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Optimal Dosing and Dynamic Distribution of Vaccines in an Influenza Pandemic

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Limited production capacity and delays inherent in vaccine development are major hurdles to the widespread use of vaccines to mitigate the effects of a new influenza pandemic. Antigen-sparing vaccines have the most potential to increase population coverage but may be less efficacious. The authors explored this trade-off by applying simple models of influenza transmission and dose response to recent clinical trial data. In this paper, these data are used to illustrate an approach to comparing vaccines on the basis of antigen supply and inferred efficacy. The effects of delays in matched vaccine availability and seroconversion on epidemic size during pandemic phase 6 were also studied. The authors infer from trial data that population benefits stem from the use of low-antigen vaccines. Delayed availability of a matched vaccine could be partially alleviated by using a 1-dose vaccination program with increased coverage and reduced time to full protection. Although less immunogenic, an overall attack rate of up to 6% lower than a 2-dose program could be achieved. However, if prevalence at vaccination is above 1%, effectiveness is much reduced, emphasizing the need for other control measures.

disease outbreaks; influenza, human; mass immunization; models, theoretical

Severe disease due to influenza is typically prevented by vaccinating vulnerable populations. A new pandemic of influenza poses 2 major problems regarding this strategy. The first is production capacity: the entire population of the world may be vulnerable to severe disease from a novel strain of influenza (1). Protecting this vulnerable population would require a massive increase in vaccine production, which currently is achievable only by dramatic reductions in antigen requirements per dose (2).

Secondly, influenza vaccines rely at present on isolation of the circulating strain prior to production. Doing so will result in a considerable delay (usually quoted as 3–6 months) from initial isolation to distribution of sizable quantities of vaccine (3). Modeling studies based on patterns of human air travel suggest that, in many countries, the first wave of the pandemic would end within this time period (4–6). Because pandemic plans in countries such as Australia and the United States still emphasize vaccine use for eventual control (7, 8), it is important to investigate the feasibility of these plans.

A potential avenue is the use of candidate (prepandemic) H5N1 vaccines prior to widespread local transmission (e.g., during overseas pandemic stage 5/6—refer to Table 1 for pandemic stages as defined by the World Health Organization). Although early versions of such vaccines were poorly immunogenic in adults (9, 10), more recent trials using novel adjuvants (11) or whole virion vaccines (12) have demonstrated high immunogenicity at low antigen volumes. Evidence of cross protection against drifted strains (11, 13) suggests that candidate vaccines will provide at least partial protection, even if unmatched to the circulating pandemic strain.

Given that supply is likely to be constrained, what amount of antigen per dose provides optimal population protection? The standard answer is the lowest that meets accepted correlates of protection, but this view implicitly assumes unrestricted supply. When an entire population requires protection, it may be preferable to use a dose that provides suboptimal individual protection in return for greater overall benefits deriving from herd immunity. This question is currently of great interest and has been examined elsewhere in the context of a stockpiled prepandemic vaccine (14). We approached this question in the context of a matched vaccine and analyzed the effects of delays and different dose schedules on the optimal vaccine dose. The methods developed here are simple to apply and could be used during

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Table 1. Pandemic Stages Defined by the World Health Organization

Stage	Definition	Description
1	Interpandemic stage	Low risk of human cases
2	New virus in animals, no human cases	Higher risk of human cases
3	Pandemic alert	No or very limited human-to-human transmission
4	New virus causes human cases	Increased human-to-human transmission
5		Significant human-to-human transmission
6	Pandemic	Sustained human-to-human transmission

pandemic stage 4/5 to inform planning, when evidence of human-to-human transmission is well established but prior to a pandemic being declared.

Our study had 2 aims. The first was to assess the optimal dose for a pandemic vaccine that protects against infection and reduces infectivity and to apply this finding to data from published trials; the second was to compare 1- and 2-dose strategies with a matched vaccine.

