

EVELOT DUIJZER

# Mathematical Optimization in Vaccine Allocation





# MATHEMATICAL OPTIMIZATION IN VACCINE ALLOCATION



# Mathematical Optimization in Vaccine Allocation

Wiskundige optimalisatie in vaccinatieallocatie

Thesis

to obtain the degree of Doctor from the  
Erasmus University Rotterdam  
by command of the  
rector magnificus

Prof.dr. H.A.P. Pols

and in accordance with the decision of the Doctorate Board

The public defence shall be held on

Friday 15 September 2017 at 09:30 hrs

by

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**ERIM Electronic Series Portal:** <http://repub.eur.nl/>

### ERIM PhD Series in Research in Management, 430

ERIM reference number: EPS-2017-430-LIS

ISBN 978-90-5892-490-2

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Design: PanArt, [www.panart.nl](http://www.panart.nl)

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# Acknowledgments

In this section, I would like to take the opportunity to thank the people who have contributed to the completion of this dissertation. I am indebted to my promotor, Rommert Dekker, for the opportunity he gave me to develop myself as a researcher. Although Rommert has a busy schedule, he had always time for a meeting and provided me with interesting new perspectives. Willem van Jaarsveld served as my daily supervisor and was always very helpful and willing to answer all kinds of questions. I am particularly thankful for all the time Willem took to read my manuscripts and for the feedback he provided in his unique handwriting. His comments undoubtedly helped me to improve my writing style. It is also nice to see how he has grown as a supervisor. Although Jacco Wallinga was technically not one of my supervisors, we have met and discussed my work multiple times during these four years. I have always appreciated Jacco's friendliness and his input and perspective were invaluable for this multidisciplinary project.

I would like to thank Prof. Joris van de Klundert and Prof. Albert Wagelmans for being part of my inner committee and for evaluating this dissertation. Prof. Odo Diekmann and Prof. Mirjam Kretzchmar agreed to participate in the opposition during the defense ceremony, which I appreciate.

Besides doing research, I also had the pleasure to assist in several courses. It was enjoyable to be part of the team for Introduction to Statistics and I admire Christiaan Heij's enthusiasm and his well-organized course. I am grateful to Rommert for giving me the freedom to develop my own teaching style and for allowing me to obtain my University Teaching Qualification.

These last four years would not have been as pleasant without my fellow PhD students in the Operations Research group and I would like to thank all of them. I have enjoyed the open atmosphere and the willingness to discuss all kinds of work and

non-work related matters. I have gathered many pleasant memories, including our table tennis and office-hockey matches and our gardening activities in the windowsill.

Although the importance of good supervisors and colleagues can hardly be overestimated, there is more in life than work. I am grateful to my parents and to my family for their support and encouragement and for helping me to clear my mind. It has been, and still is, a pleasure to go to Gorinchem for a weekend and leave all the work-related matters behind in Rotterdam. These words of thanks also extend to the Westerink family in Nunspeet and to my friends. I feel blessed to be part of two loving families and to have valuable friendships. My brother Christiaan and my colleague and friend Gert-Jaap Polinder agreed to be my paranymphs and I am glad to have them standing beside me during the defense ceremony. The final words of thanks go to Christian, to whom I am deeply grateful for more than words can say.

Looking back on these four years, I cannot but conclude that there is nothing I have that I did not receive. SOLI DEO GLORIA.

Evelot Duijzer

Rotterdam, June 2017



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# Chapter 1

## Introduction

### 1.1 Infectious diseases

Infectious diseases have heavily influenced the course of history. From the 14th until the 19th century, there were several major outbreaks of the plague, causing millions and millions of victims. Also the Spanish influenza in 1918 took the lives of over twenty million people. Nowadays, in most countries infectious diseases no longer cause such staggering death tolls and some diseases have even been eliminated. But new threats may arise from the outbreak of a new influenza pandemic (e.g., H1N1), another respiratory illness (e.g., SARS, MERS) or a viral disease (e.g., Ebola, Zika) as we have seen in the last years. Therefore, research on the prevention of a pandemic as well as on the actions to take if an outbreak occurs remains a high priority.

Infectious diseases can be transmitted directly (e.g., via air or body fluids) or indirectly (e.g., via mosquitos or ticks). In this dissertation we mainly consider direct transmission through air. This type of transmission has caused large unexpected outbreaks in the past (e.g., Spanish influenza) and can potentially do so in the future. Also the models for transmission via air do not require detailed assumptions on the population structure. Airborne diseases can spread through a population very quickly, because one infected individual can transmit the disease to many others. Even before an individual becomes symptomatic and is aware of the infection, he or she might already be infectious and able to transmit the disease. This can lead to large outbreaks, also referred to as epidemics, in a relatively short time. When an

epidemic has spread through populations across multiple countries or even continents, we speak of a pandemic. The spread of an infectious disease in a population is a complex nonlinear process, because of the population dynamics that affect the transmission. Epidemic models are used to analyze and understand this process.

## 1.2 Epidemic models

Over the years, many models are proposed to describe the time course of an epidemic. We refer to Keeling and Rohani (2008) and Diekmann et al. (2013) for detailed overviews of the many ways to model infectious disease dynamics.

**Deterministic models** A seminal paper in the field of epidemiological modelling is the work of Kermack and McKendrick (1927). The authors propose a mathematical model that describes how a disease spreads through a population and this model has been widely used since. The model divides the considered population into different compartments, each containing all the individuals that are in the same state of disease. The model is therefore referred to as a *compartmental model*. One of the simplest versions of the compartmental model is the *SIR* model, consisting of three compartments: susceptible (S), infected (I) and removed (R). This *SIR* model consists of a set of deterministic differential equations that describe the transitions in the population from one compartment to the other. Numerous extensions are proposed, some of which are analyzed by Hethcote (2000). One of the main advantages of a compartmental model is its simplicity: it is easy to understand and can be described in a few equations. However, despite the simple model description, compartmental models cannot be solved analytically due to their nonlinear dynamics.

**Stochastic models** To overcome the disadvantage of deterministic spread, there are studies that incorporate stochasticity in their models. Allen (2008) provides an overview of such stochastic epidemic models. These models make use of stochastic differential equations or they are based on Markov Chains. Stochastic models differ from deterministic models mainly in their asymptotic dynamics. There can be endemic equilibria in deterministic models, but in stochastic models any epidemic will eventually die out (Allen 2008). In addition, in deterministic models there are certain conditions under which an outbreak will always affect a large proportion of



the population, but in stochastic models there is always a probability that the outbreak will remain minor (Diekmann et al. 2013). For large populations, the dynamics of stochastic and deterministic models are approximately the same. Bortolussi and Hillston (2013) have made this result rigorous using a fluid approximation.

**Simulation models** In order to model the individuals in a population in detail, simulation models are developed. They thereby differ from the deterministic and stochastic models described earlier. The earlier described models are metapopulation models that subdivide the population into distinct subpopulations, while assuming that all individuals in a subpopulation are identical. Simulation models, and more precisely microsimulation models, differentiate between individuals by applying individual-based or agent-based modelling techniques. Examples of such models for the spread of influenza include the model proposed by Ferguson et al. (2005) for the population of Thailand and the work of Chao et al. (2010) for the United States. Although these individual-based models can capture many realistic aspects and generate case-specific results, analytical metapopulation models are better for deriving general insights.

Epidemic models were initially developed for descriptive purposes only, but they have shown to be very useful for prediction and evaluation as well. In particular, these models are often used to evaluate the effects of certain interventions on the course of an epidemic.

## 1.3 Vaccination

There are multiple ways to intervene in the course of an epidemic in order to reduce the number of infections. One can distinguish between pharmaceutical interventions such as vaccines and antivirals, and non-pharmaceutical interventions. The latter include social distancing measures like travel restrictions or school closures. In this dissertation we focus on pharmaceutical interventions, in particular on vaccination, which is one of the most effective ways to avoid a large epidemic.

Vaccination protects individuals from infection by inducing an immune response. After effective vaccination, this immune response results in long-lasting immunity to the infection (Keeling and Rohani 2008). We can distinguish between different types

of vaccination. Pediatric vaccination relates to childhood vaccination programs in which children are preventively vaccinated against diseases such as measles, mumps and polio. Pediatric vaccination is a form of pre-pandemic vaccination: individuals are vaccinated to *avoid* an outbreak. Reactive vaccination, on the other hand, takes place in response to an outbreak or a bioterror attack and aims at controlling an existing outbreak. In this dissertation we study both pre-pandemic and reactive vaccination.

## 1.4 Resource allocation problems

Policy makers are often confronted with limited resources in fighting or avoiding the outbreak of an infectious disease. They either have to deal with budget restrictions or face limited vaccine stockpiles. This brings about resource allocation problems: How should the available resources be deployed in order to achieve a desired outcome? For example, how should vaccines be divided over the age groups in a population or among multiple regions? In this dissertation, we formulate and analyze several of these resource allocation problems.

To quantify the outcome of a certain intervention we make use of two important performance measures: the reproduction ratio and the final size. These measures are often used in infectious disease epidemiology to express the potential of an infectious agent to cause an epidemic. The final size is the eventual number of people who have become infected. The reproduction ratio, denoted by  $R$ , is the average number of secondary cases produced by an average infectious individual in a completely susceptible population. In deterministic models, an outbreak will die out if  $R < 1$ , but will grow explosively if  $R > 1$  (Van den Driessche and Watmough 2002).  $R$  is considered to be one of the most important parameters in infectious disease epidemiology and has received considerable attention (cf., Diekmann et al. 2013). The effectiveness of an allocation is often expressed as the capability of the allocation to reduce the reproduction ratio or the final size.

Once a resource allocation problem is formulated, the goal is to find the allocation that performs best with respect to the selected performance measure. The nonlinear dynamics of infectious diseases significantly complicate the analysis of resource allocation problems in epidemiology.

## 1.5 Thesis outline

In this dissertation, we study decision problems concerning vaccine logistics. We start by considering a broad range of decision problems to map this field. We then focus on a specific subfield within vaccine logistics: the allocation of scarce resources to fight outbreaks of infectious diseases. In particular, we look at vaccine allocation problems. We describe the outbreak using the *SIR* model and we use an analytical approach to derive and analyze the solution. The outline of this dissertation is as follows.

Chapter 2 provides a literature review on the logistic decision problems that play a role in vaccination. We combine the priorities areas defined by the World Health Organization (WHO) with a supply chain perspective and propose a classification for the literature on vaccine logistics. Using this classification we structure this relatively new field and highlight promising research directions. With a view to this, we distinguish between the following four components: (1) product, (2) production, (3) allocation and (4) distribution. We find that the vaccine supply chain has some unique aspects, including asymmetry between the various parties and important differences between developing and developed countries.

In Chapters 3 - 5 we analyze three decision problems in the subfield of vaccine allocation. The nonlinear dynamics of epidemics render vaccine allocation problems difficult to optimize. Therefore, many studies in literature simplify their analysis by comparing a few allocation schemes (e.g., Mylius et al. 2008, Tuite et al. 2010), by enumerating all possibilities (e.g., Arino et al. 2008, Medlock and Galvani 2009, Keeling and Shattock 2012, Yuan et al. 2015) or by developing heuristics (e.g., Teytelman and Larson 2013). In contrast, in this dissertation we gain insights into vaccine allocation problems by looking at them from the perspective of mathematical optimization. This enables us to formulate structured approaches to finding the optimal allocation: the best possible allocation according to some well-defined criterion.

In Chapter 3, we study a decision maker that has a limited vaccine stockpile available to divide among multiple populations in order to minimize the final size. Public health organizations such as the National Institute for Public Health and the Environment (RIVM) in the Netherlands or the Centers for Disease Control and Prevention (CDC) in the United States face this decision problem when confronted with a sudden outbreak. To account for the suddenness of the outbreak, we mainly

focus on vaccination during an outbreak instead of before. We use the seminal *SIR* model to derive an expression for the final size. Even though the final size can only be expressed implicitly, we are able to prove a convex-concave structure in the vaccination fraction and the existence of a unique vaccination fraction that maximizes the number of people who escape infection per dose of vaccine. Our results provide new insights into vaccine allocation to multiple non-interacting or weakly interacting populations, such as regions that are geographically distant. These insights enable us to explain puzzling outcomes that were observed before in literature. We show that allocations that minimize the final size are rarely equitable, while equitable allocations may be significantly non-optimal.

In Chapter 4, we relax the assumptions of a limited vaccine stockpile and weakly or non-interacting populations. Instead, we consider a heterogeneous interacting population and are interested in the following optimization problem: minimize the required amount of vaccines to obtain an effective reproduction ratio of exactly one. This optimization problem occurs when decision makers want to preventively vaccinate a population in an efficient way. We prove that this optimization problem is equivalent to the problem of maximizing the proportion of susceptible people who escape infection during an epidemic. In doing so, we establish a clear connection between two key concepts in the literature of vaccination while those concepts have mostly been considered separately in the past. We explicitly solve the case of two populations and propose a greedy heuristic that optimally solves the problem in case of separable mixing. For the general case, we propose an efficient solution method and illustrate it in a case study for pre-pandemic vaccination in the initial phase of an influenza pandemic. This case study shows that the optimal allocation requires a much smaller vaccine stockpile to protect the population compared to allocations proposed previously.

Whereas Chapters 3 and 4 consider a single vaccination moment during or before an outbreak, respectively, Chapter 5 allows for multiple vaccination moments. More precisely, the chapter focuses on the budget allocation problem over two vaccine types: an early aspecific vaccine and a later specific vaccine. We compare the two vaccine types and surprisingly show that the decision maker should not exclusively consider *pure* strategies, i.e., strategies which spend the entire budget on one of the types. Instead, an appropriate investment should be made in both vaccine types to benefit from the early response and from the good vaccine. Numerical results show that such

*hybrid* strategies can reduce the number of infections by more than 50% compared to pure strategies. We note that both Chapter 3 and Chapter 5 give counterintuitive results that arise because of the nonlinear dynamics of the *SIR* model and that are atypical for regular allocation problems.

Finally, in Chapter 6 we summarize the main findings of this dissertation and derive conclusions.

## 1.6 Contribution

The chapters of this dissertation can be read individually. As a result, there is some overlap in the introduction and problem descriptions of the individual chapters. The chapters are based on papers that are either published in or submitted to scientific journals. These papers are the result of a cooperation between various authors. The references to these publications are given below.

**Chapter 2** The literature study for this chapter was conducted by the first author under supervision of dr. W. van Jaarsveld and prof.dr.ir. R. Dekker. It is based on:

Duijzer, Lotty E, Willem van Jaarsveld, Rommert Dekker. 2017b. Literature review - the vaccine supply chain. Tech. rep., Econometric Institute, Erasmus School of Economics. URL <https://repub.eur.nl/pub/99513>. Report number: EI 2017-01.

**Chapter 3** The research for this chapter was conducted by the first author in close cooperation with dr. W. van Jaarsveld. Prof.dr.ir. R. Dekker supervised the process and prof.dr. J. Wallinga contributed in defining the problem. It is based on:

Duijzer, Lotty E, Willem van Jaarsveld, Jacco Wallinga, Rommert Dekker. 2015a. Dose-optimal vaccine allocation over multiple populations. Tech. rep., Econometric Institute, Erasmus School of Economics. URL <https://repub.eur.nl/pub/79212>. Report number: EI 2015-29.

**Chapter 4** This chapter was primarily written by the first author under supervision of dr. W. van Jaarsveld and prof.dr.ir. R. Dekker. Prof.dr. J. Wallinga contributed in defining the problem and in the review process. It is based on:

Duijzer, Lotty E, Willem van Jaarsveld, Jacco Wallinga, Rommert Dekker. 2016. The most efficient critical vaccination coverage and its equivalence with maximizing the herd effect. *Mathematical Biosciences* **282** 68–81.

**Chapter 5** This chapter was primarily written by the first author under supervision of dr. W. van Jaarsveld and prof.dr.ir. R. Dekker. It is based on:

Duijzer, Lotty E, Willem van Jaarsveld, Rommert Dekker. 2017a. The benefits of combining early aspecific vaccination with later specific vaccination. Tech. rep., Econometric Institute, Erasmus School of Economics. URL <https://repub.eur.nl/pub/99515>. Report number: EI 2017-03.

**Summary in Dutch** This chapter was written entirely by the first author. It is based on:

Duijzer, Lotty E, Willem van Jaarsveld, Jacco Wallinga, Rommert Dekker. 2015b. Vaccinatieallocatie en de kracht van optimalisatie. *STAtOR* **3** 4–8.

## Chapter 2

# Literature Review - optimization in the vaccine supply chain<sup>1</sup>

### 2.1 Introduction

Every year millions of people are vaccinated preventively: they receive the annual influenza shot, are included in childhood immunization programs or are vaccinated against other infectious diseases. Preventive vaccination takes place before a disease emerges and is meant to avoid an outbreak. In addition to preventive vaccination there is also reactive vaccination, which can take place during an outbreak of an infectious disease or in response to a bioterror attack. Although vaccination is a medical intervention, successful vaccination campaigns are impossible without good logistics. The growing literature on vaccine logistics demonstrates that the importance of this is increasingly recognized.

In this chapter, we structure the literature on vaccine logistics, using the priority areas defined by the World Health Organization (WHO) (World Health Organization & PATH 2011). These priority areas allow us to evaluate the current state of

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<sup>1</sup>This chapter is based on Duijzer et al. (2017b).

literature on the vaccine supply chain and identify promising directions that could be further explored in order to create a flexible and robust vaccine supply chain:

- Products and packaging
- Immunization supply system efficiency
- Environmental impact of immunization supply systems
- Immunization information systems
- Human resources

We focus on the first three priorities of the WHO, as these are most related to Operations Research/Operations Management (OR/OM). The WHO clarifies these three priorities as follows: vaccine products and their packaging should be designed with characteristics that best suit the needs and constraints of countries; immunization supply systems should be designed to maximize effectiveness, agility, and integration with other supply systems, and to support continuous system improvement through learning, innovation, and leveraging synergies with other sectors; and the environmental impact of energy, materials, and processes used in immunization supply systems from the international to local levels should be assessed and minimized. The last two priorities, ‘Immunization information systems’ and ‘Human resources’, are not explicitly considered in this review because they are more general and not specific to vaccines.

The OR/OM community is increasingly interested in vaccine logistics, which is indicated by the fact that around 90% of the papers discussed in this review dates from 2005 and more than half, in fact, from 2011 (cf., Appendix 2.B). Despite the growing interest, the literature on vaccine logistics is somewhat scattered. E.g., most papers focus on a particular aspect of logistics (e.g., allocation or production) which results in separate clusters of papers with few cross citations. Moreover, there is limited attention in these papers to the broader perspective of vaccine logistics, making the papers difficult to place in the correct context. This larger context is important, because improving a single aspect of logistics without aligning with others will only lead to minor overall improvements (Privett and Gonsalvez 2014). Current literature falls short in presenting a broad overview of vaccine logistics and the vaccine supply chain, which makes it difficult to see where opportunities lie for the OR/OM community.



