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EVALUATION OF VACCINATION STRATEGIES DURING PANDEMIC OUTBREAKS

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Abstract. During pandemic influenza, several factors could significantly impact the outcome of vaccination campaigns, including the delay in pandemic vaccine availability, inadequate protective efficacy, and insufficient number of vaccines to cover the entire population. Here, we incorporate these factors into a vaccination model to investigate and compare the effectiveness of the single-dose and two-dose vaccine strategies. The results show that, if vaccination starts early enough after the onset of the outbreak, a two-dose strategy can lead to a greater reduction in the total number of infections. This, however, requires the second dose of vaccine to confer a substantially higher protection compared to that induced by the first dose. For a sufficiently long delay in start of vaccination, the single-dose strategy outperforms the two-dose vaccination program regardless of its protection efficacy. The findings suggest that the population-wide benefits of a single-dose strategy could in general be greater than the two-dose vaccination program, in particular when the second dose offers marginal increase in the protection induced by the first dose.

1. **Introduction.** While vaccination remains the most effective strategy against influenza infection [3, 12], this preventive measure may not be available during the initial spread of an emerging pandemic virus. However, upon availability, vaccines could potentially play an important role in disease mitigation. Given the possibility of genetic variation in the replication of a novel emerging virus, and the inadequacy

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of immune responses in some vaccinated individuals, a single dose of a virus-specific vaccine may provide limited protection, necessitating a second dose for boosting immunity to levels required for infection prevention. A second dose of vaccine may be administered in a 3-4 week time after the first dose [11], and this delay can be significant in the context of a rapidly spreading disease.

Decision on the most effective vaccination strategies are compounded by many factors [2, 5, 8], in addition to the likely increase in the protection efficacy induced by additional vaccine doses. Policymakers would need to take into account the possibility of inadequate vaccine supply, as well as the timelines for vaccine availability and distribution to target groups. With the pressures of a rapidly growing outbreak, and the manufacturing and logistical realities of production and delivery of large quantities of a new vaccine [6], it is unclear whether vaccines should be administered in a single-dose program (with possibly lower protection and higher coverage) or in a two-dose strategy (with likely higher protection and reduced coverage). This study aims to address this question by developing a mathematical model for the transmission dynamics of pandemic influenza.

For the purpose of this study, we develop a model to incorporate several parameters that affect the outcome of vaccination campaigns, including the number of vaccines, efficacy of single- and two-dose vaccination, the time at which vaccination starts during the outbreak, the rate at which vaccines are distributed, the delay between first and second vaccine doses, and the severity of the disease represented by the reproduction number of the pandemic virus [11]. These parameters are particularly relevant to the 2009 pandemic situation caused by the worldwide spread of an influenza A/H1N1 strain [17], but the results of this study are equally important and applicable to future emerging infectious disease challenges.

2. **The model.**

To develop the model, we divide a homogeneously mixing population into compartments of individuals that are susceptible (S), asymptomatically infected (A), symptomatically infected (I), vaccinated with a single dose (V_1), and vaccinated with two doses (V_2). We assume that the population is entirely immunologically naïve to the disease with no pre-existing immunity. In addition to susceptible individuals, asymptomatically infected individuals (who show no clinical symptoms) may also be vaccinated without gaining benefit from vaccine during the relatively short course of infection. Vaccination of asymptomatic infection will reduce the vaccine supply, and we consider this reduction by the factor $S/(S+A)$ in the constant rate at which susceptibles are vaccinated. The primary vaccination (first dose) is assumed to start at time T_s, and end at time T_e; although the second dose vaccination will continue after T_e if required. We investigate the importance of T_s, relative to the time for the onset of the outbreak, on the effectiveness of vaccination policies considered in this study.

