THE JAPANESE EXPERIENCE WITH VACCINATING SCHOOLCHILDREN AGAINST INFLUENZA

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ABSTRACT

Background Influenza epidemics lead to increased mortality, principally among elderly persons and others at high risk, and in most developed countries, influenza-control efforts focus on the vaccination of this group. Japan, however, once based its policy for the control of influenza on the vaccination of schoolchildren. From 1962 to 1987, most Japanese schoolchildren were vaccinated against influenza. For more than a decade, vaccination was mandatory, but the laws were relaxed in 1987 and repealed in 1994; subsequently, vaccination rates dropped to low levels. When most schoolchildren were vaccinated, it is possible that herd immunity against influenza was achieved in Japan. If this was the case, both the incidence of influenza and mortality attributed to influenza should have been reduced among older persons.

Methods We analyzed the monthly rates of death from all causes and death attributed to pneumonia and influenza, as well as census data and statistics on the rates of vaccination for both Japan and the United States from 1949 through 1998. For each winter, we estimated the number of deaths per month in excess of a base-line level, defined as the average death rate in November.

Results The excess mortality from pneumonia and influenza and that from all causes were highly correlated in each country. In the United States, these rates were nearly constant over time. With the initiation of the vaccination program for schoolchildren in Japan, excess mortality rates dropped from values three to four times those in the United States to values similar to those in the United States. The vaccination of Japanese children prevented about 37,000 to 49,000 deaths per year, or about 1 death for every 420 children vaccinated. As the vaccination of schoolchildren was discontinued, the excess mortality rates in Japan increased.

Conclusions The effect of influenza on mortality is much greater in Japan than in the United States and can be measured about equally well in terms of deaths from all causes and deaths attributed to pneumonia or influenza. Vaccinating schoolchildren against influenza provides protection and reduces mortality from influenza among older persons. (N Engl J Med 2001;344:889-96.)

A SERIOUS consequence of recurring influenza epidemics is excess mortality during the winter season among elderly persons and those with medical conditions that place them at high risk for complications of influenza.[1-5] Control efforts have focused primarily on the administration of inactivated influenzavirus vaccine to this target population. Several large, population-based, retrospective studies in both community[6-8] and institutional[9] settings have shown that vaccination is effective in reducing not only the rate of hospitalization because of pneumonia but also mortality from all causes during epidemic periods in the winter. Today, in virtually all developed countries, influenza vaccination is recommended for elderly persons (usually those who are 65 years old or older) and those with chronic medical conditions.[10,11]

Only one country, Japan, has ever based its policy for controlling influenza on a strategy of vaccinating schoolchildren rather than elderly persons.[12] The Asian influenza epidemic of 1957 had a powerful effect on Japan. After both winter and summer epidemics, the number of deaths attributed to influenza reached approximately 8000 — by far the largest death toll from influenza ever recorded in Japan. There were widespread school closures, with attack rates as high as 60 percent in some areas. It was clear that school attendance played an important part in amplifying the epidemic. In the aftermath, official policy on influenza vaccination in Japan was changed; the new recommendations stated that "because schoolchildren are the major disseminators of the disease, they should be immunized. Young children, elderly, high-risk patients, pregnant women and workers of essential community services may be immunized as possible."[13] In 1962, special programs of vaccination against influenza for schoolchildren were begun, and in 1977, legislation made such vaccination obligatory. From the mid-1970s to the late 1980s the levels of vaccine coverage among Japanese schoolchildren ranged from 50 percent to 85 percent. In 1987, however, new legislation allowed parents to refuse vaccination against influenza for their children, and in 1994, the government discontinued

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the program because of growing doubt about its effectiveness.[14-18] In addition, there were sensationalized reports of lawsuits alleging adverse side effects of vaccination, and the public lost confidence in the program. The use of influenza vaccine in Japan fell to very low levels.[11,14]

