PRIORITIZATION OF DELAYED VACCINATION FOR PANDEMIC INFLUENZA

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Abstract. Limited production capacity and delays in vaccine development are major obstacles to vaccination programs that are designed to mitigate a pandemic influenza. In order to evaluate and compare the impact of various vaccination strategies during a pandemic influenza, we developed an age/risk-structured model of influenza transmission, and parameterized it with epidemiological data from the 2009 H1N1 influenza A pandemic. Our model predicts that the impact of vaccination would be considerably diminished by delays in vaccination and staggered vaccine supply. Nonetheless, prioritizing limited H1N1 vaccine to individuals with a high risk of complications, followed by school-age children, and then preschool-age children, would minimize an overall attack rate as well as hospitalizations and deaths. This vaccination scheme would maximize the benefits of vaccination by protecting the high-risk people directly, and generating indirect protection by vaccinating children who are most likely to transmit the disease.

1. **Introduction.** The emergence of a pandemic strain of H1N1 influenza A in Mexico and rapid global spread made influenza pandemic preparedness a top public health priority [16]. Vaccination is critical to controlling the spread of influenza and reducing the disease burden. In the event of an influenza pandemic, the introduction of a matched vaccine (from isolation of the circulating virus) is expected to be delayed by at least three months [43]. A similar situation occurred with the 2009 H1N1 influenza A pandemic, and vaccines did not become available until late October, 2009 [35]. This resulted in relatively low vaccine coverage, approximately 20% in the US [8]. Initially, the 2009 H1N1 vaccines in the US were largely distributed to health care personnel, individuals from 6 months through 24 years of age, and individuals at high risk of medical complications [9]. When more vaccines became available and the demand for vaccine for the prioritized groups was met, vaccines were given to everyone from the ages of 25 to 64.

The 2009 H1N1 vaccination recommendations in the US were based on the infection pattern of H1N1 influenza pandemic strain. Previous studies showed that among all age groups, school-age children are the most likely to become infected, although young adults are more likely to experience serious clinical outcomes [10]. Thus, the largest numbers of H1N1 deaths occurred in the 25-to-49 age group in the US [10]. Discordantly, the elderly have been mostly protected from the H1N1 pandemic strain due to previous exposure to a similar virus in the 1940s and 1950s

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[11, 35, 41]. Thus, the risk for infection among persons aged 65 and older was less than the risk for younger age groups [23, 35].

Given that the attack rates and the risk of medical complications differ between age groups, the prioritization of vaccination needs to be carefully assessed to produce the greatest reduction in influenza illness attack rates. In this context, we propose to investigate the effectiveness of various age/risk-targeted vaccination strategies when vaccine supply is limited and delayed. Using our age-structured model of influenza transmission and vaccination, we evaluated the effectiveness of five different vaccine allocation schemes in the context of the H1N1 influenza A pandemic; (i) 'CDC-like' influenza vaccination scheme according to the 2009 H1N1 vaccine recommendations prepared by CDC's Advisory Committee on Immunization Practices (ACIP); (ii) the 'seasonal-like' influenza vaccination scheme prioritizing the high-risk group, young children (≤ 19 y) and the elderly (≥ 65 y); (iii) the morbidity-based scheme, which targets demographics with high attack rates; (iv) the mortality-based scheme, which targets those age/risk groups in which most influenza deaths occur; and (v) the mass vaccination scheme.

In this paper, we compared the reduction in overall and age-specific influenza cases that could be prevented by implementing five vaccination strategies proposed above. In addition, we considered the impact of vaccine delay on the effectiveness of vaccination programs. In order to study whether optimal strategy depended on the level of viral transmissibility, the basic reproductive ratio was varied for sensitivity analysis.

2. **Methods.** To compare the effectiveness of various vaccination schemes against H1N1 influenza A pandemic in the US, we developed an age/risk-structured deterministic model of influenza transmission and vaccination. We applied realistic assumptions regarding the delay of vaccine distribution and limited vaccine supplies. Our model is parameterized with the age-specific contact patterns [30], a proportion of people at high risk of medical complications in age groups, and population immunity profiles. The proposed model was also parameterized with transmissibility, case hospitalization ratio, and case fatality ratio of the 2009 H1N1 influenza A (Table 1). Below we describe our model, and present vaccination strategies examined.

2.1. **Mathematical model.** We constructed a mathematical model that incorporates transmission dynamics of influenza infections, vaccination, and pre-existing immunity against the pandemic strain of H1N1 influenza A. In order to track the influenza-related epidemiological status of individuals, we divided the population into five groups for ages ≤ 4, $5 - 9$, $20 - 44$, $45 - 64$, and 65+ (Table 1). Within each age group, we further subdivided the population into low- and high-risk groups in terms of influenza complications. Individuals at high risk can be identified by medical conditions such as asthma, chronic obstructive pulmonary disease, diabetes, neurologic disease, and pregnancy [9]. The proportion of high-risk people within each age group is provided in Table 1. Each of the age/risk groups is then stratified by epidemiological and vaccination status. We assume that S_k, E_k, A_k, I_k, and R_k represent the respective numbers of susceptible, latent, asymptomatic, symptomatic, and recovered individuals in age group k ($k = 1, 2, \cdots, 5$). In addition, we use the subscripts L, H, U, and V to indicate low-risk, high-risk, unvaccinated, and vaccinated individuals. For instance, $S_{LU,1}(t)$ represents the number of unvaccinated susceptible individuals at low risk in the youngest age group.

