Dose-optimal vaccine allocation over multiple populations

Econometric Institute Report 2015 - 29

Evelot Duijzer*, Willem van Jaarsveld*, Jacco Wallinga†, Rommert Dekker*

October 29, 2015

Abstract

For a large number of infectious diseases, vaccination is the most effective way to prevent an epidemic. However, the vaccine stockpile is hardly ever sufficient to treat the entire population, which brings about the challenge of vaccine allocation. To aid decision makers facing this challenge, we provide insights into the structure of this problem.

We first investigate the dependence of health benefit on the fraction of people that receive vaccination, where we define health benefit as the total number of people that escape infection. We start with the seminal SIR compartmental model. Using implicit function analysis, we prove the existence of a unique vaccination fraction that maximizes the health benefit per dose of vaccine, and that the health benefit per dose of vaccine decreases monotonically when moving away from this fraction in either direction. Surprisingly, this fraction does not coincide with the so-called critical vaccination coverage that has been advocated in literature. We extend these insights to other compartmental models such as the SEIR model.

These results allow us to provide new insights into vaccine allocation to multiple non-interacting or weakly interacting populations. We explain the counter-intuitive switching behavior of optimal allocation. We show that allocations that maximize health benefits are rarely equitable, while equitable allocations may be significantly non-optimal.

Keywords: resource allocation, optimization, vaccination, disease modelling, infectious diseases

*Econometric Institute, Erasmus University Rotterdam, The Netherlands, {duijzer, vanjaarsveld, rdekker}@ese.eur.nl

†National Institute for Public Health and The Environment (RIVM), Bilthoven, The Netherlands, jacco.wallinga@rivm.nl

1 Introduction

Infectious diseases have heavily influenced the course of history, and in recent years we have seen new emerging epidemics due to the SARS coronavirus in 2003, the novel influenza A H1N1 virus in 2009, the MERS-coronavirus in 2013, and the Ebola virus in 2014. A large outbreak brings about deaths, health losses and economic losses. Research on preventing an epidemic or mitigating its consequences is thus of high priority. Vaccination is one of the most effective ways to prevent an epidemic. However, the vaccine stockpile is hardly ever sufficient to vaccinate the entire population. This brings about an allocation problem: How should the doses of vaccine be allocated when they become available?

A reasonable objective for vaccine allocation is maximizing the number of people that escape infection. This objective may be achieved by evaluating the eventual outcome of alternative allocations by projecting the course of the epidemic numerically (e.g., Keeling and Shattock 2012, Yuan et al. 2015) or via simulation (e.g., Ferguson et al. 2005, Cooper et al. 2006). This approach may use detailed models and thus yield sophisticated allocations, but it does not give a high-level explanation of *why* certain allocations yield a higher health benefit. This is especially problematic because the resulting allocations are often inequitable and behave counter-intuitively, as illustrated in Table 1. For example, Population 1 has priority over Population 2 when 2000 doses are available, but this priority switches at 8000 doses and again at 20000 doses. Similar puzzling outcomes have been observed in various models (Rowthorn et al. 2009, Klepac et al. 2011, Keeling and Shattock 2012, Yuan et al. 2015), but remain poorly understood.

Vaccine stockpile	**Population 1**	**Population 2**	**Population 3**
2000	2000	0	0
5000	4200	800	0
8000	0	8000	0
10000	1900	8100	0
15000	0	0	15000
20000	3600	0	16400
25000	0	8200	16800
30000	4100	8500	17400

Table 1: The optimal vaccine allocation over three non-interacting populations (rounded to the nearest hundred). The sizes of population 1, 2 and 3 are respectively 10000, 20000 and 40000 and the fractions of people initially infected are 0.015, 0.012 and 0.010. (Section 3 contains a detailed description of the model and Section 5 gives the parameters used for this table.)

We propose to apply analytical methods to vaccine allocation to gain insights into the

structure of the optimal allocation. We expect that a research agenda along these lines will yield a high-level understanding of the inequitable and seemingly counter-intuitive outcomes of a broad range of models. Equity versus efficiency has been studied in various health care applications (e.g., Zaric and Brandeau 2007, McCoy and Lee 2014). In this paper we derive analytical insights that explain *why* an efficient allocation is often inequitable.

Our main contribution in this paper is making a first step towards developing such analytical insights by studying a seminal class of epidemic models: The compartmental models introduced by Kermack and McKendrick (1927). These models divide the population into different compartments that represent all people that are in the same disease state. We initially focus on the classical SIR model, which consists of three compartments that respectively contain susceptible (S), infected (I), and removed (R) people. People can be in the removed compartment because of recovery and immunity, successful vaccination or death. We define the health benefits in this model in terms of the total number of people that escape infection. Vaccination affects health benefit in two ways: directly for people that are vaccinated, and indirectly for people that are not vaccinated by reducing their disease exposure.

We first investigate the total health benefit as a function of the vaccination fraction that is used. This function has long resisted analysis because it cannot be characterized explicitly. Our analysis departs from an implicit relation that extends the *final size equation* (Diekmann et al. 2012). We completely characterize the dependence. For example, we prove that the health benefits are convex-concave in the vaccination fraction. This implies the existence of a unique vaccination fraction that maximizes the health benefits per dose of vaccine, our *dose-optimal vaccination fraction*. We show that health benefits per dose of vaccine decrease monotonically when moving away from this fraction in either direction. Surprisingly, this fraction is different from the so-called *critical vaccination coverage* that has been advocated in literature (e.g., Keeling and Shattock 2012, Plans-Rubió 2012). We next extend our analysis to other compartmental models, e.g., the so-called $SEIR$ model.

We then apply these results to optimal vaccine allocation in multiple non- and weakly interacting populations. We establish links to resource allocation literature (Ginsberg 1974, Ağralı and Geunes 2009). For the non-interacting case, we characterize the form of the optimal solution. We provide detailed insights explaining both the switching behavior of Table 1 and the highly non-equitable allocations that arise from the health benefit maximizing criterion. For cases with weak interaction, we illustrate how to apply the insights gained from the non-interactive case.

We hope that these first steps yielding high-level analytical insights into vaccine allocation invite further research into this area. A better high-level understanding of a broad

range of vaccine allocation models may aid policy-makers in grasping the sometimes puzzling outcomes of vaccine allocation models.

The remainder of the paper is organized as follows. Section 2 presents an extensive literature review to position our work. In Section 3 the vaccine allocation problem is formulated. The objective of maximizing the number of people that escape infection is further analyzed in Section 4 and the dose-optimal vaccination fraction is presented. Based on this analysis, the structure of the solution to the vaccine allocation problem is presented in Section 5. Section 6 discusses the generality of the results and the effect of the assumptions. We conclude in Section 7.

2 Literature

There are many different ways to model the spread of an epidemic in a population. These range from deterministic models with differential equations based on Kermack and McKendrick (1927), stochastic Markov formulations (e.g., Lefevre 1979) and simulation models (e.g., Ferguson et al. 2005). An excellent overview of mathematical methods to analyze epidemic models is given by Diekmann et al. (2012).

These models are often used to describe the evolution of an epidemic in multiple populations that differ geographically (e.g., Sattenspiel and Dietz 1995, Arino and Van den Driessche 2003). Others distinguish between age groups (e.g., Mylius et al. 2008, Medlock et al. 2009, Goldstein et al. 2009) or between people heavily contributing to the transmission of the disease and those who are very vulnerable (e.g., Goldstein et al. 2012). Another approach is to focus on households and see them as minor sub-populations (e.g., Becker and Starczak 1997, Ball and Lyne 2002, Keeling and Ross 2015). In this paper we study non-interacting and weakly interacting populations. Our insights thus apply to geographically distant populations.

Vaccination is one of the interventions often studied and included in epidemiological models. Some studies consider vaccination in a completely susceptible population (e.g., Keeling and Shattock 2012, Yuan et al. 2015). Others compare optimal vaccination strategies on different points in time and show how the optimal allocation depends on the moment of vaccination (Mylius et al. 2008, Medlock et al. 2009, Matrajt and Longini Jr 2010, Matrajt et al. 2013). Vaccination during an epidemic is especially realistic in the context of an unknown disease as a vaccine needs to be developed in that case (cf. Bowman et al. 2011).

There are different ways to evaluate the effect of interventions such as vaccination. One way is to use cost-effectiveness analysis or cost minimization of an allocation (Hethcote and Waltman 1973, Brandeau et al. 2003, Boulier et al. 2007, Simons et al. 2011). However, most

papers consider epidemic characteristics instead of costs. The *final size*, also referred to as the infection attack rate, is broadly used (e.g., Arino et al. 2006, Matrajt and Longini Jr 2010, Keeling and Shattock 2012). It measures the total number (or the fraction) of people infected during an epidemic. An implicit analytical expression for the final size can be derived from the Kermack and McKendrick model (cf. Diekmann et al. 2012). This *final size equation* may be shown to hold for a broad range of model specifications (Keeling and Shattock 2012, Ma and Earn 2006). Our objective also corresponds to minimizing the final size: an extension of the final size size equation serves as the starting point of our analysis. In contrast, Cairns (1989) and Goldstein et al. (2009) investigate how to minimize the basic reproduction ratio R_0 (cf. Wallinga et al. 2010). Others analyze the allocations that result in the threshold $R_0 = 1$ (e.g., Becker and Starczak 1997, Tanner et al. 2008). R_0 is a myopic criterion, because it corresponds to the initial growth rate, whereas the more traditional final size criterion considers the entire time course of the epidemic. While the former criterion leads to a much more tractable model, the latter approach may be more appropriate in many cases.

Many researchers have identified the optimal intervention strategy by determining the eventual outcome of alternatives using simulation models (e.g. Ferguson et al. 2005, Cooper et al. 2006, Germann et al. 2006, Halloran et al. 2008, Tuite et al. 2010, Uribe-Sánchez et al. 2011) or numerical evaluation (e.g. Mylius et al. 2008, Keeling and Shattock 2012, Yuan et al. 2015). But to the best of our knowledge, we are the first to use an analytical approach to provide structural insights explaining why certain interventions are eventually most effective. Our main technical contribution is providing a detailed mathematical analysis of the final size in the seminal SIR model. We show the convex-concave structure and prove that there is an unique vaccination fraction that yields the highest health benefits per dose of vaccine: the *dose-optimal* vaccination fraction. The term *dose-optimal* is also used by Ball and Lyne (2002) for a vaccine allocation that minimizes R_0 under different model specifications. In general, *dose-optimality* refers to the most efficient use of available doses of vaccine.

A result on convexity of the final size is found by Wu et al. (2007) for the significantly simplified case of vaccination in a completely susceptible population and for a limited range of vaccination fractions. We study the general model that holds for vaccination at any possible time during or before the outbreak and for all possible vaccination fractions. This general setting leads to the discovery of the *dose-optimal* vaccination fraction, which plays a crucial role in the optimal allocation. The analytical insights we obtain may help practitioners to better understand the sometimes counter-intuitive outcomes a broad range of models.

By leveraging the results we obtain for the final size of the epidemic, we analyze the vaccine allocation problem and establish a link to resource allocation literature. This literature

investigates for example the allocation of resources among several production plants of a firm (Ginsberg 1974) or the allocation of a limited budget over multiple investments (Ağralı and Geunes 2009). We show that connecting Operations Management to epidemiology yields interesting insights, which is in line with the growing interest for applications in health care and infectious diseases in the Operations Management community. Recent work in this area focuses on influenza vaccine composition (e.g. Wu et al. 2005, Cho 2010), resource allocation for HIV (e.g. Deo and Sohoni 2015) and vaccine allocation (Sun et al. 2009). In this latter paper game theory is used to analyze whether or not countries should share their vaccine stockpile with other countries.

3 Vaccine allocation

Vaccinating in multiple populations brings about the question of allocation: How should the available doses of vaccine be divided over the populations? This paper models the spread of an epidemic using the seminal deterministic SIR model, which is explained in Section 3.1. In Section 3.2, we derive an implicit analytical relation that characterizes the final state of the epidemic, which extends the so-called final size equation to arbitrary starting conditions. The vaccine allocation problem is formulated in Section 3.3. We keep ourselves to a deterministic model; for discussion of stochastic models we refer to Section 7.

3.1 The SIR model

Let J denote the set of populations. Every population is divided into three compartments for which the time course is tracked (cf. Hethcote 2000). Let $s_j(t), i_j(t)$ and $r_j(t)$ be the fractions of the population respectively susceptible, infected and removed in population j at time t. People who have died will remain in the removed compartment. By interpretation it must hold that $s_j(t) + i_j(t) + r_j(t) = 1$ for all $t \geq 0$ and all $j \in J$. The following system of differential equations is proposed by Kermack and McKendrick (1927), with the transmission rate and the rate of recovery in population j denoted by β_j and γ_j, respectively.

$$\begin{aligned} \frac{ds_j}{dt} &= -\beta_j s_j i_j \\ \frac{di_j}{dt} &= \beta_j s_j i_j - \gamma_j i_j \\ \frac{dr_j}{dt} &= \gamma_j i_j \end{aligned} \tag{1}$$

From (1) the following equation follows, which presents the relation between $i_j(t)$ and $s_j(t)$ at any time t (Hethcote 1976):

$$i_j(t) = -s_j(t) + \frac{\log(s_j(t))}{\sigma_j} + s_{0,j} + i_{0,j} - \frac{\log(s_{0,j})}{\sigma_j} \tag{2}$$

Here $i_{0,j} := i_j(0)$ and $s_{0,j} := s_j(0)$ are the initial fractions infected and susceptible, where we assume $0 < i_{0,j} < 1$, $0 < s_{0,j} < 1$ and $0 < s_{0,j} + i_{0,j} \leq 1$. We define $\sigma_j = \frac{\beta_j}{\gamma_j}$, which is assumed to be strictly positive. Note that σ_j equals the basic reproduction ratio R_0 for the SIR model (Diekmann et al. 2012). For $i_{0,j} = 0$ there is no transmission, resulting in $i_j(t) = 0$ for all $t \geq 0$. However, in the remainder of the paper we will use $i_{0,j} = 0$ to refer to the limit $i_{0,j} \downarrow 0$. Vaccination for the limit $i_{0,j} \downarrow 0$ is sometimes referred to as prophylactic vaccination (e.g Keeling and Shattock 2012, Yuan et al. 2015), but we will not use this term as this may lead to confusion with the medical definition of prophylactic vaccination.

3.2 Vaccination

To evaluate the effect of vaccination allocation, assume that at $t = \tau_{v,j}$ a fraction f_j of the susceptible population in population j is vaccinated, with $0 \leq f_j \leq 1$. Just prior to vaccination the system is in state $(s_j(\tau_{v,j}), i_j(\tau_{v,j}))$. By assumption $\frac{ds_j}{dt} < 0$ at $t = 0$, such that $0 < s_j(\tau_{v,j}) \leq s_{0,j}$ for $\tau_{v,j} \geq 0$. Assume that the vaccine is completely effective and that vaccination takes no time. Assume that it is possible to identify the susceptible people and that vaccination with a single dose results in immunity immediately. We refer to Section 6 for a discussion of these assumptions. Under our assumptions vaccination causes a shift at time $\tau_{v,j}$ from state $(s_j(\tau_{v,j}), i_j(\tau_{v,j}))$ to state $((1 - f_j)s_j(\tau_{v,j}), i_j(\tau_{v,j}))$. This implies that $r_j(\tau_{v,j})$ shifts to $r_j(\tau_{v,j}) + f_j s_j(\tau_{v,j})$.

In order to evaluate different allocations, we use the characteristics of the final state of the epidemic, i.e., the disease-free equilibrium. In particular we analyze the final fraction of susceptible people. This value fully characterizes the disease-free equilibrium, since $s_j(t) + i_j(t) + r_j(t) = 1$ and $i_j(t) = 0$ in the disease-free equilibrium.

We define $G_j(f_j)$ as the final fraction of people susceptible in population j after vaccinating a fraction f_j of the susceptible people at time $\tau_{v,j}$. More precisely,

$$G_j(f_j) = \lim_{t \to +\infty} s_j(t), \tag{3}$$

with $s_j(t)$ evolving according to (1) for $t > \tau_{v,j}$. The final fraction of people susceptible is related to a concept which is often called 'herd immunity' (cf. Fine 1993, John and Samuel 2000). In the latter paper the term 'herd effect' is used and defined as *the reduction of*

infection or disease in the unimmunized segment as a result of immunizing a proportion of the population. The function $G_j(f_j)$ measures this *herd effect* in population j. Section 4 studies the herd effect function $G_j(f_j)$ in more detail.

3.3 The vaccine allocation problem

Let N_j denote the size of population j and denote by V the size of the available vaccine stockpile. Define $F_j(f_j)$ as the fraction of people that escape infection in population j:

$$F_j(f_j) = f_j s_j(\tau_{v,j}) + G_j(f_j) \tag{4}$$

As can be seen in (4) there are two ways of escaping infection: either you will get vaccinated (the first term) or you will escape infection without being vaccinated (the second term). These two terms exactly correspond to the direct effect and the herd effect of vaccination.