MATERIALS AND METHODS

Model of vaccine response

Rates of influenza infection by prechallenge hemagglutination inhibition titers were used to calculate relative susceptibility of vaccinees. The data were drawn from a late-1960s trial by Hobson et al. (15) that was influential in establishing the 1/40 titer as a correlate for protection. In this paper, these rates are used to weight the density of hemagglutination inhibition titers (refer to the online supplementary material, which is posted on the *Journal*'s website (http://aje.oupjournals.org/)) from recent vaccine trials (9–12) to estimate a mean relative susceptibility (e_s) of vaccinees against antigenically similar viruses. A linear model of dose response provides a good fit to the data and a simple characterization of the optimal dose, provided that interpretation is limited to the tested range of doses.

We also allowed for vaccinees who acquire a breakthrough infection to be less infectious than infected nonvaccinees (relative infectivity e_i), assuming less severe infection in vaccinees. Since data to estimate e_i were not available, we explored 2 scenarios: 1) relative infectivity was equal to relative susceptibility ($e_i = e_s$), and 2) there was no reduction in infectivity for vaccinees ($e_i = 1$). Refer to the supplementary material for a formal definition of e_i and e_s.

Impact of vaccination

The impact of a limited vaccine stockpile was assessed by using a deterministic susceptible-infected-recovered–type model of influenza transmission in a hypothetical large population center. The vaccine stockpile was assumed to contain a fixed amount of antigen, which could be subdivided into different amounts of antigen per vaccine. The level of antigen per vaccine determined overall population coverage (maximum of 100%).

The optimal dose was defined as that which provided the greatest overall reduction in the eventual attack rate. To determine the theoretical maximum benefit of vaccination, we assumed that the vaccinated population had seroconverted prior to significant case numbers occurring. In this situation, attack rates among vaccinated and unvaccinated individuals can be obtained by numerically solving a 2-type attack rate formula (refer to the supplementary material).

In this model, the final attack rate is closely related to (but not completely determined by) the reproduction number, R. In particular, if R is brought below 1 by vaccination, the attack rate in both vaccinated and unvaccinated groups will be negligible. In our model,

$$R = R_0(1 - v + ve_ie_s), \quad (1)$$

where v is the dose-dependent vaccine coverage and R_0 is the basic reproduction number.

Delays to seroconversion

We also examined the situation in which vaccine distribution and seroconversion occur after local transmission has begun. The potential for rapid international spread of a new pandemic (4–6) makes this situation almost inevitable given the delays to creation of a matched vaccine. In this context, it is of interest to compare not only different doses but also 1- and 2-dose schedules, given the reduced time to seroconversion in a 1-dose schedule.

We used a deterministic susceptible-exposed-infectious-removed model of influenza transmission to determine the effect of delay to vaccination and seroconversion on the attack rate. The changing impact of vaccination on the attack rate was explored in scenarios in which the cumulative attack rate at the time of vaccination was 0.01% and 1%.

Comparison of 1- and 2-dose schedules

We based the comparison of 1- and 2-dose schedules on cross-protective immunogenicity data for the GlaxoSmithKline Biologicals (Rixensart, Belgium) adjuvanted 3.75-μg vaccine (13). Values for R_0 were in the range of 1.5–2.5, and latent and infectious periods were fixed at 1 and 2 days, respectively (sensitivity is explored in supplementary material Web Figures 1 and 2).

