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One versus two doses: What is the best use of vaccine in an influenza pandemic?

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ABSTRACT

Avian influenza A (H7N9), emerged in China in April 2013, sparking fears of a new, highly pathogenic, influenza pandemic. In addition, avian influenza A (H5N1) continues to circulate and remains a threat. Currently, influenza H7N9 vaccines are being tested to be stockpiled along with H5N1 vaccines. These vaccines require two doses, 21 days apart, for maximal protection. We developed a mathematical model to evaluate two possible strategies for allocating limited vaccine supplies: a one-dose strategy, where a larger number of people are vaccinated with a single dose, or a two-dose strategy, where half as many people are vaccinated with two doses. We prove that there is a threshold in the level of protection obtained after the first dose, below which vaccinating with two doses results in a lower illness attack rate than with the one-dose strategy; but above the threshold, the one-dose strategy would be better. For reactive vaccination, we show that the optimal use of vaccine depends on several parameters, with the most important one being the level of protection obtained after the first dose. We describe how these vaccine dosing strategies can be integrated into effective pandemic control plans.

1. Introduction

On April 1st 2013, the first cases of human infection with influenza A (H7N9) were reported in China (WHO, 2013). As of November 17th, 2014, over 450 cases have been reported (CIDRAP, 2014a), with an estimated 30% mortality rate (CIDRAP, 2014b). Studies have shown that this strain may be better adapted to mammalian hosts than other avian strains (Xu et al., 2013; Chan et al., 2013), raising a global concern that influenza A (H7N9) could acquire the ability to transmit from person to person triggering a new influenza pandemic (Uyeki and Cox, 2013). In response to this threat, several candidate vaccines are currently being tested, with most of them requiring two doses: a prime and a boost three weeks later (CIDRAP, 2013; WHO, 2013). With new cases arising continuously (WHO, 2014), avian influenza A (H5N1) remains a threat (Linster et al., 2014). Vaccination remains the most effective intervention against pandemic influenza, but in the event of a pandemic, vaccine will likely be in short supply (Osterholm et al., 2013).

We developed a mathematical model to evaluate two possible strategies for allocating limited vaccine supplies: a *one-dose strategy*, where more people are vaccinated with a single dose of vaccine, or a *two-dose strategy*, where half as many people are vaccinated with the full, required, two doses. We considered both pre-pandemic vaccination and reactive vaccination. For pre-pandemic vaccination, we demonstrated that under certain conditions, there is a threshold in the primary response level (defined as the percentage of the full vaccine efficacy that will be reached after the first dose), below which the two-dose strategy is better, but above which vaccinating the most people with a single dose would yield lower attack rates. We analyzed different parameters affecting the course of an epidemic to determine which ones carry the most weight in favoring a one-dose versus a two-dose strategy: initiation of vaccination with respect to the start of the epidemic, primary response level, vaccination coverage, the kinetics of the vaccine efficacies post-vaccination as functions of time, and transmissibility of the virus, measured through the basic reproduction number, R_0 (defined as the expected number of secondary

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infections resulting from a single typical infectious person in a completely susceptible population).

For each parameter set, we found a threshold in the value of R_0, below which the strategy of fewer vaccinees with two doses results in a smaller final illness attack rate (defined as the percentage of the population who become infected and ill) than the strategy of more vaccines with one dose. Above this threshold, our model predicts that vaccinating more people with one dose is better. Though the threshold depends on all the parameters considered, the primary response level is the most important. Because a vaccine shortage is very likely to occur for pandemic influenza, our results could provide valuable insights for allocating limited resources.

2. Methods

We used a classic susceptible–infected–removed (SIR) differential equations model to simulate an influenza epidemic in a homogeneous population. Briefly, the population is partitioned into those who are susceptible unvaccinated or vaccinated, infectious unvaccinated or vaccinated, asymptomatic or symptomatic, and recovered. A fraction of those infected will develop symptoms, while the rest remain asymptomatic. Infected asymptomatic people are less infectious than those who are symptomatic. Fig. 1A shows a schematic diagram of the model.

Vaccine is assumed to be "leaky" (Halloran et al., 1989), that is, vaccine confers partial protection to all vaccinees. The effect of vaccination in an individual is modeled following Halloran et al. (1997) in which vaccine protection has three possible components: First, vaccinated individuals have a reduced probability of becoming infected (vaccine efficacy on susceptibility, VE_S). Then, once infected, a vaccinated individual has a reduction in his/her infectiousness (vaccine efficacy to reduce infectiousness given infection, VE_I), and a reduction in the probability of developing symptoms (vaccine efficacy to prevent or diminish symptoms VE_P).

During the first two weeks after the first dose, the vaccine efficacies increase until they reach their *primary response level*, r_1, defined as the percentage of the overall maximum efficacy obtained after the full recommended two doses. For example, a *primary response level* of 50% corresponds to obtaining half of the protection after one dose, and full protection after two doses.

We further assumed that it would take only one week for the second dose to reach its full efficacy, and that the vaccine efficacy components would remain constant during the third week before the second dose.

Little is known about the pharmacodynamics of influenza vaccines and their interplay with the immune response. Since we were interested in investigating the impact of the shape and the speed of the vaccine efficacy kinetics on the population-level attack rates of the *one-* and *two-dose strategies*, we modeled vaccine efficacy building up over time and constructed, for each vaccine efficacy component, a family of functions that allows us to change these features. A concave shape corresponds to a vaccine in which protection is acquired mostly during the first few days after vaccination and then levels off. A convex shape corresponds to a vaccine efficacy in which protection takes a few days to kick in, then grows exponentially, finally leveling off during the last few days (Fig. 1B). The full description of the model, its equations, and the parameters values used here are presented in the Appendix. In the text below, the values of VE_S, VE_I, and VE_P always refer to the vaccine efficacy values obtained after the second dose of vaccine.

We analyzed vaccination under two different settings: prepandemic vaccination in which vaccination occurs well before the epidemic starts, and reactive vaccination in which vaccination occurs after the epidemic has started. We considered vaccinating 50% of the population with a single dose of vaccine or 25% of the population with two doses. A sensitivity analysis showed that our conclusions do not depend on the population coverage (Supplemental material).

3. Results

3.1. Prepandemic vaccination

In this section we assume that vaccination occurred before the beginning of the epidemic, so that vaccinated people have acquired all the protection given by a vaccine before the epidemic starts. This scenario allows us to mathematically analyze the model in full detail.

Here, we considered a variety of vaccines with different characteristics. First, assume a vaccine reducing susceptibility only (so that $VE_S > 0$ but $VE_I = 0 = VE_P$). This is the most common perception of how a vaccine works. We analytically demonstrated that for this model, there is a threshold in the primary response level, $r_1^* > 0.5$, that depends on the other parameters, at which the two strategies are equivalent. If $r_1 < r_1^*$, then the *two dose strategy* is always better, but, if $r_1 > r_1^*$ vaccinating twice as many people with one dose would result in lower attack rates (Fig. 2A and Theorem 1, Appendix).

Then, suppose that we have a vaccine that reduces either infectiousness only (so that $VE_I > 0$ but $VE_S = 0 = VE_P$) or pathogenicity only (so that $VE_P > 0$ but $VE_I = 0 = VE_S$). In both cases, we analytically proved that the threshold r_1^* in the primary response level is exactly 50%, and that this threshold is independent of all the other parameters of the model (Fig. 2B and C, and Theorems 2 and 3, Appendix).