Parameter	Ages	Value	Reference
Basic reproductive ratio ($\Re_0$)		1.4	[3, 4, 12, 16, 20] [31, 34, 35, 36, 42]
Overall vaccination coverage for Nov 1 peak for Dec 1 peak for Jan 1 peak for Feb 1 peak		20.5%* 30.1% 41.0% 41.0%	[8] By assumption By assumption By assumption
Latent period	all	3 days	[22]
Infectious period	all	4 days	[22]
Proportion of infections that become symptomatic (p)	all	0.67	[14, 17, 25, 44]
Population distribution ($N_k(0)/N(0)$)	0-4 5-19 20-44 45-64 65+	0.0691 0.2027 0.3437 0.2567 0.1278	
Proportion of population who are at high risk (ξ_k)	0-4 5-19 20-44 45-64 65+	7.61% 12.38% 19.88% 30.41% 50.15%	[27]
Proportion of population who have remote H1N1 immunity (χ_k)	0-4 5-19 20-44 45-64 65+	0.00% 0.00% 7.50% 7.50% 33.00%	[24]
Case fatality ratio (d_k)	0-4 5-19 20-44 45-64 65+	0.026% 0.030% 0.159% 0.159% 0.090%	[32]
Case hospitalization ratio (h_k)	0-4 5-19 20-44 45-64 65+	2.45% 0.93% 3.00% 3.00% 1.84%	[32]
Vaccine efficacy against infection (δ_k)	0-4 5-19 20-44 45-64 65+	75.9% 75.9% 75.9% 68.5% 66.1%	[19]
Vaccine efficacy against death (κ_k)	0-4 5-19 20-44 45-64 65+	75% 75% 70% 70% 60%	[28]

TABLE 1. Parameter values with sources. (*Age-specific vaccination coverage is shown in Table 2.)

We define λ_k as the rate at which unvaccinated susceptible individuals in age group k are exposed to the influenza virus. When individuals in age group k are vaccinated, the rate at which they are exposed to influenza viruses is reduced by age-specific vaccine efficacy, δ_k. The mean latent and infectious periods are assumed to be $1/\tau$ and $1/\gamma$, respectively. We also assume that hospitalization or deaths may occur among symptomatic cases. The influenza-induced death rates for symptomatic cases in age group k are $\alpha_{LU,k}$, $\alpha_{HU,k}$, $\alpha_{LV,k}$, and $\alpha_{HV,k}$, respectively, for unvaccinated low-risk, unvaccinated high-risk, vaccinated low-risk, and vaccinated high-risk people.

Using the definitions above, the transmission of influenza and vaccination can be described by the following differential equations:

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\begin{aligned}
\frac{dS_{LU,k}}{dt} &= -\left(\omega_{L,k}(t) + \lambda_k\right)S_{LU,k}, \\
\frac{dE_{LU,k}}{dt} &= \lambda_k S_{LU,k} - \tau E_{LU,k}, \\
\frac{dA_{LU,k}}{dt} &= \tau(1-p)E_{LU,k} - \gamma A_{LU,k}, \\
\frac{dI_{LU,k}}{dt} &= \tau p E_{LU,k} - (\gamma + \alpha_{LU,k})I_{LU,k}, \\
\frac{dR_{LU,k}}{dt} &= \gamma(I_{LU,k} + A_{LU,k}), \\
\frac{dS_{HU,k}}{dt} &= -\left(\omega_{H,k}(t) + \lambda_k\right)S_{HU,k}, \\
\frac{dE_{HU,k}}{dt} &= \lambda_k S_{HU,k} - \tau E_{HU,k}, \\
\frac{dA_{HU,k}}{dt} &= \tau(1-p)E_{HU,k} - \gamma A_{HU,k}, \\
\frac{dI_{HU,k}}{dt} &= \tau p E_{HU,k} - (\gamma + \alpha_{HU,k})I_{HU,k}, \\
\frac{dR_{HU,k}}{dt} &= \gamma(I_{HU,k} + A_{HU,k}), \\
\frac{dS_{LV,k}}{dt} &= \omega_{L,k}(t)S_{LU,k} - (1-\delta_k)\lambda_k S_{LV,k}, \\
\frac{dE_{LV,k}}{dt} &= (1-\delta_k)\lambda_k S_{LV,k} - \tau E_{LV,k}, \\
\frac{dA_{LV,k}}{dt} &= \tau(1-p)E_{LV,k} - \gamma A_{LV,k}, \\
\frac{dI_{LV,k}}{dt} &= \tau p E_{LV,k} - (\gamma + \alpha_{LV,k})I_{LV,k}, \\
\frac{dR_{LV,k}}{dt} &= \gamma(I_{LV,k} + A_{LV,k}), \\
\frac{dS_{HV,k}}{dt} &= \omega_{H,k}(t)S_{HU,k} - (1-\delta_k)\lambda_k S_{HV,k}, \\
\frac{dE_{HV,k}}{dt} &= (1-\delta_k)\lambda_k S_{HV,k} - \tau E_{HV,k}, \\
\frac{dA_{HV,k}}{dt} &= \tau(1-p)E_{HV,k} - \gamma A_{HV,k},
\end{aligned}
\tag{1}
$$

$$\frac{dI_{HV,k}}{dt} = \tau p E_{HV,k} - (\gamma + \alpha_{HV,k})I_{HV,k},$$

$$\frac{dR_{HV,k}}{dt} = \gamma(I_{HV,k} + A_{HV,k}),$$

for $k = 1, 2, \cdots, 5$.

Here we define the total population size (N) and the rate of exposure to influenza virus (λ_k) as

$$N = \Sigma_{k=1}^5 N_k$$

and

$$\lambda_k = \Sigma_{m=1}^5 \frac{\beta\phi_{km}\Psi(t)}{N}$$

where N_k is the number of individuals of age group k and $\Psi(t) = A_{LU,m} + I_{LU,m} + A_{HU,m} + I_{HU,m} + A_{LV,m} + I_{LV,m} + A_{HV,m} + I_{HV,m}$ (Table 1). Thus,

$$\begin{aligned}
N_k = &S_{LU,k} + E_{LU,k} + A_{LU,k} + I_{LU,k} + R_{LU,k} + S_{HU,k} + E_{HU,k} \\
&+ A_{HU,k} + I_{HU,k} + R_{HU,k} + S_{LV,k} + E_{LV,k} + A_{LV,k} + I_{LV,k} \\
&+ R_{LV,k} + S_{HV,k} + E_{HV,k} + A_{HV,k} + I_{HV,k} + R_{HV,k} \ (k = 1, \cdots, 5).
\end{aligned}$$

Here β is the transmission probability per contact, and ϕ_{km} is defined as the number of contacts between a person in age group k with people in age group m [30].

