

Effectiveness and Cost-Effectiveness of Vaccination Against Pandemic Influenza (H1N1) 2009

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Background: Decisions on the timing and extent of vaccination against pandemic (H1N1) 2009 virus are complex.

Objective: To estimate the effectiveness and cost-effectiveness of pandemic influenza (H1N1) vaccination under different scenarios in October or November 2009.

Design: Compartmental epidemic model in conjunction with a Markov model of disease progression.

Data Sources: Literature and expert opinion.

Target Population: Residents of a major U.S. metropolitan city with a population of 8.3 million.

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: Vaccination in mid-October or mid-November 2009.

Outcome Measures: Infections and deaths averted, costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness.

Results of Base-Case Analysis: Assuming each primary infection causes 1.5 secondary infections, vaccinating 40% of the population in October or November would be cost-saving. Vaccination in October would avert 2051 deaths, gain 69 679 QALYs, and save \$469 million compared with no vaccination; vaccination in Novem-

ber would avert 1468 deaths, gain 49 422 QALYs, and save \$302 million.

Results of Sensitivity Analysis: Vaccination is even more cost-saving if longer incubation periods, lower rates of infectiousness, or increased implementation of nonpharmaceutical interventions delay time to the peak of the pandemic. Vaccination saves fewer lives and is less cost-effective if the epidemic peaks earlier than mid-October.

Limitations: The model assumed homogenous mixing of case-patients and contacts; heterogeneous mixing would result in faster initial spread, followed by slower spread. Additional costs and savings not included in the model would make vaccination more cost-saving.

Conclusion: Earlier vaccination against pandemic (H1N1) 2009 prevents more deaths and is more cost-saving. Complete population coverage is not necessary to reduce the viral reproductive rate sufficiently to help shorten the pandemic.

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Pandemic (H1N1) 2009 has caused 182 166 confirmed infections and 1799 deaths in more than 150 countries to date (1). Both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have declared public health emergencies in response to global circulation of this virus, and the WHO has raised the influenza pandemic alert level from 3 to 6 (2).

As a result of the strain's novelty, most people lack innate immunity to pandemic (H1N1) (3); currently available vaccines do not protect against the virus; and the time needed to manufacture, test, and distribute a matched vaccine is several months (4, 5).

In the absence of a matched vaccine, infections and deaths from pandemic (H1N1) will continue globally until a sufficient proportion of the population has developed immunity through infection and recovery, inducing "herd immunity" (population immunity that decreases the effective reproductive rate of the virus below 1, ending the pandemic by epidemiologic definitions [6]). Public health officials were planning to begin vaccination campaigns in mid-October 2009 (7); however, the National Biodefense Science Board, a group of advisors to the U.S. Department of Health and Human Services, recommended moving large-scale vaccine administration to mid-September 2009 (8). Decisions on vaccination timing and distribution are

complicated: It is unclear how many individuals would require vaccination to substantially reduce transmission once vaccine is available (some scientists note that the first epidemic wave may in fact already be complete by this time [9]), and it could be expensive to manufacture and administer the vaccine and to treat its side effects.

To help guide policymakers in advising vaccine manufacturers, we developed a model of progression of the 2009 (H1N1) pandemic to determine how vaccination in October or November 2009 would affect the course of

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Context

Influenza A (H1N1) vaccine is now being distributed for use in vaccination programs.

Contribution

This decision model for vaccination suggests that vaccinating 40% of the population in October would save more lives and money than similar vaccination coverage in November.

Caution

The model makes several assumptions that may not bear out given the unpredictability of H1N1 infection this fall. However, users can test their own assumptions with a model provided by the authors (available at www.annals.org).

Implication

Earlier vaccination is estimated to prevent more deaths and cost less than would later vaccination for influenza A (H1N1).

—The Editors

the pandemic. We compared the effectiveness and cost-effectiveness of no vaccination, vaccination in mid-October, and vaccination in mid-November.

METHODS

Overview

We developed a compartmental epidemic model in conjunction with a Markov model of disease progression of the human spread of pandemic (H1N1) to elucidate the dynamics of disease transmission and progression of the first pandemic wave (**Appendix Figure A1** [all appendix figures and tables are in **Appendix 2**, available at www.annals.org]). Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine (10), we adopted a societal perspective for costs and benefits, discounted at 3% annually. We analyzed outcomes for the remaining lifetime of each individual. We expressed these outcomes in infections and deaths, costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios. We developed the simulation model and performed analyses by using Microsoft Excel, version 2003 (Microsoft, Redmond, Washington). We provide an annotated version of the model (**Appendix 1**, available at www.annals.org) so that readers can test model output for different assumptions and circumstances.