Finally, using numerical simulations, we studied prepandemic vaccination when the three vaccine efficacy components can take any non-negative value. We considered four different vaccines: a low-efficacy vaccine ($VE_S = 15\%$, $VE_I = 0\%$, and $VE_P = 24\%$), a medium-efficacy vaccine ($VE_S = 40\%$, $VE_I = 22.5\%$, and $VE_P = 62\%$), a vaccine as efficacious as a seasonal vaccine ($VE_S = 40\%$, $VE_I = 45\%$, and $VE_P = 75\%$), and a high-efficacy vaccine ($VE_S = 66\%$, $VE_I = 45\%$, and $VE_P = 100\%$). These values were taken from *Basta et al.*, where the authors used challenge and community-based study data to estimate seasonal influenza vaccine efficacy (Basta et al., 2008). When $r_1 = 30\%$, for all the vaccines considered, the *two-dose strategy* was better with a maximum absolute difference of 6% in the attack rate (for $R_0 = 1.4$ and the medium-efficacy vaccine, Fig. 3A). For $r_1 = 50\%$ and $r_1 = 70\%$ and for all these vaccines, our simulations suggested that vaccinating with a single dose would be better than vaccinating half as many people with two doses. This difference was accentuated with more efficacious vaccines, with the highest difference seen for the high-efficacy vaccine when $R_0 = 1.5$ and $r_1 = 50\%$ (10% difference in the attack rate, Fig. 3B); and for $R_0 = 1.6$ for $r_1 = 70\%$ (16% difference in the attack rate), Fig. 3C.

3.2. Reactive vaccination

Next, we considered the situation in which vaccination is provided after the epidemic has started by solving the differential equations numerically. We assumed that the three components of vaccine efficacy are non-negative, and that they all reach the same primary response level after a single dose of vaccine. We considered vaccination taking place 45, 60, 75, or 90 days after the epidemic has started (Fig. S1). We also considered a model in which vaccination campaigns are stretched over 10, 20 or 30 days, and showed that our results are robust to this change (Sensitivity Analysis, Figs. S2–S6).

Our results suggested that there is a threshold R^*, in the basic reproduction number, above which priming a large number of

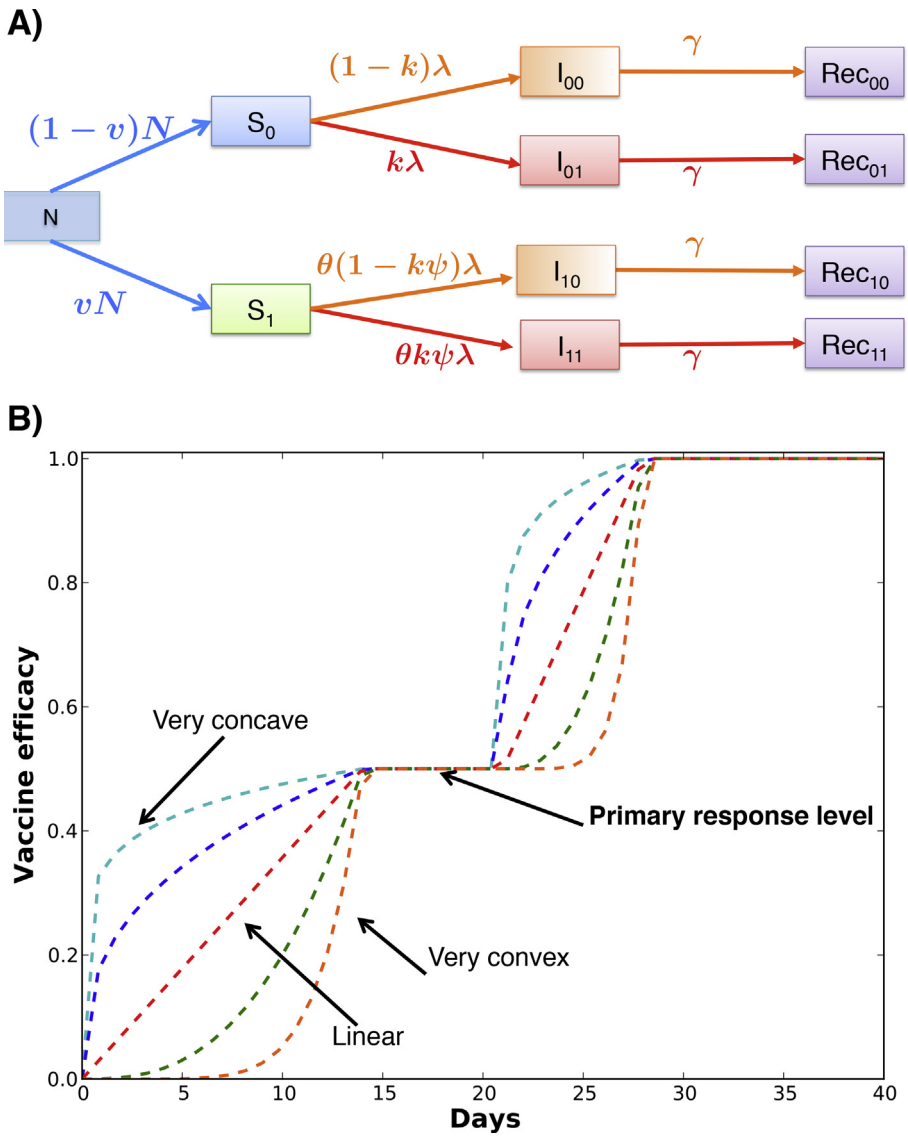

Fig. 1. (A) SIR model for influenza with vaccination with a leaky vaccine. Compartments: N total susceptible population; S_0 susceptible unvaccinated individuals; S_1 susceptible vaccinated individuals; I_{00} infected unvaccinated asymptomatic individuals; I_{01} infected unvaccinated symptomatic individuals; I_{10} infected vaccinated asymptomatic individuals; I_{11} infected vaccinated symptomatic individuals; Rec_{00} recovered unvaccinated asymptomatic individuals; Rec_{01} recovered unvaccinated symptomatic individuals; Rec_{10} recovered vaccinated asymptomatic individuals; Rec_{11} recovered vaccinated symptomatic individuals. See methods for detailed description and equations and Table 1 for parameter definitions and values. (B) Vaccine efficacy modeled as a function of time post-vaccination. We used a one-parameter family of functions to model the kinetics of the vaccine efficacies post-vaccination. Vaccine is administered at day 0 and at day 21. See Section 2 for a full description.

