Published in final edited form as:
Ann Intern Med. 2014 May 20; 160(10): 684–694. doi:10.7326/M13-2071.

HEALTH AND ECONOMIC BENEFITS OF EARLY VACCINATION FOR A HUMAN INFLUENZA A (H7N9) PANDEMIC

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Abstract

Background—2009 pandemic vaccination occurred late, limiting its benefits. Influenza A (H7N9) is causing high morbidity and mortality in China, and researchers have modified A (H5N1) to transmit via aerosol, again heightening concerns about pandemic influenza preparedness.

Objective—We sought to determine how much more quickly a vaccination program should be implemented to reduce infections, deaths, and healthcare costs in a pandemic with characteristics similar to influenza A (H7N9) and A (H5N1).

Design—We used a 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.

Perspective—Societal.

Time Horizon—Lifetime.

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Interventions—Vaccination of 30% of the population at 4 or 6 months.

Outcome Measures—Infections and deaths averted, cost-effectiveness.

Results of Base Case Analysis—48,254 would die in 12 months; vaccinating at 9 months would avert 2,365 of these deaths. Vaccinating at 6 months would save 5,775 additional lives and $51 million at a city level. Further accelerating delivery to 4 months would save an additional 5,633 lives and $50 million.

Results of Sensitivity Analysis—In the event of a vaccine delay to 9 months, increasing reductions in contacts via non-pharmaceutical interventions by 8% would yield a similar reduction in infections and deaths as vaccination at 4 months.

Limitations—The model is not designed to evaluate programs targeting specific populations such as children or individuals with comorbidities.

Conclusions—Vaccination in an influenza A (H7N9) pandemic would need to be performed far more rapidly than in 2009 to substantially reduce morbidity, mortality, and healthcare costs. Maximizing non-pharmacological interventions can substantially mitigate the pandemic until matched vaccine becomes available.

BACKGROUND

Two events have raised concerns about our preparedness for a severe influenza pandemic: (1) separate scientific groups recently published methods for genetically engineering an influenza A (H5N1) virus that may be transmissible via aerosol between humans (1,2); and (2) 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 a crucial opportunity to evaluate our response to the 2009 influenza A (H1N1) pandemic and technological advances since that time to prepare for a severe influenza pandemic.

In our prior work assessing efficacy of vaccination in the 2009 pandemic, we found that timing of pandemic vaccination was crucial, with as little as a four week delay resulting in a substantial increase in infections, deaths, and costs. Unfortunately, large-scale vaccination against 2009 influenza A (H1N1) occurred nine months after the beginning of the pandemic, substantially later than the timing we found would have maximized health and economic benefits (5). Case-fatalities of influenza A (H5N1) and A (H7N9) are remarkably high (59% and 19%, respectively) compared with the less than 0.3% case-fatality seen in 2009 (6)(7)(3). These may be overestimated due to incomplete ascertainment of cases; nonetheless, the observed mortality remains a critical concern. If either of these viruses were lethal and transmissible between humans, a resulting pandemic would have devastating health and economic consequences, much greater than in 2009.

Advances in cell-based and recombinant vaccine (8) technologies could allow more rapid mass pandemic vaccination than current egg-based methods (9). To evaluate our progress and preparedness for a more severe pandemic than the mild 2009 influenza A (H1N1) pandemic, we developed a model of a severe pandemic with characteristics similar to influenza A (H7N9) and A (H5N1) to assess the value of accelerating vaccine production

with new technologies. We evaluated effectiveness and cost-effectiveness of no vaccination, or vaccination at four months or six months, compared to nine months.

METHODS

Overview

We created a dynamic infectious disease transmission model of the progression of a severe pandemic with characteristics similar to influenza A (H7N9) and A (H5N1) in a susceptible population (**Table 1** and **Appendix Figure 1**). We evaluated vaccine interventions coupled with non-pharmaceutical interventions. Following recommendations of the Panel on Cost-Effectiveness in Health and Medicine (10), we conducted the analysis using a societal perspective, discounting costs and benefits at 3% annually. We analyzed health and economic outcomes over the individuals' remaining lifetimes. We measured outcomes in infections and deaths averted, costs, and cost-savings. We constructed the model and performed analyses in Microsoft Excel (11).