As discussed in the introduction, our objective is minimizing the *final size of the epidemic*, i.e., the total number of people that get infected. In fact, it will be more convenient to maximize the total number of people that escape infection, which can be more easily expressed in $F_j(f_j)$, $j \in J$. An allocation that maximizes this number exploits the available resources in the most effective way. This gives rise to the following *vaccine allocation problem* (cf. Keeling and Shattock 2012):

$$\begin{aligned} \max \quad & \sum_{j\in J} N_j F_j(f_j) \\ \text{s.t.} \quad & \sum_{j\in J} f_j s_j(\tau_{v,j}) N_j \quad \leq \quad V \\ & 0 \leq f_j \leq 1 \qquad\qquad\qquad\qquad \forall j \in J \end{aligned} \tag{5}$$

Theorem A.5 proves that the constraint $\sum_{j\in J} f_j s_j(\tau_{v,j}) N_j \leq V$ will always be met with equality. Thus, any optimal allocation will use the entire vaccine stockpile.

The final size of the epidemic may be expressed as $Z_j(f_j) = s_{0,j} + i_{0,j} - F_j(f_j)$ and (5) is thus formally equivalent to a minimization problem involving this final size. The relation between $Z_j(f_j)$ and the two components of $F_j(f_j)$ is illustrated in Figure 1.

4 Analysis of the objective function

In order to study Problem (5), this section analyzes the function $F_j(f_j) = f_j s_j(\tau_{v,j}) + G_j(f_j)$ and in particular the function $G_j(f_j)$. For notational convenience, the subscript j will be dropped in this section.

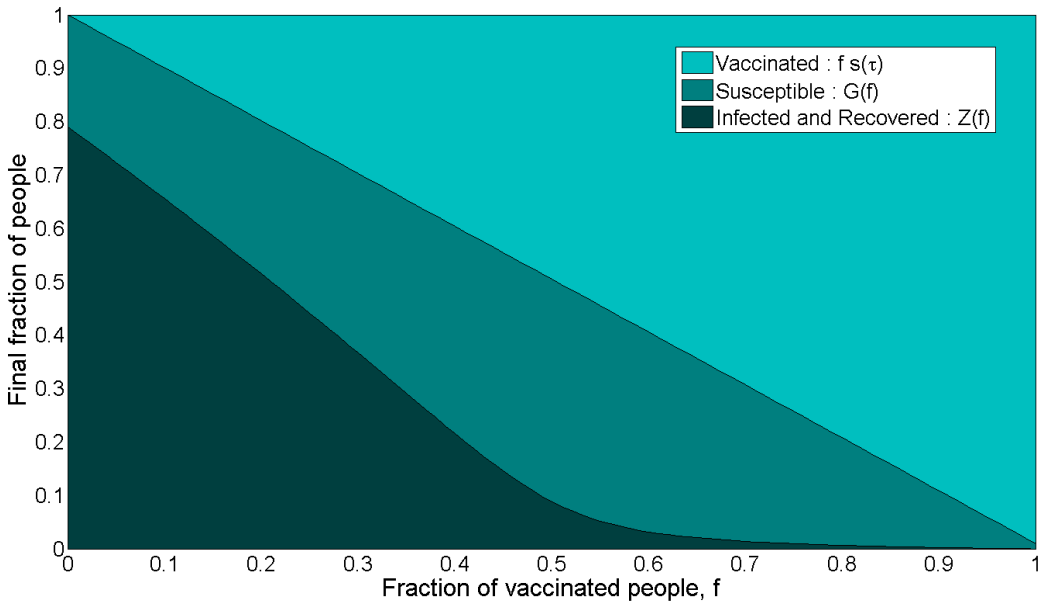

Figure 1: The final state of the epidemic for different vaccination fractions, for an epidemic with basic reproduction ratio $\sigma = 2$ with $(s_0, i_0) = (0.99, 0.01)$ and $\tau_v = 0$.

An implicit relation that characterizes $G(f)$, i.e., the herd effect, is given in Section 4.1 and this expression is analyzed in Section 4.2. Based on this analysis we present our *dose-optimal* vaccination fraction in Section 4.3. We extend our analysis to more general compartmental models in Section 4.4. A minor detail is sorted out in Section 4.5: we formally confirm that it is optimal to vaccinate as early as possible.

Figure 2 summarizes the main findings of this section and illustrates the structure of $G(f)$. In Section 4.2 and 4.3 this result is derived formally.

4.1 Implicit formulation of the function $G(f)$

We derive an implicit relation that characterizes $G(f)$ and that forms the basis of our analysis. Note that the state $((1-f_j)s_j(\tau_{v,j}), i_j(\tau_{v,j}))$ directly after vaccination can be seen as a new initial state, where $i_j(\tau_{v,j})$ can be obtained from (2). $G_j(f_j)$ is then obtained from (2) by setting $i_j(t) = 0$ and thus is the unique solution to:

$$\begin{aligned} 0 &= -G_j(f_j) + \frac{\log(G_j(f_j))}{\sigma_j} + (1-f_j)s_j(\tau_{v,j}) + i_j(\tau_{v,j}) - \frac{\log((1-f_j)s(\tau_{v,j}))}{\sigma_j} \\ \Leftrightarrow 0 &= -G_j(f_j) + \frac{\log(G_j(f_j))}{\sigma_j} + s_{0,j} + i_{0,j} - \frac{\log(s_{0,j}(1-f_j))}{\sigma_j} - f_j s_j(\tau_{v,j}) \end{aligned} \tag{6}$$

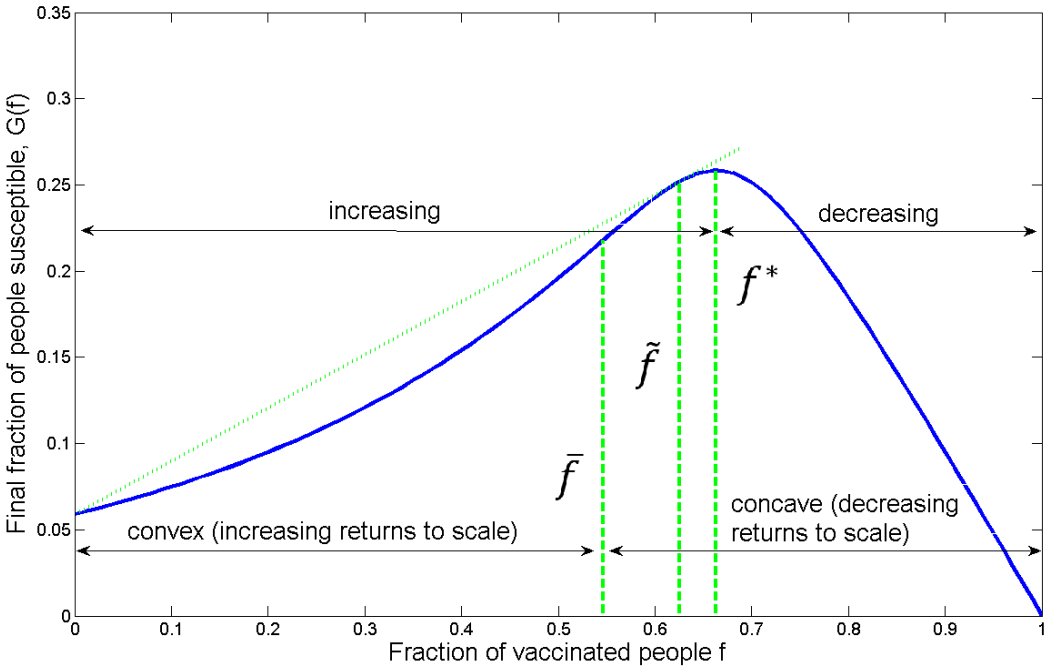

Figure 2: Illustration of the structure of $G(f)$, which is proven in Section 4: Theorems 1 and 2 establish the increasing-decreasing and convex-concave structure of $G(f)$, the fraction of non-vaccinated people that escape infection, which is illustrated in this figure using the parameters $(s_0, i_0) = (0.99, 0.01), \sigma = 3$ and $\tau_v = 0$. Dashed lines represent the important vaccination fractions $\bar{f}$ (left), f^* (right) and our dose-optimal vaccination fraction $\tilde{f}$ following from Corollary 1 (middle).

Above equation holds for all $i_{0,j} > 0$. The value of $G_j(f_j)$ in the limit $i_{0,j} \downarrow 0$ can be determined by substituting $i_{0,j} = 0$. (6) extends the *final size equation* to any initial state. The original final size equation can be recovered for $f_j = 0$, $s_{0,j} \to 1$ and $i_{0,j} \to 0$ (see e.g., Kermack and McKendrick (1927), Ma and Earn (2006), Diekmann et al. (2012) and Keeling and Shattock (2012)).

We refer to Appendix D for an alternative expression of $G(f)$ using the Lambert W function denoted by $W(x)$ (cf. Corless et al. 1996, Ma and Earn 2006).

4.2 Analysis of the herd effect

In this and the next section we present the main technical contribution of this paper: a structural analysis of the herd effect, i.e., the function $G(f)$. All proofs can be found in Appendix A. For the analysis we distinguish between two types of vaccination: vaccination in a completely susceptible population (the limit $i_0 \downarrow 0$) or vaccination in an infected population

$(i(\tau_v) > 0)$.

Lemma 1. *The function $G(f)$ is twice differentiable for all $f \in [0,1)$ in case of vaccination in an infected population $(i_0 > 0)$ and twice differentiable for all $f \in [0,1)$ with $f \neq 1 - \frac{1}{\sigma s(\tau_v)}$ in case of vaccination in a completely susceptible population (the limit $i_0 \downarrow 0$).*

Theorem 1. *For $s(\tau_v) > \frac{1}{\sigma}$ there is a unique vaccination fraction $f^* = 1 - \frac{1}{\sigma s(\tau_v)} > 0$ such that the herd effect $G(f)$ is increasing in f for all $f < f^*$, maximized for $f = f^*$ and decreasing for $f > f^*$. For $s(\tau_v) \leq \frac{1}{\sigma}$ the function $G(f)$ is decreasing for all $f \in [0,1]$. If $i_0 > 0$, then $G'(f^*) = 0$.*

Note that the vaccination fraction f^* also plays a role in the *critical vaccination coverage*, denoted by p_c (cf. Diekmann et al. (2012)). This critical vaccination coverage is defined as the smallest fraction of people that must be vaccinated in a completely susceptible population in order to prevent an outbreak (an increase in the fraction of people infected) and equals $p_c = 1 - \frac{1}{\sigma}$. Observe that $p_c = f^*$ for $s(\tau_v) = 1$.

To study the effect of one additional dose of vaccine, we consider the convexity and concavity of the function $G(f)$. We consider $G(f)$ to be convex if the second order derivative is non-negative and concave if the second order derivative is non-positive.

Theorem 2. *Denote by $W[\cdot]$ the Lambert W function (cf. Appendix D) and let C be defined as follows:*

$$C = \frac{W\left[-\sigma \exp\{-\sigma(s_0 + i_0) + \log(s_0)\}\right] + 2}{\sigma}$$

For $s(\tau_v) > C$ there exists a unique vaccination fraction $\bar{f} > 0$ such that $G(f)$ is strictly convex $(G''(f) > 0)$ for all $f < \bar{f}$ and strictly concave $(G''(f) < 0)$ for all $f > \bar{f}$. For $s(\tau_v) \leq C$ the function $G(f)$ is concave for all $f \in [0,1]$. If $i_0 > 0$, then $G''(\bar{f}) = 0$.

Recall that $G(f)$ represents the herd effect: the fraction of people that escapes infection without being vaccinated. $G'(f)$ thus represents the impact of an additional dose of vaccine on the herd effect for different vaccination fractions. By Theorems 1 and 2, this impact is initially positive and increasing, then it starts to decrease to eventually become negative.

Lemma 2 will show that $\bar{f} \leq f^*$. Using Theorems 1 and 2 we can thus distinguish three cases for the function $G(f)$: *(i)* the function is first convex and increasing, then concave and increasing and finally concave and decreasing, *(ii)* the function is always concave and is first increasing and then decreasing, or *(iii)* the function is always concave and decreasing. Figure 2 graphically illustrates the most general shape *(i)* of the function $G(f)$. Observe that for $f \uparrow 1$ the herd effect goes to zero: Vaccinating all susceptible people implies that there are no people left that could be spared from infection without being vaccinated.

4.3 The dose-optimal vaccination fraction

We introduce the function $D(f)$ as the average slope of the function $G(f)$ on the interval $[0, f]$, measuring the average herd effect per dose of vaccine:

$$D(f) = \frac{1}{f}\left[G(f) - G(0)\right] \tag{7}$$

Corollary 1. *The function $D(f)$ as defined by (7) is maximized by the unique vaccination fraction $\tilde{f}$ for which $G'(\tilde{f}) = D(f)$. The function $D(f)$ is increasing for $f < \tilde{f}$ and decreasing for $f > \tilde{f}$.*

Corollary 1 is illustrated in Figure 3. The interpretation of Corollary 1 is that $\tilde{f}$ gives the highest herd effect *per* dose of vaccine. We therefore introduce the term *dose-optimal vaccination fraction* for $\tilde{f}$. In Section 5 we will show that $\tilde{f}$ plays a central role in optimal vaccine allocation.

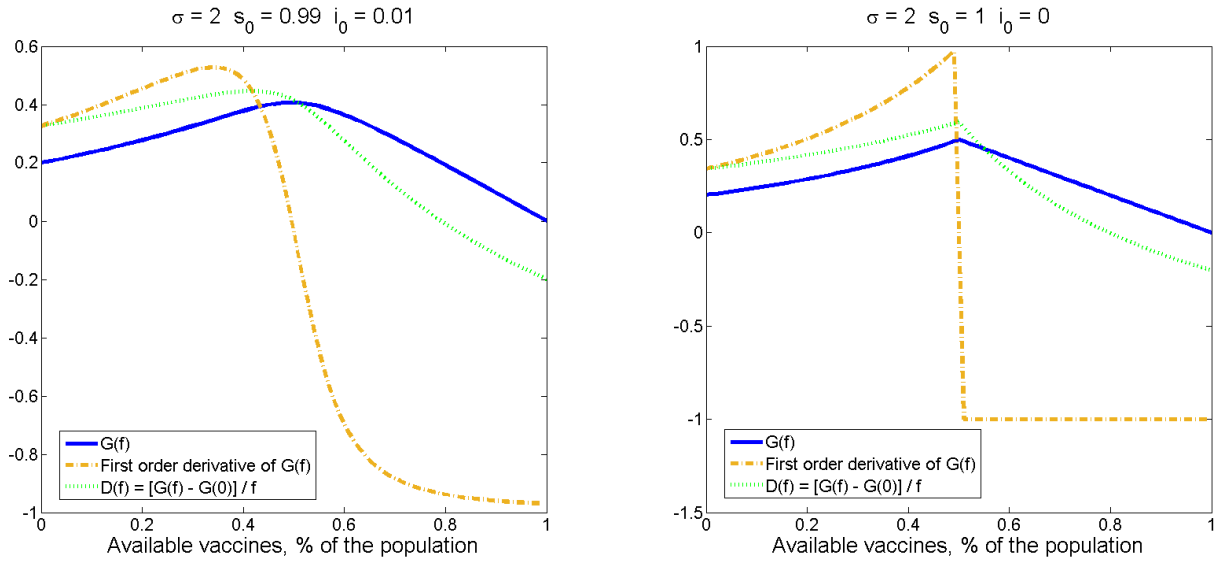

Figure 3: The function $G(f)$, its derivative $G'(f)$ and the function $D(f)$ for an infection with a basic reproduction ratio $\sigma = 2$ when vaccination is offered at time $\tau_v = 0$. The left panel shows the case of vaccination in an infected population with initial conditions $(s_0, i_0) = (0.99, 0.01)$. In this case we have $\bar{f} \approx 0.341$, the dose-optimal vaccination fraction $\tilde{f} \approx 0.417$ and the critical vaccination coverage $f^* = 0.5$. The right panel shows the case of vaccination in a completely susceptible population, with initial conditions $(s_0, i_0) = (1, 0)$. In this case we have $\bar{f} = \tilde{f} = f^* = 0.5$.

σ	2	3	5	10	15	20	25	30	50	100
f^*	0.4949	0.6633	0.7980	0.8990	0.9327	0.9495	0.9596	0.9663	0.9798	0.9899
$\tilde{f}$	0.4175	0.6255	0.7824	0.8944	0.9304	0.9481	0.9586	0.9656	0.9795	0.9898
$\bar{f}$	0.3410	0.5465	0.7158	0.8483	0.8946	0.9186	0.9333	0.9434	0.9642	0.9810

Table 2: The table illustrates that for increasing basic reproduction ratio σ the dose-optimal vaccination fraction $\tilde{f}$ converges to f^*. To calculate the numbers an initial state $(s_0, i_0) = (0.99, 0.01)$ and $s(\tau_v) = 0.99$ is used.

