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Health and Economic Benefits of Early Vaccination and Nonpharmaceutical Interventions for a Human Influenza A (H7N9) Pandemic

A Modeling Study

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Background: Vaccination for the 2009 pandemic did not occur until late in the outbreak, which limited its benefits. Influenza A (H7N9) is causing increasing morbidity and mortality in China, and researchers have modified the A (H5N1) virus to transmit via aerosol, which again heightens concerns about pandemic influenza preparedness.

Objective: To determine how quickly vaccination should be completed to reduce infections, deaths, and health care costs in a pandemic with characteristics similar to influenza A (H7N9) and A (H5N1).

Design: Dynamic transmission model to estimate health and economic consequences of a severe influenza pandemic in a large metropolitan city.

Data Sources: Literature and expert opinion.

Target Population: Residents of a U.S. metropolitan city with characteristics similar to New York City.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Vaccination of 30% of the population at 4 or 6 months.

Outcome Measures: Infections and deaths averted and cost-effectiveness.

Results of Base-Case Analysis: In 12 months, 48 254 persons would die. Vaccinating at 9 months would avert 2365 of these deaths. Vaccinating at 6 months would save 5775 additional lives and $51 million at a city level. Accelerating delivery to 4 months would save an additional 5633 lives and $50 million.

Results of Sensitivity Analysis: If vaccination were delayed for 9 months, reducing contacts by 8% through nonpharmaceutical interventions would yield a similar reduction in infections and deaths as vaccination at 4 months.

Limitation: The model is not designed to evaluate programs targeting specific populations, such as children or persons with comorbid conditions.

Conclusion: Vaccination in an influenza A (H7N9) pandemic would need to be completed much faster than in 2009 to substantially reduce morbidity, mortality, and health care costs. Maximizing nonpharmaceutical interventions can substantially mitigate the pandemic until a matched vaccine becomes available.

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Two events have raised concerns about our preparedness for a severe influenza pandemic: Separate scientific groups recently published methods for genetically engineering an influenza A (H5N1) virus that may be capable of aerosol transmission between humans (1, 2); and a novel influenza virus, A (H7N9), is causing alarming morbidity and mortality in human infections throughout China (3). In addition, a new influenza virus, A (H10N8), was recently reported and associated with a human fatality (4). These developments offer an invaluable opportunity to evaluate our response to the 2009 influenza A (H1N1) pandemic and technologic advances since then to prepare for a severe influenza pandemic.

See also:

Web-Only
Supplements

In our previous work assessing efficacy of vaccination in the 2009 pandemic, we found that timing was crucial, with as little as a 4-week delay resulting in a substantial increase in infections, deaths, and costs. However, large-scale vaccination against 2009 influenza A (H1N1) occurred 9 months after the beginning of the pandemic, which is substantially later than the timing we found would have maximized health and economic benefits (5). The mortality rates of influenza A (H5N1) and A (H7N9) are remarkably high (59% and 19%, respectively) compared with a rate of less than 0.3% from A (H1N1) in 2009 (3, 6, 7). These data may be overestimated because of incomplete ascertainment of cases; nonetheless, the observed mortality rate remains a critical concern. If these viruses were lethal and transmissible between humans, a resulting pandemic would have more devastating health and economic consequences than in 2009.

Advances in cell-based and recombinant vaccine (8) technologies could allow faster mass vaccination than current egg-based methods (9). To evaluate our progress and

preparedness for a more severe outbreak than the mild 2009 pandemic, we modeled a severe pandemic caused by a virus with characteristics similar to those of influenza A (H7N9) and A (H5N1). We wanted to assess the value of accelerating vaccine production with new technologies. We evaluated effectiveness and cost-effectiveness of no vaccination or vaccination at 4 or 6 months versus 9 months.

Context

Determining how best to prepare for future influenza pandemics is urgent.

Contribution

In a model, widespread delivery of vaccine by 4 and 6 months decreased infections and deaths while saving health care costs compared with vaccine delivery at 9 months. Nonpharmaceutical strategies, such as the use of facemasks, hand washing, and social distancing, if fully utilized, were similar to delivering vaccine by 4 months.

Caution

The model was developed for a major U.S. city.

Implication

Accelerated vaccination and maximization of nonpharmacologic measures are strategies that should be considered in planning a response to future influenza pandemics.

—The Editors

METHODS

Overview

We created a dynamic transmission model of progression of a severe pandemic caused by a virus with characteristics similar to those of influenza A (H7N9) and A (H5N1) in a susceptible population (**Table 1** and **Appendix Figure 1**, available at www.annals.org). We evaluated vaccine interventions coupled with nonpharmaceutical interventions (NPIs). In accord with recommendations from the Panel on Cost-Effectiveness in Health and Medicine (10), we conducted the analysis using a societal perspective and discounted costs and benefits at 3% annually. We analyzed health and economic outcomes over the remaining lifetimes of the population. We measured outcomes in infections and deaths averted, costs, and cost savings. We constructed the model and did analyses in Microsoft Excel, version 2010 (Microsoft, Redmond, Washington) (11). We provide an annotated version of the model (**Supplement 1**, available at www.annals.org) so that readers can test model output for different assumptions and circumstances.

Study Population and Disease Variables

Susceptible Population

We modeled a population of 8.3 million persons in a large metropolitan U.S. city with demographic characteristics similar to those of New York City (12). We assumed 1000 persons were infected at the start of the pandemic. In the absence of documented influenza A (H7N9) human infection in the United States (6), we assumed no preexisting population immunity.

Infected Population

We assumed a severe pandemic, similar to the 1918 Spanish influenza pandemic, with an R_0 (the reproductive number; secondary infections caused by each infected person in a susceptible population), of 2.0 (13). We varied R_0 between 1.8 and 2.2 in sensitivity analysis.

On the basis of previous studies (14–16), we assumed that 67% of infected persons were symptomatic and 50% of them were socially isolated, either voluntarily because of symptoms or involuntarily because of hospital admission. We assumed that the nonisolated 50% continued to infect others.

On the basis of observations of the 2009 influenza A (H1N1) outbreak (17), we assumed that the mean incubation period was 3 days. On the basis of Centers for Disease Control and Prevention (CDC) estimates (18, 19), we assumed persons to be symptomatic for 10 days and infectious for 4 days. In sensitivity analysis, we varied infectivity between 3 and 7 days. We extrapolated from previous influenza A studies (19, 20) that symptomatic persons transmitted the disease 3 times faster than asymptomatic persons.

