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# The Japanese Program of Vaccination of Schoolchildren Against Influenza: Implications for Control of the Disease

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**In 1970, vaccination of the schoolchildren of the town of Tecumseh, MI, against influenza was shown to protect not only the children of the town, but all of its citizens from influenza-derived illness. Subsequently, models suggested that not only illness, but hospitalizations and mortality might be reduced as well. However, influenza control programs in developed countries focused on direct vaccination of the elderly. Only in Japan was a program of schoolchildren vaccination undertaken. Measures used to gauge the effectiveness of that program were insufficiently sensitive to demonstrate value, set against the large social and healthcare gains in that country. The program was discontinued; but this discontinuation revealed that excess mortality had been dramatically reduced. The demonstration of this reduction has prompted expression of several lines of concern. In this review, I have examined these concerns and provided additional detail, bolstering the findings of the hidden success of the Japanese program. In addition, the implications of the vaccination of schoolchildren for augmented control of influenza are explored.**

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The influenza virus is an ancient adversary of man. The length of this association with humankind has engendered both physical and psychological accommodation. The time between recognized influenza pandemics is sufficiently long that most humans experience “the flu” as little more than a modest incapacitation. Even the influenza pandemic of 1918 lies poorly reported and remembered. Alfred Crosby<sup>1</sup> wrote, “Nothing else—no infection, no war, no famine—has ever killed so many in as short a period. And yet it has never inspired awe, not in 1918 and not since, not among the citizens of any particular land . . .”

Consistent with this lack of remembrance and recognition, measures to control this disease have developed slowly, even in healthcare systems with adequate resources. Vaccination is the principal modality of control efforts, yet the median of the fraction of the population vaccinated in 22 developed countries was approximately 5 percent in the early 1980s, rose to approximately 8 percent by 1990, and was still less than 13 percent in 1997.<sup>2</sup> Only in Japan in the early 1980s and in the United States since 1996 were as many as 20 percent of the citizenry vaccinated against influenza in any year. These figures may seem *very* low;

however, in all countries except Japan, priority for vaccination has been assigned to persons at greatest risk. The recommendations for vaccination are well summarized in Table II of Ambrosch and Fedson.<sup>2</sup> They focus on the protection of individuals in elderly age groups and those who are afflicted with an array of conditions that compromise health. Coverage of the elderly, then, proceeded at much higher percentage levels, and in recent years, coverage of the elderly has approached, even exceeded, 60 percent in several countries. Very recently, this programmatic success has been extended in several countries by lowering the age threshold above which vaccination is recommended.<sup>3</sup>

Influenza immunization policy and practice in Japan differed from those of other developed countries. In Japan, the philosophical and conceptual base for the influenza vaccination program was “to benefit the community through reducing disease transmission.”<sup>4</sup> Epidemiological studies conducted in both Japan<sup>5</sup> and the United States<sup>6</sup> demonstrated that schoolchildren were infected with influenza in the early stages of epidemics and that vaccination of schoolchildren could reduce disease attack rates in all age groups, not just in those immunized.<sup>7,8</sup> Possibly more important, however, was the popular experience with the influenza pandemic in Japan in 1957. It was unrelenting. Not only were the number of deaths attributed to influenza in the early months of that year elevated to the highest levels previously reported, but the H2N2, A-type virus struck in June, producing in the 3 summer months mortality rates that rivaled those of the worst winters. Then, as quickly as it had struck, the epidemic dissipated at the end

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of August, only to return again in synchrony with the return of children from their 1-month school vacation, to rocket to levels never before reported. No study was required. Every newspaper made the association.

## The Japanese Influenza Vaccines

The winter of 1957 to 1958 was the last time that vaccines in Japan were constructed based directly on strains recommended by the World Health Organization (WHO). Beginning in 1958, the WHO recommendations were taken as a guide to the choice of strains used in Japanese vaccines. The actual strains chosen were high-growth variants of strains indicated by Japanese virological surveillance, and the strains used in vaccine production were uniformly based on Japanese isolates, for both A and B strains. Vaccines produced were frequently tri- and even tetra- or pentavalent.