Since vaccination may not be 100% effective [11], those who receive vaccines (in single- or two-dose strategy) remain still susceptible to the disease, but at a reduced rate of acquiring infection (compared to unvaccinated individuals) corresponding to the efficacy of the vaccine. Individuals in the V_1 class leave the class either by acquiring infection (moving to I or A), or by receiving their second dose of vaccine (moving to V_2) at a fixed time a^* after primary vaccination. Individuals in V_2 may still be susceptible to the disease, and leave via infection to I or A. We assume that vaccinated individuals who become infected are less likely to develop symptoms (with an increased probability of being asymptomatic) due to the immunological

effects of vaccination [11]. Since we are only concerned with the short time-scale of a pandemic outbreak, we ignore demographics and the waning of vaccine-induced protection. Given these assumptions, the model is expressed as the following system of ordinary differential equations, along with a partial differential equation.

$$S' = -fS - V_1(t,0), \tag{1a}$$

$$A' = \Big((1-p)S + (1-p_1)\delta_1\hat{V}_1 + (1-p_2)\delta_2 V_2\Big) f - \mu_A A, \tag{1b}$$

$$I' = (pS + p_1\delta_1\hat{V}_1 + p_2\delta_2 V_2)f - \mu I, \tag{1c}$$

$$V_2' = V_1(t,a^*) - \delta_2 f V_2(t), \tag{1d}$$

$$\Big(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\Big)V_1(t,a) = -\delta_1 f V_1(t,a), \qquad 0 \le a \le a^* \tag{1e}$$

with boundary condition

$$V_1(t,0) = \begin{cases} \gamma S_0\Big(\dfrac{S(t)}{S(t)+A(t)}\Big), & T \le t \le T_e \text{ and } S > 0 \\ 0, & \text{otherwise} \end{cases} \tag{2}$$

and initial conditions $S(0) > 0$, $A(0), I(0) \ge 0$, $V_1(0,a) = 0$ for all $0 \le a \le a^*$ and $V_2(0) = 0$, and where for notational convenience we have defined

$$f = \beta(\delta_A A + I),$$

$$\hat{V}_1(t) = \int_0^{a^*} V_1(t,a)da.$$

In this model, S_0 is the initial size of the susceptible population; β is the baseline transmission rate of disease; γ is the rate at which susceptible individuals are vaccinated per day; p, p_1 and p_2 are, respectively, the probabilities that susceptible, primary vaccinated, and secondary vaccinated individuals develop symptoms upon infection; δ_1 and δ_2 are, respectively, the reduced transmission factors due to first and second dose vaccination; δ is the reduced transmissibility of asymptomatic infection; and μ and μ_A are the recovery rates of symptomatic and asymptomatic infection, respectively. We assume that recovered individuals are protected against re-infection. For the above model, the equation for removed (recovered) individuals is given by $R' = \mu_A A + \mu I$, which has no influence on other equations and the dynamics of the system, and we therefore ignore it here. The values of the model parameter with their respective ranges are given in Table 1.

The equation for V_1 in (1e) can be solved using the method of characteristics along the lines $a = s$ and $t = T + s$, with s as a new variable. Doing so, $V_1(t,a)$ is explicitly expressed as

$$V_1(t,a) = V_1(t-a,0)\ \exp\Big(\int_{t-a}^{t} -\delta_1 f(\xi)d\xi\Big). \tag{3}$$

Defining,

$$\zeta(t) = \int_0^t \delta_1 f(\xi)d\xi,$$

and substituting into (3), leads to

$$V_1(t,a) = V_1(t-a,0)e^{\zeta(t-a)-\zeta(t)},$$

which converts the distributed delay into a discrete one. Defining the new variable

$$\nu(t) = \int_0^t V_1(s,0)e^{\zeta(s)}ds,$$

the total number of individuals that have been vaccinated with a single dose is given by

$$\hat{V}_1(t) = e^{-\zeta(t)}\big(\nu(t) - \nu(t-a^*)\big).$$

Thus the model (1a)-(1e) can be written in the following form

$$S' = -fS - V_1(t,0), \tag{4a}$$

$$A' = \Big((1-p)S + (1-p_1)\delta_1\hat{V}_1 + (1-p_2)\delta_2 V_2\Big)f - \mu_{_A}A, \tag{4b}$$

