The benefits of combining early aspecific vaccination with later specific vaccination

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Decision Support

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 should be administered as quickly as possible. However, during early stages of an outbreak the information on the disease is limited and delaying the intervention enables the design of a more tailored vaccination strategy. In this paper, we study the resulting trade-off between vaccination timing and an effective response strategy.

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 invest in both vaccine types to benefit both from an early response and from an effective 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. Our numerical experiments show that a hybrid strategy can reduce the number of infections by more than 50% compared to the best pure strategy. Such experiments also substantiate our restriction to two vaccine types.

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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 vaccination timing and an effective response strategy. 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 must make a trade-off between vaccination timing and an effective response strategy. Here are three examples of decisions that

need to be made in vaccine delivery where this trade-off plays a role:

1. The production of the annual influenza vaccine starts well before the influenza season. This implies that detailed knowledge about the characteristics of the annual influenza is missing and that it is difficult to design a good vaccine. Policy makers face a 'commit-or-defer' decision: they either decide on the vaccine composition early with little knowledge available, or they defer the decision to learn more about the coming influenza season (e.g., [Cho, 2010](#); [Kornish & Keeney, 2008](#)). The advantage of the commit decision is that the vaccines are available early. However, deferring could lead to vaccines with a higher efficacy. We discuss several decision models for this commit-or-defer decision in [Section 2](#).
2. Whereas outbreaks of annual influenza occur regularly, influenza pandemics are unexpected and occur irregularly. When confronted with such an unexpected pandemic, policy makers must determine how to respond. They can often choose among multiple vaccine types: vaccines with a high efficacy or those with a lower efficacy. The latter might seem worse, but might have a lower price, a shorter delivery time, or may be

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available in larger quantities. Our discussions with policy makers from the National Institute for Public Health and the Environment of the Netherlands revealed the practical relevance of this problem (private communication, Wallinga, 2016). For example, this problem played a role in the 2009 H1N1 influenza pandemic, where governments had to negotiate with pharmaceutical companies about ordering vaccines. The companies offered different types of vaccine, each with a different expected efficacy, a different (negotiable) price, and a different (negotiable) delivery date. [Nguyen and Carlson \(2016\)](#) study a related problem and vary the time at which vaccines become available and the stockpile size to determine the effects on the epidemic. In [Section 2](#), we discuss several studies that consider the timing of vaccination and the effect of the vaccination moment on the time course of the pandemic.

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 must decide how this vaccine stockpile should be allocated: they can either give a single dose to a large number of people, or two doses to half of the group ([Matrajt, Britton, Halloran, & Longini, 2015](#)). Practitioners also confirmed the practical relevance of studying this decision problem (private communication, Wallinga, 2016). For example, it played a role in the 2009 H1N1 influenza pandemic. In case of a pandemic, it is advised to administer two doses of vaccine. For seasonal influenza, a single dose is sufficient because most people have been infected with the same influenza subtype before. In 2009 it was unclear whether one or two doses were necessary because the H1N1 subtype had been circulating for a longer time, but the virus causing the outbreak was very different. In such a case it is likely that a single dose protects relatively well, but two doses protect better. It may not be obvious how timing of vaccination plays a role in this example. However, 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, revealing the same generic trade-off as for the other two types of decisions. However, this third decision problem has a few aspects that would need to be captured by making the following two additional assumptions. Firstly, the amount of vaccines allocated for the second dose cannot be larger than the amount of vaccines allocated for the first dose. Secondly, it is no longer possible to vaccinate people randomly with the second dose, because to benefit from the higher efficacy these people should have already received the first dose.

In this paper, we synthesize these 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, although example 3 requires some additional assumptions. We therefore leave it for future research to study how our results can be translated to example 3. In this article, we consider a policy maker who has a limited budget to fight an outbreak of an infectious disease. The budget can be spent on multiple vaccine types that differ in time of availability and in their efficacy. Most of our research focuses on a simple example with two vaccine types. Type 1 is an early aspecific vaccine with low efficacy and type 2 is a late specific vaccine with high efficacy. We analyze for which combinations of parameters (moment of availability, efficacy) type 1 is preferred over type 2. 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 invest in both vaccine types to benefit both from the early response and from the effective vaccine. Such a *hybrid strategy* has received little attention in the 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 a specific virus ([Homeland Security Council, 2006](#); [U.S. Department of Health & Human Services, 2005](#)).

Our main contribution in this paper is to formally propose and analyze 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 more effective 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. Our analysis of hybrid strategies contributes to three streams of literature (see [Section 2](#)). This is because our formulation generalizes examples 1–3 above.