Study Population and Disease Parameters

Susceptible Population

We followed a hypothetical cohort of 8.3 million persons living in a large U.S. city with a sex distribution (53% women), age range (0 to 100 years), and average remaining life expectancy similar to those of the population of New

York City (11). The WHO officially declared the start of the pandemic on 11 June 2009 (2). We assumed that 10 000 individuals were infected at that time on the basis of a New York City telephone survey of influenza-like illness (12) and CDC data on cases of influenza-like illness testing positive for pandemic (H1N1) (13–15) (calculations in **Appendix 2**). We varied this number from 1000 to 50 000 in sensitivity analysis. According to data showing some preexisting population immunity to pandemic (H1N1) (3), we assumed that 10% of the population entered the model immune to the virus and that 90% of individuals entered susceptible to the virus. In sensitivity analysis, we examined scenarios in which up to 20% of individuals entered immune to the virus.

Infected Population

On the basis of available evidence (16–18), we assumed that in the base-case scenario, the R_0 (number of secondary infections caused by each primary infection in a susceptible population) of pandemic (H1N1) is approximately 1.5. As new data on infectious spread emerge, this number may change. In sensitivity analysis, we varied R_0 from 1.2 to 1.8.

New York City death rates and other epidemiologic data suggest that viral transmission may be decreased over the warm summer months (12, 19–23). Because the timing of the peak of the epidemic is an important determinant of the effectiveness of vaccination, we modeled seasonal variation (described in **Appendix 2**) by calibrating to decreased deaths confirmed in New York City over the summer (**Appendix Figure B4**). We also evaluated the effectiveness of vaccination in scenarios in which the epidemic grew more slowly or more rapidly.

According to influenza A virus infections (24–33), we assumed that 67% of infected individuals developed symptoms. Fifty percent of these individuals entered a state of isolation, either voluntarily or because of physical limitation secondary to illness or admission to a hospital. We assumed that those who were not in isolation (34) continued to infect contacts. On the basis of information to date on pandemic (H1N1) 2009 and other influenza A viruses (35, 36), we assumed that infected individuals had a mean incubation time of 3 days, had symptoms (if they were symptomatic) for 10 days, and could transmit the virus for 4 days. We evaluated infectivity of 7 days in sensitivity analyses. On the basis of studies of influenza A infection and nasal viral shedding (37, 38), we assumed that incubating individuals transmitted influenza at half the rate of symptomatic individuals and that asymptomatic infected individuals transmitted at one quarter the rate of symptomatic individuals. Consistent with published CDC assumptions (39), we estimated that 3.3% of symptomatic individuals required 5 days of hospital care and 10% of hospitalized patients required 10 days of care in the intensive care unit.

Recovered Population

Estimates of reinfection with antigenically drifted influenza A viruses range from 2% to 25% (40–43) throughout the course of epidemics. Because most reinfecting individuals are asymptomatic or have mild symptoms with a shorter duration of illness and less viral shedding, we assumed that 5% of the recovered population was once again susceptible to infection at an average of 5 months after recovery. We examined a range of reinfection from 2% to 25% in sensitivity analysis.

Death From Influenza

On the basis of the percentage of cases of influenza-like illness in the United States that have tested positive for pandemic (H1N1) (13–15, 44–54), we calculated a case-fatality proportion of 0.1% after adjusting the documented case-fatality proportions (17, 55) for underreporting nonfatal cases owing to less frequent testing of individuals with influenza-like illness as the pandemic progresses (56, 57). In sensitivity analysis, we modeled a more severe pandemic, with a 1.0% clinical case-fatality proportion (consistent with pandemic [H1N1] global case-fatality proportions [58]) and a less severe pandemic, with a 0.01% clinical case-fatality proportion. We modeled age-specific mortality with increases in deaths in newborns, young adults, and individuals older than 65 years (54, 55).

Interventions

Nonpharmaceutical Interventions

Nonpharmaceutical interventions for pandemic (H1N1) recommended by the CDC have included closing school and child care facilities, home isolation, cough etiquette, hand washing, use of alcohol-based hand gels, and use of personal protective equipment (such as facemasks) (59). Incorporating the results of a complex network model of pandemic spread through communities (60), we assumed that these nonpharmaceutical interventions are reducing contacts by 15%. A recent randomized trial of facemasks and hand washing found that under optimal circumstances, these measures reduced transmission among households by 66% (61); therefore, we evaluated reduction in contacts from 10% to 70% in sensitivity analysis (61).

Vaccination

Nonadjuvanted vaccines routinely used for seasonal influenza have had limited success in eliciting human antibodies to novel influenza A viruses. Adjuvanted vaccines have been much more successful—not only do they more frequently elicit antibody responses, they protect against different influenza clades, an important advantage in light of the virus's ability to mutate (62–65). On the basis of these properties, vaccine manufacturers have been testing adjuvanted vaccines for pandemic (H1N1) (66). Consistent with results of trials of adjuvanted pandemic (H1N1) vaccination (67, 68), we assumed a 15- μ g adjuvant-to-antigen concentration and examined concentrations from

3.8 μ g to 30 μ g (63) in sensitivity analyses. We assumed that this vaccination sequence was 75% effective, within the range of effectiveness shown in pandemic (H1N1) trials (67, 68). In sensitivity analyses, we examined ranges of vaccine effectiveness from 60% to 90%.