In the early years of influenza vaccination in the United States, there were similar questions about vaccine efficacy.[19] In 1970, Monto et al. reported that during the outbreak of type A (H3N2) influenza in 1968–1969, vaccination of 85 percent of the schoolchildren in Tecumseh, Michigan, resulted in an incidence of influenza-like illness among adults that was one third of that in a neighboring community in which schoolchildren were not vaccinated.[20] Mathematical models suggested that high rates of vaccination among schoolchildren (50 to 70 percent) might substantially reduce the community-wide effects of influenza.[21-23] Several studies conducted in Japanese schoolchildren demonstrated vaccine coverage in this range.[24-27] If, in at least some years, a degree of herd immunity was achieved in the population, the effect of influenza on older persons should have been reduced. A sensitive indicator would be a reduction in excess mortality during winter influenza seasons. We undertook this study to determine whether such a reduction occurred in Japan.

METHODS

We obtained data on the midyear populations of Japan and the United States for all years from 1949 through 1998 and on the numbers of deaths in those countries in each month during those years that were due to all causes and that were attributed to pneumonia and influenza.[28-30] The monthly totals were adjusted to a standard month of 30.4 days.

For both mortality attributed to pneumonia and influenza and mortality due to all causes, we estimated the excess number of deaths per month during the winter season as the number of deaths above a base-line number for the months during which influenza is likely to occur in the United States and Japan (November through April). The base-line level was a three-year moving average of deaths in November. The excess mortality for each winter month was estimated as the algebraic sum of the difference between the adjusted monthly mortality and the base-line level. One exception was the type A (H2N2) influenza pandemic season of 1957–1958, during which a considerable number of deaths attributable to influenza occurred in November. We excluded this month from calculation of the base line and extended the influenza period for that year to include the month of October.

We validated our method of estimating excess mortality by comparing our results with those obtained with a method developed by Simonsen et al.[5] In that model, the choice of months for each influenza season was guided by data from virologic surveillance, and the base line was the estimated level of mortality in relatively influenza-free Decembers. We could not use this method in our study, because data from virologic surveillance were not available for all study years for the United States and no such data were available for Japan. A comparison of our estimates of excess mortality attributed to pneumonia and influenza in the United States with those obtained by Simonsen et al. for the years 1968 through 1995 demonstrated an excellent correlation (Pearson r^2, 0.97; slope, 0.97; intercept, 3200). Thus, our model generated estimates of excess mortality attributed to pneumonia and influenza that differed only by a constant amount from those generated by the method of Simonsen et al. (our estimates were higher by 3200 deaths per season). Our estimates for mortality from all causes in the United States were also well correlated with those of Simonsen et al., from which they also differed only by a constant amount.

A high degree of correlation was also demonstrated between our estimates and those based on other models for estimating excess mortality.[4,31] Thus, although point estimates from various models differed in magnitude, the differences between estimates for two time points were similar regardless of which model was used. With our method, the coefficient for the correlation (r^2) between estimates of excess mortality from all causes and excess mortality attributed to pneumonia and influenza was 0.61 for the United States and 0.73 for Japan, with slopes of 0.19 and 0.21, respectively, and intercepts of 0. For both countries, estimates of excess deaths from all causes were very nearly five times as high, on average, as those for excess deaths attributed to pneumonia and influenza. The peaks, troughs, and trends in the two measures coincided. Thus, the effect of influenza on mortality can be well represented by either excess deaths from all causes or excess deaths attributed to pneumonia and influenza. Excess mortality attributed to pneumonia and influenza is a sensitive index, but it neglects deaths attributed to other causes, which account for most of the effect of the disease on mortality. We suggest that the method used in this paper generates estimates of excess mortality attributed to pneumonia and influenza and excess mortality from all causes, either of which provides an appropriate index of the severity of influenza seasons and is useful for comparing the effects of influenza both between years and between countries.

Data on the amount of influenza vaccine distributed in Japan from 1953 to 1999 were supplied by the Association of Manufacturers of Biologic Products of Japan. These data substantially extend the information that has been published previously.[10,11,14,32] Information on the use of influenza vaccine in the United States during the period from 1963 to 1997 was obtained from a report of the Centers for Disease Control and Prevention.[33] The rate of use of influenza vaccine is expressed as the number of 1-ml doses distributed per 1000 population.