Japanese vaccine titers were held at a total of 300 or 350 CCA equivalents/mL until 1972, when split virus vaccines were introduced and titers were raised to a total of 600 CCA equivalents/mL, to 700 CCA equivalents/mL in 1975 to 1976, and to 800 CCA equivalents/mL in 1991 to 1992. The chick cell agglutination (CCA) system of assessing vaccine potency was replaced in many other countries around 1976 with an assay (single radial diffusion<sup>9</sup>) that is thought to be more consistent with immunogenicity data.<sup>10</sup> This change was not made in Japan until 2000 to 2001. In part, this delay derived from the formalin treatment that was used in the inactivation step in Japanese vaccines. Formalin inactivation always induces a degree of aggregation in protein antigen, and a very significant degree of aggregation was present in early Japanese vaccines. Formalin treatment, especially in combination with certain agents used to “split” the influenza virion, inhibits the single radial diffusion assay and complicates the assessment of the potency of Japanese vaccines.<sup>11,12</sup>

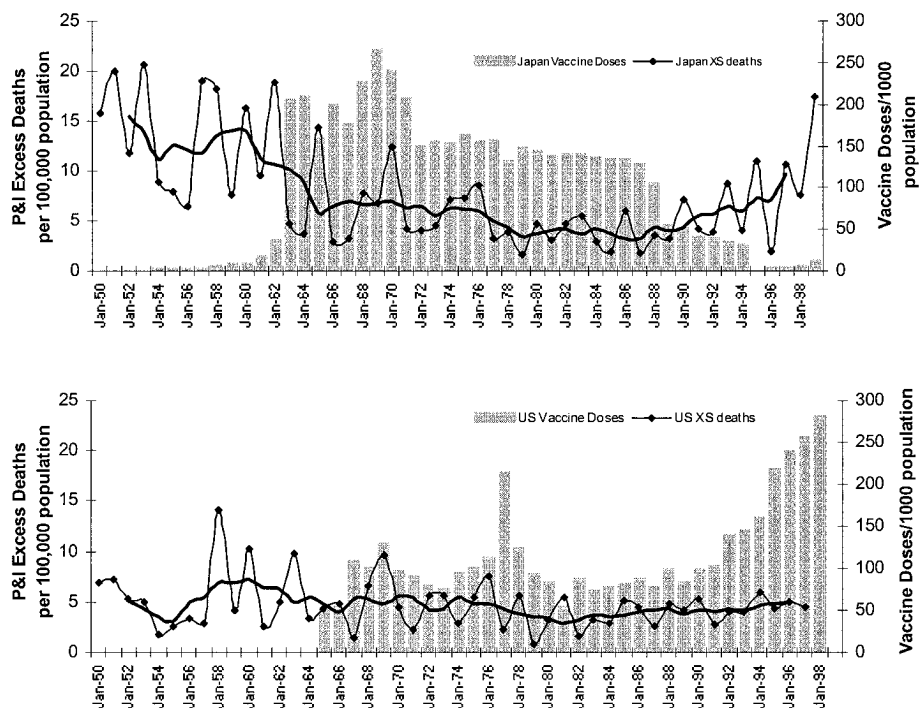
Every lot of vaccines, from every producer, was tested by the Japanese National Regulatory Laboratory. Release assays included immunogenicity testing in mice, and, of course, only vaccines that passed these potency tests were licensed and distributed to the public. Postimmunization hemagglutinin antibody also was monitored annually in human volunteers by all manufacturers. Details of this testing are being assembled for publication in another forum.

Few English-language publications discuss and document the potency of Japanese influenza vaccines. In 1970, Sugiura et al<sup>13</sup> demonstrated that, even with relatively low titer vaccines (200 CCA/mL), most youthful subjects developed antihemagglutinin antibody titers equal to or greater than 32, approximating the conventional definition of the level of antibody likely to produce an acceptable level of protection after a single vaccination (two 0.5 mL doses administered subcutaneously 9 days apart). Dowdle et al<sup>4</sup> noted that Japanese vaccine companies manufacture vaccine only from September through July, whereas the announcement of northern hemisphere strain selections by the WHO occurs in late March or early April. As a consequence, Japanese manufacturers typically began prepara-

