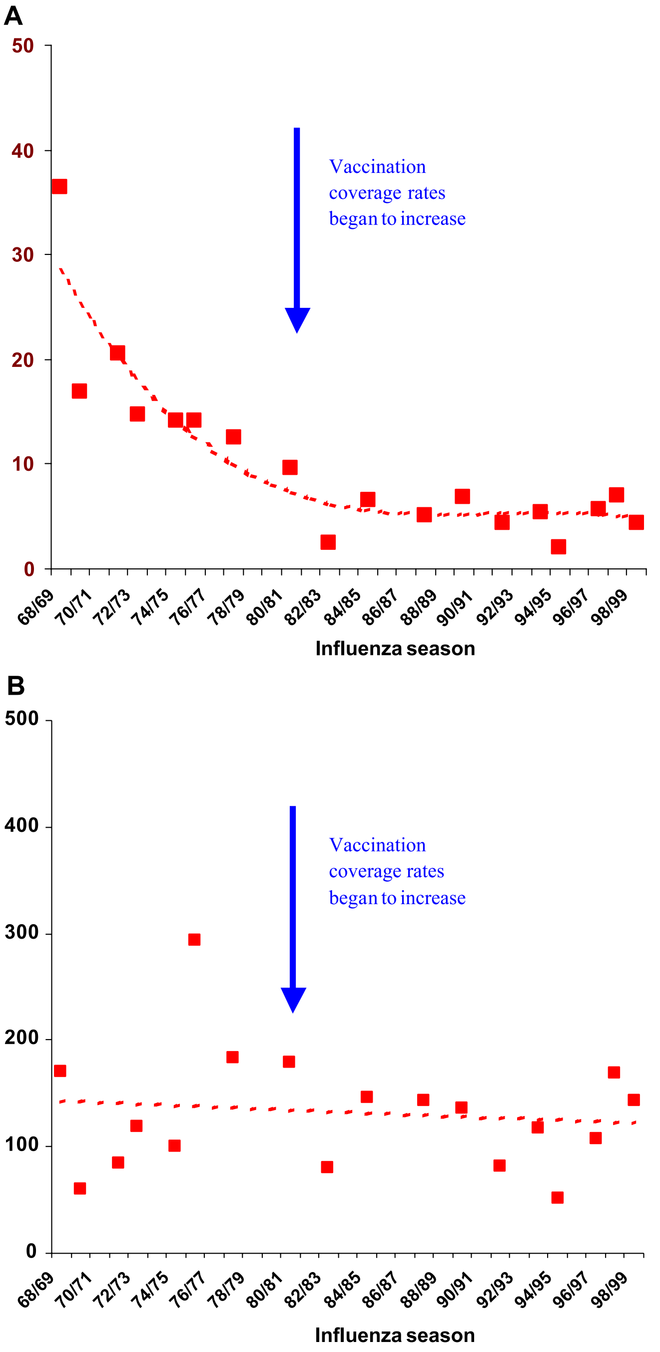

Fig. 1. (A) Trends in age-adjusted excess P&I mortality rates among the younger elderly aged 65–74 years [Panel A] and among the very elderly aged 85+ years [Panel B].

3. Results

3.1. Increasing numbers of influenza-related deaths

There was more than a doubling in the mean seasonal numbers of excess all-cause deaths over the last three decades, from 17,500 in the 1970s to 43,100 in the 1990s (Table 1). Our mean estimates of seasonal, influenza-related mortality during 1976–1999 (32,600 deaths) were very similar to the most recent estimates obtained by the CDC using a complex regression modeling approach [2]. We also noted large changes in the age distribution of influenza-related deaths over time. For example, 9% and 38% of excess all-cause deaths occurred among persons 85+ years of age in the 1968 pandemic and the 1998/1999 epidemic, respectively. This large increase in the proportion of influenza-related deaths that were in the very elderly, especially during the 1990s, reflects the aging of the US population and the higher influenza mortality risk in this group.

3.2. Trends in excess mortality rates

The unadjusted, 3-year moving average of excess P&I mortality rates among persons ≥65 years of age increased substantially from the mid-1980s, while the vaccination coverage steadily rose from ~15% to ~65%. After age adjustment, and limiting the analysis to 18 A (H3N2)-dominated seasons, this paradoxically rising trend in unadjusted data was no longer apparent. However, the temporal patterns of influenza-related mortality varied substantially between elderly age groups. For those aged 65–74 years, influenza-related mortality rates dropped precipitously during the post-pandemic decade, but stabilized after 1980 (Fig. 1A). In contrast, for those ≥85 years, age-adjusted excess mortality did not change markedly overall during 1968–1999 (Fig. 1B); the pandemic impact was moderate compared with other subsequent severe A (H3N2) seasons, due to the protective effect of childhood exposure to H3 antigens among persons born before 1892 [5]. For both age groups, there was no evidence of a reduction in influenza-related deaths during the decades of accelerated vaccine coverage after 1980.

4. Discussion

Despite great advances in influenza vaccination coverage since 1980, there was a paradoxical increase in influenza-related mortality (unadjusted) among persons ≥65 years of age during those years. We demonstrated that this was largely due to aging within the elderly population because the risk of dying of influenza increases exponentially with age [4,5]. For example, the proportion of excess all-cause deaths that occurred among persons 85+ years of age increased from 9% to 38% during the study period 1968–1999. We note that similar mean excess mortality estimates were obtained when applying the new CDC [2] and our Serfling model to the same data years, 1976–1999 (Table 1, see also Ref. [7] for further discussion).

In this study, we have adjusted measures of influenza-related mortality for aging within the elderly population, and for changes in influenza A (H3N2) virus circulation over time. We report dramatic age differences in influenza A (H3N2) mortality patterns. Those aged

65–74 years experienced a 70% decline in influenza-related mortality during the post-pandemic decade, but no further decline after 1980 when influenza vaccination coverage rates increased. For persons ≥85 years of age, there was no apparent mortality benefits during the expansion in vaccination coverage after 1980. The observed absence of a reduction in influenza-related deaths during a period of increasing influenza vaccination coverage among the elderly may be explained by a disparity in vaccination rates among frail elderly [8], combined with a reduced responsiveness to influenza vaccination with age [9].

There is a curious anomaly between our findings and those of numerous cohort studies that have consistently reported a ~50% reduction in the total mortality risk (all causes) among vaccinated elderly during winter months (reviewed in Refs. [10,11]). The next steps to explore this anomaly should include an examination of the possibility that cohort studies may systematically overestimate the effectiveness of influenza vaccination due to an unrecognized disparity in vaccination rates among frail elderly. Ultimately, a coordinated effort to interpret anomalies in available data is critical, since few randomized, placebo-controlled vaccine trials in elderly populations are available, only one of them with mortality as an end-point.

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