Using CDC data, we estimated that 10% of persons with symptomatic infection would require 5 days of hospitalization, and 10% of that population would be admitted to the intensive care unit for 10 days (21).

Recovered Population

Studies find a 2% to 25% (22, 23) risk for reinfection with influenza A viruses. Reinfected persons tend to be asymptomatic or have moderate symptoms, a shorter duration of illness, and less viral shedding (23). We assumed that 5 months after recovery, 5% of the recovered population would become susceptible to reinfection. In sensitivity analysis, we analyzed reinfection rates ranging from 2% to 25%.

Death From Influenza

The mortality rates from influenza A (H7N9) and A (H5N1) infections (6) may be overestimated because asymptomatic and mildly symptomatic infections were undercounted (24, 25). However, mortality rates may be greater in resource-limited health care settings (7). We therefore assumed a 2.5% mortality rate for our model, which is much lower than the observed naturally occurring rate. In sensitivity analysis, we examined mortality rates ranging from 0.5% to 10%. We allowed age-specific mortality to vary, with increased rates in newborns and persons older than age 65 years, which is consistent with the 1957 and 1968 pandemics and seasonal influenza epidemics

Table 1. **Variables and Sources**

Variable	Base Case (Range)	Source (Reference)
Susceptible population characteristics		
Population, *n*	8 175 133	U.S. Census Bureau (12)
Age range, *y*	0–100	U.S. Census Bureau (12)
Women, %	53	U.S. Census Bureau (12)
Preexisting population immunity, %	0 (0–10)	Assumed; WHO (56)
Infected population characteristics		
Infected persons at start of pandemic, *n*	1000 (100–10 000)	New York City Department of Health and Mental Hygiene (57), Longini et al (15)
Infectiousness		
R_0*	2.0 (1.8–2.2)	Assumed; CDC (58, 59)
Reduction in R_0 from nonpharmaceutical interventions, %*	25 (0–50)	Assumed; Davey et al (39)
Mean duration of infectiousness, *d*	4 (3–7)	Hayden et al (19), Leekha et al (20)
Probability of asymptomatic infection, %	33 (10–50)	Ferguson et al (14), Longini et al (15), Fox et al (16)
Infectiousness by asymptomatic (relative to symptomatic) persons, %	25 (10–50)	Hayden et al (19), Atkinson and Wein (60)
Probability of symptomatic infection, %	67 (10–50)	Ferguson et al (14), Longini et al (15), Fox et al (16)
Mean duration of symptomatic illness, *d*	10.0 (7.5–12.5)	CDC (18), Hayden et al (19)
Probability of isolating given symptomatic infection, %	50.0 (37.5–62.5)	Longini et al (15)
Probability of inpatient care, %	20 (2–40)	CDC (61, 62)
Mean duration of non-ICU inpatient stay, *d*	5.00 (3.75–6.25)	CDC (21), HHS (63)
Probability of ICU inpatient stay, %	20 (10–30)	CDC (21), HHS (63)
Mean duration of ICU stay, *d*	10.0 (7.5–12.5)	CDC (21), HHS (63)
Incubation		
Mean incubation time, *d*	3 (1–7)	CDC (18), WHO (56)
Reduced infectiousness by incubating persons, %	50.0 (10.0–62.5)	Hayden et al (19), Atkinson and Wein (60)
Recovered population characteristics		
Susceptibility to reinfection after recovery, %	5 (2–25)	Smith et al (22), Monto et al (23)
Timing of waning immunity, *mo*	5 (2–8)	Smith et al (22), Monto et al (23)
Mortality		
Case-fatality rate, %	2.5 (0.5–10.0)	Assumed; CDC (18), WHO (56), HHS (63), Li et al (64), Taubenberger and Morens (65)
Mortality threshold for reactive social distancing, *n per 10 000 persons*	10 (5–50)	Bootsma and Ferguson (27)
Reactive social distancing memory period, *d*†	30 (1–40)	Bootsma and Ferguson (27)
Vaccination		
Population coverage, %	30 (10–50)	Assumed
Effectiveness, %	56 (30–80)	Griffin et al (66)
Mild to moderate adverse effects, %	45 (5–75)	European Medicines Agency (30), GlaxoSmithKline Canada (31)
Duration, *d*	2 (1–7)	European Medicines Agency (30), GlaxoSmithKline Canada (31), CDC (67)
Reduction in quality of life‡§	0.05 (0.00–0.10)	European Medicines Agency (30), GlaxoSmithKline Canada (31), CDC (67)
Severe adverse effects, %	0.001 (0.000–0.010)	Neustadt and Fineberg (32), Partinen et al (33), Nohynek et al (34)
Duration of hospitalization, *d*	14 (7–28)	Chió et al (68)
Reduction in quality of life‡§	0.5 (0.0–1.0)	Assumed; Neustadt and Fineberg (32)
Risk for death, %	5 (1–10)	Chió et al (68)
Risk for long-term care, %	5 (1–10)	Mendell et al (69)
Influenza-related quality of life‡		
Uninfected or asymptomatic	0.96 (0.92–1.00)	Fryback et al (47), U.S. Census Bureau (12)
Symptomatic influenza	0.8 (0.7–0.9)	Turner et al (70)
Postinfluenza disabled state for patients requiring ICU care	0.90 (0.85–0.95)	Assumed
Costs		
Vaccine		
Cost per dose, *$*	9.04 (6.78–11.30)	CDC (71)
Administration, *$*	6.04 (6.55–10.91)	Bureau of Labor Statistics (72)
Patient time, *h*	11.64 (5.82–23.28)	Bureau of Labor Statistics (73)

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Table 1—**Continued**

Variable	Base Case (Range)	Source (Reference)
Daily health care costs, $		
Patient with severe adverse effects (treated in ICU)	3902 (2926–4877)	Desta et al (42)
General medical hospitalized patient	1910 (1433–2388)	Talbird et al (41)
ICU hospitalized patient	3902 (2927–4878)	Desta et al (42)
Long-term treatment facility costs	327 (245–408)	Metlife (74)
Long-term health expenditures	24.53 (18.40–30.66)	Centers for Medicare & Medicaid Services (46)
Other		
Annual discount rate, %	3 (0–5)	Weinstein et al (10)

CDC = Centers for Disease Control and Prevention; HHS = U.S. Department of Health and Human Services; ICU = intensive care unit; WHO = World Health Organization.
* R_0, the reproductive number, is the number of secondary infections caused by each infected person in a susceptible population.
† Historic pandemic phenomenon in which persons in the population reduce social contacts in reaction to recent high mortality in the community. The "memory period" provides a precise definition of "recent" to describe the mortality. It is a number of days over which mortality is averaged. For example, if the memory period were 2 d, persons would reduce social contacts if average mortality in the past 2 d were high. If the "mortality period" were 60 d, persons would reduce contacts if the average mortality over the past 60 d were high.
‡ Quality-of-life variables represent a person's preference for a given state of health and are scaled from 0 to 1 (perfect health).
§ Reduction of quality of life in our model represents duration of reduction multiplied by quantity of decrement.