tion of the vaccines, which contained 3 to 5 strains, as early as they could be determined with some certainty. Often, the result was the incorporation of strains either similar to the WHO strains that were found to be circulating locally in Japan by the national surveillance program and that could be selected at an earlier date or another strain would be added to the vaccine mix if the recommended strains differed immunogenically from those already selected. Potency recommendations were determined first by an unpublished study involving more than 38,000 subjects (nearly all children). A study conducted by the U.S. Food and Drug Administration (FDA) of a representative 1978 to 1979 vaccine found that “the potency of the type A components [is] similar to that of current U.S. formulations for adults.”<sup>4</sup> The next English-language publication appeared 14 years later, when Sugaya et al<sup>14</sup> demonstrated a vaccine effectiveness of 67.5 percent against clinical infection for an inactivated influenza vaccine of 350 CCA units (equivalent to 13.5  $\mu$ g of hemagglutinin) in young subjects with asthma. This level of effectiveness is appropriate, even quite good, given that the subsequent infecting strain (prototype—A/Kitakyushu/159/93) had drifted substantially from the strain used to generate the vaccine (A/Beijing/352/89). Similar, in fact lower, efficacy was reported for less-than-optimally matched vaccines given to U.S. military subjects in the same year.<sup>15</sup> No evidence exists, certainly after about 1972, that the potency of Japanese vaccines was not similar to their counterparts in the United States.

## The Japanese Program of Vaccination of Schoolchildren Against Influenza

In 1962, a special influenza vaccination program was added to the national vaccination plan. It was funded by national grants to local governments. Although influenza vaccine had been available prior to that year, it was only subsequently that usage was substantial. Figure 1 details vaccine distribution in both Japan and the United States. The availability of split virus, increased titer vaccines after 1972, was accompanied by more uniform program practice. This practice was crystallized in legislation passed in 1977 that made obligatory immunization of all children from kindergarten through senior high school. In 1977, approximately 80 percent of school-age children (17.4 million) received at least 1 dose of vaccine, and 62 percent of these children (10.8 million) received 2 doses. Dowdle et al<sup>4</sup> estimated that, in addition, 2 to 3 million adults received vaccine in 1977, but very few of them were elderly, for whom the vaccine package insert contained a contraindication.<sup>16</sup> Even in 1980, Dowdle et al warned<sup>4</sup> that “there is no proof that annual vaccination significantly reduces influenza-related deaths” and further, that “the present lack of data on the effect of annual vaccination on reduction of influenza-associated morbidity and mortality makes it difficult to establish reasonable program expectations or to measure accurately program achievements.” Oya and Nerome<sup>17</sup> later cited studies in the Japanese literature that documented reductions in attack rates and school closures, but other researchers chronicled a growing doubt about the effective-



**Figure 1.** The influenza vaccine usage history in Japan and the United States. The 5-year moving average of excess deaths (XS) attributable to pneumonia and influenza (P&I) over 50 years for each country is superimposed. Reprinted with permission<sup>32</sup>.

ness of vaccination of schoolchildren as a means of societal protection.<sup>18-20</sup> In 1987, legislation was introduced that allowed parents of children age 3 to 15 years to refuse influenza vaccination for their children.

One of the few studies of that era, reported in English,<sup>21</sup> addressed the rate of occurrence of influenza-like disease in school-age children from 8 elementary schools in a single Japanese city in the winters of 1988 to 1989, 1989 to 1990 and 1990 to 1991. Such a study was possible only because of the precipitous drop in the fraction of children vaccinated after the above-cited changes in the Preventive Vaccination Law (1987). Only 40 percent of subjects admitted were evaluable. The characteristics of the evaluable group differed significantly from that initially accessioned, and no account was made for vaccination in previous years. Nevertheless, the investigators concluded that “the preventive effect of influenza vaccination in pupils under the current programme is inconsistent, and weak” and further that “unless an influenza vaccine with greater effectiveness and more consistent results becomes available, there is no point in recommending that all pupils be inoculated to protect themselves and also their communities.”

The vaccination of children in Japan was completely discontinued in 1994, and national usage of influenza vaccine dropped to approximately zero in that year. Recommendations for influenza vaccination of risk groups were promulgated in Japan in 1997, but government reimbursement was put in place only in 2001.

