

# The benefits of combining early aspecific vaccination with later specific vaccination

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## Abstract

Timing is of crucial importance for successful vaccination. To avoid a large outbreak, vaccines are administered preferably as quickly as possible. However, in the early stages of an outbreak the information on the disease is limited and waiting with the intervention allows to design a more tailored vaccination strategy. In this paper we study the resulting tradeoff between timing of vaccination and the effectiveness of the response.

We model disease progression using the seminal *SIR* model, and consider a decision maker who allocates her budget over two vaccine types: an early aspecific vaccine and a later specific vaccine. We analytically characterize the switching curve separating the parameter space region where the late specific vaccine is preferred from the region where the early aspecific type is preferred. More importantly, we show that the decision maker should not only consider *pure* strategies, i.e., strategies which spend the entire budget on one of the types. Instead, she should suitably invest in both vaccine types to benefit both from the early response and from the good vaccine. We prove that at the switching curve, such a *hybrid* strategy is strictly better than either of the pure strategies due to the non-linear dynamics of epidemics. Numerical experiments show that the associated benefit of hybrid strategies over pure strategies in terms of reduction of the number of infections may be more than 50%. Such experiments also substantiate our restriction to two vaccine types.

**Keywords:** optimization, vaccination, mathematical modelling, infectious diseases, *SIR* model

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# 1 Introduction

One of the crucial aspects of successful vaccination is timing. As an infectious disease can spread quickly through a population, the earlier people can be immunized, the better. However, an effective response strategy cannot always be started directly, either because the characteristics of the outbreak are not yet known or because it takes time to produce and distribute the right vaccines. Thus policy makers face a trade-off between the timing of vaccination and the effectiveness of the response. The effectiveness of the response is related to the *efficacy* of a vaccine, which is a measure of relative risk in a vaccinated group compared to an unvaccinated control group. The higher the efficacy of a vaccine, the better the vaccine is able to achieve immunity in the vaccinee.

There are numerous practical situations where policy makers have to make a trade off between the efficacy of vaccines and the timing of vaccination. Here are three examples:

1. The production for the annual influenza vaccine starts well before the influenza season starts. That implies that detailed knowledge about the characteristics of the annual flu is missing and that it is difficult to design a good vaccine. Policy makers face a ‘commit-or-defer’ decision: either they should decide on the vaccine composition early with little knowledge available, or they decide to defer the decision in order to learn more about the coming influenza season (e.g., Cho, 2010; Kornish & Keeney, 2008). Quick decisions have the advantage of having the vaccines available early, but deferring could lead to vaccines with a higher efficacy.
2. Whereas the annual influenza is expected, an unexpected outbreak of influenza can also occur, potentially resulting in a pandemic. In those situations policy makers have to determine how to respond. They can often choose among multiple vaccine types: vaccines with a high efficacy or vaccines with a lower efficacy. The latter might seem worse, but might have a lower price, a shorter delivery time or may be available in larger quantities. Nguyen and Carlson (2016) vary the time at which vaccines become available and the stockpile size to determine the effects on the epidemic.
3. For some vaccines a single dose only results in limited protection. To benefit fully from the vaccine, you need multiple doses, a number of days apart. When a certain number of doses of vaccine is available, policy makers have to decide how this vaccine stockpile should be allocated: they can either give a large number of people a single dose, or two doses to half of the group (Matrajt, Britton, Halloran, & Longini, 2015). It may not be obvious how timing of vaccination plays a role in this example. But

the fact that there is a fixed time in between two doses implies that the epidemic can spread between the first and the second dose. A one-dose strategy thus corresponds to a quick response, whereas a two-dose strategy has a higher efficacy.

In this paper we synthesize these different decision problems and formulate a general problem that encapsulates all three examples. We formulate this general problem in terms of example 2, but the other examples can analogously be analyzed. We consider a policy maker who has a limited budget to fight an outbreak of an infectious disease. The budget can be spent on different vaccine types that differ in the time at which they are available and in their efficacy. The simplest example on which most of our research focuses is the case of two vaccine types: type 1 is an early aspecific vaccine, which has a low efficacy, and type 2 is a late specific vaccine, which has a high efficacy. We analyze for which combinations of parameters (efficacy, moment of availability) the late specific vaccine is preferred over the early aspecific vaccine. We first prove a rather intuitive result: the existence of a switching curve which separates the region in the parameter space where the late specific vaccine is preferred from the region where the early aspecific type is preferred. In this paper we give an analytical expression characterizing this curve.

More importantly, we show that the decision maker should not only consider spending her entire budget on one of the vaccine types. Instead, she should suitable invest in both vaccine types to benefit both from the early response and from the good vaccine. Such a *hybrid strategy* is not well taken up in literature, although some national pandemic response plans propose a similar strategy by emphasizing the importance of investing in stockpiles of vaccines for known virus types as well as expanding the vaccine manufacturing capacity for the production of pandemic vaccines tailored to the specific virus (Homeland Security Council, 2006; U.S. Department of Health and Human Services, 2005).

Our main contribution in this paper is formally proposing and analyzing such hybrid strategies. We characterize the areas in the parameter space where either of the two pure strategies or the hybrid strategy is optimal. We prove that there is an area around the switching curve where hybrid strategies are superior to pure strategies. We argue that this is due to the non-linear dynamics of an epidemic: By using both vaccine types the early vaccine can be used to reduce the initial growth in infections, while the better vaccine is used to control the epidemic. Our numerical results show that a hybrid strategy can reduce the number of infections by more than 50% compared to the best pure strategy. We note that because our formulation generalizes examples 1-3 above, our analysis of hybrid strategies contributes to three streams of literature (see Section 2.

In this article we focus on the most interesting case of hybrid strategies, namely those with two vaccine

types. Our numerical results show that this choice is not restrictive, as hybrid strategies with more than two vaccine types are not beneficial. Moreover, our results can also be applied to vaccines that become available in batches instead of instantaneously.

The remainder of the paper is structured as follows. We start with a literature review in Section 2. In Section 3 we formally define the vaccination problem. This problem is analyzed in Section 4: we compare the two vaccine types and analyze hybrid strategies. In Section 5 we derive our numerical results. We close with a discussion and conclusions in Section 6.

## 2 Literature

Extant literature considers the trade-off between timing of vaccination and vaccine efficacy in three separate practical settings. We now first discuss literature in the setting of the annual influenza vaccine, then literature on the effects of timing of vaccination and finally literature on the number of doses to use. Timing of vaccination is part of a much broader stream of literature on vaccine logistics. For a recent overview we refer to Duijzer, van Jaarsveld, and Dekker (2017).

**Annual influenza vaccine** The trade-off between timing and efficacy is well studied for the annual influenza vaccine. There exist multiple types of the influenza virus and mutations might lead to new types. Every year the World Health Organization (WHO) advises on the composition of the influenza vaccine (Silva et al., 2015), i.e., which virus types to include in the vaccine. To produce a sufficient number of doses, the composition of the vaccine must be determined well before the influenza season starts.

Wu, Wein, and Perelson (2005) discuss the ‘follow policy’, where the forecasted epidemic strain is included in the annual vaccine. The authors investigate whether this policy can be improved by including information on the strains to which the individual has been exposed in the past. The results conclude that the follow policy is only slightly suboptimal and is therefore recommended to be continued. Kornish and Keeney (2008) study when it is beneficial to defer the decision on the vaccine composition in order to buy time to gather more information about the coming influenza season. Deferring reduces uncertainty and could lead to better decisions on which strains to include in the vaccine. However, waiting too long reduces the available time for production, potentially leading to higher production costs. The authors assume that they can estimate the number of cases during the outbreak, based on the information at the current time. The authors formulate a commit-or-defer model and derive conditions on the optimal decision using dynamic programming. When

discussing their model assumptions the authors mention the disadvantage of waiting with production while gathering information on one of the strains that are included in the vaccine. They suggest a solution in which production of the other strains could start earlier and the new strain is only added to the vaccines subsequently produced. This solution can be seen as some kind of hybrid strategy, but the strategy is not formally analyzed by the authors.

Cho (2010) extend the work of Kornish and Keeney (2008) by including production yield uncertainties. Decision makers have to decide on retaining the current vaccine or shifting to updated compositions. The latter may have more production yield uncertainty. A discrete time model is proposed with three possible decisions at every time: select the current vaccine strain, update to the most prevalent new strain or postpone decision making to the next period. Özalım, Prokopyev, Schaefer, and Roberts (2011) allow for choosing among multiple possible strains for the vaccine, not only the most prevalent one. The authors use parameters to quantify the proportion of the population that got infected caused by a certain influenza strain. A multi-stage stochastic mixed integer model is formulated to integrate the composition decision and the timing of this decision. The results show that selecting a less prevalent strain might be beneficial, if this strain has higher production yields for example. All papers on the influenza composition decision consider only situations in which all vaccines are of the same type. In other words, the policy maker either decides to ‘commit’ or to ‘defer’. A hybrid strategy, in which the decision maker commits for part of the budget and defers for the remaining budget, are not analyzed apart from the brief discussion in Kornish and Keeney (2008).

**Timing of vaccination** The second example of a trade-off between timing and efficacy is the selection among multiple vaccine types with different delivery times. Matrajt and Longini Jr (2010) study a related problem and compare multiple moments of vaccination and different available stockpiles. Their results show how the vaccine stockpile size and the moment at which this stockpile becomes available affect the optimal allocation over the different age-groups and risk-groups. A similar setting is studied by Matrajt, Halloran, and Longini Jr (2013), who focus on a network of cities connected by an airline network instead of a single population. Motivated by practical considerations they shortly discuss the case of vaccines that arrive in two batches, with fixed amounts of vaccines per batch. This is a form of hybrid strategy and results show that the optimal allocation almost coincides with the pro-rata allocation over children in the different cities. Yarmand, Ivy, Denton, and Lloyd (2014) study a two-phase allocation problem with minimum required vaccination levels in each phase, where the required level for a region in the second phase only applies if the epidemic in that region is not yet contained after phase 1. They formulate a stochastic programming problem

and show how the optimal allocation depends on the minimum required levels. Nguyen and Carlson (2016) compare different vaccination strategies which differ in when and how much vaccines become available. Deterministic and stochastic models are used and the optimal allocation for two coupled populations is determined numerically. All vaccines are assumed to be available at the same time. The authors present contour plots that indicate which combinations of the vaccination fraction and the timing of vaccination result in the same final size. We extend this work by analytically describing the shape of these contour curves as well as by analyzing hybrid strategies where people can be vaccinated at multiple moments in time.

**Optimal vaccine dosage** There are some studies on determining the optimal dose for vaccines against pandemic influenza. Riley, Wu, and Leung (2007) show that a lower vaccine dose may be preferred, because it increases coverage levels. This strategy can be seen as a hybrid strategy which is advocated in the current paper. Similar results are found by Wood, McCaw, Becker, Nolan, and MacIntyre (2009), who find that the lowest dose results in the smallest attack rate. Matrajt et al. (2015) compare the effects of a one-dose and a two-dose strategy for influenza vaccination and use a more analytical approach. The authors prove that there is a threshold in the level of protection that is obtained after the first dose below which the two-dose strategy is the best. For pre-pandemic vaccination this threshold can analytically be characterized and for reactive vaccination numerical and simulation results are found. Our results contribute to this literature in two ways: we derive an analytical approach that also holds for the reactive case, but more importantly we propose hybrid strategies and show their benefits. These hybrid strategies translate to some people receiving one dose and others receiving two doses. Riley et al. (2007) briefly mention the possibility to give health care workers a higher dosage than the remainder of the population, but this strategy is not analyzed.

**Model** We now relate our modelling choices to current literature. We make use of the *SIR* model, which is a seminal model in epidemiology proposed by Kermack and McKendrick (1927). As our problem incorporates the effect of timing of vaccination, we allow for vaccination during an outbreak (see also Chowell, Viboud, Wang, Bertozzi, & Miller, 2009; Matrajt & Longini Jr, 2010; Meyers, Galvani, & Medlock, 2009; Tuite, Fisman, Kwong, & Greer, 2010). Alternatively, there are studies that focus on pre-pandemic vaccination, assuming that all vaccines are available prior to the outbreak (e.g. Duijzer, Van Jaarsveld, Wallinga, & Dekker, 2016; Keeling & Shattock, 2012; Wu, Riley, & Leung, 2007). To evaluate the effects of different vaccination strategies we focus on minimizing the *final size*, i.e., the proportion of people infected during the outbreak (e.g., Keeling & Shattock, 2012; Lee, Yuan, Pietz, Benecke, & Burel, 2015; Wang, de Véricourt,

& Sun, 2009; Wu et al., 2007). An alternative performance criterion is the reproduction ratio  $R$ , which is related to the initial growth of infections (Diekmann, Heesterbeek, & Britton, 2013). There are studies that focus on minimizing the reproduction ratio (Goldstein et al., 2009; Wallinga, van Boven, & Lipsitch, 2010) or on reaching a certain threshold value of the reproduction ratio (e.g., Gittings & Matson, 2016; Tanner, Sattenspiel, & Ntamo, 2008). The reproduction ratio differs from the final size by focusing on the short term, whereas the final size takes into account the entire time course of the epidemic. However, Duijzer et al. (2016) show that under certain conditions optimization problems involving these two performance criteria are equivalent.