RESULTS

The pattern of mortality from all causes in both Japan and the United States over a period of 50 years (Fig. 1) is a series of peaks in early winter months. The taller peaks mark the years when influenza activity reached epidemic proportions. In the graph for the United States, the base line connecting the summer troughs is relatively constant. The graph for Japan shows somewhat higher winter peaks and a U-shaped trend in the summer troughs. This trend indicates that the number of deaths in Japan in the summer months declined until about 1987, after which it again rose. The tall peaks in mortality during winter seasons, spaced at intervals of two to five years, were attenuated beginning in about 1971. From 1971 through 1989, the highest peak occurred during the winter of 1975–1976, when the emergence of the A/Victoria (H3N2) strain of influenzavirus produced substantial excess mortality worldwide. Very high peaks occurred again after 1993–1994.

Figure 2 presents a comparison of the mortality attributed to pneumonia and influenza for the two countries. The pattern of peaks was similar; however, the peaks in the Japanese curve were much higher than their counterparts in the United States before 1966, similar to their counterparts between 1966 and 1992, and once again much higher after 1994.

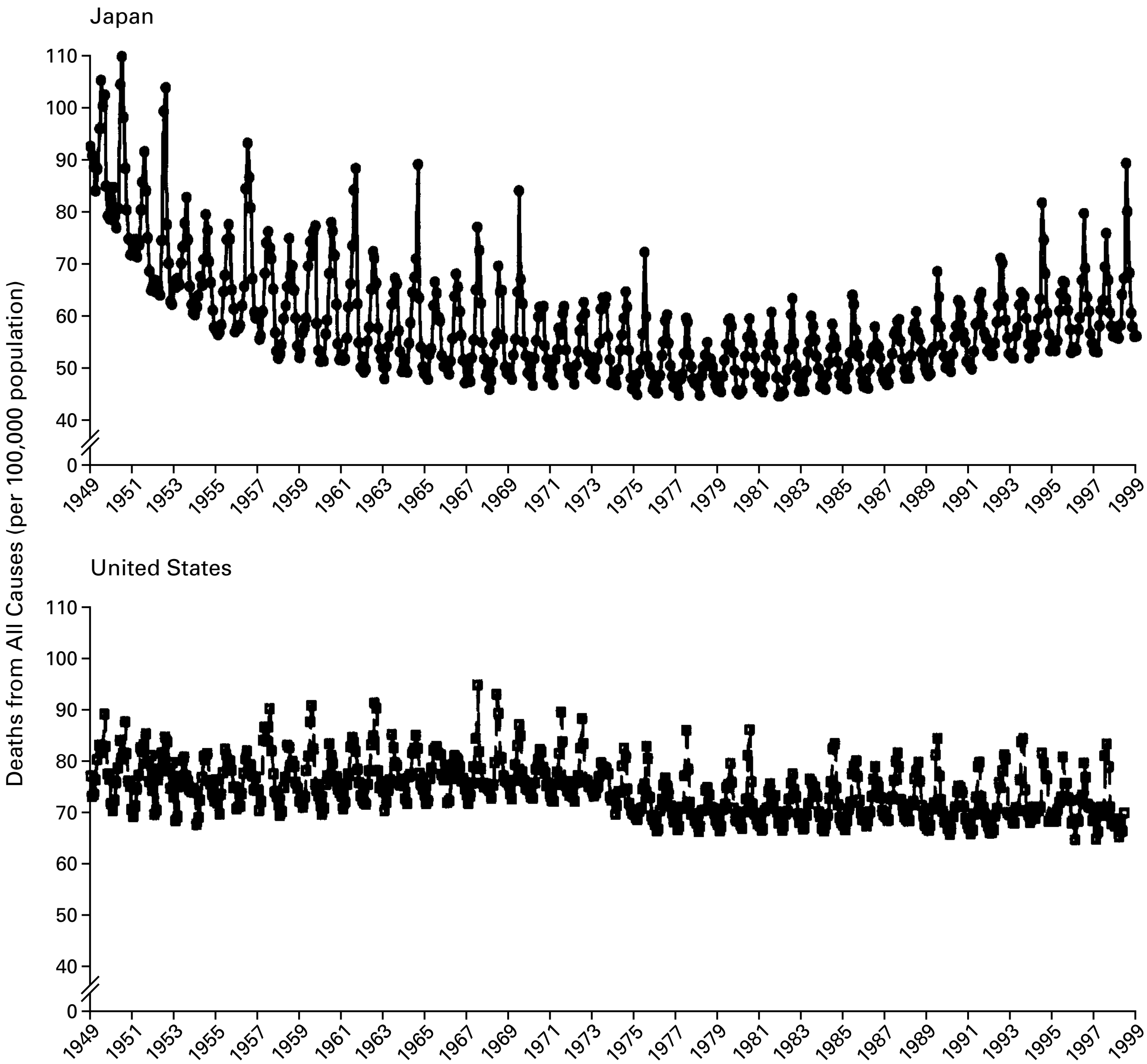

Figure 1. Monthly Mortality from All Causes in Japan and the United States, 1949 to 1999.
Tick marks represent the middle of the years indicated.

The base-line trends in the two countries were quite different; the base-line rate approximately doubled in Japan between 1980 and the mid-1990s.

The population of Japan increased linearly from 1950 to 1980, with a slower growth rate thereafter. From 1970 to 1990, the population grew from 104 million to 124 million, an increase of 19 percent, while the population of persons who were 65 years old or older doubled from 7 million to 15 million, increasing from 7 percent to 12 percent of the total population. The population of the United States also increased in a linear fashion between 1970 and 1990 and to a similar extent — from 203 million to 249 million (an increase of 23 percent). The population of persons who were 65 years old or older increased from 20 million to 31 million (a 55 percent increase), thereby growing from 10 percent to 12 percent of the total population. Thus, the overall growth of the two populations was similar, with the Japanese population about half that of the United States throughout the period, but there was a greater increase in the proportion of elderly persons in Japan.

Between 1962 and 1972, the Japanese five-year moving average of excess death rates declined by half

