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OPTIMAL CONTROL OF VACCINATION DYNAMICS DURING AN INFLUENZA EPIDEMIC

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Abstract. For emerging diseases like pandemic influenza, several factors could impact the outcome of vaccination programs, including a delay in vaccine availability, imperfect vaccine-induced protection, and inadequate number of vaccines to sufficiently lower the susceptibility of the population by raising the level of herd immunity. We sought to investigate the effect of these factors in determining optimal vaccination strategies during an emerging influenza infection for which the population is entirely susceptible. We developed a population dynamical model of disease transmission and vaccination, and analyzed the control problem associated with an adaptive time-dependent vaccination strategy, in which the rate of vaccine distribution is optimally determined with time for minimizing the total number of infections (i.e., the epidemic final size). We simulated the model and compared the outcomes with a constant vaccination strategy in which the rate of vaccine distribution is time-independent. When vaccines are available at the onset of epidemic, our findings show that for a sufficiently high vaccine efficacy, the adaptive and constant vaccination strategies lead to comparable outcomes in terms of the epidemic final size. However, the adaptive vaccination requires a vaccine coverage higher than (or equivalent to) the constant vaccination regardless of the rate of vaccine distribution, suggesting that the latter is a more cost-effective strategy. When the vaccine efficacy is below a certain threshold, the adaptive vaccination could substantially outperform the constant vaccination, and the impact of adaptive strategy becomes more pronounced as the rate of vaccine distribution increases. We observed similar results when vaccines become available with a delay during the epidemic; however, the adaptive strategy may require a significantly higher vaccine coverage to outperform the constant vaccination strategy. The findings indicate that the vaccine efficacy is a key parameter that affects optimal control of vaccination dynamics during an epidemic, raising an important question on the trade-off between effectiveness and cost-effectiveness of vaccination policies in the context of limited vaccine quantities.

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1. **Introduction.** Vaccination remains a key preventive measure for reducing the health and economic burden of influenza infection worldwide. However, the high prepotency of influenza viruses for genetic mutations could lead to the emergence of novel strains, such as pandemic viruses [54, 55, 6], for which no vaccine is available at the time of disease emergence. The herald wave of the 2009 influenza H1N1 pandemic exemplifies such an event in the absence of a strain-specific vaccine. These novel viruses tend to replace or co-circulate with predecessor strains in the subsequent epidemics [49], for which a strain-specific vaccine may become available.

There is a vast literature on the dynamics of vaccination for seasonal influenza, for which the vaccine is generally available and administered prior to the onset of epidemics [7, 42, 3]. However, such dynamics have been inadequately studied for the scenarios in which vaccines become available during the course of the outbreak [46], such as the second wave of the 2009 influenza H1N1 pandemic in northern hemisphere. The outcome of vaccination during an epidemic depends critically on several important factors, including the protection efficacy of vaccines against the circulating strain, the time at which vaccination starts, and the speed with which vaccination is administered [5]. While it is expected that vaccine reduces the susceptibility of the population, the vaccine-induced immunity may not fully protect individuals from acquiring infection. However, protective effects of vaccination may prevent the development of clinical disease with the associated symptoms. In this context, asymptomatic infection (with no clinical symptoms) may develop in vaccinated individuals who can still spread the disease in the population. While the overall disease incidence may be reduced with vaccination, low efficacy vaccines may lead to a higher incidence of asymptomatic infection compared to the scenario without vaccination.

Recent work on vaccination dynamics during an influenza epidemic [40, 47, 50, 53, 18, 52, 41, 37] has generally neglected to consider the simultaneous effects of the aforementioned factors. Much of the efforts in determining optimal vaccination strategies has been devoted to identifying age-specific vaccine allocation, optimizing vaccine distribution for minimizing infection and its outcomes (e.g., deaths or hospitalization), or in a more theoretical context, characterizing the optimal control with its type and possible singularities, and solving the optimality system. Previous work highlights the complexity of the vaccination dynamics during an emerging influenza epidemic [5]. However, optimizing vaccination strategies with important vaccine-related parameters (efficacy, timing, distribution capacity, and unintended clinical consequences such as increase in asymptomatic infection due to imperfect vaccine-induced protection) remains elusive. We propose to build upon the existing modelling frameworks, and address this question by applying control theory to determine the optimal vaccination strategy with the objective of minimizing the epidemic final size. The inadequate vaccine quantity also presents an important control parameter, since vaccination of individuals who are recovered from asymptomatic infection (but are still eligible to receive vaccine) results in wasteful use of vaccines without enhancing the level of herd immunity in the population.

For the purpose of this study, we employ a compartmental modelling framework and apply control theory to minimize both the epidemic final size and the number of asymptomatic infection. We attempt to identify the optimal vaccination profile as a function of time, and determine analytic solutions for the control problem described below. For comparison purposes, we also consider the outcome of a vaccination strategy with a constant distribution rate, which may resemble more

closely the implementation of vaccination policies during an epidemic. We present the modelling structure and simulation results of both adaptive and constant vaccination strategies, and provide details of our analyses for the control problem in the Appendix. Finally, we place the findings in the context of public health for implementation of vaccination strategies during epidemics of emerging influenza viruses.

2. **The model.** The mathematical model, schematically represented in Figure 1, describes the basic transmission dynamics of influenza infection in the presence of vaccination. Similar to the previous work [5], we divide a homogeneously mixing population into susceptible (S), symptomatically infectious (I), asymptomatically infectious (A), and vaccinated (V) classes of individuals. Transmission of disease occurs through contacts between susceptible and infectious (symptomatic or asymptomatic) individuals, at a rate $\beta(I+\delta_{_A}A)$, where β is the baseline transmission rate of the infection, and $\delta_{_A}$ is the reduction factor for transmissibility of asymptomatic infection.

In addition to susceptible individuals, asymptomatically infected individuals may be considered for vaccination during an epidemic, since the lack of clinical symptoms may classify these individuals as immunologically naïve to the infection. However, vaccination of asymptomatic infection will have virtually no effect in raising the level of herd immunity. Therefore, $S/(S+A)$ represents the fraction of vaccinated individuals who receive vaccines while being still susceptible to the disease. Thus, the dynamics of the susceptible class is governed by

$$S' = -\beta\,(I+\delta_{_A}\,A)\,S - \frac{S}{S+A}\,\gamma\,S_0, \tag{1}$$

where the prime ' ′ ' denotes the derivative of the compartment with respect to time; γ is the rate at which individuals are vaccinated per unit time; and S_0 represents the initial size of the susceptible population. The vaccination term in (1) shows that in the absence of asymptomatic infection, a maximum γS_0 number of susceptible individuals are vaccinated per unit time. In the model considered here, we omit demographics (natural birth and death rates) during the relatively short course of an epidemic compared to the average life-time.

Since vaccination may not provide full protection against infection, we assumed that the susceptibility of vaccinated individuals is reduced by a factor of $\delta_{_V}$ compared to the susceptible individuals. This gives

$$V' = \frac{S}{S+A}\,\gamma\,S_0 - \beta\,(I+\delta_{_A}\,A)\,\delta_{_V}\,V, \tag{2}$$

In our model, susceptible individuals who acquire infection will develop clinical symptoms with the probability p. We assumed that vaccine-induced immunity reduces the probability of developing clinical disease in vaccinated individuals if infection occurs. This reduction depends on the protection efficacy of vaccine, and we assumed a reduced probability of $p_{_V} = \delta_{_V}p$ for infected vaccinees to develop clinical disease. These assumptions lead to the following differential equations for the dynamics of infection

$$I' = \beta\,[p\,S + \delta_{_V}p_{_V}\,V]\,(I+\delta_{_A}\,A) - \mu\,I, \tag{3}$$

$$A' = \beta\,[(1-p)\,S + (1-p_{_V})\delta_{_V}\,V]\,(I+\delta_{_A}\,A) - \mu_{_A}\,A, \tag{4}$$