$$I' = (pS + p_1\delta_1\hat{V}_1 + p_2\delta_2 V_2)f - \mu I, \tag{4c}$$

$$V_2' = V_1(t-a^*,0)e^{\zeta(t-a^*)-\zeta(t)} - \delta_2 f V_2, \tag{4d}$$

$$\zeta' = \delta_1 f, \tag{4e}$$

$$\nu' = V_1(t,0)e^{\zeta(t)}. \tag{4f}$$

In the absence of vaccination, the model reduces to the system of ordinary differential equations $S' = -fS$, $A' = (1-p)fS - \mu_{_A}A$, and $I' = pfS - \mu I$. Using a previously established method [15], we can calculate the basic reproduction number, $\mathcal{R}_0$, of disease transmission for this reduced model, which is defined as the number of new infections generated by a single infected case introduced into a wholly susceptible population [4]. This calculation yields the expression

$$\mathcal{R}_0 = \beta S_0\Big(\frac{(1-p)\delta_{_A}}{\mu_{_A}} + \frac{p}{\mu}\Big). \tag{5}$$

2.1. **Reproduction number for the limiting model.** Suppose that $t \to \infty$. Then for sufficiently large t, we have $V_1(t,0) = V_1(t-a^*,0) = 0$. It is easy to show that the system (4a)-(4f) is well-posed with continuous nonnegative and bounded state variables, and as a consequence, it follows that

$$\int_T^{T_e} \frac{S(s)}{S(s)+I(s)}e^{\zeta(s)}ds =: K,$$

with $K \in \mathbb{R}_+$. Thus, for large t, $\nu(t) = \gamma S_0 K$, which implies $\hat{V}_1(t) = 0$. Thus, the system (4a)-(4f) takes the limiting form

$$S' = -\beta(\delta_{_A}A + I)S, \tag{6a}$$

$$A' = \beta\big((1-p)S + (1-p_2)\delta_2 V_2\big)(\delta_{_A}A + I) - \mu_{_A}A, \tag{6b}$$

$$I' = \beta(pS + p_2\delta_2 V_2)(\delta_{_A}A + I) - \mu I, \tag{6c}$$

$$V_2' = -\delta_2\beta(\delta_{_A}A + I)V_2, \tag{6d}$$

in which the delay has vanished. Note that this system should not be considered as a *de novo* system, for which initial conditions should be provided. Indeed, (4a)-(4f) is a non-autonomous system of ordinary differential equations (in which all the "non ordinary" terms make up the non autonomous component), which is asymptotically autonomous with limiting system (6a)-(6d) [14].

The disease free equilibrium in (6a)-(6d) is found by setting $A = I = 0$. This is satisfied at any (S^*, V_2^*). This equilibrium cannot be expressed explicitly, and its values depend on the history of system (4a)-(4d) prior to approaching the limiting

system. However, this equilibrium can be used to formulate the control reproduction number in the presence of vaccination. To do so, we apply a previous method [15], and re-write (6b)-(6c) as

$$\begin{pmatrix} A \\ I \end{pmatrix}' = \mathcal{F} - \mathcal{W},$$

where

$$\mathcal{F} = \begin{pmatrix} \beta\big((1-p)S + (1-p_2)\delta_2 V_2\big)(\delta_{_A} A + I) \\ \beta(pS + p_2\delta_2 V_2)(\delta_{_A} A + I) \end{pmatrix}, \qquad \mathcal{W} = \begin{pmatrix} \mu_{_A} A \\ \mu I \end{pmatrix}.$$

Computing the Fréchet derivatives of $\mathcal{F}$ and $\mathcal{W}$, and evaluating them at the disease free equilibrium, gives

$$F = \beta \begin{pmatrix} (1-p)S^* + (1-p_2)\delta_2 V_2^* & 0 \\ 0 & pS^* + p_2\delta_2 V_2^* \end{pmatrix} \begin{pmatrix} \delta_{_A} & 1 \\ \delta_{_A} & 1 \end{pmatrix}$$

and

$$W = \begin{pmatrix} \mu_{_A} & 0 \\ 0 & \mu \end{pmatrix}.$$

A simple calculation yields

$$FW^{-1} = \begin{pmatrix} (1-p)S^* + (1-p_2)\delta_2 V_2^* & 0 \\ 0 & pS^* + p_2\delta_2 V_2^* \end{pmatrix} \begin{pmatrix} \frac{\delta_{_A}}{\mu_{_A}} & \frac{1}{\mu} \\ \frac{\delta_{_A}}{\mu_{_A}} & \frac{1}{\mu} \end{pmatrix},$$

with the eigenvalues 0 and

$$\mathcal{R}_c = \beta S^* \left(\frac{(1-p)\delta_{_A}}{\mu_{_A}} + \frac{p}{\mu} \right) + \beta\delta_2 V_2^* \left(\frac{(1-p_2)\delta_{_A}}{\mu_{_A}} + \frac{p_2}{\mu} \right).$$

