Optimizing Influenza Vaccine Distribution

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The criteria to assess public health policies are fundamental to policy optimization. Using a model parametrized with survey-based contact data and mortality data from influenza pandemics, we determined optimal vaccine allocation for five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs. We find that optimal vaccination is achieved by prioritization of schoolchildren and adults aged 30 to 39 years. Schoolchildren are most responsible for transmission, and their parents serve as bridges to the rest of the population. Our results indicate that consideration of age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines. We also found that previous and new recommendations from the U.S. Centers for Disease Control and Prevention both for the novel swine-origin influenza and, particularly, for seasonal influenza, are suboptimal for all outcome measures.

Vaccination is the principal strategy for reducing the disease burden of many infectious diseases. The evaluation of vaccination policies before their implementation is essential to allocate resources and to minimize disease burden. Outcome measures applied to quantify the success of a vaccination program are fundamental to this evaluation.

Vaccination has the indirect benefit of decreasing transmission, thereby reducing the infection risk even for those who have not been vaccinated. Mathematical modelers of influenza transmission take into account this indirect protection but typically only evaluate outcomes using deaths or infections averted (*1*–*4*). By contrast, ethicists focus on the debate regarding the outcome measure that should be used to prioritize influenza vaccination. Ethicists have proposed outcome measures that incorporate valuation based on the ages of victims (*5*–*7*). For example, in terms of years of life lost, children would be valued over adults. Young adults are prioritized by measures based on surveying public values attributed to people at different ages (*7*, *8*). Another alternative outcome measure is the economic cost, including age-specific mortality costs (*9*, *10*). However, ethicists and health economists neglect the transmissible nature of influenza in making their recommendations about which age groups should be targeted for interventions (*11*). For example, children are responsible for a disproportionate amount of influenza transmission (*12*–*19*), which affects age-specific vaccination policies (*20*–*22*). Thus, it is necessary to take into account transmission dynamics to determine optimal vaccination policy for the community overall, which depends on which of the different outcome measures is used.

Levels of annual influenza vaccination were estimated from the 2007 National Health Interview Survey (*23*) as 34% for people aged 0 to 4, 20% for those aged 5 to 19, 17% for those aged 20 to 49, 35% for those aged 50 to 64, and 63% for those older than 64 years (fig. S15), totaling about 85 million vaccine doses. The influenza vaccine must be updated annually to keep pace with the antigenic evolution of influenza. In addition, zoonosis can lead to the emergence of influenza subtypes, such as the novel swine-origin influenza virus. Consequently, manufacturing of influenza vaccine follows a tight schedule to achieve sufficient doses (*24*). This schedule is also vulnerable to disruptions, as evidenced by the vaccine contamination that left the United States short on doses in 2004 to 2005 (*25*). The World Health Organization recently announced that the unusually slow growth of swine-origin H1N1 in chicken eggs may cause shortfalls in current production of vaccine this year (*26*). When vaccine availability is limited or when vaccine efficacy is low, optimal allocation of vaccines is imperative. Nonetheless, vaccine allocation can also be improved when vaccine is plentiful and highly efficacious. We evaluated current vaccine allocation policies based on the optima derived from multiple outcome measures. We also compared the outcome measures when vaccine availability and efficacy vary, an understanding of which will be fundamental to