The U.S. government expects to have 120 million doses of pandemic (H1N1) vaccine available in the autumn, a quantity sufficient to vaccinate 40% of the U.S. population (7, 69). On the basis of historical precedent (New York City, 1976 [70]) and modern mass vaccination exercises (71), we estimated that a rapid influenza vaccination campaign, using published emergency response logistic plans, could inoculate approximately 250 people per vaccination center per hour, providing coverage for all 8.3 million individuals over a 10-day period (72). On the basis of the results of studies of adjuvanted pandemic (H1N1) vaccination (67, 68), we assumed that the vaccine would provide complete immunity to 75% of recipients 14 days after vaccination.

We assumed that 85% of pandemic (H1N1)-vaccinated individuals experienced mild to moderate adverse reactions, such as pain, redness, swelling, induration, ecchymosis, low-grade fevers, arthralgias, fatigues, headaches, myalgias, shivering, or sweating for up to 7 days, on the basis of adjuvanted pandemic (H1N1) vaccination data (68). We assumed that 0.001% of the population experienced severe adverse reactions, such as angioedema, anaphylaxis, or the Guillain-Barré syndrome, consistent with 1976 vaccination data (73).

Costs and Utilities

We expressed all costs in 2009 U.S. dollars using the Gross Domestic Product deflator. Intervention costs included the cost of a vaccine, administration, the value of an individual's time receiving it, and the costs of treating individuals with severe side effects (Table 1 [74–89]). We estimated treatment costs at a hospital from the average cost of general medical hospitalization for influenza (87) or hospitalization in a medical intensive care unit (86). We based utility estimates on EuroQol and time-tradeoff ratings and included the remaining lifetime of individuals alive at the end of the year. We calculated remaining life-years from the New York census, then adjusted life expectancy for quality of life by using age- and sex-specific utilities from the Beaver Dam Health Outcomes Study (81).

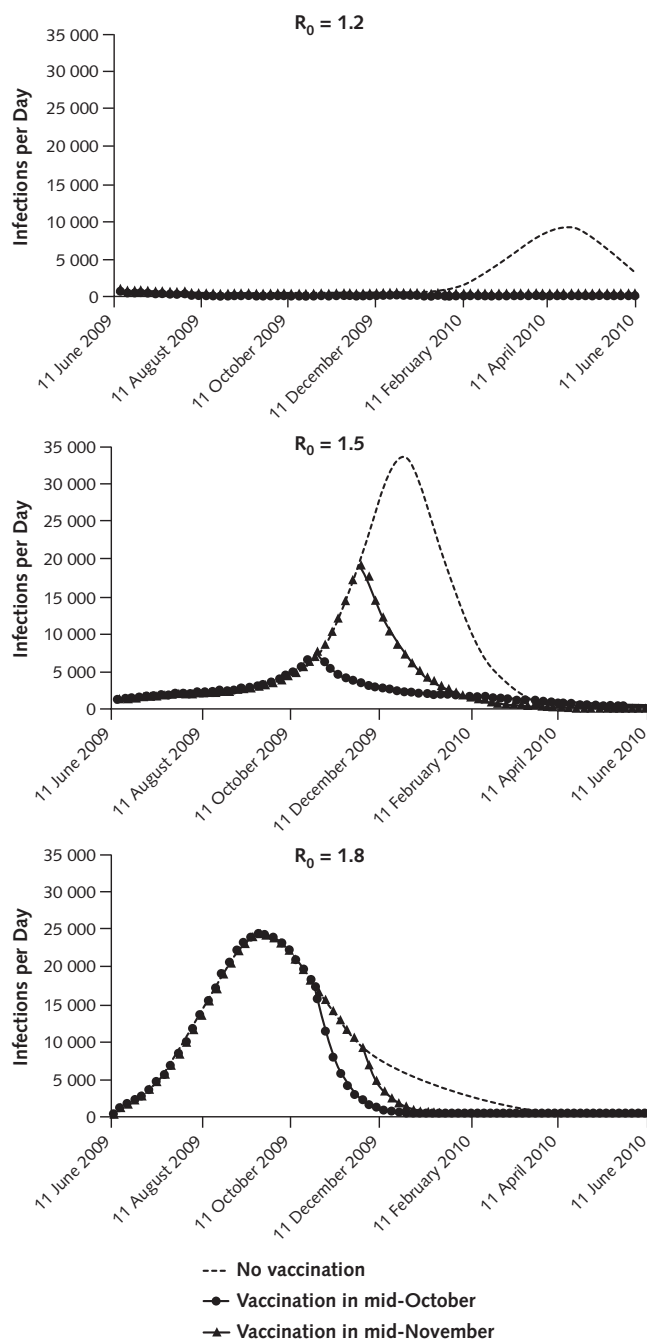
Sensitivity Analysis

We used sensitivity analysis to identify important model uncertainties. When available, we based variable ranges on reported 95% CIs from the data sources. Otherwise, we determined ranges by adding or subtracting 25% from the baseline estimate.