### What Should Be Expected of a Vaccination Program for Schoolchildren?

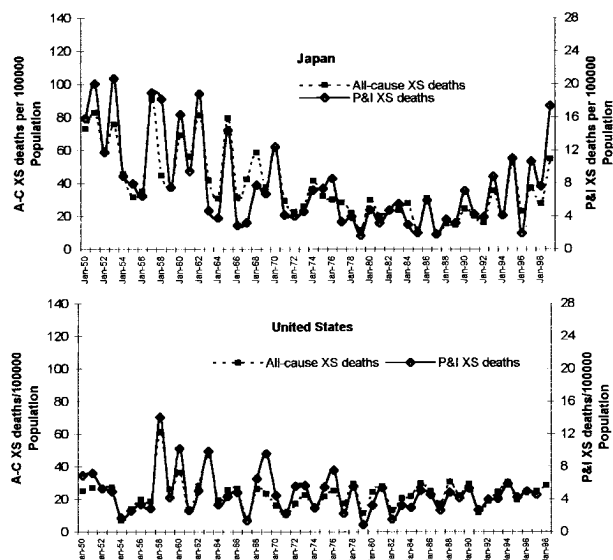
During the past 2 decades, many investigators have demonstrated the health benefits of providing influenza vacci-

nation to particular risk groups.<sup>22,23</sup> Nichol and Goodman<sup>24</sup> recently summarized and extended these analyses for elderly persons (see, in particular, their Table 1). The range of vaccine effectiveness cited for North American subjects for prevention of hospitalization is 12 to 52 percent, and it is 27 to 54 percent for prevention of death. Single studies of European elderly<sup>25,26</sup> suggested that even higher efficacies may be found. Gross et al<sup>27</sup> conducted a meta-analysis of 20 cohort studies, most of which involved institutionalized, very elderly patients. These investigators estimated that influenza vaccine efficacy was 56 percent for preventing respiratory illness, 50 percent for preventing hospitalization, and 68 percent for preventing deaths. The impression from more than 30 studies is that the effectiveness of vaccine in preventing deaths caused by all causes is at least as great, and in some cases significantly greater, than is the efficacy in preventing hospitalization or clinically measured illness.

Nichol and Goodman<sup>24</sup> directly studied data pooled over 6 seasons for a large staff model health maintenance organization. For the vaccination of persons 65 to 74 years of age, without further restriction, they found that the number needed to treat (NNT)<sup>28</sup> to prevent 1 death was 270.

The ability of vaccination against influenza to attenuate mortality was specifically assessed by Nichol et al<sup>29</sup> in an elderly population with a particular class of chronic disease. This study demonstrated that seasonal variations in both hospitalizations and deaths in patients with chronic obstructive pulmonary disease were all but eliminated by vaccination over 3 seasons. The estimated reduction in risk of death was 70 percent. Reduction in total mortality thus appears to be the most sensitive indicator of influenza vaccine effectiveness.

Finally is the matter of whether the vaccination of approximately 80 percent of Japanese children actually achieved an indirect effect, “herd immunity” (ie, a critical



**Figure 2.** Excess (XS) mortality above a baseline of November moving average expressed as rates for all-cause (A-C) mortality and that attributable to pneumonia and influenza (P&I), for both Japan and the United States. These data are not adjusted to a common age distribution.

level of protection within the community group such that infection cannot be propagated to epidemic proportions). Longini et al<sup>30</sup> developed arguments, based on mathematical models, that for a vaccine efficacy of approximately 70 percent, the vaccination rate required to stop or very substantially reduce the spread of influenza throughout a community may range from 55 to 80 percent, depending on how the virus strains spread and the social patterns within which the children interact with other age groups. Morio et al<sup>31</sup> later estimated that herd immunity can be obtained only if the vaccine efficacy exceeds 60 percent and the vaccination rate exceeds 80 percent.

Thus, in some years, and certainly in all years to some extent, a degree of herd protection possibly was present in Japan. If this was the case, then the effect of influenza should have been blunted in Japan during the period of vaccination, and this effect should have been reflected in its most sensitive indicator, total mortality. Reichert et al<sup>32</sup> demonstrated that beginning about 1962, excess mortality (both all-cause and that attributed to pneumonia and influenza) declined from a rate about twice that of the United States to rates approximating those in this country by about 1977. After 1987, excess mortality rates rose again in Japan and in 1995 reached levels approximating those of 1976. In 1999, excess mortality rose further, to the 1970 level. Figure 2 compares the excess mortality rates for the United States and Japan for 50 years, 1950-1999.

Reichert et al<sup>32</sup> estimated the number of deaths averted by vaccination in Japan to be an average of 37,000, based on the 1960 population, or 49,000, based on the 1990 population. From 2 different estimates of the number of children consistently vaccinated, the number of averted deaths corresponds to (number needed to treat) 380 to 460 vaccina-

tions of children to avoid 1 death, principally in the elderly. Given that this result was obtained as a population-wide figure, whereas the result of Nichol and Goodman<sup>24</sup> was based on a population likely to be in better health and more limited in age distribution, we consider the 2 estimates to be approximately the same.