people would result in lower attack rates but below which vaccinating half as many with the full recommended two doses would result in fewer symptomatic infections. This threshold R^* depends on key parameters, with the primary response level being the most important one. For example, if the primary response level was 20% and the vaccine was as efficacious as a seasonal vaccine, then $R^* = 1.8$ but if the primary response level was 30%, then $R^* = 1.7$ (Fig. 4). Choosing the wrong policy could result in important differences in the attack rates: If the primary response level was 20% and $R_0 = 1.4$, then vaccinating 50% of the population with a single dose of a seasonal vaccine would result in a 13% higher attack rate than vaccinating 25% of the population with two doses (Fig. 4A). However, if the primary response level was 50% and $R_0 = 1.8$, then vaccinating the same percentage of the population with a single dose would result in a 9% lower attack rate than vaccinating half as many people with two doses. As expected, difference in the attack rates is more important with vaccines that are more efficacious. Fig. 5 represents the contour lines of the absolute difference between the attack rates of the *two-dose* and *one-dose* strategies, with 50% of the population vaccinated with a single dose and vaccination on day 45 after the beginning of the epidemic. For small values of R_0, ($1 \leq R_0 \leq 1.3$), or for big values of R_0 and low values of the primary response level r_1 ($0 \leq r_1 \leq 20\%$), the absolute difference in the attack rates is minimal. This is expected, both strategies will perform well at the lower end of R_0 and poorly at the higher end. The highest absolute difference is seen for intermediate values of R_0. For these values, a very low primary response level favors the ***two-dose strategy*** as little is gain with a single dose of vaccine, and a very high primary response level favors the ***one-dose strategy*** as most of the protection would be obtained after the first dose. The contour line where both strategies agree is shown in green. Interestingly, for this particular set of parameters, the strategies yield identical attack rates for primary response levels much below 50%, with most of the plane favoring the ***one-dose strategy*** (sensitivity analysis showed that this is true

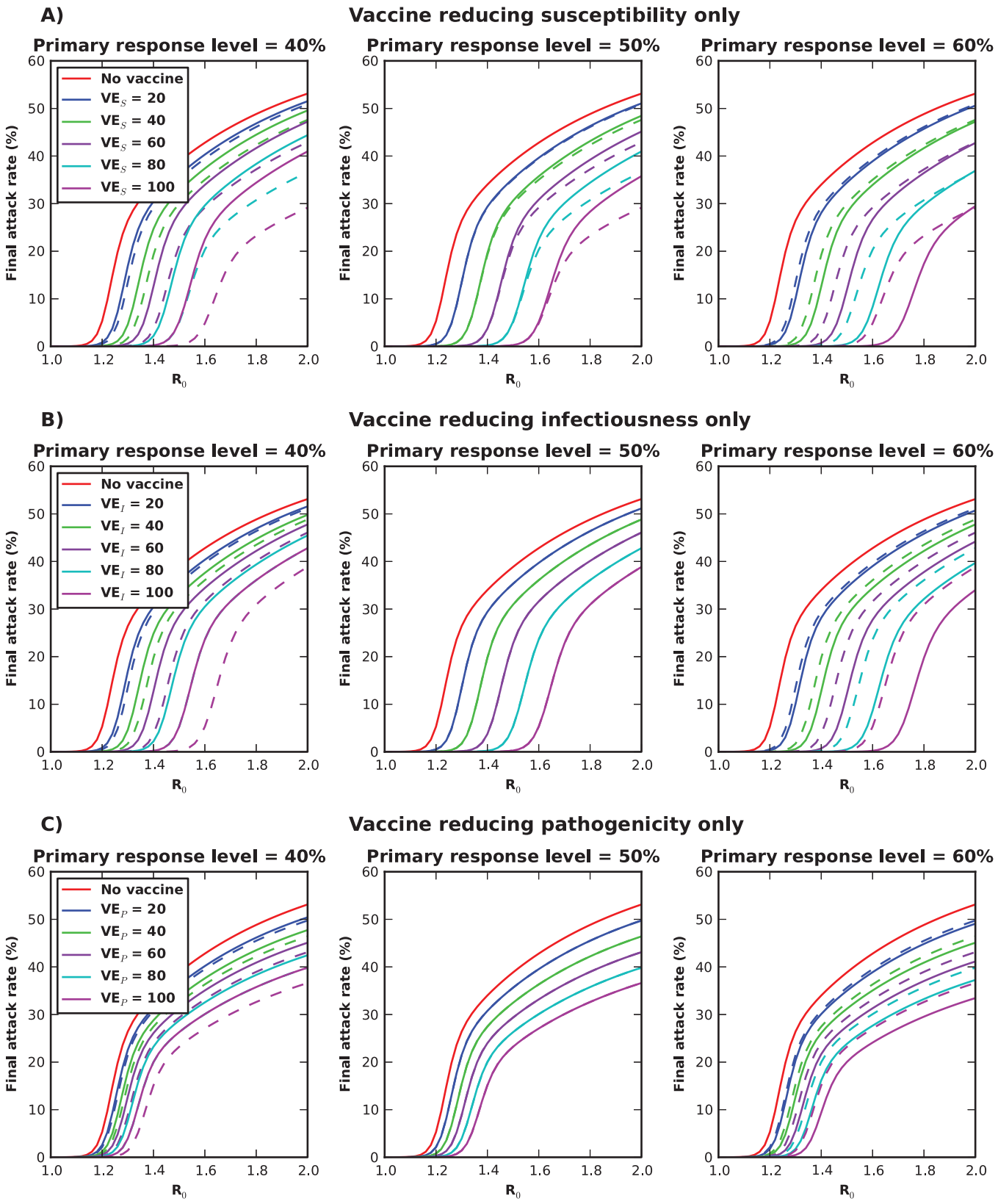

Fig. 2. Attack rates for pre-pandemic vaccination when the vaccine is efficacious (A) against susceptibility only; (B) in reducing infectiousness given infection only; (C) in reducing pathogenicity only. Solid lines indicate the final attack rate when vaccinating 50% of the population with a single dose, dashed lines indicate the final attack rates when vaccinating 25% of the population with two doses. The colors indicate the vaccine efficacy reached after the second dose.