Role of the Funding Source

The funding sources 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.

Figure 1. Progression of pandemic under different R_0 s and vaccination scenarios.



The effective viral reproductive rate decreases over time, secondary to the development of immunity in individuals in the population who recover from infection. The R_0 is the number of secondary infections caused by each primary infection in the susceptible population.

RESULTS

For a later peaking epidemic at R_0 of 1.5 (in mid-October), 285 566 of the city's 8.3 million individuals would have been symptomatically infected and 286 would have died (Table 2 and Figure 1). In November,

541 865 would have been infected and 542 would have died. Because of the development of immunity in individuals in the population who had been infected and recovered, 85% of individuals would still be susceptible to infection in October, and 80% would be susceptible to infection in November.

Varying R_0 from 1.2 to 1.8 (Table 2 and Figure 2), symptomatic infections would range from 38 304 to 1.74 million in October and 40 416 to 2.25 million in November; deaths would range from 38 to 1743 in October and 40 to 2247 in November. At R_0 of 1.2, fewer individuals would become infected and less immunity would develop; 89% of individuals would still be susceptible to infection in October and November. At R_0 of 1.8, a significant number of infections would increase population immunity, with 59% of individuals susceptible to infection in October and 50% susceptible to infection in November.

Health Outcomes

Death averted by vaccination and the number of individuals requiring vaccination to reduce R_0 below 1 (thus helping to end widespread transmission) are related to the initial R_0 for the pandemic (Table 2 and Figure 2). At a low and a high R_0 , fewer individuals require vaccination to slow the epidemic than if R_0 is 1.5. At a high R_0 , the epidemic spreads so quickly that many individuals become ill and develop immunity without vaccination. Vaccination has the largest effect on deaths averted for an intermediate R_0 .

Cost-Effectiveness

Vaccinating 40% of the population in October would slow widespread transmission and be cost-saving, adding 69 679 QALYs and saving \$469 million. Vaccinating 40% of the population in November would add 49 422 QALYs and save \$302 million relative to no vaccination (Table 3). Vaccinating 35% of the population in November would slow widespread transmission and add 45 383 QALYs, saving \$282 million relative to no vaccination. Vaccinating 40% of the population in October would be more effective and cost less than vaccinating 40% in November.

When the reproductive rate of the virus is low, the pandemic spreads more slowly, and fewer treatment costs and deaths are averted with vaccination (Figure 1 and Table 3). At R_0 of 1.2, vaccination in October would add 25 387 QALYs and save \$103 million, and vaccination in November would add 25 236 QALYs and save \$102 million relative to no vaccination. When the reproductive rate of the virus is higher, widespread transmission of the virus is already decreasing by November, leading to fewer lives saved with vaccination. At R_0 of 1.8, vaccination in October would add 20 967 QALYs, saving \$69 million, and vaccination in November would add 10 851 QALYs at \$14 million, for a cost of \$1303 per QALY relative to no vaccination.