We contribute to structuring the literature on vaccine logistics by integrating the WHO priorities with an OR/OM supply chain perspective. We propose to distinguish between the following four components in the vaccine supply chain:

1. **Product** - *What kind of vaccine should be used?*

A vaccine is administered to develop immunity against a certain disease. Before vaccination can take place, policy makers must decide which disease they are targeting and which vaccine will be used. There might be multiple vaccines available for the same disease or the characteristics of the disease might not be known at the time of production. This leads to the problem of deciding on the composition of the vaccine. For the annual influenza shot, for example, the composition decision is related to the strains of the influenza virus that should be included. Questions on what vaccines to use also play a role in designing a vaccination program for multiple diseases. In designing such programs, policy makers must decide not only which diseases to include and which vaccines to use, but also when these vaccinations are scheduled in the program. Finally, for vaccines it is of high importance to determine the right package of the product, because vaccines are sensitive to changes in temperature.

2. **Production** - *How many doses should be produced?*

Once a vaccine has been selected, it has to be produced. The production of vaccines is characterized by a high level of uncertainty in production yield and long production times. This potentially leads to inefficiencies on the vaccine market. Coordination on this market can improve the match between demand and supply.

3. **Allocation** - *Who should be vaccinated?*

The available doses of vaccine are often insufficient to vaccinate the entire population, especially in case of sudden outbreaks. This creates an allocation problem: who should be vaccinated? Within a population, one can distinguish between high-risk and low-risk individuals, but also between high-transmission and low-transmission groups. Careful analysis is needed to determine which group(s) should be prioritized. Also, (re)allocation problems among different regions and/or countries can arise when an epidemic spreads across borders.

4. **Distribution** - *How to get the vaccines to the people?*

Once vaccines are available and the allocation decision has been made, the ac-

tual distribution takes place. The doses of vaccine must be located somewhere, leading to inventory control decisions. In the event of static distribution points, logistical questions related to the positioning and layout of these points come in play. For mobile teams that deliver medical support to various locations, routing and scheduling problems occur.

Throughout the chapter we also use alternative perspectives next to the supply chain perspective. One of those alternative perspectives looks at the main challenges for vaccine logistics. By analyzing the literature, we identify three main challenges: (1) increasing the efficiency and cost-effectiveness of the supply chain for planned vaccination (2) preparing for sudden outbreaks and (3) preparing for bioterror attacks. Next to that, we also use a disease-specific perspective and investigate which decision problems play a role for which disease(s). Finally, we compare the decision problems that play a role in developing countries with those in developed countries. In Table 2.1, we derive the relation between types of outbreaks, diseases and components of the supply chain. An ‘x’ in the table indicates that there are studies in this review that consider the combination of disease and supply chain component. Based on our bibliometric analysis in Chapter 2.3, we treat the studies on childhood vaccination separately. Within our supply chain framework we discuss the differences in decision problems for existing/expected outbreaks versus sudden outbreaks and developed countries versus developing countries.

The supply chain perspective that we use enables us to compare the vaccine supply chain to other supply chains. We observe that the vaccine supply chain has several unique characteristics, which leads to some general lessons for supply chains. Other aspects of the vaccine supply chain are also apparent in general supply chains (cf., Chopra and Meindl 2007). Our analysis and structuring of the literature has led to the framework in Figure 2.1, which is discussed in Section 2.8. This framework compares the vaccine supply chain to other supply chains. Using this framework we integrate the papers discussed and synthesize their contributions. We see that the components ‘Production’ and ‘Distribution’ are comparable to other supply chains, ‘Allocation’ is unique to the vaccine supply chain and ‘Product’ is somewhat in between. Decisions on which product to use play a role in every supply chain, but the composition decisions that are important in vaccination are unique.

Based on this framework we derive promising research directions. With the WHO priorities in mind, we identify the direction in which the vaccine supply chain should

	Product	Production	Allocation	Distribution
Childhood vaccination	x			
Existing/expected outbreaks				
seasonal influenza	x	x	x	x
HIV/AIDS	x	x	x	x
malaria		x	x	x
tuberculosis		x	x	x
unspecified		x	x	x
Sudden outbreaks				
pandemic influenza			x	
unspecified			x	x
Bioterror attacks				
anthrax			x	
smallpox			x	
unspecified			x	x

**Table 2.1:** Classification of studies based on type of vaccination and position in the supply chain.

	Product	Production	Allocation	Distribution
	What type of product to use?	How many products to produce and when?	Who should get the products?	How to get the products to the people?
	<i>Right product (decision)</i>	<i>Right product (realization), Right time</i>	<i>Right place (decision)</i>	<i>Right place (realization), Right time</i>
Similarities	<ul style="list-style-type: none"><li>- Product development (R&amp;D)</li></ul>	<ul style="list-style-type: none"><li>- Long production time</li><li>- Uncertain demand</li><li>- Pull process: initiated by the customer (i.e., public health organisation)</li><li>- Uncertain yields</li></ul>		<ul style="list-style-type: none"><li>- Inventory control</li><li>- Facility location</li><li>- Routing</li><li>- Supply chain design</li><li>- Perishable product</li><li>- Temperature controlled chain</li></ul>
Particularities	<ul style="list-style-type: none"><li>- Asymmetry: product is determined by public health organisations, not by the supplier</li><li>- Public health organisations are non-profit, whereas supplier is full profit</li><li>- Product changes very frequently (yearly for annual influenza vaccine)</li><li>- Product decision is made under time pressure and high demand uncertainty</li></ul>	<ul style="list-style-type: none"><li>- Demand externalities due to disease dynamics and the protective power of vaccinations for non-vaccinated people</li></ul>	<ul style="list-style-type: none"><li>- Complex decision making: political interests, equity considerations</li><li>- End customer (i.e., ‘patient’) does not pay for the product in most cases</li><li>- Push process: initiated and performed in anticipation of end customer need</li><li>- Asymmetry: end customer has no power in this phase</li></ul>	<ul style="list-style-type: none"><li>- Mass distribution under time pressure</li></ul>

**Figure 2.1:** Framework - Classification of the vaccine supply chain and overview of its particularities.

develop and what is still needed to achieve this development. We emphasize the importance of the supply chain perspective and the integration of the different stages in the supply chain. We also observe in Table 2.1 that, in particular for the higher levels of the supply chain (i.e., product and production), there are rarely any studies on sudden outbreaks. Another topic that could be further elaborated is the asymmetry in the vaccine supply chain: multiple parties are involved that each have their own interest.

Within our classification of the vaccine supply chain, we structure and discuss 147 papers, 65 of which are from top OR/OM journals. We contribute by providing the first review that connects the different logistical components of vaccination in order to develop an integrated view of the vaccine supply chain. We are aware of two reviews on related topics, but both have a rather different scope from ours. Dasaklis et al. (2012) write an extensive review on epidemic control. Both pharmaceutical and non-pharmaceutical interventions are taken into account. As the focus is on unexpected outbreaks with a natural cause or due to a bioterror attack, logistical aspects related to seasonal influenza or other expected outbreaks are not taken into account. In contrast, we restrict ourselves to vaccination, which is a special case of pharmaceutical interventions, and we consider all kinds of outbreaks (both expected and unexpected). Lemmens et al. (2016) review general models on supply chain network design (SCND) and apply their findings to the vaccine supply chain of the rotavirus vaccine. They primarily consider the distribution phase and, to a lesser extent, the production phase. The authors investigate whether the current literature on SCND is able to deal with the characteristics of the rotavirus vaccine supply chain and they indicate a number of points where there are shortcomings.

The remainder of this chapter is structured as follows. We start in Section 2.2 with a short discussion on the search strategy and the characteristics of the included publications. In Section 2.3, we perform a bibliometric analysis to cluster and visualize the publications based on co-citations. In the remaining sections, we discuss the four components of the supply chain: Product in Section 2.4, Production in Section 2.5, Allocation in Section 2.6 and Distribution in Section 2.7. We discuss our findings and present future research directions in Section 2.8 and close with conclusions in Section 2.9.

## 2.2 Search strategy

The following search strategy is used in our review. We have searched the journal databases of the top 20 journals in the category ‘Operations Research and Management Science’ of Thomson Reuters InCites Journal Citation Reports. The journals are ranked based on Article Influence Score and the ranking is presented in Appendix 2.A. These journal databases have been searched using the keywords ‘vaccination’ and ‘vaccine’. These words have a rather unique meaning. A thesaurus does not provide words with a similar meaning. The search resulted in 285 unique publications in total. The publications that were not scientific articles were disregarded. This applied to 45 publications, for example editorial statements, descriptions of award winners and book reviews. Out of the 240 remaining publications, 96 were disregarded because of the lack of any health care related terminology in either title, abstract or keywords. These publications for example cited papers with one of the keywords in the title. We were left with 144 papers, which have been studied in more detail. After careful reading, another 79 publications were disregarded because the topics did not match the scope of this literature review, in most of those cases vaccination was mentioned just once as an example. This review discusses the remaining 65 publications in the top OR/OM journals, that deal with topics related to vaccination. We also review supporting literature: e.g., from the epidemiological or health economics community and other relevant literature that we found through citation analysis. This resulted in including over 40 publications from various fields, including Immunology, Mathematical & Computational Biology and Medicine. For these streams of literature we have been more pragmatic and the list of included papers is not exhaustive. We mainly included studies that use a quantitative approach.

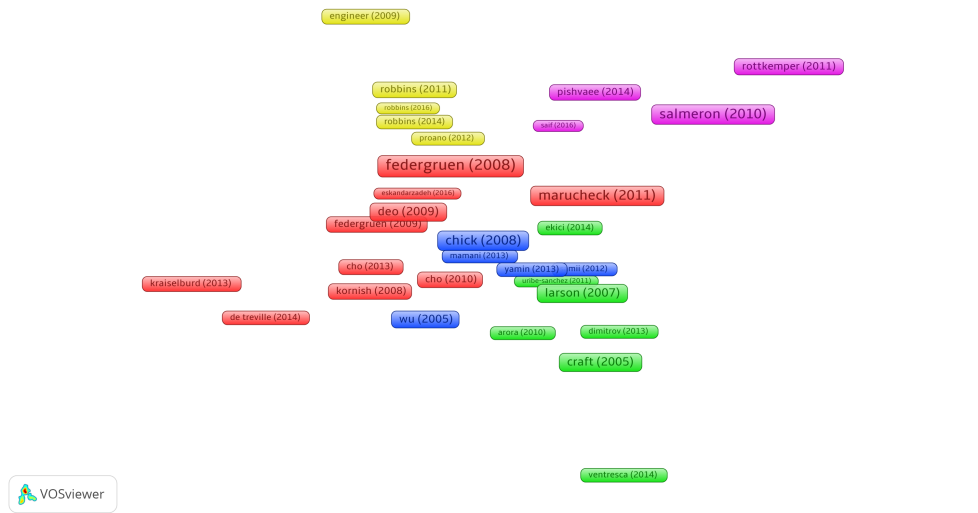
## 2.3 Bibliometric analysis

Before we discuss the papers on vaccine supply chains in detail, we perform a bibliometric analysis of the papers included in this review. The contribution of this bibliometric analysis is twofold: (1) it supports the classification of the literature that we use in the remainder of the chapter and (2) it indicates some subfields. We use the database of the Web of Science<sup>TM</sup> Core Collection to gather information (search date March 20, 2017). This chapter reviews 65 studies of which 59 are found

in this database and are hence included in the bibliometric analysis. The six papers that are not included are listed in Appendix 2.C. We use VOSViewer (cf., Van Eck and Waltman (2007) and [www.vosviewer.com](http://www.vosviewer.com)), a software tool well-established in the field of bibliometric analysis. This tool is used to structure and visualize the papers based on co-citations. VOSViewer constructs a map in which the publications are represented by labelled nodes. The map contains only the most important publications, for others the labels are omitted to avoid overlapping labels. The distances between the nodes are based on bibliographic coupling, i.e., the number of references that publications share. Hence, the closer two publications are in the map, the more shared references they have. The *weight* of a publication is measured as the total bibliographic coupling with all other publications. Node size and font size of the labels are used to express this weight. Next to the construction of the map, VOSviewer also supports clustering of the publications using a clustering algorithm. This algorithm assigns weights to each combination of publications dependent on the bibliographic coupling. The optimal clustering is determined by minimizing a weighted distance function, where the distance between publications depends on whether they are in the same cluster or not. In the map, different colors are used to distinguish between the publications in the different clusters.

The map in Figure 2.2 contains five clusters. If we analyze these clusters in more detail, we observe that the publications in each cluster are related by topic. Roughly, the clusters can be described as follows.

The yellow cluster in the top left corner captures part of the papers in the component ‘Product’, more precisely on childhood vaccination programmes. If we consider the purple cluster in the right upper corner, we conclude that there is not really a central theme that connects the publications in this cluster. We do see that most of them are related to the distribution phase of the vaccine supply chain, ranging from supply chain design to inventory decisions. The green cluster in the bottom right corner consist of papers that discuss allocation problems for unexpected outbreaks, either pandemics or bioterror attacks. The red and blue cluster are similar and are both largely formed by publications in the INFORMS journals on influenza vaccine composition and production. If we recall the three important challenges in vaccination, we observe that the yellow, red and blue cluster focus on increasing the efficiency of supply for planned vaccination. The remaining two clusters are related to papers on preparing for sudden outbreaks or bioterror attacks. We thus conclude



**Figure 2.2:** Mapping of the publications in this review, with node and font size representing the weight of a publication. The different colors represent the clusters.

that Figure 2.2 roughly confirms the challenges that we identify in vaccine logistics and our structuring of the different components of the supply chain. The way we subdivide the publications over these components qualitatively coincides with the clusters in the mapping. We also see some small subfields with a specific focus, such as bioterror response and childhood vaccination programmes. We have included these subfields in the broader components of the supply chain.

## 2.4 Product

The first decision that has to be made in the vaccine supply chain is the choice for the right product: Which vaccine should be used? For some diseases there is not yet a vaccine available (e.g., HIV/AIDS) or every year a new vaccine needs to be developed (i.e., seasonal influenza). Decision problems arise regarding the design of such vaccines. For other diseases, including the ones in childhood vaccination programs, there are often multiple suitable vaccines available. Decision makers have to decide which vaccines to use and when to schedule them in the program.

The right vaccine is a vaccine that is designed with characteristics that best suit the needs and constraints of countries (World Health Organization & PATH 2011). First and foremost, a vaccine should have the desired characteristics in terms of immunization. But also other aspects of the used vaccine can have a large influence on the supply chain, such as the volume and the temperature at which it must be stored. These characteristics particularly play a role in developing countries, where (cold) storage capacity is limited. Following the terminology of the WHO priorities, we refer to these characteristics as the ‘packaging’ of the vaccine.

In this section, we study the decision problems related to designing the right product. In Section 2.4.1, we focus on vaccine composition, i.e., on designing a vaccine such that it is able to immunize against the targeted disease. In Section 2.4.2, we consider the case that there are multiple vaccines available, but the decision maker has to select which vaccines to use. Finally, in Section 2.4.3 we study the decision problems related to packaging of vaccines.

### 2.4.1 Vaccine composition

The main goal of a vaccine is to induce immunity. To design a vaccine that achieves this goal, it is important to know the characteristics of the disease you are immunizing against. For ongoing outbreaks (e.g., AIDS, malaria) one can study the characteristics of the disease that is causing the outbreak. However, this is not the case for sudden outbreaks (e.g., of pandemic influenza) or outbreaks that are caused by bioterror attacks. Outbreaks of seasonal influenza bring about an extra challenge: Even though we know that these outbreak occur yearly, the virus strains that cause these outbreaks change every year. This leads to the following categorization of diseases: (1) diseases with unknown characteristics and a certain outbreak (seasonal influenza), (2) pandemic influenza and other sudden outbreaks and (3) diseases with known characteristics for which a vaccine is still under development (e.g., AIDS). Note that there is also a fourth category, namely the diseases with known characteristics and an available vaccine. We do not consider those diseases here, because the decision problem regarding the vaccine composition does not play a role for those diseases.

We start by considering the first group of diseases: diseases with unknown characteristics but that are known to appear in the coming future. Seasonal influenza is the most studied example for this group. Every year there is an outbreak of seasonal



influenza, but policy makers do not know beforehand which influenza virus strain will be dominant in the coming season. There exist multiple strains of the influenza virus and mutations might lead to new strains. In designing the annual influenza vaccine, policy makers therefore have to decide based on forecasts which virus strains to include in the vaccine. Due to long production times for vaccines, this decision has to be made under high uncertainty with little information about the characteristics of the coming influenza season. This results in the trade-off between deciding early based on limited information or deferring the decision to learn more. Every year the World Health Organization (WHO) advises on which virus strains to include in the influenza vaccine (Gerdil 2003, Silva et al. 2015). This combination of included virus strains is called the *vaccine composition*. At the decision moment, the most prevalent strains in the coming influenza season are still unknown, although surveillance data may be used to make predictions. Wu et al. (2005) discuss the ‘follow policy’, where the forecasted epidemic strain is included in the annual vaccine. The authors investigate whether this policy can be improved by including the antigenic history of the vaccinees, which consists of the strains to which the individual has been exposed in the past. A dynamic program is formulated to determine the optimal vaccine composition based on the antigenic history in sequential time periods. The results show that the follow policy is only slightly suboptimal and is therefore recommended to be continued. To gather more information about the coming influenza season, it could be beneficial to defer the decision on the vaccine composition. Deferring the decision reduces uncertainty and could lead to better decisions on which strains to include in the vaccine. However, there is also a deadline before which the vaccines should be produced. Waiting too long thus reduces the available time for production, potentially leading to higher production costs. Kornish and Keeney (2008) study this trade-off and formulate a commit-or-defer model. Conditions on the optimal decision are derived also using dynamic programming. Their results can be used to evaluate what-if questions related to changes in vaccine production rates, effectiveness of the vaccines, dominant strains that cause the influenza outbreak and its expected severity. Cho (2010) extends the work of Kornish and Keeney (2008) by including production yield uncertainties. Decision makers have to decide on retaining the current vaccine or shifting to updated compositions. The latter may have more production yield uncertainty. The objective is to maximize expected social welfare which is comprised of social benefits and social costs. The costs include the pro-

duction costs, which are related to production yield uncertainties. A discrete-time decision model is proposed with three possible decisions at every time: select the current vaccine strain, update to the most prevalent new strain or postpone decision making to the next period. The main contribution of their work is that they include the effects of the composition decision on the next step in the supply chain: the production of vaccines. Özaltın et al. (2011) also take the uncertain yields into account and allow for choosing among multiple possible strains for the vaccine, not only the most prevalent one. A multi-stage stochastic mixed integer model is formulated to integrate the composition decision and the timing of this decision. The results show that selecting a less prevalent strain might be beneficial, if this strain has higher production yields for example.