(18). In sensitivity analysis, we examined additional increases in mortality rates in young adults, which occurred in the 1918 and 2009 pandemics (26). On the basis of previous pandemics (27), we assumed that healthy persons would limit social interactions as mortality rates in the city increased.

Interventions

Vaccination

Consistent with information on pandemic vaccine effectiveness in 2009 (28), we assumed an effectiveness of 56% and varied effectiveness from 30% to 80% in sensitivity analysis.

On the basis of U.S. vaccination coverage in the 2009 influenza A (H1N1) pandemic and the 1947 smallpox vaccination campaign in New York City (29), we estimated that a mass vaccination exercise in a U.S. city of 8.3 million people could inoculate 30% of the population in 10 days.

We anticipated that 45% of vaccinated persons would experience mild to moderate adverse effects, such as pain, redness, swelling, fatigue, headache, arthralgia, myalgia, shivering, sweating, and low-grade fevers, on the basis of 2009 influenza A (H1N1) vaccine studies (30, 31). Although we assumed a nonadjuvanted vaccine, we drew from adjuvanted vaccination data in Europe in 2009 and vaccination campaigns in 1976 and assumed that 0.001% of vaccinated persons would have severe adverse effects, such as angioedema, anaphylaxis, narcolepsy, or the Guillain–Barré syndrome (32). We varied this number to 0.01% in sensitivity analysis, which yielded a rate of narcolepsy more than twice that seen with European adjuvanted 2009 influenza A (H1N1) vaccines (33, 34).

NPIs

The World Health Organization and CDC recommend concurrent use of nonpharmaceutical and pharmaceutical interventions to mitigate influenza pandemics (35). Nonpharmaceutical interventions include closures of school and child care facilities; home isolation; cough etiquette; hand washing; use of alcohol-based hand gels; and protective personal equipment, such as facemasks. Randomized trials of facemasks, hand hygiene, and social distancing have shown a reduction of transmission rates from 66% to 75% (36, 37). On the basis of available data (38, 39), our model assumes NPIs reduce contacts by 25%. We also examined effects of a 50% to 90% reduction in contacts in sensitivity analysis.

Cost and Utilities

We expressed all costs in 2012 U.S. dollars using the gross domestic product deflator (40). Our model incorporates costs associated with vaccination (including vaccine, administration, persons' time, and treatment of adverse effects) and normal lifetime health expenditures for all persons who survive the pandemic (**Table 1**). Treatment costs are based on an average hospitalization for symptomatic influenza infection (41) or admission to the intensive care unit (42). We used 1 hour of average wages to estimate the opportunity cost of receiving the vaccine (43). We used EuroQol-5D (44) and time-tradeoff ratings (45) for utility estimates and accounted for the average remaining lifetime of persons alive at the end of the year. We calculated long-term health expenditures by age based on personal health care expenditure from the age tables of the Centers for Medicare & Medicaid Services (46). We calculated remaining life-years using New York census data (12) and quality-of-life adjustments based on age- and sex-specific utilities from the Beaver Dam Health Outcomes Study (47).

Sensitivity Analysis

We used sensitivity analysis to account for uncertainties. We measured ranges from data sources or by adding or subtracting 25% from the base case.

Table 2. **Health and Economic Outcomes for a City of 8.3 Million Persons**

Outcome	No Vaccination	Vaccination Time*		
		9 mo	6 mo	4 mo
Symptomatic infections, *n*	1 920 514	1 834 584	1 604 262	1 378 271
Deaths, *n*	47 851	45 889	40 114	34 481
Persons still susceptible to infection, %	68	70	76	81
Deaths averted after vaccination, *n*†	–	–	5775	11 408
Reduction in contacts via NPIs required to decrease widespread transmission, %‡	50	29	34	39
Vaccination costs (millions), $	–	140	140	140
Short-term treatment cost savings (millions), $	–	–	51	50
Long-term lifetime health expenditures (millions), $§	–	–	1417	1390
Incremental total costs (millions), $	–	–	1367	1339
QALYs gained*	–	–	127 460	125 309
ICER, $/QALY†	–	–	10 722	10 689

ICER = incremental cost-effectiveness ratio; NPI = nonpharmaceutical intervention; QALY = quality-adjusted life-year.
* Since start of pandemic in target city.
† Compared with vaccination at 9 mo.
‡ R_0 (the number of secondary infections caused by each infected person in a susceptible population) ≤1. End of pandemic by epidemiologic definitions.
§ Vaccinating earlier averts infections and deaths, resulting in short-term treatment cost savings. However, this increases long-term costs because more persons survive to have average life expectancies with associated medical costs. Accounting for the health care expenditures of persons whose lives are saved, total costs increase in the long term. Long-term costs of vaccination at 4 mo are compared with those at 6 mo, and costs of vaccination at 6 mo are compared with those at 9 mo.

Role of the Funding Source

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

RESULTS

Model Validation

Compared with the 1918 pandemic (27), our model had a similar clinical attack rate (33% vs. 30% to 40%) and first pandemic wave duration (50 days vs. 55 to 60 days). Our model's clinical attack rate and first wave duration were also within the estimated ranges of other published models (39).

Health Outcomes

If no vaccination were performed, 1.92 million persons would become symptomatically infected and 48 254 would die (**Table 2**). For a mortality rate of 2.5%, vaccination can reduce daily mortality by 85% to 92% (**Figure 1**).

In the base case, assuming 9 months were needed for vaccination (an interval similar to that seen in the 2009 pandemic), the first and second waves would have passed, and vaccination would avert 85 930 infections and 2365 deaths.

If vaccination could be completed at 6 months, the original planned time frame during the 2009 pandemic (48), the first epidemic wave would already have passed. Vaccination would avert approximately 230 321 additional infections and 5775 additional deaths, relative to vaccinating at 9 months.