Table 1. Assumptions for Variables in the Model

Variable	Base Case (Range)	Source (Reference)
Susceptible population parameters		
Population, <i>n</i>	8 300 000	New York Bureau of Vital Statistics (11)
Age range, <i>y</i>	0–100	New York Bureau of Vital Statistics (11)
Female, %	53	New York Bureau of Vital Statistics (11)
Preexisting population immunity, %	10 (0–20)	CDC (3)
Infected population parameters		
R_0^*	1.5 (1.2–1.8)	CDC (16), Fraser et al (17), Pourbohloul et al (18)
Effect of season on transmission	0.2 (0–0.5)	Assumed
Reduction in contacts from nonpharmaceutical interventions, %	15 (0–70)	Assumed; Davey et al (60), Cowling et al (61)
Infected individuals at start of pandemic, <i>n</i>	10 000 (1000–50 000)	New York City Department of Health and Mental Hygiene (12), CDC (13–15)
Probability of symptomatic infection, %	67 (50–90)	Ferguson et al (32), Longini et al (33), Katz et al (24), Dinh et al (31), Vong et al (25), Buxton Bridges et al (26), Apisarnthanarak et al (27), Liem et al (28), Wang et al (30)
Reduced infectiousness by incubating persons, %	50 (10–62.5)	Hayden et al (37), Atkinson and Wein (74)
Reduced infectiousness by asymptomatic persons, %	25 (10–50)	Hayden et al (37), Atkinson and Wein (74)
Probability of isolating given symptomatic infection, %	50 (37.5–62.5)	Longini et al (75)
Mean incubation time, <i>d</i>	3 (1–7)	Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team (35), CDC (55)
Mean duration of infectiousness, <i>d</i>	4 (3–7)	Hayden et al (37), Leekha et al (38)
Mean duration of symptomatic illness, <i>d</i>	10 (7.5–12.5)	CDC (36)
Symptomatic patients requiring inpatient care, %	3.3 (1–10)	CDC (39, 77), HHS (76)
Mean duration of non-ICU hospital stay, <i>d</i>	5 (3.75–6.25)	CDC (39)
Hospitalized patients requiring ICU care, %	10 (7.5–12.5)	CDC (39)
Mean duration of ICU stay, <i>d</i>	10 (7.5–12.5)	CDC (39)
Recovered population parameters		
Susceptibility to reinfection after recovery, %	5 (2–25)	Smith et al (43), Monto et al (41), Sonoguchi et al (40), Davies et al (42)
Timing of waning immunity, <i>mo</i>	5 (2–8)	Smith et al (43), Monto et al (41), Sonoguchi et al (40), Davies et al (42)
Mortality		
Case-fatality proportion, %	0.1 (0.01–1.0)	Assumed; pandemic (H1N1) case fatalities (55, 58)
Intervention effectiveness		
Adjuvanted 1-dose vaccine, %	75 (60–90)	Greenberg et al (67), Clark et al (68)
Adjuvanted 2-dose vaccine, %	90 (70–99)	Clark et al (68)
Time to immunity, <i>d</i>	14 (7–21)	Greenberg et al (67), Clark et al (68)
Vaccination side effects, %		
Mild to moderate side effects	85 (50–100)	Clark et al (68)
Severe side effects	0.001 (0–0.01)	Neustadt and Fineberg (73)
Risk for death from severe side effects	5 (1–10)	Chio et al (78)
Risk for long-term care from severe side effects	5 (1–10)	Mendell et al (79)
Reduction in quality of life from vaccination side effects, <i>dt</i>		
Net quality-of-life decrement secondary to mild to moderate side effects‡	0.1 (0–0.7)	Treanor et al (62), Leroux-Roels et al (63), CDC (80)
Net quality-of-life decrement secondary to severe side effects§	7 (0–28)	Neustadt and Fineberg (73)
Influenza-related quality of life†		
Uninfected or asymptomatic	0.96 (0.92–1.00)	New York Census (11), Beaver Dam Health Outcomes Study (81)
Symptomatic influenza	0.8 (0.7–0.9)	Turner et al (82)
Postinfluenza disabled state for patients requiring ICU care	0.9 (0.85–0.95)	Assumed
Costs		
Vaccine		
Antigen per μ g, \$	0.45 (0.15–0.70)	HHS (83)
Adjuvant, \$	7.00 (5.25–8.75)	BARDA (Perdue M. Personal communication.)
Adjuvant per vaccine, μ g	15 (3.8–30)	Greenberg et al (67)
Administration, \$	8.73 (6.54–10.91)	Calculated; 10 min of nurse wages (84)
Patient time, \$	10.55 (5.28–21.10)	U.S. Bureau of Labor Statistics (85)

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Table 1—Continued

Variable	Base Case (Range)	Source (Reference)
Daily health care costs, \$		
Patient with severe side effects (treated in ICU)	3739.05 (2804.29–4673.82)	Dasta et al (86)
General medical hospitalized patient	1830.46 (1429.37–1870.54)	Talbird et al (87)
ICU hospitalized patient	3739.05 (2804.29–4673.82)	Dasta et al (86)
Long-term treatment facility costs for patients with severe vaccine side effects	313.05 (234.79–391.31)	MetLife survey (88)
Normal health care expenditures	19.56 (14.67–24.45)	Statistical Abstract of the United States (89)
Other variables		
Discount rate, annual %	3 (0–5)	Weinstein et al (10)

BARDA = Biomedical Advanced Research and Development Authority; CDC = Centers for Disease Control and Prevention; HHS = U.S. Department of Health and Human Services; ICU = intensive care unit.

* Number of secondary infections caused by each primary infection in a susceptible population.

† Quality-of-life variables represent a person's preference for a given state of health and are scaled from 0 to 1, with 1 equivalent to perfect health.

‡ Mild to moderate vaccine side effects were assumed to reduce quality of life by 0.05 (range, 0–0.1) for 2 days (range, 1–7 days).

§ Severe vaccine side effects were assumed to reduce quality of life by 0.5 (range, 0–1) for the duration of hospitalization, which was 7 days (range, 0–28 days).

In considering short-term local budgetary implications, at R_0 of 1.5, federal costs for vaccination in November for a city of 8.3 million individuals would be \$46 million for vaccine antigen and adjuvant; city costs would be \$29 million to administer the vaccines; and city and individual costs would be \$35 million in vaccine recipient time and \$6.4 million for treating severe short-term side effects. Savings to the city and individuals would be \$686 million in influenza treatment costs (Table 3).