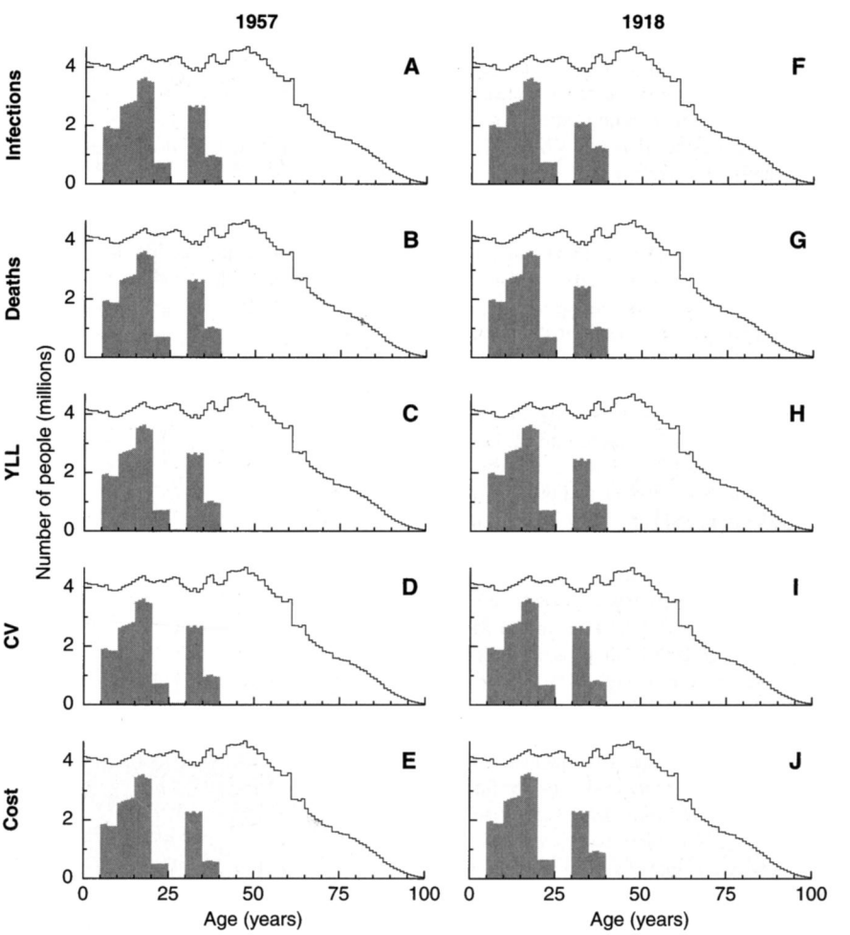

Fig. 1. (A to J) Optimal age-specific vaccine allocation with just enough vaccine doses for eradication. For an outbreak with the 1957 mortality pattern, 63 million vaccine doses lead to eradication, whereas 62 million vaccine doses were required for eradication of an outbreak with the 1918 mortality pattern. The line indicates the 2007 U.S. population by age, and the shaded area is the proportion of each age group vaccinated under the optimal strategies for each outcome measure (labeled at the far left). YLL is years of life lost.

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the allocation of vaccine doses during the current outbreak of swine-origin influenza.

To evaluate vaccination strategies for the different outcome measures, we developed an age-structured model that incorporates transmission dynamics (*27*). We applied an optimization routine that identifies the optimal strategy for each outcome measure. Rather than comparing the efficacy of just a few specific vaccination policies, as is often done in modeling, our routine allows us to find the optimal vaccine distribution, essentially evaluating all possible age-based vaccination policies. We compared patterns of influenza A transmission and mortality in the United States, parametrized with survey-based contact data (*28*) and mortality data from the 1957 and 1918 pandemics. These two pandemics had qualitatively different patterns of mortality. Both of these pandemics infected 25 to 30% of the U.S. population, but there were about 6 times as many deaths from the 1918 pandemic in a 40% smaller population, a 10-fold difference in per capita mortality (*29*). The elderly suffered the greatest mortality in the 1957 pandemic, whereas infants and young adults suffered the highest mortality during the 1918 pandemic (fig. S2) (*29*–*31*). The 1957 mortality pattern is representative both of seasonal influenza and of the 1968 pandemic. Because of the uncertainty of the mortality patterns of future outbreaks, we considered mortality based on both the 1957 and 1918 pandemics.

The model tracks 17 age groups for the 2007 U.S. population: ages 0, 1 to 4, 5 to 9, 10 to 14, ..., 70 to 74, and 75 and older. For the duration of the incubation period, we used 1.2 days and 4.1 days for the duration of the infectious period (*32*). Sensitivity analysis was also performed with regard to vaccine efficacy, but baseline age-dependent vaccine efficacy against infection was 80% for 0 to 64-year-olds and 60% for those 65 and older (*4*, *33*), and age-dependent vaccine efficacy against death, if infected, was 75% for 0 to 19-year-olds, 70% for 20- to 64-year-olds, and 60% for those 65 and older (table S1) (*4*, *34*). We assumed that the basic reproductive number (R_0), defined as the number of secondary cases caused by a single infective case in a completely susceptible population (*35*), was $R_0 = 1.4$, as estimated for the novel swine-origin H1N1 influenza outbreak (*36*), although we also considered $R_0 = 1.2$, 1.6, 1.8, and 2.0. Age-specific death rates were based on estimates of excess pneumonia and influenza deaths from the 1957 and 1918 pandemics (fig. S2) (*30*, *31*). We parametrized age-specific contact rates using data from a large-scale survey of daily contacts (*28*). These contact data show strong mixing between people of similar ages and moderately high mixing between children and people of their parents' ages (fig. S3).