The pandemic was assumed to be initiated with the entire population unvaccinated. Therefore, the initial conditions for Model (1) are

$$\begin{aligned}
&S_{LU,k} = (1 - \xi_k)(1 - \chi_k)N_k - 2, \\
&A_{LU,k} = I_{LU,k} = 1, \\
&R_{LU,k} = (1 - \xi_k)\chi_k N_k, \\
&S_{HU,k} = \xi_k(1 - \chi_k)N_k - 2, \\
&A_{HU,k} = I_{HU,k} = 1, \\
&R_{HU,k} = \xi_k\chi_k N_k, \\
&E_{LU,k} = E_{HU,k} = S_{LV,k} = E_{LV,k} = A_{LV,k} = I_{LV,k} = 0, \\
&R_{LV,k} = S_{HV,k} = E_{HV,k} = A_{HV,k} = I_{HV,k} = R_{HV,k} = 0
\end{aligned}$$

for $k = 1, 2, \cdots, 5$, where ξ_k is the proportion of age group k who are at high risk of medical complications, and χ_k is the proportion of age group k who have immunity to the H1N1 influenza A pandemic strain due to previous exposure in the distant past (Table 1).

The rates of hospitalization and death for unvaccinated individuals are derived from the empirical case hospitalization ratio (h_k) and case mortality ratio (d_k), respectively (Table 1) [32]. The demographic-specific mortality rates for H1N1 pandemic influenza vary considerably. The high-risk people are assumed to be 9 times more likely to die from an infection and 3 times more likely to be hospitalized [28]. Thus, it follows that $d_{HU,k} = 9d_{LU,k}$ $(k = 1, \cdots, 5)$ where $d_{LU,k}$ and $d_{HU,k}$ are empirical case fatality ratios for the high-risk and low-risk groups, respectively. Similarly, we have $h_{HU,k} = 3h_{LU,k}$ $(k = 1, \cdots, 5)$ where $h_{LU,k}$ and $h_{HU,k}$ are empirical case hospitalization ratios for the high-risk and low-risk groups, respectively. Thus, the case mortality ratio for people in age group k is

$$d_k = d_{LU,k}(1 - \xi_k) + d_{HU,k}\xi_k.$$

Equivalently the case mortality ratio for low-risk, unvaccinated people is

$$d_{LU,k} = \frac{d_k}{(1 - \xi_k) + 9\xi_k}. \tag{2}$$

Also the case mortality in terms of the model parameters is

$$d_{LU,k} = \frac{\alpha_{LU,k}}{\gamma + \alpha_{LU,k}},$$

leading to

$$\alpha_{LU,k} = \gamma \frac{d_{LU,k}}{1 - d_{LU,k}}. \tag{3}$$

Using Eqs. (2) and (3), the rate of influenza-related death among low-risk people in age group k, $\alpha_{LU,k}$, is calculated in terms of empirical case fatality ratio. Similarly, the rate of influenza-related death among high-risk people in age group k, $\alpha_{HU,k}$, is defined as

$$\alpha_{HU,k} = \gamma \frac{9d_{LU,k}}{1 - 9d_{LU,k}}.$$

For vaccinated individuals, it follows that

$$\alpha_{LV,k} = \gamma \frac{(1 - \kappa_k)d_{LU,k}}{1 - (1 - \kappa_k)d_{LU,k}} \text{ and } \alpha_{HV,k} = \gamma \frac{9(1 - \kappa_k)d_{LU,k}}{1 - 9(1 - \kappa_k)d_{LU,k}}$$

where κ_k is vaccine efficacy against death among people in age group k.

2.2. **Basic reproduction ratio, $\Re_0$.** The basic reproduction ratio ($\Re_0$) is defined as the average number of secondary cases generated when one infectious individual is introduced into a wholly susceptible population. The basic reproduction ratio of H1N1 influenza A was estimated to be in the range of 1.4-1.6 [3, 4, 12, 16, 20, 31, 34, 35, 36, 42]. We derived an expression of the basic reproduction ratio from our mathematical model and used this information to estimate the probability of transmission per contact, β.

2.3. **Vaccine allocation schemes.** We simulated the impact of five staggered vaccination scenarios during 2009 influenza A (H1N1) pandemic in the US. All scenarios were evaluated under the assumption that vaccination would start on October 1, 2009 [6]. In order to incorporate the scheduling of H1N1 vaccine release times in the US, we assumed that 8.9 million individuals were vaccinated every week in the order of vaccine priority list (Table 2) [8]. Further, protection was assumed to occur two weeks after vaccination [1]. Rather than explicitly incorporating the time lag between vaccination and effectiveness into the proposed model, we combined this delay time with that of vaccine distribution. In addition, an age-specific vaccine efficacy was applied (Table 1) [19, 28].

Previous studies based on confirmed cases of H1N1 pandemic inspected the course of the H1N1 influenza pandemic and concluded that the peak of a pandemic influenza in the US occurred at the beginning of November, 2009 [2, 40]. Thus, in our baseline scenarios, the peak of a pandemic wave was assumed to occur on November 1, 2009, and an overall vaccination coverage of 20.5% was assumed, in alignment with a reported vaccine coverage level for 2009 influenza A (H1N1) in the US (Table 2)[8].

We analyzed the following five vaccine allocation schemes:

Risk	Ages	CDC-like vaccination	Seasonal-like vaccination	Morbidity-based vaccination	Mortality-based vaccination	Mass vaccination
High risk	0-4	33.0%	18.8%	44.3%	7.5%	20.5%
	5-19	27.5%	11.2%	51.7%	17.6%	20.5%
	20-44	18.6%	11.9%	13.5%	26.7%	20.5%
	45-64	18.6%	20.0%	7.6%	20.5%	20.5%
	65+	11.2%	36.0%	2.5%	15.1%	20.5%
Low risk	0-4	33.0%	27.5%	44.3%	7.5%	20.5%
	5-19	27.5%	18.8%	51.7%	17.6%	20.5%
	20-44	18.6%	13.9%	13.5%	26.7%	20.5%
	45-64	18.6%	21.8%	7.6%	20.5%	20.5%
	65+	11.2%	40.6%	2.5%	15.1%	20.5%
Over-all		20.5%	20.5%	20.5%	20.5%	20.5%

TABLE 2. Vaccination coverage for five vaccination strategies evaluated [7, 10]. Based on National 2009 H1N1 Flu Survey (NHFS) [8], the percentage of US residents who reported they had received at monovalent H1N1 influenza vaccine was 20.5%, which was assumed as an overall vaccination coverage for all five schemes.