Results Under Varied Growth Scenarios

In light of significant local and regional variations in the growth of the pandemic in the United States (14–16, 45–54), we examined a slower growth scenario than in our initial analysis, based on an average of confirmed U.S. deaths to date (13–15, 44–53). In this scenario, with slower spread of the virus (Appendix Figure B1), more individuals would be susceptible to infection in the autumn: Vaccinating 40% of the population would be cost-saving, adding 89 592 QALYs and saving \$629 million relative to no vaccination in October, and adding 72 167 QALYs and saving \$486 million relative to no vaccination in November. Vaccinating 44% of the

population in October would slow widespread transmission, add 94 363 QALYs, and save \$657 million relative to no vaccination. Vaccinating 43% of the population in November would slow widespread transmission, add 76 396 QALYs, and save \$513 million relative to no vaccination.

We also examined a scenario with no reduction in viral transmission over the summer months. In this case, with faster spread of the pandemic (Appendix Figure B2), the peak of the epidemic would have passed, and widespread transmission would be decreasing without vaccination by October. Assuming that nonpharmaceutical interventions reducing infectious contacts by 15% remained in effect, vaccinating 40% of the population in October would gain 2854 QALYs at a cost of \$27 841 per QALY; vaccinating in November would increase costs by \$105 million, with a loss of 318 QALYs secondary to vaccine side effects.

Results Assuming Lesser Vaccine Availability

Recent announcements by public health officials suggest that the originally anticipated 120 million vaccine doses may not be ready for distribution in October but

Table 2. Health Outcomes Assuming No Vaccination for a City of 8.3 Million Individuals

R_0 *	Vaccination in October					Vaccination in November				
	Symptomatic Infections by 15 October 2009, n †	Deaths to Date, n †	Vaccination to Decrease Widespread Transmission, %‡	Persons Still Susceptible to Infection, %	Deaths Averted After Vaccination, n §	Symptomatic Infections by 15 November 2009, n	Deaths to Date, n	Vaccination to Decrease Widespread Transmission, %	Persons Still Susceptible to Infection, %	Deaths Averted After Vaccination, n
1.2	38 304	38	21	89	768	40 416	40	21	89	764
1.5	285 566	286	40	85	2051	541 865	542	35	80	1468
1.8	1 742 525	1743	25	59	649	2 246 591	2247	9	50	358

* Number of secondary infections caused by each primary infection in a susceptible population. R_0 s correspond to attack rates as follows: R_0 of 1.2 = 19% attack rate; R_0 of 1.5 = 36% attack rate; R_0 of 1.8 = 46% attack rate.

† From a total population of 8 300 000 in target city.

‡ $R_0 \leq 1$ (by epidemiologic definitions, end of pandemic).

§ At 12 months, compared with continuing with no vaccination.

that at least 45 million doses, a quantity sufficient to vaccinate 15% of the population, will be available (69, 90). Vaccinating 15% of the population in mid-October would avert 719 474 infections and 720 deaths, saving \$162 million versus no vaccination.

The costs and feasibility of expediting vaccination of 15% to 40% of the population in mid-October are unknown. At a willingness-to-pay threshold of \$50 000 per QALY, over an R_0 range of 1.5 to 1.8, the additional acceptable costs would range from \$2.6 billion to \$447 million for a city of 8.3 million individuals.

Results Under Differing Vaccination Strategies

As results of vaccine trials comparing 1- and 2-dose vaccination emerge, policymakers may consider 2-dose vaccination (68, 91). With a 2-dose adjuvanted vaccine, 20% of the population could be vaccinated in mid-November, averting 967 deaths and saving \$159 million, as compared with 1468 deaths averted and \$302 million saved with 1-dose vaccination.

Policymakers may also consider nonadjuvanted vaccines in light of emerging data showing equal or nearly equal efficacy to adjuvanted vaccines (91). One-dose nonadjuvanted vaccination in mid-November would save \$23 million as compared with equally efficacious adjuvanted vaccination for a city of 8.3 million individuals.

Additional Sensitivity Analyses

We conducted univariate sensitivity analysis on all variables (Appendix Table B1). If more effective nonpharmaceutical interventions were implemented, fewer individuals would become infected, and the peak of the pandemic would be delayed while the interventions were in effect. If 70% reduction in contacts were achieved through nonpharmaceutical interventions, the pandemic would be contained ($R_0 < 1$). Decreases in vaccine efficacy would increase the percentage of the population requiring vaccination to decrease widespread transmission in November (Figure 3).

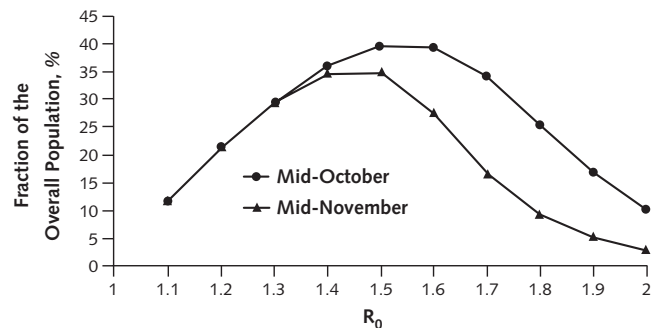
Sensitivity to Severe Vaccine Side Effects

Under our base-case assumption of severe side effects from vaccination occurring in 1 in 100 000 vaccinated individuals, vaccinating 40% of the city's population would cause approximately 2 deaths from severe vaccine side effects but would prevent 1468 influenza deaths from vaccination in November. If severe side effects from adjuvanted vaccination occur in 1 in 250 individuals, 664 deaths would result from severe side effects, approximately half the number of lives saved from vaccination in November.