Lemma 2. *Consider the following three vaccination fractions: $\bar{f}$ as defined in Theorem 2, the dose-optimal vaccination fraction $\tilde{f}$ and f^* as defined in Theorem 1. The following relation holds: $\bar{f} \leq \tilde{f} \leq f^*$*

Recall that the critical vaccination fraction $p_c = 1 - \frac{1}{\sigma}$ is equal to $f^* = 1 - \frac{1}{\sigma s(\tau_v)}$ in case of vaccination in a completely susceptible population ($s(\tau_v) = 1$). From Lemma 2 and Lemma A.2 we can derive that $\bar{f} = \tilde{f} = f^* = p_c$ in that case. This is illustrated in the right graph of Figure 3. Another relation between $\tilde{f}$ and f^* is presented in the following lemma:

Lemma 3. *For increasing σ the dose-optimal vaccine fraction $\tilde{f}$ converges to f^*.*

This lemma is illustrated in Table 2, which shows that very high σ is needed to obtain convergence.

4.4 The $SEIR$ model and other extensions

An important extension of the standard SIR compartmental model is the SI^nR model with n different consecutive infectious stages. This extension allows to include a latent period or multiple levels of infectivity. For $n = 2$ this model is often referred to as the $SEIR$ model. Let β_k and γ_k denote respectively the transmission rate and recovery rate in infectious stage k. Hyman et al. (1999) prove that $R_0 = \sum_{k=1}^{n} \frac{\beta_k}{\gamma_k}$ for this model. Ma and Earn (2006) show that the final size equation derived from the SIR model also holds for the SI^nR model for $s(0) \to 1$ and without vaccination. We extend the generality of the final size equation for the SI^nR model to any initial state and include vaccination. Proofs can be found in Appendix B.

Theorem 3. *Up to a constant, the expression for $G(f)$ given in* (6) *also applies to the SI^nR model with $\sigma = \sum_{k=1}^{n} \frac{\beta_k}{\gamma_k}$.*

Corollary 2. *The results of Lemma 1, Theorem 1, Theorem 2 and Corollary 1 also apply to the SI^nR model with $\sigma = \sum_{k=1}^{n} \frac{\beta_k}{\gamma_k}$.*

Lemma 1, Theorem 1, Theorem 2 and Corollary 1 form the basis for the analysis of the vaccine allocation problem in Section 5. By Corollary 2 the results derived in Section 5 are valid for the more general SI^nR model.

4.5 Vaccination in a single population

We sort out a minor detail by formally proving that vaccination should be carried out as soon as possible. Thereto we determine the time τ_v at which $G(f, s(\tau_v)) + fs(\tau_v)$ is maximized. Assume that we have a fixed vaccine stockpile, V, such that a fraction of the population can be vaccinated is restricted by $\frac{V}{Ns(\tau_v)}$, where N is the population size. If $s(\tau_v) \leq V/N$, all susceptible people can be vaccinated and the objective function for $f = 1$ reduces to $s(\tau_v)$, because $\lim_{f\uparrow 1} G(f) = 0$ by Theorem A.1. If $s(\tau_v) > V/N$, all available doses of vaccine are used and $f = \frac{V}{Ns(\tau_v)}$. Let $G'_{s(\tau_v)}(f, s(\tau_v))$ be the derivative of $G(f, s(\tau_v))$ with respect to $s(\tau_v)$:

$$G'_{s(\tau_v)}(f, s(\tau_v)) \left[1 - \frac{1}{\sigma G(f, s(\tau_v))}\right] = \frac{-V/N}{\sigma s(\tau_v)[s(\tau_v) - V/N]}$$

Observe that the objective function is increasing in $s(\tau_v)$, because $G(f, s(\tau_v)) < \frac{1}{\sigma}$ by Theorem A.2. Therefore, to maximize the number of people that do not get infected one should vaccinate as soon as possible.

5 Analysis of the vaccine allocation problem

In this section we analyze the vaccine allocation problem (5), using the characterization of the objective function in Theorems 1 and 2. Section 5.1 presents the central insight. Section 5.2 considers an interesting special case to obtain more insight into the structure of the solution. The general case is discussed in Section 5.3. In Section 5.4 we illustrate how the insights from the non-interactive case can be applied to populations with weak interaction.

5.1 The optimal allocation

In this section we characterize the optimal allocation, which is the solution to problem (5). We emphasize that our analysis in Section 4 is essential to obtain this insight. By Theorem 2 let $\bar{f}_j$ denote the vaccination fraction such that $F''_j(f) > 0$ for all $f < \bar{f}_j$ and $F''_j(f) < 0$ for $f > \bar{f}_j$.

Theorem 4 (Central Insight)**.** *For every optimal solution to* (5) *there exist* $J' \subseteq J$, $k \in J \backslash J'$ *and* $\omega \geq 0$ *such that:*

(i). For all $j \in J'$, f_j is the unique solution to $\frac{1}{s_j(\tau_{v,j})} F_j'(f_j) = \omega$ for which $f_j \geq \bar{f}_j$.

(ii). $\frac{1}{s_k(\tau_{v,k})} F_k'(f_k) = \omega$, and either f_k is the unique solution to this equation for which $f_k \geq \bar{f}_k$ or f_k is the unique solution for which $f_k < \bar{f}_k$.

(iii). Either $f_j = 0$ or $f_j = 1$ for all $j \in J \setminus \{J' \cup \{k\}\}$.

In case vaccination takes place before the peak in infected people is attained, i.e., $s_j(\tau_{v,j}) > \frac{1}{\sigma_j}$ for all $j \in J$, condition (iii) in Theorem 4 reduces to the following by Lemma C.2: Either $f_j = 0$ for all $j \in J \setminus \{J' \cup \{k\}\}$ or $f_j = 1$ for all $j \in J \setminus \{J' \cup \{k\}\}$.

Given a subset $J' \subseteq J$ we use the term *partial pro rata* allocation to denote an allocation that meets condition (i) of Theorem 4. The optimal vaccine allocation is thus *partial pro rata* over a subset J' of populations. Possibly some leftover vaccines are allocated to one population k. The remaining populations are completely vaccinated or not vaccinated at all. The optimal allocation is thus driven by the goal to make the best possible use of the herd effect in some populations, which is in line with the numerical results of Wu et al. (2007) and the intuitive explanation of Keeling and Shattock (2012).

5.2 The special case: identical parameters

Now consider an interesting special case: the case of identical functions $F_j(f_j) := F(f_j)$ for all $j \in J$ ($\sigma_j := \sigma$, $s_0^j := s_0$, $i_0^j := i_0$, $\tau_{v,j} := \tau_v$ and $s_j(\tau_{v,j}) = s(\tau_v)$ for all $j \in J$). In that case a *partial pro rata* allocation is a *pro rata* allocation, with *pro rata* as usual denoting an allocation in which the doses of vaccine are distributed equally with respect to population size, such that the vaccination fraction is the same in all selected populations. For this special case the optimal allocation may be characterized in more detail. In the context of investing in factories Ginsberg (1974) have derived similar results for the special case $F_j(0) = 0$ and $N_j = N$ for all j.

Observe that the dose-optimal vaccination fraction $\tilde{f}$ as defined by Corollary 1 does not only maximize the function $D(f)$. It also maximizes the average slope of the function $F(f)$ on the interval $[0, f]$, calculated as $[F(f) - F(0)]/f$, because $F(f) = fs(\tau_v) + G(f)$. Thus, $\tilde{f}$ is the allocation fraction that gives per dose of vaccine the highest total effect, which consists of the herd effect and the direct effect. The optimal allocation therefore tries to allocate as close as possible to $\tilde{f}$ in a subset of all the populations:

Theorem 5. *Consider a set of populations J with $\forall j$: $F_j(f) = F(f)$ and a total available amount of resources equal to V. Let $b = \frac{V}{s(\tau_v)}$, $|J| = n$ and order the populations such that $N_1 \leq ... \leq N_n$. The optimal allocation for particular cases is as follows:*

(a). if $b < \tilde{f}N_1$, then allocate only to the smallest population. Set $f_1 = b/N_1$ and $f_j = 0$ for $j = 2, ..., n$.

(b). if $b = \sum_{j \in K} \tilde{f}N_j$ for a subset $K \subseteq J$, then set $x_j = \tilde{f}$ for $j \in K$ and $x_j = 0$ for $j \notin K$.

(c). if $b > \sum_{j \in J} \tilde{f}N_j$, then allocate pro rata over all the populations: $x_j = \frac{b}{\sum_{j \in J} N_j}$ for all $j \in J$.

The proof of this theorem can be found in Appendix C. Theorem 5 shows that the optimal allocation tries to make the best possible use of the herd effect by vaccinating close to $\tilde{f}$ in (a subset of) the populations. All vaccines are allocated to the smallest population if the vaccination fraction $\tilde{f}$ cannot be attained in either of the populations. For very large vaccine stockpiles, the pro rata allocation is optimal. Note that Theorem 5 only specifies the allocation in specific cases of vaccine stockpiles, but can be extended to any available amount of vaccines. However, the description of the optimal allocation for a general vaccine stockpile is quite technical and less insightful and is therefore omitted.

In practice it is not always possible to vaccinate at the start of an epidemic ($\tau_v = 0$), because vaccines should be developed, ordered or produced. It is therefore useful to study the effect of τ_v on the optimal allocation, which is governed by the dose-optimal vaccination fraction $\tilde{f}$.

Theorem 6. *The value $\tilde{f}$, which maximizes $D(f) = [G(f) - G(0)]/f$, decreases when $s(\tau_v)$ decreases.*

Recall from Theorem 5 that the pro rata allocation is optimal for V large enough to reach $\tilde{f}$ in every population. Thus by Theorem 6, if vaccination takes place at a later point in time, the pro rata allocation is already optimal for smaller vaccine stockpiles.

5.3 Discussion of the general case

The insights obtained in Section 5.2 by considering the special case can be translated to the general case. Recall that a single dose of vaccine leads to a small herd effect in a population, but multiple doses together can make a difference. We prove that the herd effect is convex-concave in the vaccination fraction and thus vaccinating a second individual can have a larger effect than vaccinating a first individual. However, when a very large fraction of the population is vaccinated, the herd effect is decreasing. This leads to the dose-optimal vaccination fraction $\tilde{f}$, which gives the highest decrease in final size per dose of vaccine.

In the general case of the vaccine allocation problem the parameters may differ per population, causing the functions $F_j(\cdot)$ to be different for different populations j. This

implies that there is no longer a single value for $\tilde{f}$, but an $\tilde{f}_j$ for every population $j \in J$. Equivalent to vaccinating close to $\tilde{f}_j$, we could say that there is an optimal number of vaccines $\tilde{V}_j = \tilde{f}_j s_j(\tau_{v,j}) N_j$ for every population j. We either come close to $\tilde{V}_j$ or we do not allocate to population j. This explains the structure of the solution of the vaccine allocation problem: a subset of populations is selected and we divide the vaccines over these populations such that in these populations we vaccinate as close to $\tilde{V}_j$ as possible while respecting the conditions of Theorem 4. This explains why the smallest populations are prioritized for small vaccine stockpiles, as the required number of doses of vaccine to reach a fraction $\tilde{f}_j$ is smaller in those populations. Numerical analysis of the optimal vaccine allocation (e.g., by Keeling and Shattock (2012)) shows switch points where a small increase in vaccine stockpile results in a completely different allocation. Our analysis explains these switch points: they are related to a change in the subset of populations to approach the dose-optimal vaccination fraction.

This structure of the optimal allocation is illustrated in Figure 4 where we use the example from the introduction with three populations of size $N_1 = 10000, N_2 = 20000$ and $N_3 = 40000$ respectively. The following parameters are used: a basic reproduction ratio $\sigma_j = 2$ for $j = 1, 2, 3$ and let the initial states be $(s_0^1, i_0^1) = (0.985, 0.015), (s_0^2, i_0^2) = (0.988, 0.012)$ and $(s_0^3, i_0^3) = (0.990, 0.010)$. Furthermore, let $\tau_{v,j} = 0$ for $j = 1, 2, 3$. Observe that the number of allocated vaccines in the populations that receive vaccination is indeed close to $\tilde{V}_j$.

Table 3 presents the differences between using the equitable allocation and the optimal allocation. Since the direct effect of vaccination is not affected by the allocation, we only compare the additional herd effect:

$$\text{additional herd effect} = \sum_{j \in J} N_j (G_j(f_j) - G_j(0))$$

The table shows that the optimal allocation is significantly more effective in harnessing the herd effect.

5.4 Weak interaction

We illustrate how the results derived from the non-interacting case can be applied in the interacting case. The SIR model with interaction is given by the following differential

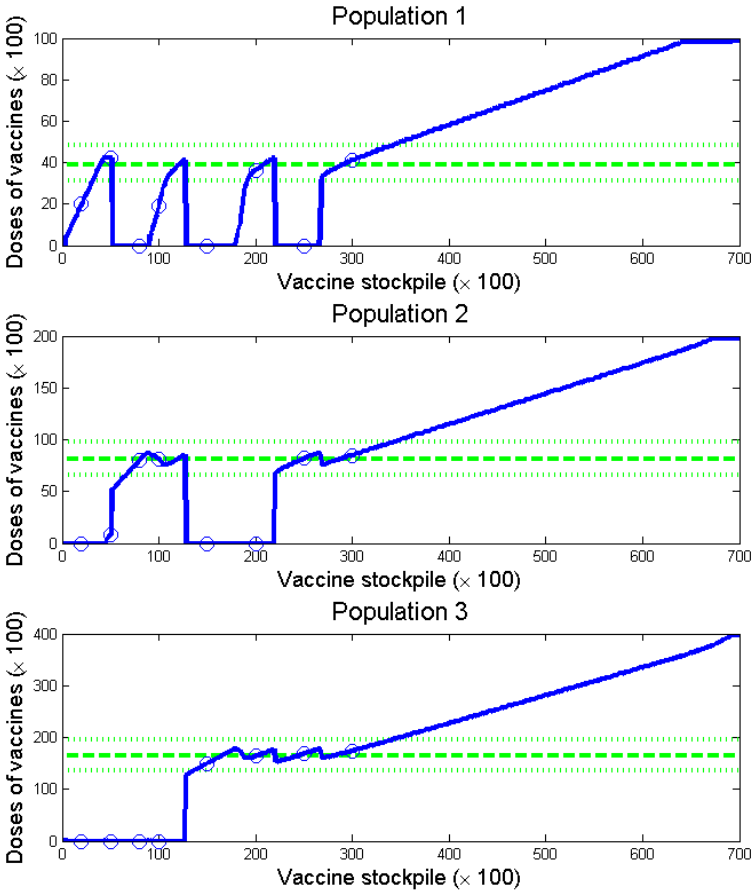

Figure 4: The graphs present the optimal vaccine allocation (the solid lines) over three populations for different sizes of vaccine stockpile. The dashed and dotted lines indicate the important vaccination fractions: the dashed line in the middle equals $\tilde{V}_j = \tilde{f}_j s_j(\tau_{v,j})N_j$, the upper dotted line equals $V_j^* = f_j^* s_j(\tau_{v,j})N_j$ and the lower dotted line equals $\bar{V}_j = \bar{f}_j s_j(\tau_{v,j})N_j$. The circles indicate the values from Table 1.

equations (Diekmann et al. 2012):

$$\begin{aligned} \frac{ds_j}{dt} &= -\sum_{k\in J} \beta_{j,k} s_j i_k \\ \frac{di_j}{dt} &= \sum_{k\in J} \beta_{j,k} s_j i_k - \gamma_j i_j \\ \frac{dr_j}{dt} &= \gamma_j i_j \end{aligned} \tag{8}$$

Vaccine stockpile	Equitable Allocation	Optimal Allocation	Relative Improvement
2000	671.76	762.14	+ 13.45%
5000	1742.47	2037.82	+ 16.95%
8000	2893.30	3511.54	+ 21.37%
10000	3707.30	4274.03	+ 15.29%
15000	5912.18	6702.56	+ 13.37%
20000	8350.69	8910.43	+ 6.70%
25000	10930.50	11170.84	+ 2.20%
30000	13255.30	13264.27	+ 0.07%

Table 3: The additional herd effect for two different allocation strategies for various vaccine stockpiles. The equitable allocation allocates pro rata over all populations and the optimal allocation is specified in Table 1 and Figure 4. The population sizes are: $N_1 = 10000$, $N_2 = 20000$ and $N_3 = 40000$.