### 3 Problem formulation

We evaluate the effects of different vaccination strategies and make use of the deterministic *SIR* model to model the time course of the epidemic. This model is explained in Section 3.1. In Section 3.2 we describe the effect of vaccination on the epidemic and the considered decision problem. We formalize this in Section 3.3. In Section 3.4 we formulate the optimization problem that is studied in this paper.

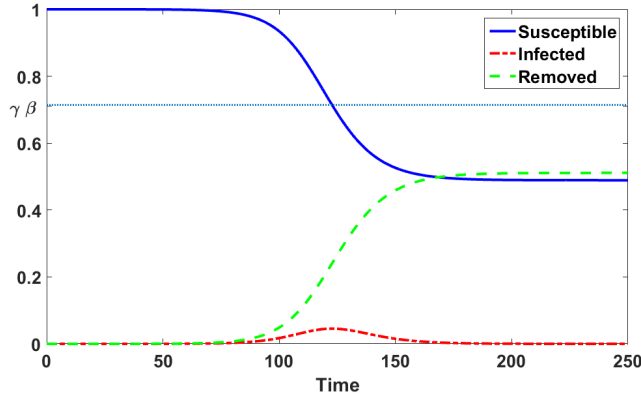
#### 3.1 The *SIR* model

The *SIR* model is a seminal model in epidemiology proposed by Kermack and McKendrick (1927). The population is divided into three compartments for which the time course is tracked (cf. Hethcote, 2000). Let  $s(t)$ ,  $i(t)$  and  $r(t)$  be the fractions of the population respectively susceptible, infected and removed at time  $t$ . In this paper we assume that the removed compartment consists of recovered individuals, deaths can be taken into account straightforwardly. By interpretation it must hold that  $s(t) + i(t) + r(t) = 1$  for all  $t \geq 0$ . The *SIR* model is described by the following system of differential equations, with the transmission rate and the rate of recovery denoted by  $\beta$  and  $\gamma$ , respectively.

$$\begin{aligned} \frac{ds}{dt} &= -\beta si \\ \frac{di}{dt} &= \beta si - \gamma i \\ \frac{dr}{dt} &= \gamma i \end{aligned} \tag{1}$$

We assume that boundary conditions  $s(0) = s_0$ ,  $i(0) = i_0$  and  $r(0) = r_0$  are given, with  $i_0 > 0$  and  $s_0 + i_0 + r_0 = 1$ . Figure 1 illustrates the time course for an epidemic that evolves according to the *SIR* model. This figure is made using the Runge-Kutta method (Kutta, 1901). The figure shows that not everybody gets infected during the outbreak. Around 50% of the population is still susceptible when the

epidemic has died out, so they have escaped infection. We also observe in the figure that the infected individuals are initially increasing until they reach a certain peak value. After the peak, the epidemic starts to die out. From the differential equations we can derive that this peak occurs when  $s(t) = \frac{\gamma}{\beta}$ . We therefore refer to an epidemic being controlled when  $s(t)$  is below the threshold  $\frac{\gamma}{\beta}$ . Although the number of infected people in a controlled epidemic can still be substantial, there are more recoveries than new infections per time unit so that the proportion of infected people is decreasing.



**Figure 1:** Illustration of the deterministic *SIR* model with parameters  $\gamma = 0.25, \beta = 0.35, i_0 = 10^{-6}$  and  $s_0 = 1 - i_0$ .

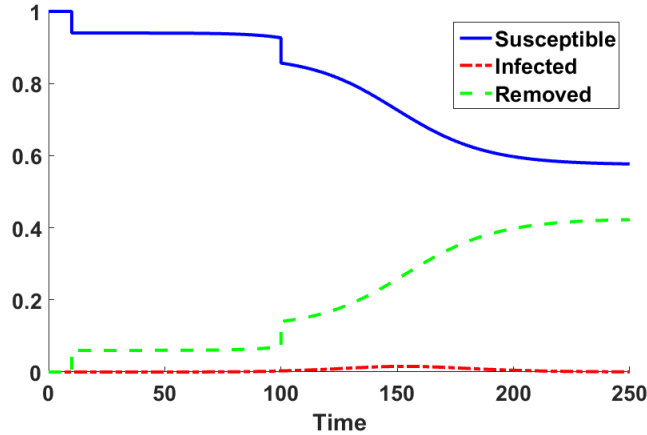
### 3.2 Problem description

Vaccination reduces the fraction of susceptible individuals, in order to control the epidemic at an earlier point in time and to avoid or reduce an increase in the fraction of infected individuals. The effect of vaccination is twofold. The people who directly benefit from vaccination are the vaccinees, because they acquire (partial) immunity due to vaccination. Indirectly also unvaccinated people benefit from the vaccination of others, as it reduces their disease exposure. This indirect effect of vaccination is known as the *herd effect* (Fine, 1993).

Consider a decision maker who has a budget available to spend on the different vaccine types in the set  $J$ . These vaccine types differ in three aspects: the price per dose of vaccine ( $p_j$ ), the efficacy of the vaccine ( $\phi_j$ ) and the time at which the vaccine becomes available ( $\tau_j$ ). The efficacy of a vaccine is the level at which the vaccine is able to induce immunity and can be interpreted as the proportion of vaccinated people that will get immune after vaccination. We assume that all vaccines can quickly be distributed as soon as they are available. Denote by  $B$  the total budget of the policy maker. Her goal is to divide this budget over the vaccine types in such a way that as few people as possible will get infected during the outbreak.



The effect of vaccination on the epidemic is illustrated in Figure 2. In this figure we consider a population of  $10^6$  individuals where 150 000 people are vaccinated at time 10 with a vaccine that has efficacy 0.4 and another 100 000 people are vaccinated at time 100 with a vaccine that has efficacy 0.7. This means that effectively  $150\,000 \times 0.4 + 100\,000 \times 0.7 = 130\,000$  people have become immune through vaccination. If we compare Figure 1 and Figure 2, we see that vaccination lowers the peak in infected individuals. Next to that, more people have escaped infection when vaccination is used: the proportion of people still susceptible when the epidemic has died out (i.e., the herd effect) has increased from 50% to almost 60%.



**Figure 2:** Illustration of vaccination in the deterministic *SIR* model with vaccination, with parameters as in Figure 1.

In the remainder of this section we give a detailed model for the problem.

### 3.3 Vaccination

To formally define vaccination, we introduce the following notation. Denote by  $B_j$  the budget allocated to vaccines of type  $j$ . Furthermore, let  $\varphi_j = \frac{\phi_j}{p_j}$  be the efficacy per dollar for vaccines of type  $j$  which are available at  $\tau_j$ . The vaccines are administered to susceptible individuals and we assume that it is possible to identify the susceptible people. Thus the fraction of people no longer susceptible and immune due to allocating  $B_j$  to vaccines of type  $j$  equals  $f_j = \frac{\varphi_j B_j}{N}$ , where  $N$  is the size of the considered population. It makes sense to consider only  $B_j \leq p_j s(\tau_j) N$ : the amount of allocated budget is at most enough to vaccinate the entire susceptible population. Under this constraint  $f_j \leq s(\tau_j) \phi_j$ . For  $B_j > p_j s(\tau_j) N$  we stipulate that  $f_j = s(\tau_j) \phi_j$ .

We also assume that vaccination takes no time, meaning that vaccination results in immunity immediately.

We refer to Section 6 for a discussion of these assumptions. Under our assumptions vaccination causes a shift at time  $\tau_j$  from state  $(s(\tau_j), i(\tau_j))$  to state  $(s(\tau_j) - f_j, i(\tau_j))$ . This implies that  $r(\tau_j)$  shifts to  $r(\tau_j) + f_j$ . This is a common way of modelling vaccination (e.g., Bansal, Pourbohloul, & Meyers, 2006; Hill & Longini Jr, 2003; Mylius, Hagenaars, Lugnér, & Wallinga, 2008).

To compare different vaccination strategies we consider the state of the system when  $t \rightarrow \infty$ . This state is also referred to as ‘disease-free equilibrium’, because  $\lim_{t \rightarrow \infty} i(t) = 0$  which can be derived from the differential equations (1). For notational convenience, we define  $\mathbf{f} = (f_1, \dots, f_n)$  and  $\tau = (\tau_1, \dots, \tau_n)$ . Let  $G(\mathbf{f}, \tau)$  denote the final fraction of people susceptible in the disease-free equilibrium. More precisely, for  $f_j \in [0, \phi_j s(\tau_j)]$  for all  $j \in J$

$$G(\mathbf{f}, \tau) = \lim_{t \rightarrow \infty} s(t), \quad (2)$$

with  $s(t)$  evolving according to (1) in between two consecutive vaccination moments and after the last vaccination moment. We determine  $G(\mathbf{f}, \tau)$  with an implicit relation called the *final size equation*, details are in Appendix A.  $G(\mathbf{f}, \tau)$  quantifies the so-called *herd effect*, which is the indirect effect of vaccination where unvaccinated people benefit from the vaccination of others. We refer to Duijzer, van Jaarsveld, Wallinga, and Dekker (2015) for a more extensive analysis of the herd effect and the function  $G(\mathbf{f}, \tau)$  for a single vaccination moment. In the remainder of this paper we focus on the *final size*, i.e., the proportion of the population that has been infected during the outbreak. The final size is denoted by  $Z(\mathbf{f}, \tau)$  and can be calculated as follows:

$$Z(\mathbf{f}, \tau) = s_0 - G(\mathbf{f}, \tau) - \sum_{j \in J} f_j + i_0 \quad (3)$$

Observe that the part  $s_0 - G(\mathbf{f}, \tau)$  in above equation determines the proportion of people that were susceptible at the beginning of the outbreak, but are no longer susceptible at the end. These people have either become infected or have become immune because of vaccination. By correcting for those that are vaccinated ( $\sum_{j \in J} f_j$ ), we remain with the number of infections during the outbreak. We add the initial infections ( $i_0$ ) to determine the final size of the outbreak. For a more detailed discussion of modelling vaccination in the *SIR* model we refer to Duijzer et al. (2015).

### 3.4 Optimization problem

In this section we formally define our decision problem. Recall that we consider a decision maker with a total budget  $B$  to spend on the vaccine types in  $J$  in order to minimize the final size of the outbreak. Using

the notation that is introduced in Section 3.3 the optimization problem can be formulated as follows:

$$\begin{aligned}
 \min \quad & Z(\mathbf{f}, \tau) \\
 \text{s.t.} \quad & N \sum_{j \in J} \frac{f_j}{\varphi_j} \leq B \\
 & f_j \geq 0 \quad \forall j \in J
 \end{aligned} \tag{4}$$

The objective is to minimize the final size. We formulate the optimization problem using the variables  $f_j$ , but the constraints can easily be rewritten in terms of  $B_j$ . The first constraint ensures that the budget  $B$  is not exceeded. The second constraint makes sure that the amount of vaccines is non-negative.

## 4 Analytical results

In this section we study Problem (4) and compare different vaccination strategies. In Section 4.1 we start with showing that a hybrid vaccination strategy can equivalently be summarized as a vaccination strategy with a single vaccination moment. The characterization of this single moment strategy enables us to analyze hybrid strategies in the following sections. In Section 4.2 we focus on comparing two vaccination strategies. We analyze pure strategies in which the entire budget is spent on one vaccine type, and we consider hybrid strategies where the budget is divided over the two vaccine types. Section 4.3 is dedicated to the analysis of two vaccine types that arrive in batches, such that vaccination does not take place at a single moment, but during a vaccination campaign.

### 4.1 Characterizing hybrid vaccination strategies

Hybrid vaccination strategies are difficult to compare, because they differ both in the times at which people are vaccinated and in the proportion of the population vaccinated at those times. To simplify the comparison, we show how to construct for each hybrid strategy a single moment strategy, *such* that the hybrid strategy and the single moment strategy have the same final size. Note that this single moment strategy differs from the pure strategies described earlier, because the vaccination moment for the single moment strategy need not, and typically is not, one of the moments at which vaccination is possible for the hybrid strategy.

The formal result is presented in the following theorem. The proof can be found in Appendix B. In this theorem  $s_{(i)}(t)$  and  $s_{(ii)}(t)$  respectively denote the proportion of people susceptible at time  $t$  in the hybrid strategy ( $i$ ) and the single moment strategy ( $ii$ ).