We use a general epidemic model, the *SIR* model. This simple model forms the basis of many other epidemiological models, such as the *SEIR* model that is often used for influenza modeling ([Arino, Brauer, Van Den Driessche, Watmough, & Wu, 2008](#); [Coburn, Wagner, & Blower, 2009](#); [Weidemann et al., 2017](#)). We see our choice for a general epidemic model as complementary to more advanced parameterized models for a specific population (e.g., [Larson & Teytelman, 2012](#); [Matrajt & Longini Jr, 2010](#); [Medlock, Meyers, & Galvani, 2009](#); [Tuite, Fisman, Kwong, & Greer, 2010](#)) and detailed simulation models (e.g., [Ferguson et al., 2005](#); [2006](#)). Our choice of a general epidemic model enables us to generate insights and understanding *why* hybrid vaccination strategies can be optimal. We expect that these insights gained with the *SIR* model carry over to models that are more advanced, despite the potential differences in the time course of the epidemic predicted by our general model and by the more advanced models. In the literature it has been established that simple compartmental models can capture the important aspects of the time course of an epidemic ([Ajelli et al., 2010](#); [Bansal, Grenfell, & Meyers, 2007](#); [Silal, Little, Barnes, & White, 2016](#)), even though the details may be different from advanced models. Thus, it seems reasonable to suspect that higher level insights derived from the *SIR* model carry over to settings that are more complex. In addition, our results advocate for the inclusion of hybrid strategies in studies that evaluate and compare a limited number of vaccination strategies using advanced models (e.g., [Chowell, Viboud, Wang, Bertozzi, & Miller, 2009](#); [Matrajt et al., 2015](#)). Specifically, we show that the optimality of hybrid strategies does not depend on a practical motivation for such strategies, but that it is inherent to the non-linear dynamics of the time course of an epidemic.

In this paper, 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 which we also discuss various epidemic models. In [Section 3](#) we formally define the

vaccination problem. This problem is analyzed in [Section 4](#), in which 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 vaccination timing and an effective response strategy in three practical settings. We first examine the research on the annual influenza vaccine, then consider papers on the effects of timing of vaccination, and finally we look at the literature on optimal vaccine dosage. 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 \(2018a\)](#).

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’ in which the predicted 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 the authors recommend that the policy be continued.

[Kornish and Keeney \(2008\)](#) study when it is beneficial to defer the decision on the vaccine composition to buy time to gather more information about the coming influenza season. Deferring reduces uncertainty and can lead to better decisions on which strains to include in the vaccine. However, delaying can reduce 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, they mention the disadvantage of delaying 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 that the new strain is only added to the vaccines subsequently produced. This solution can be seen as some kind of hybrid strategy, but the authors do not formally analyze the strategy. [Cho \(2010\)](#) extends the work of [Kornish and Keeney \(2008\)](#) by including production yield uncertainties. Decision makers must decide on retaining the current vaccine or shifting to updated compositions. The latter may have more production yield uncertainty. The author proposes a discrete time model 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. [Özaltın, 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 was infected by a certain influenza strain. They formulate a multi-stage stochastic mixed integer model 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.

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 decides either to commit or to defer. A hybrid strategy, in which the decision maker commits for part of the budget and defers for the remaining part has not been analyzed, except in a 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 available stockpiles. Their results show how vaccine stockpile size and the moment at which this stockpile becomes available affect the optimal allocation over 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 briefly 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 cities.

[Teytelman and Larson \(2013\)](#) study the case in which vaccines that become available at multiple times should be allocated among several regions. This problem setting automatically results in a hybrid vaccination strategy. The authors propose a dynamic approach that uses the most recent information on the epidemic to determine the vaccine allocation for the remaining time. Their *telescope-to-the-future* algorithm cleverly incorporates the future trajectory of the epidemic and in this way avoids myopic decision making. They use data from the 2009 H1N1 outbreak in the US to demonstrate that their vaccination strategy outperforms the CDC policy of pro-rata vaccination. [Finkelstein, Larson, Nigmatulina, and Teytelman \(2015\)](#) discuss vaccination strategies and discuss the findings of [Teytelman and Larson \(2013\)](#). [Finkelstein et al. \(2015\)](#) emphasize the importance of taking into account the status of the influenza wave when determining vaccine allocations. They argue that it is better to allocate vaccines to regions that are early in the flu wave instead of allocating vaccines pro-rata to regions.

[Yarmand, Ivy, Denton, and Lloyd \(2014\)](#) study a two-phase allocation problem with minimum required vaccination levels in each phase, in which 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. In contrast, [Nguyen and Carlson \(2016\)](#) consider only one vaccination moment, but they vary the time at which the vaccines become available. The authors compare vaccination strategies that differ in when and how many vaccines become available. They use deterministic and stochastic models and numerically determine the optimal allocation for two coupled populations. 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 and 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. [Wood, McCaw, Becker, Nolan, and MacIntyre \(2009\)](#) find similar results and 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. They show that this threshold can be analytically characterized for pre-pandemic vaccination and find numerical and simulation results for reactive vaccination.

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 of giving health care workers a higher dosage than the remainder of the population, but they do not analyze this strategy. This strategy can be seen as a hybrid strategy which is advocated in the current paper.