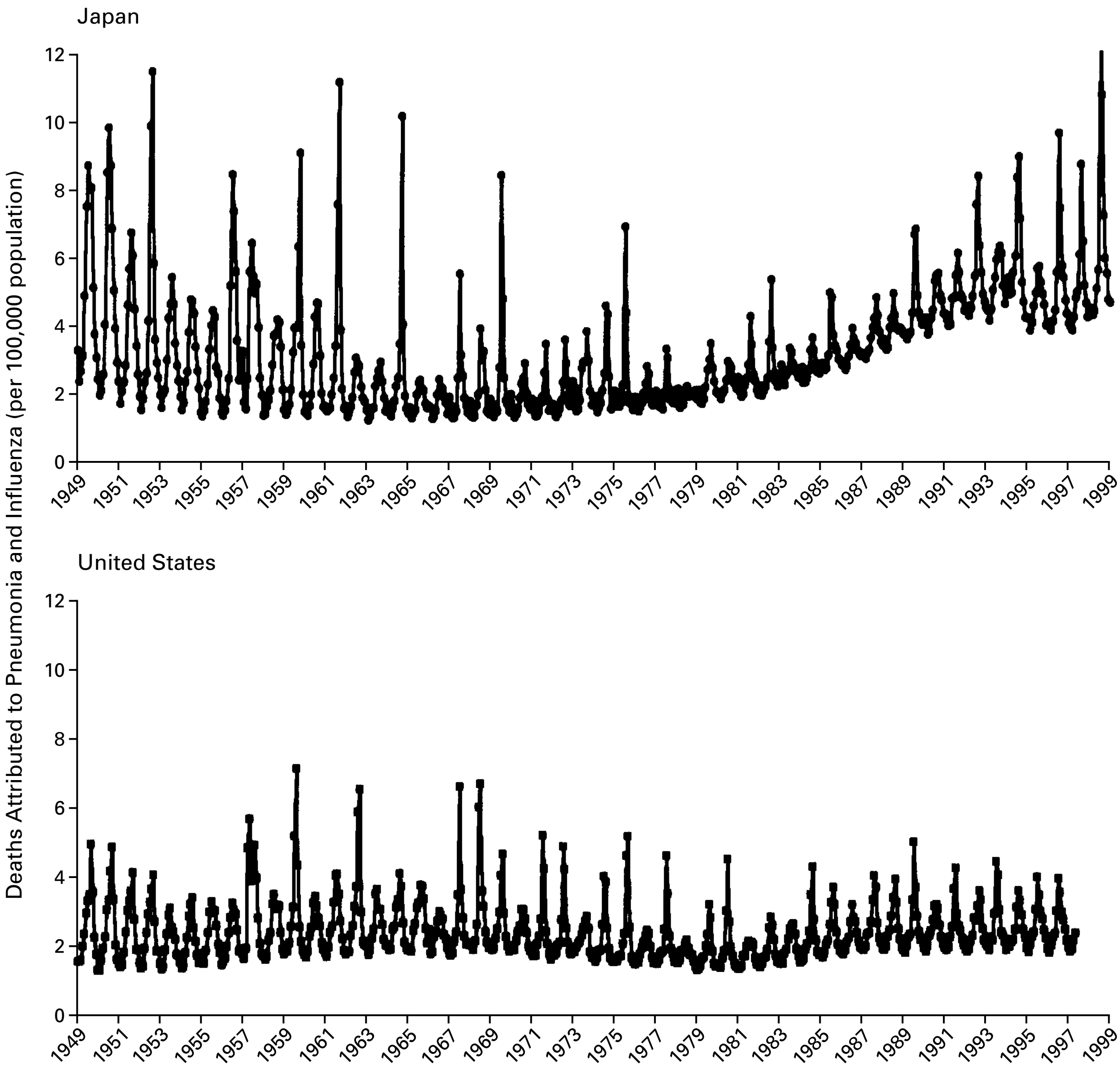

Figure 2. Monthly Mortality Attributed to Pneumonia and Influenza in Japan and the United States, 1949 to 1999. Tick marks represent the middle of the years indicated.

(Fig. 3). Between 1972 and 1987, Japanese excess death rates declined again by 40 percent, to the U.S. level. The Japanese rates rose steadily after 1987, and more steeply after 1994, to values similar to those in Japan before 1962. Figure 4 shows the rates of excess deaths attributed to pneumonia and influenza for each country superimposed on the rates of use of influenza vaccine. In the United States, year-to-year variation diminished steadily after 1970. A correspondence between these changes and the rate of use of vaccine in both countries is clear. The rate of deaths not attributable to influenza, best represented by the summer base-line rates of mortality from all causes (Fig. 1), was approximately constant in the United States and exhibited only a broad, shallow dip in Japan, with all of the decline occurring before 1962. The dramatic difference between the patterns of winter and summer deaths rules out the possibility that the drop and subsequent rise in winter-season mortality in Japan could be explained by a general post–World War II effect on mortality. During the decades of the program of vaccination for schoolchildren (broadly, 1970 through 1990), the mortality attributable to pneumonia and influenza decreased by 10,000 to