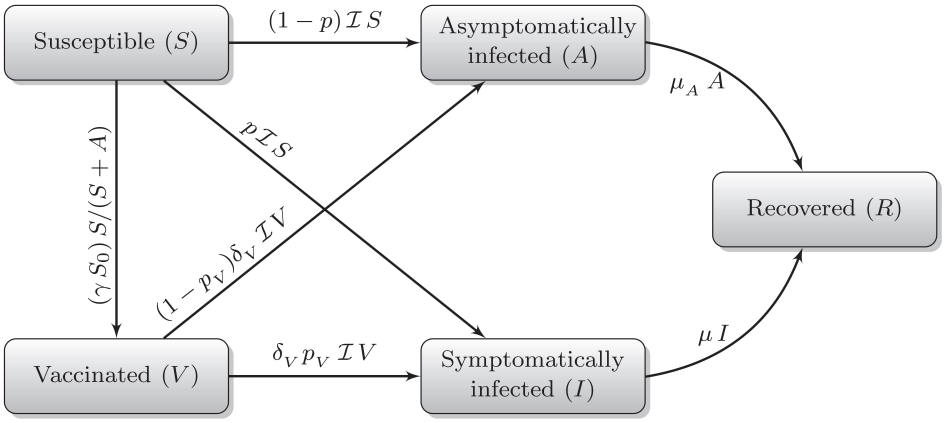

FIGURE 1. Model diagram for the transitions between subpopulations, where $\mathcal{I} = (I + \delta_{_A}\,A)$.

where μ and $\mu_{_A}$ are the recovery rates from symptomatic and asymptomatic infections, respectively. Ignoring disease-induced death, and assuming that immunity induced by natural infection provides full protection against re-infection, the equation for the class of recovered individuals (R) is given by

$$R' = \mu_{_A}\,A + \mu\,I.$$

For simplicity of our model and its analysis, we rewrite the system (1)–(4) in the following form:

$$X' = G(t, X, p), \tag{5}$$

where $X = [x_1, x_2, x_3, x_4]^\top = [S, V, I, A]^\top$ denotes the state of the control system, and $G = [g_1, g_2, g_3, g_4]^\top$ is the functional form of the corresponding response of the control system, with the initial conditions: $S(0) = S_0 > 0$, $I(0) > 0$, $A(0) > 0$ and $V(0) = R(0) = 0$. Table 1 summarizes the description and respective ranges of the model parameters used for simulations.

For the model considered here, we attempt to address an adaptive time-dependent vaccination profile as a function of the vaccine protection efficacy ($\sigma = 1 - \delta_{_V}$) and the rate of vaccination (γ), when vaccine becomes available at different times during the epidemic. Through simulation experiments, we compare the outcome of this adaptive strategy with a constant vaccination rate. Although we do not intend to imply that this modelling framework is the only approach to the optimal vaccination problem, our results about this system offer new ideas and approaches towards development of the control problem for more complex models of vaccination dynamics.

3. **Control problem and objectives.** In the following analysis, the quantity $\gamma\,S_0$ is the per-capita rate at which susceptible individuals are vaccinated per day. We denote the vaccine-induced protection by σ, which ranges from 0 to 1.

The Pontryagin Maximum Principle (a multilevel algorithm for optimizing an objective functional) will be applied to determine the analytical solutions to the control problem with respect to the change in the level of vaccination with time in the adaptive strategy. Below, we define the control problem and show the existence

of an optimal control related to the time-dependent vaccination profile. Our objective is to determine the optimal time-varying strategy that minimizes the epidemic final size, which can be mathematically expressed by

$$\min_{\gamma(t)\geq 0} J(\gamma), \tag{6}$$

where the cost functional is given by

$$J(\gamma) = \int_0^{T_f} f(t, X, \gamma)\, ds, \tag{7}$$

in which the integrant function f represents the outflow from infected classes, that is, $f(t, X, p) = (\mu\, I + \mu_{_A}\, A)$. For consistency with the published literature [22, 23, 24, 25], the upper bound of integration, T_f denotes the end of epidemic where $T_f = \inf\{t \,|\, (I+A)(t) = \kappa \ll 1\}$. For simplicity, we assumed that the recovery rates are the same for both infectious classes (i.e., $\mu = \mu_{_A}$), denoted by μ. In this case, the objective functional becomes

$$J(\gamma) = \mu \int_0^{T_f} [I + A]\ ds. \tag{8}$$

From Lemma A.4, it follows that minimizing the epidemic final size given by equation (8) is equivalent to maximizing the total number of susceptibles and vaccinated individuals $S_f + V_f$ at T_f, since the term $(S(0)+A(0)+I(0)-\kappa)$ is fixed. From now on, we consider our objective functional for minimizing $-(S_f + V_f)$ resulted from equation (10) in Appendix A.

The primary stage in the process of finding optimal control is to investigate the existence of a solution to the control problem under consideration. This will consist of multiple components and adjoint variables. The transient and long-term behaviour of the model will be affected by these variables in time, indicating that the epidemic final size will be determined by these control variables. The existence of an optimal control, namely γ^* for the rate of vaccination, can be established by applying the Fleming and Rishel theorem [17, Chapter III] (See Appendix A).

3.1. **Characterization of the optimal control.** A particular case of optimization problem, in which the system of differential equations (1)–(4) is linear in terms of the control variable γ, is considered in this subsection. The results of Pontryagin Maximum Principle indicate an optimal control of the bang-bang type for this problem. However, in Appendix A we will provide details of our arguments that the optimal control may actually consist of intervals of singular control together with intervals of bang-bang control. In this situation, we observe that the Hamiltonian function H has an explicit linear form of the control, that is, H depends linearly on the control variable during the course of epidemic $[0, T_f]$. As a result, the optimal control cannot be found directly by global minimization of the objective functional. This special case arises frequently when the Hamiltonian is an affine function of the control γ, i.e., the function H is given by $H(\gamma) = \psi(t, X, \Lambda)\,\gamma(t) + \Phi(t, X, \Lambda)$, where the control is constrained to upper and lower bounds $0 \leq \gamma(t) \leq \gamma_{\max}$, and scalar functions ψ and Φ are the remaining non-linear terms which depend only on the state and adjoint variables. The optimality condition, represented by the time-dependent *switching function*, ψ,

$$\psi \quad = \frac{\partial H}{\partial \gamma} = \frac{S_0 S}{S + A}(\lambda_{_V} - \lambda_{_S}),$$

takes positive values at some times, negative values otherwise, and is nonzero with the possible exception of at most a finite number of times t; and the solution to the control problem is easily obtained from (9). In this case, the optimal control which is referred to as *bang-bang* control switches from 0 to $\gamma_{\max}$ at finite number of times corresponding to sign changes in $\psi(t)$ at each switch [51, 57]. However, a case of singularity for the control problem may arise when $\psi(t)$ is zero on a time interval $t_1 \leq t \leq t_2$. In this case, the minimization of the Hamiltonian function with respect to the control γ does not provide any solution within the time interval $[t_1, t_2]$. The common technique for an explicit characterization of the control function is to recurrently take the derivative of $\partial H/\partial\gamma$ with respect to time, which guarantees to generate the explicit solution [8]. Setting the expression for $\psi(t)$ to zero, the control γ is determined by the requirement that the singularity condition continues to hold. This characterizes the optimal control as follows

$$\gamma^*(t) = \begin{cases} 0 & \text{if } \psi(t) > 0, \\ ? & \text{if } \psi(t) = 0, \\ \gamma_{\max} & \text{if } \psi(t) < 0. \end{cases} \tag{9}$$

Clearly, when $\psi(t) = 0$, the Hamiltonian function H is globally minimized for all γ in some nonempty interval $[0, \gamma_0]$. An approach to circumvent the singularity in this situation follows from the fact that, with $\psi \equiv 0$ in the same time interval, all derivatives of the switching function ψ along the optimal trajectory must vanish in this time interval, i.e., $\psi^{(n)} \equiv 0$ for $n = 1, 2, 3, \cdots$. One may apply the differentiation process until the control variable γ explicitly appears in a derivative. We apply the Kelly theorem [26, 32, 34] in Appendix A to find the switching function explicitly from the adjoint and state variables.