Thus, the control reproduction number of the limiting systems is given by

$$\mathcal{R}_c = \mathcal{R}_0 \frac{S^*}{S_0} + \beta\delta_2 V_2^* \left(\frac{(1-p_2)\delta_{_A}}{\mu_{_A}} + \frac{p_2}{\mu} \right).$$

3. **Simulations and results.** Using parameter values given in Table 1, we simulated the model to draw a comparison between the outcome of single-dose and two-dose vaccination strategies. To test the robustness of our results, we performed a sensitivity analysis over a range of key model parameters, including the rate at which vaccines are distributed and the probability of developing symptoms. In this analysis, using the Latin Hypercube Sampling technique [10], samples of size $n = 100$ were generated in which parameters are uniformly distributed and sampled within their respective ranges. In what follows, we summarize the results of our simulations and sensitivity analysis.

We assumed that the epidemic is triggered by the introduction of $I(0) = 1$ infected case in an entirely susceptible population of $S_0 = 100,000$ individuals. Early findings for the transmissibility of the novel H1N1 infection provided the range $1.2 - 1.8$ for $\mathcal{R}_0$ [7, 13, 18], and we assumed $\mathcal{R}_0 = 1.6$ that lies within the estimated range. This value of $\mathcal{R}_0 = 1.6$ seems to be a plausible choice as recent studies have not significantly changed the early estimated range. For simplicity, we use σ_1 and σ_2 to represent the protection efficacy induced by single-dose and two-dose vaccination, respectively. Figure 1 shows the fractional difference in the final size of the epidemic (total number of infections) between single-dose and two-dose vaccination as a function of vaccine-induced protection in each strategy. The colorbars display the increase in final size of the two-dose vaccine strategy, relative to

TABLE 1. Model parameters with their values (ranges) [1, 11]. For a given value of the basic reproduction number, the transmission rate β can be obtained by substituting parameter values into the expression (5).

parameter	description	value (range)
β	baseline transmission rate	variable
σ_1	efficacy of first dose of vaccine	0.2 (0.1 – 0.5)
σ_2	efficacy of second dose of vaccine	0.8 (0.5 – 0.9)
γ	fraction of population vaccinated per day	0.01 (0.01 – 0.04)
δ_1	level of susceptibility after one dose of vaccine	$1-\sigma_1$
δ_2	level of susceptibility after two doses of vaccine	$1-\sigma_2$
p	probability of developing symptoms without vaccination	0.67 (0.5 – 0.75)
p_1	probability of developing symptoms after one dose of vaccine	$p\delta_1$
p_2	probability of developing symptoms after two doses of vaccine	$p\delta_2$
δ_A	relative transmissibility of asymptomatic infection	0.142
μ_A	recovery rate of asymptomatic infection	1/4.1 day^{-1}
μ	recovery rate of symptomatic infection	1/4.1 day^{-1}
a^*	time between first and second dose of vaccine	30 days
$\mathcal{R}_0$	basic Reproduction number	1.6

that of a single-dose vaccination program. Above the solid curve (positive values in colorbars), a single-dose vaccination outperforms the two-dose strategy with smaller final size. This situation is reversed for the region below the solid curve (negative values in the colorbars). The dashed curve corresponds to the scenario in which $\sigma_2 = 2\sigma_1$, and clearly illustrates a single-dose vaccination as the favoured strategy. These simulations demonstrate that, in addition to the relative efficacy of the second dose, the time at which vaccination begins is crucial. For a longer delay in start of vaccination after the onset of the epidemic, a substantially higher σ_2 is required for the two-dose vaccination to outperform, as shown by the increasing gap between solid and dashed curves in Figure 1. If the vaccination is initiated too late during the epidemic, a single-dose vaccination leads to a lower final size even when the second-dose induces full protection. The relative importance of the vaccine-induced protection (with respect to the time for start of vaccination) is further illustrated in the sensitivity analysis (Figure 2), which is performed to determine the minimum value of σ_2 that results in a lower final size of epidemic when two-dose vaccination is implemented (compared to a single-dose strategy), as a function of delay in start of vaccination.