We focused on comparing 1- and 2-dose strategies with coverage of 100% and 50%, respectively. A range of 60–180 days was assumed for the delay from the first local case until vaccination with the first (or only) dose, with seroconversion occurring 21 days after the first and second doses were given (note that in the 2-dose program, vaccinees achieve 1- and 2-dose protection in sequence). This assumption may underestimate protection since it increases continuously between vaccination and these time points. We also assumed that control measures (e.g., antivirals and social distancing) for reducing transmission were ongoing and reduced the effective R_0 by 30%. These measures were assumed to cease after

Table 2. Parameters, Typical Values, and Sources Used in the Dynamic Model

Parameter	Value	Source (Reference Numbers)/Justification
Reproduction number (R_0)	1.5–2.5 used in dynamic simulations	Estimates based on 1918 and 1957 pandemic data (22–24)
Mean latent period (L)	1 day	Similar to Ferguson et al. (25) and recent analysis of challenge trials (26); varied in sensitivity analysis
Mean infectious period (D)	2 days	Assumption—lies between (25) and (18); varied in sensitivity analysis
Initial prevalence of infection	1 per million	Assumption
Seroconversion delay (τ_s)	21 days	Based on trial data (11)
Delay to vaccine (τ_0)	2–6 months	Similar to range quoted by Daems et al. (3), taking into account a delay of about 1 month for the pandemic to arrive (23)
Mean relative susceptibility for vaccinees (e_s)	0.53 (1 dose), 0.13 (2 doses)	Estimates based on 3.75-μg vaccine in Leroux-Roels et al. (11)
Mean relative infectivity for vaccinees (e_i)	1 or equal to e_s	Assumption (also consider $e_i = (1 + e_s)/2$ in sensitivity analysis)
Mean reduction in R_0 due to other control measures	30%	Conservative assumption—other modeling papers suggest that larger reductions are possible (18, 27)

seroconversion from the final dose of vaccine. Table 2 lists the parameter values used in the model.

Our analysis showed that prevalence of infection at the time of vaccination, given by a linearized model in which depletion of susceptibles is ignored, is useful as a single predictor of the impact of vaccination. We denote this variable by $I_l(t_0) \sim \exp(r\,t_0)$, where r is the epidemic growth rate and t_0 is the delay until vaccination (refer to the supplementary material for a definition of r in terms of R_0 and infectious and latent periods).

RESULTS

Generic properties of optimal doses

Figure 1 summarizes assumptions, inputs, and outputs from the model of vaccination prior to significant case numbers occurring. In panel A, we sketch the linear model of dose response, whereas panel B shows that this model fits well to the trial data. The fitted data come from Sanofi Pasteur (Lyon, France) (9) and Sinovac Biotech Co., Ltd. (Bejing, China) (12) adjuvanted trials, with estimated efficacy e_s plotted against antigen for 2 doses of vaccine.

Panels C–F show how 2 key parameters, the effective R (panels C and D) and the attack rate (panels E and F), depend on vaccine dose and efficacy ($R_0 = 2$ in each graph) when the stockpile is fixed at 20% coverage with the maximum dose. Contour lines display constant values of the effective R (panels C and D) and the attack rate (panels E and F). As the dose is reduced, coverage increases, and vice versa, up to a maximum of 100% coverage. Overlayed on the graphs are the estimates of 2-dose efficacy for the Sanofi (9) (triangles) and Sinovac (12) (+) vaccines.

The shape of the contour lines differs between the graphs, implying that the optimal dose for reducing the attack rate may not be optimal for reducing the effective R and that the optimal dose can be strongly influenced by assumptions about the infectivity of breakthrough cases. Higher efficacy/lower coverage vaccine programs are more effective at reducing the attack rate than at reducing the effective R. Conversely, if the infectivity of breakthrough cases is reduced by as much as their susceptibility, low-dose vaccines become much more effective at reducing both R and the attack rate.

However, based on the estimates of efficacy from the Sanofi (9) and Sinovac (12) trials, the optimal dose was consistently the lowest (or the lowest at which 100% coverage could be achieved if the stockpile was sufficiently large) regardless of whether the outcome variable was attack rates or the effective R or whether the infectivity of breakthrough cases was reduced (results not shown).