We determine the optimal allocation for an example with three populations. Let N_j denote the population size of population $j \in J$. We use the following parameters: $\gamma_j = 1$ and $\beta_{j,j} = \beta = 2$ for all $j \in J$. The interaction is determined as follows: $\beta_{j,k} = 0.01\beta \frac{N_k}{\sum_{m \neq j} N_m}$ for $j, k \in J$ and $j \neq k$, such that $\sum_{k \neq j} \beta_{j,k} = 0.01\beta$ for all $j \in J$: interaction between populations is a factor 100 weaker than interaction within populations. This assumption of week interaction between populations conforms to Wu et al. (2007) who note that individuals spend on average more than 97% of their time in their home regions. Analogous to the non-interacting case we denote by f_j the fraction of susceptible people that is vaccinated at time $\tau_{v,j}$ in population j. We use the same initial states and population sizes as in Section 5.3.

To apply our insights from Section 5.3 we consider the populations $j \in J$ one by one, varying the vaccination fraction for that population while fixing $f_k = 0$ for $k \neq j$. Perhaps surprisingly, we still observe the convex-concave relation between the final fraction of people susceptible and the used vaccination fraction in that population. This enables us to compute the important vaccination fractions $\bar{f}_j$, $\tilde{f}_j$ and f_j^* by numerical evaluation of (8), taking $\tau_{v,j} = 0$ for all $j \in J$. To investigate the relation between the optimal allocation and the important vaccination fractions, we graphically illustrate them in Figure 5. The optimal allocation is determined via enumeration.

Note that the optimal allocation follows the same pattern as in the non-interacting case (Figure 4), where the values $\tilde{V}_j$ determine the structure of the solution. In Figure 6 we illustrate the relative performance of the solution to the non-interacting problem in the model with interaction. We evaluate the additional herd effect and observe that the non-interacting solution performs close to optimal and outperforms the pro rata allocation. Note that the additional herd effect becomes negative for large vaccine stockpiles, because vaccinating

many people leaves very few people susceptible. This implies that herd effect can be lower for large vaccine stockpiles than for no vaccination, resulting in a negative additional herd effect.

In Appendix E we analyze the optimal allocation for somewhat stronger interaction. The figures with the optimal allocation are given in case interaction between populations is respectively 0.02, 0.05 and 0.1 times the interaction within a population. From these figures we conclude that as the interaction between populations increases, the switching behaviour eventually disappears. For an interaction factor of 0.02 the switching pattern is still clearly visible up to vaccine stockpiles of around 30% of the total population size. For a factor 0.05 switching priorities occur only for relatively small stockpiles and for a factor 0.1 the optimal allocation does no longer display any switching behaviour. Yet for all compared levels of interaction the optimal allocation of small vaccine stockpiles remains unequitable, prioritizing only a subset of the populations.

6 Discussion

In this section we discuss the effect of modelling assumptions, extensions and the generality of the results.

Our results hold under several relaxations of assumptions. We assume that vaccination is completely effective and results in immunity directly. The effectiveness of a vaccine can be incorporated with an additional parameter (Hill and Longini Jr 2003, Mylius et al. 2008, cf.) and a delay in attained immunity can be incorporated in the parameter $s(\tau_v)$. These small adjustments in the parameters do not change the structure of our results. We have completely characterized the final size expression for the SIR model, but this expression is also valid for other compartmental models such as the SI^nR model (see Section 4.4). This implies that our results can be generalized to other model choices. We assume that the susceptible people can be identified and that no vaccines are waisted on infected people. This assumption is more justifiable for the SIR model than for the SI^nR model, as the latter possibly contains latent phases. However, this assumption can be relaxed to vaccinating a fraction of the total population instead of only the susceptible population. Vaccines are then waisted on individuals that are already infected or immune. Under this adjusted assumption our results still hold.

Numerical results show that the convex-concave pattern in the final fraction of people susceptible also holds for a stochastic SIR model. This is an indication that the insights of this paper carry over, although proving convexity is more difficult for the stochastic model. Also for populations with weak interaction we numerically illustrate that the insights gained

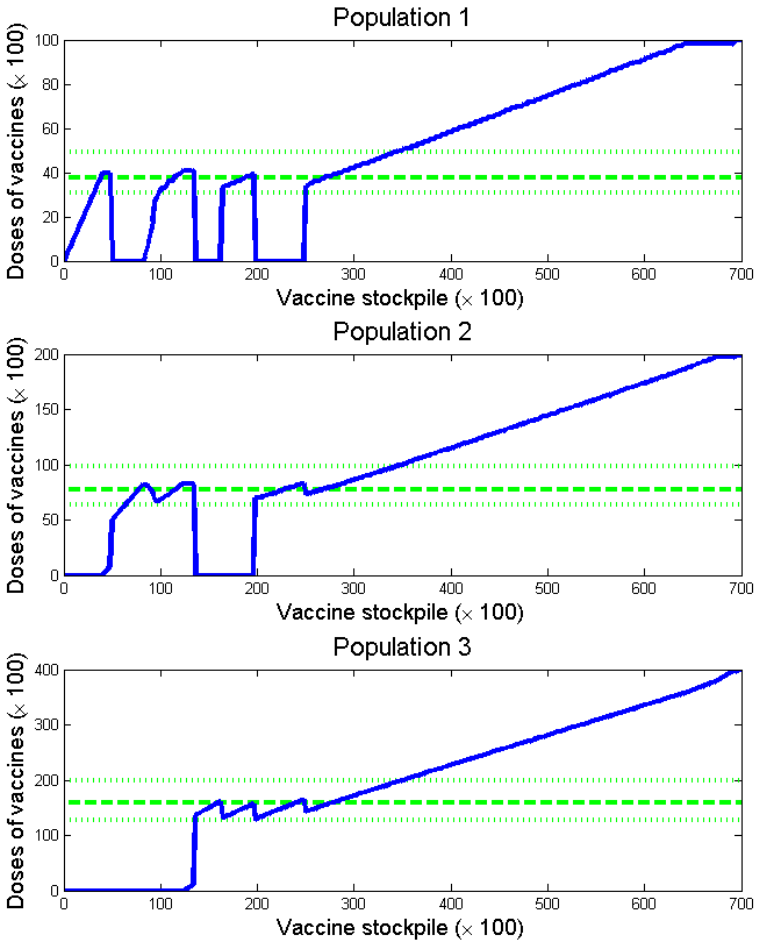

Figure 5: The graphs present the optimal vaccine allocation (the solid lines) over three interacting populations for different sizes of vaccine stockpile. The dashed and dotted lines indicate the important vaccination fractions: the dashed line in the middle equals $\tilde{V}_j = \tilde{f}_j s_j(\tau_{v,j})N_j$, the upper dotted line equals $V_j^* = f_j^* s_j(\tau_{v,j})N_j$ and the lower dotted line equals $\bar{V}_j = \bar{f}_j s_j(\tau_{v,j})N_j$.

from the non-interacting case can still be applied, which is in line with the findings of Wu et al. (2007).

The results in this paper are established under the assumption that vaccination is the only intervention used. However, in practice vaccination is often combined with treatment or isolation of infected patients. These other interventions change the course of the epidemic by influencing for example the transmission rate or the recovery rate. Further research is needed to investigate how the results derived in this paper carry over when multiple interventions

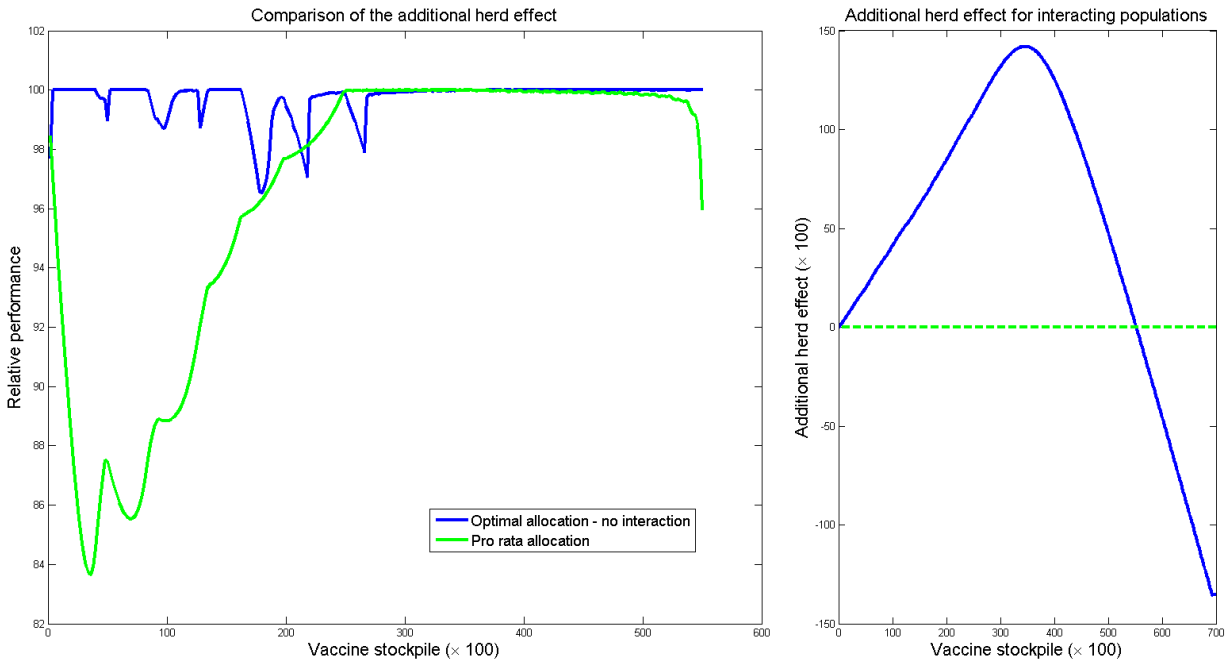

Figure 6: The left figure illustrates the relative performance of the optimal allocation for the non-interacting case (Figure 4) and the pro rata allocation evaluated in the model with interaction as described in Section 5.4. We evaluate the additional herd effect for vaccine stockpiles up to size 550, because the right figure shows that for larger vaccine stockpiles the additional herd effect becomes negative.

are combined.

Vaccination allocation has an ethical dimension, unlike many other resource allocation problems where equity does not play a role. This paper shows that for small vaccine stockpiles it is optimal to allocate only to a limited subset of populations. Only for large vaccine stockpiles it is optimal to allocate to all populations. The policy that we describe as optimal need not be the best policy if we also take equity considerations into account. Nevertheless, the vaccination policies derived in this paper can be used as a benchmark to determine the effects on the final size of an epidemic if a suboptimal policy is selected motivated by fairness. Another possibility is to reserve a part of the vaccine stockpile for pro rata allocation and allocate the remaining vaccines optimally (cf. Kaplan and Merson 2002, Wu et al. 2007). In this way policymakers are able to make a trade off between equity and health benefits.

7 Conclusions and future directions

In this paper we analyze the optimal allocation of a vaccine stockpile in order to maximize the health benefit, where we define health benefit as the total number of people that escape infection. We prove that the health benefit is convex-concave in the vaccination fraction. We then prove the existence of a unique vaccination fraction that results in the highest health benefit per dose of vaccine and introduce the term *dose-optimal* for this fraction. Based on this result we characterize the solution of the vaccination allocation problem and provide links to resource allocation literature.

This study uses an analytical approach to determine the essential problem characteristics that govern the structure of the solution. This implies that the structure of the solution can be generalized to problems with the same characteristics. Further research may thus yield an understanding of the optimal vaccine allocation for a broad range of models, including interaction and stochasticity. Eventually, such a high level understanding of a range of vaccine allocation models may increase the adoption of such models by policy-makers, who may hesitate accepting puzzling modelling outcomes without knowing what causes these outcomes.

Applying Operations Management in Health Care is increasingly becoming popular, also in the context of infectious diseases (e.g., Ekici et al. 2013, Deo and Sohoni 2015). This paper gives rise to many interesting research directions for multidisciplinary and potentially high impact research.

References

Ağralı, Semra, Joseph Geunes. 2009. Solving knapsack problems with S-curve return functions. *European Journal of Operational Research* **193**(2) 605–615.

Arino, Julien, Fred Brauer, P Van Den Driessche, James Watmough, Jianhong Wu. 2006. Simple models for containment of a pandemic. *Journal of the Royal Society Interface* **3**(8) 453–457.

Arino, Julien, P Van den Driessche. 2003. A multi-city epidemic model. *Mathematical Population Studies* **10**(3) 175–193.

Ball, Frank G, Owen D Lyne. 2002. Optimal vaccination policies for stochastic epidemics among a population of households. *Mathematical Biosciences* **177&178** 333–354.

Becker, Niels G, Dianna N Starczak. 1997. Optimal vaccination strategies for a community of households. *Mathematical Biosciences* **139**(2) 117–132.

Boulier, Bryan L, Tejwant S Datta, Robert S Goldfarb. 2007. Vaccination externalities. *The B.E. Journal of Economic Analysis & Policy* **7**(1).

Bowman, Christopher S, Julien Arino, Seyed M Moghadas. 2011. Evaluation of vaccination strategies during pandemic outbreaks. *Mathematical Biosciences and Engineering* **8**(1) 113–122.

Brandeau, Margaret L, Gregory S Zaric, Anke Richter. 2003. Resource allocation for control of infectious diseases in multiple independent populations: beyond cost-effectiveness analysis. *Journal of Health Economics* **22**(4) 575–598.

Cairns, Andrew JG. 1989. Epidemics in heterogeneous populations: aspects of optimal vaccination policies. *Mathematical Medicine and Biology* **6**(3) 137–159.

Cho, Soo-Haeng. 2010. The optimal composition of influenza vaccines subject to random production yields. *Manufacturing & Service Operations Management* **12**(2) 256–277.

Cooper, Ben S, Richard J Pitman, W John Edmunds, Nigel J Gay. 2006. Delaying the international spread of pandemic influenza. *PLoS Medicine* **3**(6) e212.

Corless, Robert M, Gaston H Gonnet, David EG Hare, David J Jeffrey, Donald E Knuth. 1996. On the Lambert W function. *Advances in Computational Mathematics* **5**(1) 329–359.

Deo, Sarang, Milind Sohoni. 2015. Optimal decentralization of early infant diagnosis of HIV in resource-limited settings. *Manufacturing & Service Operations Management* **17**(2) 191–207.

Diekmann, Odo, Hans Heesterbeek, Tom Britton. 2012. *Mathematical tools for understanding infectious disease dynamics*. Princeton University Press.

Ekici, Ali, Pinar Keskinocak, Julie L Swann. 2013. Modeling influenza pandemic and planning food distribution. *Manufacturing & Service Operations Management* **16**(1) 11–27.

Ferguson, Neil M, Derek AT Cummings, Simon Cauchemez, Christophe Fraser, Steven Riley, Aronrag Meeyai, Sopon Iamsirithaworn, Donald S Burke. 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* **437**(7056) 209–214.

Fine, Paul EM. 1993. Herd immunity: history, theory, practice. *Epidemiologic Reviews* **15**(2) 265–302.

Germann, Timothy C, Kai Kadau, Ira M Longini, Catherine A Macken. 2006. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Sciences* **103**(15) 5935–5940.

Ginsberg, William. 1974. The multiplant firm with increasing returns to scale. *Journal of Economic Theory* **9**(3) 283–292.

Goldstein, E, A Apolloni, B Lewis, JC Miller, M Macauley, S Eubank, M Lipsitch, J Wallinga. 2009. Distribution of vaccine/antivirals and the least spread line in a stratified population. *Journal of the Royal Society Interface* **7**(46) 755–764.

Goldstein, E, J Wallinga, M Lipsitch. 2012. Vaccine allocation in a declining epidemic. *Journal of The Royal Society Interface* **9**(76) 2798–2803.

Halloran, M Elizabeth, Neil M Ferguson, Stephen Eubank, Ira M Longini, Derek AT Cummings, Bryan Lewis, Shufu Xu, Christophe Fraser, Anil Vullikanti, Timothy C Germann, et al. 2008.

Modeling targeted layered containment of an influenza pandemic in the United States. *Proceedings of the National Academy of Sciences* **105**(12) 4639–4644.

Hethcote, Herbert W. 1976. Qualitative analyses of communicable disease models. *Mathematical Biosciences* **28**(3) 335–356.

Hethcote, Herbert W. 2000. The mathematics of infectious diseases. *SIAM Review* **42**(4) 599–653.

Hethcote, Herbert W, Paul Waltman. 1973. Optimal vaccination schedules in a deterministic epidemic model. *Mathematical Biosciences* **18**(3) 365–381.

Hill, Andrew N, Ira M Longini Jr. 2003. The critical vaccination fraction for heterogeneous epidemic models. *Mathematical Biosciences* **181**(1) 85–106.

Hyman, James M, Jia Li, E Ann Stanley. 1999. The differential infectivity and staged progression models for the transmission of HIV. *Mathematical Biosciences* **155**(2) 77–109.

John, T Jacob, Reuben Samuel. 2000. Herd immunity and herd effect: new insights and definitions. *European Journal of Epidemiology* **16**(7) 601–606.

Kaplan, Edward H, Michael H Merson. 2002. Allocating HIV-prevention resources: balancing efficiency and equity. *American Journal of Public Health* **92**(12) 1905–1907.