4. **Simulation results.**

To illustrate the effect of adaptive vaccination profile, we simulated the model for the dynamics of influenza infection to determine the total number of infections in each class (i.e., symptomatic and asymptomatic) as a function of the vaccine efficacy (σ) and the rate of vaccine distribution in the population (γ). For comparative purposes, we also calculated these numbers for a vaccination strategy with a constant (time-independent) distribution rate. For this comparison, we used the ratio of the total infections in the adaptive strategy to the total infections in constant vaccination. A ratio below 1 indicates that the adaptive vaccination outperforms the constant strategy. The ratio of the quantity of vaccines used in each strategy was also calculated. We simulated the model for two plausible scenarios: (i) vaccine is available at the onset of epidemic (no delay); (ii) vaccine becomes available at some point of time during the epidemic (with delay). Parameter values used for simulation scenarios are summarized in Table 1.

4.1. **Vaccination with no delay.**

For simulating the model in each scenario, we considered two different values of $p = 0.4, 0.8$ corresponding to the fraction of infected individuals who develop symptomatic infection. For the ratio of the total number of infections in the adaptive vaccination strategy to that in the constant vaccination strategy (R_a/R_c), Figure 2a ($p = 0.4$) shows that for sufficiently low vaccine efficacy (below 80% in our simulations), the adaptive strategy outperforms the constant vaccination, giving a ratio R_a/R_c below 1. However, for $\sigma < 0.8$, this ratio depends on the rate of vaccine distribution (γ). For a relatively low vaccine efficacy (approximately below 30%), increasing γ in the range $0 - 0.5$ will reduce the ratio R_a/R_c, and the effect of adaptive vaccination becomes more pronounced.

TABLE 1. Values of the model parameters obtained from the published literature.

Parameter	Description	Value (Range)	References
β	baseline transmission rate	variable (day people)$^{-1}$	[1, 5, 14, 15, 48, 43, 44]
γ	vaccination rate	variable (day)$^{-1}$	[1, 5, 15, 43, 44]
δ_V	level of susceptibility after vaccination	$[0, 1]$	[1, 5, 14, 43, 44]
σ	vaccine protection efficacy	$1 - \delta_V$	[1, 5, 14, 43, 44]
p	probability of developing symptoms without vaccination	$[0, 1]$	[5]
p_V	probability of developing symptoms after vaccination (if infected)	$\delta_V p$	[5]
δ_A	relative transmissibility of asymptomatic infection	$[0, 1]$	[5]
μ	rate of recovery from infection	0.244 day^{-1}	[1, 2, 5, 15, 43, 44]

In terms of vaccine usage, this ratio corresponds to a significantly higher vaccine coverage in the adaptive strategy compared to that in the constant strategy, as illustrated in Figure 2c. Faster distribution of vaccines with γ above 0.5 will have virtually no impact in further reduction of R_a/R_c for any given $\sigma < 0.3$. As vaccine efficacy increases in the range $0.3 - 0.7$, increasing γ will decrease R_a/R_c with relatively sharp changes and with small increases in the rate of vaccine distribution. In this range, there is a threshold curve above which increasing γ will have little or no impact on decreasing R_a/R_c (blue region). The adaptive strategy still requires a higher vaccine coverage compared to the constant strategy, but lower than the corresponding scenario for a given distribution rate when vaccine efficacy is below 30%. When vaccine efficacy is sufficiently high (approximately above 80%), the outcome of constant strategy is comparable to that of the adaptive strategy. Given the larger vaccine quantities required for the adaptive strategy, constant vaccination appears more cost-effective for $\sigma > 0.8$, especially if vaccine quantities are limited. We observed similar results (Figures 2b,d) for the case where 80% of infected individuals develop symptomatic infection ($p = 0.8$).

Comparing the ratios of asymptomatic and symptomatic infections in each strategy, we observed patterns that closely resemble those of the total infections (Figures 3a-d). Not surprisingly, when higher fraction ($p = 0.8$) of infected individuals develop clinical symptoms (Figures 3d), some reduction in the ratio of I_a/I_c may not be achievable for sufficiently low vaccine efficacy (below 10%) as it would be possible for $p = 0.4$ (Figures 3b).

4.2. **Vaccination with delay.** We simulated the model to compare the outcomes when vaccines become available with a delay of 30 days after the onset of epidemic. The results are largely similar to the case of vaccination with no delay (Figures 4,5). However, the range of vaccine efficacy σ in which the adaptive strategy outperforms the constant vaccination strategy shrinks (compared to the scenario with no delay) to below approximately 60% (Figures 4a,b). For a very low vaccine efficacy (below 10%), increasing vaccine distribution has virtually no impact on raising the performance of the adaptive vaccination strategy, but leads to a substantial increase in the vaccine coverage, requiring as much as 6 times higher vaccine quantities compared

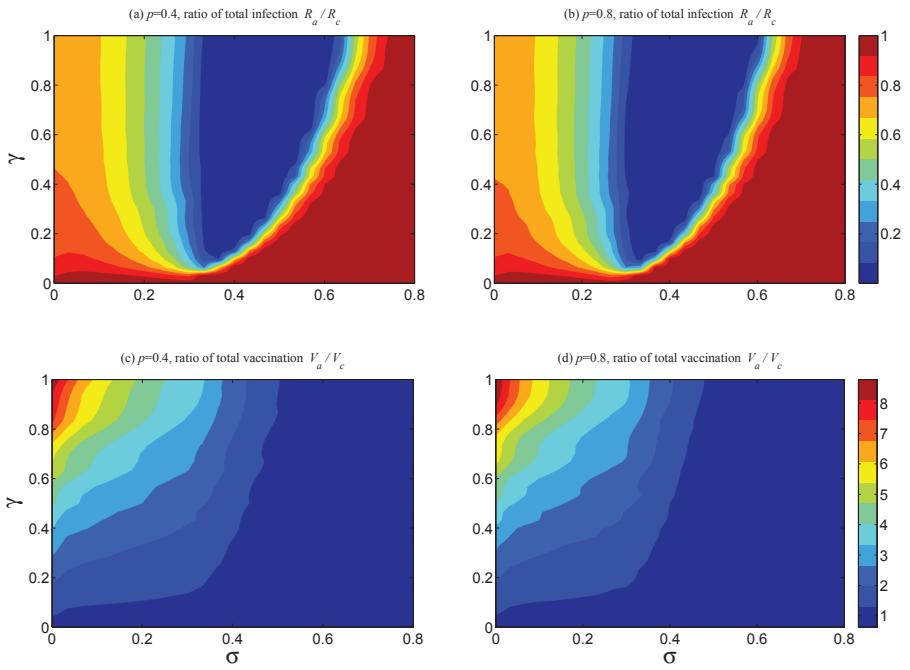

FIGURE 2. Ratio of the total number of infections in the adaptive vaccination strategy to the total number of infections in the constant vaccination strategy (R_a/R_c) as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (a) $p = 0.4$; and (b) $p = 0.8$. Ratio of the total number of vaccinated individuals in the adaptive strategy to the total number of vaccinated individuals in the constant strategy (V_a/V_c) as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (c) $p = 0.4$; and (d) $p = 0.8$. Vaccination started at the onset of epidemic with no delay.

to the constant strategy. For a vaccine efficacy in the range $0.1 - 0.6$, the reduction in the ratio R_a/R_c depends on the rate of vaccine distribution. For a sufficiently high vaccine efficacy (above 60%), the outcome of constant strategy is comparable to that of the adaptive strategy, with virtually identical vaccine coverage. The ratio of vaccine coverage (V_a/V_c) is generally higher when $p = 0.4$ than when $p = 0.8$ (Figures 4c,d). Comparing the two strategy for the ratios of asymptomatic and symptomatic infections, we found similar results for the range of vaccine efficacy below 60%, and comparable outcomes for a vaccine efficacy above 60% (Figures 5a-d).