Study Population and Disease Parameters

Susceptible Population—We modeled a population of 8.3 million individuals in a large metropolitan U.S. city with demographics comparable to New York City (12). We assumed 1,000 individuals 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 pre-existing population immunity.

Infected Population—We assumed a severe pandemic, comparable to 1918, with a reproductive number (R_0, the number of secondary infections caused by each infected individual in a susceptible population) of 2.0 (13). We varied R_0 between 1.8 and 2.2 in sensitivity analysis.

Based on prior studies (14)(15)(16), we assumed 67% of infected individuals were symptomatic, and 50% of them socially isolated, either voluntarily due to symptoms, or due to hospital admission. We assumed that the other 50% continued to infect others.

Based on observations of the 2009 influenza A (H1N1) outbreak (17), we assumed that the mean incubation period was 3 days. Based on Centers for Disease Control and Prevention (CDC) estimates (18)(19), individuals were assumed 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 individuals transmitted the disease at three times the rate of asymptomatic individuals.

Using CDC data, we estimated that 10% of symptomatic infections would require 5 days of hospitalization, and 10% of those hospitalized would be admitted to the intensive care unit (ICU) for 10 days (21).

Recovered Population—Studies find a 2 to 25% (22)(23) risk of re-infection with influenza A viruses. Re-infected individuals tend to be asymptomatic or have moderate symptoms, a shorter duration of illness, and less viral shedding (23). We assumed that 5

months following recovery, 5% of the recovered population once again become susceptible to infection. In sensitivity analysis, we analyzed a range of re-infection rates from 2% to 25%.

Death from influenza—The estimated case-fatality proportions of influenza A (H7N9) and A (H5N1) (6) may be too high due to undercounting of asymptomatic and mildly symptomatic infections (24)(25). However, mortality may be greater in resource-limited healthcare settings (7). We therefore assumed a 2.5% case fatality proportion for our model, well below the observed naturally occurring proportion. In sensitivity analysis, we examined case fatality rates ranging from of 0.5% to 10%. We allowed age-specific mortality to vary, with greater mortality rates in newborns and individuals over 65 years, consistent with the 1957 and 1968 pandemics and seasonal influenza epidemics (18). In sensitivity analysis, we examined additional increases in mortality in young adults, as occurred in the 1918 and 2009 pandemics (26). Based on prior pandemics (27), we assumed that healthy individuals 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 56% effectiveness, and varied effectiveness from 30% to 80% in sensitivity analysis.

Based on 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 45% of vaccinated individuals would experience mild to moderate adverse side effects such as pain, redness, swelling, fatigue, headache, arthralgia, myalgia, shivering, sweating, and low-grade fevers based on 2009 influenza A (H1N1) vaccine studies (30)(31). Although we assumed an unadjuvanted vaccine, we drew upon vaccination data from adjuvanted vaccination data in Europe in 2009 as well as vaccination campaigns in 1976, and assumed that 0.001% of vaccinated individuals would experience severe adverse effects like angioedema, anaphylaxis, narcolepsy, or Guillain-Barré Syndrome (32). We varied this number to 0.01% in sensitivity analysis, more than twice the adverse event rate of narcolepsy observed in European adjuvanted 2009 influenza A (H1N1) vaccines (33)(34).

Non-pharmaceutical interventions—The World Health Organization (WHO) and CDC recommend concurrent use of non-pharmaceutical and pharmaceutical interventions to mitigate influenza pandemics (35). Non-pharmaceutical interventions (NPIs) include closures of school and childcare 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 demonstrated a reduction of transmission rates from 66 to 75% (36)(37). Based on available data (38)(39), our model assumes NPIs reduce contacts by 25%.We also examined effects of 50 - 90% reduction in contacts in sensitivity analysis.