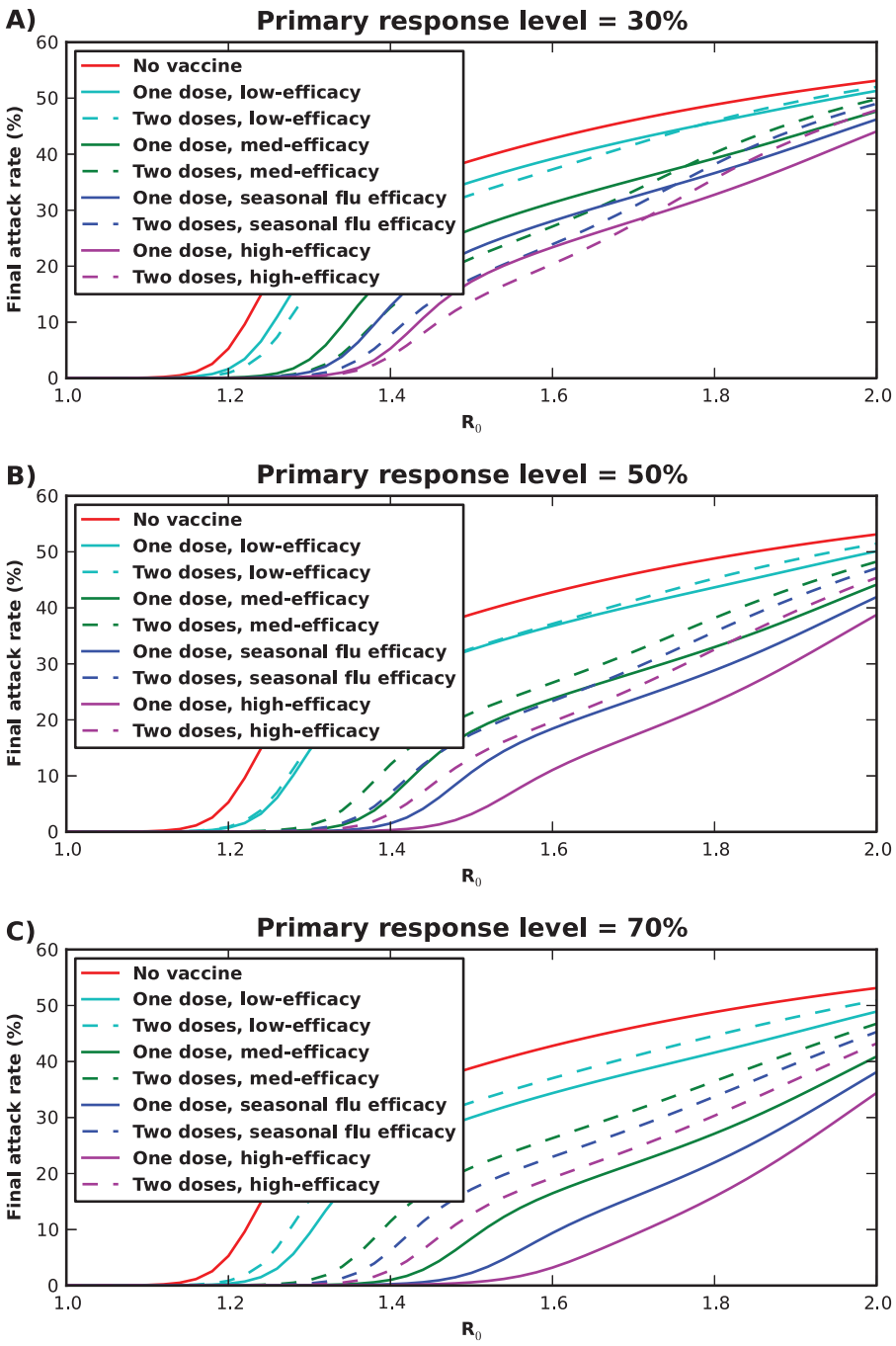

Fig. 3. Prepandemic vaccination when the primary response is set to (A) 30%; (B) 50%; (C) 70%. We considered vaccination of 50% of the population with a single dose or 25% of the population with two doses, and four different vaccines: a low-efficacy vaccine (VE_S = 15%, VE_I = 0%, and VE_P = 24%), a medium-efficacy vaccine (VE_S = 40%, VE_I = 22.5%, and VE_P = 62%), a vaccine as efficacious as a seasonal vaccine (VE_S = 40%, VE_I = 45%, and VE_P = 75%), and a high-efficacy vaccine (VE_S = 66%, VE_I = 45%, and VE_P = 100%).

for other relevant parameter sets as well). Our results suggest that the differences in the absolute attack rates are greater for reactive vaccination than for pre-pandemic vaccination.

If the primary response is lower than 50%, then our simulations showed that the best strategy will depend on key parameters of infection. We then considered other parameters affecting the course of an epidemic. For these results, we considered a vaccine that would be as good as the current seasonal vaccine, and used the vaccine efficacy values provided in Basta et al. (2008) and a primary response level of 30%. However, sensitivity analysis showed that our conclusions are not sensitive to these assumptions (Figs. S7–S10). In Fig. 6A, we considered different vaccination dates: the later vaccination occurs, the lower the threshold value R^* becomes. For example, if vaccination were to occur on day 45 after the beginning of the epidemic, then $R^* = 1.7$, but if vaccination occurred on day 75, then $R^* = 1.4$. Furthermore, the absolute difference between the attack rates of the ***two-dose strategy*** and the ***one-dose strategy*** is more important if vaccination occurs early, and it is attenuated as vaccination gets delayed. If vaccination started on or after day 90, this difference is less than 3% (Fig. S3). We analyzed the influence of the vaccine efficacy kinetics after vaccination on the threshold R^*. As expected, concave vaccine efficacy components yield smaller attack rates than convex ones. In addition, the more concave the vaccine efficacy components are, the lower the threshold values of R^* are, but the difference both in the values of R^* and the absolute difference between the attack rates were minimal (Figs. 6B and S4).

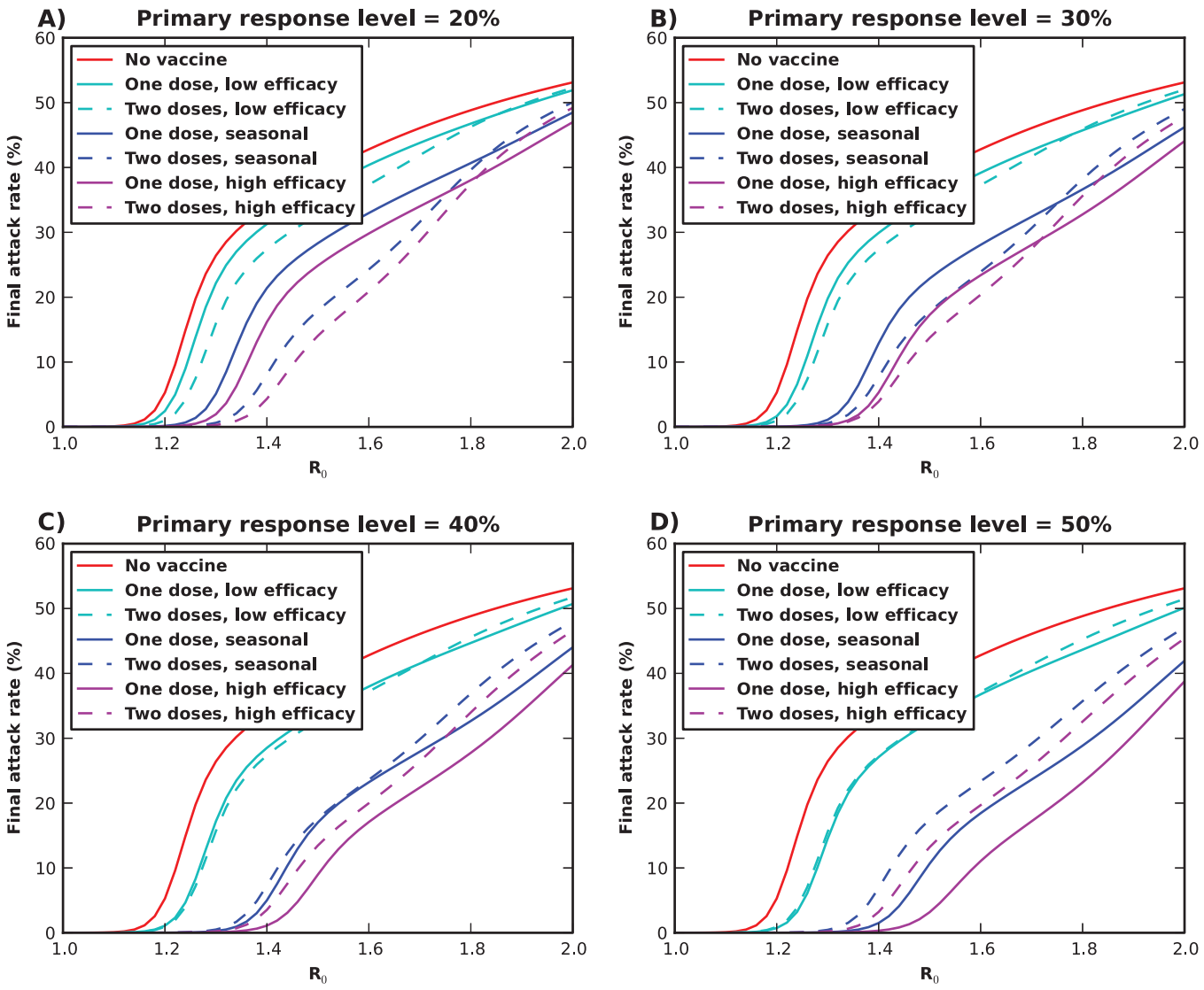

Fig. 4. Final attack rates for 50% coverage with one dose (solid lines) or 25% coverage with two doses (dashed lines) when vaccination occurs 45 days after the beginning of the epidemic. (A) Primary response level = 20%. (B) Primary response level = 30%. (C) Primary response level = 40%. (D) Primary response level = 50%. Three vaccines were considered: a low-efficacy vaccine (VE_S = 15%, VE_I = 0%, and VE_P = 24%), a vaccine as efficacious as a seasonal vaccine (VE_S = 40%, VE_I = 45%, and VE_P = 75%), and a high-efficacy vaccine (VE_S = 66%, VE_I = 45%, and VE_P = 100%).