We now consider the second group of diseases: unknown diseases that might suddenly result in an outbreak. Designing vaccines for those diseases suffers from two types of uncertainty. It is not certain what type of disease will cause the outbreak nor do we know when there will be an outbreak, if at all. The current policy for sudden outbreaks is therefore often to design a vaccine only after an outbreak has emerged. This is for example the case for pandemic influenza (Özaltın et al. 2011). However, acting only when the outbreak has emerged might result in many infections, due the long production times of a vaccine. Decision makers can therefore decide to stockpile vaccines in order to prepare for a pandemic. Several researchers in the medical/epidemiological community have discussed the development of a ‘pre-pandemic’ vaccine for influenza (e.g., Jennings et al. 2008, Stöhr 2010, Scorza et al. 2016). Such a vaccine is tailored to the vaccine strain(s) that is (are) most likely to cause the next influenza pandemic.

Finally, there are known infectious diseases for which there is not yet a vaccine available, such as HIV/AIDS. Developing new vaccines requires medical and epidemiological expertise, but also OR techniques might be helpful. We discuss a number of studies that consider the development of new vaccine. Ding and Eliashberg (2002) study the pipeline problem for new development of products. This problem concerns a company that has to decide in which products to invest, while it is still uncertain whether the development will be successful. The authors motivate their problem with describing potential approaches for developing an HIV vaccine. The model assists policy makers in deciding in which of these approaches they should invest. Maher and Murray (2016) consider a specific technique to develop an HIV

vaccine, namely gene sequencing. Gene sequencing can be used to identify structures in the HIV virus that could potentially be used for vaccine development. A vaccine should target those antibodies that are responsible for the early stages of HIV. The authors use integer programming to characterize the key antibodies that determine the differences between initial and chronic sequences of the virus. Porco and Blower (1998) state that one of the complicating factors for the development of a HIV vaccine is the fact that there are multiple subtypes that are genetically different from each other. Even though there is no vaccine available for HIV, Porco and Blower (1998) consider HIV vaccination and formulate a simulation model to control two subtypes of HIV. A prophylactic vaccine is considered that is effective for one subtype and results in vaccine-induced cross immunity for the other. Focusing on multiple subtypes is particularly important for developing countries in which more than one subtype is present. Dependent on the characteristics of the vaccine the authors determine whether mass vaccination leads to eradication of both HIV subtypes or to the existence of one or two of the subtypes.

### 2.4.2 Vaccine selection

In case there is already a vaccine, or multiple vaccines, available for a certain disease, policy makers have to determine which vaccine to use. A significant proportion of annual vaccinations takes place within childhood vaccination programs. Public health facilities and governments can buy the required vaccines for childhood vaccination programmes on the pediatric vaccine market. Robbins and Jacobson (2011) study the pediatric vaccine market from the perspective of the federal government which can negotiate prices and quantities with vaccine producers. The authors formulate a MINLP formulation which minimizes the costs of immunizing a full birth cohort while guaranteeing a sufficient profit for producers to stimulate research and development. Robbins et al. (2014) differentiate between the multiple vaccines offered on the market, where each vaccine contains one or more antigens. They study the problem where every customer (i.e., public health facility) wants to purchase at least one of each antigen while minimizing cost. This leads to a set covering game and conditions for the existence of equilibria are discussed. Robbins and Lunday (2016) extend Robbins et al. (2014) and formulate a bilevel mathematical program with the upper level consisting of the manufacturer and the customer on the lower level. The manufacturer wants to maximize profit and faces a pricing problem for the produced

vaccines. The customer can choose among a set of available vaccines each of which immunizes against one or more diseases. The objective of the customer is to minimize cost while selecting a number of vaccines that together immunize against a set of diseases. The authors propose three heuristics to solve the problem.

Once decision makers have decided which vaccines to use, they have to design a vaccination program, which involves solving combinatorial problems. A classical example of such large combinatorial problems appears in the design of childhood vaccination programs. These programs aim at immunizing a child against a number of infectious diseases by scheduling multiple vaccination moments during a certain period of time. Since there are different vaccines available which immunize each against a certain combination of diseases, constructing an effective and affordable childhood vaccination program is a challenging scheduling problem. To avoid that children need numerous injections, multiple vaccines can be combined into a single injection, a so-called ‘combination vaccine’. Combination vaccines are not only beneficial, they also have potential negative side effects. An injection with multiple vaccines might overwhelm the immune system and can result in overdoses of vaccine antigen. Hall et al. (2008) express the adverse effects of extrimmunization in terms of costs and aim to minimize the total costs of the childhood vaccination program. To solve the resulting combinatorial problem a solution method based on dynamic programming is proposed as well as heuristics. Once a vaccination program has been designed, not all children will adhere to this program. Due to parental misunderstanding or logistical difficulties, vaccinations may be delayed or even missed. In those cases a catch-up vaccination schedule must be constructed. Engineer et al. (2009) propose a dynamic programming algorithm to construct catch-up schedules within a short amount of time. Based on this algorithm Smalley et al. (2011) provide a decision tool that constructs the best catch-up schedule given the vaccination history and age of a child.

While combination vaccines are preferred in high-income countries, they are often not affordable in low-income countries. Proano et al. (2012) study the ‘antigen-bundling pricing’ problem which determines for a set of producers which combination vaccines to produce, how many to supply to each market and for what price, in order to maximize total profit and consumer surplus. The authors propose a constructive heuristic to solve the problem. Based on their solutions they conclude that organisa-

tions such as the WHO could serve as an intermediary to encourage the introduction of affordable vaccines for developing countries.

### 2.4.3 Packaging

The WHO emphasizes the importance of designing vaccine packages with the right characteristics. Vaccines are packaged in vials, which are small glass or plastic bottles that can contain liquid medicine, such as vaccine. The number of doses per vial highly influences the required storage capacity and the wastage of vaccine. Determining the vial size is particularly challenging in developing countries when people are vaccinated in small communities. In those settings it is extremely difficult to predict the number of people who will show up for an immunization session. Consequently, determining the number of needed doses is complicated, which often results in partially used vials and lost doses. In the epidemiological community there are several studies that evaluate the effects of changing the vaccine vial size on the supply chain. Lee et al. (2010) develop a general spreadsheet model to evaluate the effects of changing vial sizes on the costs in the supply chain (inventory costs, disposal costs, costs of administering vaccines and costs of doses wasted). They show that the optimal vial size depends on the patient demand. If the demand is high, greater vials are preferred and the reduced wastage costs outweigh the increased medial waste and storage requirements. When demand is low, smaller vial sizes are preferred. Lee et al. (2011) and Assi et al. (2011) use discrete event simulation models for respectively Niger and Thailand's Tang province to analyze the best vial size for measles vaccine. They conclude that it is not beneficial to replace the currently used 10-dose size with smaller vial sizes, even though the waste of vaccines could be reduced. Dhamodharan and Proano (2012) apply optimization techniques to this problem and determine the optimal vial size. They use a Monte Carlo Simulation model to account for stochastic demand and solve an integer programming problem to find optimal ordering policies and the best vial size. Their model can generally be applied by decision makers.

Next to the vial size, also the storage conditions of vaccines heavily influence the supply chain. In developing countries cold storage capacity is scarce and electricity to provide refrigeration is often unreliable. Lee et al. (2012) therefore study the effects of making vaccines thermostable, meaning that cold storage is no longer required. They construct a large discrete event simulation model for the Niger vaccine supply chain. Their result show that even making a single vaccine thermostable reduces the

pressure in the bottlenecks in the supply chain and thereby improves the availability for other vaccines as well.

#### **2.4.4 Discussion**

In this section, we analyzed the decision problems related to vaccine composition, selection and packaging. We observe that many studies in the OR/OM community focus on expected outbreaks in developed countries. Studies on the composition of a vaccine all consider seasonal influenza, which is a yearly recurrent outbreak. It would be interesting to study how the derived methods and results could be applied to vaccines for pandemic influenza, especially given the discussion on developing a pandemic vaccine.

Also the works on childhood immunization programmes consider developed countries, with one exception being Proano et al. (2012). In general, in developed countries one can expect that a designed program can be executed as planned. In case children miss certain vaccinations, a catch-up schedule can be constructed (Engineer et al. 2009, Smalley et al. 2011). However, in developing countries childhood vaccination programmes face many more operational limitations. For example, in rural areas medical staff visits villages occasionally, which implies that all medical procedures are performed at the same time in a village. The WHO emphasizes that a growing number of vaccines will be available for low-income countries in the coming years. It is therefore of interest to determine how these new vaccines should be integrated in existing childhood vaccination schedules and which catch-up schedules should be used.

Although the current studies on vaccine composition use advanced OR techniques such as dynamic programming or stochastic programming, they are somewhat behind in using models for disease progression to evaluate the effects of a vaccine. They assume that the number of cases is known (Kornish and Keeney 2008) or use very general functions to express the social benefits of vaccination (Cho 2010). More advanced models for disease progression are available in the epidemiological literature, but also in the OR/OM community (e.g., Larson 2007, Teytelman and Larson 2012, Aleman et al. 2011). Further research should try to incorporate these disease progression models into the vaccine composition decision, because evaluating the time course of an epidemic is essential to properly quantify the impact of vaccination.

To develop new vaccines researchers are applying new technologies, such as genomics (Seib et al. 2009, Liao et al. 2017). The technological developments might change current decision problems or bring about new problems. For example, with the large amount of genomic data that becomes available, analytical approaches are likely to become much more important. Maher and Murray (2016) demonstrate the valuable contribution of applying OR techniques in analyzing sequence data for vaccine development and further research opportunities in this direction should be investigated.

In Section 2.4.3, we emphasized the importance of designing packages with the desired characteristics. In the epidemiological community there are some studies on determining a good vial size and evaluating the effects of the used vial size on the supply chain. However, the results of these studies are often very case specific. The OR/OM community can contribute to these decision problems with their general models and supply chain perspective. Another important characteristic of vaccines is their required storage temperature. Liquid vaccines typically need to be stored at a temperature of 2-8 degrees Celsius and the storage of vaccines is therefore sometimes referred to as the ‘cold chain’. Recent research shows that new approaches and technologies are being developed to allow vaccines to be stored at higher temperatures (e.g., Chen and Kristensen 2009, Wang et al. 2013). Future research could evaluate the effects of making vaccines thermostable on the entire supply chain. Another interesting research direction is the coordination of the discussion between manufacturers and public health decision makers on determining the desired characteristics of a vaccine. These two parties have their own interest and coordination might be needed. Solutions have been proposed for related coordination problems on vaccine production (see Section 2.5.2) and further research could extend these solution methods to the packaging of vaccines.

## 2.5 Production

The production of vaccine is characterized by various types of uncertainty. In the production phase there are multiple stake holders involved: for-profit manufacturers and non-profit governments, public health organizations et cetera. Every stakeholder has their own interest and is affected by the uncertainties in different ways. The production process itself has a long production time and suffers from yield uncertainty.

But also the demand of vaccines is highly uncertain. For seasonal influenza, for example, the immunization season is short and there are frequent changes in the vaccine composition. In Section 2.5.1, we discuss these uncertainties and how they can be reduced. Especially the uncertain yields are one of the main causes for the undersupply on the vaccine market (Chick et al. 2008, Deo and Corbett 2009). As vaccines are public goods with positive externalities, governments and other non-profit organizations may want to influence the vaccine market to achieve a social optimum. We distinguish between two ways to achieve this: via market coordination or through funding. Market coordination is discussed in Section 2.5.2 and mainly plays a role in developing countries. In Section 2.5.3, we discuss funding, which is also of importance for developing countries.

### **2.5.1 Production uncertainties**

There are various types of uncertainty that appear in vaccine production and that are important for vaccine manufacturers. The most eminent are the natural uncertainties that are related to the production process. For example, influenza vaccines are grown in embryonated eggs, which is a process that is characterized by uncertain production yields. An additional complicating factor for influenza vaccines is that they last for only one season, in contrast to other vaccines. They can therefore be seen as one-time newsvendor products, whereas other vaccines are closer to perishable products (Chick et al. 2008). Also malaria vaccines are produced through natural production processes that suffer from yield uncertainties. The most effective malaria treatment nowadays uses medication that is produced using artemisia leaves. The market of this agricultural product is characterized by high volatility in supply and price, which directly influences the market for malaria medication (Kazaz et al. 2016).

The safety and quality regulations for vaccines also contribute to the yield uncertainty. After vaccine is produced, it is stored in a tank and a number of tests need to be performed. Only vaccines that pass the tests, can be sold. For vaccine manufacturers this brings about a decision problem: they have to decide on the timing of bottling vaccines. This can be done before test results are available, partially before and after or only after the results are known. Quick bottling reduces the required tank capacity, but also limits the possibilities of rework and hence possibly leads to lost sales. Teunter and Flapper (2006) compare four bottling alternatives and present closed form expressions for important performance criteria for each of



the alternatives. The results show for which types of vaccines postponing bottling is beneficial.

Not only the production yield itself is uncertain, also the vaccine demand fluctuates. On the one hand there is the demand from the governments or public health organizations. This demand can be regulated via tenders. Vaccine producers can bid on a tender and learn only a few months before delivery whether or not the tender was won. Due to the long production times of vaccines, the production has to be started well before knowing the outcome of the tender. Shortening lead times allows the company to start production at a later time when the estimated probability of winning the tender is higher. De Treville et al. (2014) study the GlaxoSmithKline vaccine supply chain. They show that investing in lead time reduction is beneficial and accordingly managers have extensively explored ways to achieve this. On the other hand there is the demand of individuals that can decide themselves whether or not to get vaccinated. In developed countries this demand is dependent on the perceived risk of getting infected and the perceived safety of the vaccine. Public health organizations and governments have to take this individual demand into account when deciding how many vaccines to order.

The vaccine manufacturer has several options to reduce the uncertainty resulting from the randomness in both production yield and demand. Begen et al. (2016) analyze the effects and potential benefits of reducing supply or demand uncertainty. Results show that supply uncertainty reduction effort is more efficient. Supply uncertainty can be reduced by influencing the uncertain yields. Federgruen and Yang (2009) investigate suppliers that influence their uncertain yields and they use the vaccine supply chain as an illustration throughout their paper. They analyze the equilibrium of the total market. Kazaz et al. (2016) determine how uncertainty can be reduced in the production process of malaria vaccines, a process in which artemisia leaves are used. They develop a model for the artemisia supply chain to study the consequences of several interventions to reduce the volatility in the market. They show for example that improving the average yield or offering a support price has significant impact.

Another way to manage the supply chain uncertainties is to adjust the pricing and selling strategy. Cho and Tang (2013) study three selling strategies: advance, regular and dynamic selling. In the first two strategies, selling and price setting takes place respectively before or after demand and supply are realized. The authors show

that the dynamic strategy, which combines advance and regular selling, is preferred by the manufacturer. Eskandarzadeh et al. (2016) extend this work to controlling the risk of the producer in the case that the price is set before the yield is realized. The authors study a production planning problem for a risk averse producer and propose a solution algorithm. They illustrate their solution approach for an influenza producer and determine the optimal price and production quantities for different risk profiles.

The production uncertainty faced by the vaccine manufacturer also affects the public health decision maker. Federgruen and Yang (2008) studies such a decision maker who has to satisfy the uncertain demand for a single season from several suppliers. The planning problem that he faces relates to determining how much to order from which supplier, taking into account the uncertain yield of the suppliers. Goal is cost minimization while guaranteeing that the uncertain demand is satisfied with a certain probability. The authors motivate their model by the case of influenza vaccine delivery, where an unexpected drop-out of one of the two suppliers in 2004 led to a significant reduction in the US vaccine stockpile.

### **2.5.2 Market coordination**

Vaccines are public goods with positive externalities. Governments and public health organizations therefore want to achieve high immunization levels. But due to supply and production uncertainties, the amount of vaccines produced may be below socially optimal levels. Via contracts and subsidies governments can try to coordinate the vaccine market. Tools such as mechanism design and game theory are useful in studying this coordination problem. Chick et al. (2008) show that a lack of coordination on the vaccine market for annual influenza leads to high production risks for the manufacturers of vaccines. Without government intervention the vaccine coverage is below the socially optimal level. Different types of contracts are studied in order to align the incentives of both governments and manufacturers. The authors show that a cost-sharing contract, in which the risks for yield uncertainty are shared, is able to globally optimize vaccine supply. Arifoğlu et al. (2012) extend Chick et al. (2008) to include rational consumer behavior. Vaccination brings about a positive externality effect because it reduces the infection risk for individuals that are close contacts of the vaccinee. In addition, negative externality effects can occur: self-interested individuals ignore that vaccinating high-risk individuals is more beneficial when supply is limited. The positive externalities can lead to free-riding, when individuals do not

get vaccinated because they expect to benefit from the vaccination of others (Ibuka et al. 2014). The vaccine market suffers from inefficiencies because of these disregarded externality effects on the demand side and the yield uncertainty on the supply side. Arifoğlu et al. (2012) model the vaccine market as a game between the manufacturer and the individuals and study the effect of government interventions either on the supply or on the demand side. Adida et al. (2013) extend the coordination of the vaccine market to contracts that affect both the supply and the demand side. They show that a fixed two-part subsidy is not able to align the quantity and pricing decisions simultaneously. A two-part menu is proposed with subsidies depending on the vaccination coverage. The analysis shows that this subsidy menu can result in a socially optimal level of vaccine coverage.

The need for coordination on the vaccine market is the result of asymmetry: what is beneficial for the supplier, is often not beneficial for the public health organization and vice versa. This also applies to the timing of production. The supplier has little incentive to start production early, because the public health organization benefits the most from on time delivery. Late delivery can result in a vaccine shortage, even though supply is sufficient. Dai et al. (2016) show that existing supply contracts fail in coordinating the supply chain in this respect. A new contract is proposed that both coordinates the supply chain and allows for flexible profit division. In addition to the asymmetry in interests, there is also asymmetry in information. Chick et al. (2017) contributes to this stream of literature by explicitly taking this asymmetric information into account. They consider a government who wants to minimize expected social costs and a for-profit manufacturer who has private information about his productivity. The study shows that the manufacturer can command information rent from the government, due to the asymmetric information. A menu of contracts is proposed that minimizes the overall costs of the government.