5. **Discussion.** In this study, we investigated optimal vaccination scenarios during an epidemic episode, when vaccines become available after the onset of epidemic. This is generally the case for novel influenza viruses with pandemic potential, where identification of the specific strain is required for vaccine production. We applied a population dynamical model of influenza infection to determine optimal control of vaccination dynamics. We found that the optimality of an adaptive vaccination strategy, as characterized by the time-dependent control problem, depends on

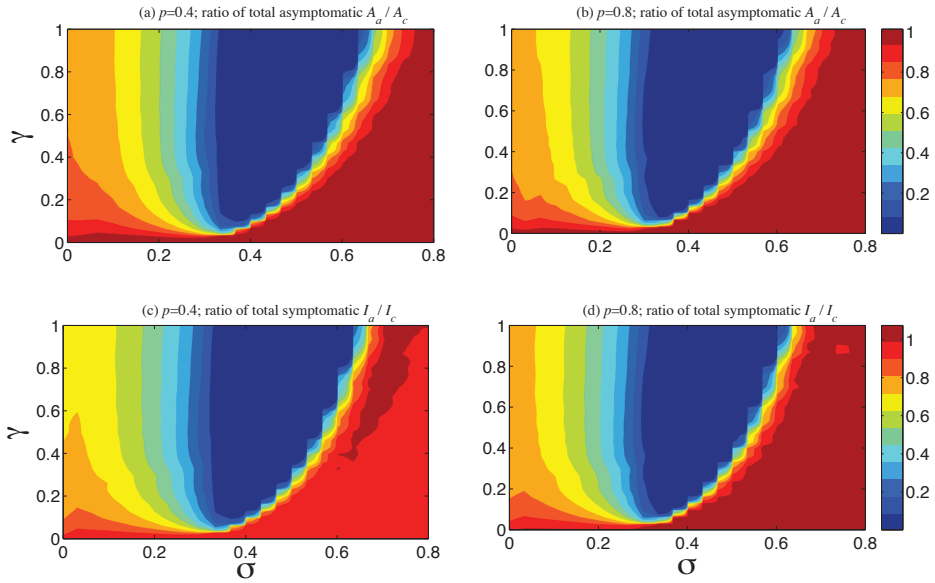

FIGURE 3. Ratio of the total number of asymptomatic infections in the adaptive vaccination strategy to the total number of asymptomatic infections in the constant vaccination strategy (A_a/A_c) as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (a) $p = 0.4$; and (b) $p = 0.8$. Ratio of the total number of symptomatic individuals in the adaptive strategy to the total number of symptomatic individuals in the constant strategy (I_a/I_c) as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (c) $p = 0.4$; and (d) $p = 0.8$. Vaccination started at the onset of epidemic with no delay.

two key parameters of the system, namely: vaccine efficacy, and the rate of vaccine distribution. Vaccine efficacy reflects the protection induced by vaccination against infection which may not be complete. The immune response generated by vaccination may prevent the development of symptomatic infection (if a vaccinated individual is infected), and we therefore considered this imperfect protection as an increased rate of developing asymptomatic infection. The rate of vaccine distribution reflects the capacity of the healthcare system to implement vaccination or the rate at which vaccines become available.

Our results indicate that, for a given delay in start of vaccination during the epidemic, if the vaccine efficacy is above a certain threshold (determined by parameterization of the model), the adaptive and constant vaccination strategies lead to virtually identical outcomes in terms of the total numbers of asymptomatic and symptomatic infections. However, adaptive vaccination generally requires a higher (or equivalent) vaccine coverage compared to the constant strategy with a given distribution rate. Below the threshold of vaccine efficacy, the adaptive strategy outperforms the constant vaccination in reducing the total number of infections. However, this reduction depends on both the efficacy and distribution rate of vaccines, and may require a significantly larger vaccine coverage. Nevertheless, our

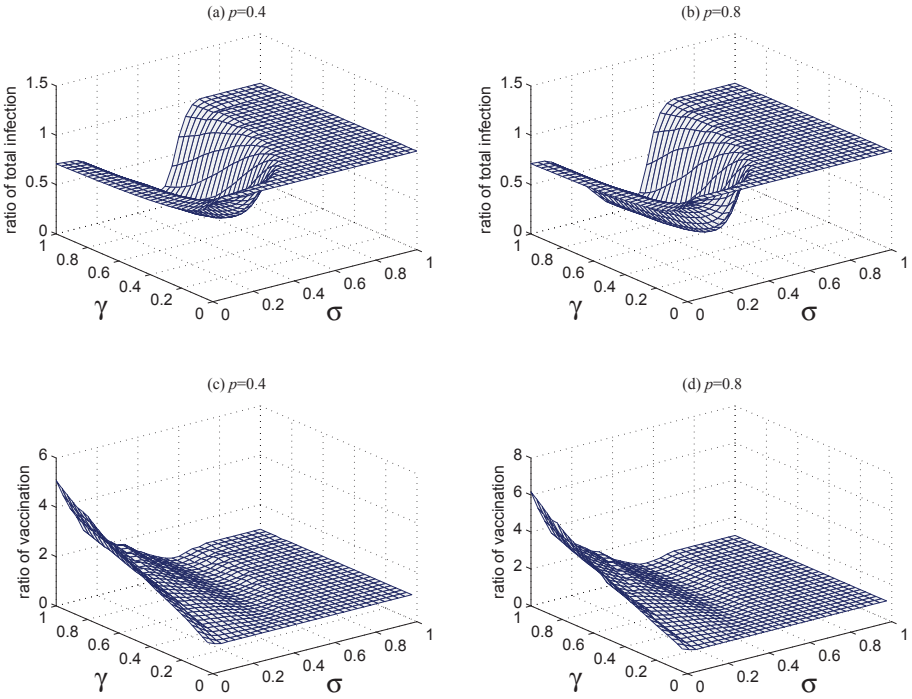

FIGURE 4. Ratio of the total number of infections in the adaptive vaccination strategy to the total number of infections in the constant vaccination strategy as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (a) $p = 0.4$; and (b) $p = 0.8$. Ratio of the total number of vaccinated individuals in the adaptive strategy to the total number of vaccinated individuals in the constant strategy as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (c) $p = 0.4$; and (d) $p = 0.8$. Vaccination started 30 days after the onset of epidemic.

results suggest that, for a vaccine efficacy below the threshold, increasing vaccine distribution rate could increase the benefits of the adaptive vaccination strategy.

Although this study provides a comparative evaluation of vaccination strategies, our model does not fully address the optimality of vaccination dynamics during an epidemic. Determining optimal vaccination, especially for emerging diseases, is a challenging task [9], and may not be addressed with the use of a simple deterministic model. For example, in the context of influenza, most excess mortality occurs in older individuals and those with comorbid illnesses; vaccination provides real but limited protection against infection and disease outcomes in these vulnerable groups [10, 11, 45]. However, most disease is likely to be transmitted by younger, healthier individuals who are at low risk of severe disease outcomes. In the context of limited vaccine supplies, it is not clear whether to vaccinate younger individuals [20, 56], as a means of disrupting disease transmission, or older individuals, as a means of reducing mortality and other severe outcomes. The optimal vaccine distribution also depends upon the criterion used to assess effectiveness [5, 13]. In