The number of deaths averted estimated by Reichert et al<sup>32</sup> is approximately twice as many as the average number of excess all-cause deaths estimated for the United States.<sup>33</sup> However, as Dowdle et al note,<sup>4</sup> during the 10-year period 1961 to 1970, the absolute number of excess deaths during influenza epidemics was 2 to 3 times greater in Japan than that in the United States. Moreover, the seasonal variation in all-cause mortality in many countries (eg, Spain and the United Kingdom) is similar to that observed for Japan; the estimated excess mortality for the United Kingdom for the decade of the 1990s is approximately 3 times that observed in the United States.<sup>34</sup> Therefore, a plausible conclusion is that very large numbers of deaths might be averted by vaccination programs that involve schoolchildren and that are sufficiently comprehensive to achieve herd immunity.

Carrat and Valleron<sup>35</sup> provided a model for estimating the deaths averted by vaccination as a multiple of the observed excess deaths. Their formula multiplies the excess number of deaths determined by the quantity  $[VE \cdot p / (1 - VE \cdot p)]$ , where VE is the vaccine effectiveness and p is the coverage in a directly vaccinated cadre. Reichert et al<sup>32</sup> found that excess mortality (both all-cause and pneumonia and influenza) was reduced by one-half to two-thirds by vaccination of Japanese schoolchildren. If we assume that the Carrat-Valleron model also is an appropriate estimator for deaths averted in the setting of herd immunity for the protection of the elderly population (for the case in which coverage is sufficiently great that herd immunity is present), then the factor in brackets falls in the range of 2 to 3, for values of  $VE \cdot p$  between 0.667 and 0.75. For coverage of 0.8, this implies that herd immunity could provide an effective vaccine effectiveness (VE) of 0.84 to 0.94 for the prevention of mortality in the elderly population, which is at the upper end of what has been achieved in studies of direct vaccination. This corroboration is further substantiated by Longini et al,<sup>30</sup> who projected the efficacy rate for herd protection via vaccination of schoolchildren to be similar to that of direct vaccination.

## How Robust Is the Japanese Schoolchildren Result?

Comments<sup>36,37</sup> on the paper of Reichert et al<sup>32</sup> have focused on 3 alternative hypotheses that might be invoked to explain the observed phenomenon:

1. The model used by Reichert et al<sup>32</sup> to estimate excess mortality produced values that were 3,200 deaths higher than those of earlier models, labeled as "more rigorous." Conceding a high correlation, the critics were concerned that comparisons between seasons could be distorted.
2. The dramatic increase in the elderly population in Ja-

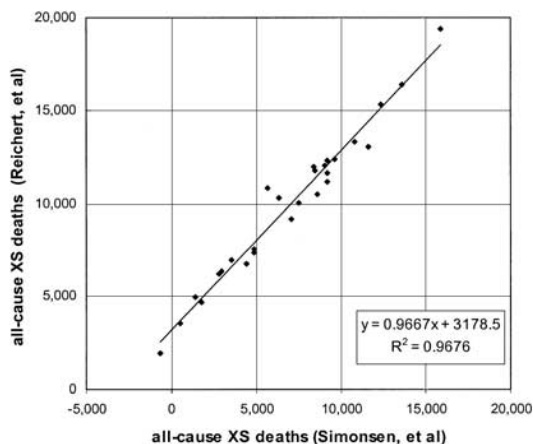
pan, especially after 1990, might explain the observed rise in excess mortality.

3. The “economic miracle” of Japan produced a dramatic decline in overall deaths before 1962. How can this effect be separated from that assigned to the vaccination of schoolchildren?