We determined the optimal age-specific distribution of a limited number of vaccine doses for five different outcome measures. The first two were simply total infections averted and total deaths averted. We also used years of life lost, weighing deaths by the expected remaining years of life for different ages. An additional measure was "contingent valuation" (*10*), derived from a survey of 3000 U.S. households (*8*) to give the disutility of deaths at each age. This measure resulted in a valuation similar to "the investment refinement" principle (*7*), wherein young adults are most valued. Finally, for the outcome measure of economic cost, we included costs associated with

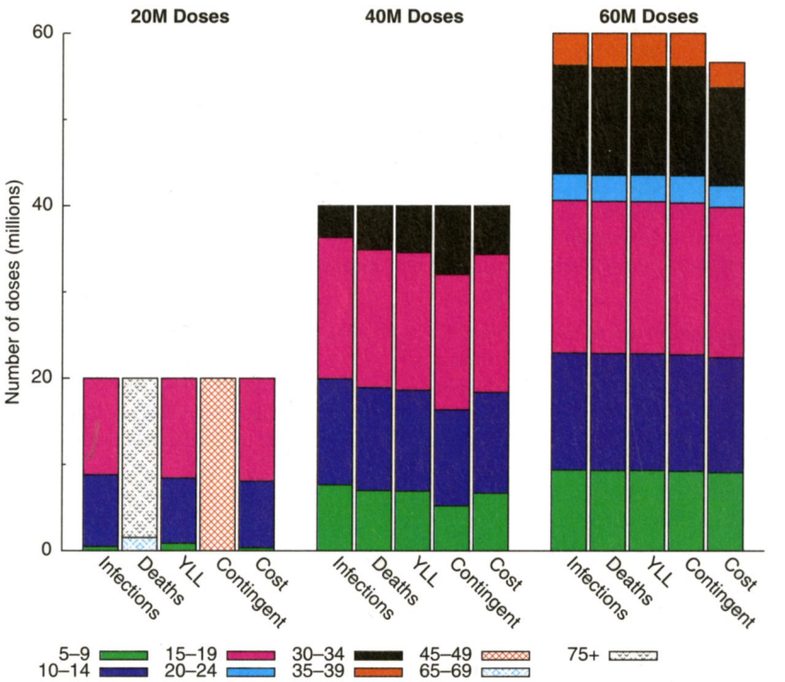

Fig. 2. Number of vaccines optimally distributed to each age group under the 1957 mortality pattern for 20 million, 40 million, and 60 million available vaccine doses, based on each outcome measure. Fewer than 60 million vaccine doses are used for the outcome measure of cost because the cost of vaccination (including side effects) is larger than its benefits when infection is unlikely because of herd immunity.