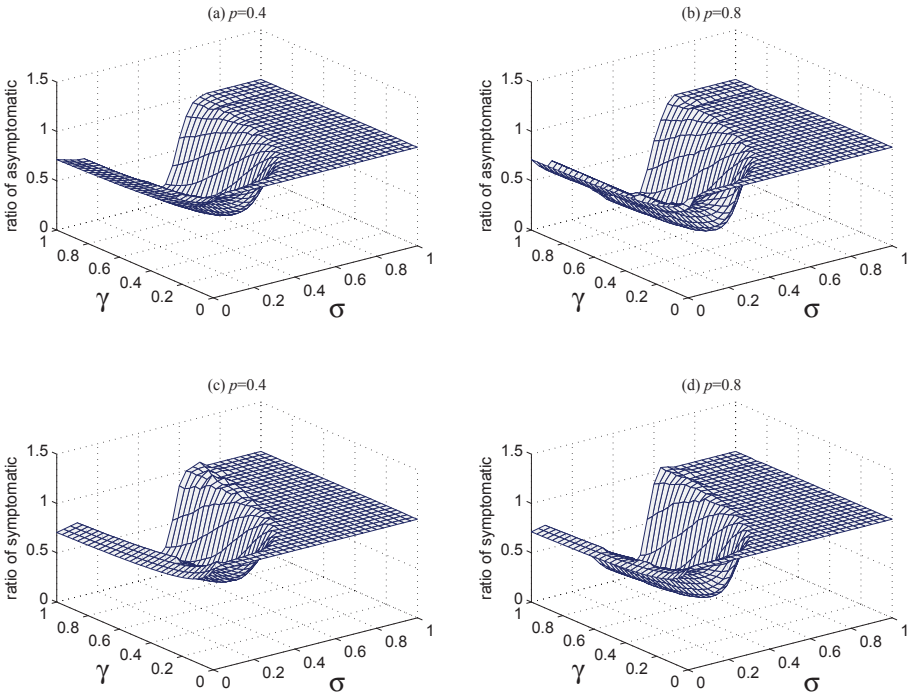

FIGURE 5. Ratio of the total number of asymptomatic infections in the adaptive vaccination strategy to the total number of asymptomatic infections in the constant vaccination strategy as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (a) $p = 0.4$; and (b) $p = 0.8$. Ratio of the total number of symptomatic individuals in the adaptive strategy to the total number of symptomatic individuals in the constant strategy as a function of vaccine efficacy (σ) and the rate of vaccine distribution (γ) for (c) $p = 0.4$; and (d) $p = 0.8$. Vaccination started 30 days after the onset of epidemic.

this context, vaccination dynamics depends on decisions regarding allocation of potentially limited vaccine supplies among specific groups with varying risk factors for serious morbidity or mortality. Acceptance of vaccination will determine the coverage of a given group, and acceptance may be affected by divergent perceptions about the risks of vaccine versus the risks of infection, resulting in conflict between individual and societal optimal approaches to vaccination [4]. Furthermore, other factors influence optimality of vaccination strategies, such as transmission patterns, population demographics, and the composition of risk groups that may widely vary between different population settings. Recent work shows that in a non-crowded setting with relatively low average persons-per-household, vaccination of young individuals remains a key factor in determining epidemic outcomes, regardless of the age distribution of the population [36].

Our study highlights other parameters that should be included in the modelling efforts for investigating vaccination dynamics, including the level of vaccine-induced protection (which may be affected by health status of vaccinated individuals), the

rate of vaccination (which may depend on the capacity of the healthcare system and other factors involved in competing health priorities), and the timing of vaccine availability (which may depend on the type of disease and vaccine production capacity). These factors merit further consideration in future modelling studies.

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Appendix A. **Existence of a feasible solution.** In this Appendix, we aim to investigate an optimal control solution to system (5) that minimizes the epidemic final size. The existence of an optimal control, $\gamma^* \in [0, \gamma_{\max}]$, is a necessary condition required before the use of the Pontryagin Maximum Principle to reduce the objective functional (8). We apply the theorem of Fleming and Rishel [17, Chapter III] to show the existence of a solution. To this end, let Γ be a bounded subset of $\mathbb{R}$ as the collection of all admissible controls, γ, with values in $\mathbb{R}$, where admissible controls $\gamma : [0, T] \to \Gamma$ are measurable functions. We introduce

$$\Gamma(T) = \{\gamma : [0, T] \longrightarrow \mathbb{R} |\ \gamma \text{ is measurable and bounded}\},$$

as the set of all bounded measurable functions with values in $\mathbb{R}$ for arbitrary positive time T, where T is the time of completion for the control program.

Theorem A.1 ([17, 21])**.** *Let Γ be a bounded subset of $\mathbb{R}$ and $\gamma \in \Gamma$. Consider the control problem (5) when $G : \mathbb{R}^n \times \Gamma \to \mathbb{R}^n$ is continuous on both arguments X and γ. Suppose there exist positive constants C_1 and C_2 such that*

(i) $\|G(t, X, \gamma)\| \leq C_1 (1 + \|(X, \gamma)\|)$;
(ii) $\|G(t, X_1, \gamma) - G(t, X_2, \gamma)\| \leq C_2 \|X_1 - X_2\|$ *for all* $t \in \mathbb{R}$, $X_1, X_2 \in \mathbb{R}^n$, *and* $\gamma \in \Gamma$;
(iii) $f : \mathbb{R}^n \times \Gamma \to \mathbb{R}$ *is continuous (where f is given in equation (7));*
(iv) Γ *is compact;*
(v) the set of admissible pairs (X, γ) is not empty;
(vi) the set of allowable boundary values is compact (the set of possible values for the initial and final state values is called the set of allowable boundary values);
(vii) $\{(Z_0, Z) \,|\, Z_0 \geq f(X, \gamma),\ Z = G(X, \gamma),\ \gamma \in \Gamma\}$ *is convex.*

Then there exists a solution (X^*, γ^*) minimizing $J(\gamma)$ given by (7) corresponding to the problem (5).

Here we explicitly show the existence of an optimal solution for the control problem.

Theorem A.2. *There exists an optimal solution for the control problem corresponding to system (1)–(4) with constant initial values $(S_0, A(0), I(0), 0)$, $(I + A)(0) > \kappa > 0$ and $T_f = \inf\{t \,|\, (I + A)(t) = \kappa \ll 1\}$.*

Proof. A direct application of Theorem A.1 leads to the proof. The reader may consult [24, 25] for further details. □

We now discuss the necessary conditions of optimality by introducing the Pontryagin Maximum Principle (PMP) [16, 17, 22, 27, 28, 29, 30, 31, 35, 38, 39]. The main technique in the PMP is to determine an admissible set of necessary conditions for an optimal control problem. This admissible set decreases the cost functional given by (7) provided that the adjoint variable and the corresponding state variables hold under some general conditions imposed as follows.

Theorem A.3 (PMP [38, 17, 33]). *Let the pair $(\gamma^*(t), X^*(t))$ be an admissible control for the corresponding solution of system (1)−(4). Then there exists an absolutely continuous function*

$$\Lambda(t) = [\lambda_0, \lambda_{_S}(t), \lambda_{_V}(t), \lambda_{_I}(t), \lambda_{_A}(t)]^\top \in \mathbb{R}^5,$$

such that $\Lambda(t) \neq 0$ for $t \in [0, T_f]$ with $\lambda_0 \in \{0, 1\}$ and

$$H(t, X^*, \Lambda, \gamma^*) \;=\; \min_{\gamma \in \Gamma} H(t, X^*, \Lambda, \gamma) \qquad \textit{Minimization Principle}$$

for all admissible controls γ at each time t, where the Hamiltonian function is defined by

$$H(t, X, \Lambda, \gamma) = \lambda_0\, f(t, X, \gamma) + \langle G(t, X, \gamma), \Lambda(t, X, \gamma)\rangle,$$

in which the map $\langle \cdot, \cdot \rangle$ represents the standard inner product and the adjoint variables are obtained from

$$\lambda'_{x_i}(t) = -\frac{\partial H(t, X, \Lambda, \gamma)}{\partial x_i}, \qquad (i = 1,\, 2,\, 3,\, 4).$$

Furthermore, $\Lambda(T_f)$ is orthogonal to $ker(D\Psi(X(T_f)))$ where $D\Psi$ denotes the Jacobian of the sets of possible values for the final states.

Lemma A.4. *Minimizing the cost function given by (7) is equivalent to reducing the influx rates from susceptible and vaccinated classes to symptomatic and asymptomatic infections, i.e., the cost function can be written as*

$$\begin{aligned} J(\gamma) \;&=\; \int_0^{T_f} \left[\beta\, (S + \delta_{_V}\, V)\, (I + \delta_{_A}\, A)\right] ds + (A(0) + I(0) - \kappa) \\ &=\; (S(0) + A(0) + I(0) - \kappa) - S_f - V_f \end{aligned} \tag{10}$$

where $S_f = S(T_f)$ and $V_f = V(T_f)$.