Effect of delayed vaccination

These results are useful for a prepandemic vaccine that could be administered prior to a local epidemic. A matched vaccine, however, will be delayed by at least 3 months from isolation of the circulating virus. Models of worldwide spread indicate that many countries will experience their first pandemic case within a month of the first identified cluster in the source country. In the next section of this paper, we focus on use of a matched vaccine and the effect of delays to vaccination and seroconversion.

Figure 2 shows attack rates for dose-response pairs with the same assumptions as in Figure 1 ($R_0 = 2$, 20% coverage at the maximum tested dose) but with vaccination occurring when the cumulative attack rate has reached 0.01% (panels A and B) and 1% (panels C and D) of the population. Infectivity of breakthrough cases is reduced ($e_i = e_s$) in panels B and D, which show that even if the attack rate is small when the vaccine is delivered, the effectiveness of the vaccination campaign is substantially decreased.

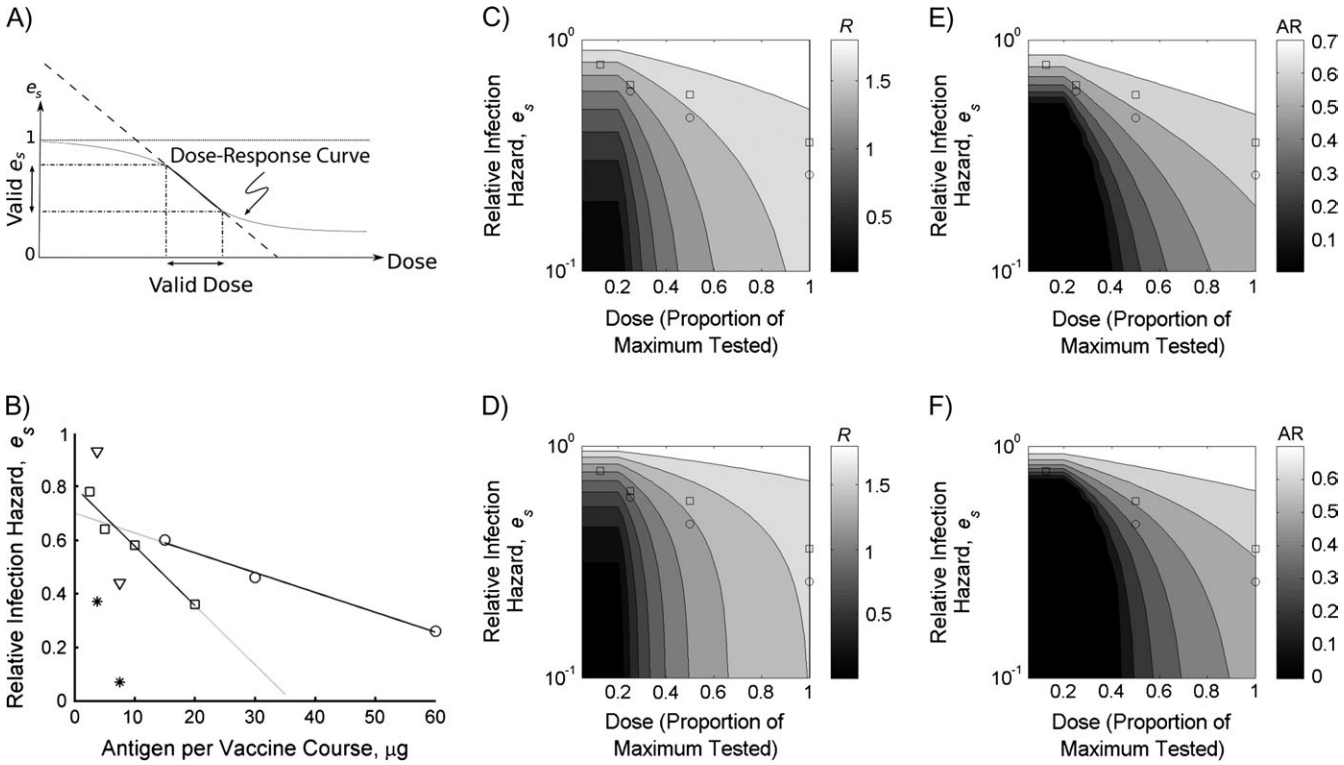

Figure 1. A: Schematic of dose response and interpretation of the linear model fits, indicating valid dose—domain for linear models; B: fits to estimated susceptibilities for Sinovac Biotech Co., Ltd. (Bejing, China) (12) (squares) and Sanofi Pasteur (Lyon, France) (9) (circles) adjuvanted vaccines, as well as estimated cross-protective (triangles) and matched (asterisks) values for GlaxoSmithKline Biologicals (Rixensart, Belgium) 1- and 2-dose (3.75 μg/dose) adjuvanted vaccines; C, D: effective reproduction number, R, for a given dose-response pair, with a fixed stockpile giving 20% coverage at the maximum tested dose; E, F: attack rate (AR) for a given dose-response pair, again with 20% coverage at the maximum tested dose. In panels C and E, $e_i = 1$; in panels D and F, $e_i = e_s$; $R_0 = 2$ in panels C–F. Squares and circles in panels C–F correspond to estimated relative susceptibilities for Sanofi and Sinovac vaccines, respectively, and appear at x values given by the tested dose divided by the maximum tested dose in the trial (30 μg and 10 μg, respectively, for the Sanofi and Sinovac trials). e_i, mean relative infectivity; e_s, mean relative susceptibility.