Keeling, Matt J, Joshua V Ross. 2015. Optimal prophylactic vaccination in segregated populations: When can we improve on the equalising strategy? *Epidemics* **11** 7–13.

Keeling, Matt J, Andrew Shattock. 2012. Optimal but unequitable prophylactic distribution of vaccine. *Epidemics* **4**(2) 78–85.

Kermack, WO, AG McKendrick. 1927. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London. Series A* **115**(772) 700–721.

Klepac, Petra, Ramanan Laxminarayan, Bryan T Grenfell. 2011. Synthesizing epidemiological and economic optima for control of immunizing infections. *Proceedings of the National Academy of Sciences* **108**(34) 14366–14370.

Lefevre, Cl. 1979. Optimal control of the simple stochastic epidemic with variable recovery rates. *Mathematical Biosciences* **44**(3) 209–219.

Ma, Junling, David JD Earn. 2006. Generality of the final size formula for an epidemic of a newly invading infectious disease. *Bulletin of Mathematical Biology* **68**(3) 679–702.

Matrajt, Laura, M Elizabeth Halloran, Ira M Longini Jr. 2013. Optimal vaccine allocation for the early mitigation of pandemic influenza. *PLoS Computational Biology* **9**(3) e1002964.

Matrajt, Laura, Ira M Longini Jr. 2010. Optimizing vaccine allocation at different points in time during an epidemic. *PLoS ONE* **5**(11) e13767.

McCoy, Jessica H, Hau L Lee. 2014. Using fairness models to improve equity in health delivery fleet management. *Production and Operations Management* **23**(6) 965–977.

Medlock, Jan, Lauren Ancel Meyers, Alison Galvani. 2009. Optimizing allocation for a delayed influenza vaccination campaign. *PLoS Currents* **1** RRN1134.

Mylius, Sido D, Thomas J Hagenaars, Anna K Lugnér, Jacco Wallinga. 2008. Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. *Vaccine* **26**(29) 3742–3749.

Plans-Rubió, Pedro. 2012. The vaccination coverage required to establish herd immunity against influenza viruses. *Preventive Medicine* **55**(1) 72–77.

Rowthorn, Robert E, Ramanan Laxminarayan, Christopher A Gilligan. 2009. Optimal control of epidemics in metapopulations. *Journal of the Royal Society Interface* **6**(41) 1135–1144.

Sattenspiel, Lisa, Klaus Dietz. 1995. A structured epidemic model incorporating geographic mobility among regions. *Mathematical Biosciences* **128**(1) 71–91.

Simons, Emily, Molly Mort, Alya Dabbagh, Peter Strebel, Lara Wolfson. 2011. Strategic planning for measles control: using data to inform optimal vaccination strategies. *Journal of Infectious Diseases* **204**(suppl 1) S28–S34.

Sun, Peng, Liu Yang, Francis de Véricourt. 2009. Selfish drug allocation for containing an international influenza pandemic at the onset. *Operations Research* **57**(6) 1320–1332.

Tanner, Matthew W, Lisa Sattenspiel, Lewis Ntaimo. 2008. Finding optimal vaccination strategies under parameter uncertainty using stochastic programming. *Mathematical Biosciences* **215**(2) 144–151.

Tuite, Ashleigh R, David N Fisman, Jeffrey C Kwong, Amy L Greer. 2010. Optimal pandemic influenza vaccine allocation strategies for the Canadian population. *PloS ONE* **5**(5) e10520.

Uribe-Sánchez, Andrés, Alex Savachkin, Alfredo Santana, Diana Prieto-Santa, Tapas K Das. 2011. A predictive decision-aid methodology for dynamic mitigation of influenza pandemics. *OR Spectrum* **33**(3) 751–786.

Wallinga, Jacco, Michiel van Boven, Marc Lipsitch. 2010. Optimizing infectious disease interventions during an emerging epidemic. *Proceedings of the National Academy of Sciences* **107**(2) 923–928.

Wu, Joseph T, Steven Riley, Gabriel M Leung. 2007. Spatial considerations for the allocation of pre-pandemic influenza vaccination in the United States. *Proceedings of the Royal Society B: Biological Sciences* **274**(1627) 2811–2817.

Wu, Joseph T, Lawrence M Wein, Alan S Perelson. 2005. Optimization of influenza vaccine selection. *Operations Research* **53**(3) 456–476.

Yuan, Edwin C, David L Alderson, Sean Stromberg, Jean M Carlson. 2015. Optimal vaccination in a stochastic epidemic model of two non-interacting populations. *PloS ONE* **10**(2) e0115826.

Zaric, Gregory S, Margaret L Brandeau. 2007. A little planning goes a long way: multilevel allocation of HIV prevention resources. *Medical Decision Making* **27**(1) 71–81.

Supplement - Dose-optimal vaccine allocation over multiple populations

Appendix A Analysis of the herd effect - Lemmas and theorems

This appendix consists of theorems that describe the characteristics of the function $G(f)$. The proofs for Lemma 1, Theorem 1 and Theorem 2 are presented as well as other results required for these proofs.

We need that the differential equations (1) have a solution $s(t), i(t)$ and $r(t)$ for all t which conforms to intuition: all fractions are between 0 and 1, $s(t)$ is non-increasing over time and $r(t)$ non-decreasing over time. We omit this technical result for brevity.

Theorem A.1. *It holds that* $G(f) > 0$ *for all* $f \in [0, 1)$ *and* $\lim_{f\uparrow 1} G(f) = 0$.

Proof. Consider the characterization of $G(f)$ in (22). Note that $W[0] = 0$ and $W[x] < 0$ for $\frac{-1}{e} \leq x < 0$ (Appendix D). In our case $x = -\sigma \exp\{-\sigma B(f, \sigma)\}$, with $\lim_{f\uparrow 1} B(f, \sigma) = +\infty$. Thus, $x < 0$ for $f \in [0, 1)$ and approaches 0 for $f \uparrow 1$. Therefore, $W[x] < 0$ and $G(f) > 0$ for $f \in [0, 1)$ and $\lim_{f\uparrow 1} G(f) = 0$.

□

Theorem A.2. *It holds that* $G(f) < \frac{1}{\sigma}$ *for all* $f \in [0, 1]$ *under the assumption that* $i_0 > 0$.

Proof. The differential equations in (1) show that $i(t)$ is maximized when $s(t) = 1/\sigma$. Note that $G(f)$ describes the fraction of people susceptible, when the pandemic has died out. Therefore, if $G(f) = 1/\sigma$, the function $i(t)$ is maximal when the pandemic has died out, so $i(t)$ is at most equal to 0. This contradicts our assumption that $i_0 > 0$. Using the same argument, it can be noted that it is not possible for $G(f)$ to be greater than $1/\sigma$. As long as $s(t) > 1/\sigma$, the number of infectives is increasing, thereby reducing $s(t)$. In a final state, when $i(+\infty) = 0$, it must always hold that the fraction of susceptible people is below $1/\sigma$, which completes the proof.

□

Theorem A.3. *It holds that* $G(f) < (1 - f)s(\tau_v)$ *for all* $f \in [0, 1)$ *for vaccination in an infected population.*

Proof. Upon vaccination the system changes from state $(s(\tau_v), i(\tau_v))$ to state $((1 - f)s(\tau_v), i(\tau_v))$. By assumption we have that $s(\tau_v) > 0$ and $i(\tau_v) > 0$ for vaccination in

an infected population. By the differential equations in (1) this implies that the derivative of $s(t)$ directly after vaccination is negative. As $G(f) = \lim_{t\to+\infty} s(t)$ (3) and $s(t)$ is non-increasing over time, we have that $G(f) < s(\tau_v + \epsilon) = (1-f)s(\tau_v)$.

□

Lemma 1. *The function $G(f)$ is twice differentiable for all $f \in [0,1)$ in case of vaccination in an infected population ($i_0 > 0$) and twice differentiable for all $f \in [0,1)$ with $f \neq 1 - \frac{1}{\sigma s(\tau_v)}$ in case of vaccination in a completely susceptible population (the limit $i_0 \downarrow 0$).*

Proof. We prove the following four statements consecutively:

(i). The function $G(f)$ is differentiable for all $f \in [0,1)$ for vaccination in an infected population.

(ii). In case of vaccination in a completely susceptible population (i.e., $s_0 > 0$, $i_0 = 0$ and $s(\tau_v) = s_0$) the function $G(f)$ is indifferentiable if and only if $f^* = 1 - \frac{1}{\sigma s(\tau_v)}$ or $f = 1$.

(iii). The function $G(f)$ is twice differentiable for all $f \in [0,1)$ in case of vaccination in an infected population.

(iv). The function $G(f)$ is twice differentiable for all $f \in [0,1)$ except for $f = f^* = 1 - \frac{1}{\sigma s(\tau)}$ in case of vaccination in a completely susceptible population.

We start the proof:

(i). Note that vaccination in an infected population means $i(\tau_v) > 0$ and $i_0 > 0$ which implies $G(f) < \frac{1}{\sigma}$ by Theorem A.2. Denote by $G'(f)$ the first order derivative of the function $G(f)$ with respect to f which can be obtained by taking the derivative of (6):

$$G'(f)\left[1 - \frac{1}{\sigma G(f)}\right] = \frac{1}{\sigma(1-f)} - s(\tau_v) \tag{9}$$

For $G(f) = \frac{1}{\sigma}$ the function $G'(f)$ is not defined as can be seen in (9). However, this does not occur for vaccination in an infected population (Theorem A.2). The function $G(f) : [0,1] \to \mathbb{R}$, we analyze the boundaries $f = 0$ and $f = 1$. Because $G(0) < \frac{1}{\sigma}$ by Theorem A.2:

$$\lim_{f\downarrow 0} G'(f) = \frac{1}{\left[1 - \frac{1}{\sigma G(0)}\right]}\left(\frac{1}{\sigma} - s(\tau_v)\right) \tag{10}$$

By Theorem A.1 we have $\lim_{f\uparrow 1} G(f) = 0 < \frac{1}{\sigma}$ and thus $\lim_{f\uparrow 1} G'(f) < 0$.

(ii). First we will prove that the given vaccination fractions indeed render $G(f)$ to be indifferentiable. Consider the explicit expression for $G(f)$ in (22) and insert the parameter settings for vaccination in a completely susceptible population and the value for f^*:

$$G(f) = \frac{-1}{\sigma} W\left[-\sigma \exp\{-\log(\sigma) - 1\}\right] = \frac{-1}{\sigma} W[-\exp\{-1\}] = \frac{1}{\sigma}$$

By (i) the function $G(f)$ is indifferentiable at f^*, because $G(f^*) = \frac{1}{\sigma}$. The same theorem also states that $G(f)$ is indifferentiable at $f = 1$. Now we will also prove that for vaccination in a completely susceptible population $G(f)$ is differentiable for all $f \in [0, 1)$ for which $f \neq f^*$. By definition of the Lambert W function, $W(y(f))$, this function is differentiable for all $y(f) \notin \{0, -1/e\}$ (Corless et al. 1996). Let $G(f) = \frac{-1}{\sigma} W[y(f)]$, with $y(f) = -\sigma s(\tau_v)(1-f)\exp\{-\sigma s(\tau_v)(1-f)\}$ for vaccination in a completely susceptible population (22). Clearly $y(f) < 0$, since $s(\tau_v) = s_0 > 0$ by assumption and $f < 1$. Thus, we only need to investigate for which f the function $y(f) = -\exp\{-1\}$. Note that this only holds for: $\sigma s(\tau_v)(1-f) = 1 \Leftrightarrow f = 1 - \frac{1}{\sigma s(\tau_v)} = f^*$

(iii). By (9) and (11) $G(f)$ is twice differentiable unless one of the following conditions holds: $G(f) = \frac{1}{\sigma}, f = 1, G(f) = 0$. In Theorem A.1 we showed that $G(f) > 0$ for all $f \in [0, 1)$. By Theorem A.2 we know that $G(f) < \frac{1}{\sigma}$ for vaccination in an infected population and since $\lim_{f \uparrow 1} G(f) = 0$, part (iii) follows directly.

(iv). For vaccination in a completely susceptible population we showed that $G(f) = \frac{1}{\sigma} \Leftrightarrow f = f^*$ in part (ii), which proves part (iv).

□

Theorem 1. *For $s(\tau_v) > \frac{1}{\sigma}$ there is a unique vaccination fraction $f^* = 1 - \frac{1}{\sigma s(\tau_v)} > 0$ such that the herd effect $G(f)$ is increasing in f for all $f < f^*$, maximized for $f = f^*$ and decreasing for $f > f^*$. For $s(\tau_v) \leq \frac{1}{\sigma}$ the function $G(f)$ is decreasing for all $f \in [0, 1]$. If $i_0 > 0$, then $G'(f^*) = 0$.*

Proof. Denote by $G'(f)$ the first order derivative of the function $G(f)$ with respect to f which can be obtained from (6) (see (9)). By Theorem A.1 we have $\lim_{f \uparrow 1} G(f) = 0$ and thus the function $G'(f)$ is not defined for $f = 1$. Because $G(f) < \frac{1}{\sigma}$ for all $f \in [0, 1]$ (Theorem A.2), the function $G(f)$ is maximized for $f = f^* = 1 - \frac{1}{\sigma s(\tau_v)}$. It is increasing for $f < f^*$ and decreasing for $f > f^*$. Note that for $s(\tau_v) \leq \frac{1}{\sigma}$ we get $f^* \leq 0$ and thus the function $G(f)$ is only decreasing in that case.

□

Lemma A.1. *Let $G''(f)$ be the second derivative of the function $G(f)$ with respect to f. Then for $i_0 > 0$ the following holds:*

(i). $G''(f) = 0$ if and only if $G(f) = \frac{2}{\sigma} - (1-f)s(\tau_v)$.

(ii). $G''(f) > 0$ if and only if $G(f) > \frac{2}{\sigma} - (1-f)s(\tau_v)$.

(iii). $G''(f) < 0$ for $f \geq 1 - \frac{1}{\sigma s(\tau_v)}$ and $G''(f) < 0$ if and only if $G(f) < \frac{2}{\sigma} - (1-f)s(\tau_v)$ for $f < 1 - \frac{1}{\sigma s(\tau_v)}$.

Proof. The function $G''(f)$ can be derived from (9):

$$\begin{aligned} G''(f)\left[1 - \frac{1}{\sigma G(f)}\right] = &\quad \frac{1}{\sigma(1-f)^2} - \frac{1}{\sigma}\left[\frac{G'(f)}{G(f)}\right]^2 \\ G''(f) = &\quad \frac{G(f)^2 - [G'(f)(1-f)]^2}{(\sigma G(f) - 1)G(f)(1-f)^2} \end{aligned} \tag{11}$$

Because $\lim_{f\uparrow 1} G(f) = 0$ (Theorem A.1), the function $G''(f)$ is not defined for $f = 1$. We prove the three statements of the lemma:

(i). We analyze $G''(f) = 0$ and consider that $G(f) < \frac{1}{\sigma}$ (Theorem A.2):

$$\begin{aligned} G''(f) = 0 &\Leftrightarrow \frac{G(f)^2 - [G'(f)(1-f)]^2}{(\sigma G(f) - 1)G(f)(1-f)^2} = 0 \\ &\Leftrightarrow G(f)^2 - [G'(f)(1-f)]^2 = 0 \\ &\Leftrightarrow G(f)^2 = \left[\frac{[1 - \sigma(1-f)s(\tau_v)]G(f)}{[\sigma G(f) - 1]}\right]^2 \\ &\Leftrightarrow [1 - \sigma(1-f)s(\tau_v)]^2 = [\sigma G(f) - 1]^2 \end{aligned} \tag{12}$$

In the second step we use that $(\sigma G(f) - 1)G(f)(1-f)^2 \neq 0$, which holds for all $f < 1$ by Theorems A.1 and A.2. In the third step we substitute (9). Thus $G''(f) = 0$ if and only if one of the following two relations holds:

$$1 - \sigma(1-f)s(\tau_v) = \sigma G(f) - 1 \Leftrightarrow G(f) = \frac{2}{\sigma} - (1-f)s(\tau_v) \qquad \text{if } f < 1 - \frac{1}{\sigma s(\tau_v)}$$

$$1 - \sigma(1-f)s(\tau_v) = 1 - \sigma G(f) \Leftrightarrow G(f) = (1-f)s(\tau_v) \qquad \text{if } f > 1 - \frac{1}{\sigma s(\tau_v)}$$

By Theorem A.3 $G(f) < (1-f)s(\tau_v)$ which implies that the second relation does not hold. Thus, $G''(f) = 0$ if and only if the first relation holds. The function $G''(f) = 0$ on the interval $[0, 1 - \frac{1}{\sigma s(\tau_v)}]$ for the value of f which satisfies $G(f) = \frac{2}{\sigma} - (1-f)s(\tau_v)$.