Monte Carlo Probabilistic Sensitivity Analysis

In 45% of Monte Carlo probabilistic sensitivity analysis simulations (Appendix Figure B3), vaccinating 40% of the population in November is cost-saving compared with no vaccination; in 69% of simulations, vaccinating 40% of the population in November has an estimated incremental cost less than \$50 000 per QALY saved and in 71% of

Figure 2. Percentage vaccination required to decrease widespread transmission in October and November.



At R_0 (number of secondary infections caused by each primary infection in a susceptible population) of 1.2, fewer individuals would become infected, so less immunity would develop and more individuals would require vaccination to decrease widespread transmission. However, at R_0 of 1.8, a significant number of infections would occur, increasing population immunity and decreasing the number of individuals who would require vaccination to decrease widespread transmission.

simulations, an estimated incremental cost less than \$100 000 per QALY saved. In 26% of simulations, no vaccination is more cost-effective than vaccinating 40% of the population in November.

DISCUSSION

We examined the costs and benefits of vaccination in the autumn for the ongoing 2009 (H1N1) pandemic. Our analysis suggests that absent additional harms, earlier vaccination, as advised by the National Biodefense Science Board (8), would be more cost-saving and avert more deaths than vaccination later in the autumn. Because accelerating large-scale vaccination efforts in this time frame may be costly, we have provided a range of acceptable costs of vaccination, given different reproductive rates, to guide policymakers in situations in which they might consider speeding up vaccine production and administration. We defined the number of individuals requiring vaccination to reduce widespread transmission in a metropolitan city under a broad range of possible reproductive rates, and we note that regardless of the timing of vaccination, complete population coverage is not necessary to reduce the viral reproductive rate sufficiently to help shorten the pandemic. These results have important ramifications both for vaccine production goals and preparations for a potentially unprecedented fall vaccination campaign.

We found that the effectiveness and cost-effectiveness of vaccination are most dependent on the speed at which the pandemic grows. Our finding that earlier vaccination saves more costs and averts more deaths may be most important for areas with faster growth of the pandemic. Of note, the virus is not spreading at the same rate throughout the United States but appears to be evolving as different

Table 3. Economic Outcomes After Vaccination for a City of 8.3 Million Individuals*

R_0 †	Vaccination in October						Vaccination in November					
	Vaccination Costs (in Millions), \$	Treatment Costs (in Millions), \$	Normal Health Care Costs (in Millions), \$‡	Total Costs (in Millions), \$	QALYs	ICER, \$/QALY	Vaccination Costs (in Millions), \$	Treatment Costs (in Millions), \$	Normal Health Care Costs (in Millions), \$‡	Total Costs (in Millions), \$	QALYs	ICER, \$/QALY
1.2	116	(358)	135	(103)	25 387	Cost-saving	116	(356)	135	(102)	25 236	Cost-saving
1.5	116	(959)	365	(469)	69 679	Cost-saving	116	(686)	261	(302)	49 422	Cost-saving
1.8	116	(304)	116	(69)	20 967	Cost-saving	116	(167)	64	14	10 851	1303

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

* All outcomes are relative to no vaccination. Numbers in parentheses indicate cost savings.

† Number of secondary infections caused by each primary infection in a susceptible population. R_0 s correspond to attack rates as follows: R_0 of 1.2 = 19% attack rate; R_0 of 1.5 = 36% attack rate; R_0 of 1.8 = 46% attack rate.

‡ Accounting for normal health care expenditures, total costs will increase in situations where deaths are averted.

regional and local epidemics (13–15, 44–53). Several factors may delay the peak of the pandemic, leaving a greater proportion of the population susceptible to infection and increasing the effectiveness and cost-effectiveness of vaccination later in the autumn. Viral characteristics that would delay the peak include a lower reproductive rate, a longer incubation period, and a shorter duration of infectiousness. Nonpharmaceutical interventions could also have a marked effect on the speed at which the pandemic grows: Our analysis shows that increased implementation of highly effective nonpharmaceutical interventions, such as early use of hand hygiene and surgical masks (61), can significantly delay the peak of the pandemic, increasing the effectiveness and cost-effectiveness of delayed vaccination.

In contrast, if the epidemic grows rapidly and peaks in October, as some authorities have suggested (92), vaccination becomes substantially less effective and less cost-effective. Our analysis evaluated an epidemic with a peak later than October, but we also evaluated the alternative scenario of an early peaking epidemic. Both are

plausible, and the possibility of an epidemic that peaks as early as October underscores the urgency of rapid vaccine distribution.