This delay, however, has no impact on the choice of optimal dose based on the Sanofi (9) and Sinovac (12) data. The optimal dose remained the lowest dose, or the lowest dose at which 100% coverage was achieved if the stockpile were sufficiently large (results not shown).

Up to this point, the comparisons have been between vaccines delivered in a 2-dose program with delays in seroconversion between each dose. However, it is also interesting to compare the effectiveness of 1- and 2-dose programs. We investigate this issue in terms of achieving twice the coverage with a less efficacious 1-dose vaccine but with a shorter delay to full seroconversion.

Comparison of 1- and 2-dose strategies for matched vaccines

The effect of 1-dose (100% coverage) and 2-dose (50% coverage) vaccination campaigns with a matched vaccine is shown in Figure 3. Note that the effective R in this example is 70% of R_0 since it was assumed that other control measures were in place until vaccinees seroconverted.

The first key feature is that the attack rate for the 1-dose campaign is lower than for the 2-dose campaign, and the difference can be as much as 6% of the population (Figure 3, panel B). This difference occurs despite lower immunogenicity (a reduction in the hazard of infection of 65% for 1 dose and 93% for 2 doses) because twice the coverage is achieved 21 days earlier. Note that the shaded contours show differences in attack rates according to the gray-scale bar (right of panel).

The impact of vaccination is predicted well by the expected prevalence of infection at the time of vaccination, calculated by using a linearized model in which depletion of susceptibles is assumed to be negligible. The relation between the overall attack rate and this variable is shown in Figure 3, panel C. This linearized prevalence (I_v) depends on only the case growth rate and the expected delay to vaccination and therefore has the potential to be estimated early in a pandemic if case ascertainment is good. The attack rates from 1- and 2-dose programs (dots and crosses, respectively) using the same ranges in R_0 and time to vaccination as in panel A are viewed as functions of I_v, creating the