(ii). Consider the second expression in (11), by Theorems A.1 and A.2 we have: $(\sigma G(f) - 1)G(f)(1-f)^2 < 0$ for $f < 1$ From (12) we derive:

$$\begin{aligned} G''(f) > 0 &\Leftrightarrow G(f)^2 - [G'(f)(1-f)]^2 < 0 \\ &\Leftrightarrow G(f)^2 < \left[\frac{[1-\sigma(1-f)s(\tau_v)]G(f)}{[\sigma G(f)-1]}\right]^2 \\ &\Leftrightarrow [1-\sigma(1-f)s(\tau_v)]^2 > [\sigma G(f)-1]^2 \end{aligned}$$

Thus $G''(f) > 0$ if and only if one of the following two relations hold:

$$1-\sigma(1-f)s(\tau_v) < \sigma G(f) - 1 \Leftrightarrow G(f) > \frac{2}{\sigma} - (1-f)s(\tau_v) \qquad \text{if } f < 1 - \frac{1}{\sigma s(\tau_v)}$$

$$1-\sigma(1-f)s(\tau_v) > 1 - \sigma G(f) \Leftrightarrow G(f) > (1-f)s(\tau_v) \qquad \text{if } f \geq 1 - \frac{1}{\sigma s(\tau_v)}$$

By Theorem A.3 the second relation cannot hold and thus $G''(f) > 0$ if and only if $G(f) > \frac{2}{\sigma} - (1-f)s(\tau_v)$, which can only hold for $f < 1 - \frac{1}{\sigma s(\tau_v)}$.

(iii). Analogous to the previous proof we have: $G''(f) < 0 \Leftrightarrow [1-\sigma(1-f)s(\tau_v)]^2 < [\sigma G(f) - 1]^2$ Thus, $G''(f) < 0$ if and only if one of the following two relations hold:

$$1-\sigma(1-f)s(\tau_v) > \sigma G(f) - 1 \Leftrightarrow G(f) < \frac{2}{\sigma} - (1-f)s(\tau_v) \qquad \text{if } f < 1 - \frac{1}{\sigma s(\tau_v)}$$

$$1-\sigma(1-f)s(\tau_v) < 1 - \sigma G(f) \Leftrightarrow G(f) < (1-f)s(\tau_v) \qquad \text{if } f \geq 1 - \frac{1}{\sigma s(\tau_v)}$$

By Theorem A.3 the second relation is satisfied and thus $G''(f) < 0$ for all $f \geq 1 - \frac{1}{\sigma s(\tau_v)}$. For $f < 1 - \frac{1}{\sigma s(\tau_v)}$ we have that $G''(f) < 0$ if and only if $G(f) < \frac{2}{\sigma} - (1-f)s(\tau_v)$.

□

Theorem A.4. *The derivative of $G(f)$ with respect to f, denoted by $G'(f)$, is bounded from above by $s(\tau_v)$, with $s(\tau_v) \geq 0$, i.e., $G'(f) < s(\tau_v) \quad \forall f \in [0,1]$*

Proof. From (9) we have:

$$G'(f)\left[1 - \frac{1}{\sigma G(f)}\right] = \frac{1}{\sigma(1-f)} - s(\tau_v) \Leftrightarrow G'(f) = \frac{\sigma G(f)}{\sigma G(f) - 1} \cdot \frac{1-\sigma(1-f)s(\tau_v)}{\sigma(1-f)} \tag{13}$$

From Lemma A.1 we note that $G'(f)$ has an extreme under the following condition:

$$G(f) = \frac{2}{\sigma} - (1-f)s(\tau_v) \tag{14}$$

By contradiction we assume that there exists a vaccination fraction $\bar{f}$ for which $G'(\bar{f}) \geq s(\tau_v)$ and assume that $\bar{f}$ meets condition (14), then:

$$G'(\bar{f}) = \frac{2 - \sigma(1-\bar{f})s(\tau_v)}{\sigma(1-\bar{f})} \geq s(\tau_v) \Leftrightarrow \bar{f} > 1 - \frac{1}{\sigma s(\tau_v)}$$

We arrive at a contradiction, because by Theorem 1 we have that $G'(f) < 0$ for all $f > 1 - \frac{1}{\sigma s(\tau_v)}$ and $s(\tau_v) \geq 0$. Thus, $G'(f) < s(\tau_v)$ for all f that are an extreme for $G'(f)$. This completes the proof that $G'(f) < s(\tau_v)$ for all $f \in (0,1)$. We consider the two boundary cases: $f = 0$ and $f = 1$. From Lemma 1 we know that $\lim_{f \uparrow 1} G'(f) < 0$ and thus the lemma is satisfied for $f = 1$. For $\lim_{f \downarrow 0} G'(f)$, we distinguish between three cases:

(i). if $G''(0) = 0$: then $f = 0$ is an extreme of the function $G'(f)$ for which the derivative is strictly smaller than $s(\tau_v)$.

(ii). if $G''(0) > 0$: then for a very small $\epsilon > 0$ we have $G'(\epsilon) > \lim_{f \downarrow 0} G'(f)$ and $G'(f) < s(\tau_v)$ for all $f \in (0,1]$. Thus also $\lim_{f \downarrow 0} G'(f) < s(\tau_v)$.

(iii). if $G''(0) < 0$: then from Lemma A.1 we have that $G(0) < \frac{2}{\sigma} - s(\tau_v)$. By (10) we have:

$$\lim_{f \downarrow 0} G'(f) = \frac{1}{\left[1 - \frac{1}{\sigma G(0)}\right]} \left(\frac{1}{\sigma} - s(\tau_v)\right)$$

Since $G(f) < \frac{1}{\sigma}$ by Theorem A.2, we have $\lim_{f \downarrow 0} G'(f) < 0$ in case $s(\tau_v) < \frac{1}{\sigma}$. In that case the theorem is satisfied. For $s(\tau_v) > \frac{1}{\sigma}$ we substitute $G(0) < \frac{2}{\sigma} - s(\tau_v)$ in (10):

$$\lim_{f \downarrow 0} G'(f) < \left[\frac{2 - \sigma s(\tau_v)}{1 - \sigma s(\tau_v)}\right] \left(\frac{1 - \sigma s(\tau_v)}{\sigma}\right) = \frac{2}{\sigma} - s(\tau_v) < s(\tau_v)$$

This completes the proof that $G'(f) < s(\tau_v)$ for all $f \in [0,1]$.

□

Theorem 2. *Denote by $W[\cdot]$ the Lambert W function (cf. Appendix D) and let C be defined as follows:*

$$C = \frac{W\left[-\sigma \exp\{-\sigma(s_0 + i_0) + \log(s_0)\}\right] + 2}{\sigma}$$

For $s(\tau_v) > C$ there exists a unique vaccination fraction $\bar{f} > 0$ such that $G(f)$ is strictly convex ($G''(f) > 0$) for all $f < \bar{f}$ and strictly concave ($G''(f) < 0$) for all $f > \bar{f}$. For $s(\tau_v) \leq C$ the function $G(f)$ is concave for all $f \in [0,1]$. If $i_0 > 0$, then $G''(\bar{f}) = 0$.

Proof. We first prove the convex-concave shape of the function $G(f)$ an then derive the value C. By (11) note that $G''(f)$ is a continuous function for $f < 1$, because both $G(f)$ and $G'(f)$

are continuous by Lemma 1. Consider the function $M(f) = G(f) - \frac{2}{\sigma} + (1-f)s(\tau_v)$. From Lemma A.1 we have that $\bar{f}$ must satisfy $G(\bar{f}) = \frac{2}{\sigma} - (1-\bar{f})s(\tau_v)$, i.e. $M(\bar{f}) = 0$. Denote by $M'(f)$ the derivative of $M(f)$ with respect to f: By Theorem A.4 we have $M'(f) < 0$. This implies that $M(f) = 0$ has only one solution and thus there is only one $\bar{f}$ for which $G''(\bar{f}) = 0$. As $G''(f)$ is a continuous function this implies that on either side of $\bar{f}$ the function $G(f)$ is either convex or concave.

By Lemma A.1 we have $G''(f) < 0$ for $f \geq 1 - \frac{1}{\sigma s(\tau_v)}$ and thus $G(f)$ is concave for $f > \bar{f}$. Since $M'(f) < 0$ and $M(\bar{f}) = 0$ it holds that $M(f) > 0$ for $f < \bar{f}$. By Lemma A.1 this implies that $G(f)$ is convex for all $f < \bar{f}$, which proves the convex-concave shape of the function $G(f)$.Note that this prove only holds for $i_0 > 0$. In case $i_0 = 0$ we refer to Lemma A.2.

We now derive the value C. For certain parameter settings the function $G(f)$ has a convex and a concave part. By Lemma A.1 the following condition must hold for $G(f)$ to be convex: $G(f) > \frac{2}{\sigma} - (1-f)s(\tau_v)$. Since $G(f)$ is convex for all values f below a certain threshold, the following condition requires that the function $G(f)$ has a convex part:

$$G(0) > \frac{2}{\sigma} - s(\tau_v) \tag{15}$$

We solve above inequality with equality to obtain the value C. By substituting in (6) this results in the following, where $H(x) = -x + \frac{1}{\sigma}\log(x)$:

$$\begin{aligned} 0 &= -\frac{2}{\sigma} + s(\tau_v) + \frac{1}{\sigma}\log\left(\frac{2}{\sigma} - s(\tau_v)\right) + s_0 + i_0 - \frac{1}{\sigma}\log(s_0) \\ H\left[\frac{2}{\sigma} - s(\tau_v)\right] &= H[s_0] - i_0 \\ s(\tau_v) &= \frac{W\left[-\sigma\exp\{k\sigma\}\right] + 2}{\sigma} = C \text{ with } k = H[s_0] - i_0 \end{aligned}$$

We know that $-1 < W\left[-\sigma\exp\{k\sigma\}\right] < 0$ (cf. Appendix D) and thus $\frac{1}{\sigma} < C < \frac{2}{\sigma}$. Note that for $s(\tau_v) \leq \frac{1}{\sigma}$ condition (15) is never met by Theorem A.2. By Theorem A.1 the condition is always met for $s(\tau_v) \geq \frac{2}{\sigma}$. Thus only for $s(\tau_v) > C$ the function $G(f)$ has a convex part and for $s(\tau_v) = C$ we have $\bar{f} = 0$.

□

Lemma A.2. *In case of vaccination in a completely susceptible population, the function $G(f)$ is convex for all $f < f^*$ and concave for all $f > f^*$, where $f^* = 1 - \frac{1}{\sigma s(\tau_v)}$.*

Proof. By Lemma 1(ii) we have that $G(f^*) = \frac{1}{\sigma}$ for vaccination in a completely susceptible population. Since the vaccination fraction f^* also maximizes the function $G(f)$ (Theorem 1),

it holds that $G(f) < \frac{1}{\sigma}$ for all $f \neq f^*$. In Lemma A.1 we derived conditions for $G(f)$ to be convex or concave where we needed that $G(f) < \frac{1}{\sigma}$. These conditions can still be used if we apply them only to $f \neq f^*$.

$$G''(f) > 0 \Leftrightarrow G(f) > \frac{2}{\sigma} - (1-f)s(\tau_v) \quad \text{and} \quad G''(f) < 0 \Leftrightarrow G(f) < \frac{2}{\sigma} - (1-f)s(\tau_v)$$

Note that for f^* we have $G(f^*) = \frac{1}{\sigma} = \frac{2}{\sigma} - (1-f^*)s(\tau_v)$. By Theorem 1 the function $G(f)$ is decreasing for $f > f^*$, whereas the expression $\frac{2}{\sigma} - (1-f)s(\tau_v)$ is increasing in f. This implies that $G(f)$ is concave for all $f > f^*$. The function $G(f)$ is increasing for $f < f^*$, just as the expression on the right hand side in the conditions for convexity and concavity. By Theorem A.4 the expression $\frac{2}{\sigma} - (1-f)s(\tau_v)$ increases with a faster rate than $G(f)$. This implies that $G(f)$ is convex for all $f < f^*$.

□

Theorem A.5. *The fraction of people not infected during the epidemic, $F(f) = fs(\tau_v) + G(f)$, is increasing in f for all $f \in [0, 1)$.*

Proof. Let $F'(f)$ denote the derivative of $F(f)$ with respect to f: $F'(f) = \frac{d}{df}F(f) = s(\tau_v) + G'(f)$ By Theorem 1 $G'(f) > 0$ for all $f < 1 - \frac{1}{\sigma s(\tau_v)}$ and $G'(f) < 0$ for all $f > 1 - \frac{1}{\sigma s(\tau_v)}$. Because $s(\tau_v) > 0$ the function $F(f)$ is increasing for all $f < 1 - \frac{1}{\sigma s(\tau_v)}$. The function $F(f)$ is increasing under the following condition:

$$\begin{aligned} F'(f) = s(\tau_v) + G'(f) &= \frac{\sigma G(f)}{\sigma G(f) - 1}\left[\frac{1}{\sigma(1-f)} - s(\tau_v)\right] + s(\tau_v) \\ &= \frac{1}{\sigma G(f) - 1}\left[\frac{G(f)}{\sigma(1-f)} - s(\tau_v)\right] > 0 \end{aligned}$$

By Theorem A.2 $F'(f) > 0$ if and only if $G(f) < (1-f)s(\tau_v)$, which holds by Theorem A.3 for all $f \in [0, 1)$. Thus the function $F(f)$ is increasing for all $f \in [0, 1)$.

□

Corollary 1. *The function $D(f)$ as defined by (7) is maximized by the unique vaccination fraction $\tilde{f}$ for which $G'(\tilde{f}) = D(f)$. The function $D(f)$ is increasing for $f < \tilde{f}$ and decreasing for $f > \tilde{f}$.*

Proof. The function $D(f)$ is defined as follows: $D(f) = \frac{1}{f}\left[G(f) - G(0)\right]$.

$$\begin{aligned} \frac{d}{df}D(f) &= \frac{1}{f}\left[G'(f) - D(f)\right] \\ \frac{d^2}{df^2}D(f) &= \frac{1}{f}G''(f) - \frac{2}{f^2}[G'(f) - D(f)] \end{aligned}$$

By the first derivative of $D(f)$, $\tilde{f}$ is clearly an extreme of the function $D(f)$. Observe that in the limit $f \downarrow 0$ is always a solution of the condition $G'(\tilde{f}) = D(f)$, by definition of the derivative. For parameter settings for which the function $G(f)$ does not have a convex part, the function $D(f)$ only decreases and is thus maximal for $f = 0$. However, if $G(f)$ has a convex domain, it holds that $G'(f) > D(f)$ as long as $G(f)$ is convex and increasing is, such that $D(f)$ is also increasing. This implies that $f = 0$ cannot maximize the function $D(f)$ if $G(f)$ has a convex domain and that $\tilde{f}$ is in the concave domain of $G(f)$.

Assume that $\tilde{f}$ is the first value in the concave domain for which $G'(\tilde{f}) = D(f)$. Because of concavity it holds that $G(f)$ for all $f > \tilde{f}$ is below the line through $G(0)$ and $G(\tilde{f})$. For all $f > \tilde{f}$ this implies:

$$\frac{1}{f}[G(f) - G(0)] < \frac{1}{\tilde{f}}\left[G(\tilde{f}) - G(0)\right]$$

Let f_1 be an arbitrarily selected value greater than $\tilde{f}$. Because of concavity the function $G(f)$ for all $f > f_1$ is below the line through $G(0)$ and $G(f_1)$. This implies that $D(f)$ is decreasing for $f > \tilde{f}$. Thus, there is only one strictly positive solution for the condition $G'(f) = D(f)$, which is in the concave and increasing domain of $G(f)$. By the second derivative of $D(f)$, $\tilde{f}$ gives a maximum.

□

Lemma 2. *Consider the following three vaccination fractions: $\bar{f}$ as defined in Theorem 2, the dose-optimal vaccination fraction $\tilde{f}$ and f^* as defined in Theorem 1. The following relation holds: $\bar{f} \leq \tilde{f} \leq f^*$*

Proof. By Lemma A.1 we know that $G''(f) \leq 0 \Leftrightarrow G(f) \leq \frac{2}{\sigma} - (1 - f)s(\tau_v)$. Filling in the expression for $f^* = 1 - \frac{1}{\sigma s(\tau_v)}$ results in $G(f^*) \leq \frac{1}{\sigma}$. This clearly holds by Theorem A.2 and thus $\bar{f} \leq f^*$, due to Theorem 2. The optimal vaccination fraction $\tilde{f}$ is defined as the fraction that maximizes the function $D(f)$ and meets the condition $G'(\tilde{f}) = D(\tilde{f})$. Observe that $D(\tilde{f}) \geq 0$, because $\lim_{f \downarrow 0} D(f) = 0$. This implies that $G'(\tilde{f}) \geq 0$ and thus $\tilde{f} \leq f^*$ by Theorem 1. By argument we showed in Corollary 1 that $\tilde{f}$ cannot be in the convex domain of the function $G(f)$, such that $\bar{f} \leq \tilde{f}$.