Nearly 85% of the population would still be susceptible to infection 4 months after the start of the pandemic. If DNA and cell-based vaccine technologies allowed vaccination to be completed in 4 months (49), it would have the most substantial effect and avert 225 992 additional infections and 5633 additional deaths, relative to vaccinating at 6 months (**Table 2**).

Costs of Vaccination

Vaccinating 30% of the population at 9 months would cost the government $5.3 billion nationally or $140 million for a city like New York: $45 million for the vaccine, $30 million for distribution, $55 million in persons' time receiving the vaccine, and $10 million to treat short-term adverse effects.

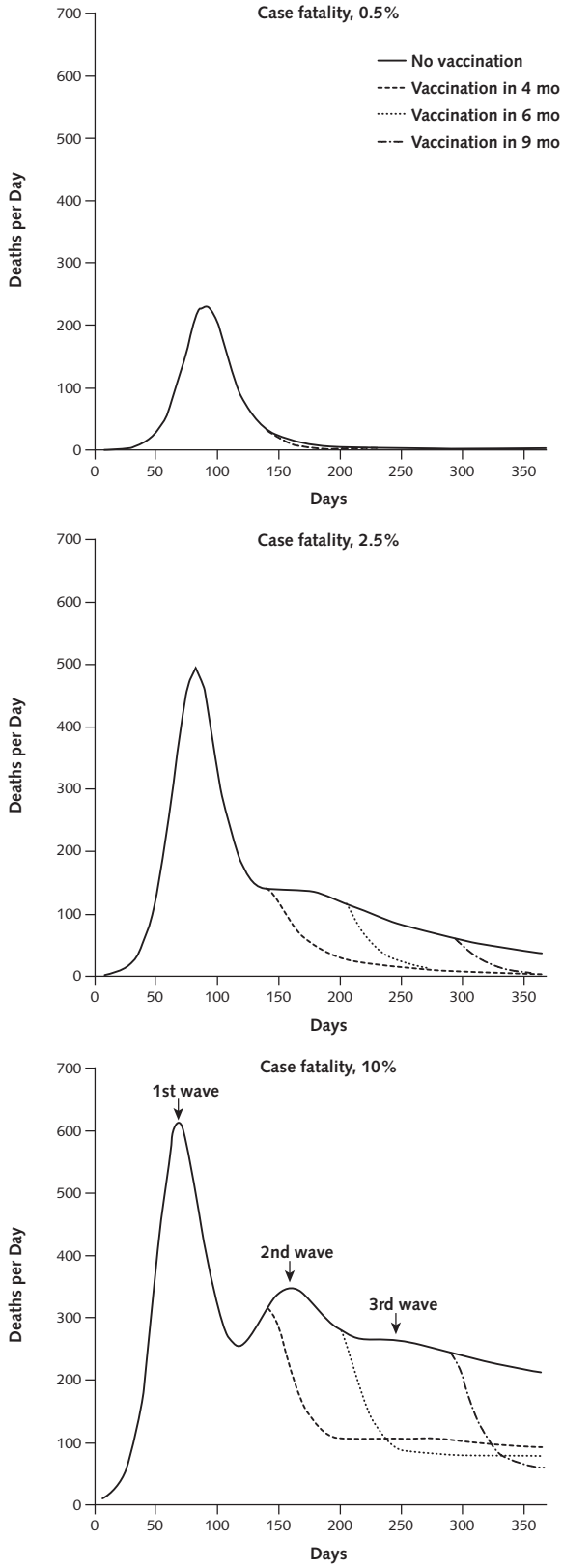
Value of Accelerating Vaccine Delivery

The costs to expedite vaccine delivery are unknown. We did a threshold analysis to assess the value of accelerating delivery. Vaccinating at 6 instead of 9 months would save $1.9 billion in treatment costs on a national level or $51 million at a city level. Further accelerating delivery to 4 months would save an additional $1.9 billion in treatment costs nationally or $50 million city-wide, relative to 6 months.

Cost-Effectiveness

Vaccinating earlier averts infections and deaths, which results in savings on short-term treatment. However, overall long-term costs increase because the lifetime expected medical costs outweigh the savings on short-term treatment. For example, every infection averted by vaccination saves about $220 in treatment costs, but if the intervention saves someone from dying, that person will now incur about $245 000 in medical costs over a typical lifetime. Completing the vaccination program at 6 versus 9 months would cost $10 722 per quality-adjusted life-year (QALY)

Figure 1. **Infections and deaths per day depending on timing of vaccination and mortality rate.**



saved, and completing the vaccination program at 4 versus 6 months would cost $10 689 per QALY saved (**Table 2**).

Sensitivity Analysis

We did univariate sensitivity analysis on all variables in our model (**Supplement 2**, available at www.annals.org). The variables that most substantially affect health and economic outcomes are mortality rate and the effect of NPIs.

Mortality Rates

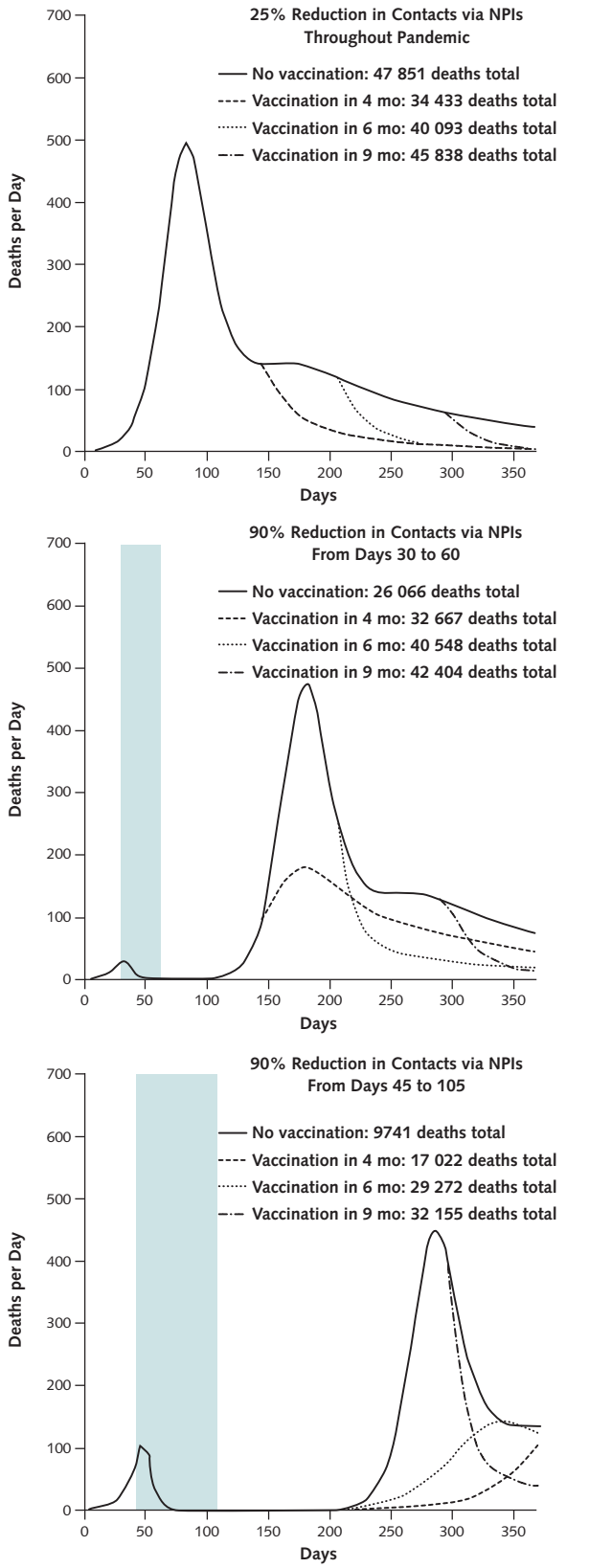
In our baseline analysis, we examined a mortality rate of 2.5%. Varying the mortality rate from 0.5% to 10% affects the magnitude of benefit seen with early vaccination (**Figure 1**).