Model. We make use of the *SIR* model, which is a seminal model in epidemiology proposed by Kermack and McKendrick (1927). The *SIR* model that we use is a deterministic compartmental model. Alternatively, there are studies that consider stochastic epidemic models (e.g., Nguyen & Carlson, 2016; Wu, Riley, & Leung, 2007). Stochastic models differ from deterministic models mainly in their asymptotic dynamics. There can be endemic equilibria in deterministic models, but in stochastic models any epidemic will eventually die out (Allen, 2008). In addition, in deterministic models there are certain conditions under which an outbreak will always affect a large proportion of the population, but in stochastic models there is always a probability that the outbreak will remain minor (Diekmann, Heesterbeek, & Britton, 2013). For large populations, the dynamics of stochastic and deterministic models are approximately the same. Bortolussi and Hillston (2013) have made this result rigorous using a fluid approximation.

The *SIR* model consists of three compartments: people are either susceptible, infected or recovered. This general compartmental model forms the basis of many other epidemic models (Dimitrov & Meyers, 2010). One extension of the *SIR* model is to include an additional latent compartment with people who are infected, but not yet infectious. This extension results in the *SEIR* model that is often used to model influenza (cf. Arino et al., 2008; Coburn et al., 2009; Weidemann et al., 2017). Compartmental models are based on the assumption that all individuals in a compartment are identical. This assumption is no longer valid if subgroups in the population differ substantially in terms of transmission, recovery or vaccine response. This is for example the case when geography plays an important role in the transmission or when the efficacy of the vaccine differs in subgroups. To account for this heterogeneity, some studies use heterogeneous compartmental models that stratify the population based on age (e.g., Chowell et al., 2009; Matrajt & Longini Jr, 2010; Medlock et al., 2009; Tuite et al., 2010) or geography (e.g., Larson & Teytelman, 2012; Nguyen & Carlson, 2016). Other studies model the individuals in a population in detail by applying individual-based or agent-based modelling techniques for influenza outbreaks (e.g., Chao, Halloran, Obenchain, & Longini Jr, 2010; Ferguson et al., 2005).

The analytical description of the *SIR* model enables us to derive structural insights into optimal vaccination strategies. A similar analytical approach is used by Matrajt et al. (2015) and Duijzer, van Jaarsveld, Wallinga, and Dekker (2018b). Alternatively, models that are more detailed can be used for deriving case-specific numerical results. These models can incorporate data on previous outbreaks or on contact patterns in specific countries (e.g., Chowell et al., 2009; Larson & Teytelman, 2012; Matrajt & Longini Jr, 2010; Medlock et al., 2009; Tuite et al., 2010). These detailed models can capture many realistic aspects of the transmission process, but are more difficult to analyze. Papers that use such models therefore often rely on numerical evaluation of vaccination strategies (e.g., Medlock et al., 2009; Nguyen & Carlson, 2016) or on scenario analysis (e.g., Chowell et al., 2009; Tuite et al., 2010). We see our analytical model and approach as complementary to the more detailed

models. The structural results that can be derived analytically enable us to gain insights into certain situations. These insights can also be valuable when using detailed models to analyze vaccination strategies.

We now relate our modeling choices to current literature. As our problem incorporates the effect of timing of vaccination, we allow for vaccination during an outbreak (see also Chowell et al., 2009; Matrajt & Longini Jr, 2010; Medlock et al., 2009; Tuite et al., 2010). Alternatively, some studies 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 et al., 2007). To evaluate the effects of 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_0 , which is related to the initial growth of infections (Diekmann et al., 2013). Some studies 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 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 commonly used in epidemiology and is 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. Since the duration of an epidemic is short compared to the life of an individual, we can assume that the population size remains constant (Kermack & McKendrick, 1927). This implies 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 recovery rate denoted by β and γ , 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 $s_0 + i_0 + r_0 = 1$. Fig. 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

Table 3.1
List of parameters.

Parameter	Explanation	Value	Source
γ	Recovery rate	0.25	Matrajt et al. (2015)
σ	Reproduction ratio	1.4	Coburn et al. (2009) Matrajt et al. (2015)
β	Transmission rate	0.35	follows from γ and σ
i_0	Proportion of initially infected people	10^{-6}	Matrajt et al. (2015)
N	Population size	10^6	Matrajt et al. (2015)
τ_j	Time at which vaccines become available	[0, 90]	Matrajt et al. (2015)
p_j	Price per dose of vaccine	1	by assumption
ϕ_j	Efficacy of vaccine	[0.4, 0.7]	Basta et al. (2008) Matrajt et al. (2015)
φ_j	Efficacy per dollar	[0.4, 0.7]	follows from p_j and ϕ_j
B	Budget available for vaccines	$\frac{p_j N}{2}$	Matrajt et al. (2015)

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 that the number of infected initially increases until it reaches 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 decreases.

3.2. Problem description

Vaccination reduces the fraction of susceptible individuals 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. In addition, unvaccinated people indirectly benefit from the vaccination of others, as it reduces their disease exposure. This indirect effect of vaccination is known as the *herd immunity effect* (Fine, 1993). In the remainder of this paper, we use the term ‘herd effect’ for brevity.