□

Lemma 3. *For increasing σ the dose-optimal vaccine fraction $\tilde{f}$ converges to f^*.*

Proof. The basic reproduction ratio is denoted by σ. By Lemma 2 it suffices to show that $\lim_{\sigma \uparrow +\infty} f^* - \bar{f} = 0$. By definition we have $\lim_{\sigma \uparrow +\infty} f^* = \lim_{\sigma \uparrow +\infty} 1 - \frac{1}{\sigma s(\tau_v)} = 1$. Clearly, for $\sigma \uparrow +\infty$ and $\bar{f} = 1$ the condition $G(\bar{f}) = \frac{2}{\sigma} - (1 - \bar{f}s(\tau_v))$ is satisfied. This completes the proof.

□

Theorem 6. *The value $\tilde{f}$, which maximizes $D(f) = [G(f) - G(0)]/f$, decreases when $s(\tau_v)$ decreases.*

Proof. Let $K(f)$ and $K'(f)$ denote respectively the derivative of $G(f)$ and $G'(f)$ with respect to $s(\tau_v)$. The functions $K(f)$ and $K'(f)$ can be determined from (6):

$$K(f)\left[1 - \frac{1}{\sigma G(f)}\right] = -f \quad \text{and} \quad K'(f)\left[1 - \frac{1}{\sigma G(f)}\right] = -1 - G'(f)K(f)\frac{1}{\sigma G(f)^2}$$

Remark that $G(f)$ is increasing in $s(\tau_v)$, because $G(f) < \frac{1}{\sigma}$ by Theorem A.2 and thus $K(f) > 0$.

Define the function $C(f) = G(f) - G(0) - fG'(f)$. The vaccination fraction $\tilde{f}$ is characterized by the unique solution to $C(f) = 0$. For $f < \tilde{f}$ we have $C(f) < 0$ and for $f > \tilde{f}$ we have $C(f) > 0$. We consider how the function $C(f)$ changes with $s(\tau_v)$:

$$\frac{\partial}{\partial s(\tau_v)}C(f) = \frac{\partial}{\partial s(\tau_v)}\left(G(f) - G(0) - fG'(f)\right) = K(f) - fK'(f) = \frac{fG'(f)K(f)\frac{1}{\sigma G(f)^2}}{\left[1 - \frac{1}{\sigma G(f)}\right]}$$

Above expression is negative at $\tilde{f}$, because $G(f)$ is increasing for $\tilde{f}$, $K(f) > 0$ and $G(f) < \frac{1}{\sigma}$. This implies that $C(\tilde{f}) > 0$ for any $s < s(\tau_v)$. Thus, the peak of $D(f)$ for $s < s(\tau_v)$ is attained at a value $f < \tilde{f}$, for $\tilde{f}$ maximizing $D(f)$ for $s(\tau_v)$. This completes the proof.

□

Theorem A.6. *Let $\bar{f}$ be the value for which $G''(\bar{f}) = 0$ and f^* for which $G'(f^*) = 0$. Both $\bar{f}$ and f^* decrease when $s(\tau_v)$ decreases.*

Proof. The peak of $G(f)$ is attained at $f^* = 1 - \frac{1}{\sigma s(\tau_v)}$. Thus, f^* decreases when $s(\tau_v)$ decreases. For $\bar{f}$ it holds that $G(\bar{f}) = \frac{2}{\sigma} - (1 - \bar{f})s(\tau_v)$. When $s(\tau_v)$ decreases to $s_2(\tau_v)$, the right side of this expression increases. From Theorem 6 we know that $G(f)$ is increasing in $s(\tau_v)$, because the derivative $K(f) > 0$. With $s(\tau_v)$ decreasing, also $G(\bar{f})$ decreases to $G_2(\bar{f})$. This implies that $G_2(\bar{f}) < \frac{2}{\sigma} - (1 - \bar{f})s_2(\tau_v)$. This implies that our initial $\bar{f}$ is already in the concave part when $s(\tau_v)$ decreases and thus the value for f where the function $G(f)$ goes from concave to convex, denoted by $\bar{f}$ also decreases if $s(\tau_v)$ decreases.

□

Appendix B Generality of the function $G(f)$

One of the extensions to the standard SIR compartmental model, is the SI^nR 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 susceptible in every state are given by $i_k(t)$ for $k = 1, ..., n$. Interpretation dictates that $s(t)+\sum_{k=1}^{n} i_k(t)+r(t) = 1$ for all t. Let β_k and γ_k denote respectively the transmission rate and recovery rate in infectious stage k. The differential equations for the SI^nR model are:

$$\begin{aligned}
\frac{ds}{dt} &= -s\sum_{k=1}^{n}\beta_k i_k \\
\frac{di_1}{dt} &= s\sum_{k=1}^{n}\beta_k i_k - \gamma_1 i_1 \\
\frac{di_k}{dt} &= \gamma_{k-1} i_{k-1} - \gamma_k i_k \quad k = 2, ..., n \\
\frac{dr}{dt} &= \gamma_n i_n
\end{aligned} \tag{16}$$

Theorem 3. *Up to a constant, the expression for $G(f)$ given in (6) also applies to the SI^nR model with $\sigma = \sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}$.*

Proof. The following relation can be derived from (16), using $\sigma = \sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}$.

$$\begin{aligned}
\int_0^\infty \frac{1}{s(t)}ds &= -\sum_{k=1}^{n}\beta_k\int_0^\infty i_k(t)dt \\
\log(s(t)) - \log(s(0)) &= -\sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}\left[G_k(t) - G_k(0)\right] \\
&= \sigma\left[s(t) + \sum_{k=1}^{n} i_k(t)\right] - \sigma\left[s(0) + \sum_{k=1}^{n} i_k(0)\right] - \sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}\left[\sum_{m=k+1}^{n} i_m(t) - i_m(0)\right]
\end{aligned} \tag{17}$$

We let $t \to \infty$ and assume that $i_k(\infty) = 0$ for $k = 1, ..., n$. This results in the following expression, which is equal to the expression for the SIR model up to a constant:

$$0 = -s(\infty) + \frac{1}{\sigma}\log(s(\infty)) - \frac{1}{\sigma}\log(s(0)) + s(0) + \sum_{k=1}^{n} i_k(0) - \frac{1}{\sigma}\sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}\sum_{m=k+1}^{n} i_m(0) \tag{18}$$

Assume that we vaccinate a fraction f of the susceptible people at time τ_v. Analogous to the analysis of the SIR model, we let $((1-f)s(\tau_v), i_1(\tau_v), ..., i_n(\tau_v))$ be a new initial state and define the value $s(\infty)$ according to (18). The values for $i_k(\tau_v)$ for $k = 1, ..., n$ can be calculated according to (17). We define $G(f) = \lim_{t\to\infty} s(t)$, where $s(t)$ follows (16) for

$t > \tau_v$. This results in the following:

$$0 = -G(f) + \frac{1}{\sigma}\log(G(f)) - \frac{1}{\sigma}\log(s(0)(1-f)) + s(0) + \sum_{k=1}^{n} i_k(0) - fs(\tau_v) - \frac{1}{\sigma}\sum_{k=1}^{n}\frac{\beta_k}{\gamma_k}\sum_{m=k+1}^{n} i_m(0) \tag{19}$$

Above expression equals the expression for the SIR model (6) up to a constant.

□

Corollary 2. *The results of Lemma 1, Theorem 1, Theorem 2 and Corollary 1 also apply to the SI^nR model with $\sigma = \sum_{k=1}^{n} \frac{\beta_k}{\gamma_k}$.*

Proof. By Theorem 3 the expression for $G(f)$ in the SI^nR model is equal to the expression in the SIR model up to a constant. This constant disappears after taking the derivative, implying that the first and second order derivative do not change. The structural properties of the function $G(f)$ thus carry over.

□

Appendix C Optimal vaccine allocation - Theorems and proofs

Theorem 2 establishes that Problem (5) is a resource allocation problem with an S-shaped objective function: non-decreasing and convex for all x smaller than some value $\hat{x}$ and concave for all $x > \hat{x}$ (cf. Ginsberg (1974) and Ağralı and Geunes (2009)). As the vaccine allocation problem is a maximization problem with inequality constraints, necessary conditions for the optimum are given by the Karush-Kuhn-Tucker (KKT) conditions. Let ω be the KKT multiplier for the capacity constraint, λ_j for the non-negativity constraint $f_j \geq 0$ for all $j \in J$ and μ_j for the constraint $f_j \leq 1$ for all $j \in J$. Denote by $\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}$ the vectors with the variables f_j, λ_j and μ_j respectively. Let $\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \omega)$ denote the Lagrange function of the maximization problem. The KKT conditions for this problem are given in (20). Observe that the term *partial pro rata* follows from the KKT condition that the partial derivative of $\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \omega)$ with respect to f_j equals 0 for all $j \in J$.

$$\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \omega) = \sum_{j \in J} N_j F_j(f_j) - \omega\left(\sum_{j \in J} f_j s_j(\tau_{v,j}) N_j - V\right) - \sum_{j \in J}\left(\mu_j(f_j - 1) - \lambda_j f_j\right)$$

$$
\begin{aligned}
\frac{\partial}{\partial f_j}\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \omega) &= 0 \quad \forall j \in J \\
\omega \left(\sum_{j \in J} f_j s_j(\tau_{v,j}) N_j - V \right) &= 0 \qquad\qquad \omega \geq 0 \\
\lambda_j f_j &= 0 \quad \forall j \in J \qquad \lambda_j \geq 0 \quad \forall j \in J \\
\mu_j (f_j - 1) &= 0 \quad \forall j \in J \qquad \mu_j \geq 0 \quad \forall j \in J
\end{aligned}
\tag{20}
$$

Lemma C.1. *The vaccine allocation problem always has a solution for which* $\sum_{j \in J} f_j s_j(\tau_{v,j}) N_j = V$.

Proof. Let x_j for all $j \in J$ be a solution of the vaccine allocation problem and assume that $\sum_{j \in J} x_j s_j(\tau_{v,j}) N_j < V$. Let y_j for all $j \in J$ be the solution for which $y_j \geq x_j$ for all $j \in J$, such that $\sum_{j \in J} y_j s_j(\tau_{v,j}) N_j = V$. By Lemma A.5 the functions $F_j(f)$ are non-decreasing and thus $F_i(y_i) \geq F_j(x_j)$ for all $j \in J$. This implies:$\sum_{j \in J} N_j F_j(y_j) \geq \sum_{j \in J} N_j F_j(x_j)$ Above relation proves that the proposed solution y_j for all $j \in J$ for which $\sum_{j \in J} y_j s_j(\tau_{v,j}) N_j = V$ is also an optimal solution.

□

Theorem 4 (Central Insight)**.** *For every optimal solution to* (5) *there exist* $J' \subseteq J$, $k \in J \backslash J'$ *and* $\omega \geq 0$ *such that:*

(i). For all $j \in J'$, f_j *is the unique solution to* $\frac{1}{s_j(\tau_{v,j})} F_j'(f_j) = \omega$ *for which* $f_j \geq \bar{f}_j$.

(ii). $\frac{1}{s_k(\tau_{v,k})} F_k'(f_k) = \omega$, *and either* f_k *is the unique solution to this equation for which* $f_k \geq \bar{f}_k$ *or* f_k *is the unique solution for which* $f_k < \bar{f}_k$.

(iii). Either $f_j = 0$ *or* $f_j = 1$ *for all* $j \in J \setminus \{J' \cup \{k\}\}$.

Proof. The proof of this theorem consists of the following steps:

(a). Let $J' \subseteq J$ such that $0 < f_j < 1$ for all $j \in J' \cup \{k\}$. We prove that $\frac{1}{s_j(\tau_{v,j})} F_j'(f_j) = \omega$ for all $j \in J' \cup \{k\}$.

(b). We prove that for at most one population there is a strictly positive vaccination fraction in the strictly convex domain, i.e. $0 < f_j < \bar{f}_j$ for at most one $j \in J' \cup \{k\}$.

We proof the two steps consecutively:

(a). This result follows from the KKT conditions. Note that for any population j for which $0 < f_j < 1$ the KKT conditions require that $\mu_j = 0$ and $\lambda_j = 0$. This gives the

following:

$$\frac{\partial}{\partial f_j}\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \omega) = N_j F_j'(f_j) - \omega s_j(\tau_{v,j}) N_j - \mu_j + \lambda_j$$
$$= N_j \left[F_j'(f_j) - \omega s_j(\tau_{v,j})\right] = 0 \Leftrightarrow \frac{1}{s_j(\tau_{v,j})} F_j'(f_j) = \omega$$

(b). By contradiction assume there is an optimal solution with at least two strictly positive variables in the convex domain. W.l.o.g. let $0 < f_j < \bar{f}_j$ for $j = 1, 2$, i.e. the functions $F_1(f)$ and $F_2(f)$ are convex at respectively f_1 and f_2. By the KKT conditions $F_1'(f_1) = F_2'(f_2)$. Choose an $0 < \epsilon < \min\left\{f_1, f_2 \frac{N_2 s_2(\tau_{v,2})}{N_1 s_1(\tau_{v,1})}, \bar{f}_1 - f_1, (\bar{f}_2 - f_2)\frac{N_2 s_2(\tau_{v,2})}{N_1 s_1(\tau_{v,1})}\right\}$ and let $\delta = \epsilon \frac{N_1 s_1(\tau_{v,1})}{N_2 s_2(\tau_{v,1})}$ such that:

$$f_1 s_1(\tau_{v,1}) N_1 + f_2 s_2(\tau_{v,1}) N_2 = (f_1 + \epsilon) s_1(\tau_{v,1}) N_1 + (f_2 - \delta) s_2(\tau_{v,2}) N_2$$

By convexity of $F_1(f_1)$ and $F_2(f_2)$ the following can be derived:

$$N_1 F_1(f_1+\epsilon) + N_2 F_2(f_2-\delta) > N_1 F_1(f_1) + N_2 F_2(f_2) + \epsilon N_1 [F_1'(f_1) - F_2'(f_2)] = N_1 F_1(f_1) + N_2 F_2(f_2)$$

Above relation shows that the objective function can be improved by a small change in the allocation. Thus, a solution with more than one strictly positive variable in the convex domain can never be optimal.

□

Lemma C.2. *If $s_j(\tau_{v,j}) > \frac{1}{\sigma_j}$ for all $j \in J$, then there is no optimal solution to (5) for which $f_j = 0$ and $f_k = 1$ for two populations $j, k \in J$. This implies that (iii) of Theorem 4 changes into: Either $f_j = 0$ for all $j \in J \setminus \{J' \cup \{k\}\}$ or $f_j = 1$ for all $j \in J \setminus \{J' \cup \{k\}\}$.*

Proof. By contradiction assume that $f_1 = 0$ and $f_2 = 1$ w.l.o.g. Let $\epsilon > 0$ and $\delta = \epsilon \frac{N_1 s_1(\tau_{v,1})}{N_2 s_2(\tau_{v,1})}$ such that:

$$f_1 s_1(\tau_{v,1}) N_1 + f_2 s_2(\tau_{v,2}) N_2 = (f_1 + \epsilon) s_1(\tau_{v,1}) N_1 + (f_2 - \delta) s_2(\tau_{v,2}) N_2$$

The following holds:

$$N_1 F_1(\epsilon) + N_2 F_2(1-\delta) - N_1 F_1(0) - N_2 F_2(1) = N_1 [G_1(\epsilon) - G_1(0)] + N_2 [G_2(1-\delta) - G_2(1)] > 0$$

By Theorem A.1 $G_j(f_j) > 0$ for all $0 \leq f_j < 1$ and $\lim_{f_j \uparrow 1} G_j(f_j) = 0$. This implies that the second term is positive. Furthermore, for $s_j(\tau_{v,j}) > \frac{1}{\sigma_j}$ the function $G_j(f)$ is initially

increasing by Theorem 1, implying that $G_1(\epsilon) > G_1(0)$. Thus, a small change in allocation can improve the solution. We arrive at a contradiction and thus the proof of the lemma is completed. □

Theorem 5. *Consider a set of populations J with $\forall j$: $F_j(f) = F(f)$ and a total available amount of resources equal to V. Let $b = \frac{V}{s(\tau_v)}$, $|J| = n$ and order the populations such that $N_1 \leq ... \leq N_n$. The optimal allocation for particular cases is as follows:*

(a). if $b < \tilde{f}N_1$, then allocate only to the smallest population. Set $f_1 = b/N_1$ and $f_j = 0$ for $j = 2, ..., n$.

(b). if $b = \sum_{j \in K} \tilde{f}N_j$ for a subset $K \subseteq J$, then set $x_j = \tilde{f}$ for $j \in K$ and $x_j = 0$ for $j \notin K$.

(c). if $b > \sum_{j \in J} \tilde{f}N_j$, then allocate pro rata over all the populations: $x_j = \frac{b}{\sum_{j \in J} N_j}$ for all $j \in J$.