- Allocation Scheme 1 (CDC-like influenza vaccination): Vaccination of individuals is implemented according to the United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC's ACIP) recommendations [9]. With 'CDC-like influenza vaccination' scheme, first the high-risk groups are vaccinated in the order of $0-4$ and $5-19$ years, followed by the low-risk group in the same order. Next, the high-risk groups are vaccinated in the order of $20-44$ and $45-64$ years, followed by the low-risk group in the same order. Last, the high-risk and low-risk groups in 65+ years are vaccinated. The age-specific vaccination coverage levels are based on the vaccine coverage estimates reported in the National 2009 H1N1 Flu Survey (NHFS) (Table 2) [8].
- Allocation Scheme 2 (Seasonal-like influenza vaccination): In this vaccination scheme, individuals that are of priority for vaccination against seasonal influenza are vaccinated first. This vaccination scheme focuses on those who are at high risk of having serious seasonal influenza-related complications or those who have a high activity rate. Thus, the priority list includes children 19 years of age or younger, older adults, and people of any age with chronic medical conditions [15]. Specifically, in this scheme, first the high-risk groups are vaccinated in the order of ages $5-19$, $0-4$, $45-64$, 65+, and $20-44$ years, then the low-risk groups in the same order. We implemented age-specific vaccination coverage in proportion to estimated seasonal influenza vaccine coverage levels reported in the 2007-8 Behavioral Risk Factor Surveillance System (BRFSS) [7].
- Allocation Scheme 3 (Morbidity-based vaccination): This scheme prioritizes the vaccination of individuals with high-risk of infection. That is, vaccines are also distributed to age groups proportionally corresponding to case reports (Figure 1). Thus, first the high-risk groups are vaccinated in the order of ages

$5 - 19$, $0 - 4$, $20 - 44$, $45 - 64$, and $65+$ years, and then the low-risk groups
in the same order. Vaccine coverage in age group k (v_k) is proportional to
the number of case reports per $100,000$ (a_k): $a_k = qv_k$. Considering the total
number of vaccine doses available, T^*, it follows that

$$\Sigma_{k=1}^{5} v_k N_k = T^*.$$

Therefore we can calculate the vaccine coverage in age group k;

$$v_k = \frac{a_k}{q} = \frac{a_k T^*}{\Sigma_{k=1}^{5} a_k N_k}.$$

- Allocation Scheme 4 (Mortality-based vaccination): With this scheme, vac-
  cination of individuals with high-risk of mortality is the objective. The age
  distribution of H1N1 influenza A-related mortality is a very different pattern
  from what is seen in seasonal influenza, where an estimated 90% of influenza-
  related deaths occur in people 65 years of age and older [10]. The age-specific
  vaccine coverage levels are determined in proportion to the number of H1N1
  influenza A - related deaths, which is the highest among people 25 to 49 years
  of age (39%). The next group with the highest number of deaths is ages 50
  to 64 (25%) and people 5 to 24 years of age (16%) (Figure 1). Thus, in this
  scenario, the high-risk groups are vaccinated first, in the order of ages $20 - 44$,
  $45 - 64$, $5 - 19$, $65+$, and $0 - 4$ years, followed by the low-risk groups in the
  same order. The age-specific vaccine coverage levels are calculated based on
  influenza mortality in a similar fashion to Allocation Scheme 3.
- Allocation Scheme 5 (Mass vaccination): 'Mass vaccination' scheme involves
  uniform vaccine distribution without prioritization. That is, high-risk and
  low-risk groups are combined by age, and vaccine is allocated to everyone
  randomly.

The effectiveness of a vaccination program is highly dependent on some of char-
acteristics of H1N1 pandemic influenza, such as the peak of a pandemic wave and
the magnitude of an outbreak. To highlight the impact of uncertainties in these
parameters on the outcomes, we conducted a sensitivity analysis by varying the
magnitude of the basic reproduction ratio ($\Re_0$). In addition, in order to study the
impact of initiating vaccination at an earlier stage of the outbreak, we considered
various pandemic peaks and increased vaccine coverage accordingly (Table 1).

3. **Results.** For a moderate pandemic scenario ($\Re_0 = 1.4$) in the absence of vac-
cination, our model predicts an overall population attack rate of 34.4%. Based on
our assumptions that on average 67% of infected people become symptomatic, this
would correspond to $23,000$ clinical influenza infections, 777 hospitalizations, and
25 deaths per $100,000$. The age-group specific attack rates predicted by the model
prove that the relationship between age and attack rate of the model predictions is
similar to the observations (Figures 1 and 2). We found that school-age children
(with a 37% attack rate) and young adults (with a 24% attack rate) would be most
severely hit by the H1N1 pandemic in the absence of vaccination. The attack rate
would be the lowest for the elderly (age 65+) with a 8% attack rate; this could be
explained in part by pre-existing immunity that has been reported among the el-
derly (Figures 2a and 2b) [21]. In addition to the attack rate, both hospitalizations
and deaths were estimated to be the lowest in the elderly. In contrast, the number
of both hospitalizations and deaths in the absence of vaccination were the highest
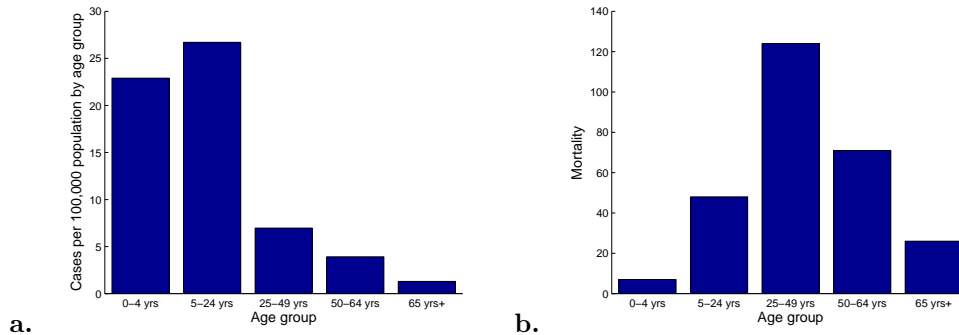among the high-risk group, followed by younger adults of age 20-44 (Figures 2c and

FIGURE 1. Novel H1N1 cases and deaths in the US, by age group
[10]. (a) The estimated rate of novel H1N1 cases per 100,000 people
from April 15 to July 24, 2009 is shown based on novel H1N1
infections reported to the CDC. (b) The number of deaths caused
by novel H1N1 influenza infections early on during the outbreak.