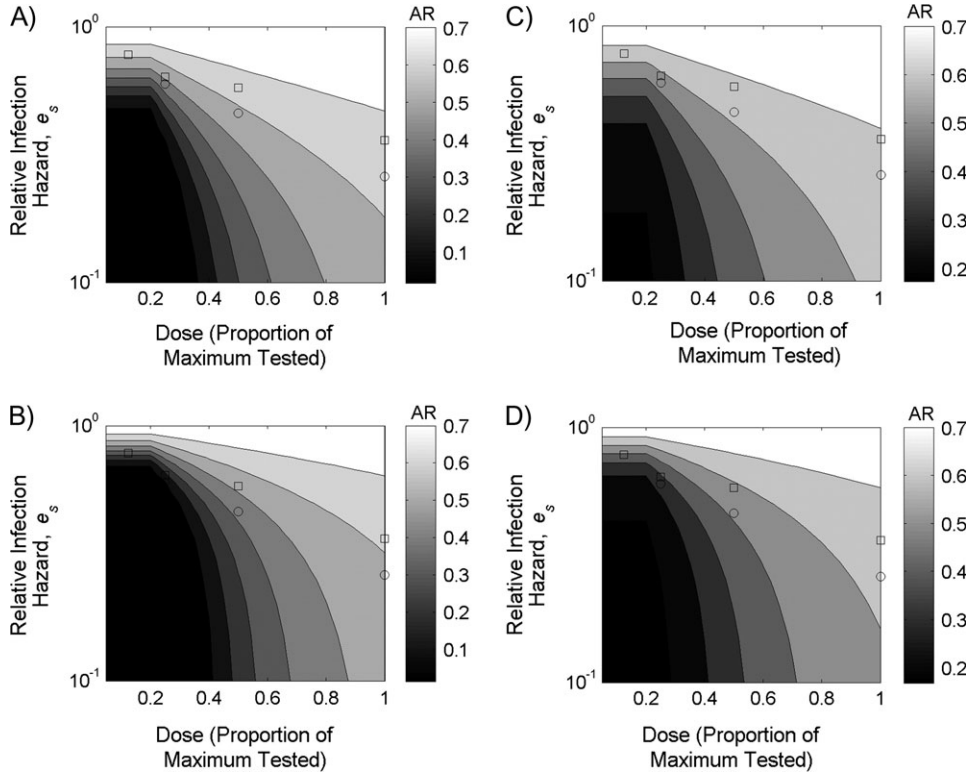

Figure 2. Attack rate (AR) for a given dose-response pair with 20% coverage at the maximum tested dose, with $R_0 = 2$ and vaccination delayed until the current attack rate is 0.01% (panels A and B) and 1% (panels C and D). In panels A and C, $e_i = 1$; in panels B and D, $e_i = e_s$. Squares and circles correspond to estimated relative susceptibilities for the Sanofi Pasteur (Lyon, France) (9) and Sinovac Biotech Co., Ltd. (Bejing, China) (12) vaccines, respectively, and appear at *x*-axis values given by the tested dose divided by the maximum tested dose in the trial (30 μg and 10 μg, respectively, for the Sanofi and Sinovac trials). e_i, mean relative infectivity; e_s, mean relative susceptibility; *R*, effective reproduction number.

scatter effect. When the prevalence is below 10^{-4}, both 1- and 2-dose programs would contain the pandemic. The 1-dose program is clearly superior when prevalence is between 10^{-4} and 10^{-2}. Beyond this level of prevalence, the differences are reduced, as is the predictive value of the linearized model.