Proof. (a). Step (b) in the proof of Theorem 4 shows that an optimal allocation results in at most one strictly positive vaccination fraction in the convex domain. By this result, the proposed allocation follows directly from convexity of the function $G(f)$ for all $f < \bar{f} < \tilde{f}$.

(b). The proposed allocation results in the maximum attainable value for the objective function for $V = bs(\tau_v)$ available vaccines and is thus optimal.

(c). We prove the optimality of the proposed allocation using the items of Theorem 4. Consider item (iii): for the special case an allocation with $f_j = 1$ and $f_k < 1$ for arbitrary populations $j, k \in J$ cannot be optimal:

$$N_j F(f_j - \epsilon) + N_k F\left(f_k + \epsilon \frac{N_j}{N_k}\right) - N_j F(f_j) - N_k F(f_k) = \epsilon N_j (F(f_k) - F(f_j)) > 0$$

The same holds for an allocation with $f_j > \bar{f}$ and $f_k < \bar{f}$. For the given amount of vaccines this also implies that $f_j > \tilde{f}$, such that:

$$\begin{aligned} &N_j F(f_j - \epsilon) + N_k F\left(f_k + \epsilon \frac{N_j}{N_k}\right) - N_j F(f_j) - N_k F(f_k) \\ &= N_j [F(f_j - \epsilon) - F(f_j)] + N_k \left[F\left(f_k + \epsilon \frac{N_j}{N_k}\right) - F(f_k)\right] > 0 \end{aligned}$$

By item (i) and (ii) of Theorem 4 the optimal allocation for $b > \sum_{j \in J} \tilde{f}N_j$ is thus a pro rata allocation over the populations $K \subseteq J$. Remains to prove that it is optimal

to allocate pro rata over all populations, i.e. $K = J$. Let z_j denote the pro rata allocation over $K \subset J$ and x_j the pro rata allocation over all populations in J. Denote $\hat{z} = \frac{b}{\sum_{j\in K} N_j}$ and $\hat{x} = \frac{b}{\sum_{j\in J} N_j}$ and remark that $\hat{z} > \hat{x} > \tilde{f}$. This implies the following:

$$\begin{aligned}
[F(\hat{z}) - F(0)]/\hat{z} &< [F(\hat{x}) - F(0)]/\hat{x} \\
\sum_{j\in K} N_j F(\hat{z}) - \sum_{j\in K} N_j F(0) &< \sum_{j\in J} N_j F(\hat{x}) - \sum_{j\in J} N_j F(0) \\
\sum_{j\in K} N_j F(\hat{z}) + \sum_{j\notin K} N_j F(0) &< \sum_{j\in J} N_j F(\hat{x})
\end{aligned}$$

Above inequality proves that if b is allocated pro rata over the populations of a subset of J, every strict subset will result in a lower objective function. Therefore, it is best to allocate the available amount pro rata over all the populations.

□

Appendix D The Lambert W function

This appendix considers the Lambert W function, or product log function (cf. Corless et al. (1996)). The Lambert W function, $W(x)$, solves $x = W(x)e^{W(x)}$. In this study we consider only real valued x and the function $W(x)$ is then defined only for $x \geq -\frac{1}{e}$. For $x \in [-\frac{1}{e}, 0]$ the function $W(x)$ has two values, but two branches of $W(x)$ can be defined that are both single valued. The constraint $W(x) \leq -1$ can be added to construct the branch $W_{-1}(x)$ defined only for $x \in [-\frac{1}{e}, 0]$. The other branch $W_0(x)$ holds for all $x \geq -\frac{1}{e}$ and meets the constraint $W(x) \geq -1$. This branch is also referred to as the principal branch, denoted by $W_p(x)$.

D.1 Lambert W function for the final size

To study the final size in an epidemic, the fraction of people still susceptible when the pandemic has died out, denoted by $G(f)$ can be expressed using the Lambert W function (cf. Ma and Earn (2006)). Let $W_p(x)$ be the principal branch of the Lambert W function which by definition solves the following expression for $x \geq -\frac{1}{e}$:

$$x = W(x)e^{W(x)}. \tag{21}$$

Using the Lambert W function, the function $G(f)$ can be expressed as:

$$\begin{aligned} G(f) &= \frac{-1}{\sigma} W\left(-\sigma \exp\{-\sigma B(f)\}\right) \\ \text{with } B(f) &= s_0 + i_0 - \frac{1}{\sigma}\log(s_0(1-f)) - f s(\tau_v) \end{aligned} \tag{22}$$

which can be verified by substituting (22) into (21), which leads to (6).

Let $G(f) = \frac{-1}{\sigma} W[y(f)]$, with $y(f) = -\sigma s_0 (1-f) \exp\left\{-\sigma(s_0 + i_0 - f s(\tau_v))\right\}$ (22). We will study $y(f)$ in more detail to determine which branch of the Lambert W function is needed for the calculation of $G(f)$.

Theorem D.1. $-\frac{1}{e} \leq y(f) \leq 0$

Proof. Because $\sigma > 0$, we have $y(f) \leq 0$. Analyze the extreme values of $y(f)$:

$$\frac{d}{df} y(f) = \sigma s_0 \exp\left\{-\sigma(s_0 + i_0 - f s(\tau_v))\right\}\left[1 - \sigma s(\tau_v)(1-f)\right] = 0 \Leftrightarrow f = 1 - \frac{1}{\sigma s(\tau_v)}$$

It suffices to show that $y(f) \geq -\frac{1}{e}$ for $f = 1 - \frac{1}{\sigma s(\tau_v)}$:

$$\begin{aligned} -\frac{s_0}{s(\tau_v)} \exp\{-\sigma(s_0 + i_0 - s(\tau_v)) - 1\} &\geq -\frac{1}{e} \\ \log(s_0) - \sigma\left(s_0 + i_0 - s(\tau_v)\right) &\leq \log(s(\tau_v)) \\ 0 &\leq -s(\tau_v) + \frac{1}{\sigma}\log(s(\tau_v)) + s_0 + i_0 - \frac{1}{\sigma}\log(s_0) \end{aligned}$$

By (2) above relation holds, because $i(\tau_v) \geq 0$.

□

By Theorem A.2 we know that $G(f) < \frac{1}{\sigma}$ and thus $-1 < W(-\sigma \exp\{-\sigma B(f,\sigma)\}) < 0$. By Theorem D.1 we have that only the principal branch $W_0(x)$ is needed for $G(f)$ (22).

Appendix E Interacting populations

In Section 5.4 the optimal allocation is analyzed for weakly interacting populations. In this appendix three figures are presented with the optimal allocation for increasing levels of interaction. Figures 7, 8 and 9 display the optimal allocation in case interaction between populations is respectively 0.02, 0.05 and 0.1 times the interaction within a population. This corresponds to interaction between populations being a factor 50, 20 or 10 times weaker than interaction within a population. The figures are discussed in Section 5.4.

Each of the graphs present the optimal vaccine allocation (the solid lines) over three interacting populations for different sizes of vaccine stockpile. The dashed and dotted lines indicate the important vaccination fractions: the dashed line in the middle equals $\tilde{V}_j = \tilde{f}_j s_j(\tau_{v,j}) N_j$, the upper dotted line equals $V_j^* = f_j^* s_j(\tau_{v,j}) N_j$ and the lower dotted line equals $\bar{V}_j = \bar{f}_j s_j(\tau_{v,j}) N_j$.

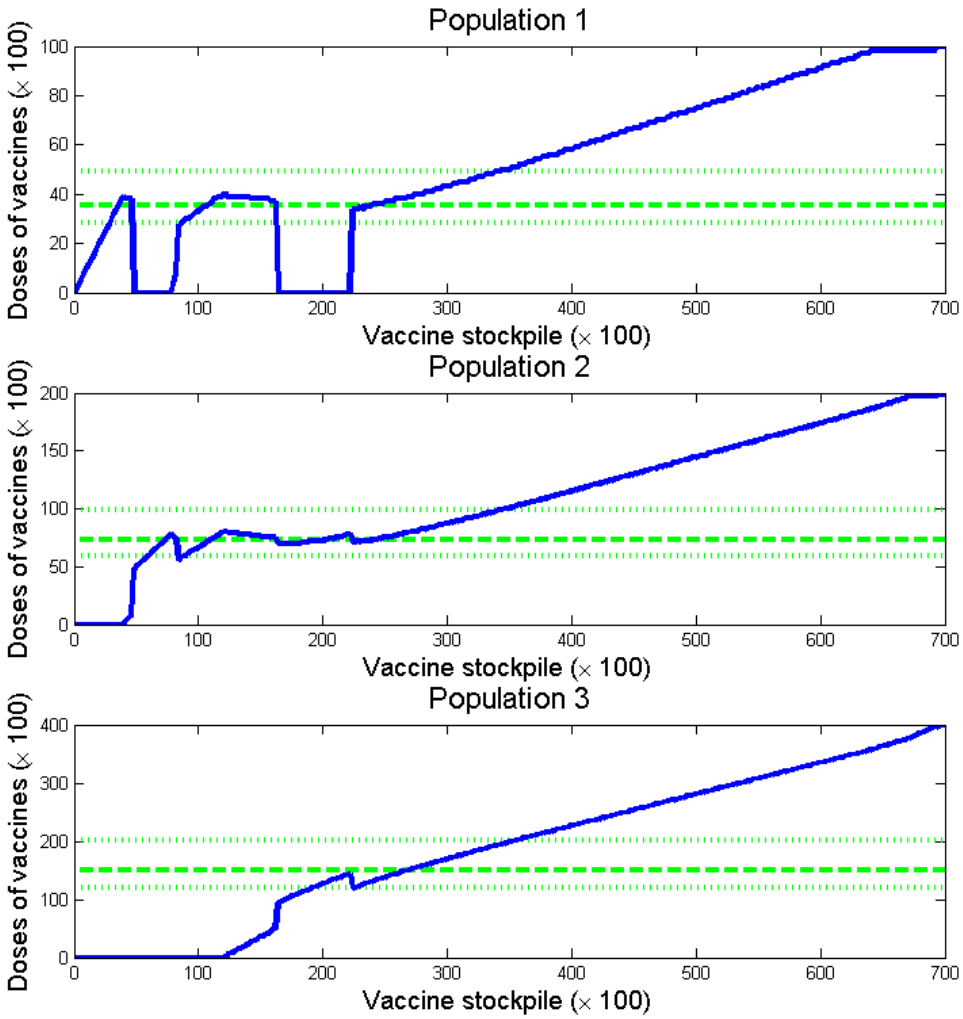

Figure 7: The optimal allocation in case interaction between populations is 0.02 times the interaction within a population.

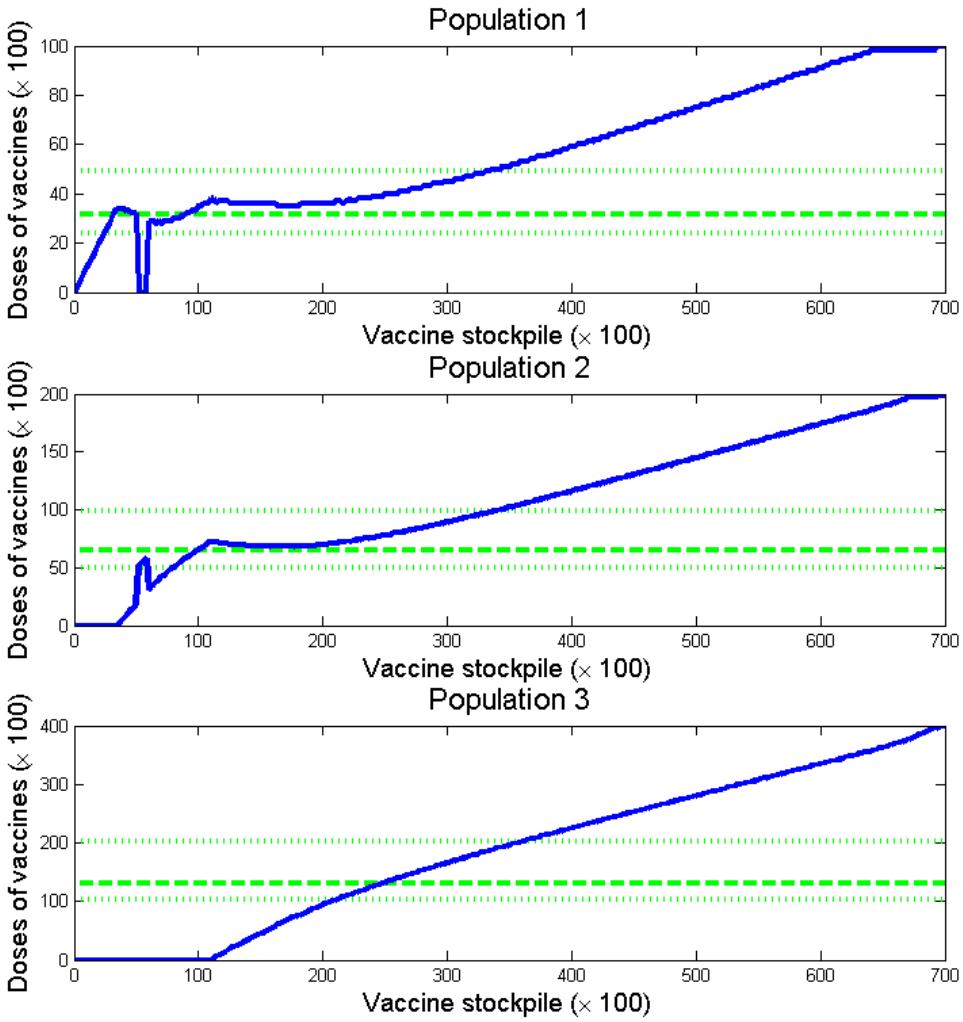

Figure 8: The optimal allocation in case interaction between populations is 0.05 times the interaction within a population.

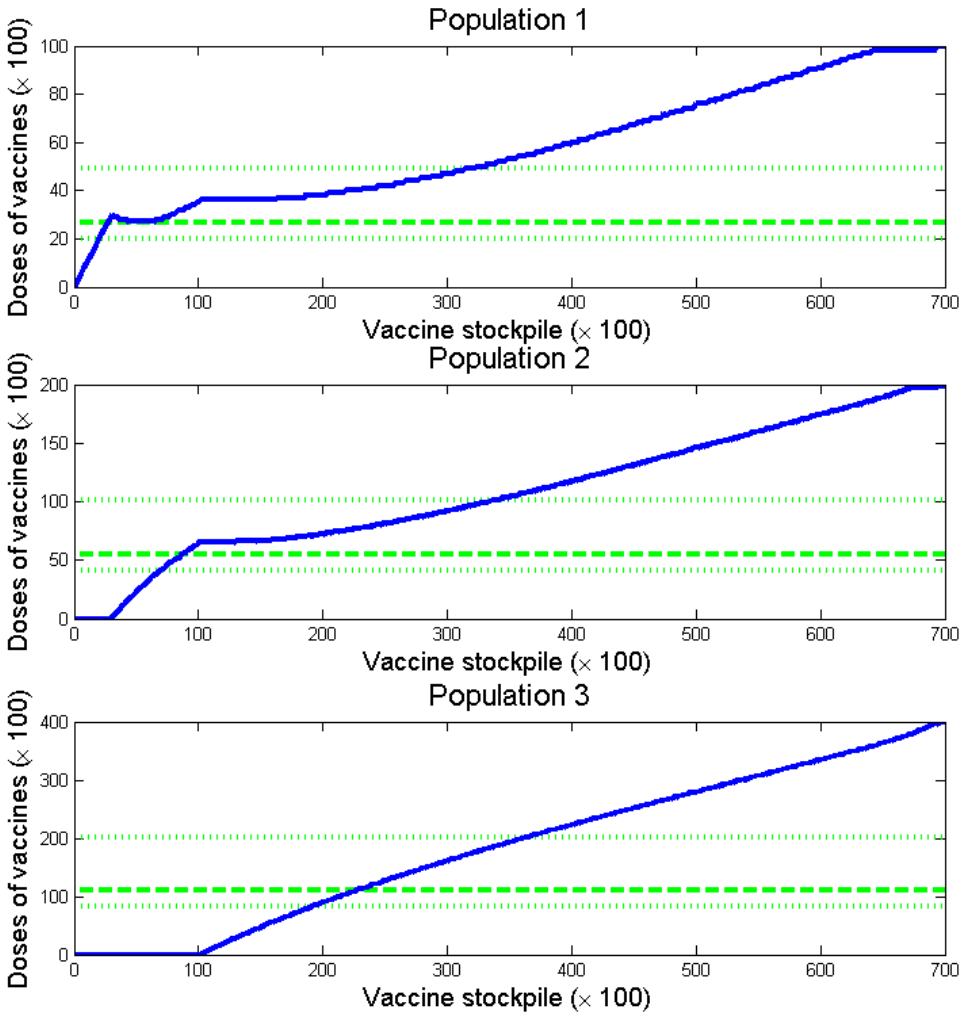

Figure 9: The optimal allocation in case interaction between populations is 0.1 times the interaction within a population.