### 2.5.3 Funding

Beside market coordination also funding or sponsoring plays an important role in influencing the vaccine market. There are sometimes donors who are willing to subsidize the vaccine production process in order to increase access to health care in developing countries. Taylor and Xiao (2014) consider malaria vaccinations and study donor subsidies that are either used for increasing the sales or lowering the production costs. The latter can be done via a purchase subsidy. A model is formulated

where the donor wants to maximize the average sales to customers under a budget constraint. The optimal size and type of subsidies dependent on the perishability of the product are determined. The results show that for products with a long shelf life a donor should only subsidize purchases. Levi et al. (2016) complement this work on subsidizing malaria medication by studying the setting of a central planner who aims to increase the market consumption. The authors study the effectiveness of a uniform copayment and derive conditions when this is optimal. The two papers together show that policy makers should not only consider subsidizing the manufacturer. Instead, allocating uniform subsidies to individual firms can (more) efficiently increase market consumption.

Vaccines are examples of public interest goods. Demirci and Erkip (2017) study the supply chain for public interest goods in which a central authority wants to maximize utility in society. They develop a model that determines how much the central authority should invest in demand-increasing strategies and how much in rebates that increase the revenue per unit sold. A bilevel program is formulated that also takes into account the manufacturers profit. Results show that applying the model outcomes can considerably increase utility. Berenguer et al. (2016) consider subsidy programs that either target at a not-for-profit firm or at a for-profit firm. Their results show that a limited budget available for subsidies is best spent when a not-for-profit firm is subsidized.

Despite the funding for vaccines, many developing countries are often confronted with stockouts. Gallien et al. (2016) develop a discrete event simulation model based on historical data to study the relation between drug availability and the fund disbursement policy of the global health organisation ‘The Global Fund to Fight AIDS, Tuberculosis and Malaria’. They find that adjusting the disbursement amounts to make them compatible with the duration of monitoring periods has a higher potential to reduce expected stockouts than using regional buffer stocks or bridge financing (i.e., providing funds for the period between grant approval and disbursement).

#### **2.5.4 Discussion**

The vaccine supply chain is characterized by asymmetry in multiple dimensions: the manufacturer does not fully design its own product and the end user is typically not the one paying for the product. Furthermore, the buyers of vaccines are often non-profit organisations whereas suppliers are for-profit companies (Herlin and

Pazirandeh 2012). The supply chain asymmetries have inspired research on market coordination mechanisms. It may be interesting to explore the implications of this research for other supply chains with similar asymmetries.

Most papers on production study seasonal influenza vaccines, for which the production time is uncertain due to biological processes and quality and safety tests (Gerdil 2003). Recently, new technologies are being developed to reduce the production uncertainties of vaccines. One of these technologies is the development of cell based instead of egg-based production processes for vaccines, in which vaccines are developed from animal cells (Centers for Disease Control and Prevention 2016a). One of the main advantages of cell-based production over egg-based production is that one can start the production process more rapidly. These new developments will affect the decision problems related to influenza vaccine composition and vaccine production. Further research should therefore incorporate these new developments to aid decision makers in preparing for the changes that new technologies will bring about.

When considering the classification in Table 2.1 it is interesting to observe that there are no studies in the OR/OM literature regarding the production of vaccines for sudden outbreaks. Although the timing of production is perhaps less of a question for sudden outbreaks (production should start immediately), it is important to think about a production plan (where, how much). Such a plan can be executed in case of a sudden outbreak and is part of a broader pandemic preparedness plan. Time plays a very crucial role in that case: it is important to react quickly to a sudden outbreak, but the production lead times are uncertain and the demand might drop over time if vaccines arrive too late. Hence, decisions have to be made under time pressure. The OR/OM community can aid decision makers in these complex decisions by designing production plans for sudden outbreaks.

In addition, it is important for decision makers to think about how much they are willing to invest in production for vaccines for sudden outbreaks. In case of an emergency there are two responses possible: (1) use the existing stockpile and (2) start production for more vaccines. We see these two aspects also in some US pandemic response plans (U.S. Department of Health and Human Services 2005, Homeland Security Council 2006). But apart from our analysis in Chapter 5 there is little to no research about this budget allocation plan.

The role of funding in vaccination is discussed in Section 2.5.3. Gallien et al. (2016) interestingly show that the way funding is organized can have a large influence on the supply chain. Their work might provide a good starting point for future research in this direction. Also with the development of new and more costly vaccines, it becomes more and more important to investigate who should pay for these vaccines (Seib et al. 2017).

## 2.6 Allocation

Before the vaccines can actually be distributed, decision makers have to decide how the available vaccines will be allocated. This allocation decision is made by governments or public health organizations. Vaccines are scarce, which particularly holds in case of unexpected outbreaks. Therefore decision makers face a complex resource allocation problem in which they have to determine who is entitled to be vaccinated and who is not. The vaccine allocation problem thus has an important ethical dimension, unlike other resource allocation problems. One of the most crucial ethical issues in vaccine allocation is the fact that equity and efficiency are often competing objectives. An allocation that significantly reduces the total number of infections, might be very unequitable (cf., Keeling and Shattock 2012, Teytelman and Larson 2013). The OR/OM community does not resolve these ethical issues, but provides support in the decision making process. The final decision is made by public health organizations such as the Centers for Disease Control and Prevention in the US who have detailed ethical guidelines (e.g., Kinlaw and Levine 2007). We are aware of the ethical dimensions in vaccine allocation, but restrict attention to the logistical challenges in the remainder of this section.

In some situations there are multiple decision makers that together have to determine the allocation. These decision makers can for example correspond to multiple countries or regions. They can either decide to act selfishly and keep their own vaccine stockpile or they can decide to allocate some vaccines to other populations in order to reduce transmission across borders. Besides the decision of the individual decision maker, we can also study the coordination between them. In Section 2.6.1, we discuss this case of coordination between multiple decision makers. In other situations there is just one decision maker, for example a government or global health organization. In that case, the vaccine allocation decision boils down to determining

which subpopulations (e.g., regions or age groups) should be prioritized (see Section 2.6.2). Often different allocation schemes are primarily compared in terms of disease related characteristics, such as the number of infected individuals. In Section 2.6.3, we discuss another way of analyzing vaccine allocations, namely by using cost-effectiveness analysis.

Most studies on vaccine allocation consider allocations to fight natural outbreaks of infectious diseases. In contrast, in Section 2.6.4 we review a class of papers that considers allocating limited resources in case of a bioterror attack. Preparing for an attack is complex, because a lot of uncertainty is involved regarding the location of the attack, the number of victims et cetera.

### 2.6.1 Multiple decision makers

In some situations there are multiple decision makers involved in deciding on the allocation of vaccines or other scarce health resources. These decision makers can either be on the same hierarchical level, such that they must come to a decision together. Or they are on different hierarchical levels and their decisions are made consecutively. The allocation of funds for HIV prevention is an example of a multilevel decision problem. The allocation over multiple regions is decided globally, but the regions themselves decide on the allocation over the several risk-groups within their region. Lasry et al. (2007) study this multilevel decision problem and compare an equity-based heuristic with the optimal allocation. The equitable allocation allocates proportionally with respect to numbers of infected cases. Since there is currently no vaccine available for HIV, the funds are spent on general interventions that reduce transmission. The objective in the optimal allocation is to minimize the number of new infections. The analysis shows that if optimization can only be applied to one level, better results are obtained if the lower level is optimized instead of the upper level.

In case the decision makers are all on the same hierarchical level, coordination might be needed. Sun et al. (2009) use game theory to coordinate the allocation of vaccine stockpiles among different countries. Prior to an outbreak every country is assumed to have its own vaccine stockpile. During an outbreak countries face the question of whether or not they are willing to give up parts of their stockpile to help other countries in containing the epidemic. A Reed-Frost model is used to describe the spread of an epidemic and only the initial stage of epidemic growth is considered.

The authors study Nash equilibria and compare the situation with and without a central planner, such as the WHO. In addition to Sun et al. (2009), Mamani et al. (2013) evaluate the entire time course of the epidemic. The amount of vaccines ordered and distributed in one country can influence the evolution of an outbreak in another country due to transmission across the borders. They study multiple countries that each want to minimize total costs related to the number of infections and allocated vaccines. A contract is proposed to achieve system optimality. The results show that a lack of coordination leads to a shortage of vaccines in some regions and an excess in others.

### 2.6.2 Central coordination

In case of a single decision maker, allocation decisions are related to prioritizing between multiple subgroups. These subgroups correspond for example to geographical regions or age groups. Policy makers have to decide which subgroups to vaccinate. The main difference between distinguishing between regions or age groups is the role of interaction between the subgroups. Interaction between geographical regions plays a much smaller role in the transmission of an infectious disease than interaction between age groups.

**Regions** Outside the OR/OM literature there are many papers that consider vaccine allocation over multiple regions (e.g., Wu et al. 2007, Araz et al. 2012, Keeling and Shattock 2012, Matrajt et al. 2013). These papers make little use of OR tools such as optimization, but usually use approaches like scenario analysis or enumeration. Some of them cluster the population in smaller groups, such as communities or households (e.g., Becker and Starczak 1997, Ball and Lyne 2002, Ball et al. 2004, Ball and Lyne 2006, Tanner et al. 2008).

Within the OR/OM community there is more emphasize on developing models and solution methods. Tanner and Ntaimo (2010) present a technological extension to Tanner et al. (2008) to solve stochastic problems with joint chance constraints. They add new optimality cuts to the problem and apply branch-and-cut. They show that the new method significantly reduces computation time and is also able to derive solutions for larger instances of the vaccine allocation problem. Other techniques used in the OR/OM community for solving vaccine allocation problems are simulation or stochastic programming. For example, Uribe-Sánchez et al. (2011) construct



a simulation model and determine the resource allocation that limits the impact of ongoing epidemics and the potential impact of new outbreaks in multiple regions. Teytelman and Larson (2013) develop several heuristics to allocate a limited vaccine stockpile over the states of the US in order to fight an influenza outbreak. They evaluate their heuristics by using Monte Carlo Simulation. Their results show that their telescope-to-the-future algorithm, which takes into account regional differences, is best at reducing infections. Yarmand et al. (2014) study a two-stage stochastic programming decision framework for vaccine allocation over multiple locations. In the first stage, a predefined amount of vaccines is allocated to every location. The second stage decision is based on the outcome of the first stage allocation: the epidemic is either contained or not. The authors show that their problem can be reformulated as a news vendor type of model.

The papers discussed so far did not assume a special structure on the connection between the different regions. In contrast to these papers, there are also some studies that consider network models, where a graph is used to represent regions (or individuals) and their connections. Ventresca and Aleman (2014a) consider a network structure and investigate the optimal removal of nodes. When the network represents a population, node removal can be interpreted as either vaccination or quarantining. More theoretical work on link or node removal can be found in Arulselvan et al. (2009), Ventresca (2012), Ventresca and Aleman (2014b), Nandi and Medal (2016).

**Age groups** Dividing the population based on geographical criteria, results in physical distance between the groups. This distance enables to consider limited or no interaction between the groups. Ignoring interaction is not possible when the population is grouped based on age or disease specific characteristics, because it is exactly the interaction between these groups that significantly contributes to the spread of a disease. Many studies in the medical/epidemiological literature consider vaccine allocation over different age-groups (e.g., Patel et al. 2005, Mylius et al. 2008, Medlock and Galvani 2009, Wallinga et al. 2010, Goldstein et al. 2009). Others differentiate between vulnerable groups and more active groups, who contribute to the spread of the disease (e.g., Dushoff et al. 2007, Matrajt and Longini Jr 2010, Goldstein et al. 2012, Lee et al. 2015b).

In some situations it is not the vaccine stockpile that is limiting the vaccine coverage, but the participation of the population in vaccination programmes. Yamin

and Gavius (2013) study how the level of influenza coverage can be increased using a game model with a central planner who can give a financial incentive given to encourage people to get vaccinated. Results indicate that the incentives should be higher for non-elderly as well as in years when the seasonal influenza is less contagious. The more vulnerable groups, such as the elderly, will benefit from the increased coverage in the groups that contribute significantly to transmission.

### **2.6.3 Cost-effectiveness**

Cost-effectiveness analysis is a way to compare vaccine allocations differently than in terms of infected cases or other health care related performance criteria. This approach assigns costs to both the intervention and the achieved health benefit and determines which interventions are cost effective (i.e., the benefits are higher than the cost). Cost-effectiveness of vaccination programmes is widely studied in communities outside the OR/OM community. In the health economics literature and the epidemiological literature this approach is often used (e.g., Siddiqui and Edmunds 2008, Jit et al. 2008, 2014). Also within the OR/OM community there are some studies that use cost-effectiveness analysis. These studies make use of epidemic models to determine the effect of certain interventions on the time course of an epidemic, on the number of infected cases et cetera. Some studies aim at comparing a predefined set of interventions and determine which are cost-effective (Frerichs and Prawda 1975, Edwards et al. 1998, Rauner 2002, Hutton et al. 2011), others try to find the optimal actions under budget constraints (Dimitrov et al. 2013). The latter paper makes use of Markov Decision Processes and not only advises what vaccination strategy to use, but also presents detailed geographic intervention plans and informs where to locate the supply centers.

Instead of explicitly performing a cost-effectiveness analysis, there are also studies that take into account the costs for the considered interventions or other socioeconomic measures differently. Parker (1983) uses a multiobjective approach and includes socioeconomic measurements such as infant mortality rate, calorie intake levels, and degree of standard housing and potable water. Reveller et al. (1969) focus on cost minimization while achieving a certain reduction in disease incidence. The authors propose a linear approximation of the transmission model for tuberculosis. Linear programming is used with the objective of minimizing the total costs of the intervention strategy. Four schedules for the reduction of active tuberculosis

cases are given and for each schedule the optimal intervention is determined. These interventions consist both of vaccination and prophylaxis, where the latter refers to medication that reduces the severity of (potential) infection. Denysiuk et al. (2015) also study tuberculosis, but combine costs and disease related measures in a multi-objective optimization problem. The goal is to minimize both costs for the active infections as well as the costs of the control strategy. To determine the optimal intervention, the authors apply optimal control theory using a transmission model consisting of a set of differential equations.

The allocation phase of vaccination is studied for a broad range of diseases, which is also apparent from the papers that apply cost-effectiveness analyses. Already in the OR/OM community there are studies on hepatitis B (Hutton et al. 2011), HIV (Edwards et al. 1998, Rauner 2002), malaria (Parker 1983, Dimitrov et al. 2013), polio (Thompson et al. 2015), rabies (Frerichs and Prawda 1975) and tuberculosis (Reveller et al. 1969, Denysiuk et al. 2015).

In most cases the goal of a vaccination program is to contain an outbreak as much as possible. However, for some diseases policy makers even strive for complete eradication. Tebbens and Thompson (2009) analyze different decision rules for the allocation of resources for eradicable diseases. A model for two diseases is considered and the effects of switching priorities from one disease to another are investigated using cost-effectiveness analysis. The results show that a long-term strategy is more cost-effective than regularly switching priorities to the most pressing disease. Thompson et al. (2015) analyze the efforts that are needed to attain polio eradication. A simple allocation model is used to choose among a set of possible allocations those options that either minimize the incremental cost-effectiveness ratio or maximize net benefit.

#### 2.6.4 Bioterror or emergency response

In this section, we analyze the allocation of vaccines and other scarce health resources in case of a bioterror attack or an unexpected emergency. Allocation decisions in this case have to be made under high time pressure and suffer from uncertainty in many dimensions (e.g., location of attack/outbreak, magnitude and severity of outbreak).

**Bioterror attacks** A bioterror attack is a form of terrorism in which terrorists intentionally release infectious viruses or bacteria. Examples are the anthrax attacks

in 2001 in the United States. After these attacks several studies were performed to develop response plans in case of a new anthrax attack. These studies develop models that can predict the transmission of anthrax and that can be used to evaluate different response plans. Craft et al. (2005) propose an extensive model that consists among others of a disease progression model, queueing models for antibiotics distribution and a queueing model for hospitalization. This model is a simplification of the model proposed by Wein et al. (2003) and is used to estimate the number of infections and the number of deaths resulting from the attack. Chen et al. (2006) compare an agent-based model and a population based simulation model for the evaluation of disease progression after a anthrax attack. The more complex agent-based model is aligned with the simple population-based model such that the former can be used to derive policy recommendations in more detail. With their model, Craft et al. (2005) show that the fraction of deaths among infected people is more or less constant per region. Based on these results Craft et al. (2005) report that policy makers decided to focus on measures that can lower the proportion of deaths among infections instead of focusing on lowering the actual number of deaths, also motivated by the fact that it is very difficult to predict the magnitude of an attack. Next to anthrax attacks, also smallpox attacks are considered in the literature. Miller et al. (2006) propose a discrete event simulation to evaluate different intervention strategies including vaccination and social distancing. They consider a case study for San Antonio Texas and show that the most robust response plan contains a mixture of public health interventions. A special case of a bioterror attack, namely on an airport, is considered by Berman et al. (2012). In that setting the authors study the allocation of limited emergency resources. They use an approximation of a compartmental epidemic model to determine the number of cases dependent on the allocated resources. Under certain assumptions the resource allocation problem of minimizing the number of cases is convex and they propose a greedy algorithm to find the optimal allocation.

The studies discussed so far reason from the perspective of the government. Berman and Gavius (2007) present an interesting addition and also take the perspective into account of the terrorist who plans to commit the attack. A two-player game is formulated that models the interaction between a terrorist and the state and incorporates the actions that both players can take. The state is able to locate facilities that contain the resources to respond quickly in case of an attack. If necessary,

available resources can be transported through the network via shortest paths. The terrorist decides at which location to commit an attack. The authors formulate a leader-follower game where the state acts first. Best strategies for both players as well as system equilibria are derived. These equilibria are illustrated in a case study of a terrorist attack in one of the metropolitan areas in the United States.

**Emergencies** Next to bioterror attacks, there are other emergency situations related to infections that require complex decision making. Wein (2009) discusses four topics related to homeland security: response to a bioterror attack either with anthrax or on the food supply chain, the control of pandemic influenza and border analyses to keep terrorists out of the country. The author discusses the contributions made in these four areas and shows that applying OR methods in these fields helps to quantify the effects of an attack and to derive policy implications. Fogli and Guida (2013) design a decision support system for general emergency management using knowledge-centered design. This approach iteratively updates the knowledge about the domain and the users of the decision support system and adjusts the support system accordingly. The authors illustrate their results with a case study for pandemic influenza, where important decisions are for example how to plan emergency vaccination and how to distribute vaccines. In order to make it easier for planners to use OR/OM models for emergency response, Herrmann (2008) develops simple and accessible spreadsheet models. These models can aid decision makers in evaluating multiple response plans.