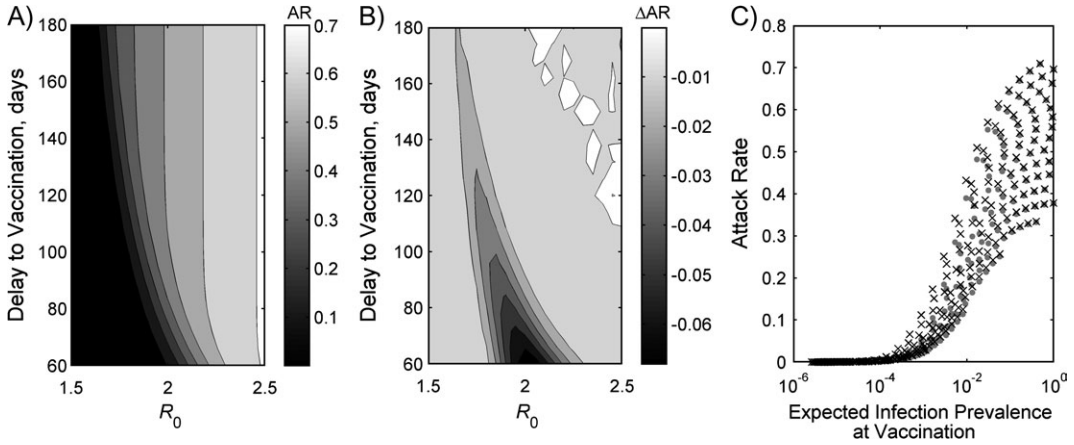

Figure 3. Contours representing the overall serologic attack rate (AR) in the 1-dose program (panel A) and the difference in attack rate (ΔAR) after an epidemic between the 1- and 2-dose programs (panel B) as a function of delay to vaccination and R_0. Antigen supply is constrained, with 1-dose coverage = 100% and 2-dose coverage = 50%. In each panel, $e_i = 1$. The attack rates vary according to the gray-scale bar (right of panel). Negative values in panel B are due to a lower attack rate with the 1-dose program. In panel C, the attack rate is graphed in terms of the expected prevalence of infection when the vaccine is delivered. Attack rates are represented by dots for the 1-dose program and by crosses for the 2-dose program. e_i, mean relative infectivity; *R*, effective reproduction number.

DISCUSSION

Models can be used to plan the best use of pandemic vaccines. This research addresses 2 key aspects of pandemic vaccines under current scrutiny: 1) the use of antigen-sparing vaccines and 2) the effect of timing on the use of matched vaccine. Antigen-sparing vaccines are a means of increasing population coverage at the price of reduced efficacy. Our approach of estimating efficacy by fitting linear models to trial data provides a simple means of comparing vaccines on the basis of their population impact, taking into account both efficacy and coverage.

This process was illustrated by calculating the effect on R_0 and attack rates, both of which were minimized by the lowest tested dose when based on existing adjuvanted trial data (Figures 1 and 2). This result is consistent with that of Riley et al. (14), who also found that the lowest tested dose was optimal for reducing attack rates for prepandemic vaccination. An exception is when supply is sufficient to provide 100% coverage at a higher dose. Their analysis focused on an R value of 1.8 and a small stockpile sufficient to vaccinate 10% of the population with the maximum tested dose in a multitype-vaccinated population with uniform mixing. They also examined semistructured populations including the case of a subpopulation with elevated transmission. Under most circumstances, these results supported their main conclusion.

Our analysis took a different approach to estimating vaccine efficacy, adding the element of delays due to seroconversion and delivery, enabling comparison of 1- and 2-dose vaccine programs. We fitted linear models to trial data, enabling simple characterization of the optimal dose for reducing R and the attack rate. Estimates of vaccine efficacy were applied to infection hazards, which is more appropriate than a relative risk measure when modeling partially protective vaccines. We showed how vaccines that also reduce infectivity of breakthrough vaccinated cases can alter the expression for the optimal dose and the expected magnitude of the reduction in R and the attack rate. This assumption is supported by evidence of greatly reduced viral loads and symptoms in challenge trials in the closest animal models (16), although the size of the reduction is unclear. The effect of a vaccine on transmission is greater if infectivity of breakthrough cases is also reduced (Figure 1, panels D and F compared with panels C and E; and Figure 2, panels B and D compared with panels A and C). If true, this finding would further support the use of low-antigen vaccines.

The time delay to vaccination has a critical effect on the impact of a vaccine matched to the pandemic strain. Campaigns based on matched vaccines are expected to occur during pandemic phase 6, when local transmission is well established. Our results showed that, even under the optimistic assumption of matched vaccination occurring at cumulative attack rates of 0.01% or 1% of the population, the effect of vaccination was substantially reduced (Figure 2).