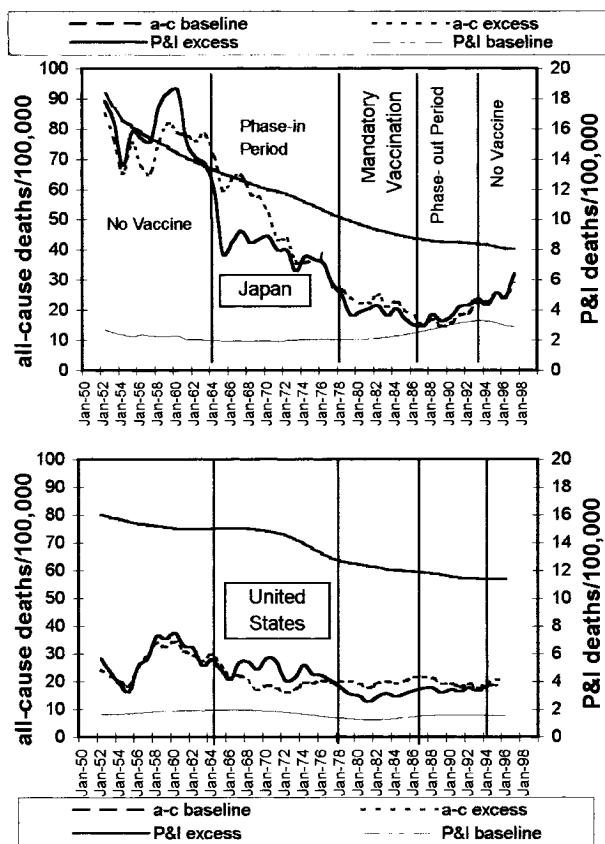
The article describing the “more rigorous model”<sup>38</sup> cited by Fukuda et al<sup>37</sup> was led by one of the coauthors of the paper by Reichert et al.<sup>32</sup> A comparison of the results for excess mortality for the United States, for data allowing the use of both models, demonstrates that the 2 models produce not just a high correlation, but nearly perfect correspondence (Fig 3). Thus, not only will the year-by-year patterns produced by these models be highly similar, except for the shift of 3,200 deaths, but parameters such as deaths averted, which are calculated as a difference between point estimates, will be nearly identical.

Reichert et al<sup>39</sup> demonstrated (cf, their Fig 1) that the summer baseline of both all-cause and pneumonia and influenza mortality rates declined in Japan until 1962 and then rose to the present time. The 5-year moving average for both forms of excess mortality had a form entirely different from the baseline mortalities. During the interval when baseline death rates were falling, excess mortality rates were constant. Then, while baselines began their rise to the present time, excess mortalities fell to one-third of their earlier values for the entire length of the schoolchildren vaccination program. Only when the schoolchildren program was made voluntary and vaccine usage plummeted 50 percent in a single year (1988) did excess mortality rise. The timing of the changes in excess mortality is completely consonant with the elements of the schoolchildren vaccination program. The baseline changes, which were driven by the Economic Miracle and the aging of the population, clearly are unrelated.

Fukuda et al<sup>37</sup> expressed concern that patterns of aging were not addressed specifically and even questioned the conclusion that vaccinating children actually reduced mortality in the elderly. Figure 4 displays the 5-year moving average of summer baseline and excess mortality data for



**Figure 3.** Comparison of estimates of excess (XS) all-cause mortality produced by the method of Reichert et al<sup>32</sup> and that of Simonsen et al<sup>38</sup> for the United States and the years 1968-1995.



**Figure 4.** Five-year moving averages for summer baseline and excess mortality for all-cause deaths and those attributed to pneumonia and influenza (P&I); averages adjusted for shifts in age distribution ( $\leq/\geq 65$  years of age) using annual mortality-by-age data for both Japan and the United States. See footnote. The reference age distribution is that of the United States in 1970.

all-cause and pneumonia and influenza mortality for both Japan and the United States adjusted for population distribution (above and below age 65) using annual mortality-by-age data and referenced to the population age distribution of the United States in 1970.\* Notice that all 4 mortality

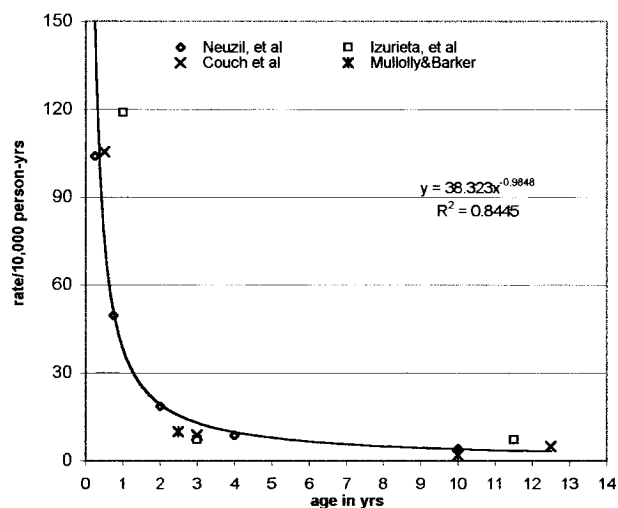
\*Figure 4 is an approximation to the true age adjustment because monthly mortality-by-age data are not yet available for Japan and we did not adjust for aging within the elderly population. The Japanese population aged 85 years and older doubled about every 10 years during the 50 years studied. Age-specific death rates increase with age above 10 to 14 years of age. Given that the fraction of deaths that occur in the elderly is expected to increase during the winter season relative to that in summer, monthly mortality-by-age data should manifest an increase in death rate during the season when excess deaths are measured for those older than 85. Therefore, the use of monthly mortality-by-age data will tend to raise the age-adjusted value. On the other hand, all age-specific death rates have declined over time in both Japan and the United States. This will tend to lower the age-adjusted value for dates near the present. Given these opposing effects, Figure 4 is unlikely to differ substantially from the true result.