### 2.6.5 Discussion

The allocation of vaccines differs slightly from the other components in the vaccine supply chain. In contrast to the production and distribution of vaccines, allocation is not a tangible process but a decision problem on a higher level. As can be seen in Table 2.1 allocation is the only component of the supply chain that is studied for both expected/existing outbreaks and sudden outbreaks. The allocation problem plays a role in all three challenges for vaccination that were mentioned in the introduction: (1) increasing the efficiency and cost-effectiveness of supply for planned vaccination (2) preparing for sudden outbreaks and (3) preparing for bioterror attacks. A possible explanation for this is that the allocation problem is quite general and can be studied for multiple situations and types of diseases with comparable models. Naturally,

papers that study vaccine allocation assume that there is a stockpile available. For sudden outbreaks or in response to a bioterror attack, this might be problematic (see our discussion in Section 2.5.4). In those cases it could be interesting to study the allocation of vaccines that become available in batches over time.

As mentioned in the previous sections the topic of vaccine allocation is extensively studied in the epidemiological literature. Although there is already some work in the OR/OM community on this topic, the epidemiological literature could benefit from further applying OR tools. The high level modelling and use of optimization methods in the OR/OM community have potential to result in insights and understanding of the complex allocation problems that could not be obtained with simulation or numerical methods (cf., Chapter 3). Furthermore, with OR tools explicit solutions of optimal allocations or efficient solutions approaches can be derived (cf., Chapter 4). As data is scarce and model parameters are difficult to determine for disease transmission models, these results are very valuable when performing sensitivity analyses.

The asymmetry in the vaccine supply chain also plays a role in the allocation phase. Where decision makers specify the allocation, individuals can have multiple reasons not to participate. Vaccine hesitancy or vaccine refusal is studied a lot in the medical/epidemiological literature (Omer et al. 2009, Larson et al. 2014), but hardly incorporated in the OR/OM papers on allocation. As the attitude towards vaccination might differ across (sub)populations, this might affect the allocation decision. Future research is needed to incorporate this aspect.

The decision problems that we have discussed in Section 2.6.4 are closely related to the decision problems in disaster management and humanitarian logistics (e.g., Altay and Green 2006, Tomasini et al. 2009, Kunz and Reiner 2012, Galindo and Batta 2013, Leiras et al. 2014). This field focuses on organizing the supply of relief items in case of a disaster, which includes setting up preparedness plans (e.g., Duran et al. 2013) and coordination between multiple parties (e.g., Ergun et al. 2014). The models and results in this field could also be useful for the allocation and distribution of vaccines after unexpected outbreaks.

## 2.7 Distribution

In this section, we analyze the final component of the vaccine supply chain: the distribution phase. In this phase, the vaccines are distributed from the manufacturer

to the end user (i.e., the ‘patient’). The distribution of vaccines involves many logistical questions on the operational level. First, it is important to determine how this part of the chain must be organized. How many layers are needed in the chain and where should hubs and storage locations be positioned? In Section 2.7.1, we discuss these questions. In Section 2.7.2, we consider inventory control for vaccines: When policy makers decide to keep vaccine stockpiles, they have to decide how large these stockpiles should be and where they should be located. Finally, the vaccines should be distributed to the end user. This can be done either through fixed locations, so-called ‘points of dispensing’ (PODs), or via mobile facilities, respectively discussed in Section 2.7.3 and 2.7.4. PODs bring about many logistical questions ranging from facility location, to staffing levels and facility lay-out. When mobile facilities or mobile medical teams are used, routing problems play a role.

### 2.7.1 Supply Chain Design

In the past years, the number of vaccines that is available for low and middle income countries has increased considerably and this trend is expected to continue in the coming years. Vaccine supply chains in those countries cannot keep up with this increase unless investments in the logistic systems are made. Kaufmann et al. (2011) present recommendations for strengthening the vaccine supply chains. They distinguish between two segments in the vaccine supply chain in low and middle income countries: (1) the process of sending vaccines to the receiving country and (2) the distribution of vaccines from the entrance in the receiving country to inventory points and finally to the health care provider. The first segment partly takes place in developed countries, whereas the second segment is completely organized within the developing countries. One of their main messages is to strengthen the coordination between the two segments of the vaccine supply chain. Zaffran et al. (2013) and Privett and Gonsalvez (2014) discuss the main challenges for the vaccine supply chain in developing countries. They both address the importance of coordination, motivated personnel and information systems to improve decision making. Privett and Gonsalvez (2014) emphasize that advanced improvement in a single aspect of the supply chain without focusing on the coordination will only lead to minor overall improvements. Maruchek et al. (2011) focus on product safety and security and illustrate some risks for several supply chains, including the pharmaceutical supply chain. One of the main risks is the long supply chain with many activities at different locations.

Other problems are the risk of counterfeiting or the case of stockpiling medication with the goal to sell at higher prices when shortages occur. The authors present four focus areas for the OR/OM community to contribute to safety and security in supply chains, including supplier relations and product life cycle management.

In Section 2.4.3, we have seen that the product characteristics of vaccines heavily impact the supply chain. This is particularly true for the perishability of vaccine and the fact that vaccines should be kept in a temperature controlled environment. Masoumi et al. (2012) take the perishability into account when studying a supply chain network model. The model incorporates multiple firms that are competing in different markets, with the product flows on their supply chain networks as strategies. The authors present an algorithm to find supply chain equilibria. Chung and Kwon (2016) extend this work and derive insightful supply chain decision rules from the necessary conditions for the equilibria. Pishvaei et al. (2014) propose a method to design a sustainable medical supply chain taking into account the complete life cycle of medical supplies and waste. Careful design of the medical waste supply chain is in particular critical for supplies that have been used for infectious patients, where the risk of further transmission is always imminent. Saif and Elhedhli (2016) also take environmental considerations into account when studying the design of a cold supply chain, i.e., a supply chain for goods that have to stay in a temperature controlled environment such as vaccines. They illustrate their model for the vaccine supply chain in Ontario and show that there is a trade-off between transportation costs and inventory costs.

In the epidemiological literature there are many studies that analyze the design of the vaccine supply chain and the multiple storage levels. Many of these studies use a similar approach in which a simulation model is developed for a specific country, for example using HERMES software (highly extensible resource for modeling supply chains) (e.g., Haidari et al. 2013, Assi et al. 2012, 2013). A common conclusion is that removing levels can reduce supply chain costs and increase vaccine availability (e.g., Assi et al. 2013, Brown et al. 2014, Lee et al. 2015a).

To increase the efficiency of the vaccine supply chain, the WHO recommends to integrate the supply chain with other health supply chains and possibly even with the private sector (World Health Organization & PATH 2011). Yadav et al. (2014) study the possibilities of integration. Although integration is expected to increase efficiency, it also brings about some challenges as different products differ in supply and demand



characteristics. Several case studies are discussed to illustrate examples of countries where integration of the supply chain has been implemented. Lydon et al. (2015) even go a step further and analyze the option of outsourcing some activities of the supply chain to the private sector. Because there is limited information available on the potential benefits of outsourcing, a case study from Western Cape Province in South Africa is presented. In this case study, the storage and transport of vaccines was outsourced to a third party. From this case the authors conclude that outsourcing can be beneficial, although it is highly important to consult all stakeholders beforehand and to carefully determine which parts of the supply chain should be outsourced and to whom. These studies provide illustrations of successful integration from which lessons can be learnt on best practices.

### 2.7.2 Inventory control

Inventories of vaccines are used to guarantee supply system efficiency and to deal with uncertainties in demand and supply (see Section 2.5.1). For planned vaccination (e.g., seasonal influenza vaccination or pediatric vaccination) inventories can increase effectiveness. Jacobson et al. (2006) consider inventory control for pediatric vaccines in the United States. The current stockpiles are sufficient to handle disruptions in production that last for around 6 months. However, when disruptions last longer, the inventory level is inadequate. This potentially leads to underimmunization and consequently to epidemic outbreaks. The risk of epidemics could be reduced by making moderate investments in inventories. Shrestha et al. (2010) develop a spreadsheet model for the inventory control of pediatric vaccines in the United States. This model can be used to evaluate different stockpile sizes and the potential shortages that might occur. Samii et al. (2012) connect allocation schemes for influenza vaccines to inventory control policies. Three allocation schemes are compared that all reserve a proportion of the available vaccines for the high-risk groups, but differ in the way the unreserved proportion is allocated. Every allocation scheme is related to an inventory control policy and the corresponding service levels and fill rates are determined.

In case of sudden outbreaks, stockpiles of vaccines can increase agility and allow to respond quickly. There are several studies that focus on inventories for disaster response. Salmerón and Apte (2010) consider pre-disaster planning for a general type of disaster. A two stage stochastic programming formulation is proposed to minimize

the expected casualties. The first stage is related to building capacity, whereas the second stage considers the logistics of the problem, related to transporting victims and resources. The analysis reflects the importance of using stochastic models, because of the uncertainty in the location of the disaster. In addition to pre-disaster planning, one can also study the situation *during* a disaster when resources might need to be (re)distributed. Arora et al. (2010) consider this problem and include both delivery from a central stockpile and lateral transshipments. The authors assume the available stockpile to be limited and do not take into account newly produced and supplied inventories. Rottkemper et al. (2011) consider a similar model, but assume an unlimited inventory at the central depot. The paper studies the relocation of inventories in case of an emergency in certain areas. In these areas, the demand for relief goods then suddenly increases, but at the same time ongoing operations in other areas must continue. The authors formulate an inventory relocation model and solve it using a rolling horizon to incorporate uncertainties. To illustrate the policy recommendations that can be generated, a case study for meningitis vaccine in Burundi is used.

### 2.7.3 Points of Dispensing

In the final stage of the vaccine supply chain, the vaccines are distributed to the end users (i.e., the ‘patients’). For vaccination in case of sudden outbreaks, there are pandemic response plans that describe how to execute this stage. These plans often include the setup of local clinics for the distribution of medication and vaccines, so-called Points-of-Dispensing (PODs).

When designing PODs there are three important decision problems that play a role: Where should they be located? How should their lay-out be? What are the required staffing levels? Some studies focus on one of these decision problems. For example, Ekici et al. (2014) look at facility location, Aaby et al. (2006) and Luangkesorn et al. (2012) restrict attention to the design and lay-out of clinics and McCoy and Johnson (2014) evaluate clinic capacity. However, since the decision problems on PODs are very much connected, there are also many studies that analyze them together. Ramirez-Nafarrate et al. (2015) simultaneously study the location problem and capacity planning for points of care. A mathematical program is formulated and a solution approach is proposed based on a genetic algorithm. The results show that simultaneously determining location, staffing and population assignment can reduce

waiting times compared to sequential decision making. Lee et al. (2006, 2009, 2013) develop the emergency response decision tool RealOpt<sup>®</sup> for PODs that are used in response to bioterrorist attacks or pandemics. This tool supports the decision making with respect to locating the facilities, determining the required labor resources and the floor plans of the facilities. RealOpt<sup>®</sup> is a generally applicable tool that has been used for numerous events, including anthrax preparedness and seasonal influenza.

Instead of developing a general model, some studies focus on case specific results. Aaby et al. (2006) consider vaccination clinics for Montgomery County and Luangkesorn et al. (2012) look at health care centers for prevention and screening in Abu Dhabi. The latter paper uses queueing and simulation models and propose an adjusted design that reduces the size of the area needed for waiting. The decisions on location of clinics, lay-out and staffing levels directly affect the people who visit these clinics. Therefore, McCoy and Johnson (2014) explicitly take adherence into account, which is assumed to depend on the travel distance to the facility. They study a clinic which has a fixed budget that can be allocated over a number of time periods to assign capacity for patients. During these time periods the epidemic continues to spread with a speed dependent on the allocation decisions. An optimization problem is formulated where the size of the infected population is minimized under a budget restriction. For two special cases of adherence the solution is determined analytically. The results show that incorporating adherence may significantly improve outcomes.

Most studies consider the setup of clinics in response to a pandemic and dedicated to medical services. Alternatively, Whitworth (2006) designs a response plan for a bioterror attack. The author analyzes candidate points, design and staffing levels of PODs for a specific case study of one community. Ekici et al. (2014) consider a pandemic, but specifically focus on food distribution. A disease spread model is used and combined with a facility location model for the location problem of food distribution points. To find close to optimal solutions, a heuristic is proposed which can help policy makers in preparing for a pandemic. Although most studies analyze PODs as a way to distribute medical supplies, there are also alternative distribution possibilities. Richter and Khan (2009) compare some of these alternatives to dispense prophylaxis to the population in a metropolitan area. Using multicriteria decision analysis, the authors show that the current method of drive-thru is outperformed by distribution via postal offices or via commercial pharmacies.

We next discuss the research in the OR/OM community on the distribution of vaccines in case of planned vaccination. In developing countries, populations can be hard to reach (see the next section), but in developed countries this final stage of the supply chain does not bring large logistical problems. We already discussed childhood vaccination programs in Section 2.4.2, which account for a substantial part of the annual planned vaccinations in developed countries. There is another class of vaccines, namely travel vaccines, for which also a scheduling problem arises. Travel vaccines are intended to protect travellers against diseases that are prevalent in their destination country. The demand for these vaccines is relatively low, which brings about the following trade-off. Vaccines come in vials and multi-dose vials are cheaper, but potentially result in waste as vaccine spoils rapidly. Abrahams and Ragsdale (2012) study the scheduling problem for a travel clinic that aims to minimize the total cost of the vaccination schedule while taking scheduling preferences of the patients into account. The results show that their method results in significantly lower costs compared to simple scheduling heuristics.

#### 2.7.4 Mobile facilities

If possible, one prefers individuals go to PODs to get vaccinated. But there are situations in which it is more efficient to bring the vaccines to the people instead of the other way around. This can for example apply to mass vaccination campaigns or vaccination in rural areas where mobile medical teams go from one location to another. The central question for such mobile teams is how to route them. Halper and Raghavan (2011) define the mobile facility routing problem, with moving facilities to serve demand at different nodes in a network. A facility at a node can serve a subset of all the other nodes, for example those within a certain distance. The demand of every node is assumed to depend on time. The satisfied demand thus depends on the routing schedule. In case of multiple facilities the routing problem is  $\mathcal{NP}$ -hard and a heuristic is proposed to solve the problem. Rachaniotis et al. (2012) study the same routing problem, with the significant simplification of only one mobile medical team. This team consecutively visits subpopulations in which an epidemic is ongoing. The authors determine the optimal order for visiting the subpopulations such that the total number of new infections is minimized. The optimal schedule significantly outperforms random scheduling.

In developing countries mobile medical teams are crucial in reaching rural areas. The organisation Riders for Health provides reliable transportation to health care workers in sub-Saharan Africa, who are then able to visit more rural areas to provide medical care such as vaccination. McCoy and Lee (2014) investigate the trade-off between equity and effectiveness for this organisation. They propose a model that can aid decision makers in deciding to which region newly available vehicles should be allocated.

### 2.7.5 Discussion

Time is of high importance in the vaccine supply chain, also in the distribution phase. When vaccines are distributed during an outbreak it is crucial that the distribution can be done efficiently and quickly to avoid an explosive increase in infections. Large scale vaccination campaigns, also known as mass vaccination campaigns, can be used in case of a sudden outbreak with natural cause or due to a bioterror attack (Kaplan et al. 2002). Performing a mass vaccination campaign is a huge logistical challenge with decision problems related to vaccination locations, facility lay-out, the order in which the population is vaccinated, staffing levels et cetera. The decision tool RealOpt<sup>®</sup> is an important contribution towards solving some of these decision problems, but the OR/OM community can further contribute here. In particular, from our overview we observe that there are quite some studies on vaccine allocation for sudden outbreaks, but the literature on how to actually distribute vaccines according to this allocation is limited. Different allocation decisions might have different effects on the operational level of vaccine distribution and some allocations might be easier to distribute than others. Current literature does not integrate these two decision problems, which provides research opportunities for the OR/OM community.

The discussion on the design of the supply chain particularly plays a role in developing countries. In these countries the supply chains are often insufficiently able to incorporate the introduction of new vaccines. This is partly due to a lack of coordination between the multiple supply chain levels that each have their own stockpiles. In the epidemiological literature there are quite some papers that study this coordination and the redesign of the supply chain (Assi et al. 2013, Brown et al. 2014, Lee et al. 2015a). But within the OR/OM community this topic has not been considered yet. Since this community has experience in studying general supply chain models, there are research opportunities to apply this knowledge to the

vaccine supply chain and derive general insights on the structure of a robust vaccine supply chain. Our review of the vaccine supply chain, which identifies the important logistical problems that play a role, could serve as guideline.

Also the inventory control of vaccines in developing countries is only minimally considered in the OR/OM community. Studying the vaccine supply chain results in new perspectives on supply chain management in general. For the vaccine supply chain, and in particular the distribution phase, there are significant differences between developing and developed countries. The existing literature on inventory control could therefore be expanded to also be applicable to developing countries that often suffer from unreliable electricity systems and unreliable transportation.

## 2.8 Discussion and future research directions

The research in this literature review has led to some interesting observations. In the Sections 2.4.4, 2.5.4, 2.6.5 and 2.7.5 we have already discussed the observations related to the individual components of the supply chain. In this section, we summarize and present common findings.

We have analyzed vaccine logistics and developed a supply chain perspective. This allows to structure different classes of papers that all study logistic decision problems related to vaccination. Our supply chain perspective also revealed the importance of integrated analyses. Namely, the decisions made in one component of the supply chain affect the downward components. In the epidemic literature there are already some case studies that use a more integrated approach, e.g., the studies on the effects of the used vial size on the supply chain (see Section 2.4.3). But these results are very case specific and the OR/OM community can contribute here with general models. The supply chain perspective can also aid governments or NGO's who want to invest in vaccine supply chains, for example in developing countries. We present an overview of the supply chain challenges that should be considered when introducing new vaccines or improving existing chains. Focusing on the entire supply chain is expected to have more effect than optimizing individual components.

A second observation is the crucial importance of time (see also Figure 2.1): composition decisions have to be made under time pressure, production is subject to uncertain production times and a swift response is needed in case of an outbreak. The combination of time pressure and extreme uncertainty, which is especially the case

for sudden outbreaks, complicates decision making processes. Future research should focus on these aspects to aid decision makers in these processes. Regarding research on sudden outbreaks, we see a gap in literature in the first two components of the supply chain ('Product' and 'Production') (see also Table 2.1). Further research is needed to address questions regarding the development and production of vaccines for sudden outbreaks.