To compare the vaccination strategies for the peak time and magnitudes of epidemics, we simulated the model for the time-courses of infection, with $\sigma_1 = 0.2$, $\sigma_2 = 0.8$, and $\mathcal{R}_0 = 1.6$. Assuming a 20% vaccine stockpile (coverage of single-dose-vaccination), Figure 3 shows that early start of vaccination (at the onset of epidemic) can decelerate the spread of disease in the population and significantly reduce the magnitude of the outbreak. This reduction is more pronounced in a two-dose strategy due to much higher protection efficacy σ_2. A longer delay in start of vaccination (on day 30) results in an earlier peak times in both vaccination programs, and reduces the effect of two-dose vaccine strategy due to the fact that a sizable portion of the population has already been infected before the administration of the second dose of vaccine. These simulations indicate that for longer delay in vaccine administration (on day 50), a single-dose vaccine strategy outperforms

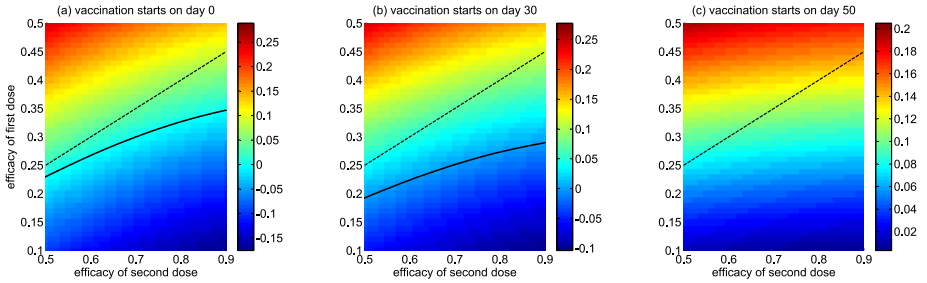

FIGURE 1. Simulations showing the relative difference in final size of the epidemic between the single-dose and two-dose vaccination strategies, as a function of σ_1 and σ_2. The solid curve denotes the points where both strategies are equally effective at reducing the final size. The dashed curve corresponds to the scenarios in which $\sigma_2 = 2\sigma_1$. Baseline values of the parameters are given in Table 1.

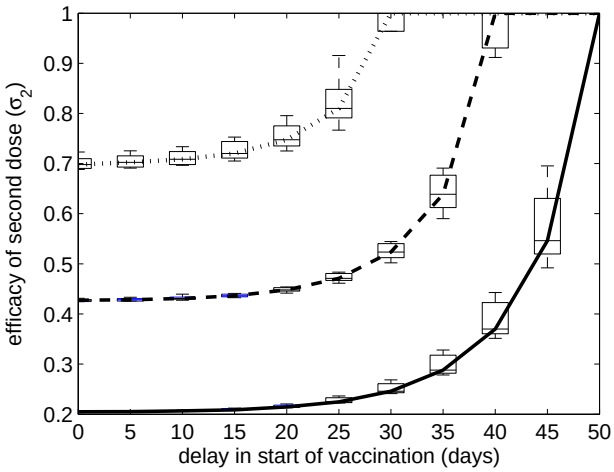

FIGURE 2. Sensitivity analysis showing the minimum value of σ_2 required for the two-dose vaccination to outperform the single-dose vaccine strategy, as a function of the delay in start of vaccination. Solid, dashed, and dotted curves passing through the median values of boxplots correspond, respectively, to values of $\sigma_1 = 0.1$, $\sigma_1 = 0.2$ and $\sigma_1 = 0.3$. The range of parameter values used for sampling are: $1\% - 4\%$ for the rate at which susceptible individuals are vaccinated per day; $5\% - 40\%$ for the coverage of vaccination in a single-dose strategy (i.e., the total vaccine stockpile); $0.5 - 0.75$ for the probability of developing clinical symptoms; with $\mathcal{R}_0 = 1.6$. Baseline values of other parameters are given in Table 1.

the two-dose program with reduced benefits from both strategies, while there is no difference between the peak times in the presence or absence of vaccination.