2d). Among high-risk individuals, the number of hospitalizations and deaths were
estimated to be 970 and 73 per 100,000, respectively. Among young adults of age
20-44, 520 hospitalizations and 15 deaths were estimated to occur per 100,000.

Because different activity levels differ between age groups, individuals in each
age group reach their highest incidence at different timing (Figure 2a). Our model
predictions show that the school-age children take the lead, followed by adults and
preschool-age children. Here again, the elderly (age 65+) are the last ones to reach
maximum incidence.

We simulated the impact of the five vaccine allocation schemes for a moderate
pandemic scenario (Figure 3a). Among five vaccine allocation schemes considered,
the morbidity-based allocation scheme achieved the largest reduction in the number
of influenza cases, yielding a reduction of 27% in the number of clinical influenza
cases. Thus, in order to minimize infections, the optimal policy is to distribute
vaccines to high-risk people, followed by school-age children (ages 5-19) and then
preschool-age children. The next age groups to be vaccinated are younger adults
(ages 25-49), older adults (ages 50-64), and finally, the elderly (ages 65+). The
same strategy would also minimize hospitalizations and deaths (Figures 7 and 8).
Nevertheless, if the public health objective is to delay an influenza pandemic wave,
the mortality-based vaccination scheme was found to be the most effective strategy.

In the event of an influenza pandemic, there are numerous uncertainties in rapidly
evolving circumstances, such as the peak in influenza cases and the possibility of a
second (or third) pandemic wave. In order to study the effect of these uncertainties
amidst epidemiological features of a pandemic wave, we compared the impact of five
allocation schemes under different scenarios, wherein the peak in pandemic influenza
cases is delayed. This is, in fact, equivalent to studying the impact of delayed
vaccination. Indeed we showed that outperformance of morbidity-based scheme
was robust to these changes (Figure 3). In other words, even with higher vaccine
coverage with a shorter delay in vaccine delivery, the morbidity-based vaccination
strategy still outperforms the other four strategies in minimizing the extent of an
outbreak. However, the difference in the impacts of various allocation schemes on
the number of influenza cases becomes smaller if the peak of a pandemic wave occurs
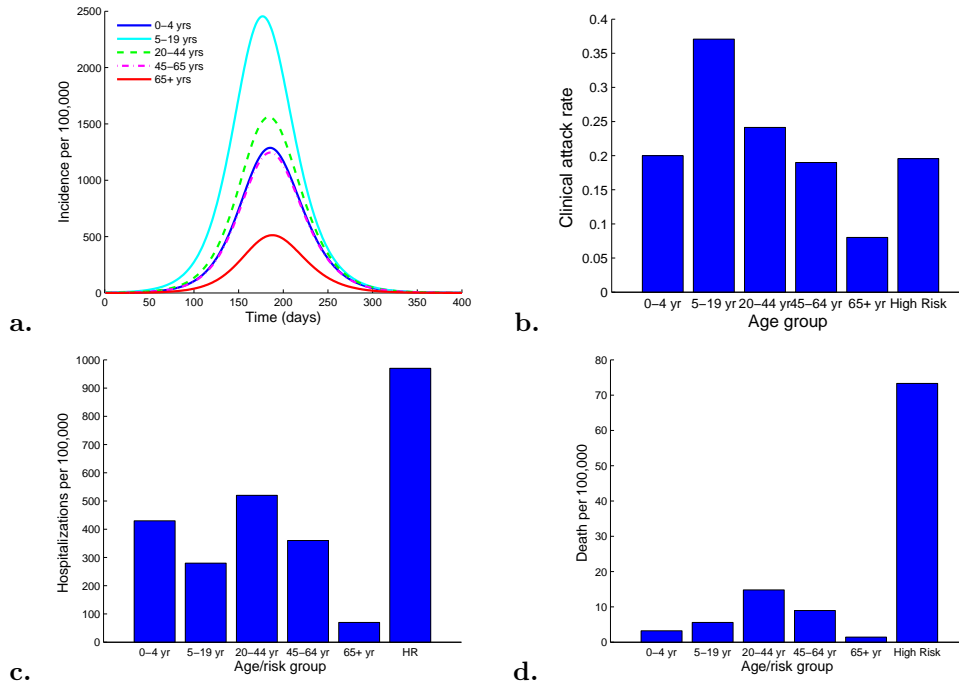
FIGURE 2. The age- and risk-specific outcomes in the absence of vaccination. (a) Model predictions of age-specific incidence for H1N1 influenza pandemic in the current US population. The timing of peaks for different age groups is shown. (b) Predicted age and risk-specific clinical attack rates for H1N1 influenza pandemic in the current US population. The low-risk group is further stratified by ages of individuals. (c) Predicted number of hospitalizations per 100,000 in age/risk groups during H1N1 influenza pandemic. (d) Predicted number of deaths per 100,000 in age/risk groups during H1N1 influenza pandemic.

relatively early. For instance, if the peak of pandemic occurs on November 1, 2009, it would allow only a month of vaccine distribution before pandemic peak, and the performance of a morbidity-based scheme is only marginally better than the other four schemes.