Consider a decision maker who has an available budget to purchase the 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 (ϕ_j), and the time at which the vaccine becomes available (τ_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 who will be immune after vaccination. We assume that all vaccines can be quickly distributed as soon as they are available. The budget available for vaccines is denoted by B . The policy maker's goal is to divide this budget over the vaccine types in such a way that as few people as possible will be infected during the outbreak.

Table 3.1 presents an overview of the parameters that we use in this paper.

The effect of vaccination on the epidemic is illustrated in Fig. 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. This means that 6% of the population is effectively vaccinated at time 10. Another 100,000 people are vaccinated at time 100 with a vaccine that has efficacy 0.7, which results in 7% of the population becoming immune through vaccination at time 100. If we compare Figs. 1 and 2, we see that vaccination lowers the peak of infected individuals. In addition, 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%.

Fig. 1. Illustration of the deterministic SIR model with parameters $\gamma = 0.25$, $\beta = 0.35$, $i_0 = 10^{-6}$ and $s_0 = 1 - i_0$ (Matrajt et al., 2015).

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

3.3. Vaccination

To define vaccination formally, we introduce the following notation. Denote by B_j the budget allocated to type j vaccines. Furthermore, let $\varphi_j = \frac{\phi_j}{p_j}$ be the efficacy per dollar for type j vaccines which are available at τ_j . The vaccines are administered to susceptible individuals. We assume that these can be identified. Thus, the fraction of people no longer susceptible and immune due to allocating B_j to type j vaccines 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 τ_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 modeling vaccination (e.g., Bansal, Pourbohloul, & Meyers, 2006; Hill & Longini Jr, 2003; Mylius, Hagenaaars, Lagnér, & Wallinga, 2008).

To compare multiple vaccination strategies, we consider the state of the system when $t \rightarrow \infty$. This state is also referred to

Fig. 2. Illustration of vaccination in the deterministic SIR model with vaccination, with parameters $\gamma = 0.25$, $\beta = 0.35$, $i_0 = 10^{-6}$ and $s_0 = 1 - i_0$ (Matrajt et al., 2015). For the situation without vaccination we refer to Fig. 1.

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 Eq. (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*. For details see Appendix A. $G(\mathbf{f}, \tau)$ quantifies the so-called *herd (immunity) effect* which is the indirect effect of vaccination when unvaccinated people benefit from the vaccination of others. We refer to Duijzer et al. (2018b) 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 (cf. Diekmann et al., 2013). 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 Eq. (3) determines the proportion of people who 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 modeling vaccination in the SIR model, we refer to Duijzer et al. (2018b).

3.4. Optimization problem

In this section, we formally define our decision problem. Recall that we consider a decision maker with a budget B to purchase vaccine types in J to minimize the final size of the outbreak. Using the notation that was introduced in Section 3.3, the optimization

problem can be formulated as follows:

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

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 ensures that the quantity of vaccines is non-negative.

4. Analytical results

In this section, we study the optimization problem of Section 3.4 and compare multiple vaccination strategies. In Section 4.1, we show 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 allocated to one vaccine type, and we consider hybrid strategies in which 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. Finally, in Section 4.4 we derive some results for the case that vaccine efficacy is stochastic.

4.1. Characterizing hybrid vaccination strategies

Hybrid vaccination strategies are difficult to compare, because they differ both in times at which people are vaccinated and in the proportion of the population vaccinated at these times. To simplify the comparison, we show how a single moment strategy is constructed for each hybrid 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 in 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 τ^T and a vaccination fraction $f^T = \sum_{j=1}^n f_j$ if and only if τ^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 Eq. (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 τ^T . Although the existence of τ^T may be intuitive, its characterization in Eq. (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.

Condition (5) that characterizes $s_{(ii)}(\tau^T)$ has the following interpretation. Upon vaccination at time τ_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 τ^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 τ^T allows us to compare multiple hybrid strategies with each other and with pure strategies. To compute the actual value for τ^T , we numerically evaluate the differential equations in (1) to determine at which time the proportion of susceptible people equals $s_{(ii)}(\tau^T)$.

Note that we compare vaccination strategies only in terms of their final size. This implies that the two vaccination strategies in Theorem 1 are only equivalent in this respect. They can differ in terms of other measures such as the initial growth of infections, the time at which infections reach their peak, or the duration of the outbreak.