Cost and Utilities

We expressed all costs in 2012 dollars using the GDP deflator (40). Our model incorporates long-term lifetime health expenditures and costs associated with vaccination (including vaccine, administration, cost of individuals' time, and costs of treating adverse side effects) (**Table 1**). Treatment costs are based on the average cost of hospitalization due to symptomatic influenza infection (41) or ICU admission (42). We used one hour of average wages to estimate the opportunity cost of an individual's time receiving vaccine (43). We used EuroQol (44) and Time Trade-Off ratings (45) for utility estimates and accounted for the average remaining lifetime of individuals alive at the end of the year. We calculated long-term health expenditures by age based on personal health care expenditure from the Centers for Medicare and Medicaid Services Age Tables (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 determined ranges from data sources, or by adding or subtracting 25% from the base case.

Role of the Funding Source

The funding organization 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 to the 1918 Pandemic (27), our model had a similar clinical attack rate (33% vs. 30-40%) and first pandemic wave duration (50 vs. 55-60 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 individuals would become symptomatically infected and 48,254 would die (**Table 2**). For a 2.5% case-fatality, vaccination can reduce daily mortality by 85-92% (**Figure 1**).

In the base case, assuming vaccination were to take 9 months, 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 2,365 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 and vaccination would avert approximately 230,321 additional infections and 5,775 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 by 4 months time (49), it would have the most substantial impact, averting 225,992 additional infections and 5,633 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 vaccine, $30 million for distribution, $55 million in individuals' time receiving the vaccine and $10 million to treat short-term adverse effects.

Value of Accelerating Vaccine Delivery

The costs to speed vaccine delivery are unknown. We performed 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, resulting in short-term treatment cost savings. However, overall long-term costs increase because the lifetime expected medical costs outweigh short-term treatment cost savings. For example, every infection averted by vaccination saves about $220 in treatment costs, but if the intervention saves someone from dying, the person will now incur about $245,000 in lifetime normal medical costs. Completing the vaccination program at 6 months versus 9 months would cost $10,722 per quality adjusted life year saved, and completing the vaccination program at 4 months versus 6 months would cost $10,689 per quality adjusted life year saved (**Table 2**).

SENSITIVITY ANALYSES

We performed univariate sensitivity analysis on all variables in our model (**Appendix Table 1**). The parameters most substantially affecting health and economic outcomes are case-fatality proportion and impact of NPIs.

Case-Fatality Proportion

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

A lower case-fatality of 0.5% would cause 12,525 deaths in a population of 8 million individuals in 12 months. Vaccination at 4 months would avert 373 deaths and save $16.5 million of treatment costs in the short term, whereas **v**accination at 6 months would avert only 61 deaths and save $2.7 million of treatment costs in the short term.

With a case-fatality proportion of 10%, 92,879 deaths would occur in a population of 8 million individuals in 12 months. In response to the high mortality, individuals reduce interpersonal contacts; as mortality decreases, individuals resume contacts, leading to sequential pandemic waves. In this setting, vaccination can reduce daily mortality by 63-72% (**Figure 1**). Vaccination at 4 months would prevent 33,605 deaths, and save $ 72 million of treatment costs in the short term. Vaccination at 6 months would prevent 24,778 deaths, and save $ $52 million of treatment costs in the short term. These interventions increase long-term healthcare costs because substantially more people survive to have average life expectancies, with associated medical costs. If long-term healthcare costs were not included, vaccination at 4 or 6 months would be cost-saving versus vaccination at 9 months (**Appendix Table 2**).

Non-Pharmaceutical Interventions

The impact of NPIs is substantial. Under a case-fatality of 2.5% without NPIs, 75,018 deaths (vs. *48,254*) would occur in a population of 8 million individuals in 12 months.

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

In case vaccine coverage is delayed to 6 or 9 months, we considered alternative 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% over pandemic days 30 to 60 would delay the peak of the first wave to 6 months; increasing to 90% over days 45 to 105 would delay the peak to 9 months (**Figure 2**).

Vaccine Effectiveness and Additional Costs of Earlier Vaccination

We performed 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 individual vaccinated at the earlier time point. If the additional cost of vaccination were less than $925 per individual and the vaccine were at least 30% effective, the cost of vaccinating at 4 months (relative to 6 months) would be less than $50,000 per quality adjusted life-year gained.