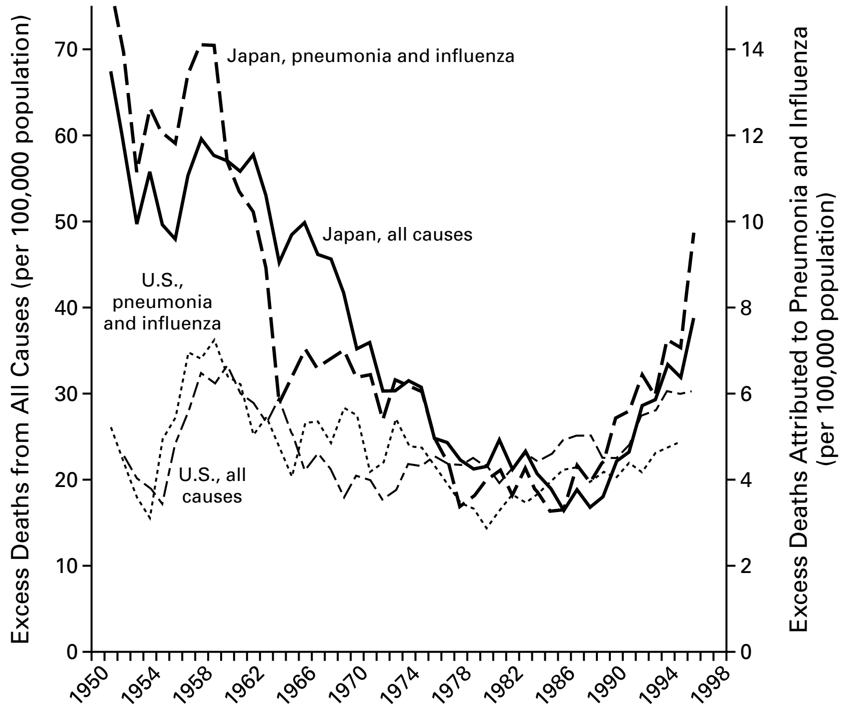

Figure 3. The Five-Year Moving Average of Excess Deaths Attributed to Both Pneumonia and Influenza and All Causes, for Japan and the United States.

Tick marks represent the beginning of the years indicated.

12,000 deaths per year, and mortality from all causes declined by 37,000 to 49,000 deaths per year.

DISCUSSION

The aim of the Japanese influenza vaccination program was to protect schoolchildren and reduce the rate of transmission of infection within the community, particularly to the elderly and those with chronic, high-risk conditions.[17] Unfortunately, assessments of the effectiveness of the program were not focused on older persons or others at high risk, and the methods used to assess morbidity in schoolchildren were insufficiently sensitive to demonstrate a beneficial effect. Only with the discontinuation of the program have its effects become clear.

The number of excess deaths during the winter season in Japan decreased from 1962 until 1987, despite a large increase in the number of elderly people. The number of excess deaths began to rise after 1987, and the increase became quite rapid after 1994. The most likely explanation for this changing pattern of seasonal mortality is that the herd immunity produced by the mass immunization of schoolchildren protected elderly persons. However, there may have been other factors. There was substantial economic development in Japan during this period. Both the social infrastructure and the standard of living improved markedly, and important advances were made in medical science and technology.[34] By 1994, the average life expectancy in Japan had become the longest in the world. These factors may have contributed to the observed decrease in excess deaths. However, none of these factors were reversed, and no other social change occurred that might account for the increase in excess mortality in the late 1990s. The fact that there was a rapid increase in excess deaths after 1994, the year in which mass immunization formally ended, supports the conclusion that the effects observed in earlier years were due to vaccine-induced herd immunity, although it is possible that social factors may have amplified the effects of this program. The proportion of elderly persons living with their children was high in Japan, as compared with other developed countries. This large proportion decreased, but only slowly, from 69 percent in 1980 to 60 percent in 1990 and 50 percent in 1998.[33] Among such households, 60 to 70 percent also included grandchildren. Thus, the high levels of vaccine coverage achieved among schoolchildren could have directly prevented the transmission of influenza-virus to their grandparents.