**Theorem 1.** We consider an initial state denoted by  $(s_0, i_0)$  and use the *SIR* model to evaluate the epidemic. A hybrid vaccination strategy (i) with  $n$  vaccination moments at times  $\tau_1, \dots, \tau_n$  and corresponding vaccination fractions  $f_1, \dots, f_n$  results in the same final size as a single moment vaccination strategy (ii) with one vaccination moment at time  $\tau^T$  and a vaccination fraction  $f^T = \sum_{j=1}^n f_j$  if and only if  $\tau^T$  satisfies the following condition:

$$1 - \frac{f^T}{s_{(ii)}(\tau^T)} = \prod_{j \in J} \left(1 - \frac{f_j}{s_{(i)}(\tau_j)}\right) \quad (5)$$

There is always exactly one  $\tau^T \in [\tau_1, \tau_n]$  satisfying (5).

The interpretation of Theorem 1 is as follows. Effectively vaccinating a certain number of people divided over  $n$  moments in the time interval  $[\tau_1, \tau_n]$  results in the same final size as effectively vaccinating this same number of people at once at some time  $\tau^T$ . Although the existence of  $\tau^T$  may be intuitive, its characterization in (5) is not trivial. The contribution of Theorem 1 is therefore that we characterize the single moment vaccination strategy: we describe the vaccination fraction and the time at which vaccination should take place.

The condition (5) that characterizes  $s_{(ii)}(\tau^T)$  has the following interpretation. Upon vaccination at time  $\tau_j$  in strategy (i) the susceptible population reduces from  $s_{(i)}(\tau_j)$  to  $s_{(i)}(\tau_j) - f_j = s_{(i)}(\tau_j) \left(1 - \frac{f_j}{s_{(i)}(\tau_j)}\right)$ , i.e.,  $s_{(i)}(\tau_j)$  is multiplied with the factor  $\left(1 - \frac{f_j}{s_{(i)}(\tau_j)}\right)$ . The time  $\tau^T$  is such that multiplying  $s_{(ii)}(\tau^T)$  with the product of all these factors for  $j = 1, \dots, n$  results in a reduction of  $f^T$ . The characterization of  $\tau^T$  allows us to compare different hybrid strategies with each other and with pure strategies. To compute the actual value for  $\tau^T$ , we numerically evaluate of the differential equations in (1) to determine at which time the proportion of susceptible people equals  $s_{(ii)}(\tau^T)$ .

In Appendix C we show that the result of Theorem 1 also holds for a more general epidemic model, namely the *SI<sup>n</sup>R* model with  $n$  consecutive infectious stages. The *SI<sup>n</sup>R* model can also take into account a latent period or multiple levels of infectivity. Since the characterization of  $s(\tau^T)$  in Theorem 1 underlies the other results in this paper, we conjecture that these results also extend to this more general epidemic model. If this conjecture is true, our choice for the simple *SIR* model is not restrictive.

## 4.2 Comparison of vaccination strategies

In this section we focus on comparing vaccination strategies for which two vaccine types can be used, i.e.,  $|J| = 2$ . Consider a policy maker that has a certain budget available to spend on these two vaccine types. We start with considering strategies in which all budget is spent on one vaccine type (Section 4.2.1). We

refer to these vaccination strategies as ‘pure strategies’. Next, we extend these results to hybrid strategies in which the budget may be divided over the two types (Section 4.2.2).

#### 4.2.1 Pure strategies

The two considered vaccine types are characterized by a vaccine efficacy and a time at which the vaccines become available, respectively denoted by  $\varphi_j$  and  $\tau_j$  for  $j = 1, 2$ . We refer to vaccine type 1 as the vaccine type which is available early, but has a low efficacy per dollar and to type 2 as the vaccine type which is available at a later point in time, but has a high efficacy per dollar. Hence,  $\tau_1 < \tau_2$  and  $\varphi_1 < \varphi_2$ . Let us assume that the characteristics are fixed for vaccine type 1. We analyze the effects of varying the availability and efficacy per dollar of type 2 to see which vaccine type is preferred.

If the vaccines of type 2 are available very early, i.e., just after  $\tau_1$ , hardly any new infections will occur in the interval  $[\tau_1, \tau_2]$ . The higher efficacy per dollar of type 2 outweighs the delayed availability, because it allows to effectively vaccinate more people and possibly even to control the epidemic directly at  $\tau_2$ . On the other hand, if the vaccines of type 2 are available when the epidemic is already declining, they are of little use. In a declining epidemic the risk of becoming infected is low and you would almost only vaccinate people that would not have become infected anyways. Thus, when type 2 is available very late, we prefer type 1 vaccines because they are available in time to reduce the growth in infections and lower the risk of infection for unvaccinated people.

We thus see that type 1 is preferred when type 2 is available very late, but also that type 2 is preferred if this type is available early. This implies that there is a specific time for the availability of type 2 at which the two pure strategies are equally good. Theorem 2 derives a formal result along these lines and characterizes the curve where the pure strategies are equally good. In this theorem  $\tau_2$  is implicitly defined through  $s_2(\tau_2)$ , with  $s_j(t)$  denoting the proportion of people susceptible in strategy  $j$  at time  $t$ .

**Theorem 2.** *The pure strategies 1 and 2 result in the same final size under the following condition:*

$$s_2(\tau_2) = \frac{s_1(\tau_1)\varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)(\varphi_2 - \varphi_1)} \quad (6)$$

*If  $s_2(\tau_2)$  is smaller (larger) than the right-hand side in above expression, then strategy 2 is worse (better).*

Recall that the proportion of people susceptible is decreasing over time, such that a lower  $s_2(\tau_2)$  implies a later availability (i.e., a higher  $\tau_2$ ). Thus, Theorem 2 confirms our finding that strategy 2 is worse if the vaccines of this type are available late, but better if they are available early. We can derive the following managerial implications from Theorem 2. First, we observe that if the two vaccine types have the same

efficacy per dollar, the best vaccine is the one that is available at the earliest time. Secondly, if the two vaccine types are available at the same time such that  $s_1(\tau_1) = s_2(\tau_2)$ , the vaccine with the highest efficacy per dollar results in the lowest final size. In short, vaccinating early is better and vaccines with a higher efficacy per dollar are better. These conclusions also imply that later available vaccine types with a lower efficacy per dollar are always dominated by vaccine types that are available at an earlier time and have a higher efficacy. This confirms our choice to consider vaccine types for which  $\tau_1 < \tau_2$  and  $\varphi_1 < \varphi_2$ .

If the epidemic can be controlled with only vaccines of type 1, then there are not many new infections after  $\tau_1$  and  $G(f_1, \tau_1)$  is only slightly smaller than  $\left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)$ . By (6) in that case vaccines of type 2 can only be preferred if  $\tau_2$  is very close to  $\tau_1$ .

In condition (6) the two parameters that characterize type 2 appear: the availability and the efficacy per dollar. For strategy 1 and 2 to be equally good, there is a trade-off between those two parameters. Delaying should be compensated by a higher efficacy per dollar. Though if the availability is too far delayed, there is no compensation possible.

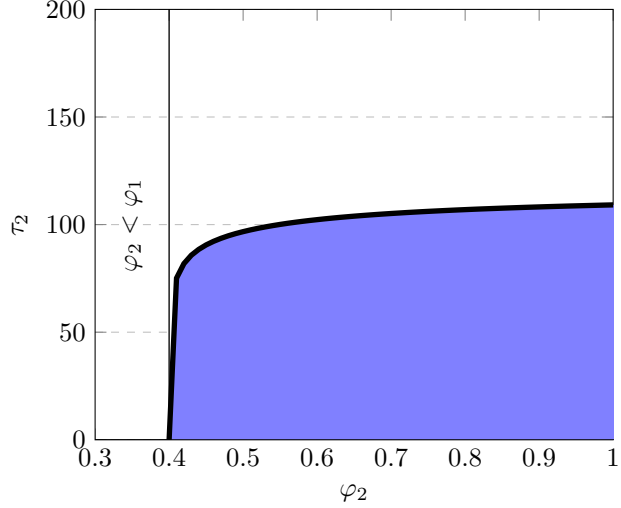
**Corollary 3.** *The value for  $\tau_2$  that satisfies (6) is increasing in  $\varphi_2$ .*

We illustrate the switching curve for two vaccination strategies in Figure 3. We can compute  $\tau_2$  easily from (6) by numerical evaluation of the differential equations (1). The parameters for this figure are as follows:  $B/N = 0.5$  and  $\beta = 0.35, \gamma = 0.24$ . Both vaccines have a price of 1 dollar per dose. Vaccines of type 1 have efficacy per dollar  $\varphi_1 = 0.4$  and are available at time 0 when  $i_0 = 10^{-6}$  and  $s_0 = 1 - i_0$ . To construct the figure, we use (6) to determine the relation between  $s_2(\tau_2)$  and  $\varphi_2$  and we evaluate the differential equations to derive  $\tau_2$  from  $s_2(\tau_2)$ . The figure shows the same structure as described before. We also see that vaccines which become available very late are never preferred, regardless of their efficacy per dollar.

#### 4.2.2 Hybrid strategies

In addition to the pure strategies that are analyzed in the previous section, we can also consider hybrid strategies. In hybrid strategies the budget is partly spent on vaccines of type 1 and partly on vaccines of type 2. Intuitively one might think that one of the vaccine types is better than the other, such that only a pure strategy can be optimal. However, in this section we prove and explain that the opposite is true.

To investigate when hybrid strategies can be optimal, we take the efficacy per dollar of type 2 as fixed and vary the time at which these vaccines become available. We start with  $\tau_2$  high, such that it is best to spend the entire budget on vaccines of type 1. By advancing the availability of type 2, we will reach a point



**Figure 3:** Illustration of the switching curve. In the white area strategy 1 results in the lowest final size and is therefore the best and in the dark area this holds for strategy 2.

at which these vaccines are so attractive, that it is no longer optimal to spend the entire budget on vaccines of type 1. The following theorem shows under which condition this happens. To derive this condition, we make use of Theorem 1 which provides a useful characterization of the hybrid strategy.

**Theorem 4.** *Consider the pure strategy where all vaccines are of type 1. It is better to shift  $\epsilon$  vaccines to type 2, with  $\epsilon > 0$  small, under the following condition:*

$$\frac{\varphi_2}{\varphi_1} > \frac{[s_1(\tau_1^v) - G(f_1, \tau_1)] / s_1(\tau_1^v)}{[s_1(\tau_2) - G(f_1, \tau_1)] / s_1(\tau_2)}, \quad (7)$$

where  $s_1(\tau_1^v)$  denotes the proportion of people susceptible just after vaccination at time  $\tau_1$ .

By spending some of the budget on vaccines of type 1 and some on vaccines of type 2, the population can benefit from the advantages of both vaccine types. The early vaccination with type 1 reduces the initial growth in infections and with the high efficacy per dollar of type 2 many people can achieve immunity due to vaccination. Such a hybrid strategy is only beneficial if the epidemic is still ongoing when the vaccines of type 2 become available and if the efficacy per dollar of type 2 is high enough. This can also be seen if we analyze the condition in Theorem 4. The term on the right-hand side represents the proportion of the total number of infections after  $\tau_1$  that occurs while waiting for the vaccines of type 2, i.e., in the interval  $[\tau_1, \tau_2]$ . This proportion is an indication of the additional infections experienced if the decision maker decides to wait for vaccines of type 2. It is beneficial to wait if the gain in efficacy per dollar, captured by the ratio  $\frac{\varphi_2}{\varphi_1}$ , outweighs the additional infections during this waiting time.

If the vaccines of type 2 become available when the epidemic has almost died out, then almost all infections have already taken place in the interval  $[\tau_1, \tau_2]$  and the higher efficacy per dollar of type 2 does not compensate for the late availability. On the other hand, if the epidemic is still ongoing and infections are increasing when type 2 becomes available, only a small part of the infections has already taken place while waiting for type 2 and it is worth waiting for this better vaccine.