In Appendix C, we show that the result of Theorem 1 also holds for a more general epidemic model, namely the S^{mR} model with n consecutive infectious stages. The S^{mR} model can incorporate a latent period or multiple levels of infectivity (Ma & Earn, 2006). A special type of the S^{mR} model is the SEIR model, which is often used for modeling influenza outbreaks (Arino et al., 2008; Coburn et al., 2009; Weidemann et al., 2017). 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 budget to purchase these two vaccine types. We first consider strategies in which all the 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 φ_j and τ_j for $j = 1, 2$. Type 1 vaccines are available early, but have a low efficacy per dollar. Type 2 vaccines are available at a later point in time, but have 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 type 2 vaccines are available very early, i.e., just after τ_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 τ_2 . On the other hand, if type 2 vaccines 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 who would not have become infected anyway. Thus, if 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 it 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, τ_2 is implicitly defined through $s_j(\tau_2)$, with $s_j(t)$ denoting the proportion of people susceptible at time t in vaccination strategy j . The proof of this theorem can be found in Appendix D.

Theorem 2. *There exists a time $\tau^* > \tau_1$ such that:*

- (a) *strategy 1 outperforms strategy 2 if $\tau_2 > \tau^*$,*
- (b) *strategy 2 outperforms strategy 1 if $\tau_2 < \tau^*$,*
- (c) *strategy 1 and strategy 2 have equal performance $\tau_2 = \tau^*$.*

Moreover, τ^* can implicitly be characterized with the following expression:

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

Theorem 2 confirms our finding that strategy 2 is worse if the type 2 vaccines 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 vaccine types that are available at an earlier time and have a higher efficacy always dominate later available vaccine types with a lower efficacy per dollar. 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 type 1 vaccines, then there are not many new infections after τ_1 , and $G(f_1, \tau_1)$ is only slightly smaller than $\left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)$. In that case, type 2 vaccines can only be preferred if τ_2 is very close to τ_1 by Eq. (6).

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

Corollary 3. *The value for τ_2 that satisfies Eq. (6) is increasing in φ_2 .*

We illustrate the switching curve for two vaccination strategies in Fig. 3. We can compute τ_2 easily from Eq. (6) by numerical evaluation of the differential equations (1). The parameters for this figure are as follows: $B/N = 0.5$ and $\beta = 0.35$, $\gamma = 0.25$. Both vaccines cost 1 dollar per dose. Type 1 vaccines have an 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 Eq. (6) to determine the relation between $s_2(\tau_2)$ and φ_2 and we evaluate the differential equations to derive τ_2 from $s_2(\tau_2)$. The figure shows the same structure as described before. We also see that vaccines that 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 were analyzed in the previous section, we can also consider hybrid strategies. In hybrid strategies, part of the budget is allocated to type 1 vaccines, the other part to type 2 vaccines. Intuitively one might think that one of the vaccine types is better than the other, such that only a pure

Fig. 3. Illustration of the switching curve for different parameter values of vaccine type 2. In the white area, strategy 1 results in the lowest final size and is therefore the best. In the dark area, strategy 2 results in the lowest final size.

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 τ_2 high, such that it is best to spend the entire budget on type 1 vaccines. By advancing the availability of type 2, we will reach a point at which these vaccines are so attractive, that it is no longer optimal to spend the entire budget on type 1 vaccines. 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 in which all vaccines are of type 1. It is better to shift some vaccines to type 2 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 τ_1 .

In [Section 5](#), we numerically analyze hybrid strategies. There we see that it can be optimal to shift a substantial part of the budget to type 2 vaccines. By allocating part of the budget to type 1 vaccines, and part to type 2 vaccines, the population can benefit from the advantages of both vaccine types. The early vaccination with type 1 reduces the initial growth in infections, and the high efficacy per dollar of type 2 results in many people achieving immunity due to vaccination. Such a hybrid strategy is only beneficial if the epidemic is ongoing when type 2 vaccines 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 τ_1 that occurs while waiting for the type 2 vaccines, i.e., in the interval $[\tau_1, \tau_2]$. This proportion is an indication of the additional infections if the decision maker decides to wait for type 2 vaccines. 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 type 2 vaccines 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 will be worth waiting for this better vaccine.

Fig. 4. This figure illustrates the optimal strategy. In the white area, strategy 1 results in the lowest final size and is therefore the best. In the dark area, strategy 2 results in the lowest final size. The dashed area between the two dashed lines is the region in which a hybrid strategy is optimal. The solid curve represents the switching curve from [Fig. 3](#).

One could argue that if the decision maker should shift ϵ vaccines from type 1 to type 2, why not allocate the entire budget to type 2 vaccines? There are two main reasons why this would not result in a good strategy. Firstly, type 2 vaccines are available at a later point in time. By using only these vaccines, the epidemic can spread freely until τ_2 , which might cause many infections. The second reason is related to type 2's high efficacy per dollar 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 fewer vaccines. Allocating the entire budget to type 2 vaccines results in vaccinated people who would not have become infected in the first place. These vaccines are not used effectively. It would be better to allocate part of the budget to reducing the initial growth by vaccinating some people at τ_1 , such that the epidemic can be controlled at τ_2 by allocating the rest of the budget to type 2 vaccines. The following two theorems formally describe the relation between pure and hybrid strategies:

Theorem 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.