We also examined increased costs for earlier vaccination under a wide range of case-fatalities. As the case-fatality increases, additional lives can be saved through earlier vaccination. For example, at a case-fatality proportion of 10%, an additional cost of $1,000 to vaccinate each individual at 4 versus 6 months would have an incremental cost of $24,000 per quality adjusted life year gained. When the case-fatality is lower than 0.5%, however, fewer lives are saved through earlier vaccination, and even an additional cost of $125 per individual would result in an incremental cost greater than $50,000 per quality adjust life-year gained to vaccinate at 4, rather than 6 months.

Vaccine Coverage

Because treatment costs decrease with increasing population vaccine 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, while vaccinating 10% of the population at the same time point would only save $23 million in treatment costs. (**Appendix Table 3**).

Vaccine Rollout

Rollout of vaccines using new technologies may occur 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 4**). Compared to our base case analysis of distribution over 10 days, mortality increased by 1-8%, but economic outcomes were similar (**Appendix Table 4).**

Behavior Change in Vaccinated Individuals

Vaccinated individuals believe that they are less susceptible to infection and are less likely to reduce contacts. Our base case assumes 56% vaccine effectiveness, and many of these individuals will still be susceptible to influenza infection and transmission. If individuals who were vaccinated performed 20% or less social distancing of non-vaccinated individuals, and if 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 simulation, varying all parameters simultaneously for 1,000 simulations. Comparing vaccination at 4 months to alternative vaccination strategies and no vaccination, vaccination at 4 months is preferred 88% of the time. Since vaccinating earlier would likely cost more due to accelerating vaccine production and delivery, we also performed analyses assuming additional costs of $10, $100, or $1,000 per individual vaccinated earlier (**Appendix Figure 3a**). 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 an optimal window exists 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 even a true pandemic , vaccination occurred far later than the optimal window to avert infections, deaths, and decrease costs, and in the time frame when much of the population had been infected and developed natural immunity, limiting large

scale benefits of vaccination. Four years later, it is unclear whether we are better prepared for such an event, or—more concerning—for a far more severe pandemic.

In light of the recent end to an international ban on experiments genetically modifying strains of influenza A (H5N1) that may spread between humans, and an ongoing high mortality from novel influenza A (H7N9), we assessed how the timing of a vaccination program would impact health and economic outcomes in a severe pandemic scenario that these viruses could cause. Large-scale vaccination in the U.S. occurred 9 months after the start of the 2009 pandemic. Comparing our findings to those of 2009 influenza A (H1N1), we note that the higher reproductive number and case-fatality associated with a severe pandemic virus would cause the pandemic to progress even more rapidly, further narrowing the optimal window for vaccination. To substantially reduce infections, deaths, and influenza treatment costs, vaccinating must occur much earlier than it did in 2009.

Pandemic egg-based vaccine development begins with a 2-month process of identification, preparation, and verification of the vaccine strain at WHO Collaborating Centers. In the next 3 months, manufacturers optimize viral growth conditions, manufacture bulk vaccine, perform quality control, fill vaccines, and perform 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 vaccine development, such as the use of cell- or recombinant- rather than egg-based vaccines (51)(52). Additional novel technologies, such as generation of synthetic vaccine seeds, could further speed development in the setting of a pandemic (53). While costs of such a program are unknown, we examined the value of earlier vaccination, and find 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 refuse influenza vaccination. Based on 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 population at an early time point can substantially reduce the health and economic impacts of a severe pandemic.

While 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 use of NPIs will be important to vaccinated as well as unvaccinated individuals. Our study demonstrates the potential for increased use of NPIs not only as an effective supplemental intervention to vaccination, but as a bridge to decrease widespread transmission of the pandemic in the absence of a vaccine. If approximately 33% reductions in contacts are achieved via NPIs over 9 months, reductions in infections, deaths and costs would be similar to vaccinating 30% of the population at 4 months with our baseline assumptions regarding NPIs. Institution of more intensive NPIs (such as school closures or home quarantine) between pandemic days 30 to 60, or 45 to 105, can respectively delay

pandemic peaks to 6 and 9 months, again serving as a bridge to vaccination. Since current egg-based vaccine technology takes at least 6 months, our analysis suggests that NPIs may be crucial in mitigating the pandemic while awaiting development and distribution.