One could argue that if the decision maker should shift  $\epsilon$  vaccines from type 1 to type 2, why not spend the entire budget on vaccines of type 2? There are two main reasons why this would not result in a good strategy. Firstly, the vaccines of type 2 are available at a later point in time. By using only these vaccines, the epidemic can spread freely until  $\tau_2$ , which might cause a lot of infections. The second reason is related to the high efficacy per dollar of the vaccines of type 2 through which many people can be effectively vaccinated. This seems to be advantageous, but it might also mean that the epidemic can easily be controlled with less vaccines. Spending the entire budget on vaccines of type 2 results in vaccinated people that would not have become infected in the first place. These vaccines are not effectively used and it is better to use part of the budget for reducing the initial growth by vaccinating some people at  $\tau_1$ , such that the epidemic can be controlled at  $\tau_2$  by spending the remaining budget on vaccines of type 2. The following two lemmas formally describe the relation between pure and hybrid strategies:

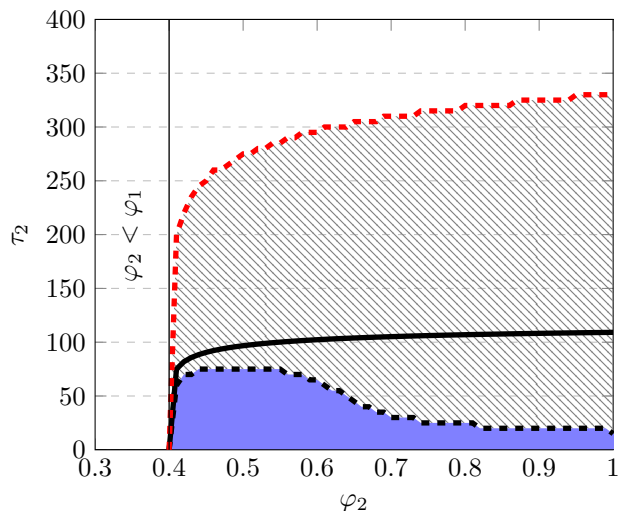
**Lemma 5.** *At the indifference curve, when the two pure strategies are equally good, the hybrid strategy is strictly better and results in a lower final size.*

**Lemma 6.** *If the two pure strategies are equally good for vaccines of type 2 that become available at time  $T$ , then there exists a  $T^* > T$  such that it is optimal to shift  $\epsilon$  vaccines to type 2 when the vaccines of type 2 become available at time  $T^*$ .*

The interpretation of Lemma 6 is that while advancing the availability of type 2, you will first reach the point where it is optimal to shift a little bit of the budget to type 2 before you reach the switching curve. Thus, even if the pure strategy with only type 2 is worse than the pure strategy with only type 1, it can be beneficial to use vaccines of type 2 in a hybrid strategy. Lemma 5 confirms that the hybrid strategy is optimal around the switching curve. The structure described by these two lemmas is also illustrated in Figure 4, which is determined with enumeration. We observe that the solid switching curve lies in the dashed region where hybrid strategies are optimal. The parameters for this figure are the same as in Section 4.2.1.

We observe the following in Figure 4. If pure strategy 1 is optimal for some  $\tau_2$ , it is also optimal when the vaccines of type 2 are available even later. Delaying the availability of type 2 results in even more infections



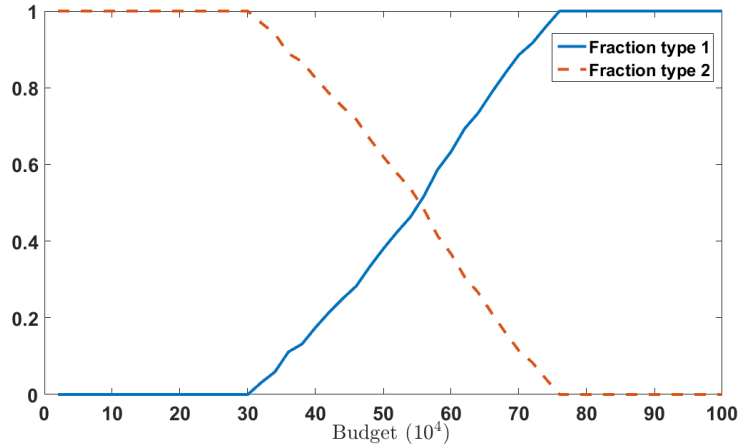


**Figure 4:** This figure illustrates the optimal strategy. In the white area strategy 1 results in the lowest final size and is therefore the best and in the dark area this holds for strategy 2. The dashed area between the two dashed lines is a sketch of the region in which a hybrid strategy is optimal. The solid curve represents the switching curve from Figure 3.

while waiting for this type which are not outweighed by the gain in efficacy per dollar. Analogously, pure strategy 2 remains optimal if  $\tau_2$  is reduced. The reduced waiting time results in less infections, so the gain in efficacy per dollar will surely compensate that. Next to that, if  $\tau_2$  is smaller there are still more people susceptible when the vaccines of type 2 become available, such that more vaccines are needed to control the epidemic at  $\tau_2$ . This implies that there is no incentive to reduce the vaccination fraction at  $\tau_2$  by shifting some vaccines to type 1. We also see that by increasing  $\varphi_2$  we can move from a region where pure strategy 2 is optimal to a region where the hybrid strategy is optimal. For these higher values of  $\varphi_2$ , pure strategy 2 is no longer optimal, because the type 2 vaccines became so efficacious that spending the entire budget on these vaccines would lead to vaccinating people that would not have become infected in the first place.

Finally, the figure shows that the dashed area lies around the solid switching curve. Thus, the decision maker should consider spending the budget on both vaccine types when the two types are equally attractive. Clearly, if one vaccine type avoids much more infections than the other, this type should be used. But if the two types are comparable, our results show that it is suboptimal to arbitrarily choose one of the types. By dividing the budget and investing in both types, even more people can be saved from infection.

As a final part of this section, we analyze the effects of an increasing budget in Figure 5. The figure shows that for small budgets, the optimal strategy is to order only the vaccines with the highest efficacy per dollar.



**Figure 5:** Optimal division of the budget over the two vaccine types with the following characteristics:  $\tau_1 = 0$ ,  $\varphi_1 = 0.4$ ,  $\tau_2 = 90$  and  $\varphi_2 = 0.7$ .

In those cases the budget is insufficient to control the epidemic, so it is best to effectively vaccinate as many people as possible. However, when the budget increases, it becomes beneficial to use a hybrid strategy. For a sufficiently large budget the epidemic can already be controlled at  $\tau_1$  and the optimal strategy is to use only the vaccines of type 1.

The results in Sections 4.2.1 and 4.2.2 are derived for a homogeneous population. In the discussion in Section 6 we discuss how our results are expected to carry over to heterogeneous populations, for example populations with multiple age-groups.

### 4.3 Two vaccination campaigns

In this section we present one more result that follows from Theorem 1. This result is an extension of our results on pure strategies in Section 4.2.1. Instead of considering vaccines that are all allocated at once, we consider vaccines that are allocated in a vaccination campaign consisting of multiple vaccination moments. There are multiple reasons why a single vaccination moment might not be possible. Logistical considerations may play a role, which render it practically infeasible to allocate all vaccines at the same time (e.g., Rachaniotis, Dasaklis, & Pappis, 2012; Ramirez-Nafarrate, Lyon, Fowler, & Araz, 2015). Next to that, the production of vaccine is a complex process, amongst others characterized by random yields (cf., Adida, Dey, & Mamani, 2013; Eskandarzadeh, Eshghi, & Bahramgiri, 2016). Together with capacity constraints, this can result in production processes or technologies that produce vaccines in batches, such

that the vaccines become available over time. In this section we extend some of our results to the case of vaccination campaigns.

Let us consider two vaccination campaigns which differ in the efficacy per dollar of the used vaccine and in the time at which the campaign starts. These differences are for example attributed to different production technologies. Denote by  $\varphi_i$  and  $\tau_i$  respectively the efficacy per dollar of the vaccine and time at which the campaign starts for  $i = 1, 2$ . Assume that during the vaccination campaign a total budget of  $B$  is spent over  $n$  vaccination moments, such that  $B/n$  dollar is spent each time. The time in between two vaccination moments is  $T$  for both campaigns, which implies that the  $j$ -th vaccination moment takes place at time  $\tau_i + (j - 1)T$  for campaign  $i$ . Let  $s_j^i$  denote the proportion of susceptible people at the  $j$ -th vaccination moment in the campaign  $i$ . The two vaccination campaigns result in the same final size if the following condition is satisfied, where  $G(\varphi_1, \tau_1)$  denotes the herd effect of campaign 1:

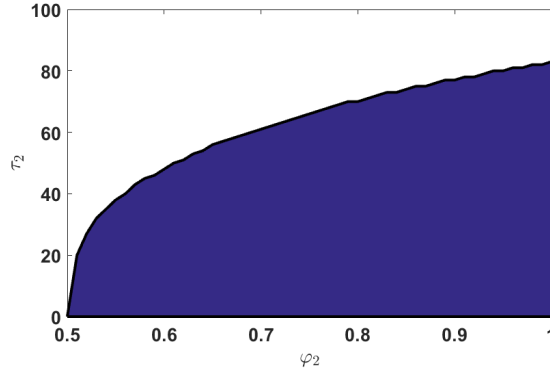
$$1 - \frac{(\varphi_2 - \varphi_1)B}{NG(\varphi_1, \tau_1)} - \prod_{j=1}^n \left( \frac{s_j^1}{s_j^2} \right) \left( \frac{nNs_j^2 - \varphi_2 B}{nNs_j^1 - \varphi_1 B} \right) = 0 \quad (8)$$

If the left-hand side is positive (negative), strategy 1 is better (worse). The derivation of this condition can be found in Appendix D.3 and makes use of Theorem 1. Note that condition 8 implicitly defines the relation between  $\tau_2$  and  $\varphi_2$ , as  $s_j^2$  for all  $j$  depend on  $\tau_2$ . We can compute this relation through numerical analysis. Figure 6 illustrates the relation for the parameters  $\varphi_1 = 0.5$ ,  $\tau_1 = 0$ ,  $n = 4$ ,  $T = 30$  and  $B = 0.2N$ . As expected, we see that campaign 2 is better than campaign 1 if either campaign 2 does not start too late, or if the corresponding vaccines have a high efficacy. Again, we see that for  $\tau_2$  above a certain threshold, around 80 in this case, vaccines of campaign 2 are too late to be optimal. Since a campaign with multiple moments is already some kind of hybrid strategy in itself, we do not consider partially investing in two campaigns.

If a vaccination campaign is used instead of instantaneous mass vaccination, then preferences for the vaccine types can change. For example, the advantage of an early aspecific vaccine type might disappear if it is distributed through a lengthy vaccination campaign.

## 5 Numerical experiments

In this section we perform some numerical experiments. Our analytical results in Section 4 show theoretically that hybrid strategies can outperform pure strategies for two vaccine types. The objective of our numerical experiments in this section is twofold: firstly, we want to know how many infections can actually be saved by using a hybrid strategy and secondly we investigate whether it is beneficial to use a hybrid strategy with



**Figure 6:** The switching curve for the two vaccination campaigns. In the white area campaign 1 is optimal and in the dark area campaign 2. The initial state and disease parameters are the same as in Figure 3.

more than two vaccine types.

We use data on an influenza outbreak and influenza vaccines from Matrajt et al. (2015). The parameters for the outbreak are as follows:  $N = 10^6$ ,  $i_0 = 10^{-6}$ ,  $s_0 = 1 - i_0$ ,  $\beta = 0.35$  and  $\gamma = 0.25$ . They do not consider prices of the vaccines and assume that there are enough vaccines to vaccinate half of the population. In terms of our model we let the price be  $p$  dollar per dose of vaccine for all vaccine types and use a budget of  $B = pN/2$ . Matrajt et al. (2015) study vaccines that have an effect on susceptibility, infectiousness and on the symptoms in case of infection. In our paper we only consider the effect on susceptibility. Matrajt et al. (2015) study vaccines that become available 0, 45, 60, 75 or 90 days after the start of the outbreak and that have an efficacy in the range of 0.4-0.66. Likewise, we analyze the following seven vaccine types, assuming that  $p = 1$ :

<b>Type</b>	1	2	3	4	5	6	7
$\tau_j$	0	45	60	60	75	75	90
$\varphi_j$	0.4	0.5	0.5	0.6	0.6	0.7	0.7

We study all subsets of three vaccine types in which no vaccine type(s) is/are dominated by others. This means that we do not consider those subsets which include two vaccine types that have the same time at which the vaccines become available or the same efficacy per dollar. For example, if a decision maker has to choose between vaccines of type 4 and 5, she will always prefer the vaccines of type 4 because they are available earlier and have the same efficacy per dollar. Analogously, type 6 will always be preferred if one has to choose between type 5 and 6, because both vaccine types are available at the same time, but type 6 has a higher efficacy per dollar. Taking these considerations into account, we find 14 subsets consisting of three vaccine types each. For these subsets we analyze the best pure strategy, the best hybrid strategy

with at most 2 types and the best hybrid strategy with at most 3 types. Note that the pure strategies are also included in the hybrid strategies. For the hybrid strategies we use enumeration and a stepsize of  $1000 = 10^{-3}N$  vaccines. The results are reported in Table 1. In this table the final size for the pure strategies is reported as a population fraction. For the hybrid strategies the relative performance compared to the best pure strategy is presented. Recall that our goal is to minimize the final size. Hence, if the reported value in the table is below 100, it means that the hybrid strategy is better and results in a lower final size than the pure strategy.