trends are similar for the United States, whereas for Japan the 2 excess mortality trends are similar to one another but are very different from the baseline trends, which also are not similar to one another. Moreover, the change in the trend in excess mortality during each period of the Japanese schoolchildren vaccination program is that which would be expected.

With the information that Japanese influenza vaccines were of low titer from 1962 to 1972, that titers were then raised and again in 1977—a reasonable assumption is that the accumulation of herd immunoprotection was a gradual process, which is another feature of expressed concern.<sup>36</sup> In Fig 4, age-adjusted excess mortality rises at the end of the schoolchildren vaccination program and against the continuing fall of age-adjusted, baseline, all-cause mortality. To be sure, the increase after 1990 in excess mortality is reduced from that seen in the unadjusted curves; however, an important perspective to keep is that even age-adjusted, excess mortality in Japan in 1998 was greater than any year since 1970 for pneumonia and influenza and since 1976 for all-cause deaths. 1970 was the redux of the pandemic of 1968, whereas 1976 was the year when the antigenically drifted strain, A/Victoria, eluded vaccine control and caused significant mortality worldwide. In the final analysis, the character of the excess mortality curves for Japan is quite complex and is completely unlike the time course of baseline mortality, unadjusted or adjusted for age, but it is completely consonant with the timing of the schoolchildren vaccination program. For the United States, where no such program was in effect, and where a similar if somewhat lessened aging of the population took place, excess mortality curves and baseline curves vary smoothly and together. The conclusion is inescapable that the Japanese schoolchildren vaccination program reduced mortality in the elderly. The time has come to move forward and integrate this information.

### Should Schoolchildren Be Vaccinated to Protect Society?

The answer to this question has 2 sides. The first side, the case for benefit balanced by hazard and, to a lesser extent, cost, has been discussed at some length.<sup>40,38</sup> That vaccination of children against influenza prevents at least the majority of hospitalizations caused by influenza and is approximately 50 percent effective in preventing respiratory infections sufficiently severe that daily activities are attenuated is without question.<sup>41,42</sup> White et al<sup>40</sup> demonstrated that vaccination of schoolchildren is cost-effective if indirect costs are reasonably accounted for and vaccination is administered in outpatient clinics, but they point out further that the cost-benefit relationship is clear, even without considering indirect costs, if vaccine is administered in a group setting. Costs due to hospitalization are not included in the analysis of White et al because “these events are rarely associated with influenza in healthy children.”<sup>40</sup> At least 4 groups of authors<sup>43-46</sup> have analyzed the risk of excess hospitalization of children for acute respiratory dis-



**Figure 5.** Estimates of excess rates of hospitalization for acute respiratory disease (see footnote) attributable to influenza among non-high risk children during periods in which influenza predominated; data are from 4 groups of authors. Methodologies differ, but the results are consistent and well-characterized by the same relationship with age. The data points are placed at the midpoints of the intervals cited by the authors. Annual hospitalizations of schoolchildren are determined by integrating between 5 and 18 years of age.

ease,<sup>†</sup> and, despite methodological differences, their data are quite similar. At first glance, the assertion of White et al would appear to be correct. However, using the functional trend underlying these data (Fig 5), we estimate the number of excess hospitalizations attributable to influenza for school-age children to be approximately 3.6 per 10,000 children per year. Approximately 54 million children in the United States today are in the age range of 5 to 18 years. If the average cost per hospitalization is approximately \$10,000, then the hospitalization cost for the projected 19,600 annual hospitalizations is \$196 million, or \$3.63 per child. Given the 56 percent effectiveness of the vaccine assumed by White et al, the additional cost savings from the neglected averted excess hospitalizations for acute respiratory disease is sufficient to fund approximately 50 percent of a universal schoolchildren vaccination program. Analyses of other problems, which are very significant in younger children, exhibit a declining incidence in children of school age (for example otitis media), and in which substantial evidence exists for the benefit of influenza vaccination, are certain to produce additional benefits (ie, real cost savings). By dint of a number of such efforts, a determined analyst could incrementally move the balance of evidence arbitrarily further toward the case for vaccination.