Proof. From (3)−(4), it follows that (μ is the recovery rate for both infectious classes)

$$\mu(I + A) \;= \beta\, (S + \delta_{_V}\, V)(I + \delta_{_A}\, A) - (I' + A'). \tag{11}$$

Integrating each side of (11) from 0 to T_f gives the desired result. □

It is worth noting that minimizing the cumulative number of infections (final size of the epidemic) given by equation (7) is equivalent to maximizing the final number of susceptible and vaccinated individuals $S_f + V_f$ since the term $(S(0) + A(0) + I(0) - \kappa)$ is fixed. The quantities $t_0 = 0$ and T_f are the start and end times of the outbreak, respectively. With the aid of our newly developed objective, we state that the outbreak will end as soon as the total number of (asymptomatic and symptomatic) infections is equal to or less than 1.

Based on the PMP Theorem, the Hamiltonian for the optimal control theory can simply be expressed by

$$\begin{aligned} H(t, X, \Lambda, p) \;&=\; \lambda_0\, f(t, X, \gamma) + \langle g(t, X, p), \Lambda(t, X, p)\rangle \\ &=\; S'\lambda_{_S} + A'\, \lambda_{_A} + I'\, \lambda_{_I} + V'\, \lambda_{_V} \end{aligned} \tag{12}$$

where $\lambda_0 \in \{0, 1\}$. From the PMP, the adjoint equations corresponding to system (1)−(4) are obtained from

$$\lambda_S'(t) = \beta\,(\lambda_S - p\lambda_I - (1-p)\,\lambda_A)\,(I + \delta_A A) + \left(\frac{\gamma S_0}{S+A} - \frac{\gamma S_0 S}{(S+A)^2}\right)(\lambda_S - \lambda_V) \tag{13}$$

$$\lambda_V'(t) = \beta\,\delta_V\,(-\lambda_I p_V + (p_V - 1)\,\lambda_A + \lambda_V)\,(\delta_A A + I) \tag{14}$$

$$\begin{aligned}\lambda_A'(t) = {} & (\lambda_S S - ((1-p)\,S + (1-p_V)\,\delta_V V)\,\lambda_A - (pS + p_V\delta_V V)\,\lambda_I + \delta_V V\lambda_V)\,\delta_A\beta \\ & + \lambda_A\mu_A + \frac{\gamma S_0 S}{(S+A)^2}(\lambda_V - \lambda_S)\end{aligned} \tag{15}$$

$$\begin{aligned}\lambda_I'(t) = {} & (-p\lambda_I + (-1+p)\,\lambda_A + \lambda_S)\,\beta\,S \\ & + (-\lambda_I p_V + (p_V - 1)\,\lambda_A + \lambda_V)\,\delta_V\,\beta V + \lambda_I\mu\end{aligned} \tag{16}$$

where the transversality conditions are given by

$$(\lambda_S(T_f), \lambda_V(T_f), \lambda_A(T_f), \lambda_I(T_f)) = (-1, -1, q, q),$$

with $q \geq 0$. The Hamiltonian function can then be represented by multiple identities which will be used to study the dynamical model of influenza infection associated with the following system:

$$\begin{aligned}H(t, X, \Lambda, \gamma) &= \langle G(t, X, \gamma), \Lambda(t, X, \gamma)\rangle \\ &= \left(-\beta\,S\,(I + \delta_A A) - \frac{\gamma S_0 S}{S+A}\right)\lambda_S \\ &\quad + (\beta\,(I + \delta_A A)\,((1-p)\,S + (1-p_V)\,\delta_V V) - \mu_A A)\,\lambda_A \\ &\quad + (\beta\,(I + \delta_A A)\,(pS + p_V\delta_V V) - \mu\,I)\,\lambda_I \\ &\quad + \left(\frac{\gamma S_0 S}{S+A} - \beta\,(I + \delta_A A)\,V\right)\lambda_V\end{aligned} \tag{17}$$

Note that $\lambda_V(T_f) \neq 0$ (or $q \neq 0$); otherwise, using the Hamiltonian at T_f results in $q = 0$ ($\lambda_S(T_f) = 0$) which contradicts the fact that $\Lambda(t) \neq 0$ for all $t \in [0, T_f]$ in the PMP Theorem A.3.

The optimality condition represented by the *switching function*, ψ, is given by

$$\psi = \frac{\partial H}{\partial \gamma} = \frac{S_0 S}{S+A}(\lambda_V - \lambda_S), \tag{18}$$

where the optimal control can be found using the following strategy

$$\gamma^*(t) = \begin{cases} 0 & \text{if } \psi(t) > 0, \\ ? & \text{if } \psi(t) = 0, \\ \gamma_{\max} & \text{if } \psi(t) < 0. \end{cases} \tag{19}$$

Obviously, when $\psi(t) = 0$, all $\gamma \in [0, \gamma_0]$ globally minimize the Hamiltonian function H in some nonempty interval. A plan to circumvent the singularity in this situation follows from the Kelly theorem [26, 32, 34]. We need to differentiate $\psi \equiv 0$ within the same time interval several times to obtain an explicit form for the switching function ψ. Applying the Kelly theorem gives

$$\psi' = \left(\frac{\lambda_S(t)\,S_0 S(t)}{(S(t) + A(t))^2} + \frac{S_0\lambda_V(t)}{S(t) + A(t)} - \frac{\lambda_S(t)\,S_0}{S(t) + A(t)} - \frac{S_0 S(t)\,\lambda_V(t)}{(S(t) + A(t))^2}\right) S'(t)$$

$$
\begin{aligned}
&-\frac{\left(\lambda_S'(t)\right) S_0 S(t)}{S(t)+A(t)}+\frac{S_0 S(t)\lambda_V'(t)}{S(t)+A(t)}+\frac{\lambda_S(t) S_0 S(t) A'(t)}{(S(t)+A(t))^2}\\
&-\frac{S_0 S(t)\lambda_V(t) A'(t)}{(S(t)+A(t))^2}\\
=\;& \frac{S_0 S(t)}{S(t)+A(t)}(-\lambda_S'(t)+\lambda_V'(t))\\
=\;& \frac{S_0 S(t)}{S(t)+A(t)}(-\lambda_S''(t)+\lambda_V''(t))\\
=\;& [-\beta(\lambda_S-p\lambda_I-(1-p)\lambda_A)(I+\delta_A A)]'\\
&+[+\beta\delta_V(-\lambda_I p_V+(p_V-1)\lambda_A+\lambda_V)(\delta_A A+I)]'\\
=\;& \Theta_1(I,A)\lambda_I'+\Theta_2(I,A)\lambda_A'+\Theta_3(I,A,I',A',\Lambda,\lambda_S',\lambda_V')=0, \qquad (20)
\end{aligned}
$$

where the two scalar-valued functions Θ_1 and Θ_2 are the coefficients of λ_I' and λ_A' obtained from differentiation of the previous equation. Also the scalar-valued function Θ_3 contains non-linear terms which depend only on the state and adjoint variables for I, A and λ_S, λ_V. Using (20), we can now determine values of the control γ for singular cases, since

$$
\begin{aligned}
\psi'=\psi'' &= \Theta_1(I,A)\lambda_I'+\Theta_2(I,A)\lambda_A'+\Theta_3(I,A,I',A',\Lambda,\lambda_S',\lambda_V')\\
&= \Theta_1(I,A)\lambda_I''+\Theta_2(I,A)\lambda_A''+\Theta_4(I,A,I',A',\Lambda,\Lambda'), \qquad (21)
\end{aligned}
$$

and the second derivative of adjoint variables λ_I'' and λ_A'' are functions of S' and V'. Thus, we can solve (21) for γ and get an explicit form for the control $\gamma(t)$ which depends on X, I', A', Λ and Λ', although this function is very complex with several non-linear terms.