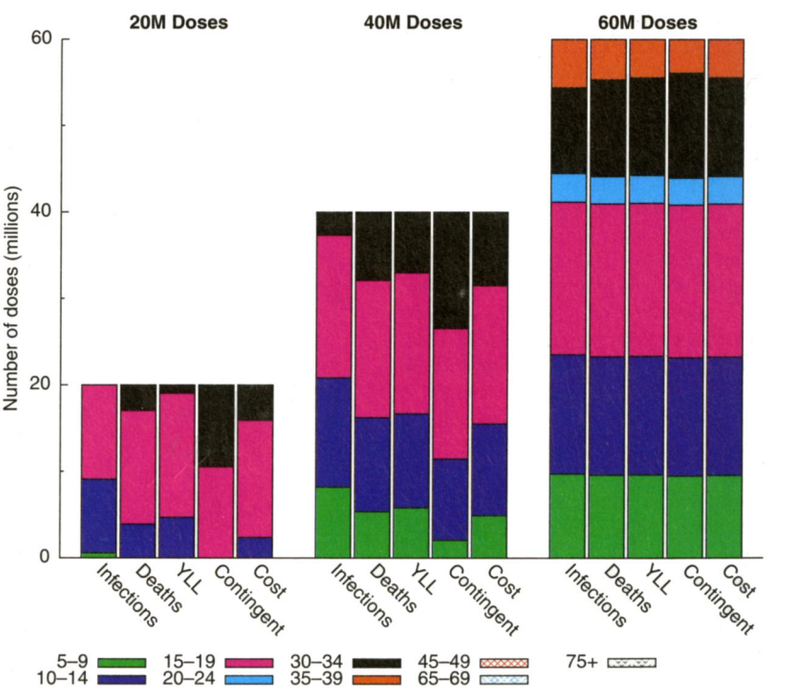

Fig. 3. Number of vaccines optimally distributed to each age group under the 1918 mortality pattern for 20 million, 40 million, and 60 million available vaccine doses, based on each outcome measure.

vaccination, as well as those associated with illness (table S2) (*4*, *34*), and valued death using net present value of future lifetime earnings (*9*). Given that the value of future earnings is highest for young adults, this age group is most valued. The optimal vaccine distribution was then calculated using a numerical optimization routine for each outcome measure.

For our model influenza outbreak with R_0 = 1.4 and a mortality pattern similar to that in 1957, the optimal distribution of 63 million vaccine doses can extinguish the outbreak, whereas for the model influenza outbreak with a 1918 mortality pattern, 62 million vaccine doses can prevent the outbreak (fig. S14). Both of these totals are less than the 85 million vaccine doses that are currently administered annually for seasonal influenza. The optimal vaccine distribution in both cases is vaccination of people aged 5 to 19 and 30 to 39 (Fig. 1). Children 5 to 19 (*37*) are responsible for most transmission and for the spread of infection to their parents' age groups. Thus, both those most responsible for transmission and those they are most likely to infect are prioritized, which in turn protects the remainder of the population. These results indicate that transmission must be explicitly considered when optimizing vaccine allocation.

To assess the effect of vaccine supply, we determined the optimal allocation of a range of available vaccine doses for both outbreaks (Figs. 2 and 3). When at least 37 million vaccine doses are available, all outcome measures prioritized vaccinating people aged 5 to 19 and 30 to 39 for the 1957 mortality pattern (Fig. 2 and fig. S7). Below 37 million vaccine doses, the outcome based on total deaths switched to prioritizing the elderly. Below 36 million vaccine doses, contingent valuation switched to prioritizing those aged 45 to 49 due to a combination of the economic productivity and greater infection severity of this age group. For the 1918 mortality pattern, all outcome measures were optimized by vaccinating people aged 5 to 19 and 30 to 39 (Fig. 3 and fig. S8).

Among the most fundamental characteristics of an influenza outbreak is its basic reproductive number, R_0. The baseline scenario assumed R_0 = 1.4, chosen as an estimate for swine-origin H1N1 influenza (*36*). We also considered one less severe outbreak (with R_0 = 1.2) and three more severe outbreaks (R_0 = 1.6, 1.8, and 2.0) (*27*). When R_0 = 1.2, optimal vaccination only included ages 5 to 19 for all levels of vaccine availability and for both mortality patterns (figs. S16 and S17). For increased R_0 values, the outcome measure of infections averted continued to be optimized by allocation to children (ages 5 to 19) and added vaccination of adults 20 to 44 as more vaccine became available (figs. S18 to S23). Generally, for the outcome measures other than infections averted, as R_0 increased above, more vaccine doses were allocated to those at greatest risk of mortality. For 1957 mortality, older adults were added to some of the optimal allocations, first ages 65 and older, and then ages 45 to 64 for higher R_0. Young adults 20 to 44 were added for higher R_0 for the 1918 mortality pattern. In addition, for 1918 mortality, it was never optimal to vaccinate adults 45 and older for any level of R_0 or vaccine availability. For all values of R_0, when vaccine supply was plentiful, optimal allocation was vaccinating children and younger adults (20 to 44). The switch from protecting those at risk of mortality to those responsible for transmission occurred at higher levels of vaccine availability as R_0 increased. In all cases, deaths averted was the last outcome measure to switch to children and younger adults; other outcome measures switched markedly earlier in some cases.