<sup>†</sup>Neuzil et al<sup>43</sup> studied acute cardiopulmonary disease but did not state the specific ICD codes used. The specific diseases listed as included (beyond acute respiratory disease), acute heart failure and myocarditis, are rare occurrences in children.

Why then do those who editorialize on the subject<sup>8,47</sup> so often come down on the side of prudence and restraint? They cite the potential of hazards yet unseen in 1 of the most widely used healthcare interventions known to man, yet side effects in adults are entirely negligible. In the Japanese schoolchildren program, the incidence of significant, severe side effects was estimated to be less than 1 per 5 million vaccinations. This low rate is not significantly different from zero.

The inverse proportionality of attack rate with age generally is appreciated. This observation, coupled with the social pattern in all economically developed societies of bringing children together for group care and education, guarantees that children will be the principal carriers of this pathogen to those less able to withstand its effects. Indeed, this matter, too, has been cited for more than 50 years.<sup>48</sup> Models predict that universal vaccination of schoolchildren (~90% coverage) would reduce attack rates by two-thirds in children and by nearly 80 percent in older adults.<sup>49</sup> Reichert et al<sup>32</sup> estimated that all-cause excess mortality was reduced by two-thirds during the Japanese program. Thus, what we have is an intervention of little to no risk with admitted great societal value and of neutral to arbitrarily positive benefit to children, themselves, but for which some unstated basis for counterargument remains. The evidence is clear; nevertheless, arguments for caution clutch at reeds such as concerns for “pincushion fear” in adding one more annual vaccination.<sup>8</sup>

Perhaps, it is time to look at the second side of the question. The other side of benefit is risk and menace. Unvaccinated children are the group most susceptible to influenza within a population. In simulated pandemics,<sup>49</sup> as many as 40 percent of schoolchildren became infectious to others 1 week into the epidemic, whereas no other group ever developed as many as 10 percent infectious members. Furthermore, in all types of pandemics, the peak of school-age infectivity occurred dramatically earlier than did that for other population groups. Reducing school contact to zero attenuated epidemics to 10 percent of the value they would otherwise attain, whereas closing schools for a short period merely prolonged the duration of the epidemic. These simulations suggested that immunization of schoolchildren reduces overall attack rates almost linearly. Therefore, each unvaccinated schoolchild can be considered to represent equal menace to his or her society. Elveback et al<sup>49</sup> found that attack rates were reduced by 8.5 percent for each 10 percent of the schoolchildren cadre vaccinated. A reasonable assumption is that the total cost of the epidemic would be reduced in direct proportion to the attack rate. The pandemic of 1968 to 1969 was estimated by Kavet<sup>50</sup> to have cost the United States \$3.88 billion. The unadjusted excess mortality rates for the population 65 years of age and older for 1997 and 1998 were quite close to the excess mortality rates for this mild pandemic. Therefore, to estimate that the influenza epidemics of 1997 and 1998 each cost the United States a similar amount is not unreasonable. Assuming an inflation rate of 2 percent, this cost translates into \$6.9 billion in 1997 to 1998 for each of these years. The incremental increase in cost to society for each unvaccinated schoolchild is thus approximately [(\$6.3 bil-

lion)/(54 million children)] · (8.5%/10%) or about \$100 per schoolchild. In strict monetary terms, the penalty for *not* vaccinating a schoolchild should be this amount. Parents could be free to choose either to vaccinate their children or to compensate society for the potential harm their unvaccinated children will perpetrate.

Influenza is the “Rodney Dangerfield” of diseases—it gets no respect. Alfred Crosby’s elegant lament skews our entire society, including its epidemiology and clinical medical communities. Perhaps, however, it is that influenza seems to have developed a strategy optimal for a predator, a strategy so subtle that its effects are denied in their magnitude and consequence by its prey.

## Acknowledgment

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