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

The interpretation of [Theorem 6](#) is that while advancing the availability of type 2, you will first reach the point where it is optimal to shift some of the budget to type 2 before reaching 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 type 2 vaccines in a hybrid strategy. [Theorem 5](#) confirms that the hybrid strategy is optimal around the switching curve. The structure described by these two theorems is also illustrated in [Fig. 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 [Fig. 4](#). If pure strategy 1 is optimal for some τ_2 , it is also optimal when the type 2 vaccines are available even later. Delaying the availability of type 2 results in even more infections while waiting for this type. These additional infections are not outweighed by the gain in efficacy per dollar. Analogously, pure strategy 2 will remain optimal if τ_2 is reduced. The reduced waiting time results in fewer infections, so the gain

Fig. 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 efficacy per dollar will surely compensate. In addition, if τ_2 is smaller, more people will be susceptible when the type 2 vaccines become available, such that more vaccines will be needed to control the epidemic at τ_2 . This implies that there is no incentive to reduce the vaccination fraction at τ_2 by shifting some vaccines to type 1. We also see that by increasing φ_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 φ_2 , pure strategy 2 is no longer optimal, because the type 2 vaccines became so efficacious that allocating the entire budget to these vaccines would lead to vaccinating people who 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 allocating the budget to both types of vaccine if the two are equally attractive. Clearly, if one vaccine type avoids many more infections than the other, this type should be used. However, if the two types are comparable, our results show that it will be 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.

In the final part of this section, we analyze the effects of an increasing budget in Fig. 5. The figure shows that for small budgets, the optimal strategy is to order only the vaccines with the highest efficacy per dollar. In these 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. With a sufficiently large budget, the epidemic can already be controlled at τ_1 , and the optimal strategy is to use only the type 1 vaccines.

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). In addition, the production of vac-

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

cine 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 that differ in 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 φ_i and τ_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 allocated 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 will be better (worse). The derivation of this condition can be found in Appendix D and makes use of Theorem 1. Note that condition 8 implicitly defines the relation between τ_2 and φ_2 , as s_j^2 for all j depend on τ_2 . We can compute this relation through numerical analysis. Fig. 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 τ_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 could change. For example, the advantage of an early aspecific vaccine type might disappear if it is distributed through a lengthy vaccination campaign.

4.4. Stochastic efficacy

In the previous sections, we assumed that the vaccine efficacy of all vaccine types is known. However, if later availability of a vaccine is caused by delaying production to learn more about the disease and develop a better vaccine, the gain in efficacy that is obtained through waiting is unknown in advance. This is, for example, the case with the commit-or-defer decision of the annual influenza vaccine. In this section, we therefore study the case that the type 2 vaccines have a stochastic efficacy per dollar Φ_2 with a cumulative distribution function $F(\varphi_2)$. We assume that vaccine type 1 is available at time 0 and has a known efficacy per dollar φ_1 and that type 2 will become available at time τ_2 . We include the possibility that the realized efficacy per dollar of type 2 is below φ_1 , because the setting of our problem is such that the decision maker orders vaccines in advance. Even if the type 2 vaccines would be worse than the type 1 vaccines, the order for type 2 is already placed and it is not possible to resort to type 1.

Note that the curves in Figs. 3 and 4 are quite flat. This indicates that the optimal vaccination strategy is not very sensitive to the exact value of Φ_2 . For a fixed value of τ_2 , there is often quite a broad range of values for Φ_2 that result in the same optimal vaccination strategy. Based on this, we conjecture that the structure of our main results continues to hold under stochastic efficacy. In this section, we study to what extent our conjecture is true. More precisely, we study whether there is still a switching curve between the two pure strategies and whether a hybrid vaccination strategy can still be optimal. We find an analytical result that extends the switching curve between the two pure strategies and we present numerical results for the analysis of hybrid vaccination strategies.

To derive a switching curve similar to the result in Theorem 2, we introduce the following notation. Let $Z(f_1, \tau_1)$ denote the final size after using type 1 vaccine. Denote by $Z(f_2(\Phi_2), \tau_2)$ the final size that is the result of vaccination with type 2, such that a fraction $f_2(\Phi_2) = \frac{\Phi_2 B}{N}$ of the population is effectively vaccinated at time τ_2 . By rewriting Eq. (6) we extend Theorem 2 as follows:

Theorem 7. *The probability that strategy 2 outperforms strategy 1 in terms of the final size is equal to:*

$$\begin{aligned} P(Z(f_2(\Phi_2), \tau_2) < Z(f_1, \tau_1)) \\ &= P\left(\Phi_2 > \frac{s_2(\tau_2)\varphi_1[G(f_1, \tau_1) - (s_1(\tau_1) - \frac{\varphi_1 B}{N})]}{G_1(f_1, \tau_1) - s_2(\tau_2)(s_1(\tau_1) - \frac{\varphi_1 B}{N})}\right) \\ &= 1 - F\left(\frac{s_2(\tau_2)\varphi_1[G(f_1, \tau_1) - (s_1(\tau_1) - \frac{\varphi_1 B}{N})]}{G_1(f_1, \tau_1) - s_2(\tau_2)(s_1(\tau_1) - \frac{\varphi_1 B}{N})}\right). \end{aligned} \quad (9)$$

A decision maker can use the above expression to estimate the probability that waiting for the second vaccine will result in a lower final size. In practice, a decision maker probably does not know the complete probability distribution for the efficacy of the second vaccine, but an approximation can be used to estimate whether it is better to wait or to order the existing vaccine.