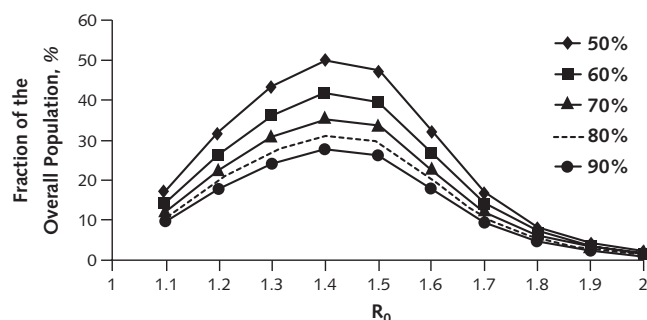
The U.S. Food and Drug Administration is awaiting results of ongoing trials of adjuvanted and nonadjuvanted pandemic (H1N1) to determine which type of vaccine to administer (91). We chose to examine an adjuvanted vaccine as a conservative estimate in light of potentially increased vaccine side effects and costs with an adjuvant. However, we examined vaccine efficacy consistent with nonadjuvanted pandemic (H1N1) trial results (67), so the decision to use nonadjuvanted vaccine would not affect our conclusions other than decreasing costs, as we describe in our sensitivity analyses.

Although complete population coverage with an effective vaccine for pandemic (H1N1) may be desirable (93), this goal does not seem to be logistically feasible for the autumn vaccination campaign. Our analysis suggests that over a wide range of viral reproductive rates and pandemic growth scenarios, vaccinating up to 44% of the population can be sufficient to slow widespread viral transmission by inducing herd immunity within the population, thereby shortening the pandemic.

We assumed that severe pandemic (H1N1) vaccine side effects could occur in 1 in 100 000 vaccinated individuals (73). Under these assumptions, vaccinating 40% of the city's population in November would cause approximately 1 death secondary to severe vaccine side effects for every 884 lives saved from vaccination. We emphasize that our analysis assumes that vaccination would not cause additional harms, and we encourage thorough testing and evaluation of vaccines before large-scale vaccination campaigns (94).

Key limitations of the analysis include an assumption that disease transmission occurs with homogenous mixing; all individuals, regardless of age and occupation, have the same frequency of contacts, and our model is not designed to make recommendations about the effects of prioritizing vaccination for different groups. In the 1918 and 1957

Figure 3. Percentage vaccination to decrease widespread transmission in November with varying vaccine efficacy.



The percentage of the population requiring vaccination to reduce widespread transmission increases with decreases in vaccine efficacy. The R_0 is the number of secondary infections caused by each primary infection in the susceptible population.

pandemics, influenza was transmitted more readily in children in proximity, such as in schools (95). If this pattern occurs in the 2009 (H1N1) pandemic, heterogeneous mixing would result in a faster initial spread of the pandemic, followed by slowing as it spreads to groups with decreased contact rates (96). Although individuals older than 60 years are most likely to have preexisting immunity to the virus (3), we assume uniform immunity across age groups. Our analysis provides insights into the magnitude of the pandemic and the response to vaccination (97); however, policymakers may wish to prioritize vaccination on the basis of differing patterns of transmission in specific age groups, as well as groups noted to have higher morbidity and mortality from pandemic (H1N1) infection.

We did not account for all costs to uninfected individuals in the setting of the 2009 (H1N1) pandemic; costs incurred by uninfected individuals from school and workplace closures, decreased tourism and group recreation, and loss of institution-specific knowledge may be greater than costs to sick individuals (98). We did not include potential savings of effective vaccination, such as limiting displacement of hospitalized patients, or decreasing school and workplace closures. However, including these costs and savings would make vaccination even more cost-effective or cost-saving. In addition, we account for normal health care expenditures, which significantly increase total costs for each life saved through vaccination; not including costs of long-term normal health care in our analysis would also make pandemic (H1N1) vaccination more cost-saving.

Covering most of the population with an effective vaccine for pandemic (H1N1) would prevent the most illness and death from influenza but will not be achievable within the short time frame for vaccine development and with projected supplies (69, 90). Our analysis suggests that vaccination can be a valuable and effective intervention even if it reaches less than half the population. Many uncertainties remain about the transmissibility and mortality of pandemic (H1N1) 2009; however, absent serious vaccine side effects, vaccination earlier in the autumn is likely to be cost-saving and avert more deaths than later vaccination. This highlights the urgency of vaccine development, with attention to safety. On 24 June 2009, President Obama signed into law an emergency spending bill devoting \$2 billion in additional funding to 2009 (H1N1) pandemic mitigation efforts (99); our analyses suggest that vaccination strategies could be a valuable component of such efforts.

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Reproducible Research Statement: An annotated version of the model is available in **Appendix 1** (available at www.annals.org) so that others can test the authors' findings and conclusions.

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