Third, we see that the development of new technologies can have a large impact on the decision problems in the vaccine supply chain. The introduction of cell-based vaccines with shorter production times potentially changes existing decision problems on vaccine composition and vaccine production. Also the development of thermostable vaccines affects inventory control decisions and supply chain design. Other new technologies, such as the use of genomics for the development of vaccines, might bring new decision problems in which the OR/OM community can contribute.

The analysis of the vaccine supply chain is a contribution to general supply chain literature. We see two important aspects in which the vaccine supply chain differs from other supply chains. The first is that the vaccine supply chain is affected by the consequences of distributed decision making and asymmetry, which can also be seen in Figure 2.1. There are many parties involved in the vaccine supply chain, each with their own interests. The 'Product' and 'Production' components of the supply chain could be characterized as a pull-process in which public health organizations and governments request the vaccines from the manufacturer. However, the allocation and distribution phase are more related to a push-process where public health organizations determine the planning for the end user (i.e., the 'patient'). Coordination between policy makers and manufacturers is relatively well studied for the production phase, but coordination regarding the packaging of vaccines is not studied. Also, the role of the end customer (i.e., the 'patient') is hardly taken into account. As vaccine hesitancy or even vaccine refusal will directly affect the effects of vaccination, future research should incorporate this aspect in the models.

The second aspect in which the vaccine supply chain differs from many other supply chains is the quantitative difference between developed and developing countries. This difference is most apparent in the distribution phase. Since most vaccines have to be stored at low temperatures, reliable electricity systems to provide refrigeration is crucial. Unfortunately, in many developing countries such reliable systems are not available. Also transportation is often less reliable in developing countries, with

poor road quality, frequent vehicle breakdowns and fuel shortages. At the same time transportation of vaccines and medical teams is highly important, because is the only way to reach communities in rural areas. The distribution of vaccines in developing countries thus brings about different decision problems than in developed countries. In extant supply chain literature, there is little attention for this difference. Studying the vaccine supply chain thus reveals this possible future research direction.

## 2.9 Conclusions

In this review, we discuss publications on the vaccine supply chain. This topic originates in the epidemiological community, but has recently also found its way into the OR/OM community. By analyzing the different aspects of the vaccine supply chain, we connect the logistical questions that play a role in vaccination.

Based on our extensive literature review, we conclude that the vaccine supply chain can benefit from the OR/OM perspective and ample examples of interesting studies are presented in this chapter. The OR/OM community can contribute in different dimensions to improving the vaccine supply chain in both developed and developing countries. For example, this community has experience in presenting an integrated view over a whole supply chain and in formally defining decision problems. These problems can be studied with OR tools to gain insights and to derive specific decision support systems. Also we see that the epidemiologic literature often makes use of case studies and scenario analysis. Although this approach provides case specific insights, decision makers could benefit from the more general OR/OM models and insights. General insights are particularly useful because similar decision problems occur for similar types of outbreaks (e.g., expected or sudden), even if the diseases of the outbreaks are different.

When analyzing current literature, some observations repeatedly appear over the different components of the supply chain. We see the importance of the supply chain perspective and the integration of the different components. We also observe that time is of crucial importance and that the time pressure combined with uncertainty makes decision problems complex. New technologies that emerge should be taken into account as well, because they change current decision problems and bring up new ones. We contribute to supply chain literature by demonstrating the unique



characteristics of the vaccine supply chain: asymmetry between the various parties and the quantitative difference between the developed and developing countries.

The papers discussed in this review show the valuable contribution that the OR/OM community has already made to logistical problems in vaccination. Further research in this area is promising and we present interesting research directions. The growing availability of vaccines in developing countries results in ample opportunities to use expertise on logistics and supply chains, such that medical developments will not be hindered by logistical constraints.

## Appendix

### 2.A Journal list

For this review we considered the top 20 journals in the category ‘Operations Research and Management Science’ by Thomson Reuters’ InCites Journal Citation Reports<sup>2</sup>. The following ranking is based on the Article Influence Score (AIS), with in brackets the number of papers discussed in this review:

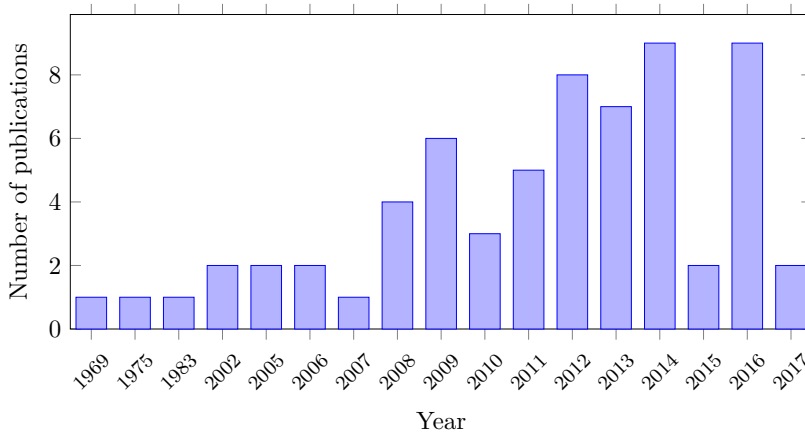
- Management Science (11)
- Journal of Operations Management (3)
- Mathematical Programming (0)
- Operations Research (11)
- Mathematics of Operations Research (0)
- Manufacturing & Service Operations Management (5)
- Transportation Science (0)
- Transportation Research part B (0)
- Journal of Quality Technology (0)
- Omega - International Journal of Management Science (3)
- Systems & Control Letters (0)
- European Journal of Operational Research (10)
- Computational Optimization and Applications (0)
- Transportation Research part E (2)
- Production and Operations Management (8)
- OR Spectrum (3)
- INFORMS Journal on Computing (1)
- Decision Support Systems (4)
- Optimization Methods and Software (1)
- Computers & Operations Research (3)

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<sup>2</sup>See [jcr.incites.thomsonreuters.com](http://jcr.incites.thomsonreuters.com)

## 2.B Chronological analysis of publications

The 65 publications are published between 1969 and 2017. 3 publications fall inside the time interval [1969-2000], 4 within the interval [2000-2005], 16 within the interval [2006-2010] and the remaining 42 publications date from [2011-2017]. The histogram in Figure 2.3 displays the number of publications over time.



**Figure 2.3:** The relation between time and the publications on the vaccine supply chain that are reviewed in this chapter.

## 2.C Bibliometric analysis

Six articles could not be found in the database of the Web of Science<sup>TM</sup> Core Collection (search date March 20, 2017): Reveller et al. (1969), Berenguer et al. (2016), Gallien et al. (2016), Levi et al. (2016), Demirci and Erkip (2017) and Chick et al. (2017). Except from the first paper, all papers are very recent, which is probably the reason that they are not (yet) included in the database.

## Chapter 3

# Dose-optimal vaccine allocation over multiple populations<sup>1</sup>

### 3.1 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 control the spread of a sudden epidemic. However, the vaccine stockpile is hardly ever sufficient to vaccinate the entire population (e.g., for influenza: Monto 2006, Berkman 2009, Roos 2009, Centers for Disease Control and Prevention 2016b).

In this chapter, we investigate vaccine allocation problems. Specifically, we consider a sudden outbreak in a population consisting of subgroups that differ geographically, and we investigate the allocation of a vaccine stockpile that is insufficient to vaccinate the entire population. Two examples of such problems are the allocation of

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<sup>1</sup>This chapter is based on Duijzer et al. (2015a).

vaccines in case of a sudden outbreak (e.g., pandemic influenza, Ebola or an unknown disease) or in response to a bioterror attack.

To illustrate the problem that is studied in this chapter, we examine a policy maker who is confronted with a sudden outbreak of pandemic influenza. For such a sudden outbreak, vaccination is one of the most effective ways to control the spread. However, the available vaccine stockpile is insufficient to vaccinate the entire population and the development of additional vaccines may take months (Centers for Disease Control and Prevention 2016b). Thus, the policy maker must solve an allocation problem: How should the doses of vaccine be allocated? During the 2009 H1N1 pandemic the US Centers for Disease Control and Prevention (CDC) used a pro rata allocation (Centers for Disease Control and Prevention 2009a) in which vaccines were allocated among states relative to their population size. However, the spread of the outbreak differed substantially per state, which motivates the study of alternative allocations of vaccines over multiple regions, also referred to as ‘populations’ (see also Teytelman and Larson 2013).

A reasonable objective for vaccine allocation is maximizing the number of people who escape infection. This objective may be achieved by evaluating the eventual outcome of alternative allocation methods by projecting the course of the epidemic numerically (e.g., Keeling and Shattock 2012, Yuan et al. 2015), simulation (e.g., Ferguson et al. 2005, Cooper et al. 2006) or by *telescoping-to-the-future* (Teytelman and Larson 2013). Such approaches may use detailed models and thus yield sophisticated allocations, but they do 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 3.1. 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 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.

We apply analytical methods to study vaccine allocation for 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 who 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) individuals. People can be in the

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 3.1:** 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 3.3 contains a detailed description of the model and Section 3.5 gives the parameters used for this table.)

removed compartment because of recovery and immunity, successful vaccination or death. Health benefits in this model are defined in terms of the total number of people who escape infection. Vaccination affects health benefit in two ways: directly for people who are vaccinated, and indirectly for people who are not vaccinated by reducing their disease exposure throughout the epidemic.

Our analytical approach yields several new structural results and general insights that cannot be derived via numerical or simulation methods. We first investigate the total health benefit for a population as a function of the vaccination fraction that is used. This function has long resisted analysis because it cannot be characterized explicitly. We derive an implicit relation that extends the *final size equation* (Diekmann et al. 2013) and that forms the basis of our subsequent analysis. We contribute to the extant literature by proving that the health benefits are in general convex-concave and increasing-decreasing in the vaccination fraction, and that the convex part arises only in populations where the disease has made limited progression yet. The insight that the health benefit has a convex-concave response to the vaccination fraction has crucial consequences for allocation. We provide an intuitive explanation for convexity-concavity to arise that is based on the effect that vaccination has on the peak of the proportion of infected.

Our second contribution consists of exploring in detail the important implications of these results for policy makers, which we summarize as follows. A single dose of vaccination may be like a drop in the ocean, but multiple doses together can have a substantial effect. To conceptualize this idea, we define our *dose-optimal vaccination fraction*, a unique fraction that maximizes the health benefits per dose of vaccine in a population. Health benefits per dose of vaccine decrease when moving away from this fraction in either direction. This leads to a crucial implication for policy makers: in order to effectively use the limited vaccine stockpile available after an outbreak, they should focus exclusively on a few populations where dose-optimal coverage is (closely) attainable.

Selecting the populations which should receive focus is a challenging combinatorial problem, and our third contribution is exploring this problem for multiple non- and 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. This leads to an explanation of the switching behavior of Table 3.1. For cases with interaction, we illustrate how to apply the insights gained from the non-interacting case.

We note that our dose-optimal fraction is conceptually different from the critical vaccination coverage advocated in extant literature (e.g., Keeling and Shattock 2012, Plans-Rubió 2012). The critical vaccination coverage aims at avoiding an increase in infected individuals and is suitable to determine vaccination fractions when sufficient vaccines are available in a pre-pandemic situation. It has also been advocated for vaccine allocation under the assumption of scarce vaccines. However, we show that our dose-optimal fraction is the right concept for allocating vaccines in this latter case, and that it gives superior results compared to critical coverage.

Our first steps yielding high-level analytical insights into vaccine allocation may aid policy-makers in grasping the sometimes puzzling outcomes of vaccine allocation models, which may support their adoption in practice. With our insights, we also contribute to the ethical debate on vaccine allocation in which policy makers have to make complex trade-offs between equity and efficiency.

The remainder of the chapter is organized as follows. Section 3.2 presents an extensive literature review to position our work. In Section 3.3, the vaccine allocation problem is formulated. The objective of maximizing the number of people who escape infection is further analyzed in Section 3.4 and the dose-optimal vaccination fraction

for a population is presented. Based on this analysis, the structure of the solution to the vaccine allocation problem is presented in Section 3.5. Section 3.6 discusses the generality of the results and the effect of the assumptions. We conclude in Section 3.7.

## 3.2 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. (2013).

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 chapter, we study non-interacting and interacting populations. In particular we focus on geographically distant populations (cf., Sun et al. 2009, Mamani et al. 2013).

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 a sudden outbreak, of pandemic influenza for example, as a vaccine needs to be developed and produced in that case (cf. Bowman et al. 2011).

There are different approaches to evaluating the effects of interventions such as vaccination. One set of approaches focuses on the costs and uses cost-effectiveness analysis or cost minimization. Many papers use such approaches. We discuss a few of them with a topic or approach that is similar to ours. Hethcote and Waltman

(1973) look for the least cost vaccination program that can prevent an epidemic. Brandeau et al. (2003) use an analytical approach to study the allocation of a limited budget on programs that affect the transmission rate. Boulier et al. (2007) analyze the externalities of vaccination in the *SIR* model and their effects on the decision problem for individuals who have to pay for their vaccination. Simons et al. (2011) develop a tool based on the *SIR* model to derive the cost-effectiveness of vaccination strategies for measles. These papers have in common that they explicitly take into account the costs of certain interventions and compare these costs to the gain in health.

Next to more cost-oriented approaches, a vast group of papers focusses on epidemic characteristics, while taking into account costs only implicitly or not at all. These epidemic characteristics are measures to quantify the severity of an outbreak. 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 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. 2013). 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 equation serves as the starting point of our analysis. In contrast, Cairns (1989) and Goldstein et al. (2009) investigate how to minimize another epidemic characteristic: the basic reproduction ratio  $R_0$  (cf. Wallinga et al. 2010).  $R_0$  is defined as the number of new infections caused by a single infectious individual in a completely susceptible population. In the initial phase of an epidemic there are very few infected individuals, so the population is almost completely susceptible.  $R_0$  is therefore related to the exponential initial growth rate of an epidemic (cf. Wallinga and Lipsitch 2007). Other studies analyze vaccine allocations that result in the threshold  $R_0 = 1$  (e.g., Becker and Starczak 1997, Tanner et al. 2008). In Chapter 4, we consider vaccination before an outbreak in an age structured population and minimize the required vaccine stockpile to achieve  $R_0 = 1$ .  $R_0$  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). Teytelman and Larson (2013) develop heuristic algorithms to solve the vaccine allocation problem. They show that these heuristic algorithms outperform a pro rata strategy by taking into account regional differences in the flu wave that can be the result of differences in school holidays and school openings. They use a dynamic approach in which vaccination decisions are updated over time to incorporate incoming information about the epidemic. 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 a unique vaccination fraction that yields the highest health benefits per dose of vaccine in a population: 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. Simulation models and numerical analysis are incapable of deriving insightful structural results. Our analytical approach is therefore essential to derive and formally proof the convex-concave structure and the dose-optimal vaccination fraction. The structural insights that we obtain may help practitioners to better understand the sometimes counter-intuitive outcomes of a broad range of models.

By taking advantage of 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 bud-

get over multiple investments (Ağralı and Geunes 2009). Both Ginsberg (1974) and Ağralı and Geunes (2009) study a knapsack problem with S-shaped return functions and the latter paper proves it to be NP-hard. Srivastava and Bullo (2014) derive a constant factor approximation algorithm with polynomial running time for the same problem. Our results in Section 3.4 establish the applicability of this algorithm for our vaccine allocation problem, but we do not explore this further because the main purpose of this chapter is developing high-level insights into the problem.

Our research is in line with the growing interest for decision problems related to the vaccine supply chain in the Operations Management community. In Chapter 2, we characterize the following four components of the vaccine supply chain: product (e.g., Cho 2010, Özaltın et al. 2011), production (e.g., Mamani et al. 2013, Adida et al. 2013), allocation (e.g., Sun et al. 2009) and distribution (e.g., McCoy and Johnson 2014). This chapter contributes to the literature on allocation.

### 3.3 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 chapter models the spread of an epidemic using the seminal deterministic *SIR* model, which is explained in Section 3.3.1. In Section 3.3.2, we explain the effect of vaccination on the time course of an epidemic. The vaccine allocation problem is formulated in Section 3.3.3.

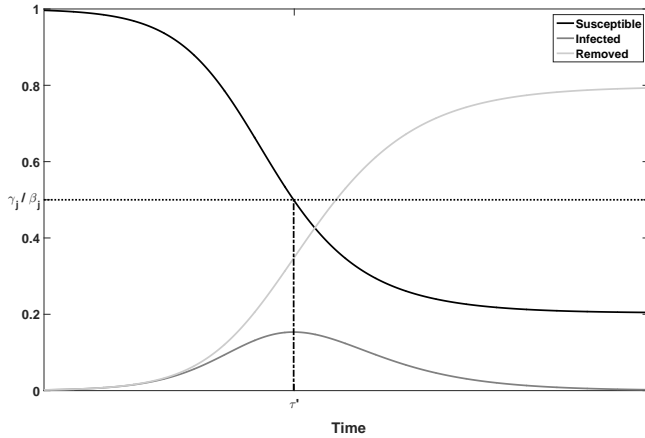
#### 3.3.1 The *SIR* model

The *SIR* model is a classic model in epidemiology proposed by Kermack and McKendrick (1927). 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  $t$ . In this chapter, we consider the removed compartment consisting of recovered individuals, deaths can be taken into account straightforwardly. 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 *SIR* model is described by the following system of differential equations, with the transmission rate and the rate of recovery in population

$j$  denoted by  $\beta_j$  and  $\gamma_j$ , respectively.

$$\begin{aligned}\frac{ds_j}{dt} &= -\beta_j s_j i_j \\ \frac{di_j}{dt} &= \beta_j s_j i_j - \gamma_j i_j \\ \frac{dr_j}{dt} &= \gamma_j i_j\end{aligned}\tag{3.1}$$

We assume that boundary conditions  $s_j(0) = s_0^j$ ,  $i_j(0) = i_0^j$  and  $r_j(0) = r_0^j$  are given, with  $i_0^j > 0$  and  $s_0^j + i_0^j + r_0^j = 1$ . (The limit  $i_0^j \downarrow 0$  is discussed in Section 3.4.3.)



**Figure 3.1:** Illustration of the deterministic *SIR* model for population  $j$  with parameters  $\gamma_j = 1.5$ ,  $\beta_j = 3$ ,  $i_0 = 10^{-6}$ .