We now study hybrid strategies. For computational reasons we do not analyze all possible divisions of the budget B over the two vaccine types, but only the following splits (0%, 100%), (10%, 90%), (20%, 80%), ..., (90%, 10%), (100%, 0%). We determine the final size for these strategies for all combinations of $\tau_2 \in [0, 5, 10, \dots, 400]$ and $a \in [0, 0.02, 0.04, \dots, 1]$. We assume that $\Phi_2 \sim U(a - w, a + w)$ with the mean and half width denoted by a and w respectively. In our analysis we vary the mean a . We motivate our choice for w from the literature. Basta, Halloran, Matrajt, and Longini Jr (2008) analyze the efficacy of influenza vaccine on susceptibility and find a 95% confidence interval with a half width of 0.25. To guarantee that the efficacy Φ_2 always lies in the interval [0,1], we let $w = \min\{a, 1 - a, 0.25\}$. In Fig. 7, we display the strategy that

minimizes the expected number of infections for a range of parameters. Fig. 8 shows the probability that each strategy is, in hindsight, optimal.

Figs. 7 and 8 provide evidence of our conjecture that the introduced stochasticity does not change the structure of our results. Both figures resemble the shape of the curves in Fig. 4. If we compare Figs. 4 and 7 to analyze the effects of increasing uncertainty by changing w from 0 to 0.125, we observe that the area where pure strategy 2 is optimal increases for $a \in [0.6, 0.7]$. The probability that Φ_2 is higher than a is worth the risk of using a pure strategy with only this second vaccine type. When the uncertainty around a increases even more and w increases to 0.25, we observe that the area in which the hybrid strategy is optimal increases. For small values of a , $P(\Phi_2 < \varphi_1)$ is large. In those cases, a hybrid strategy can be a way to reduce the risk of the uncertain efficacy. By using the type 1 vaccine early in the epidemic, the population receives a certain level of protection even if the efficacy of vaccine type 2 were to be disappointing.

Alternatively, the decision maker could try to transfer part of the risk to the supplier by negotiating a contract in which the price per vaccine depends on the achieved efficacy. This would reduce the uncertainty in Φ_2 , but this is beyond the scope of this paper.

5. Numerical experiments: the value of hybrid strategies

In this section, we perform some more 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 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 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 vaccine prices 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 $B = pN/2$. Indeed, note that Fig. 5 shows that a budget sufficient to vaccinate half of the population lies in the region where hybrid strategies can be optimal. 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 $p = 1$:

Type	1	2	3	4	5	6	7
τ_j	0	45	60	60	75	75	90
φ_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 that 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 must choose between type 4 and type 5 vaccines, she will always prefer type 4 vaccines because they are available earlier and have the same efficacy per dollar. Analogously, type 6 will always be preferred to type 5, 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 two types, and the best hy-

Fig. 7. This figure illustrates the strategy that minimizes the expected number of infections with Φ_2 following a uniform distribution on the interval $[a - w, a + w]$. We vary the uncertainty w : $w = \min\{a, 1 - a, 0.125\}$ (left) and $w = \min\{a, 1 - a, 0.25\}$ (right). In the white area, strategy 1 results in the lowest final size and is therefore the best. In the dark area, strategy 2 results in the lowest final size. The dashed area between the two dashed lines is the region in which a hybrid strategy is optimal. The parameters for the type 1 vaccines are $\tau_1 = 0$, $\varphi_1 = 0.4$.

Fig. 8. This figure provides an analysis of the pure and hybrid strategies with $\Phi_2 \sim U(a - w, a + w)$ with $w = \min\{a, 1 - a, 0.25\}$. The contour plots present the probability that each strategy is optimal in hindsight. The parameters for type 1 vaccines are $\tau_1 = 0$, $\varphi_1 = 0.4$. For a given combination of τ_2 and a , the figures give the probability (because of Φ_2 being uncertain) that a strategy is optimal by comparing the point with the closest contour line.

brid strategy with at most three types. Note that the pure strategies are also included in the hybrid strategies. For the hybrid strategies, we use enumeration and a stepsize of $1,000 = 10^{-3}N$ vaccines. The results are reported in Table 5.1. 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.

We start by discussing the column on hybrid strategies with at most two vaccine types in Table 5.1. The results show that a hybrid strategy is preferred in most cases. 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. The final size of the best hybrid strategy

is the same as the final size of the best pure strategy for a few vaccine type combinations. This implies that the pure strategy is optimal in these cases. We conclude from Table 5.1 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 5.1 and compare hybrid strategies with at most two types and those with at most three vaccine types, the final sizes will be the same for all subsets of vaccine types. The additional freedom that is introduced by allocating the budget over three vaccine types does not reduce 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 few additional benefits.