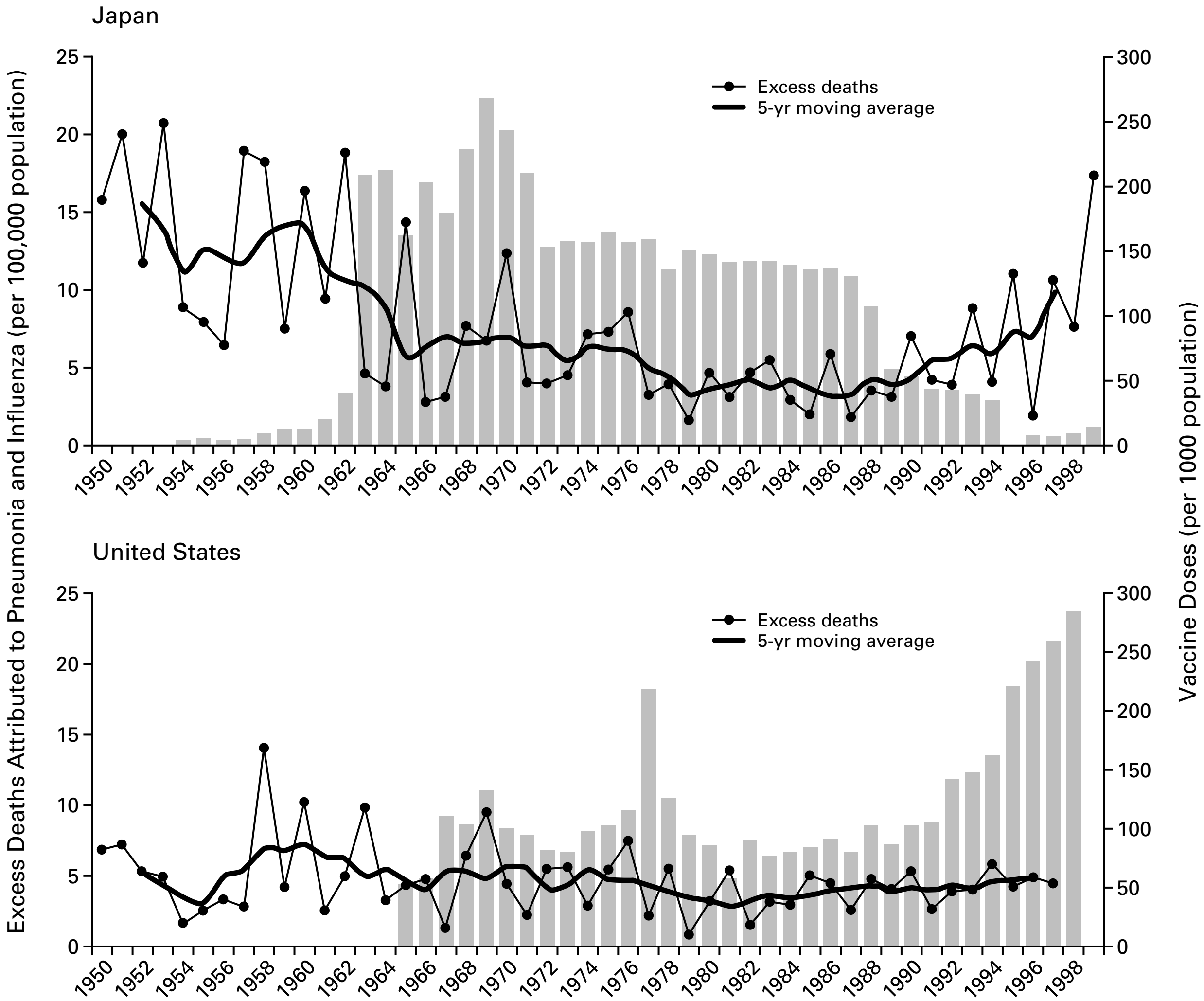

Figure 4. Excess Deaths Attributed to Pneumonia and Influenza over a 50-Year Period in Japan and the United States.
The five-year moving average is also shown. The history of the rates of use of vaccine in each country is superimposed (shaded bars). Tick marks represent the beginning of the years indicated.