We investigated how population coverage would affect the threshold R^* (Fig. 6C). Increasing the proportion of the population being vaccinated had some effect in the threshold value R^*. For example, when 20% of the population was vaccinated with a single dose, R^* = 1.9, but this value decreased to 1.7 if 80% of the population was vaccinated with one dose. In addition, for medium and high values of R_0, the absolute difference in the attack rates increased as population coverage increased (Fig. S5). Finally, we analyzed the effect of the values of the vaccine efficacy components on the threshold R^*, and found that the threshold R^* decreases very little as the vaccine becomes better (that is, if any of the vaccine efficacy components increase, the threshold R^* decreases, Fig. 6D). However, vaccine efficacy components had an interesting effect in the absolute difference in the attack rates. At both ends (low vaccine efficacy or high vaccine efficacy), both strategies yield similar differences in the attack rates, with less than 5% absolute difference for all values of R_0. However, when vaccine efficacy is moderate and R_0 has an intermediate value, the ***two-dose strategy*** would yield 5% less attack rate than the ***one-dose strategy*** (Fig. S6).

In contrast to our previous results, when the primary response level was set to 50% or higher, we found numerically that the *one-dose strategy* always resulted in lower attack rates than the *two dose strategy* in all the scenarios considered for reactive vaccination (varying vaccination dates, vaccine efficacy kinetics, vaccine efficacy values or vaccination coverage). This suggests that if the first dose of vaccine yields a strong immune response, then for reactive vaccination, priming a larger proportion of the population may be a better use of resources than vaccinating half as many with the full two doses (Fig. S11).

4. Discussion

We used a mathematical model to determine the best use of resources when vaccine supplies are constrained in the event of an influenza A (H7N9) epidemic. Our results can also be used in the event of an influenza A (H5N1) epidemic. Given that the current vaccines being tested are supposed to be administered in two doses, we examined the strategy of vaccinating a large number of people with a single dose versus vaccinating half as many with the recommended full two doses of vaccine. We performed a thorough analysis to investigate under which circumstances each strategy yields lower attack rates. We found that there is not a

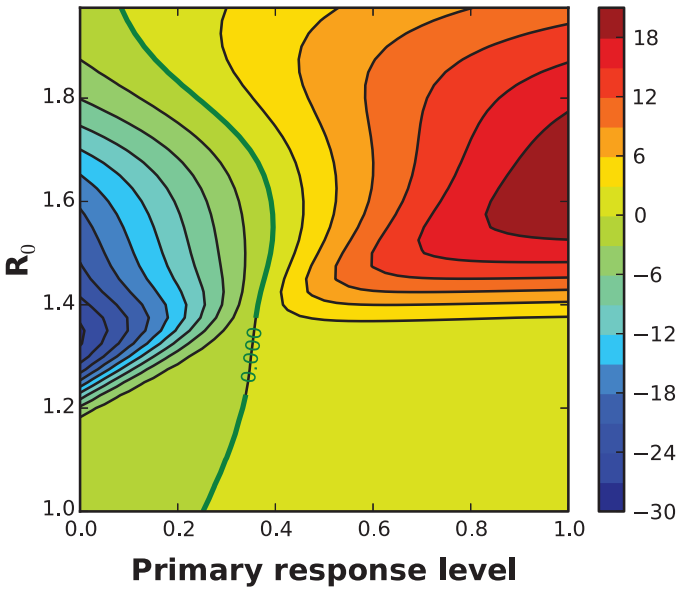

Fig. 5. Contour lines of the absolute difference between the attack rates of the *two-dose* and *one-dose* strategies as a function of the primary response level and R_0. Here, we considered vaccinating 50% of the population with a single dose of a seasonal vaccine and vaccination on day 45 after the beginning of the epidemic or 25% of the population with two doses of vaccine.

universal answer to this question, and that the best use of resources depends most of all, on the protection obtained after the first dose of vaccine (the primary response level), on the timing of the delivery of vaccine, and on the transmissibility of the virus (measured through R_0). To a lesser extent, the optimal strategy depends on the vaccine efficacy components and on the shape of the vaccine efficacy components building up once an individual is vaccinated.

If the vaccine-induced immunity after the first dose is half as good as that of the full recommended dose (so the primary response level is 50%), then we found some surprising results: If the vaccine is protective against susceptibility only, then our analytical results showed that prepandemic vaccination should be done with the full recommended two doses of vaccine, as this would yield lower attack rates. However, if vaccination occurs after the epidemic has started, then numerical results suggest that the best strategy would be to vaccinate as many people as possible with a single dose. If in addition the vaccine reduces infectiousness or pathogenicity, then numerical results suggest that the one-dose strategy would be better in both cases. If, on the other hand, the primary response level is below 50%, then our results suggest that there is a threshold in the values of R_0, below which the ***two − dosestrategy*** is better, and above it the ***one − dosestrategy*** yields lower attack rates. This threshold is dynamic, and it depends on when vaccine is administered, how good the vaccine is, the shape of the vaccine efficacy components after vaccination, and the vaccination coverage. Our results are in alignment with previous work (Riley et al., 2007; Wood et al., 2009).

Candidate vaccines against influenza A (H7N9) are currently in clinical trials (NIH, 2014), thus vaccine-induced immune responses have not been characterized yet. Our results highlight the importance of obtaining more information before taking any decision about the best use of resources. In particular, it is crucial to know the level of protection obtained after a single dose, as this seems to be a determining factor in deciding which strategy is better. In this sense, better and more complete studies need to be performed during clinical trials, where in addition to evaluating the standard vaccine safety and immunogenicity, other key parameters of vaccine efficacy and its interactions with the immune system could be measured at several time points.

A number of candidate two-dose influenza H5N1 vaccines have gone through phase I and II safety and immunogenicity trials (Bresson et al., 2006; Lin et al., 2006; Leroux-Roels et al., 2007; Treanor et al., 2006). These vaccine trials have included arms at different antigen doses ranging from 3.75 to 40 μg, with and without adjuvants, and with both homologous and heterologous testing. The main measures of immunogenicity have been based on serum hemagglutination inhibition (HAI) titers and neutralization antibody titers. Results varied considerably among the trials, but on average, for all doses tested, the use of vaccine with adjuvant resulted in geometric mean titers that were roughly twice as high just after the second dose, compared to just after the first dose; the same was true for seroconversion proportions (Leroux-Roels et al., 2007). Although it is currently unknown exactly how these immune measures predict vaccine efficacy (VE), the HAI titers have been shown to be a good correlate of protection for infection and influenza-like illness for both natural and vaccine induced immunity to seasonal influenza (Coudeville et al., 2010). This would imply that the primary response level for these vaccines could be in the region of 50%, further supporting vaccination with a single dose to as many people as possible. However, additional work needs to be done in this area to determine more precise estimates of both the primary response level and VE parameters, VE_S, VE_P and VE_I, from immunogenicity data. Furthermore, these conclusions were obtained for influenza H5N1, and extrapolation might be inadequate. Equivalent studies would be needed specifically aimed at influenza H7N9.