Limitations of our analysis include our assumption of homogenous 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 individuals such as children; transmission rates can be affected by social networks such as children in school (54). Similarly, our model cannot evaluate the impact of targeting vaccination to individuals who, due to age or comorbidities, may be at higher risk of morbidity or mortality following influenza illness. To optimize resource allocation, policymakers may consider prioritizing vaccination by age groups as well as comorbidities. 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 their transmissibility, morbidity, and mortality in humans. We examined mortality rates far lower than currently reported for these two viruses; even at a case-fatality proportion of 2.5%, our analysis reveals an unprecedented numbers infections, deaths, and health care costs in the event of an influenza A (H5N1) or A (H7N9) pandemic. Encouragingly, we also find that early vaccination and use of NPIs can have a important impact in averting these losses. The acceleration of large-scale vaccination development is a current challenge for public health and has not yet been achieved in the 4-month interval in which we found the greatest benefits. Our findings call attention to the need for investment in vaccine development and distribution strategies as well as public health messages to promote the widespread use of NPIs in the event of a severe pandemic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank our talented friend and colleague Charlotte Chae for her assistance with our graphics.

GRANT SUPPORT:

This research was supported by the Agency for Healthcare Research and Quality (5 K08 HS 019816, Dr. Khazeni) and the National Institutes of Health (5 R01 DA015612-12, Dr. Owens). Dr. Owens was supported by the Department of Veterans Affairs. The funding organization had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Funding Source: Agency for Healthcare Research and Quality; National Institutes of Health (5 R01 DA015612-12), Department of Veterans Affairs.

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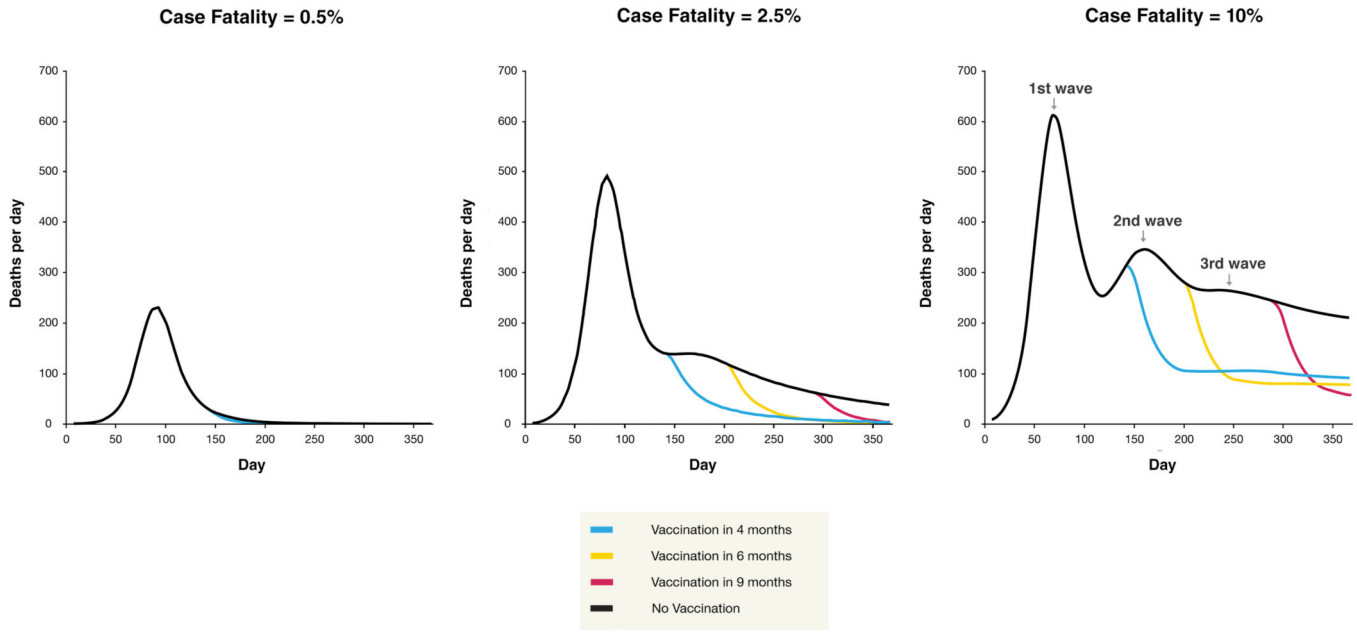