For a more severe pandemic scenario ($\Re_0 = 1.6$), we estimated an overall population attack rate and clinical attack rate would be 47% and 31%, respectively (Figure 4). We observed that the best performance of morbidity-based scheme among five proposed schemes (with respect to minimizing total infections) was robust to increasing a basic reproductive ratio. In contrast, if the public health objective is to minimize deaths from the H1N1 influenza and the pandemic peak occurs relatively early (November 1 2009, for example), the mortality-based vaccination scheme outperforms the other four schemes. That is to say, in that case, the earliest vaccine priority should be given to high-risk people in the order of ages 20-44, 45-64, 5-19, 65+, and 0-4 years, followed by the low-risk groups in the same order.
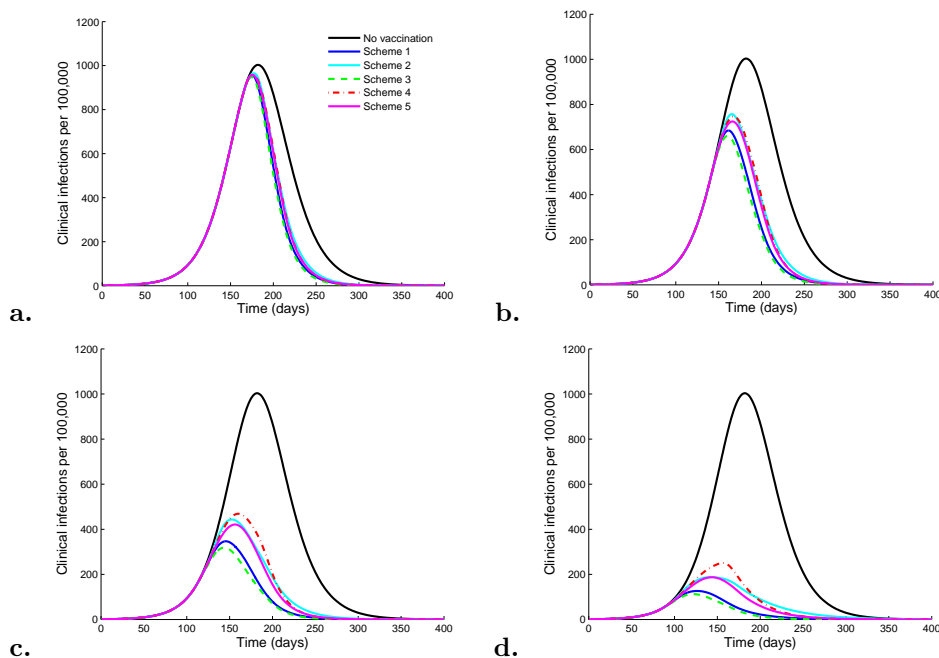
FIGURE 3. The number of clinical infections per 100,000 is presented when basic reproductive ratio ($\Re_0$) is 1.4 and the peak of H1N1 pandemic occurs on (a) Nov 1, 2009; (b) Dec 1, 2009; (c) Jan 1, 2010; (d) Feb 1, 2010. Vaccination was assumed to start on Oct 1, 2009.

The benefits of vaccination increase with a higher basic reproductive ratio if vaccination is initiated relatively early (Figures 3 and 4). For instance, if vaccines become available 8 weeks before the pandemic peak, the morbidity-based scheme would reduce the number of infections to 50% if $\Re_0 = 1.4$, and to 53% if $\Re_0 = 1.6$ (Figures 3b and 4b). However, if vaccines become available 16 weeks before the peak in pandemic influenza cases, the morbidity-based scheme would reduce the size of pandemic to 10% if $\Re_0 = 1.4$, and to 6% if $\Re_0 = 1.6$ (Figures 3d and 4d).

Figure 5 shows the estimated impact of the vaccination programs on the age-specific incidence of influenza illness caused by novel influenza A (H1N1). The incidence in the youngest group is minimized with 'CDC-like pandemic influenza vaccination scheme'. For young adults (ages 20-44), however, the mortality-based vaccination scheme would lead to the greatest reduction in influenza cases (Figure 5). Still, the estimated numbers of cases prevented among school-age children and high-risk people were maximized by the morbidity-based vaccination scheme, preventing $11,652$ and $6,321$ infections per $100,000$ in these age groups, respectively (Figure 5).

The predictions for relative epidemiological impacts through various vaccination strategies under a severe pandemic scenario ($\Re_0 = 1.6$) are qualitatively similar to those under a mild pandemic scenario ($\Re_0 = 1.4$) (Figures 6-8). For both mild and severe pandemic scenarios, the morbidity-based scheme yielded the highest reductions in clinical cases and hospitalizations, regardless of the peak of an influenza
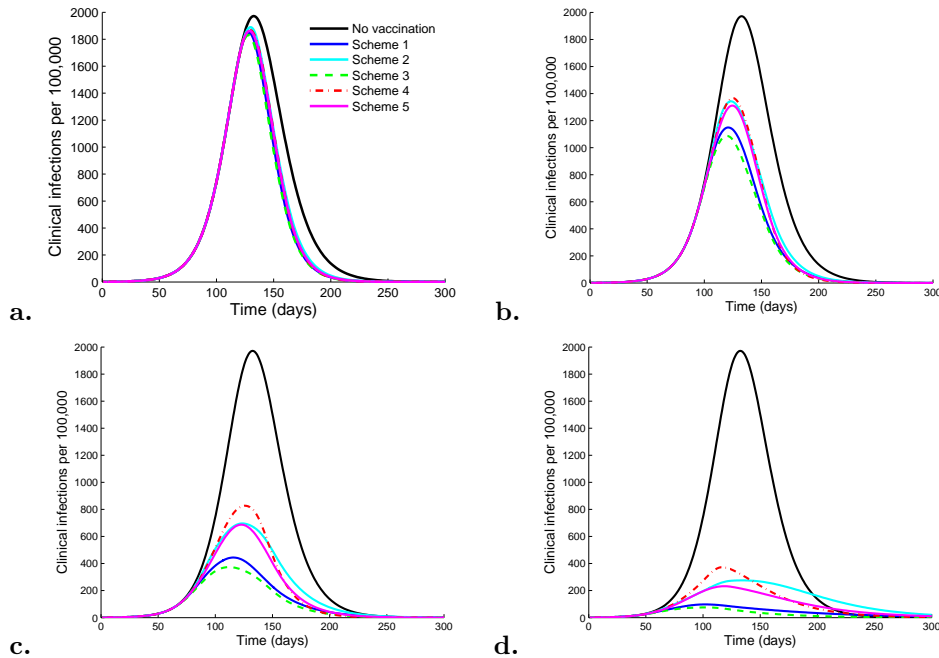
FIGURE 4. The number of clinical infections per 100,000 is presented when basic reproductive ratio ($\Re_0$) is 1.6 and the peak of H1N1 pandemic occurs on (a) Nov 1, 2009; (b) Dec 1, 2009; (c) Jan 1, 2010; (d) Feb 1, 2010. Vaccination was assumed to start on Oct 1, 2009.