A lower mortality rate of 0.5% would cause 12 525 deaths in a population of 8 million persons in 12 months. Vaccination at 4 months would avert 373 deaths and save $16.5 million in treatment costs in the short term, whereas vaccination at 6 months would avert only 61 deaths and save $2.7 million in short-term treatment costs.

With a mortality rate of 10%, 92 879 deaths would occur in a population of 8 million persons in 12 months. In response to this rate, persons reduce interpersonal contacts. As the rate decreases, persons resume contacts, and this leads to sequential pandemic waves. In this setting, vaccination can reduce daily mortality by 63% to 72% (**Figure 1**). Vaccination at 4 months would prevent 33 605 deaths and save $72 million in treatment costs in the short term. Vaccination at 6 months would prevent 24 778 deaths and save $52 million in short-term treatment costs. These interventions increase long-term health care costs because substantially more people survive to have average life expectancies with associated medical costs. If such costs were not included, vaccination at 4 or 6 months would be cost-saving versus vaccination at 9 months (**Appendix Table 1**, available at www.annals.org).

At high mortality rates, persons begin to reduce social interactions in response to the increased deaths—this reduces the number of infections per day but lengthens the epidemic. As this reactive social distancing decreases deaths, persons resume contacts, and that leads to sequential pandemic waves over time. The lines in this figure show deaths per day (areas under the curves represent cumulative deaths), which are generally higher for vaccination at 6 mo than 4 mo; however, with a mortality rate of 10%, after day 240, deaths per day for vaccination at 6 mo decrease below those per day for vaccination at 4 mo. By that time, more persons in the 6-mo vaccination category have been infected and developed immunity, which leads to fewer susceptible people and therefore fewer deaths. We see this only when we use the 10% mortality rate. When persons reduce social interactions because of a higher mortality rate, the epidemic lasts longer and influenza transmission is still sustained at day 240 and beyond. The total number of deaths for a 6-mo vaccination policy (represented by the total area under the curves) is always equal to or greater than that for a for 4-mo vaccination policy. The same reasoning explains why, later in the epidemic, daily death rates for vaccination at 9 mo decrease below those for 6 mo.

Figure 2. **Infections and deaths per day with increasing NPIs.**



NPIs

The effect of NPIs is substantial. With a mortality rate of 2.5% and no NPIs, 75 018 deaths (vs. 48 254) would occur in a population of 8 million persons in 12 months.

If vaccination cannot be completed until 9 months, decreasing contacts through NPIs can reduce widespread transmission and serve as a bridge to mass vaccination. To achieve a benefit similar to that of vaccination at 4 months, NPI coverage through such measures as hand hygiene and cough etiquette would need to decrease contacts by 33%.

If vaccine coverage is delayed to 6 or 9 months, we considered alternate times at which public health officials could announce and implement the most restrictive NPIs, such as school closures or home quarantines, as a bridge to vaccination. Increasing NPIs to 90% during pandemic days 30 to 60 would delay the peak of the first wave to 6 months, and increasing to 90% during days 45 to 105 would delay the peak to 9 months (**Figure 2**).

Vaccine Effectiveness and Additional Costs of Earlier Vaccination

We did additional analyses to determine the value of vaccinating earlier at different levels of vaccine effectiveness. We examined additional costs ranging from $10 to $1000 per person vaccinated at the earlier time point. If the additional cost were less than $925 per person and the vaccine were at least 30% effective, the cost at 4 months (relative to 6 months) would be less than $50 000 per QALY gained.

We also examined increased costs for earlier vaccination with a wide range of mortality rates. As the mortality rate increases, additional lives can be saved through earlier vaccination. For example, at a mortality rate of 10%, an additional cost of $1000 to vaccinate each person at 4 versus 6 months would have an incremental cost of $24 000 per QALY gained. When this proportion is lower than 0.5%, however, fewer lives are saved through earlier vaccination, and an additional cost of $125 per person would result in an incremental cost greater than $50 000 per QALY gained to vaccinate at 4 versus 6 months.

If mass vaccination is delayed, public health officials could announce and implement the most restrictive NPIs (e.g., school closures or home quarantines) to mitigate the pandemic while vaccination is awaited. Increasing NPIs to 90% during pandemic days 30 to 60 would delay the first wave to 6 mo, and increasing to 90% during days 45 to 105 would delay the first wave to 9 mo. The lines in this figure show deaths per day (areas under the curves represent cumulative deaths). Deaths per day for vaccination at 6 mo are generally higher than those for vaccination at 4 mo; however, in the case of a 90% reduction in contacts because of NPIs, the daily deaths for vaccination at 6 mo decrease below those for vaccination at 4 mo later in the epidemic. By that time, more persons in the 6-mo vaccination category have been infected and developed immunity after infection, which leads to fewer susceptible people and therefore fewer deaths. The total number of deaths in a 6-mo vaccination policy (represented by the total area under the curves) is always equal to or greater than that in a 4-mo policy. The same reasoning explains why, later in the epidemic, daily death rates for vaccination at 9 mo decrease below those for 6 mo. NPI = nonpharmaceutical intervention.