Dowdle et al. reported that in 1977 about 20 million persons were vaccinated in Japan, including 17 million schoolchildren.[12] Very little influenza vaccine was administered to the elderly and other persons at high risk. Oya and Nerome[15] later suggested that the number of schoolchildren vaccinated may have been somewhat lower (approximately 14 million) and that levels of coverage may have reached only 50 to 65 percent. However, the denominator they used to estimate vaccine coverage was the population of children who were between 3 and 18 years of age, whereas the vaccination program focused on schoolchildren who were 7 to 15 years of age, among whom levels of coverage of approximately 80 percent were regularly reached. Oya and Nerome also noted that attack rates due to the type A virus were reduced by about 50 percent among primary-school children and by about 80 percent among children in junior high schools.[15] A long-standing policy in Japan is that school classes are canceled and schools are closed when more than 30 percent of the pupils are absent. Oya and Nerome cite reports that class cancellations and school closures were reduced by 50 percent when vaccine coverage reached 50 percent and by 75 percent when coverage levels were higher than 70 percent.

On the basis of the observed reductions in death rates and the size of the Japanese population between 1960 and 1990, we estimate that 37,000 to 49,000 excess deaths from all causes were averted annually when the Japanese program of mass immunization of schoolchildren against influenza was in effect. These numbers are large, when compared with the excess mortality reported in the United States. For example, Simonsen et al. have estimated that, on average, only 21,000 excess deaths from all causes (range, 0 to 46,000) occurred during each of the 20 influenza epidemics in the United States between 1972–1973 and 1991–1992.[4] However, such models measure the relative severity of influenza epidemics and should not be used to estimate the absolute effect of individual outbreaks. Most important, our method, the estimates of Simonsen et al.,[4,5] peri-seasonal models, and even models based on the use of a summer base line (rather than a November base line) produce results that are highly correlated with each other, differing from one another by little more than constant amounts. Since the number of deaths averted is calculated as a difference in the numbers of excess deaths, all these models yield similar results. Thus, our estimates can be considered robust.

In the interpandemic periods, most excess deaths occur in older, unvaccinated persons. We see no alternative to the conclusion that the vaccination of schoolchildren in Japan disrupted the spread of influenza to older persons. It appears that 1 death was prevented by the vaccination of approximately 420 schoolchildren (range, 380 to 460). As a rough comparison, in a study of direct vaccination among the enrollees in a managed-care group in the United States who were 65 to 74 years old, Nichol and Goodman estimated that every 270 vaccinations prevented 1 death.[35] Since the population they studied is likely to have had better health and a higher level of health care than the general population, it appears that the effect of directly vaccinating the older at-risk population was similar to the level of protection afforded by the herd immunity induced by vaccinating schoolchildren in Japan.

In 1997, Japan issued recommendations for the administration of influenza vaccine to elderly persons and those with chronic medical conditions. If these recommendations are implemented over a short time and a level of vaccine coverage similar to that attained among schoolchildren is achieved, the result should be rapid reductions in excess mortality from all causes and excess mortality attributed to pneumonia and influenza. Such an implementation would permit a straightforward assessment of the benefit of administering vaccine directly to the population at greatest risk and could elucidate whether the effects of these two vaccination strategies are overlapping, additive, or synergistic. The reduction in mortality with comprehensive vaccination of elderly and chronically ill persons in Japan is likely to be similar to that observed with the vaccination of schoolchildren. Rapid implementation of the new vaccination strategy would provide valuable data from the only country where the effects of vaccinating schoolchildren are already known.

Recently, studies have demonstrated that outbreaks of influenza are associated with increases in the rate of hospitalization for cardiopulmonary conditions in children under the age of two years and probably in older children as well.[36-38] In preschool children, the live attenuated influenzavirus vaccine provides approximately 90 percent protection against influenza-induced illness.[39,40] Modeling efforts suggest that vaccinating 70 percent of preschool and school-aged children with either inactivated or live attenuated influenzavirus vaccine would be highly likely to prevent community-wide epidemics.[22,41] Other studies have demonstrated that vaccinating school-aged children in the United States, even with an inactivated vaccine, could be cost effective.[42] Clinical trials are under way to test whether vaccinating 85 percent of schoolchildren and 50 percent of preschool children who are 18 months old or older can control the spread of influenza. Our findings, together with the results of ongoing studies, should prompt a reconsideration of the current recommendations for the use of inactivated and live attenuated influenza vaccines in both children and adults.[43]

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