	Pure strategy		Hybrid with at most two types		Hybrid with at most three types*
Types 1, 2, 4	0.0140	(0, 0, 500)	100	(0, 0, 500)	100
Types 1, 2, 5	0.0387	(0, 0, 500)	88.63	(69, 0, 431)	88.63
Types 1, 2, 6	0.0207	(0, 0, 500)	55.56	(147, 0, 353)	55.56
Types 1, 2, 7	0.0666	(0, 0, 500)	39.19	(186, 0, 314)	32.43
Types 1, 3, 5	0.0387	(0, 0, 500)	88.63	(69, 0, 431)	88.63
Types 1, 3, 6	0.0207	(0, 0, 500)	55.56	(147, 0, 353)	55.56
Types 1, 3, 7	0.0666	(0, 0, 500)	39.19	(186, 0, 314)	39.19
Types 1, 4, 6	0.0140	(0, 500, 0)	82.14	(147, 0, 353)	82.14
Types 1, 4, 7	0.0140	(0, 500, 0)	100	(0, 500, 0)	100
Types 1, 5, 7	0.0387	(0, 500, 0)	67.44	(186, 0, 314)	67.44
Types 2, 4, 6	0.0140	(0, 500, 0)	97.86	(0, 425, 75)	97.86
Types 2, 4, 7	0.0140	(0, 500, 0)	100	(0, 500, 0)	100
Types 2, 5, 7	0.0387	(0, 500, 0)	74.16	(282, 0, 218)	74.16
Types 3, 5, 7	0.0387	(0, 500, 0)	100	(0, 500, 0)	100

**Table 1:** Table with the final sizes achieved with the different vaccination strategies. In brackets the optimal allocation over the three considered types with a step size  $10^3$  doses of vaccine. \* the allocations for hybrid strategies with a most two and at most three vaccine types are the same.

We start with discussing the column on hybrid strategies with at most two vaccine types in Table 1. The results show that in most cases a hybrid strategy is preferred. We see that the hybrid strategy often combines the earliest available vaccine with the vaccine that has the highest efficacy per dose. By using a hybrid strategy the final size can be reduced with even more than 60% for vaccine types 1,2,7 and 1,3,7.

Only for a few vaccine type combinations the final size of the best hybrid strategy is the same as the final size of the best pure strategy, which implies that the pure strategy is optimal in those cases. We conclude from Table 1 that using a hybrid strategy can result in a substantially lower final size and is therefore worth investigating.

The second goal of this section is to investigate hybrid strategies with more than two vaccine types. Interestingly, if we analyze Table 1 and compare hybrid strategies with at most two types with hybrid strategies with at most three vaccine types, the final sizes are the same for all subsets of vaccine types. The additional freedom that is introduced by allowing to divide the budget over three vaccine types does not result in further reductions of the final size. Additional experiments not reported here have also supported the conclusion that hybrid strategies with more than two vaccine types typically give no or very little additional benefits

In this section we do not analyze hybrid strategies with more than three vaccine types. Nevertheless we can draw conclusions for those situations. Consider a hybrid vaccination strategy with  $n$  vaccine types. By applying Theorem 1 to types 3, ...,  $n$  and summarizing them in one moment, the strategy with  $n$  vaccine types is equivalent to a vaccination strategy with three vaccine types. In our numerical results we do not find situations where a hybrid vaccination strategy with three vaccine types is better than a hybrid strategy with at most two vaccine types. It is therefore unlikely that hybrid strategies with more than three vaccine types are optimal.

Hence, we can conclude this section as follows. Consider a decision maker that can choose between multiple vaccines types. Based on our results decision makers can expect significant benefits by considering hybrid strategies with two types of vaccine. However, hybrid strategies that invest in more than two vaccine types are expected to provide little to no additional benefit and the decision maker does not have to investigate those hybrid strategies.

## 6 Discussion

In this section we discuss modelling assumptions, the generality of our results and possible directions for future research.

The results in this paper are established under some assumptions. We model vaccination as an immediate transition of people from the susceptible compartment to the removed compartment. This assumption could be relaxed to studying the case where vaccination takes more time, which can be modelled as a vaccination campaign (cf., Section 4.3). In our analysis we assume that the vaccine efficacy is known for every vaccine

type. Further research is needed to extend the analysis to environments where efficacy is uncertain, e.g., situations where the delayed availability is caused by a vaccine development phase with unknown outcome. Furthermore, we base our analysis on the *SIR* model, but show in Appendix C how some results extend to the more general *SI<sup>n</sup>R* model. In the *SIR* model we consider a homogeneous population. Alternatively, a model for a heterogeneous population could be used, for example a population that is subdivided in multiple age-groups (e.g., Medlock, Meyers, & Galvani, 2009; Teytelman & Larson, 2012). In a heterogeneous population the final size is the result of an optimization problem that is used to determine which allocation over the age-groups is best. We conjecture that a switching curve result similar to Theorem 2 can be derived in the case of a heterogeneous population, i.e., that there exists a curve separating the region where a pure type 1 strategy is optimal from the region where a pure type 2 strategy is optimal. Making the vaccines of type 2 more attractive by increasing their efficacy, reducing their price or by advancing their availability will reduce the final size, as the original allocation is still feasible. Another interesting research direction is incorporating high-risk and high-transmission groups (e.g., Lee et al., 2015; Samii, Pibernik, Yadav, & Verecke, 2012).

## 7 Conclusions

In this paper we study the trade-off between the timing of vaccination and the effectiveness of the response. This trade-off plays a role in several vaccination problems of which three examples are discussed in the introduction. We focus on a problem with an early aspecific vaccine and a late specific vaccine. We derive an analytical expression for the switching curve separating the region where the early aspecific vaccine is preferred from the region where the late specific vaccine is preferred. We demonstrate that it is not always optimal to spend the entire budget on one of the two vaccine types, but that a hybrid strategy can reduce the final size with more than 50%.

The derived insights are useful for decision makers. We show the importance of the trade-off between timing and efficacy and the effects on controlling the epidemic. Early vaccination is able to reduce the initial increase in infections, but a vaccine with a higher efficacy per dollar can achieve higher immunity levels in the population such that the epidemic can be controlled quickly. When the epidemic can already be controlled with the early aspecific vaccine, the decision maker should use only this vaccine. But when this is not possible, either only the specific later vaccine should be used or a hybrid strategy should be considered. By applying a hybrid strategy the target population benefits from both a quick response and a efficacious vaccine. Such a solution can also be helpful for decision makers who balance between the public pressure to respond quickly and the aim to spend the budget on the best possible vaccine.

Extant literature mentions some practical considerations for using hybrid strategies. E.g., starting production earlier for some influenza strains allows to have sufficient time to produce vaccines against these strains while buying time to learn more about the other strains and allowing higher vaccine dosages for health care workers protects them from getting infected by patients. In this paper we give an important motivation for hybrid strategies even in the absence of such practical considerations. We show that a hybrid strategy may in many cases make more efficient use of resources than any pure strategy, due to the non-linear dynamics of an epidemic. This paper thus provides an additional and more generally applicable motivation for the use of hybrid strategies which supersedes the practical arguments used in literature or in the US national pandemic response plan. Our results encourage to study hybrid vaccination strategies in any application where the trade-off between timing and efficacy plays a role, even if a direct practical necessity is missing.

## **Acknowledgements**

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# Appendices

## Appendix A SIR model

In this paper we use the final size to compare the severity of different vaccination strategies. In Section 3.3 we show that the herd effect, denoted by the function  $G(\mathbf{f}, \tau)$ , is an important determinant in the final size. The herd effect is defined as the final fraction of people susceptible after a vaccination strategy characterized by vaccination fractions  $\mathbf{f}$  and times  $\tau$ . More precisely, for  $f_j \in [0, \varphi_j s_j(\tau)]$

$$G(\mathbf{f}, \tau) = \lim_{t \rightarrow \infty} s(t), \quad (9)$$

with  $s(t)$  evolving according to (1) for  $t > \tau_n$ . In this appendix we present and analyze an alternative formulation of the herd effect, which forms the basis of the structural analysis of the herd effect.

Based on the differential equations of the *SIR* model we derive an implicit expression for the herd effect. From (1) the following equation follows, which presents the relation between  $i(t)$  and  $s(t)$  at any time  $t$  (Hethcote, 1976):

$$\begin{aligned} i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s_0 + i_0 - \frac{\log(s_0)}{\sigma} \\ \Leftrightarrow s(t) &= s_0 \exp\{-\sigma(s_0 + i_0 - s(t) - i(t))\} \end{aligned} \quad (10)$$

Above relation characterizes the state of the system at any point in time, but prior to vaccination. In Theorem 1 we show that for any vaccination strategy with multiple vaccination moments, there is a single-moment strategy resulting in the same final size. In this single-moment strategy a fraction  $f^T$  of the population is vaccinated at time  $\tau^T$ . In the remainder of this section we will use the parameters of the single-moment vaccination strategy to analyze  $G(\mathbf{f}, \tau)$ .

Upon vaccination at time  $\tau^T$  the state of the system changes from state  $(s(\tau^T), i(\tau^T))$  to state  $(s(\tau^T) - f^T, i(\tau^T))$ . Hence, the state  $(s(\tau^T) - f^T, i(\tau^T))$  directly after vaccination can be seen as a new initial state, where  $i(\tau^T)$  can be obtained from (10). Since  $\lim_{t \rightarrow \infty} i(t) = 0$ , the function  $G(\mathbf{f}, \tau)$  can be derived from (10) by setting  $i(t) = 0$  and thus is the unique solution to:

$$\begin{aligned} 0 &= -G(\mathbf{f}, \tau) + \frac{\log(G(\mathbf{f}, \tau))}{\sigma} + s(\tau^T) - f^T + i(\tau^T) - \frac{\log(s(\tau^T) - f^T)}{\sigma} \\ \Leftrightarrow 0 &= -G(\mathbf{f}, \tau) + \frac{\log(G(\mathbf{f}, \tau))}{\sigma} + s_0 + i_0 - \frac{1}{\sigma} \log\left(s_0 \left(1 - \frac{f^T}{s(\tau^T)}\right)\right) - f^T \end{aligned} \quad (11)$$

Above equation holds for all  $i_0 > 0$ . Denote by  $Z(\mathbf{f}, \tau)$  the final size according to (3). Rewriting (11) gives the following:

$$G(\mathbf{f}, \tau) = s_0 \left(1 - \frac{f^T}{s(\tau^T)}\right) \exp\{-\sigma Z(\mathbf{f}, \tau)\} \quad (12)$$

Observe that (11) and (12) are implicit definitions of the herd effect. Alternatively, we can derive a definition based on the Lambert W function (Corless, Gonnet, Hare, Jeffrey, & Knuth, 1996; Ma & Earn, 2006). This definition can be used to calculate the herd effect:

$$G(\mathbf{f}, \tau) = \frac{-1}{\sigma} W \left[ -s_0 \left( 1 - \frac{f^T}{s(\tau^T)} \right) \exp\{-\sigma(s_0 + i_0 - f^T)\} \right] \quad (13)$$

An early response is always better than a later response, as shown in the following lemma:

**Lemma A.1.** *For fixed  $f^T$ , the herd effect  $G(\mathbf{f}, \tau)$  is increasing in  $s(\tau^T)$  and the final size  $Z(\mathbf{f}, \tau)$  is decreasing in  $s(\tau^T)$ .*

*Proof.* See Section 4.5 of Duijzer et al. (2015). □

## Appendix B Multiple vaccination moments

In this Appendix we prove Theorem 1. Thereto we first present two supporting results: a result on the dynamics of an epidemic in Lemma B.1 and a technical result in Lemma B.2.

Recall that we have  $n$  moments of vaccination, respectively at time  $\tau_1, \tau_2, \dots, \tau_n$ . The vaccination fractions at these moments are denoted by  $f_1, \dots, f_n$  and  $s(\tau_j)$  denotes the fraction of susceptible people just prior to vaccination at time  $\tau_j$  for  $j = 1, \dots, n$ . For notional convenience we add two vaccination moments at  $\tau_0 = 0$  and  $\tau_{n+1} = +\infty$  at which no vaccination takes place, such that  $f_0 = f_{n+1} = 0$ . The following theorem shows that in between two vaccination moments this system follows the time course of a system without vaccination and with a different initial state.