In this section, we do not analyze hybrid strategies with more than three vaccine types. Nevertheless, we can draw conclusions

Table 5.1

Table with the final sizes achieved with the vaccination strategies. For the hybrid strategies, we present the final size relative to the pure strategy. 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 at most two and at most three vaccine types are the same.

	Pure strategy		Hybrid with at most two types		Hybrid with at most three types*
	Final size	Allocation	Relative final size	Allocation	Relative final size
Types 1, 2, 4	0.0140	(0, 0, 500)	100	dominated	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)	39.19
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	dominated	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	dominated	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	dominated	100

for these situations. Consider a hybrid vaccination strategy with n vaccine types. By applying [Theorem 1](#) to types $3, \dots, n$ 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 among 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.

6. Discussion

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

The results in this paper are established under some assumptions. We assume that the disease parameters do not change over time, because we consider vaccination as the only intervention. We do not consider non-pharmaceutical interventions, such as social distancing measures or hygiene measures, which would likely have an effect on the transmission parameters. Further research is needed to investigate how our results carry over to situations where parameters change over time. A potential direction is to adjust the vaccination strategy when new information that indicates that the parameters have changed, becomes available (cf. [Teytelman & Larson, 2013](#)).

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 modeled as a vaccination campaign (cf. [Section 4.3](#)). We first assume that the vaccine efficacy is known for every vaccine type, but we extend our results to the case that the efficacy of the second vaccine type is uncertain. This could be the case in situations where the delayed availability is caused by a vaccine development phase with unknown outcome. We show that there still is a wide range of parameters for which hybrid vaccination strategies are optimal when the efficacy is unknown. Using a hybrid vaccination strategy even seems to be a good way to reduce the uncertainty caused by the unknown efficacy.

We base our analysis on the *SIR* model, but show in [Appendix C](#) how some results extend to the more general *SIR* 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 et al., 2009](#); [Teytelman & Larson, 2012](#)). Instead of considering only age groups, it is also interesting to incorporate high-risk and high-transmission groups (e.g., [Lee et al., 2015](#); [Samii, Pibernik, Yadav, & Vereecken, 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 in which a pure type 1 strategy is optimal from the region where a pure type 2 strategy is optimal. Making the type 2 vaccines 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.

We show that hybrid strategies can be beneficial in the *SIR* model, and explain this intuitively: (1) early vaccination is used to buy time by reducing the rate of exponential growth in infections at the start of the epidemic and (2) late vaccination is used to eradicate the disease. We conjecture that this intuitive explanation for the benefit of hybrid vaccination is general, and not only valid for the *SIR* model. This conjecture is based on the following observations from the literature. In general, it has been shown repeatedly that simple models, such as the *SIR* model, can capture structures in the time course of the epidemic that hold in general ([Chick, 2007](#); [Silal et al., 2016](#)). Such structures include an initial exponential growth of infections, a flattening of the growth and extinction over time, and the fact that not all susceptible individuals will become infected. Other studies have shown that simple differential equation models and advanced models, such as agent-based simulation models and network models, harmonize quite well ([Ajelli et al., 2010](#); [Bansal et al., 2007](#)). Finally, the policy advice derived from these two modeling approaches are comparable, despite differences in the predictions of the time course of the epidemic ([Rahmandad & Sterman, 2008](#); [White et al., 2009](#)). One particular reason why we believe that our hybrid strategy will work well outside of the *SIR* model context is that the initial exponential growth of infections is observed across a wide range of epidemic models, including detailed simulation models. And our qualitative explanation for the value of the hybrid policies is based on precisely this exponential growth of infections. In conclusion, we

expect that hybrid vaccination strategies may be valuable under a wide range of modeling assumptions.

7. Conclusions

In this paper, we study the trade-off between vaccination timing and an effective response strategy. 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 allocate the entire budget to one of the two vaccine types but that a hybrid strategy can reduce the final size by 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 can 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. If the epidemic can be controlled with the early aspecific vaccine, the decision maker should use only this vaccine. However, if this is not possible, 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 an efficacious vaccine. Such a solution can also be helpful for decision makers who balance between public pressure to respond quickly and the aim to allocate the budget to the best possible vaccine.

Extant literature mentions some practical considerations for using hybrid strategies (e.g., Kornish & Keeney, 2008; Riley et al., 2007). For example, starting production earlier for some influenza strains allows for sufficient time to produce vaccines against these strains while buying time to learn more about other strains. In addition, allowing higher vaccine dosages for health care workers protects them from getting infected by patients. In this paper, we give a broader motivation for hybrid strategies. We show that such strategies can often 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 the literature or in the US national pandemic response plan. Our results encourage studying 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.

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Supplementary material

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