Vaccine Coverage

Because treatment costs decrease with increasing population coverage, the relative incremental cost-effectiveness of vaccinating from 10% to 50% of the population does not vary substantially. Covering higher percentages of the population increases vaccine costs: $47 million to cover 10% of the population versus $233 million to cover 50%. Increasing coverage also increases cost savings by decreasing influenza infection and treatment costs. Vaccinating 50% of the population at 6 months, for example, saves $59 million in treatment costs, whereas vaccinating 10% of the population at the same time point would only save $23 million in treatment costs (**Appendix Table 2**, available at www.annals.org).

Vaccine Rollout

New technologies may roll out vaccines over an extended time frame. Using CDC estimates of influenza vaccine delivery over 5 seasons (50), we examined distributing vaccines over 60 days (**Appendix Figure 2**, available at www.annals.org). Compared with our base-case analysis of distribution over 10 days, the mortality rate increased by 1% to 8%, but economic outcomes were similar (**Appendix Table 3**, available at www.annals.org).

Behavior Change in Vaccinated Persons

Vaccinated persons believe that they are less susceptible to infection and are less likely to reduce contacts. Our base case assumes 56% vaccine effectiveness, thus many of these vaccinated persons will still be susceptible to influenza infection and transmission. If vaccinated persons reduced social contacts by 20% or less and vaccine effectiveness were only 25% effective, vaccination would cost more than $50 000 per QALY.

Monte Carlo Probabilistic Sensitivity Analysis

To account for uncertainties in our cost-effectiveness analysis, we used a Monte Carlo probabilistic analysis and varied all parameters simultaneously for 1000 simulations. When vaccination at 4 months is compared with alternative vaccination strategies and no vaccination, the former strategy is preferred 88% of the time. Because vaccinating earlier would likely cost more due to accelerating vaccine production and delivery, we also did analyses assuming additional costs of $10, $100, or $1000 per person vaccinated earlier (**Appendix Figures 3** [*top*] and **4**, available at www.annals.org). At $10 more, vaccination at 4 months would cost less than $50 000 per QALY 87% of the time and less than $100 000 per QALY 88% of the time.

DISCUSSION

In previous work, we found that there is an optimal window for large-scale pandemic vaccination—a delay of even 4 weeks leads to a substantial increase in infections, deaths, and costs. As weeks pass, the susceptible population develops immunity through natural infection and recovery. In the 2009 influenza A (H1N1) pandemic, an event so mild that many question whether it was a true pandemic, vaccination occurred far later than the optimal window to avert infections, deaths, and decrease costs and in the time frame when most of the population had been infected and developed natural immunity. This limited large-scale benefits of vaccination. Four years later, it is unclear whether we are better prepared for such an event or, more concerning, a far more severe pandemic.

In light of the recent end to the ban on genetic modification of strains of influenza A (H5N1) that are transmissible between humans and an ongoing high mortality rate from novel influenza A (H7N9), we assessed how the timing of a vaccination program would affect health and economic outcomes in a severe pandemic scenario. Large-scale vaccination in the United States occurred 9 months after the start of the 2009 pandemic. Comparing our findings with those from 2009, we note that the higher reproductive number and mortality rate associated with a particularly virulent virus would cause the pandemic to progress more rapidly, further narrowing the optimal window for vaccination. To substantially reduce infections, deaths, and influenza treatment costs, vaccination must be completed much earlier than it was in 2009.

Pandemic egg-based vaccine development begins with a 2-month process of identification, preparation, and verification of the vaccine strain at the World Health Organization Collaborating Centres. In the next 3 months, manufacturers optimize viral growth conditions, manufacture bulk vaccine, perform quality control, fill vaccines, and do clinical trials. Regulatory agencies then review and release the vaccines. In a best-case scenario, egg-based vaccine delivery is completed in 5 months (48). Accelerating large-scale vaccination in the setting of a pandemic would require changes in development, such as the use of cell- or recombinant-based rather than egg-based vaccines (51, 52). Additional novel technologies, such as generation of synthetic vaccine seeds, could further expedite development during a pandemic (53). Although costs of such a program are unknown, we examined the value of earlier vaccination and found that on a national level, vaccinating at 6 rather than 9 months would save $1.9 billion in treatment costs, and vaccinating at 4 rather than 6 months would save an additional $1.9 billion in treatment costs. These figures may help policymakers decide what scenarios warrant a concerted effort between vaccine manufacturers and the government to speed production and administration.

Some people will decline influenza vaccination. On the basis of vaccine acceptance during seasonal epidemics and the 2009 influenza A (H1N1) pandemic, we analyzed vaccination rates between 10% and 50% of the population. We found that vaccinating even 10% of the popula-

tion at an early time point can substantially reduce the health and economic effects of a severe pandemic.

Although we find early vaccination to be an effective intervention that saves treatment costs in the event of a severe pandemic, public health messages promoting reductions in contacts through NPIs will be important to vaccinated as well as unvaccinated persons. Our study shows the potential for increased NPIs not only as an effective supplement to vaccination but also as a bridge to decrease widespread expansion of the pandemic in the absence of a vaccine. If approximately 33% reductions in contacts are achieved via NPIs over 9 months, decreases in infections, deaths, and costs would be similar to vaccinating 30% of the population at 4 months with our baseline assumptions about NPIs. Institution of more intensive NPIs (such as school closures or home quarantine) between pandemic days 30 to 60 or 45 to 105 can delay pandemic peaks to 6 and 9 months, respectively, again serving as a bridge to vaccination. Because current egg-based vaccine technology takes at least 6 months, our analysis suggests that NPIs may be crucial in mitigating the pandemic while development and distribution are awaited.

Limitations of our analysis include the assumption of homogeneous mixing of contacts. Our model does not account for differences in contact frequency between age groups and is not designed to evaluate the differential impact of targeting vaccination to specific groups, such as children. Transmission rates can be affected by social networks, such as children in school (54). Similarly, our model cannot evaluate the effect of targeting vaccination to persons who, because of age or comorbid conditions, may be at higher risk for morbidity or mortality after contracting influenza. To optimize resource allocation, policymakers may consider prioritizing vaccination by age groups and comorbid conditions. Nevertheless, previous research shows that models similar to ours can effectively guide policy decisions (55). Our analysis also does not account for indirect pandemic costs, such as school and workplace closures; decreases in recreation as a result of social distancing; or loss of specific skills, training, and knowledge. Vaccination may prevent some of these losses, increasing its cost-effectiveness.