Figure 3.1 illustrates the time course of an epidemic that evolves according to the differential equations of the *SIR* model. (Figure 3.1 and 3.2 are computed with the Runge-Kutta method (Greenbaum and Chartier 2012).) Two observations should be made from this figure: 1) the epidemic eventually dies out and 2) not all susceptible individuals become infected. As the fraction of susceptible individuals decreases over time, it becomes less and less likely for an infected individual to come into contact with such a susceptible individual. This eventually leads to a decrease in the fraction of infected individuals. Specifically, we see that  $i_j(t)$  increases for  $s_j(t) > \frac{\gamma_j}{\beta_j}$  and

decreases for  $s_j(t) < \frac{\gamma_j}{\beta_j}$ . Accordingly, we refer to populations being pre-peak in the first case and post-peak in the second case. Let  $\tau'$  be the time at which  $s_j(\tau') = \frac{\gamma_j}{\beta_j}$ , i.e., at  $\tau'$  the peak in infectious is reached.

### 3.3.2 Vaccination

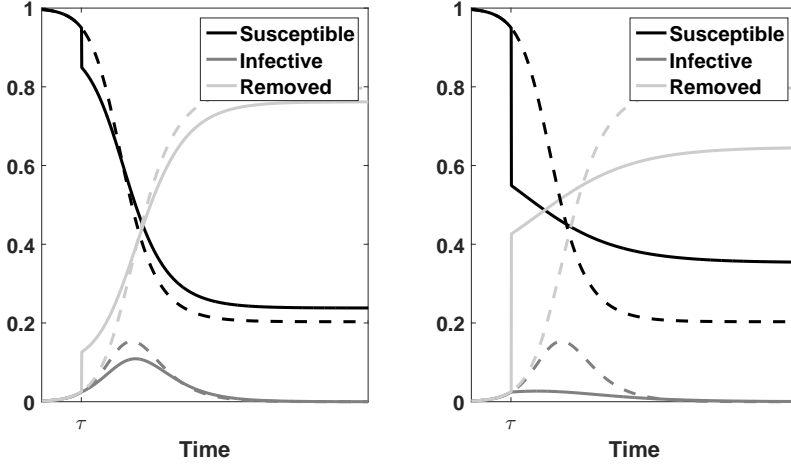
Vaccination reduces the fraction of susceptible individuals, in order to avoid or reduce an increase in the fraction of infected individuals. To formally define vaccination, we introduce the following notation. Let  $\tau$  denote the time at which a fraction  $f_j$  of population  $j$  is vaccinated, with  $0 \leq f_j \leq s_j(\tau)$ . Just prior to vaccination the system is in state  $(s_j(\tau), i_j(\tau))$ . Assume that the used vaccine is completely effective after a single dose and that vaccination takes no time, meaning that vaccination results in complete immunity immediately. Assume also that it is possible to identify the susceptible people. We refer to Section 3.6 for a discussion of these assumptions. Under our assumptions vaccination causes a shift at time  $\tau$  from state  $(s_j(\tau), i_j(\tau))$  to state  $(s_j(\tau) - f_j, i_j(\tau))$ . This implies that  $r_j(\tau)$  shifts to  $r_j(\tau) + f_j$ . Figure 3.2 illustrates the changes at time  $\tau$ .

To evaluate different vaccine allocations we base ourselves on the state of the system when  $t \rightarrow \infty$ . This state is also referred to as disease-free equilibrium, because  $\lim_{t \rightarrow \infty} i_j(t) = 0$ . 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  $\tau$ . More precisely, for  $f_j \in [0, s_j(\tau)]$

$$G_j(f_j) = \lim_{t \rightarrow \infty} s_j(t), \quad (3.2)$$

with  $s_j(t)$  evolving according to (3.1) for  $t > \tau$ . The final fraction of people susceptible is closely related to the following concepts, that we define here explicitly for future use:

**Herd immunity:** the protection of susceptible individuals against infection because they are surrounded by a sufficient number of immune individuals. The immunity from the latter group may result either from vaccination or from recovery from infection (cf. Fine 1993).



**Figure 3.2:** Illustration of the deterministic *SIR* model for population  $j$  with parameters  $\gamma_j = 1.5, \beta_j = 3, i_0 = 10^{-6}$ . Dashed lines represent the time course without vaccination. The solid lines represent the time course when either a fraction  $f_j = 0.1$  (left panel) or  $f_j = 0.4$  (right panel) is vaccinated at time  $\tau$  when  $s_j(\tau) = 0.95$ .

**Herd effect:** the proportion of all people who are spared from infection because of herd immunity. i.e., the proportion of all people who are still susceptible when the epidemic has died out.

Thus,  $G_j(f_j)$  measures the herd effect in population  $j$ . Section 3.4 studies  $G_j(f_j)$  in more detail.

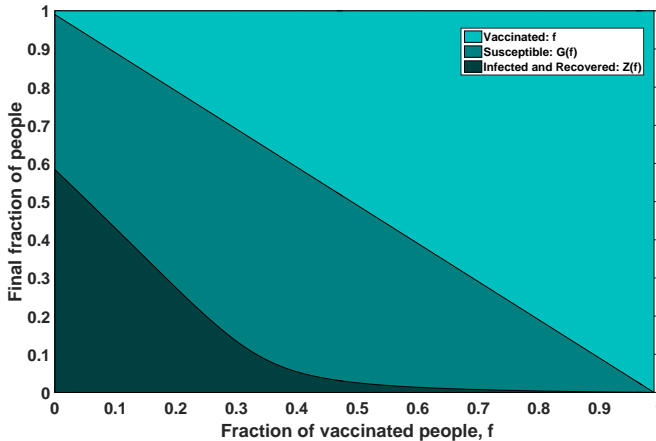
### 3.3.3 The vaccine allocation problem

We are interested in allocating a limited amount of vaccines  $V$  in order to maximize health benefit, defined as the total number of people who escape infection:

$$\begin{aligned}
 \max \quad & \overbrace{\sum_{j \in J} N_j G_j(f_j)}^{\text{herd effect}} + \overbrace{\sum_{j \in J} N_j f_j}^{\text{direct effect}} \\
 \text{s.t.} \quad & \sum_{j \in J} N_j f_j \leq V \\
 & 0 \leq f_j \leq s_j(\tau) \quad \forall j \in J
 \end{aligned} \tag{3.3}$$

Here,  $N_j$  denotes the size of population  $j$ . The objective function reflects that there are two ways to escape infection: either you are vaccinated (direct effect) or you escape infection without being vaccinated (indirect effect). Note that the fraction of people escaping infection without being vaccinated in population  $j$  is precisely the final fraction of susceptible people, i.e. the herd effect  $G_j(f_j)$  introduced in Section 3.3.2.

We discuss two equivalent formulations of the above allocation problem using different objective functions in order to demonstrate the relation of our work to epidemiological literature. Firstly, in Theorem 3.D.1 we prove that it is optimal to always use the complete vaccine stockpile, i.e., constraint  $\sum_{j \in J} N_j f_j \leq V$  will always be met with equality. This implies that the objective could be changed from maximizing the *total* effect of vaccination to maximizing only the *herd effect*. Secondly, maximizing the total effect of vaccination is equivalent to minimizing the *final size of the epidemic*, i.e., the total number of people who get infected. The final size of the epidemic may be expressed as  $Z_j(f_j) = s_j(0) + i_j(0) - f_j - G_j(f_j)$  and (3.2) is thus formally equivalent to a minimization problem involving this final size (e.g., Wu et al. 2007, Keeling and Shattock 2012). The relation between  $Z_j(f_j)$ ,  $f_j$  and  $G_j(f_j)$  is illustrated in Figure 3.3. Note that the fraction  $G_j(f_j)$  may in fact increase for smaller values of  $f_j$ .



**Figure 3.3:** 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  $\tau = 0$ .

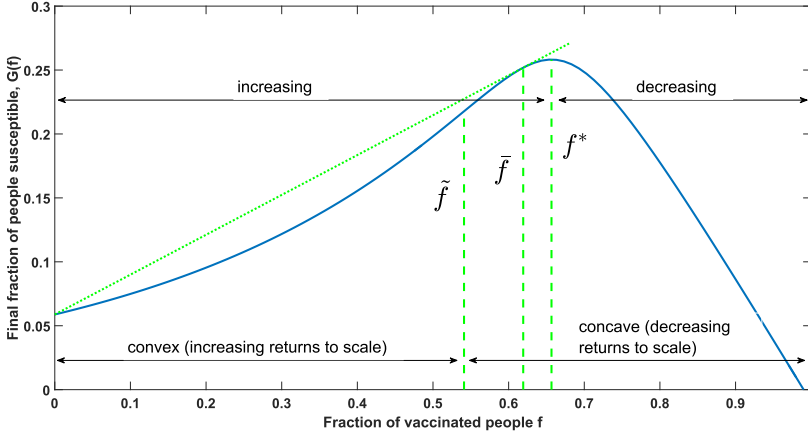
### 3.4 Analysis of the herd effect

In order to study the allocation problem (3.2), Section 3.4.1 analyzes and interprets the structure of the herd effect  $G(f)$  (we drop the subscript  $j$  for convenience). Based on this analysis, we present our *dose-optimal* vaccination fraction for a population in Section 3.4.2 and compare this fraction to the so-called critical vaccination fraction from literature in Section 3.4.3. We extend our analysis to more general compartmental models in Section 3.4.4. A minor detail is sorted out in Section 3.4.5: we formally confirm that it is optimal to vaccinate as early as possible.

Figure 3.4 summarizes the main findings of this section and illustrates the structure of  $G(f)$ . In Section 3.4.1 and 3.4.2 these results are derived formally.

#### 3.4.1 Analysis of the structure of the herd effect

In this and the next section, we present the main technical contribution of this chapter: a structural analysis of the herd effect  $G(f)$ . Let  $\sigma := \frac{\beta}{\gamma}$ . The overall structure of  $G(f)$  is established in the following theorems:



**Figure 3.4:** Illustration of the structure of  $G(f)$ , which is proven in Section 3.4: Theorems 3.1 and 3.2 establish the increasing-decreasing and convex-concave structure of  $G(f)$ , which is illustrated in this figure using the parameters  $(s_0, i_0) = (0.99, 0.01)$ ,  $\sigma = 3$  and  $\tau = 0$ . Dashed lines represent the important vaccination fractions  $\bar{f}$  (left),  $f^*$  (right) and our dose-optimal vaccination fraction  $\tilde{f}$  (middle). The latter follows from Corollary 3.1. The straight dotted line illustrates that  $\tilde{f}$  is the only non-zero vaccination fraction for which the tangent line contains the point  $(0, G(0))$ .

**Theorem 3.1.** *There is a unique vaccination fraction  $f^* = \max(s(\tau) - \frac{1}{\sigma}, 0)$  that maximizes the herd effect: the herd effect  $G(f)$  is increasing in  $f$  for all  $f < f^*$ , maximized for  $f = f^*$  and decreasing for  $f > f^*$ .*

**Theorem 3.2.** *There exists a unique vaccination fraction  $\bar{f}$  with  $0 \leq \bar{f} \leq f^*$  such that  $G(f)$  is strictly convex ( $G''(f) > 0$ ) for all  $f < \bar{f}$  and strictly concave ( $G''(f) < 0$ ) for all  $f > \bar{f}$ .*

We first briefly discuss how these results are derived. The proofs for these results and the supporting lemmas can be found in Appendix 3.B. We had to overcome a number of significant challenges, particularly because no explicit formulation of the herd effect  $G(f)$  exists. We develop an implicit relation characterizing  $G(f)$ , and our proof departs from that relation. We note that despite almost 90 years of research on



the *SIR* model, the convex-concave shape and its repercussions for vaccine allocation have not been considered.

We next discuss the intuition behind these theorems, and the consequences that these results have for practice. The peak in the infections, illustrated in Figure 3.2, plays a critical role in determining the herd effect. At this peak the proportion of susceptibles is equal to  $\gamma/\beta = 1/\sigma$  and so infections decrease for  $s(t) < 1/\sigma$ . Note that vaccinating with the fraction  $f^* = s(\tau) - 1/\sigma$  exactly results a proportion of susceptibles equal to  $1/\sigma$  directly after vaccination, which leads to the following definition (cf, Keeling and Shattock 2012, Plans-Rubió 2012):

**Critical vaccination coverage:** the smallest vaccination fraction that results in a decrease of infections directly after vaccination, denoted by  $f^*$  as in Theorem 3.1.

Vaccination *beyond*  $f^*$  thus protects individuals that would not be likely to contract the disease anyhow and expanding coverage beyond  $f^*$  actually reduces the herd effect.

The primary effect of vaccination is that it reduces the number of people to be infected until the peak of infected is reached at  $s(t) = 1/\sigma$ . The convex-concave structure results because this primary effect interacts with a secondary effect:  $f$  affects the *specific time* at which the peak occurs. This secondary effect is non-monotonic, because it consists of two competing phenomena: (1) Vaccination lowers  $s(\tau)$ , thus reducing the further reduction in susceptibles needed until  $s(t)$  reaches  $1/\sigma$  and (2) Vaccination reduces the rate of initial exponential growth of infected people, thus inhibiting the speed of reduction of  $s(t)$ . For small  $f$  the second effect dominates, resulting in a delayed peak as can be seen in Figure 3.2. For larger vaccination fractions, when  $s(\tau)$  comes close to  $1/\sigma$ , the first effect dominates rendering the peak to be advanced. A delayed peak is beneficial, since more time allows for more recoveries and consequently results in fewer infections at the peak. Small vaccination fractions benefit from the delayed peak, in addition to the primary effect, which results in the convex and increasing herd effect. For larger vaccination fractions the secondary benefit is reversed, which explains the concave increase.

The structure of the herd effect has some interesting practical consequences. Consider for example a policy maker that faces a pandemic influenza outbreak where the vaccine stockpile should be allocated over multiple populations with a comparable

pre-peak state. It is better to concentrate on one or few of these populations instead of allocating equally over all. By restricting attention to a few populations both the primary effect and the secondary effect can be fully exploited for a few populations resulting in a higher overall herd effect. Our results thus yield understanding why equitable allocations are often not efficient. This increased understanding is a contribution to the ethical debate on vaccine allocation.

Note that Theorem 3.2 does not rule out that  $\bar{f} = 0$ , in which case there is no convex part of  $G(f)$ . Similarly, by Theorem 3.1 we may have  $f^* = 0$ , in which case  $G(f)$  is never increasing. The following theorem investigates these issues. It features the constant  $C$  that is defined as  $C = 2/\sigma + W[-\sigma \exp\{-\sigma(s_0 + i_0) + \log(s_0)\}]/\sigma$ , where  $W[\cdot]$  is the Lambert W function and  $C > 1/\sigma$  (cf. Appendix 3.E).

**Theorem 3.3.** *For the structure of  $G(f)$  we can distinguish three cases based on  $s(\tau)$ , the proportion of susceptibles at the moment of vaccination  $\tau$ :*

- (i)  $C < s(\tau) < 1$ : *We have  $f^* > \bar{f} > 0$ . Thus  $G(f)$  is increasing and convex between 0 and  $\bar{f}$ , increasing and concave between  $\bar{f}$  and  $f^*$ , and decreasing and concave above  $f^*$ .*
- (ii)  $1/\sigma < s(\tau) \leq C$ : *We have  $f^* > 0$  and  $\bar{f} = 0$ . Thus  $G(f)$  is increasing and concave between 0 and  $f^*$ , and decreasing and concave above  $f^*$ .*
- (iii)  $0 \leq s(\tau) < 1/\sigma$ : *We have  $\bar{f} = f^* = 0$ . Thus  $G(f)$  is decreasing and concave everywhere.*

Figure 3.4 graphically illustrates the herd effect  $G(f)$  with parameters for which  $C = 0.7092$ . Since we use  $s(\tau) = s_0 = 0.99$ , the figure shows the most general shape (i). Theorem 3.3 follows from the intuitive discussion earlier in this section. For  $s(\tau)$  high enough (more precisely higher than  $C$ ) the peak in infections can be delayed with small vaccination fractions, resulting in the convex increase in the herd effect. When  $s(\tau)$  is below  $C$  the peak can not be delayed through vaccination and the herd effect has no convex part. If  $s(\tau) < 1/\sigma$ , the population is already in a post-peak state with infections declining. This implies that the risk of getting infected for the people who are still susceptible is relatively low. In that case  $f^* = 0$  and vaccination reduces the herd effect, because you vaccinate people who were unlikely to get infected in the first place.

Thus, policy makers that face an outbreak of pandemic influenza for example, should resist the pressure to vaccinate in areas with many infected people. Indeed, when infections are close to the peak, the effect of vaccination is lower. Vaccinating in post-peak areas is even less effective, because the people who are vaccinated were not likely to become infected anyhow (cf., Teytelman and Larson 2013). Thus, it is best to vaccinate in pre-peak areas where  $s(\tau) \gg 1/\sigma$ . But to achieve most in such populations, concentration of effort is needed. In Sections 3.4.2 and 3.5.1 we will discuss this in more detail.

### 3.4.2 The dose-optimal vaccination fraction

In this section, we present a third important vaccination fraction, next to the vaccination fractions  $f^*$  and  $\bar{f}$  defined in Theorems 3.1 and 3.2. To explore the impact of vaccination we should take into account that susceptible people will escape infection even without vaccination. Accordingly, we define:

**Additional herd effect:** the herd effect achieved through vaccination minus the herd effect that would already be present without vaccination; denoted by  $G(f) - G(0)$ .

We introduce the function  $D(f)$  to measure the average additional herd effect per dose of vaccine:

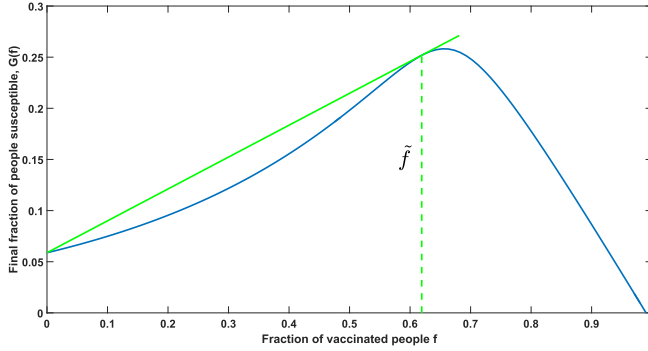
$$D(f) = \frac{1}{f} [G(f) - G(0)] \quad (3.4)$$

Note that  $D(f)$  can also be interpreted as the average slope of the herd effect  $G(f)$  on the interval  $[0, f]$ . We derive following result:

**Corollary 3.1.** *The function  $D(f)$  as defined by (3.4) is maximized by the unique vaccination fraction  $\tilde{f}$  for which  $G'(\tilde{f}) = D(\tilde{f})$ . The function  $D(f)$  is increasing for  $f < \tilde{f}$  and decreasing for  $f > \tilde{f}$ .*

We have thus determined three important vaccination fractions of which the relation is presented in the following lemma:

**Lemma 3.2.** *Consider the following three vaccination fractions:  $f^*$  as defined in Theorem 3.1,  $\bar{f}$  as defined in Theorem 3.2 and  $\tilde{f}$  as defined in Corollary 3.1. The following relation holds:  $\bar{f} \leq \tilde{f} \leq f^*$*



**Figure 3.5:** Illustration of the dose-optimal vaccination fraction  $\tilde{f}$  using the parameters  $(s_0, i_0) = (0.99, 0.01)$ ,  $\sigma = 3$  and  $\tau = 0$ . The slope of the straight line represent the value of  $D(f)$  for  $\tilde{f}$ . Observe that any other line starting at  $G(0)$  and intersecting with  $G(f)$  would be less steep and not tangent to  $G(f)$ .