**Lemma B.1.** *For all  $k = 1, \dots, n$  we consider the following two systems, that both follow the dynamics of the SIR model. Note that (i) is a system with vaccination and (ii) a system without vaccination:*

(i) *let  $(s(t), i(t))$  denote the state at time  $t$  of the system with initial state  $(s(0), i(0)) = (s_0, i_0)$  when a fraction  $f_j$  of the susceptible people is vaccinated at time  $\tau_j$  for  $j = 1, \dots, k$ .*

(ii) *let  $s^k(t)$  and  $i^k(t)$  denote the state at time  $t$  of a system without vaccination and with initial state  $s^k(0) = s_0^k := s_0 \cdot \prod_{j=1}^k \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right]$  and  $i^k(0) = i_0^k := s_0 + i_0 - s_0^k$ .*

*The time course of system (i) on the interval  $t \in (\tau_k, \tau_{k+1})$  is the same as the time course of system (ii) on the shifted interval  $[t_k^*, t_k^* + \tau_{k+1} - \tau_k]$  for some  $t_k^*$ . More precisely,  $s^k(t + t_k^* - \tau_k) = s(t)$  and  $i^k(t + t_k^* - \tau_k) = i(t)$  for  $\tau_k < t < \tau_{k+1}$ .*

*Proof.* This theorem will be proven by induction. We start with proving that it holds for  $k = 1$ . Consider system (i) and note that the relation between  $i(\tau_1)$  and  $s(\tau_1)$  just prior to vaccination at time  $\tau_1$  can be described by (10) as follows:

$$i(\tau_1) = -s(\tau_1) + \frac{\log(s(\tau_1))}{\sigma} + s_0 + i_0 - \frac{\log(s_0)}{\sigma} \quad (14)$$

On the interval  $t \in [\tau_1, \tau_2)$  we can see system (i) as a system that starts at time  $\tau_1$  with initial state  $[(s(\tau_1) - f_1), i(\tau_1)]$ . We can use (10) again to derive the relation between  $i(t)$  and  $s(t)$  for  $t \in [\tau_1, \tau_2)$ :

$$\begin{aligned} i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s(\tau_1) - f_1 + i(\tau_1) - \frac{\log(s(\tau_1) - f_1)}{\sigma} \\ \Leftrightarrow i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s_0 + i_0 - f_1 - \frac{1}{\sigma} \log\left(1 - \frac{f_1}{s(\tau_1)}\right) - \frac{\log(s_0)}{\sigma} \\ \Leftrightarrow s(t) &= s_0 \left(1 - \frac{f_1}{s(\tau_1)}\right) \exp\{\sigma f_1\} \exp\{-\sigma[s_0 + i_0 - s(t) - i(t)]\} \end{aligned} \quad (15)$$

In the second line of above derivation we substitute  $s(\tau_1)$  and  $i(\tau_1)$  from (14) and in the third line we take the exponent. We can verify with (10) that the states  $(s(t), i(t))$  for  $t \in [\tau_1, \tau_2)$  that satisfy (15) are also part of the time course of system (ii) for  $k = 1$  by substituting in (10) the following initial state for system (ii):  $s^1(0) = s_0^1 := s_0 \cdot \left(1 - \frac{f_1}{s(\tau_1)}\right) \exp\{\sigma f_1\}$  and  $s_0^1 + i_0^1 := s_0 + i_0$ . Let  $t_1^*$  denote the time at which system (ii) is in the state  $(s(\tau_1) - f_1, i(\tau_1))$ . Such time  $t_1^*$  must exist, because the state  $(s(\tau_1) - f_1, i(\tau_1))$  is part of the time course of system (ii). Then the time course of system (i) on the interval  $(\tau_1, \tau_2)$  is equivalent to that of system (ii) on the interval  $(t_1^*, t_1^* + \tau_2 - \tau_1)$ . This completes the base case of the proof by induction.

We perform the inductive step and assume that the theorem holds for  $k$ . In that case we can determine the state of systems (i) and (ii) at time  $\tau_{k+1}$  with (10) as follows, using that  $s_0^k + i_0^k = s_0 + i_0$  per definition:

$$\begin{aligned} s^k(\tau_{k+1} + t_k^* - \tau_k) &= s_0^k \exp\{-\sigma[s_0^k + i_0^k - s^k(\tau_{k+1} + t_k^* - \tau_k) - i^k(\tau_{k+1} + t_k^* - \tau_k)]\} \\ \stackrel{\text{by induction}}{\Leftrightarrow} s(\tau_{k+1}) &= s_0^k \exp\{-\sigma[s_0^k + i_0^k - s(\tau_{k+1}) - i(\tau_{k+1})]\} \\ &= s_0 \prod_{j=1}^k \left[ \left(1 - \frac{f_j}{s(\tau_j)}\right) \exp\{\sigma f_j\} \right] \exp\{-\sigma[s_0 + i_0 - s(\tau_{k+1}) - i(\tau_{k+1})]\} \end{aligned} \quad (16)$$

We now prove that above relation implies that the theorem also holds for  $k + 1$ . Thereto, we analyse system (i) for  $t \in (\tau_{k+1}, \tau_{k+2})$ . We make use of (10) and take the state at time  $\tau_{k+1}$  just after vaccination,  $(s(\tau_{k+1} - f_{k+1}), i(\tau_{k+1}))$ , as the initial state. Then the following holds for  $t \in (\tau_{k+1}, \tau_{k+2})$ :

$$\begin{aligned} s(t) &= (s(\tau_{k+1}) - f_{k+1}) \exp\{-\sigma[s(\tau_{k+1}) - f_{k+1} + i(\tau_{k+1}) - s(t) - i(t)]\} \\ &= s_0 \prod_{j=1}^{k+1} \left[ \left(1 - \frac{f_j}{s(\tau_j)}\right) \exp\{\sigma f_j\} \right] \exp\{-\sigma[s_0 + i_0 - s(t) - i(t)]\} \end{aligned} \quad (17)$$

In the second step we use (16) to substitute  $s(\tau_{k+1})$  and  $i(\tau_{k+1})$ . We can again verify with (10) that the states  $(s(t), i(t))$  for  $t \in (\tau_{k+1}, \tau_{k+2})$  that satisfy (17) are part of the time course of system (ii) for  $k+1$ , as before for the case  $k=1$ . Let  $t_{k+1}^*$  denote the time at which system (ii) is in the state  $(s(\tau_{k+1}) - f_{k+1}, i(\tau_{k+1}))$ , then the time course of system (i) on the interval  $(\tau_{k+1}, \tau_{k+2})$  is equivalent to that of system (ii) on the interval  $(t_{k+1}^*, t_{k+1}^* + \tau_{k+2} - \tau_{k+1})$ . This completes the proof of this theorem.  $\square$

**Lemma B.2.** *The following relation holds for all  $n \geq 1$ , where we define  $\prod_{k=1}^{j-1} (1 - x_k) = 1$  for  $j = 1$ :*

$$1 - \prod_{j=1}^n (1 - x_j) = \sum_{j=1}^n x_j \prod_{k=1}^{j-1} (1 - x_k)$$

*Proof.* Proof by induction. The lemma clearly holds for  $n = 1$ :  $1 - (1 - x_1) = x_1$ . The inductive step: suppose the lemma holds for  $n = 1, \dots, L$ , then it also holds for  $L + 1$ .

$$\begin{aligned} 1 - \prod_{j=1}^{L+1} (1 - x_j) &= 1 - (1 - x_{L+1}) \prod_{j=1}^L (1 - x_j) \\ &= 1 - \left[ 1 - \sum_{j=1}^L x_j \prod_{k=1}^{j-1} (1 - x_k) \right] + x_{L+1} \prod_{j=1}^L (1 - x_j) \\ &= \sum_{j=1}^{L+1} x_j \prod_{k=1}^{j-1} (1 - x_k) \end{aligned}$$

$\square$

**Theorem 1.** *We consider an initial state denoted by  $(s_0, i_0)$  and use the SIR model to evaluate the epidemic. A hybrid vaccination strategy (i) with  $n$  vaccination moments at times  $\tau_1, \dots, \tau_n$  and corresponding vaccination fractions  $f_1, \dots, f_n$  results in the same final size as a single moment vaccination strategy (ii) with one vaccination moment at time  $\tau^T$  and a vaccination fraction  $f^T = \sum_{j=1}^n f_j$  if and only if  $\tau^T$  satisfies the following condition:*

$$1 - \frac{f^T}{s_{(ii)}(\tau^T)} = \prod_{j \in J} \left( 1 - \frac{f_j}{s_{(i)}(\tau_j)} \right) \quad (5)$$

*There is always exactly one  $\tau^T \in [\tau_1, \tau_n]$  satisfying (5).*

*Proof.* Note that strategy (i) and (ii) allocate in total the same amount of vaccines, because  $f^T = \sum_{j=1}^n f_j$ . Hence, to show that the final sizes for both strategies are the same, it suffices to show that both strategies result in the same herd effect, i.e.  $\lim_{t \rightarrow +\infty} s(t)$  is equal for these two systems.

Denote by  $s_1(\infty)$  and  $s_2(\infty)$  the final fraction of people susceptible in system (i) and (ii) respectively. Note that for  $t \rightarrow +\infty$  the fraction of infected individuals goes to zero. From Lemma B.1 and the fact that

$i_1(\infty) = 0$  we derive that  $s_1(\infty)$  follows from the following expression:

$$s_1(\infty) = s_0 \prod_{j=1}^n \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right] \exp \left\{ -\frac{\beta}{\gamma} [s_0 + i_0 - s_1(\infty)] \right\} \quad (18)$$

In case of a single vaccination moment we can use the final line of (15):

$$s_2(\infty) = s(0) \left( 1 - \frac{f^T}{s(\tau^T)} \right) \exp \{ \sigma f^T \} \exp \left\{ -\frac{\beta}{\gamma} [s_0 + i_0 - s_2(\infty)] \right\} \quad (19)$$

For  $f^T = \sum_{i=1}^n f_i$  and  $\frac{f^T}{s(\tau^T)} = 1 - \prod_{i=1}^n \left( 1 - \frac{f_i}{s(\tau_i)} \right)$  it holds that (18) and (19) are equal to each other, which implies that  $s_1(\infty) = s_2(\infty)$ . With the equal herd effects and the same amount of effectively allocated vaccines, the final sizes of the two strategies are equal.

It remains to show that  $\tau^T \in [\tau_1, \tau_n]$ . We prove this in the following two steps: (i) we show that  $s_1(\tau_n) < s(\tau^T) < s(\tau_1)$  and (ii) we show that  $\tau_1 < \tau^T < \tau_n$ .

- (i) Observe that  $s_1(\tau_j) < s_1(\tau_{j-1}) - f_{j-1}$  for  $j = 2, \dots, n$ , which also implies that  $s_1(\tau_j) < s_1(\tau_1) \prod_{k=1}^{j-1} \left( 1 - \frac{f_k}{s_1(\tau_k)} \right)$  for  $j = 2, \dots, n$ . We can derive the following, using Lemma B.2:

$$\frac{f^T}{s(\tau^T)} = 1 - \prod_{j=1}^n \left( 1 - \frac{f_j}{s_1(\tau_j)} \right) = \sum_{j=1}^n \frac{f_j}{s_1(\tau_j)} \prod_{k=1}^{j-1} \left( 1 - \frac{f_k}{s_1(\tau_k)} \right) > \frac{1}{s_1(\tau_1)} \sum_{j=1}^n f_j = \frac{f^T}{s_1(\tau_1)}$$

Above relation implies that  $s(\tau^T) < s_1(\tau_1)$ . Analogously, we can prove that  $s(\tau^T) > s_1(\tau_n)$ , by noting that  $s_1(\tau_j) > s_1(\tau_n) \frac{1}{\prod_{k=j}^{n-1} \left( 1 - \frac{f_k}{s_1(\tau_k)} \right)}$ . This implies the following:

$$\frac{f^T}{s(\tau^T)} = \sum_{j=1}^n \frac{f_j}{s_1(\tau_j)} \prod_{k=1}^{j-1} \left( 1 - \frac{f_k}{s_1(\tau_k)} \right) < \frac{\left( 1 - \frac{f^T}{s(\tau^T)} \right)}{s_1(\tau_n)} \sum_{j=1}^n f_j = \left( 1 - \frac{f^T}{s(\tau^T)} \right) \frac{f^T}{s_1(\tau_n)} < \frac{f^T}{s_1(\tau_n)}$$

We thus proved that  $s_1(\tau_n) < s(\tau^T) < s_1(\tau_1)$ .

- (ii) Given that  $s(t)$  is decreasing over time,  $s(\tau^T) < s_1(\tau_1)$  implies that  $\tau^T > \tau_1$ . Furthermore, by Lemma B.1 strategies (i) and (ii) are equivalent for time  $t > \tau_n$ . This implies that  $\tau^T < \tau_n$  and hence,  $\tau^T \in [\tau_1, \tau_n]$

This completes the proof of this theorem. □

## Appendix C Generality of Theorem 1

One of the extensions to the standard *SIR* compartmental model, is the *SI<sup>n</sup>R* model with  $n$  different consecutive infectious stages. Let  $s(t)$  and  $r(t)$  denote the fraction of people respectively susceptible and

removed at time  $t$ . The fractions of people infected in every state are given by  $i_k(t)$  for  $k = 1, \dots, n$ . Interpretation dictates that  $s(t) + \sum_{k=1}^n i_k(t) + r(t) = 1$  for all  $t$ . Let  $\beta_k$  and  $\gamma_k$  denote respectively the transmission rate and recovery rate in infectious stage  $k$ . The differential equations for the  $SI^nR$  model are:

$$\begin{aligned}\frac{ds}{dt} &= -s \sum_{k=1}^n \beta_k i_k \\ \frac{di_1}{dt} &= s \sum_{k=1}^n \beta_k i_k - \gamma_1 i_1 \\ \frac{di_k}{dt} &= \gamma_{k-1} i_{k-1} - \gamma_k i_k \quad k = 2, \dots, n \\ \frac{dr}{dt} &= \gamma_n i_n\end{aligned}\tag{20}$$

Hyman, Li, and Stanley (1999) prove that  $R_0 = \sum_{k=1}^n \frac{\beta_k}{\gamma_k}$  for this model, with  $R_0$  denoting the basic reproduction ratio.