pandemic. Yet, the indirect benefit of the morbidity-based vaccination scheme over the other vaccination schemes were significantly greater when the peak in influenza cases was later in the season. For instance, the morbidity-based strategy would yield a reduction of 27% in the overall number of clinical influenza cases if the peak of H1N1 influenza pandemic occurs one month after the initiation of vaccination, and vaccination reaches 20% of the population (Figure 6A). If the peak of pandemic occurs three months after the initiation of vaccination and vaccine coverage reaches 40%, the morbidity-based strategy would yield a reduction of 74% in the number of clinical cases (Figure 6A). Therefore the most considerable benefits of the morbidity-based vaccination strategy were found at higher $\Re_0$ values and earlier implementation of vaccination campaigns in line with higher vaccine coverage.

4. **Discussion.** In order to evaluate the effectiveness of various age/risk-targeted vaccination strategies for pandemic influenza A (H1N1) in the US, we proposed an age-structured model of influenza transmission and vaccination. Using our model, the impact of the vaccine delay was assessed. Based on the schedule of vaccine availability projected by the CDC, we examined the various age- and risk-specific allocation of vaccine doses, and compared the effectiveness of various vaccination schemes to the vaccination strategies recommended by the CDC's ACIP for H1N1 pandemic influenza A. The 2009 H1N1 vaccine guidelines proposed by the CDC
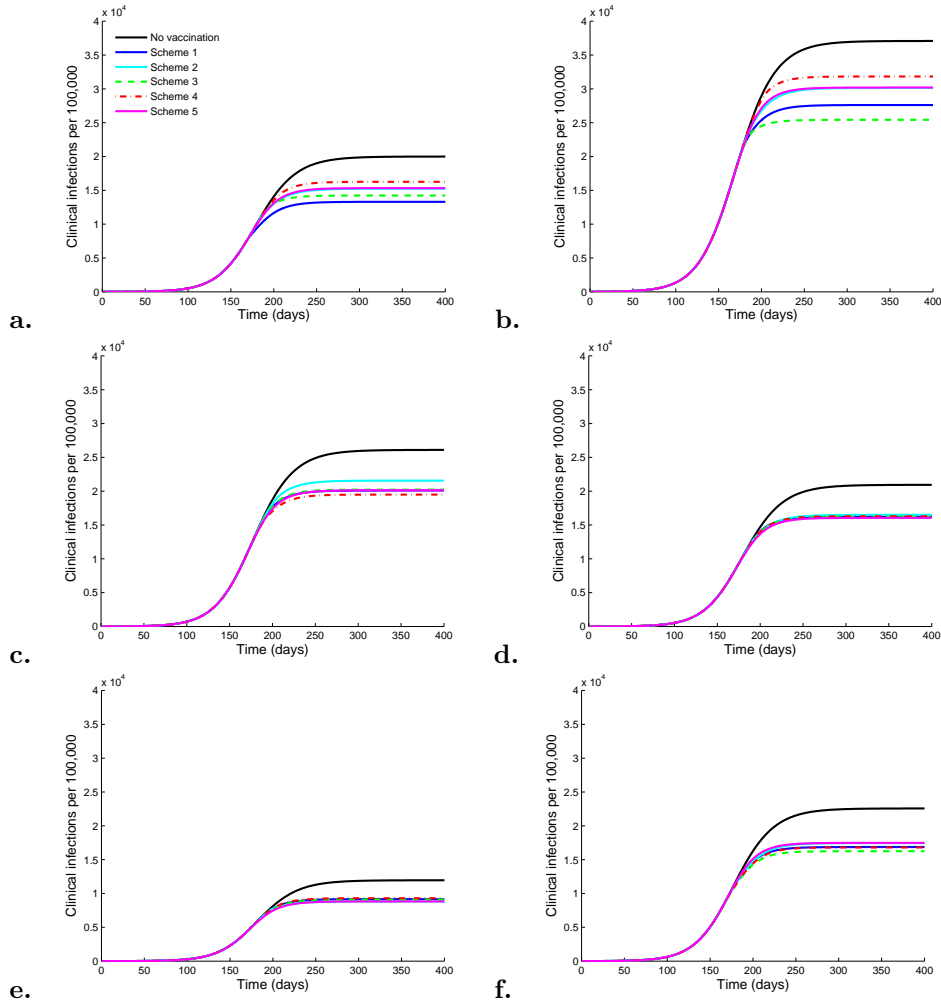
FIGURE 5. Predicted age group-specific attack rates for H1N1 influenza pandemic in relation to the different vaccination strategies. These attack rates are compared with the no-vaccination alternative among (a) individuals of ages 4 and under, (b) individuals between ages 5 and 19, (c) individuals between ages 20 and 44, (d) individuals between ages 45 and 64, (e) individuals of ages 65+, and (f) high-risk individuals. We assumed that the peak of H1N1 influenza pandemic occurs 30 days after the implementation of vaccination, and that 20% of the population was vaccinated.

prioritized high-risk people aged 0-19 years and low-risk people aged 6 months through 24 years [9].