Theorem A.5. *Suppose $\beta S_0 > \mu$ and $\gamma(0)=0$, and let $(\gamma^*(t), X^*(t))$ be an optimal control for the corresponding solution of system (1)–(4). Then a switch in the level of vaccination (from $\gamma=0$ to $\gamma>0$) must occur before T_f for minimizing the epidemic final size and the expression for the final size satisfies the following inequalities:*

$$
\delta_A\,\delta_V\,\frac{\beta S_0}{\mu}\left[1-\frac{S_f+V_f}{N_0}\right]\le \ln\left(\frac{S_0}{S_f}\right)\le \frac{\beta S_0}{\mu}\left[1-\frac{S_f+V_f}{N_0}\right]. \qquad (22)
$$

Proof. The proof is similar to Theorem 4 of [24, 25] and will be omitted. □

Remark. We denote the ratio $\beta S_0/\mu$ by R_0, the so-called basic reproduction number. In the epidemiological context, R_0 is defined as the number of secondary infectious cases generated by a single infected case introduced into an entirely susceptible population $N_0 \simeq S_0$ (assuming $I(0)$ is small compared to S_0) [12]. If $R_0>1$, then the outbreak will occur, and if $R_0<1$, then the outbreak is expected to die out.

Theorem A.6. *Let the pair $(\gamma^*(t), X^*(t))$ be an optimal control for the corresponding solution of system (1)–(4). Then there is a $t_0>0$ such that the optimal control value is given by $\gamma^*(t)>0$ for $t\in[0,t_0]$. In addition, there is no singularity before the first switch, that is, $\gamma^*(t)=\gamma_{\max}$ on this interval.*

Proof. Suppose the pair $(\gamma^*(t), X^*(t))$ is an optimal control for the corresponding solution of system (1)–(4). Assume to the contrary that $\gamma(t)>0$ on some interval $t\in[0,t_0]$; therefore the Hamiltonian function is independent of V on the the same

interval, and thus, the adjoint variable corresponding to this state equation is zero, i.e. $\lambda_V' = 0$. Using the adjoint variables (13)–(14), it follows that

$$\lambda_S'(t) = \beta\,(\lambda_S - p\lambda_I - (1-p)\,\lambda_A)\,(I + \delta_A\,A), \tag{23}$$

$$\lambda_V'(t) = \beta\,\delta_V\,(-\lambda_I p_V + (p_V - 1)\,\lambda_A + \lambda_V)\,(\delta_A\,A + I) = 0. \tag{24}$$

We claim that no singularity occurs before the first switch. If a singularity occurs, then based on the switching function, we must have $\lambda_S = \lambda_V$ and $\lambda_S' = \lambda_V' = 0$, from which and system (23)–(24) it follows that

$$\lambda_S = p\lambda_I + (1-p)\,\lambda_A, \tag{25}$$

$$\lambda_V = p_V\lambda_I + (1-p_V)\,\lambda_A. \tag{26}$$

Taking derivatives of both sides of above equations gives

$$\lambda_I' = -(1-p)\,\lambda_A'/p, \tag{27}$$

$$\lambda_I' = -(1-p_V)\,\lambda_A'/p_V. \tag{28}$$

Clearly we have $\lambda_I' = \lambda_A' = 0$. In view of the adjoint variable (16), we have $\lambda_I = 0$. From system (25)–(26) it follows that $\Lambda(t) \equiv 0$ on $[0, t_0]$ which contradicts the result of PMP. This shows that our claim holds true, that is, $\gamma(t) = \gamma_{\max}$ on some positive interval $[0, t_0]$. □

Theorem A.7. *Let the pair $(\gamma^*(t), X^*(t))$ be an optimal control for the corresponding solution of system (1)−(4). Then there exists some $t_1 < T_f$ such that the optimal control value is given by $\gamma^*(t) = \gamma_{\max}$ for $t \in [t_1, T_f]$ provided that the size of the susceptible class is positive.*

Proof. Assume that the pair $(\gamma^*(t), X^*(t))$ is an optimal control for the corresponding solution of system (1)−(4). If the susceptible class S is depleted before the end of epidemic, that is, there exits some nonempty interval $[t_1, T_f]$ $(t_1 < T_f)$ where $S = 0$, then $\gamma = 0$ on $[t_1, T_f]$. However, if S is positive for all $t < T_f$, then from system (1)−(4) it follows that there exists some $[t_2, T_f] \subset [t_1, T_f]$ such that $S' < 0$, $V' > 0$, $A' < 0$, and $I' < 0$. The transversality conditions for sufficiently large t $(t \to T_f)$ gives $\lambda_S(T_f) = \lambda_V(T_f) = -1$ and $\lambda_A(T_f) = \lambda_I(T_f) = q > 0$. Substituting these conditions into system (13)–(14), we get

$$\lambda_S'(T_f) = \beta\,(-1-q)\,(I(T_f) + \delta_A\,A(T_f)), \tag{29}$$

$$\lambda_V'(T_f) = \beta\,\delta_V\,(-qp_V + (p_V - 1)\,q - 1)\,(I(T_f) + \delta_A\,A(T_f)), \tag{30}$$

$$= \beta\,\delta_V\,(-q-1)\,(I(T_f) + \delta_A\,A(T_f)). \tag{31}$$

Since $\delta_V < 1$, we have

$$\begin{aligned}\lambda_S'(T_f) &= \beta\,(-1-q)\,(I(T_f) + \delta_A\,A(T_f)) \\ &< \beta\,\delta_V\,(-q-1)\,(I(T_f) + \delta_A\,A(T_f)) = \lambda_V'(T_f).\end{aligned} \tag{32}$$

Thus $\lambda_S'(T_f) < \lambda_V'(T_f) < 0$, which implies that there exists some t_1 $(< T_f)$, such that $\lambda_S(t) > \lambda_V(t)$ for $t \in [t_1, T_f)$ from which the desired result is obtained, i.e., $\gamma^*(t) = \gamma_{\max}$ for $t \in [T_0, T_f]$. □

REFERENCES

[1] J. Arino, C. S. Bowman and S. M. Moghadas, Antiviral resistance during pandemic influenza: Implications for stockpiling and drug use, *BMC Infectious Diseases*, **9** (2009).

[2] J. Arino, F. Brauer, P. van den Driessche, J. Watmough and J. Wu, A model for influenza with vaccination and antiviral treatment, *Journal of Theoretical Biology*, **253** (2008), 118–130.

[3] N. E. Basta, D. L. Chao, M. E. Halloran, L. Matrajt and I. M. Jr. Longini, Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United State, *American Journal of Epidemiology*, **170** (2009), 679–686.

[4] C. T. Bauch, A. P. Galvani and D. J. Earn, Group interest versus self-interest in smallpox vaccination policy, *Proceedings of the National Academy of Sciences of the United States of America*, **100** (2003), 10564–10567.

[5] C. S. Bowman, J. Arino and S. M. Moghadas, Evaluation of vaccination strategies during pandemic outbreaks, *Mathematical Biosciences and Engineering*, **8** (2011), 113–122.

[6] R. M. Bush, Influenza evolution, in *Encyclopedia of Infectious Diseases: Modern Methodologies* (ed. M. Tibayrenc, Chapter 13), John Wiley & Sons, Inc., 2007, 199–214.

[7] M. Baguelin, M. Jit, E. Miller and W. J. Edmunds, Health and economic impact of the seasonal influenza vaccination programme in England, *Vaccine*, **30** (2012), 3459–3462.

[8] A. E. Jr. Bryson and Y. C. Ho, *Applied Optimal Control: Optimization, Estimation and Control*, Taylor & Francis, 1975.

[9] M. G. Cojocaru, C. T. Bauch and M. D. Johnston, Dynamics of vaccination strategies via projected dynamical systems, *Bulletin of Mathematical Biology*, **69** (2007), 1453–1476.

[10] R. B. Couch, et al., Respiratory viral infections in immunocompetent and immunocompromised persons, *The American Journal of Medicine*, **102** (1997), 2–9.

[11] N. J. Cox and K. Subbarao, Influenza, *Lancet*, **354** (1999), 1277–1282.

[12] O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, John Wiley & Sons, 2000.

[13] J. Dushoff, et al., Vaccinating to protect a vulnerable subpopulation, PLOS Medicine, **4** (2007), e174.

[14] N. M. Ferguson, S. Mallett, H. Jackson, N. Roberts and P. Ward, A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals, *Journal of Antimicrobial Chemotherapy*, **51** (2003), 977–990.