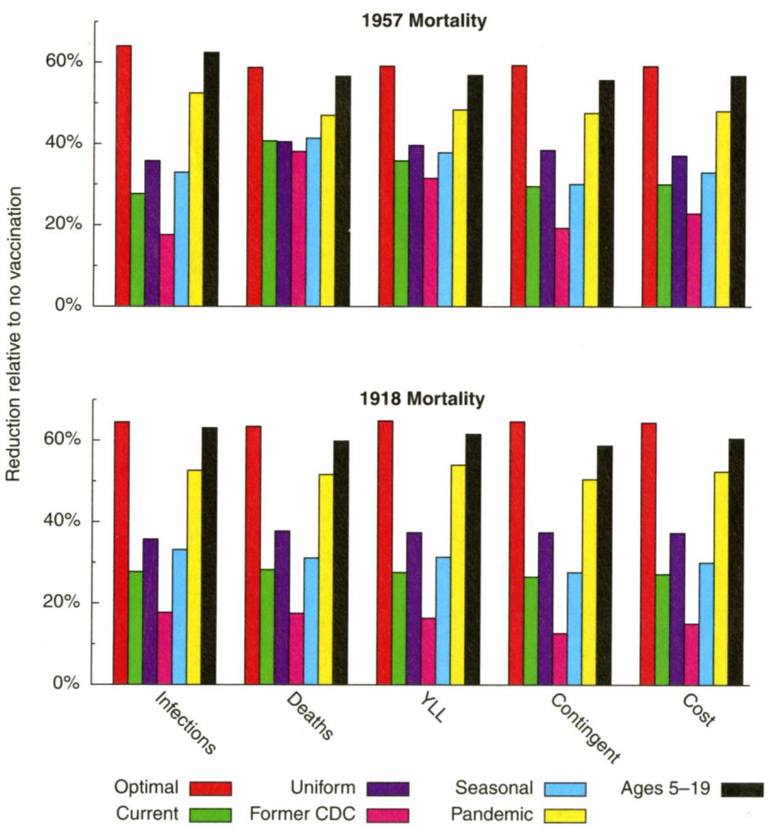

Fig. 4. Comparison of outcomes between optimal and alternative vaccination strategies for 40 million vaccine doses relative to a pandemic in an unvaccinated population for both 1957 (**top**) and 1918 (**bottom**) mortality patterns. We compare reductions in the five outcome measures resulting from the allocation of 40 million vaccine doses for seven different strategies: the strategy that optimizes the outcome measure (Optimal), the current levels of vaccination in the U.S. population (Current), uniform coverage of all age groups (Uniform), the former CDC age-based recommendations (Former CDC), the new CDC age-based recommendations for seasonal influenza (Seasonal), the new ACIP age-based recommendations for the novel swine-origin influenza (Pandemic), and uniform coverage of ages 5 to 19 (Ages 5–19). For each measure, the optimal distribution did markedly better than the strategies based on the CDC and ACIP recommendations.

The efficacy of the influenza vaccine varies from year to year. It is likely to be low for a zoonotic influenza strain, such as the currently circulating swine-origin influenza, and it is useful to be able to predict what might happen if vaccination strategies have reduced efficacy. Under these circumstances, we separated vaccine efficacy against infection and vaccine efficacy against mortality in our sensitivity analysis (*27*). For all outcome measures except infections averted, reducing vaccine efficacy against infection elevated prioritization of vaccinating those at greatest risk of mortality when vaccine supply was very limited (figs. S24 and S25). Reduced vaccine efficacy against death had a small effect on vaccine distribution when optimizing for any of the outcome measures (figs. S26 and S27). For novel influenza strains, older people may have acquired immunity from distant previous exposure. Such reduced susceptibility to the novel swine-origin H1N1 influenza may be present in the elderly (*38*). Incorporating this effect into our model resulted in the optimal vaccination no longer including the elderly for the one setting in which they were included in the baseline case: the 1957 mortality pattern with the outcome measure of deaths averted. Otherwise, the effect of reduced susceptibility on optimal vaccine allocation in the elderly was minimal (figs. S28 and S29). We also tested the impact of vaccination reducing the severity of infection by shortening the duration of infection and by decreasing infectiousness. Both shortened infection duration and reduced

infectiousness among vaccinees had little effect on optimal vaccine allocation (figs. S30 to S33).