In (10) we present a relation between  $s(t)$  and  $i(t)$ . A similar relation can be derived for the  $SI^nR$  model (Appendix C of Duijzer et al., 2015):

$$\begin{aligned}\log(s(t)) - \log(s(0)) &= \sigma \left[ s(t) + \sum_{k=1}^n i_k(t) \right] - \sigma \left[ s(0) + \sum_{k=1}^n i_k(0) \right] \\ &\quad - \sum_{k=1}^n \frac{\beta_k}{\gamma_k} \left[ \sum_{m=k+1}^n i_m(t) - i_m(0) \right]\end{aligned}\tag{21}$$

Using (21) we can derive that the result of Theorem 1 also holds for the  $SI^nR$  model. The proof is identical, we only need to use an adjusted version of Lemma B.1. Next, we show how the result of this latter theorem carries over to the more general  $SI^nR$  epidemic model.

**Lemma C.1.** *For all  $k = 1, \dots, m$  we consider the following two systems, that both follow the dynamics of the  $SI^nR$  model. Note that (i) is a system with vaccination and (ii) a system without vaccination:*

(i) *let  $(s(t), i_1(t), \dots, i_n(t))$  for  $t \in (\tau_k, \tau_{k+1})$  denote the state at time  $t$  of the system with  $(s(0), i_1(0), \dots, i_n(0))$  as initial state for which a fraction  $f_j$  of the susceptible people is vaccinated at time  $\tau_j$  for  $j = 1, \dots, k$ .*

(ii) *let  $(s^k(t), i_1^k(t), \dots, i_n^k(t))$  correspond to a system without vaccination with  $s^k(0) = s_0 \cdot \prod_{j=1}^k \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right]$ ,  $i_1^k(0) = s(0) + i_1(0) - s_0^k$  and  $i_l^k(0) = i_l(0)$  for  $l = 2, \dots, n$ .*

*The time course of system (i) on the interval  $t \in (\tau_k, \tau_{k+1})$  is the same as time course of system (ii) on the shifted interval  $[t^*, t^* + \tau_{k+1} - \tau_k]$  for some  $t^*$ . More precisely,  $s^k(t) = s(t + t^* - \tau_k)$  and  $i_l^k(t) = i_l(t + t^* - \tau_k)$  for  $l = 1, \dots, n$  and  $\tau_k < t < \tau_{k+1}$ .*

*Proof.* The proof is analogous to the proof of Theorem 1, now only using the relation between  $s(t)$  and  $i_1(t), \dots, i_n(t)$  from (21) instead of the relation for the  $SIR$  model (10).  $\square$

## Appendix D Analytical results

### D.1 Pure strategies

In this section we derive the switching curve which is presented in Theorem 2. To prove this theorem, we propose a function that can be used to compare the two pure vaccination strategies. In the supporting result of Lemma D.1 we show how this function can be used to determine which strategy is best, i.e., which strategy results in the lowest final size. We define this function  $H(f_1, f_2, s_1, s_2)$  as follows:

$$H(f_1, f_2, s_1, s_2) = \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) [f_1 - f_2],$$

with  $G(f_1, \tau_1)$  denoting the herd effect for strategy 1. The following result can be derived:

**Lemma D.1.** *The sign of the function  $H(f_1, f_2, s_1, s_2)$  determines which strategy is best: if the function value equals zero, the two strategies are equally good and if the function value is positive (negative) strategy 1 is better (worse).*

*Proof.* We prove this theorem in the following three steps:

- (i) Strategy 1 and 2 are equally good if and only if  $H(f_1, f_2, s_1, s_2) = 0$ ,
- (ii) Strategy 1 is better than strategy 2 if and only if  $H(f_1, f_2, s_1, s_2) > 0$ ,
- (iii) Strategy 2 is better than strategy 1 if and only if  $H(f_1, f_2, s_1, s_2) < 0$ .

The proof is as follows:

(i)

$$\begin{aligned} Z(f_1, \tau_1) - Z(f_2, \tau_2) &= 0 \\ \Leftrightarrow G(f_1, \tau_1) + f_1 - G(f_2, \tau_2) - f_2 &= 0 \quad \text{substitute (3)} \\ \Leftrightarrow s_0 \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) \exp\{-\sigma Z(f_1, \tau_1)\} + f_1 - f_2 &= 0 \quad \text{substitute (12) and} \\ &\quad \text{use that } Z(f_1, \tau_1) = Z(f_2, \tau_2) \\ \Leftrightarrow \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) [f_1 - f_2] &= 0 \quad \text{substitute (12)} \end{aligned}$$

(ii) Observe that the condition  $H(f_1, f_2, s_1, s_2) = 0$  can equivalently be formulated as:

$$s_2 = \frac{s_1 f_2 G(f_1, \tau_1)}{f_1 G(f_1, \tau_1) + (s_1 - f_1)(f_2 - f_1)}$$

By Lemma A.1 we know that the final size  $Z(f, \tau)$  is monotonically decreasing in  $s(\tau)$ . Hence, if  $s_2$  is slightly lower than the expression above, then  $Z(f_2, \tau_2) > Z(f_1, \tau_1)$ .

$$s_2 < \frac{s_1 f_2 G(f_1, \tau_1)}{f_1 G(f_1, \tau_1) + (s_1 - f_1)(f_2 - f_1)} \Leftrightarrow H(f_1, f_2, s_1, s_2) > 0$$

(iii) Analogous to (ii). □

**Theorem 2.** *The pure strategies 1 and 2 result in the same final size under the following condition:*

$$s_2(\tau_2) = \frac{s_1(\tau_1) \varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right) (\varphi_2 - \varphi_1)} \quad (6)$$

If  $s_2(\tau_2)$  is smaller (larger) than the right-hand side in above expression, then strategy 2 is worse (better).

*Proof.* The results follows directly from Lemma D.1. □

**Corollary 3.** *The value for  $\tau_2$  that satisfies (6) is increasing in  $\varphi_2$ .*

*Proof.* We proof this result by taking the derivative of the switching curve (6) with respect to  $\varphi_2$ :

$$\frac{\partial}{\partial \varphi_2} s_2(\tau_2) = \frac{s_1(\tau_1) \varphi_1 G(f_1, \tau_1) \left[ G(f_1, \tau_1) - \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) \right]}{\left[ \varphi_1 G(f_1, \tau_1) + \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) (\varphi_2 - \varphi_1) \right]^2}$$

Above expression is negative, if  $G(f_1, \tau_1) < \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right)$  which means that the final fraction of people susceptible is smaller than the fraction of people susceptible just after vaccination. This holds, because the proportion of people susceptible is decreasing over time. Hence,  $s_2(\tau_2)$  is decreasing in  $\varphi_2$ . By the same argument this means that the value for  $\tau_2$  that satisfies (6) is increasing in  $\varphi_2$ . This completes the proof. □

## D.2 The hybrid strategy

In this section we analyze the hybrid strategy that consists of an early aspecific vaccine and a late specific vaccine. We respectively denote by strategy 1 and 2 the two pure strategies for the considered vaccine types. We start this section with Theorem 4 in which we derive under which condition the hybrid strategy outperforms strategy 1. We know that strategy 1 and 2 are equally good at the switching curve. Hence, if the condition derived in Theorem 4 holds at the switching curve, then the hybrid strategy is better than both pure strategies at the switching curve. We show in Lemma 5 that this is indeed the case. Before we prove this lemma, we first present two auxiliary results on the dynamics of the *SIR* model in Lemma D.2 and Lemma D.3.



In this section we use the following notation: strategy 3 denotes the hybrid strategy with  $V_1$  vaccines of type 1 and  $V - V_1$  vaccines of type 2, with  $V_1 \in (0, V)$ . In Table 2 we summarize the three strategies, and formulate the hybrid strategy in terms of a pure strategy by applying Theorem 1. We denote by  $s_i(t)$  the proportion of people susceptible at time  $t$  in strategy  $i = 1, 2, 3$ .

Strategy	$f$ at $\tau_1$	$f$ at $\tau_2$	$f_i$	$s_i$
1	$\frac{V\varphi_1}{N}$	0	$f_1 = \frac{V\varphi_1}{N}$	$s_1 = s_1(\tau_1)$
2	0	$\frac{V\varphi_2}{N}$	$f_2 = \frac{V\varphi_2}{N}$	$s_2 = s_2(\tau_2)$
3	$\frac{V_1\varphi_1}{N}$	$\frac{(V-V_1)\varphi_2}{N}$	$f_3 = \frac{V_1\varphi_1 + (V-V_1)\varphi_2}{N}$	$s_3 = \frac{f_3}{\frac{V_1\varphi_1}{Ns_1(\tau_1)} + \left(1 - \frac{V_1\varphi_1}{Ns_1}\right) \left(\frac{(V-V_1)\varphi_2}{Ns_3(\tau_2)}\right)}$

**Table 2:** This table describes the three vaccination strategies. The last two columns with  $f_i, s_i$  characterize the vaccination strategy by Theorem 1 with only one vaccination moment and the same final size.

**Theorem 4.** *Consider the pure strategy where all vaccines are of type 1. It is better to shift  $\epsilon$  vaccines to type 2, with  $\epsilon > 0$  small, under the following condition:*

$$\frac{\varphi_2}{\varphi_1} > \frac{[s_1(\tau_1^v) - G(f_1, \tau_1)] / s_1(\tau_1^v)}{[s_1(\tau_2) - G(f_1, \tau_1)] / s_1(\tau_2)}, \quad (7)$$

where  $s_1(\tau_1^v)$  denotes the proportion of people susceptible just after vaccination at time  $\tau_1$ .

*Proof.* In this proof we compare strategy 1 and strategy 3 of Table 2. These strategies are identical, and therefore equally good, in case  $V_1 = V$ . By Lemma D.1 the following condition holds if these strategies are equally good:

$$H(f_1, f_3, s_1, s_3) = \left(\frac{f_3}{s_3} - \frac{f_1}{s_1}\right) G(f_1, \tau_1) + \left(1 - \frac{f_1}{s_1}\right) [f_1 - f_3] = 0$$

We evaluate the derivative of  $H(f_1, f_3, s_1, s_3)$  with respect to  $V_1$  at the point  $V_1 = V$ . If this derivative is positive, then decreasing  $V_1$  results in a decrease of  $H(f_1, f_3, s_1, s_3)$ , rendering it negative and implying that  $\exists \epsilon > 0$  such that strategy 3 with  $V_1 = V - \epsilon$  is better than strategy 1 by Lemma D.1.

We now investigate this derivative with respect to  $V_1$ . Note that  $V_1$  only plays a role in strategy 3, such

that  $s_1, f_1$  and  $G_1(f_1, \tau_1)$  are not affected by changes in  $V_1$ . We use the following notation:  $s_3'(t) = \frac{\partial}{\partial V_1} s_3(t)$ .

$$\begin{aligned}
& \frac{\partial}{\partial V_1} H(f_1, f_3, s_1, s_3) \\
&= \frac{\partial}{\partial V_1} \left\{ \left( \frac{f_3}{s_3} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) [f_1 - f_3] \right\} \\
&= G(f_1, \tau_1) \frac{\partial}{\partial V_1} \frac{f_3}{s_3} - \left( 1 - \frac{f_1}{s_1} \right) \frac{\partial}{\partial V_1} f_3 \\
&= G(f_1, \tau_1) \frac{\partial}{\partial V_1} \left( \frac{V_1 \varphi_1}{N s_1} + \left( 1 - \frac{V_1 \varphi_1}{N s_1} \right) \left( \frac{(V - V_1) \varphi_2}{N s_3(\tau_2)} \right) \right) - \left( 1 - \frac{f_1}{s_1} \right) \frac{\partial}{\partial V_1} \frac{V_1 \varphi_1 + (V - V_1) \varphi_2}{N} \\
&= G(f_1, \tau_1) \left( \left( 1 - \frac{V_1 \varphi_1}{N s_1} \right) \left( \frac{(V - V_1) \varphi_2 N s_3'(\tau_2) - N s_3(\tau_2) \varphi_2}{N^2 s_3(\tau_2)^2} \right) + \frac{\varphi_1}{N s_1} \left( 1 - \frac{(V - V_1) \varphi_2}{N s_3(\tau_2)} \right) \right) \\
&\quad - \left( 1 - \frac{f_1}{s_1} \right) \frac{\varphi_1 - \varphi_2}{N}
\end{aligned}$$

We now evaluate the condition  $\frac{\partial}{\partial V_1} H(f_1, f_3, s_1, s_3)|_{V_1=V} > 0$  by substituting  $V_1 = V$  in above expression. For  $V_1 = V$  strategy 1 and 3 are identical, which implies that  $s_3(\tau_2) = s_1(\tau_2)$ .

$$\begin{aligned}
& \frac{\partial}{\partial V_1} H(f_1, f_3, s_1, s_3) &> 0 \\
\Leftrightarrow & G(f_1, \tau_1) \left( \frac{\varphi_1}{N s_1} + \left( 1 - \frac{V \varphi_1}{N s_1} \right) \left( \frac{-\varphi_2}{N s_1(\tau_2)} \right) \right) - \left( 1 - \frac{V \varphi_1}{N s_1} \right) \frac{\varphi_1 - \varphi_2}{N} &> 0 \\
\Leftrightarrow & \frac{G(f_1, \tau_1)}{N^2 s_1(\tau_2) s_1} (\varphi_1 N s_1(\tau_2) - \varphi_2 (N s_1 - V \varphi_1)) - \left( 1 - \frac{V \varphi_1}{N s_1} \right) \frac{\varphi_1 - \varphi_2}{N} &> 0
\end{aligned}$$

Let  $s_1(\tau_1^v)$  denote the proportion of people susceptible directly after vaccination, i.e.,  $s_1(\tau_1^v) = \left( s_1 - \frac{V \varphi_1}{N} \right)$ .