Figure 1. Infections and deaths per day depending on timing of vaccination and case-fatality

At high case-fatality proportions, individuals begin to reduce social interactions in response to increasing mortality, reducing the number of infections per day, but lengthening the epidemic. As this reactive social distancing decreases mortality, individuals resume contacts, leading to sequential pandemic waves over time..

The lines in this figure demonstrate deaths per day (the areas under the curves represent cumulative deaths). Deaths per day are generally higher for vaccination at 6 months than those for vaccination at 4 months; however, with a case-fatality proportion of 10%, deaths per day for vaccination in 6 months drops below deaths per day for vaccination in 4 months after day 240. This occurs because by that point, a greater number of individuals in the 6-month vaccination category have been infected and developed immunity following infection, leading to fewer susceptible people and therefore fewer deaths. We see this only under the 10% case-fatality proportion, because as individuals reduce social interactions due to higher mortality, the epidemic lasts longer and there is still sustained influenza transmission at day 240 and beyond. The total cumulative deaths under the policy of vaccination in 6 months (represented by the total area under the curves) are always equal to or greater than those under the policy of vaccination in 4 months. The same reasoning explains daily death rates for vaccination at 9 months dropping below vaccination in 6 months later in the epidemic.

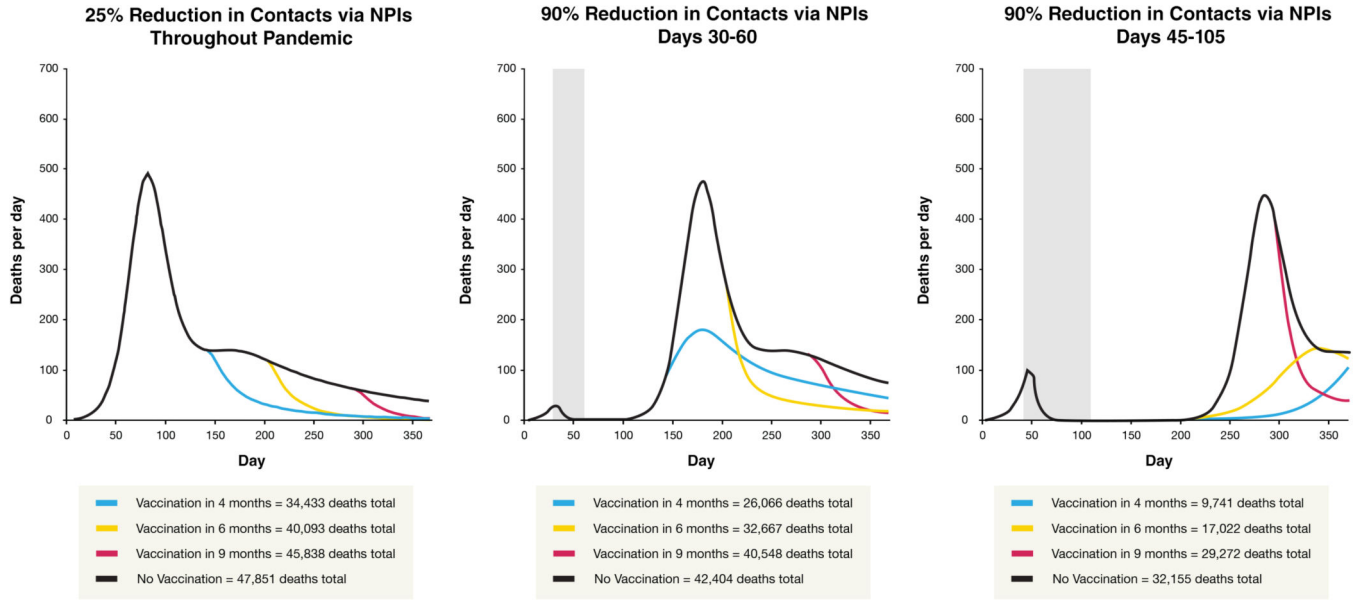

Figure 2. Infections and deaths per day with increasing non-pharmaceutical interventions

In case of delays to mass vaccination, public health officials could announce and implement the most restrictive NPIs (e.g., school closures or home quarantines) to mitigate the pandemic while awaiting vaccination. Increasing NPIs to 90% over pandemic days 30 to 60 would delay the first wave to 6 months; increasing to 90% over days 45 to 105 would delay the first wave to 9 months.

The lines in this figure demonstrate deaths per day (the areas under the curves represent cumulative deaths). Deaths per day for vaccination in 6 months are generally higher than those for vaccination in 4 months; however, in the case of 90% reduction in contacts due to NPIs, the daily deaths for vaccination in 6 months decrease below the deaths per day for vaccination in 4 months later in the epidemic. This occurs because by that point, a greater number of individuals in the 6-month vaccination category have been infected and developed immunity following