Our results have some limitations. Our model is intentionally simple to avoid possible confounders and to allow us to derive mathematical thresholds and general conclusions. The aim of the present work was to investigate the importance and impact of key parameters in determining the best use of vaccine under a one versus two-dose scenario. Models including age-groups or high-risk groups are more realistic, but such models introduce more variables and different questions to consider: how to prioritize vaccine among high and low transmission groups (e.g give one dose to adults and full dosage to children), how to prioritize vaccine among high and low risk groups, trade-offs between transmission-reducing versus mitigation strategies in the resulting attack rates, how to model morbidity and mortality in different age-groups, etc. These questions are highly important and are the subject of future research. We assumed that vaccine efficacies would induce the same protection across age-groups. Evidence based on seasonal influenza vaccines suggest, however, that this might not be the case, with the elderly obtaining lower protection (Jefferson et al., 2010; Osterholm et al., 2012). We based our decisions on illness attack rates, but other measures, like mortality or morbidity, could be useful in preparing for a pandemic. In reality, the optimal use of vaccine probably involves vaccinating high-risk groups with two doses and low-risk ones with a single dose. We assumed that a vaccine for either H5N1 or H7N9 influenza strains would require two doses (indeed, all vaccines ongoing clinical trials currently have a two-dose schedule). This assumption is based on immune responsiveness for seasonal vaccines, and we actually do not know if the established correlations between immune responsiveness and vaccine efficacy for seasonal vaccines can be translated for pandemic or zoonotic vaccines.

With new cases of influenza A (H7N9) arising, it is important for public health officials to have a clear vaccination policy in place as part of a prepandemic preparedness plan. The methods proposed here could help guiding this policy. As a shortage of vaccine is likely to occur, it is important to maximize the benefits that the available vaccine can give to the entire population.

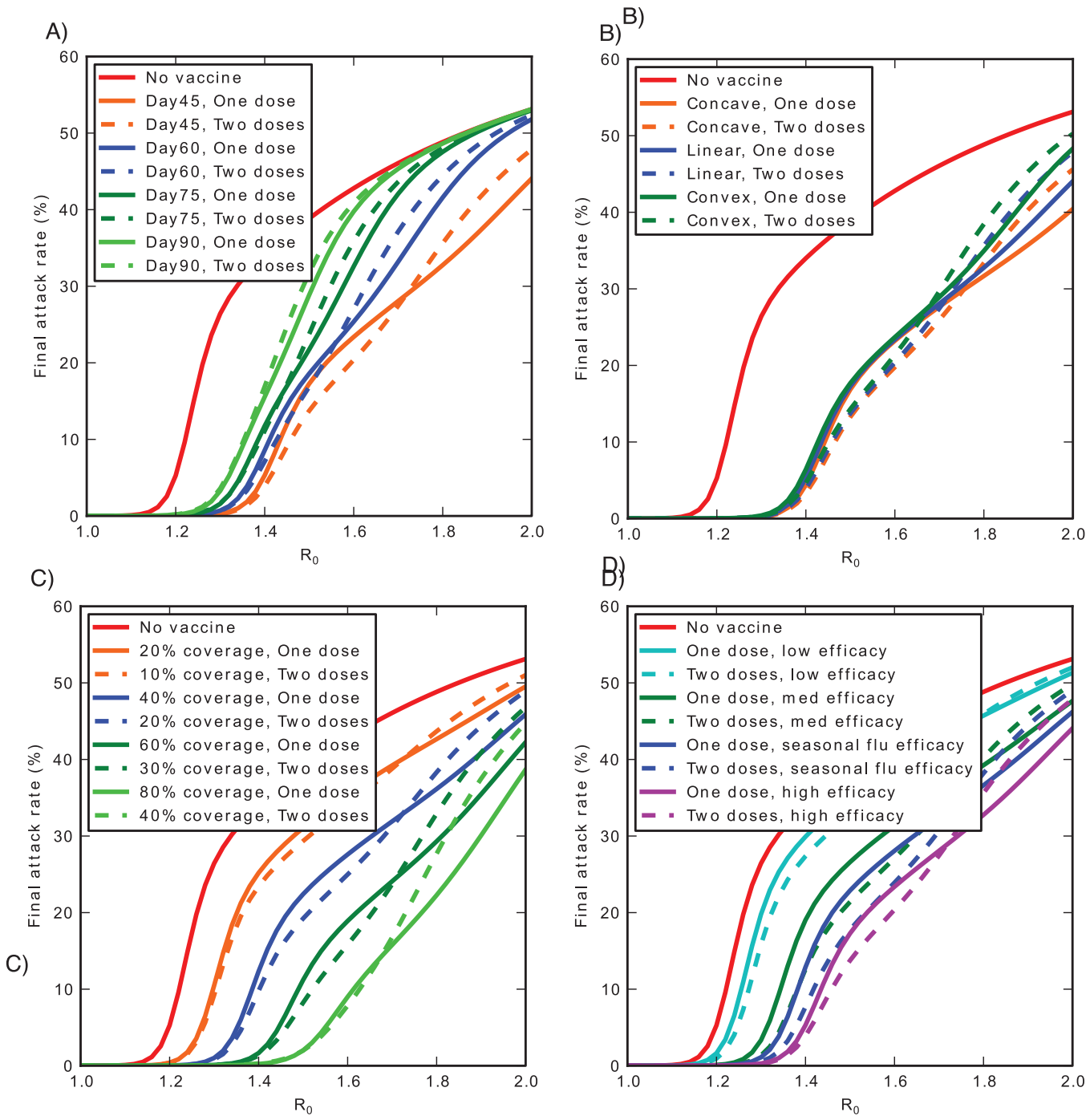

Fig. 6. Final attack rates for one dose (solid lines) and two doses (dashed lines) varying (A) vaccination dates; (B) the kinetics of the vaccine efficacies; (C) vaccination coverage; (D) vaccine efficacy values. For (D), four different vaccines were considered: a low-efficacy vaccine (VE_S = 15%, VE_I = 0%, and VE_P = 24%), a medium-efficacy vaccine (VE_S = 40%, VE_I = 22.5%, and VE_P = 62%), a vaccine as efficacious as a seasonal vaccine (VE_S = 40%, VE_I = 45%, and VE_P = 75%), and a high-efficacy vaccine (VE_S = 66%, VE_I = 45%, and VE_P = 100%). The primary response level was set to 30%.

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Appendix A.