Influenza A (H5N1) and A (H7N9) have the potential to cause severe influenza pandemics. Many uncertainties remain about transmissibility, morbidity, and mortality in humans. We examined mortality rates far lower than those currently reported for these 2 viruses. Even at a mortality rate of 2.5%, our analysis reveals unprecedented numbers of infections, deaths, and health care costs in a pandemic caused by either virus. Encouragingly, we also found that early vaccination and NPIs can substantially avert these losses. The acceleration of large-scale vaccine development is a current challenge in public health and has not yet been achieved in the 4-month interval in which we found the most benefit. Our findings call attention to the need for investment in vaccine development, distribution strategies, and public health messages to promote the widespread use of NPIs in the event of a severe pandemic.

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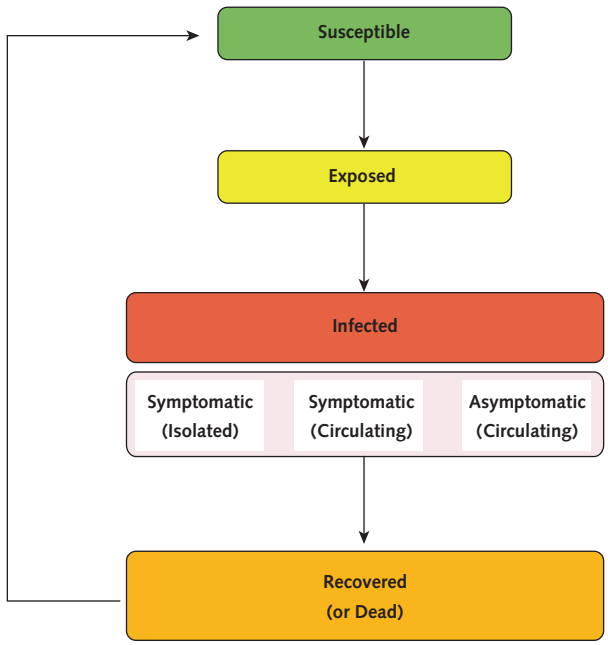
Appendix Figure 1. **SEIR model.**



Dynamic infectious disease transmission model of progression of a severe pandemic with characteristics similar to influenza A (H7N9) and A (H5N1) in a susceptible population. We used a basic deterministic SEIR model with modifications to allow for various population groups (who receive pharmaceutical and nonpharmaceutical interventions). SEIR = susceptible, exposed, infected, and recovered.

Appendix Table 1. **Economic Outcomes Without Long-Term Health Care Costs After Vaccination for a City of 8.3 Million Persons With 30% Vaccine Coverage**

Vaccination Time*	Vaccination Costs (Millions), $	Treatment Cost Savings (Millions), $	Total Costs (Millions), $	QALYs Gained	ICER, $/QALY†
No vaccination	0	–	426	–	–
9 mo	140	18‡	548	51 056‡	2388
6 mo	140	51§	498	127 460§	399
4 mo	140	50‖	447	125 309‖	69

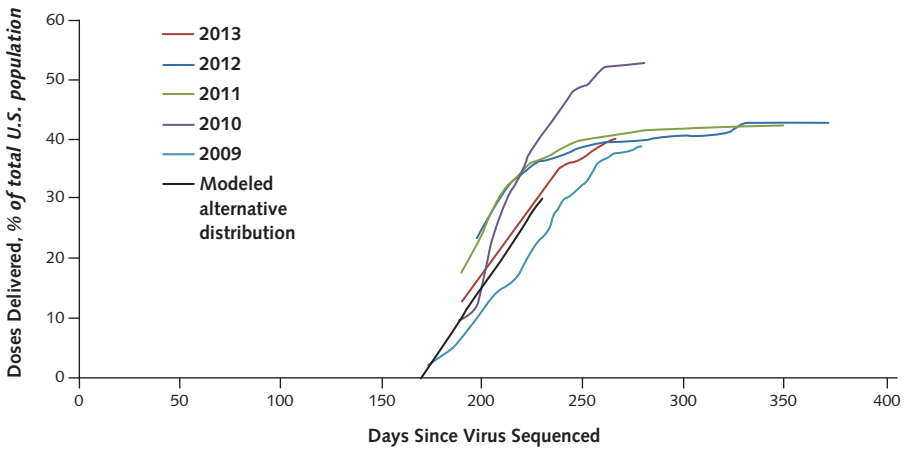
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* Since start of pandemic in target city.
† If long-term health care costs were not included, vaccination at 4 or 6 mo would be cost-saving vs. vaccination at 9 mo.
‡ Relative to no vaccination.
§ Relative to vaccination at 9 mo.
‖ Relative to vaccination at 6 mo.

Appendix Table 2. Economic Outcomes After Vaccination for a City of 8.3 Million Persons

Vaccination Time*	Vaccination Costs (Millions), $	Treatment Cost Savings (Millions), $	Added Normal Health Care Costs (Millions), $†	Total Costs (Millions), $	QALYs Gained	ICER, $/QALY
10 mo% vaccine coverage						
9 mo	47	–	–	–	–	–
6 mo‡	47	23	636	613	57 162	10 718
4 mo§	47	14	363	349	32 820	10 643
50% vaccine coverage						
9 mo	233	–	–	–	–	–
6 mo‡	233	59	1649	1589	148 297	10 718
4 mo§	233	65	1797	1732	162 028	10 692

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* Since start of pandemic in target city.
† Accounting for normal health care expenditures, total costs will increase in situations where deaths are averted.
‡ Relative to vaccination at 9 mo.
§ Relative to vaccination at 6 mo.

Appendix Figure 2. Alternative vaccine distribution strategy (60-d rollout).