Our model predicts that the impact of vaccination was attenuated by the delay in vaccine production and delivery, as well as its limited supply. This prediction is consistent with previous modeling studies which have shown that the benefit of vaccination in mitigating a potential pandemic highly depends on the time it is
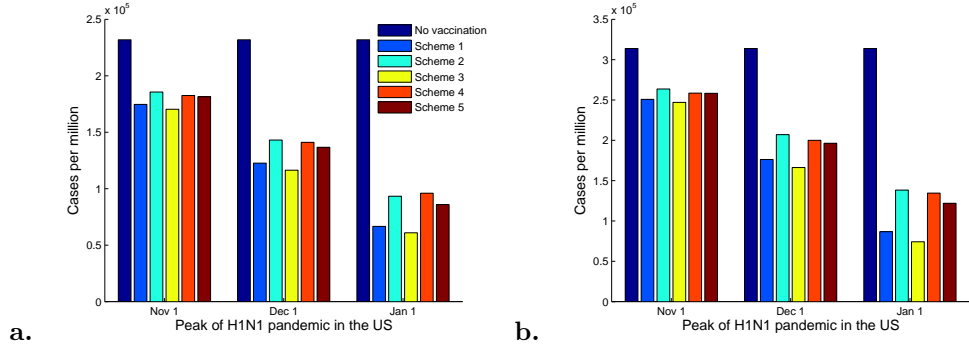
FIGURE 6. Age specific incidence rates for various vaccination schemes with (a) $\Re_0 = 1.4$; and (b) $\Re_0 = 1.6$ when the peak of H1N1 in the US is varied.
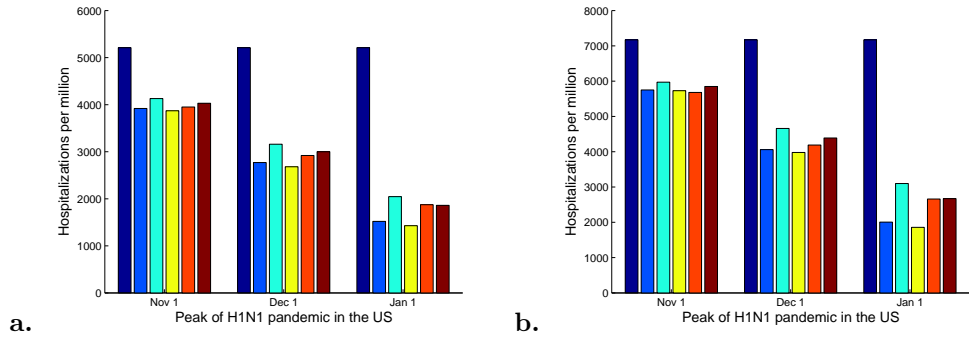

FIGURE 7. Age specific hospitalization rates for various vaccination schemes with (a) $\Re_0 = 1.4$; and (b) $\Re_0 = 1.6$ when the peak of H1N1 in the US is varied.
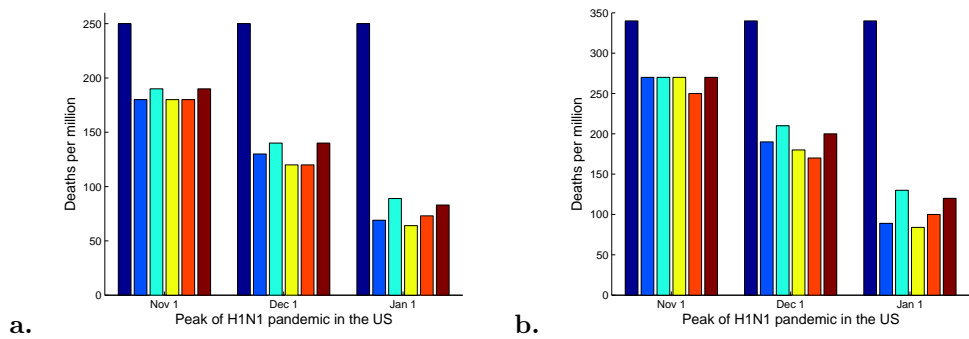

FIGURE 8. Age specific mortality for various vaccination schemes with (a) $\Re_0 = 1.4$; and (b) $\Re_0 = 1.6$ when the peak of H1N1 in the US is varied.

initiated and that containment of pandemic influenza would be unlikely to succeed unless multiple interventions are applied [5, 13, 14, 25, 37, 40].

Our analysis suggests that some modification to the planned CDC vaccination campaign might improve the performance of the vaccination program. In fact, the morbidity-based strategy was found to outperform the other four strategies considered for a range of parameter values, reducing disease incidence most effectively. In this scheme, the earliest priority is given to high-risk people in all age groups, followed by school-age children (5-19 years old) and then preschool-age children (under the age of 4). The next age groups to be vaccinated are individuals of age 20-44, 45-64, and then 65+ years. This optimal vaccine allocation differs from the CDC recommendations by excluding preschool-age children and including high-risk people over the age of 25 in the highest priority. This strategy is also found to minimize hospitalizations and deaths. In fact, the relative performance of this morbidity-based strategy was even more beneficial with early delivery of vaccines. Vaccinating the groups recommended by the CDC is predicted to be the "next-best" strategy in terms of reducing infections, hospitalizations, and deaths.

Previous studies have found that school-age children are the most responsible for influenza transmission [26, 29, 33, 38]. Thus an advantage of vaccinating school-age children is significant indirect protection in the age groups that are not vaccinated. As a result, vaccination of school-age children is considered to be essential in order to minimize the magnitude of an influenza outbreak, if vaccines are available and allocated early in the outbreak. Our analysis confirmed that this method is still critical in the event of delayed vaccination. This is in part because the young are most vulnerable to the novel 2009 H1N1 influenza, unlike the elderly who have cross-immunity from prior infections. In addition, our analysis suggests protecting the high-risk group directly in order to minimize hospitalizations and deaths. If the objective is to minimize the potency of an influenza pandemic as well as deaths, our results suggest that low-risk individuals of age 65 and older receive the lowest priority for vaccination. This group is the least likely to transmit, and is known to have residual immunity against the novel 2009 H1N1 influenza strain [32].

In conclusion, we show that vaccination strategy based on age-specific morbidity would lead to substantial effects through both direct and indirect protection. Such conclusion was found to be robust to the increase in the transmissibility of influenza virus. Thus, if vaccine becomes available in a limited supply during the pandemic, priority should be given to groups at a high-risk of developing complications and school-age children first, with an objective being to minimize infections. Although our model assumed that a pandemic evolves in a single wave, influenza pandemics typically happen in multiple waves [18, 39]. As a result, the model prediction of reduction in the overall attack rate through vaccination is conservative, since vaccination might contribute to aborting the second and third waves even when vaccination is not introduced early during the ongoing outbreak [37].

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