infection, leading to fewer susceptible people and therefore fewer deaths. The total cumulative deaths under the policy of vaccination in 6 months (represented by the total area under the curves) are always equal to or greater than those under the policy of vaccination in 4 months. The same reasoning explains daily death rates for vaccination at 9 months dropping below vaccination in 6 months later in the epidemic.

Table 1

Variables and Sources

Variable	Base Case (Range)	Source
Susceptible Population Parameters		
Population	8,175,133	New York Quick Facts, US Census Bureau (12)
Age (range, years)	0-100	New York Quick Facts, US Census Bureau (12)
Percent female	53	New York Quick Facts, US Census Bureau (12)
Pre-existing population immunity	0% (0-10%)	Assumed, WHO (56)
Infected Population Parameters		
Number of infected individuals at start of pandemic	1,000 (100-10,000)	New York City Department of Health and Mental Hygiene (57), CDC (15),
Infectiousness		
Secondary infections caused by an infected individual (R_0)	2.0 (1.8-2.2)	Assumed, CDC MMWR (58) (59)
Non-pharmaceutical interventions reduction in R_0	25% (0-50%)	Assumed, Davey et al. (39)
Mean duration of infectiousness (days)	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 individuals)	25% (10-50%)	Hayden et al. (19), Wein et al. (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 (days)	10 (7.5-12.5)	CDC (18), (19)
Probability of isolation if symptomatic	50% (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 (days)	5 (3.75-6.25)	CDC (21), HHS (63)
Probability of ICU care	20% (10-30%)	CDC (21), HHS (63)
Mean duration of ICU stay (days)	10 (7.5-12.5)	CDC (21), HHS (63)
Incubation		
Mean incubation time (days)	3 (1-7)	Novel Swine-Origin Influenza A Virus Investigation Team (56), CDC (18), WHO influenza A (H5N1) data (56)
Infectiousness by incubating (relative to symptomatic individuals)	50% (10-62.5%)	Hayden et al. (19), Wein et al. (60)
Recovered Population Parameters		
Susceptibility to re-infection following recovery	5% (2-25%)	Smith et al. (22), Monto et al. (23)
Timing of waning immunity (months)	5 (2-8)	Smith et al. (22), Monto et al. (23)
Mortality		
Case-fatality proportion	2.5 (0.5%-10%)	Assumed, Current influenza A (H5N1) Case Fatality (56), Seasonal flu clinical case-fatality (18), CDC Severity Index 5 Case Fatality (63), Li FCK (64), Taubenberger and Morens (65)
Mortality threshold for reactive social distancing	10 per 10,000 (5-50 per 10,000)	Bootsma and Ferguson (27)
Reactive social distancing memory period*	30 days (1-40)	Bootsma and Ferguson (27)
Vaccination		
Population coverage	30% (10-50%)	Assumed
Effectiveness	56% (30-80%)	Griffin et al. (66)