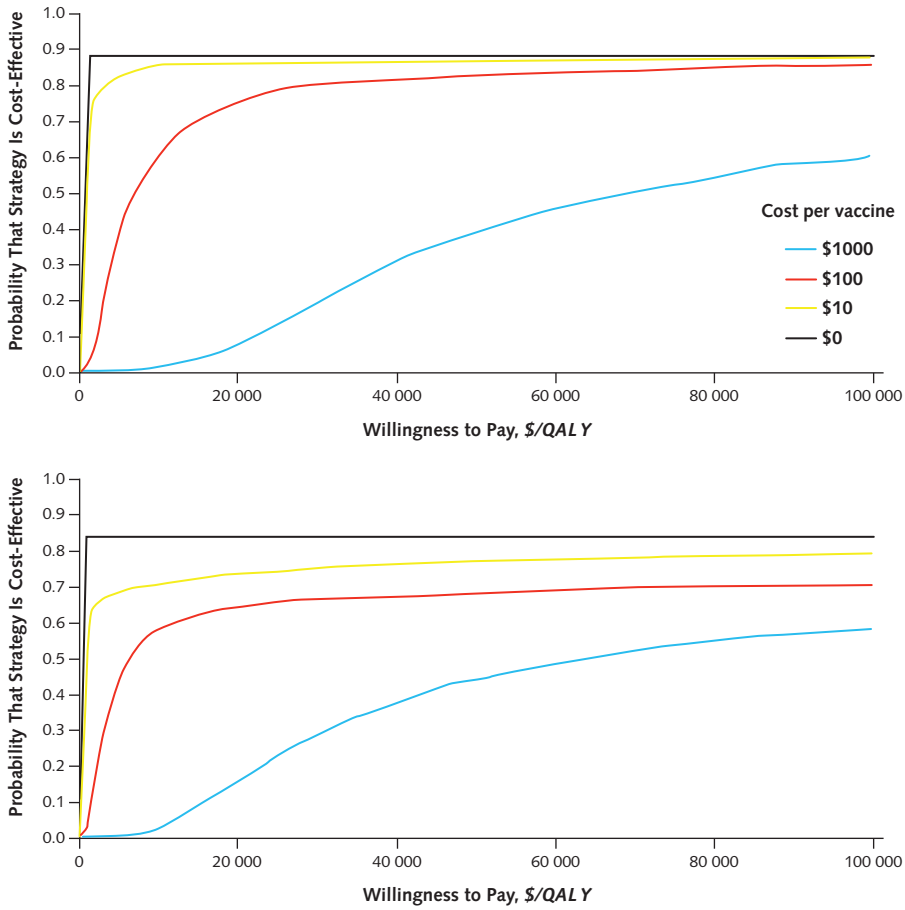
Rollout of vaccines by using new technologies may occur over an extended time frame. We examined distributing vaccines over 60 d by averaging the Centers for Disease Control and Prevention's estimates of vaccine delivery over 5 seasons. ICER = incremental cost-effectiveness ratio.

Appendix Table 3. **Health and Economic Outcomes After Alternate Timing for Vaccine Distribution for a City of 8.3 Million Persons**

Outcome, Assuming That Vaccination of 30% of the Population Takes 60 d	No Vaccination	Vaccination Time*		
		9 mo	6 mo	4 mo
Symptomatic infections, *n*	1 920 514	1 876 565	1 688 043	1 489 219
Deaths, *n*	48 254	46 973	42 210	37 244
Persons still susceptible to infection, %	68	70	76	81
Deaths averted after vaccination, *n*†	–	–	4763	9729
Reduction in contacts via NPIs required to decrease widespread transmission, %‡	50	29	34	39
Vaccination costs (millions), $	–	140	140	140
Short-term treatment cost savings (millions), $	–	–	41	44
Long-term lifetime health expenditures (millions), $§	–	–	1167	1223
Incremental total costs (millions), $	–	–	1126	1179
QALYs gained*	–	–	104 864	110 141
ICER, $/QALY†	–	–	10 737	10 702

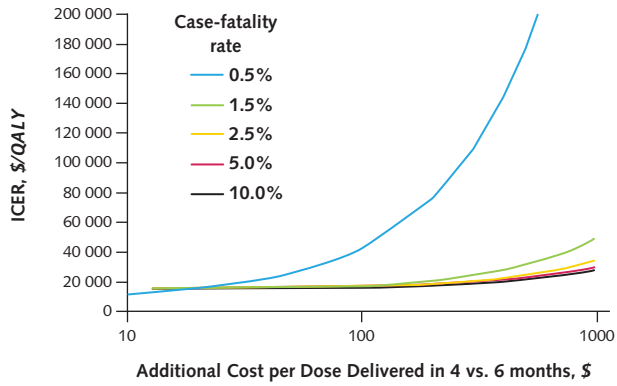
ICER = incremental cost-effectiveness ratio; NPI = nonpharmaceutical intervention; QALY = quality-adjusted life-year.
* Since start of pandemic in target city.
† Compared with vaccination at 9 mo.
‡ R_0 (the number of secondary infections caused by each infected person in a susceptible population) ≤1. End of pandemic by epidemiologic definitions.
§ Vaccinating earlier averts infections and deaths, resulting in short-term treatment cost savings. However, this increases long-term costs because more persons survive to have average life expectancies with associated medical costs. Accounting for the health care expenditures of persons whose lives are saved, total costs increase in the long term. Long-term costs of vaccination at 4 mo are compared with those at 6 mo, and costs of vaccination at 6 mo are compared with those at 9 mo.

Appendix Figure 3. **Cost-effectiveness acceptability curves for vaccine availability at 4 mo (*top*) and for vaccine availability at 4 mo with 60-d distribution, alternative levels of NPIs, and additional costs (*bottom*).**



Additional investments would be necessary for a vaccine to be available at 4 mo. We conducted an analysis of several possible costs of a vaccine, per person vaccinated, assuming that 30% of the population is vaccinated. The cost-effectiveness acceptability curves show the likelihood that a vaccine at 4 mo would be cost-effective. Typically, cost-effectiveness acceptability curves show lines for each strategy. In this case, vaccination at 4 mo is compared with no vaccination and all other vaccination strategies (with no additional costs). The lines for the policies of "no vaccination," "vaccination at 9 mo," and "vaccination at 6 mo" are not shown for clarity. We also examined 60-d vaccine distribution schedules, alternative levels of NPIs, and additional costs for expediting vaccine delivery ranging from $10 to $1000. NPI = nonpharmaceutical intervention.

Appendix Figure 4. **Additional costs of vaccination at 4 mo versus 6 mo for different mortality rates.**



As the rate increases, additional lives can be saved through earlier vaccination. At a rate of 10%, an additional cost of $1000 to vaccinate each person at 4 vs. 6 mo would have an incremental cost of $24 000 per QALY gained. When this proportion is lower than 0.5%, however, fewer lives are saved through earlier vaccination, and even an additional cost of $125 per person would result in an incremental cost >$50 000 per QALY gained to vaccinate at 4 vs. 6 mo. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.