A.1. Model

We use a differential equations model to simulate an influenza epidemic. We partitioned the population into those who are susceptible unvaccinated or vaccinated (S_i, i = 0, 1 for unvaccinated and vaccinated respectively), infectious I_{ij} with vaccinated status i and symptomatic status j, and recovered Rec_{ij} with vaccinated status i

and symptomatic status j ($j=0$ for asymptomatic and $j=1$ for symptomatic). A fraction k of those infected will develop symptoms, while the rest become asymptomatic. Infected asymptomatic people have their infectiousness reduced by a factor m ($m \in [0,1]$). All the infected people recover at the same rate, γ. The model consists of a system of eight ordinary differential equations:

Unvaccinated	Vaccinated
$\frac{dS_0}{dt} = -\lambda S_0$	$\frac{dS_1}{dt} = -\lambda\theta S_1$
$\frac{dI_{00}}{dt} = (1-k)\lambda S_0 - \gamma I_{00}$	$\frac{dI_{10}}{dt} = \theta(1-k\psi)\lambda S_1 - \gamma I_{10}$
$\frac{dI_{01}}{dt} = k\lambda S_0 - \gamma I_{01}$	$\frac{dI_{11}}{dt} = \theta k\psi\lambda S_1 - \gamma I_{11}$
$\frac{dRec_{00}}{dt} = \gamma I_{00}$	$\frac{dRec_{10}}{dt} = \gamma I_{10}$
$\frac{dRec_{01}}{dt} = \gamma I_{01}$	$\frac{dRec_{11}}{dt} = \gamma I_{11}$

subject to the conditions

$$\lambda(t) = \frac{cp}{N}(mI_{00} + I_{01} + m\phi I_{10} + \phi I_{11}),$$

with c being the contact rate and p is the probability of infection. The value of cp was varied to obtain different values of R_0. Vaccination is modeled with a leaky vaccine with three different components, $VE_S = 1-\theta$, $VE_I = 1-\phi$, and $VE_P = 1-\psi$ (Table 1).

We constructed a one-parameter family of functions to model vaccine efficacy components increasing over time,

$$f(t) = \begin{cases} VE * r_1(t/14)^{\exp(s_1)} & \text{for } 0 \le t \le 14 \\ VE * r_1 & \text{for } t \ge 14 \end{cases} \quad (1)$$

for one dose of vaccine and

$$f(t) = \begin{cases} VE * r_1(t/14)^{\exp(s_1)} & \text{for } 0 \le t \le 14 \\ VE * r_1 & \text{for } 14 \le t \le 21 \\ VE * (r_1 + (1-r_1)(t-21/7)^{\exp(s_2)}) & \text{for } 21 \le t \le 28 \\ VE & \text{for } t \ge 28 \end{cases} \quad (2)$$

for two doses of vaccine. VE is the vaccine efficacy, s_1 and s_2 are free parameters that allow us to vary the convexity of the function $f(t)$ ($s_i = 0$ results in a linear function), and r_1 is the primary response level. For all the results, except those where the shape of the vaccine efficacies was studied, we assumed that vaccine efficacies develop linearly in time, and assumed that the primary response level would be the same for all three efficacies.

A.2. Reproduction number and final size relation: the general case

Results shown below concern pre-pandemic vaccination only.

The basic reproduction number R_0 in the absence of vaccination for this model has been previously shown (Matrajt and Longini, 2012) to be given by

$$R_0 = ((1-k)m + k)r_0 \quad (3)$$

where $r_0 = cp/\gamma$. If a fraction v of the population is vaccinated, then the effective reproduction number R_v is

$$R_v = r_0\left\{(1-v)((1-k)m+k) + \theta\phi v((1-\psi k)m + \psi k)\right\}. \quad (4)$$

Similarly to Arino et al. (2006), we derived the final size relations for this model. Here, we obtain two balance equations, one for the unvaccinated and one for the vaccinated populations. Let p_u be the fraction of the unvaccinated who got infected (among these a fraction k are symptomatic), and p_v be the fraction among the vaccinated who got infected (and a fraction ψk among them become symptomatic).

$$1-p_u = \exp\left[-r_0\left((1-v)p_u((1-k)m+k) + vp_v\phi((1-\psi k)m+\psi k)\right)\right], \quad (5)$$

$$1-p_v = \exp\left[-r_0\theta\left((1-v)p_u((1-k)m+k) + vp_v\phi((1-\psi k)m+\psi k)\right)\right]. \quad (6)$$

From this we see that $(1-p_v) = (1-p_u)^\theta$ as expected.

A.3. Vaccine reducing susceptibility only

Suppose now that vaccination produces no reduction in infectivity or probability of symptomatic influenza so that $VE_I = VE_P = 0$. This corresponds to $\phi = \psi = 1$. Further, suppose that the first dose reduces susceptibility by a factor e_1 (so the relative susceptibility is $(1-e_1)$ and the second dose reduces susceptibility even further by a factor e_2. Then, the vaccine efficacy for susceptibility VE_S (after two doses) is given by

$$VE_S = 1-\theta = 1-(1-e_1)(1-e_2) = e_1 + e_2 - e_1e_2 \quad (7)$$

with the primary response level r_1 given by:

$$r_1 = \frac{e_1}{e_1 + e_2 - e_1e_2}. \quad (8)$$

Note that here the primary response level is expressed as a fraction rather than a percentage.

Assume that a fraction v of the population is vaccinated with one dose. The reproduction number R_1 is given by

$$R_1 = R_0(1-e_1v), \quad (9)$$

and the balance Eqs. (5) and (6) become

$$1-p_u = \exp\left[-r_0((1-k)m+k)((1-v)p_u + vp_v)\right], \quad (10)$$

$$1-p_v = \exp\left[-(1-e_1)r_0((1-k)m+k)((1-v)p_u + vp_v)\right]. \quad (11)$$

If we take the weighted average $p_1 = (1-v)p_u + vp_v$ of the two equations we get an equation for the overall fraction infected p_1:

$$p_1 = 1-(1-v)e^{-R_0p_1} - ve^{-R_0(1-e1)p_1}. \quad (12)$$

Analogously, when a fraction $v/2$ is vaccinated with two doses with a vaccine efficacy for susceptibility $VE_S = 1-(1-e_1)(1-e_2)$ the reproduction number R_2 is given by

$$R_2 = R_0\left(1-(\frac{e_1+e_2-e_1e_2}{2}v)\right), \quad (13)$$

and the final size relation becomes

$$\begin{aligned} p_2 &= 1-(1-\frac{v}{2})e^{-R_0p_2} - \frac{v}{2}e^{-R_0(1-e_1)(1-e_2)p_2} \\ &= 1-e^{-R_0p_2} + \frac{v}{2}e^{-R_0p_2} - \frac{v}{2}e^{-R_0(1-e_1)(1-e_2)p_2} \\ &= 1-(1-v)e^{-R_0p_2} - \frac{v}{2}\left(e^{-R_0p_2} + e^{-R_0(1-e_1)(1-e_2)p_2}\right). \end{aligned} \quad (14)$$

Theorem 1. *If a vaccine reduces susceptibility only (so that $VE_S > 0$ but $VE_I = 0 = VE_P$), then there is a value $r_1^* > 0.5$, such that $p_2 < p_1$ if and only if $r_1 < r_1^*$ (and $p_2 = p_1$ if and only if $r_1 = r_1^*$).*

Proof. First, when $r_1 = 0.5$, we have that $(1-e_1)(1-e_2) = 1-2e_1$ and the expressions (12) and (14) become

$$p_1 = 1-(1-v)e^{-R_0p_1} - ve^{-R_0(1-e1)p_1} \quad (15)$$

Table 1
Parameter values.