Variable	Base Case (Range)	Source
Mild-moderate side-effects	45% (5-75%)	European Medicines Agency (30), GlaxoSmithKline (31)
Duration (days)	2 (1-7)	European Medicines Agency (30), GlaxoSmithKline (31), CDC (67)
Reduction in quality of life[†‡]	0.05 (0-0.1)	European Medicines Agency (30), GlaxoSmithKline (31), CDC (67)
Severe side effects	0.001% (0-0.01%)	Neustadt and Fineberg (32), Partinen et al. (33), Nohynek et al. (34)
Duration of hospitalization (days)	14 (7-28)	Chio et al. (68)
Reduction in quality of life	0.5 (0-1)	Assumed, Neustadt and Fineberg (32)
Risk of death	5% (1-10%)	Chio et al. (68)
Risk of long-term care	5% (1-10%)	Kissel et al. (69)
Influenza-related quality of life		
Uninfected/Asymptomatic	0.96 (0.92-1.00)	Beaver Dam Health Outcomes (47), New York Quick Facts, US Census Bureau (12)
Symptomatic Influenza	0.8 (0.7-0.9)	Turner et al. (70)
Post-influenza disabled state for patients requiring ICU care	0.9 (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)	Calculated: 10 minutes of nurse wages, Bureau of Labor Statistic (72)
Patient Time	11.64 (5.82-23.28)	U.S. Bureau of Labor Statistics (73)
Daily health care costs ($)		
Patient with severe side effects (treated in ICU)	3902 (2,926-4,877)	Desta et al. (42)
General medical hospitalized patient	1910 (1,433-2,388)	Talbird et al. (41)
ICU hospitalized patient	3902 (2,927-4,878)	Desta et al. (42)
Long-term treatment facility costs	327 (245-408)	Metlife Survey (74)
Long-term health expenditures	24.53 (18.40-30.66)	National Health Expenditure Data (46)
Other variables		
Discount Rate (annual)	3% (0-5%)	Weinstein et al. (10)

[*] Reactive social distancing describes historic pandemic phenomenon in which individuals 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, individuals would reduce social contacts if average mortality in the last two days were high. If the “mortality period” were 60, individuals would reduce contacts if the average mortality over the last 60 days were high.

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

[‡] Reduction of quality of life in our model represents duration of reduction multiplied by quantity of decrement.

Table 2

Health and economic outcomes for a city of 8.3 million individuals

Outcome	No Vaccination	Vaccination Time* (months):		
		9	6	4
Symptomatic infections	1,920,514	1,834,584	1,604,262	1,378,271
Deaths	47,851	45,889	40,114	34,481
Individuals still susceptible to infection	68%	70%	76%	81%
Deaths averted following vaccination†	-	-	5,775	11,408
% Reduction in contacts via NPIs‡ required to decrease widespread transmission§	50%	29%	34%	39%
Vaccination Costs (USD, millions)	-	140	140	140
Short-Term Treatment Cost Savings (USD, millions)	-	-	51	50
Long-Term Lifetime Health Expenditures ** **(USD, millions)**	-	-	1,417	1,390
Incremental Total Costs (USD, millions)	-	-	1,367	1,339
QALYs Gained††	-	-	127,460	125,309
ICER (USD/QALY)‡‡	-	-	10,722	10,689

*Since start of pandemic in target city

†Compared to vaccination at 9 months

‡NPI = Non-pharmaceutical intervention

§$R_0 \leq 1$. 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 people survive to have average life expectancies, with associated medical costs. Accounting for the healthcare expenditures of individuals whose lives are saved, total costs increase in the long term. Long-term costs of vaccination at 4 months are compared to 6 months, and costs of vaccination at 6 months are compared to 9 months.

††QALY = quality-adjust life year

‡‡Incremental cost-effectiveness ratio