[15] N. M. Ferguson, D. A. T. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, Strategies for containing an emerging influenza pandemic in Southeast Asia, *Nature*, **437** (2005), 209–214.

[16] K. R. Fister and J. C. Panetta, Optimal control applied to cell-cycle-specific cancer chemotherapy, *SIAM Journal on Applied Mathematics (SIAP)*, **60** (2000), 1059–1072.

[17] W. H. Fleming and R. W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer-Verlag, New York, 1975.

[18] H. Gaff and E. Schaefer, Optimal control applied to vaccination and treatment strategies for various epidemiological models, *Mathematical Biosciences and Engineering*, **6** (2009), 469–492.

[19] M. E. Halloran, F. G. Hayden, Y. Yang, I. M. Jr. Longini and A. S. Monto, Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials, *American Journal of Epidemiology*, **165** (2006), 212–221.

[20] M. E. Halloran and I. M. Jr. Longini, Community studies for vaccinating schoolchildren against influenza, *Science*, **311** (2006), 615–616.

[21] E. Hansen, *Applications of Optimal Control Theory to Infectious Disease Modeling*, Ph.D. Thesis, Queen's University, 2011.

[22] E. Hansen and T. Day, Optimal control of epidemics with limited resources, *Journal of Mathematical Biology*, **62** (2011), 423–451.

[23] E. Hansen and T. Day, Optimal antiviral treatment strategies and the effects of resistance, *Proceedings of the Royal Society B*, **278** (2011), 1082–1089.

[24] M. Jaberi-Douraki, J. M. Heffernan, J. Wu and S. M. Moghadas, Optimal treatment profile during an influenza epidemic, *Differential Equations and Dynamical Systems*, **21** (2013), 237–252.

[25] M. Jaberi-Douraki and S. M. Moghadas, Optimality of a time-dependent treatment profile during an epidemic, *Journal of Biological Dynamics*, **7** (2013), 133–147.

[26] C. D. Johnson, Singular solutions in problems of optimal control, *Automatic Control, IEEE Transactions,* **8** (1963), 4–15.
[27] H. R. Joshi, Optimal control of an HIV immunology model, *Optimal Control Applications and Methods*, **23** (2002), 199–213.
[28] H. R. Joshi, S. Lenhart and H. Gaff, Optimal harvesting in an integro-difference population model, *Optimal Control Applications and Methods*, **27** (2006), 61–75.
[29] H. R. Joshi, S. Lenhart, H. Lou and H. Gaff, Harvesting control in an integro-difference population model with concave growth term, *Nonlinear Analysis: Hybrid Systems*, **1** (2007), 417–429.
[30] E. Jung, S. Lenhart and Z. Feng, Optimal control of treatments in a two-strain tuberculosis model, *Discrete and Continuous Dynamical Systems B*, **2** (2002), 473–482.
[31] E. Jung, Y. Takeuchi and T. C. Jo, Optimal control strategy for prevention of avian influenza pandemic, *Journal of Theoretical Biology*, **260** (2009), 220–229.
[32] H. J. Kelley, R. E. Kopp and H. G. Moyer, *Singular extremals*, in *Topics in Optimization* (ed. G. Leitmann), Academic Press, New York, 1967, 63–101.
[33] D. E. Kirk, *Optimal Control Theory: An Introduction*, Dover Publications Inc., Mineola., New York, 2004.
[34] R. E. Kopp and H. G. Moyer, Necessary conditions for singular extremals, *American Institute of Aeronautics and Astronautics (AIAA) Journal*, **3** (1965), 1439–1444.
[35] E. G. Kyriakidis and A. Pavitsos, Optimal intervention policies for a multidimensional simple epidemic process, *Mathematical and Computer Modelling*, **50** (2009), 1318–1324.
[36] M. Laskowski, et al., The impact of demographic variables on disease spread: Influenza in remote communities, *Scientific Reports: Nature*, **1** (2011), 105.
[37] S. Lee, M. Golinski and G. Chowell, Modeling optimal age-specific vaccination strategies against pandemic influenza, *Bulletin of Mathematical Biology.*, **74** (2012), 958–980.
[38] S. Lenhart and J. T. Workman, *Optimal Control Applied to Biological Models*, Chapman & Hall, CRC Press, 2007.
[39] D. L. Lukes, *Differential Equations: Classical to Controlled*, Mathematics in Science and Engineering, 162, Academic Press, New York, 1982.
[40] L. Matrajt and I. M. Jr. Longini, Optimizing vaccine allocation at different points in time during an epidemic, PLoS ONE, **5** (2010) e13767.
[41] J. Medlock and A. P. Galvani, Optimizing influenza vaccine distribution, *Science*, **325** (2009), 1705–1708.
[42] G. N. Mercer, S. I. Barry and H. Kelly, Modelling the effect of seasonal influenza vaccination on the risk of pandemic influenza infection, *BMC Public Health*, **11** (2011), S11.
[43] S. M. Moghadas, Management of drug resistance in the population: Influenza as a case study, *Proceedings of the Royal Society B*, **275** (2008), 1163–1169.
[44] S. M. Moghadas, C. S. Bowman, G. Röst and J. Wu, Population-Wide Emergence of Antiviral Resistance during Pandemic Influenza, *PLoS ONE*, **3** (2008), e1839.
[45] A. S. Monto, K. Hornbuckle and S. E. Ohmit, Influenza vaccine effectiveness among nursing home residents: A cohort study, *American Journal of Epidemiology*, **154** (2001), 155–160.
[46] K. L. Nichol, K. Tummers, A. Hoyer-Leitzel, J. Marsh, M. Moynihan and S. McKelvey, Modeling seasonal influenza outbreak in a closed college campus: Impact of pre-season vaccination, in-season vaccination and holidays/breaks, *PLoS ONE*, **5** (2010), e9548.
[47] R. Patel, I. M. Jr. Longini and M. E. Halloran, Finding optimal vaccination strategies for pandemic inflenza using genetic algorithms, *Journal of Theoretical Biology*, **234** (2005), 201–212.
[48] R. R. Regoes and S. Bonhoeffer, Emergence of drugresistance influenza virus: Population dynamical considerations, *Science*, **312** (2006), 389–391.
[49] A. H. Reid, T. A. Janczewski, R. M. Lourens, A. J. Elliot, R. S. Daniels, C. L. Berry, J. S. Oxford and J. K. Taubenberger, 1918 influenza pandemic caused by highly conserved viruses with two receptor-binding variants, *Emerging Infectious Diseases*, **9** (2003), 1249–1253.
[50] L. B. Shaw and I. B. Schwartz, Enhanced vaccine control of epidemics in adaptive networks, *Physical Review E: Statistical, Nonlinear, and Soft Matter Physics*, **81** (2010), 046120.
[51] H. J. Sussmann, A bang-bang theorem with bounds on the number of switchings, *SIAM Journal on Control and Optimization (SICON)*, **17** (1979), 629–651.
[52] R. Ullah, G. Zaman and S. Islam, Prevention of influenza pandemic by multiple control strategies, *Journal of Applied Mathematics*, (2012), Art. ID 294275, 14 pp.

[53] E. Verriest, F. Delmotte and M. Egerstedt, Control of epidemics by vaccination, *Proceedings of the American Control Conference,* **2** (2005), 985–990.
[54] R. G. Webster, Influenza: An emerging disease, *Emerging Infectious Diseases*, **4** (1998), 436–441.
[55] R. G. Webster, W. J. Bean, O. T. Gorman, T. M. Chambers and Y. Kawaoka, Evolution and ecology of influenza A viruses, *Microbiology and Molecular Biology Reviews*, **56** (1992), 152–179.
[56] D. Weycker, D. Weycker, J. Edelsberg, M. E. Halloran, I. M. Jr. Longini, A. Nizam, V. Ciuryla and G. Oster, Population-wide benefits of routine vaccination of children against influenza, *Vaccine*, **23** (2005), 1284–1293.
[57] K. Wickwire, Optimal immunization rules for an epidemic with recovery, *Journal of Optimization Theory and Applications*, **27** (1979), 549–570.

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