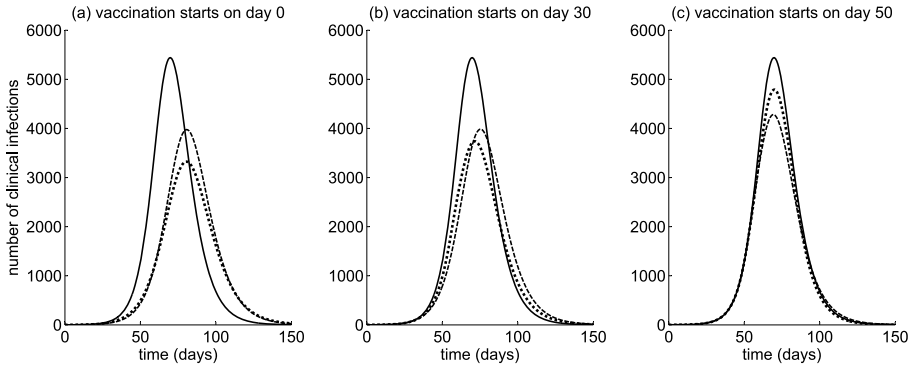

FIGURE 3. Time-courses of epidemics with $\sigma_1 = 0.2$, $\sigma_2 = 0.8$, and $\mathcal{R}_0 = 1.6$, where vaccination starts on (a) day 0 at the onset of epidemic; (b) day 30; and (c) day 50 during the epidemic. Solid, dashed, and dotted curves represent the scenarios of no vaccination, single-dose vaccination, and two-dose vaccination strategies, respectively. Baseline values of other parameters are given in Table 1.

4. **Discussion.** Existing literature on evaluating influenza vaccination strategies through modelling is mainly concerned with the situation in which vaccination ends before the onset of the outbreak [2, 16], which is most relevant to seasonal influenza epidemics. However, in case of pandemic influenza, a strain-specific vaccine cannot be developed before identification of the pandemic virus. Considering timelines for vaccine production and distribution, vaccination campaigns will likely start during the outbreak [9]. In this study, we developed a theoretical framework to investigate strategies with delay in start of vaccination after the onset of the outbreak.

Our comparison of single-dose and two-dose vaccination programs highlights the importance of two critical parameters, namely, the time at which vaccination starts, and the protection efficacy of secondary dose of vaccine compared to that of the primary dose. When vaccine supply is limited, our results show that if vaccination begins sufficiently early (within 30 days after the onset of the outbreak), then the two-dose strategy could potentially lead to a larger reduction in the final size of the epidemic compared to the single-dose vaccination. This, however, requires a considerable increase in the protection efficacy induced by the second dose of vaccine (Figure 2). Further delay in start of vaccination reduces the benefits from both strategies, and clearly favours the single-dose program with lower magnitude of the outbreak (Figure 3).

In the scenario of limited supply, the single-dose program appears to have several advantages over the two-dose strategy. Most conspicuous is that in a single-dose strategy, twice as many individuals will receive vaccine. Less obvious, but also important, is the fact that vaccines can be deployed into the community more quickly in a single-dose strategy. Due to the delay between the administration of the first and second doses, a supply of vaccine must be held in reserve to be allocated towards the secondary vaccination, thereby decelerating the rate of vaccine deployment. Furthermore, a two-dose strategy must contend with the inevitable drop-out from the vaccination program, whether due to acquiring infection after

receiving the first dose, or simply due to individuals voluntarily forgoing the second dose. This drop-out leads to waste in the form of unused vaccines at the end of the epidemic. It may be possible to compensate for this drop-out by allocating larger vaccine supply for the first dose, but this involves many logistical challenges with substantial uncertainty for the required vaccine doses.

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