Until the 2008 to 2009 influenza season, the U.S. Centers for Disease Control and Prevention (CDC) recommended for seasonal influenza the vaccination of children aged 6 months to 5 years old and of adults aged 50 and over. The CDC recommendations for seasonal influenza vaccination were expanded in 2008 to include children through age 18 (*33*). Recently, the CDC's Advisory Committee on Immunization Practices (ACIP) proposed guidelines for vaccinating against the novel swine-origin influenza that prioritize young people aged 6 months to 25 years (*39*), excluding the elderly due to their apparent reduced susceptibility (*38*).

We found that the previous as well as the new CDC policies for seasonal influenza performed substantially worse than our optimal strategies for all outcome measures (Fig. 4). For example, when at least 40 million vaccine doses are available for an outbreak with $R_0 = 1.4$, the entire population would be better protected by vaccinating schoolchildren (Figs. 2 and 3), who were not targeted by the previous CDC policy. In our model, the allocation of 40 million vaccine doses according to the previous CDC policy during an outbreak with the 1957 mortality pattern resulted in 102 million infections, 162,000 deaths, and a total cost of $99 billion. The new CDC policy for seasonal influenza led to 83 million infections, 153,000 deaths, and $86 billion in cost. The ACIP policy for swine-origin influenza resulted in 59 million infections, 139,000 deaths, and $67 billion in cost. In contrast, the optimal strategies resulted in only 44 million infections, 108,000 deaths, and a total cost of $53 billion. For the 1918 mortality pattern with 40 million vaccine doses, the previous CDC recommendations resulted in 102 million infections, 1.5 million deaths, and a total cost of $1.7 trillion. The new CDC seasonal-influenza policy led to 83 million infections, 1.2 million deaths, and $1.4 trillion in cost. The ACIP policy for swine-origin influenza produced 59 million infections, 853,000 deaths, and $939 billion in cost. Our proposed optimal strategies resulted in 44 million infections, 645,000 deaths, and a cost of $703 billion. The strategy of distributing vaccines uniformly to ages 5 to 19 also performed markedly better than the CDC and ACIP policies. Moreover, with the exception of the outcome measure of deaths averted when the mortality pattern is based on 1957, the CDC policies for seasonal influenza even performed worse than uniform allocation across all age groups, primarily as a result of the inefficient allocation of vaccine doses to the elderly and newborns. The CDC and ACIP's age-based recommendations could be substantially improved by reducing the prioritization of the elderly and children under age 5, although the recent vaccination recommendations for swine-origin H1N1 show marked improvement over the recommendations for seasonal influenza.

For this particular comparison ($R_0 = 1.4$ with 40 million vaccine doses), the optimal allocations prevent substantial transmission, whereas the CDC and ACIP recommended policies do not, particularly those for seasonal influenza. For an outbreak with higher R_0, when fewer vaccine doses are available, or when vaccine efficacy is low, the CDC and ACIP policies may be closer to optimal, depending on the outcome measure used. [The CDC and ACIP policies are likely closer to optimal for deaths averted (figs. S7, S18, S20, and S22.)] However, given the broad conditions under which vaccination of children and younger adults is optimal, such a policy is likely optimal except during severe vaccine shortages.

An age-structured mathematical model of influenza transmission has allowed us to determine the optimal allocations of vaccine doses for a variety of measures of population morbidity and mortality. Our results illustrate the importance of explicitly considering transmission when allocating vaccines, regardless of how vaccination outcomes are quantified. Our comparison with CDC and ACIP recommendations for both seasonal influenza and the novel swine-origin influenza suggest that CDC and ACIP recommendations are below optimum for all outcome measures, although recommendations for swine-origin H1N1 are a substantial improvement.

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References

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