When we varied R_0 and the delay to vaccination in the ranges of 1.5–2.5 months and 2–6 months, respectively, most simulations showed a modest reduction in attack rates, even with high vaccine effectiveness and coverage (Figure 3, panels A and C). We compared 1- and 2-dose programs based on immunogenicity data from the GlaxoSmithKline Biologicals 3.8-μg adjuvanted vaccine. Our assumption of being able to obtain twice the coverage with the 1-dose vaccine, combined with a relatively high estimate for vaccine efficacy and seroconversion occurring just once, meant that a 1-dose program was favored in our analysis. This preference could change if the 1-dose program had a substantially lower vaccine efficacy. We also found that the benefit of a 1-dose program over a 2-dose program was greatest when the vaccine was delivered while prevalence was above 0.1% but prior to its peak.

If the delay to vaccination were known in advance, then one could in principle assess whether a 1- or 2-dose program would be better while case numbers were small, since prevalence at this time point can be estimated on the basis of the epidemic growth rate. Currently, 2 doses of vaccine are required for high immunogenicity, even when the vaccine involves a novel adjuvant. However, our results show that a 1-dose program can lead to a lower attack rate by trading off lower immunogenicity against higher coverage.

Further benefits can be derived by increasing vaccine coverage through reducing the antigen required per dose. Efficacy of a single dose of vaccine could be aided either by priming individuals with a stockpiled H5N1 vaccine during pandemic phase 5/6 or by incorporating a H5N1 component in seasonal vaccines.

Our analysis focused on strategies designed to protect an entire population, and calculations of the optimal dose apply only when supply is constrained. The analysis does not apply to vaccination strategies aimed at protecting subsets of the population, where individual protection is the paramount concern and vaccine supply is adequate.

Limitations to our model include uniform seroconversion 21 days after each vaccination and the assumption of uniform mixing in a homogenous population. Titers rise continuously after vaccination, potentially more rapidly after the second dose, implying that our model may be biased slightly in favor of 1-dose programs. Subgroups, such as children, have been identified that display increased influenza transmission, and targeting transmitters has been shown to be an efficient use of influenza vaccine (17–19). In these circumstances, the optimal strategy may differ from that indicated by a homogenous mixing model, with higher dose, low-coverage strategies becoming more favorable. We did not account for stochastic behavior or importations of cases, both of which are influential during the early stages of an outbreak. Our estimates of optimal doses were based on a small number of data points for antigen volume and an assumed perfect correlation between infection rates in historic challenge trials and in a new pandemic as a function of titers of hemagglutination inhibition. This correlation is unlikely to be the case but reflects the unavoidable difficulty of estimating efficacy for H5N1 vaccines. Vaccination could also assume a staged form based on perceived disease or transmission risks (8, 20), and correlations between this order and transmission between different subgroups of the population cannot be assessed in a homogeneously mixed model. Also note that a focus on attack rates can sometimes be misleading in terms of prevention of severe disease and death (20).

The many limitations do suggest a role for carefully designed studies to improve estimates of model parameters. The infectivity of breakthrough-vaccinated cases seems particularly amenable, given that similar estimation studies have been performed with antiviral prophylaxis to prevent influenza (21). A household-based design in a moderately to highly vaccinated population, with recruitment based on a positive rapid test during the influenza season, might be a good start to addressing this question.

In conclusion, our results suggest that population benefits can accrue from low-antigen vaccination strategies that provide greater herd immunity but reduced individual protection. These benefits increase if the vaccine reduces both infectivity and susceptibility, as supported by studies performed on animal models of influenza. However, the effectiveness of a matched vaccine during pandemic phase 6 falls with both increasing R_0 and the delay to vaccine distribution. Once prevalence is greater than about 1%, the benefit of a matched vaccine falls away. If other control measures can slow the increase in prevalence, antigen-sparing vaccination strategies including a 1-dose vaccination campaign can reduce the overall attack rate.

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