We substitute this expression and obtain the following:

$$\begin{aligned}
& G(f_1, \tau_1) (\varphi_1 s_1(\tau_2) - \varphi_2 s_1(\tau_1^v)) - s_1(\tau_2) s_1(\tau_1^v) (\varphi_1 - \varphi_2) &> 0 \\
\Leftrightarrow & \frac{[s_1(\tau_1^v) - G(f_1, \tau_1)] / s_1(\tau_1^v)}{[s_1(\tau_2) - G(f_1, \tau_1)] / s_1(\tau_2)} &< \frac{\varphi_2}{\varphi_1}
\end{aligned}$$

This completes the proof of this theorem. □

**Lemma D.2.** Consider two systems  $s_j(t)$  and  $i_j(t)$  for  $j = 1, 2$  and assume that they both follow the dynamics of the deterministic SIR model. If  $s_1(0) = (1 - f_1) s_2(0)$  and  $i_1(0) = i_2(0)$ , then  $s_1(t) > (1 - f_1) s_2(t)$  for all  $t > 0$ .

*Proof.* We proof this lemma as follows:

- At time 0 it holds that  $i_1(0) = i_2(0)$  and  $s_1(0) = (1 - f_1) s_2(0)$ .
- As long as  $s_1(t) < s_2(t)$  we can show that also  $i_1(t) < i_2(t)$  and that  $s_1(t) > (1 - f_1) s_2(t)$ .
- When  $s_1(t) \geq s_2(t)$  the lemma clearly holds.

- By Lemma D.3 the curves  $s_1(t)$  and  $s_2(t)$  intersect at most once. This proves the lemma for all  $t > 0$ .

It suffices to prove the claim in the second bullet point. We start with  $s_1(0) = (1-f)s_2(0)$  and  $i_1(0) = i_2(0)$ . Since  $s_1(0) < s_2(0)$  this implies that  $\frac{\partial}{\partial t}i_1 < \frac{\partial}{\partial t}i_2$ . Hence, as long as  $s_1(t) < s_2(t)$  we also have that  $i_1(t) < i_2(t)$ .

We prove the lemma by induction, using the following inductive step: if  $s_1(t) \geq (1-f_1)s_2(t)$  and  $i_1(t) < i_2(t)$ , then  $s_1(t+\epsilon) > (1-f_1)s_2(t+\epsilon)$ . We prove this step using the differential equations:

$$\begin{aligned} (1-f_1)s_2(t+\epsilon) &= (1-f_1)s_2(t)[1-\epsilon\beta i_2(t)] \\ &\leq s_1(t)[1-\epsilon\beta i_2(t)] \\ &< s_1(t)[1-\epsilon\beta i_1(t)] \\ &= s_1(t+\epsilon) \end{aligned}$$

Since the requirements for the inductive step are satisfied at  $t = \epsilon$ , the proof of the lemma is completed.  $\square$

**Lemma D.3.** *Consider two different initial states  $(s_0^j, i_0^j)$  for  $j = 1, 2$  and assume that  $s_j(t)$  and  $i_j(t)$  follow the dynamics of the deterministic SIR model. Then  $s_1(t) = s_2(t)$  for at most one  $t \in [0, \infty)$ . i.e., the curves for the proportion of people susceptible intersect at most once.*

*Proof.* Define the function  $H(x) = -x + \frac{1}{\sigma} \log(x)$ . Then the following can be derived from (10):

$$i(t) = H(s(t)) + i_0 - H(s_0)$$

When the curves for the proportion of people susceptible intersect, it holds that  $s_1(t) = s_2(t)$  and hence:

$$i_1(t) - i_2(t) = i_0^1 - i_0^2 + H(s_0^2) - H(s_0^1) \quad (22)$$

Observe that the right-hand side of above equation is a constant that only depends on the initial state. When two curves intersect, the derivative of the one must be larger than the other. Using the differential equations we find that:

$$\frac{\partial}{\partial t}s_2(t) - \frac{\partial}{\partial t}s_1(t) = -\beta i_2(t)s_2(t) + \beta i_1(t)s_1(t) = \beta s_1(t)(i_1(t) - i_2(t))$$

By contradiction assume that  $s_1(t)$  and  $s_2(t)$  intersect at both  $t_1$  and  $t_2$ , with  $t_1 < t_2$  W.l.o.g. let  $s_0^1 > s_0^2$ , such that  $s_1(t) > s_2(t)$  for  $t \in [0, t_1)$  and  $t > t_2$  and  $s_1(t) < s_2(t)$  for  $t \in (t_1, t_2)$ . Then at  $t_1$  the following must hold:

$$\left. \frac{\partial}{\partial t}s_2(t) \right|_{t=t_1} - \left. \frac{\partial}{\partial t}s_1(t) \right|_{t=t_1} > 0 \Leftrightarrow i_1(t_1) - i_2(t_1) > 0$$

If above condition is satisfied, the constant at the right-hand side of (22) must be positive. Now consider the intersection at  $t_2$ , where we need the following:

$$\left. \frac{\partial}{\partial t} s_2(t) \right|_{t=t_2} - \left. \frac{\partial}{\partial t} s_1(t) \right|_{t=t_2} < 0 \Leftrightarrow i_1(t_2) - i_2(t_2) < 0$$

This condition can only be satisfied if the right-hand side of (22) is negative. Since this right-hand side is a constant, it cannot be positive and negative at the same time. Hence, it is not possible to have two intersections. We arrive at a contradiction and conclude that the curves  $s_1(t)$  and  $s_2(t)$  can intersect at most once, which completes the proof of this lemma.  $\square$

**Lemma 5.** *At the indifference curve, when the two pure strategies are equally good, the hybrid strategy is strictly better and results in a lower final size.*

*Proof.* The outline of the proof is as follows:

- We use Lemma D.1 to find an expression for  $G(f_1, \tau_1)$  making use of the fact that the two pure strategies, strategy 1 and 2, are equally good.
- This expression for  $G(f_1, \tau_1)$  is substituted in the condition of Theorem 4 and we show that the resulting expression is positive.

By Lemma D.1 the following condition holds if strategy 1 and 2 are equally good:

$$\begin{aligned} & \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) (f_1 - f_2) = 0 \\ \Leftrightarrow & \frac{V}{N} \left[ \frac{\varphi_2}{s_2(\tau_2)} - \frac{\varphi_1}{s_1(\tau_1)} \right] G(f_1, \tau_1) + \frac{V}{N} \left( 1 - \frac{V\varphi_1}{s_1(\tau_1)N} \right) (\varphi_1 - \varphi_2) = 0 \\ \Leftrightarrow & G(f_1, \tau_1) = \frac{s_2(\tau_2)(N s_1(\tau_1) - V\varphi_1)(\varphi_2 - \varphi_1)}{N(s_1(\tau_1)\varphi_2 - s_2(\tau_2)\varphi_1)} \end{aligned}$$

We insert above expression for  $G(f_1, \tau_1)$  the second to last condition of Theorem 4 to show that the hybrid strategy is better.

$$\begin{aligned} & s_1(\tau_2) \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) (\varphi_2 - \varphi_1) + G_1(f_1, \tau_1) \left[ \varphi_1 s_1(\tau_2) - \varphi_2 \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) \right] > 0 \\ \Leftrightarrow & s_1(\tau_2) + \frac{s_2(\tau_2) \left[ \varphi_1 s_1(\tau_2) - \varphi_2 \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) \right]}{(s_1(\tau_1)\varphi_2 - s_2(\tau_2)\varphi_1)} > 0 \\ \Leftrightarrow & s_1(\tau_2)(s_1(\tau_1)\varphi_2 - s_2(\tau_2)\varphi_1) + s_2(\tau_2) \left[ \varphi_1 s_1(\tau_2) - \varphi_2 \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right) \right] > 0 \\ \Leftrightarrow & s_1(\tau_2) - s_2(\tau_2) \left( 1 - \frac{V\varphi_1}{N s_1(\tau_1)} \right) > 0 \end{aligned}$$

In the second step we substitute the expression for  $G(f_1, \tau_1)$ . To show that above condition holds, we apply Lemma D.2 and note that until  $\tau_1$  the two epidemics follow the same time course. Hence, the hybrid strategy with  $V_1 = V - \epsilon$  is better than the pure strategies. This completes the proof of this theorem.  $\square$

**Lemma 6.** *If the two pure strategies are equally good for vaccines of type 2 that become available at time  $T$ , then there exists a  $T^* > T$  such that it is optimal to shift  $\epsilon$  vaccines to type 2 when the vaccines of type 2 become available at time  $T^*$ .*

*Proof.* Observe that  $T$  and  $T^*$  are respectively characterized by (6) and (7). In both expressions the time is implicitly characterized via  $s_2(T)$  or  $s_1(T^*)$ . In condition (7) we used the following notation  $s_1(\tau_1^v)$  is the proportion of people susceptible just after vaccination at time  $\tau_1$ . i.e.,  $s_1(\tau_1^v) = \left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right)$ . Substituting this expression in (7) and rewriting gives the following:

$$s_1(T^*) = \frac{\left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right) \varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right) (\varphi_2 - \varphi_1)} = s_2(T) \left(1 - \frac{V\varphi_1}{N s_1(\tau_1)}\right) \quad (23)$$

The second equation is derived from (6). Note that  $s_1(\tau_1^v) = s_1(\tau_1) \left(1 - \frac{V\varphi_1}{s_1(\tau_1)N}\right)$  and  $s_2(\tau_1) = s_1(\tau_1)$ . By Lemma D.2 at time  $T$  it holds that  $s_1(T) > s_2(T) \left(1 - \frac{V\varphi_1}{N s_1(\tau_1)}\right)$ . Since the proportion of people susceptible is decreasing over time, this implies that  $T < T^*$ , which completes the proof.  $\square$

### D.3 Two vaccination campaigns

In Section 4.3 we describe two technologies that can be used for the production of vaccines for a vaccination campaign. The resulting vaccination campaigns have each  $n$  vaccination moments. To analyze the campaigns and the corresponding final sizes, we apply the result of Lemma B.1. Using the notation of that theorem, we have that  $f_i^T = \frac{\varphi_i B}{N}$  and  $1 - \frac{f_i^T}{s_i(\tau_i^T)} = \prod_{j=1}^n \left(1 - \frac{\varphi_j B}{s_j^i}\right)$  for  $i = 1, 2$ . We make use of expression (6) to derive the switching curve that compares two single-moment vaccination strategies. We use that  $f_j^i = \frac{\varphi_j B}{nN}$  for  $i = 1, \dots, n$ .

$$\begin{aligned} s_2(\tau_2^T) &= \frac{\varphi_2 G(\varphi_1, \tau_1)}{(\varphi_2 - \varphi_1) \prod_{j=1}^n \left(1 - \frac{f_j^1}{s_j^1}\right) + \left[1 - \prod_{j=1}^n \left(1 - \frac{f_j^1}{s_j^1}\right)\right] G(\varphi_1, \tau_1) \frac{N}{B}} \\ \Leftrightarrow \prod_{j=1}^n \left(1 - \frac{f_j^2}{s_j^2}\right) &= \left[1 - \frac{(\varphi_2 - \varphi_1)B}{NG(\varphi_1, \tau_1)}\right] \prod_{j=1}^n \left(1 - \frac{f_j^1}{s_j^1}\right) \\ \Leftrightarrow \prod_{j=1}^n \left(\frac{s_j^1}{s_j^2}\right) \left(\frac{s_j^2 - \frac{\varphi_2 B}{nN}}{s_j^1 - \frac{\varphi_1 B}{nN}}\right) &= 1 - \frac{(\varphi_2 - \varphi_1)B}{NG(\varphi_1, \tau_1)} \end{aligned}$$

In the second step, we substitute the expression for  $s_2(\tau_2^T)$ . The derivation above leads to condition (8), which is presented in Section 4.3.

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