Parameter	Description	Value	Reference
γ	Recovery rate	0.25	Longini et al. (2004)
k	Fraction of symptomatic	2/3	Longini et al. (2004)
m	Reduction of infectiousness for asymptomatics	0.5	Longini et al. (2004)
cp	Contact rate, probability of transmission	–	Calculated to obtain the desired R_0
v	Fraction vaccinated	–	Varied throughout text
$VE_S = 1-\theta$	Vaccine efficacy for susceptibility for seasonal influenza	40	Basta et al. (2008)
$VE_I = 1-\phi$	Vaccine efficacy for infectiousness for seasonal influenza	45	Basta et al. (2008)
$VE_P = 1-\psi$	Vaccine efficacy for pathogenicity for seasonal influenza	75	Basta et al. (2008)
N	Total population	1,000,000	Assumption
	Initially infected fraction of the population	1/1,000,000	Assumption

$$p_2 = 1-(1-v)e^{-R_0 p_2} - \frac{v}{2}\left(e^{-R_0 p_2} + e^{-R_0(1-2e_1)p_2}\right). \quad (16)$$

Consider the function $f(x) = e^{-R_0(1-x)p_1}$. If $x_1 \le x_2$, then $f(x_1) \le f(x_2)$, so that

$$e^{-R_0(1-x_1)p_1} \le e^{-R_0(1-x_2)p_1} \text{ and}$$
$$1-(1-v)e^{-R_0 p_1} - ve^{-R_0(1-x_1)p_1} \ge$$
$$1-(1-v)e^{-R_0 p_1} - ve^{-R_0(1-x_2)p_1}.$$

This implies that p_1 is monotonically decreasing in e_1 (the more effective vaccine the fewer get infected) and hence in r_1. Now, the function $f(x)$ is convex, so we have

$$e^{-R_0(1-e1)p_1} \le \frac{1}{2}\left(e^{-R_0(1-2e_1)p_1} + e^{-R_0 p_1}\right).$$

This implies that $p_2 \le p_1$ if $r_1 \le 0.5$, and it follows that there exists r_1^*, such that $r_1^* > 0.5$, for which $p_2 = p_1$.

Note: the value of this threshold depends on R_0 as well, so it depends indirectly on other parameters of the model other than the primary response level. □

A.4. Vaccine reducing infectiousness only

Assume now a vaccine reduces infectiousness only (so that $VE_I > 0$ but $VE_S = 0 = VE_P$). Suppose, as before, that a single dose reduces infectivity by a factor e_1 and a second dose reduces it by an additional factor e_2. The relative infectivity is hence $(1-e_1)$ for one dose and $(1-e_1)(1-e_2)$ for two doses, and the primary response level (for infectivity) equals $r_1 = e_1/(e_1+e_2-e_1e_2)$.

Since the vaccine has no effect on susceptibility, the fraction infected among the vaccinated and unvaccinated populations will be identical. We hence obtain a single balance equation from Eqs. (5) and (6) for the fraction p_1 of the population getting infected when a fraction v of the population is vaccinated with a single dose,

$$1-p_1 = e^{-R_0(1-e_1 v)p_1}. \quad (17)$$

If instead a fraction $v/2$ is vaccinated with 2 doses, the final fraction infected, now denoted p_2, solves the equation

$$1-p_2 = e^{-R_0(1-(e_1+e_2-e_1e_2)v/2)p_2}. \quad (18)$$

Theorem 2. *Assume a vaccine that reduces infectiousness only (so that $VE_I > 0$ but $VE_S = 0 = VE_P$). Vaccinating with two doses a fraction $v/2$ of the population yields lower attack rates than vaccinating a fraction v of the population with a single dose if and only if the primary response level is less than 50%. Mathematically: $p_2 \le p_1$ if and only if $r_1 \le 0.5$.*

Proof.

$$p_2 \le p_1 \quad \text{iff } -R_0\left(1-\frac{(e_1+e_2-e_1e_2)v}{2}\right) \le -R_0(1-e_1v)$$
$$\text{iff} \quad \frac{e_1}{e_1+e_2-e_1e_2} \le \frac{1}{2}.$$

Note that here the inequality depends only on the primary response level, hence this result is independent of all the other parameters of the model. □

A.5. Vaccine reducing pathogenicity only

Suppose now instead that the vaccine has no effect on susceptibility, nor on infectivity for symptomatic and asymptomatic cases, but that the only effect is that it increases the chance of having no symptoms (i.e. becoming asymptomatic). As before we let e_1 and e_2 respectively be the reduction factors for one dose and an additional vaccine dose.

More precisely, without vaccination an infected person becomes symptomatic with probability k. If vaccinated with one dose this probability then becomes $(1-e_1)k$ and after 2 doses it becomes $(1-e_1)(1-e_2)k$. As in the previous case there is no reduction in susceptibility, and the equation for the fraction p_1 of the population getting infected when a fraction v of the population is vaccinated with a single dose is given by

$$1-p_1 = \exp\left[-r_0\left((1-v)(k+(1-k)m) + v((1-e_1)k + (1-(1-e_1)k)m)\right)p_1\right]. \quad (19)$$

If instead a fraction $v/2$ of the population is vaccinated with 2 doses, the fraction p_2 who got infected is given by

$$1-p_2 = \exp\left[-r_0\left((1-v/2)(k+(1-k)m) + (v/2)((1-e_1) \times (1-e_2)k + (1-(1-e_1)(1-e_2)k)m)\right)p_2\right]. \quad (20)$$

Theorem 3. *Assume a vaccine that reduces pathogenicity only (so that $VE_P > 0$ but $VE_S = 0 = VE_I$). Vaccinating with two doses a fraction $v/2$ of the population yields lower attack rates than vaccinating a fraction v of the population with a single dose if and only if the primary response level is less than 50%. Mathematically: $p_2 \le p_1$ if and only if $r_1 \le 0.5$.*

Proof.

$$p_2 \le p_1 \Leftrightarrow$$

$$(1-\frac{v}{2})(k+(1-k)m)+\frac{v}{2}((1-e_1)(1-e_2)k+(1-(1-e_1)(1-e_2)k)m) \le (1-v)(k+(1-k)m)+v((1-e_1)k+(1-(1-e_1)k)m) \Leftrightarrow$$

$$(1-\frac{v}{2})(k+(1-k)m)+\frac{v}{2}((1-e_1)(1-e_2)k+(1-(1-e_1)(1-e_2)k)m \le (1-\frac{v}{2}-\frac{v}{2})(k+(1-k)m)+v((1-e_1)k+(1-(1-e_1)k)m \Leftrightarrow$$

$$\frac{1}{2}((1-e_1)(1-e_2)k+(1-(1-e_1)(1-e_2)k)m) \le -\frac{1}{2}(k+(1-k)m)+m((1-e_1)k+(1-(1-e_1)k) \Leftrightarrow$$

$$\frac{k}{2}-\frac{ke_2}{2}-\frac{ke_1}{2}+\frac{m}{2}+\frac{ke_1e_2}{2}-\frac{km}{2}-\frac{kme_2}{2}-\frac{kme_1}{2}+\frac{kme_1e_2}{2} \le -\frac{k}{2}-\frac{m}{2}+\frac{km}{2}+k-ke_1+m-km+kme_1 \Leftrightarrow$$

$$-\frac{1}{2}(1-m)(e_1+e_2-e_1e_2) \le -e_1(1-m) \Leftrightarrow$$

$$\frac{1}{2} \ge \frac{e_1}{e_1+e_2-e_1e_2} \Leftrightarrow$$

$$r_1 \le \frac{1}{2}$$

□

Appendix B. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2015.06.001

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