Corollary 3.1 and Lemma 3.2 are illustrated in Figure 3.5. Observe that at  $\tilde{f}$  the line connecting  $G(0)$  and  $G(\tilde{f})$  is also the tangent line at  $G(\tilde{f})$ . Because of the convex-concave structure of the herd effect  $G(f)$  there is only a single vaccination fraction  $\tilde{f}$  for which this holds, and this fraction must lie between  $\bar{f}$  and  $f^*$ . The interpretation of Corollary 3.1 is that  $\tilde{f}$  gives the highest additional herd effect *per* dose of vaccine, which leads to the following definition:

**Dose-optimal vaccination fraction:** the vaccination fraction that maximizes the average additional herd effect per dose of vaccine in a population, denoted by  $\tilde{f}$ .

A discussion of the implications of Corollary 3.1, and a comparison of the dose-optimal  $\tilde{f}$  with the critical vaccination coverage  $f^*$  are provided in the next section.

### 3.4.3 Dose-optimal and critical vaccination coverage

Our dose-optimal vaccination fraction  $\tilde{f}$  and the vaccination fraction  $f^*$  represent two different concepts in vaccine allocation. We compare the dose-optimal vaccination fraction  $\tilde{f}$  with the critical vaccination coverage  $f^*$  and illustrate these fractions for different values of  $\sigma$  in Table 3.2. The table shows that  $\tilde{f}$  and  $f^*$  are indeed quite

$\sigma$	2	3	5	10	20	30	50	100
$\tilde{f}$	0.3376	0.5411	0.7086	0.8398	0.9094	0.9340	0.9546	0.9712
$\tilde{f}$	0.4134	0.6193	0.7746	0.8855	0.9386	0.9560	0.9697	0.9799
$f^*$	0.4900	0.6567	0.7900	0.8900	0.9400	0.9567	0.9700	0.9800

**Table 3.2:** Illustration of the three important vaccination fractions  $\tilde{f}$ ,  $\tilde{f}$  and  $f^*$  for increasing  $\sigma$ . To calculate the numbers an initial state  $(s_0, i_0) = (0.99, 0.01)$  and  $s(\tau) = 0.99$  is used.

different. For  $\sigma$  growing large, both  $\tilde{f}$  and  $f^*$  converge to  $s(\tau)$  (cf., Lemma 3.B.4 in Appendix 3.B.3), but this limit is not very interesting because  $\sigma$  is between 2 and 20 for most diseases. For example,  $\sigma \approx 3$  for influenza,  $\sigma \approx 3.5 - 6$  for smallpox,  $\sigma \approx 6 - 7$  for rubella and  $\sigma \approx 16 - 18$  for measles (Keeling and Rohani 2008).

As discussed in Section 3.4.2, the vaccination fraction  $\tilde{f}$  results in the most efficient allocation *per* dose of vaccine in a population. The vaccination fraction  $f^*$  on the other hand is attractive from another perspective and has been advocated in literature (e.g., Keeling and Shattock 2012, Plans-Rubió 2012). It does not only maximize the herd effect, but also directly results in a decrease in infected individuals at time  $\tau$ .

Corollary 3.1 and Lemma 3.2 clearly show that  $\tilde{f}$  makes more efficient use of vaccines than  $f^*$ . This can be intuitively understood as follows. Note that  $f^* > \tilde{f}$ . Our intuitive interpretation of Theorem 3.2 reveals that while vaccination initially delays the timing of the peak of infected, vaccinating with higher vaccination fractions will actually render the peak to be advanced. As a consequence, vaccines issued to expand coverage from  $\tilde{f}$  to  $f^*$  in a population are used inefficiently. We give an example using the settings of Table 3.2 and  $\sigma = 3$ . In that case, the vaccines between 0 and  $\tilde{f}$  result in an average herd effect of 0.31 per dose, whereas this average is only 0.17 per dose for the vaccines between  $\tilde{f}$  and  $f^*$ . Hence, vaccinating beyond  $\tilde{f}$  to achieve  $f^*$  is costly, and not a good use of a limited vaccine stockpile.

In literature optimal vaccination has often been explained in terms of avoiding the further increase in infected individuals, which relates to vaccinating with  $f^*$  (cf., Wu et al. 2007, Keeling and Shattock 2012, Yuan et al. 2015). Avoiding an increase of infected people is suitable when there are initially no infected individuals, i.e., for ‘pre-pandemic vaccination’ (the limit  $i_0 \downarrow 0$ ). However, allocating a limited vaccine

stockpile typically goes hand in hand with a sudden outbreak: the limited stockpile arises because not enough time is available to produce more. This arguably renders pre-pandemic vaccination unrealistic in combination with allocating a limited vaccine stockpile. In the case of influenza, this implies that the assumption of a limited stockpile is more realistic for pandemic influenza than for seasonal influenza. Extant literature has focused mainly on the less realistic case of a limited stockpile and pre-pandemic vaccination, for which  $f^*$  and  $\tilde{f}$  coincide numerically as we show in Appendix 3.B.3, and has thus missed the conceptual distinction between critical and dose-optimal vaccination. In general, the concepts of dose-optimal vaccine allocation and avoiding an increase in infections are substantially different. The explanation of literature is therefore not generalizable.

#### 3.4.4 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. Let  $\beta_k$  and  $\gamma_k$  denote respectively the transmission rate and recovery rate in infectious stage  $k$ . A special case of the  $SI^nR$  model for which  $n = 2$  is the  $SEIR$  model. Compared to the  $SIR$  model the  $SEIR$  model has an additional compartment  $E$  containing the individuals that are exposed and hence infected, but not yet infectious. We derive our results for the general  $SI^nR$  model, in which there are arbitrary many additional compartments:

**Lemma 3.3.** *The results of Theorem 3.1, Theorem 3.2, Theorem 3.3 and Corollary 3.1 also apply to the  $SI^nR$  model with  $\sigma = \sum_{k=1}^n \frac{\beta_k}{\gamma_k}$ . In particular, for each  $SI^nR$  model with given initial conditions there exist vaccination fractions  $\bar{f}, \tilde{f}$  and  $f^*$  that together characterize the convex-concave and increasing-decreasing shape of the herd effect.*

Theorem 3.1, Theorem 3.2, Theorem 3.3 and Corollary 3.1 form the basis for the analysis of the vaccine allocation problem in Section 3.5. By Corollary 3.3 the results derived in Section 3.5 are valid for the more general  $SI^nR$  model. The interested reader is referred to Appendix 3.C, where we formally analyze the  $SI^nR$  model.

### 3.4.5 The optimal timing of vaccination

We sort out a minor detail by formally proving that vaccination should ideally be carried out as soon as possible. Thereto we determine the time  $\tau$  at which the total effect of vaccination, i.e.,  $G(f, s(\tau)) + f$ , is maximized. Assume that we have a fixed vaccine stockpile,  $V$ , such that a fraction of the population can be vaccinated is restricted by  $\frac{V}{N}$ , where  $N$  is the population size. If  $s(\tau) \leq V/N$ , all susceptible people can be vaccinated and the objective function for  $f = s(\tau)$  reduces to  $s(\tau)$ , because  $\lim_{f \uparrow s(\tau)} G(f) = 0$  by Theorem 3.B.1. If  $s(\tau) > V/N$ , all available doses of vaccine are used and  $f = \frac{V}{N}$ . In Lemma 3.B.6 we derive that the herd effect  $G(f, s(\tau))$  is increasing in  $s(\tau)$  in that case. Therefore, to maximize the number of people who escape infection one should vaccinate as soon as possible in an ideal world. A policy maker that has to allocate a limited vaccine stockpile over a number of populations that face an outbreak of pandemic influenza should therefore concentrate on the population in which the outbreak has least progressed.

## 3.5 Analysis of the vaccine allocation problem

In this section, we analyze the vaccine allocation problem (3.2), using the characterization of the objective function in Theorems 3.1, 3.2 and 3.3. These theorems establish that our vaccine allocation problem is a combinatorial optimization problem that is likely difficult to solve to optimality (cf., Srivastava and Bullo 2014). However, in this section we show that there is an interesting structure in the optimal solution. Section 3.5.1 presents this central insight. Section 3.5.2 considers an interesting special case to gain more understanding of the structure of the solution. Section 3.5.3 translates the results gained in Sections 3.5.1 and 3.5.2 into insights and simple guideline for arriving at an efficient allocation. In Section 3.5.4, we illustrate how the insights from the non-interactive case can be applied to geographically distant populations that interact with each other.

### 3.5.1 The optimal allocation

We characterize the optimal allocation, which is the solution to problem (3.2). We will make a few non-restrictive assumptions to allow us to focus on the most interesting cases. Firstly, we assume that  $V < V^*$ , where  $V^* = \sum_{j \in J} N_j f_j^*$ , reflecting

our focus on severe shortages of vaccines. As argued in Section 3.4.3, this is a realistic assumption in case of a sudden outbreak such as pandemic influenza. Indeed, with  $V \geq V^*$  all locations can reach critical vaccination coverage  $f_j^*$ , stopping any further increase of infections. Moreover, we observed in Section 3.4.1 that post-peak populations (with  $s_j(\tau) < 1/\sigma_j$ ) should not receive vaccination until all pre-peak populations receive at least  $f_j^*$ . Thus, here we assume that all populations are pre-peak ( $s_j(\tau) > 1/\sigma_j$ ). We refer to Appendix 3.D for a description of the optimal allocation in case these assumptions are relaxed.

We will show that every optimal solution to problem (3.2) is linked to a certain *marginal efficiency*  $\omega$ :

**Marginal efficiency:** the increase in herd effect if one additional dose of vaccine would be allocated to a population, calculated as the derivative of  $G_j(f_j)$  with respect to  $f_j$ .

Populations  $j \in J$  are vaccinated with marginal efficiency  $\omega$  if  $G'_j(f_j) = \omega$ . In the optimal solution, by KKT conditions every population that is partially vaccinated must be vaccinated with marginal efficiency  $\omega$ . However, potentially *two* vaccination fractions  $f_j$  may satisfy  $G'_j(f_j) = \omega$ :

**Regular fraction:** the vaccination fraction  $f_j$  that results in a marginal efficiency  $\omega$  and lies in the domain where the herd effect is concave, i.e.,  $f_j > \bar{f}_j$ .

**Exceptional fraction:** the vaccination fraction  $f_j$  that results in a marginal efficiency  $\omega$  and lies in the domain where the herd effect is convex, i.e.,  $f_j < \bar{f}_j$ .

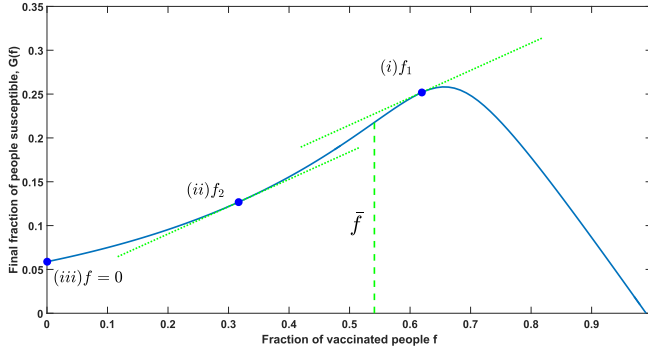
In the optimal solution there are three possible vaccination fractions for every population  $j \in J$ : (i) the regular fraction, (ii) the exceptional fraction or (iii)  $f_j = 0$  and population  $j$  is not vaccinated at all. Figure 3.6 illustrates these three possibilities for population  $j$ .

**Theorem 3.4** (Central Insight). *Every optimal solution to (3.2) can be characterized as follows:*

- (i). *A subset of populations  $J' \subseteq J$  is vaccinated with the regular fraction that corresponds to marginal efficiency  $\omega$ .*
- (ii). *Possibly another population  $k$  is also vaccinated with marginal efficiency  $\omega$ , but with the exceptional fraction for which  $f_k < \bar{f}_k$ .*



(iii). The remaining populations are not vaccinated at all.



**Figure 3.6:** Illustration of the structure of the optimal allocation, using the parameters  $(s_0, i_0) = (0.99, 0.01)$ ,  $\sigma = 3$  and  $\tau = 0$ .

Determining  $\omega$  for a specific problem is difficult, which relates back to the combinatorial nature of Problem 3.2. Still, a key insight can be derived from Theorem 3.4: A policy maker should focus on a subset of populations when allocating vaccines and leave other populations unvaccinated. By doing so the benefits of the herd effect are best exploited, because only a concentrated effort can fully harness both the primary and the secondary effects of vaccination. The structure of the optimal allocation thus clearly brings about complex decisions for policy makers, who also have to take equity considerations into account. Our results show that mathematically optimal allocations are *inherently* inequitable due to the nonlinear dynamics of epidemics. Hence, policy makers are to some extent forced to choose between equity and efficiency. For a further discussions of the ethical dimension of vaccine allocation we refer to Section 3.7.

### 3.5.2 The special case: identical parameters

We illustrate the intuition behind the central insight for an interesting special case: the case of populations having identical disease parameters. This special case implies identical functions  $G_j(f_j) := G(f_j)$  for all  $j \in J$  ( $\sigma_j := \sigma$ ,  $s_0^j := s_0$ ,  $i_0^j := i_0$  for all  $j \in J$ ). In that case, the regular fraction  $f_j$  for a certain marginal efficiency  $\omega$

is the same for all populations  $j$ . This implies that the allocation described in (i) of Theorem 3.4 is a *pro rata* allocation over the subset  $J'$ , 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.

Based on the results derived in Section 3.4, we conclude that our optimization problem is a knapsack problem with convex-concave return functions. Ginsberg (1974) study an investment problem over multiple factories with convex-concave production functions. Mathematically, this problem is equivalent to our vaccine allocation problem for the special case  $G_j(0) = 0$  and  $N_j = N$  for all  $j \in J$ . Intuitively, this special case corresponds to a situation with a shifted herd effect and all sub-populations having the same size. We build upon the results of Ginsberg (1974) to characterize the optimal vaccine allocation in the following theorem.

**Theorem 3.5.** *Consider a set of populations  $J$  with  $\forall j: G_j(f) = G(f)$  and a total available amount of resources equal to  $V$ . Let  $|J| = n$  and order the populations such that  $N_1 \leq \dots \leq N_n$ . The optimal allocation for particular cases is as follows:*

- (a). *if  $V < \tilde{f}N_1$ , then allocate only to the smallest population. Set  $f_1 = V/N_1$  and  $f_j = 0$  for  $j = 2, \dots, n$ .*
- (b). *if  $V = \sum_{j \in K} \tilde{f}N_j$  for a subset  $K \subseteq J$ , then set  $f_j = \tilde{f}$  for  $j \in K$  and  $f_j = 0$  for  $j \notin K$ .*
- (c). *if  $V > \sum_{j \in J} \tilde{f}N_j$ , then allocate pro rata over all the populations:  $f_j = \frac{V}{\sum_{j \in J} N_j}$  for all  $j \in J$ .*

The proof of this theorem can be found in Appendix 3.D. Theorem 3.5 shows that in order to make the best possible use of the herd effect, decision makers should try to vaccinate close to  $\tilde{f}$  in (a subset of) the populations. They should allocate all vaccines to the smallest population if the vaccination fraction  $\tilde{f}$  cannot be attained in any of the populations (case (a)). For very large vaccine stockpiles, policy makers do best in selecting the pro rata allocation over all populations (case (c)). Note that Theorem 3.5 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 general, the optimal allocation changes continuously for small changes in  $V$ . For larger changes, discontinuities may arise when jumping from one subset  $K$  to the other in item (b) of Theorem 3.5.

### 3.5.3 Discussion of the general case - The switching behavior

The vaccine allocation problem that we study is NP-hard, but we have derived an interesting structure in Theorem 3.4 and Section 3.5.2. In this section, we translate this structure to insights and a simple guideline for arriving at an efficient allocation.

Recall that in the special case discussed in Section 3.5.2 a decision maker should look for a subset of populations such that it is feasible to vaccinate these populations close to the fraction  $\tilde{f}$  that yield the highest additional herd effect per allocated dose. In the general case, the parameters may differ per population, causing the functions  $G_j(\cdot)$  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  $j \in J$ . The additional herd effect per dose of vaccine in population  $j$  is the highest at  $\tilde{f}_j$  and decreases as the vaccination fraction moves away from  $\tilde{f}_j$  in either direction. This has the following implications for the optimal allocation: a decision maker should select a subset of populations and divide the vaccines over them such that these populations are vaccinated with a fraction *close to* their dose-optimal fractions  $\tilde{f}_j$ . The marginal efficiency  $\omega$  of Theorem 3.4 determines how close the vaccination fraction exactly is to the dose-optimal fraction. In any case, Theorem 3.4 guarantees that the vaccination fraction lies in the interval  $[\tilde{f}_j, f_j^*]$  for the populations in the selected subset, except for at most one population which can be vaccinated with a fraction below  $\tilde{f}_j$ .

The recommendation given by Wu et al. (2007), Keeling and Shattock (2012), Yuan et al. (2015) to maximize the herd effect in some populations by setting  $f_j = f_j^*$  is thus incorrect in typical practical settings of a limited vaccine stockpile, e.g., during an outbreak of pandemic influenza. A decision maker should vaccinate close to  $\tilde{f}_j$  to use the vaccines efficiently in every population; any additional vaccinations used to reach critical coverage  $f^*$  in  $j$  are ineffective as discussed in Section 3.4.3.

Using the above characterization of the optimal allocation we can also explain the switching behavior. The smallest populations are prioritized for small vaccine stockpiles, as the number of doses of vaccine required to reach  $\tilde{f}_j$  is smaller in those populations. When the stockpile size increases, we can vaccinate *close to* the dose-optimal vaccination fraction in larger populations and hence priority shifts to these

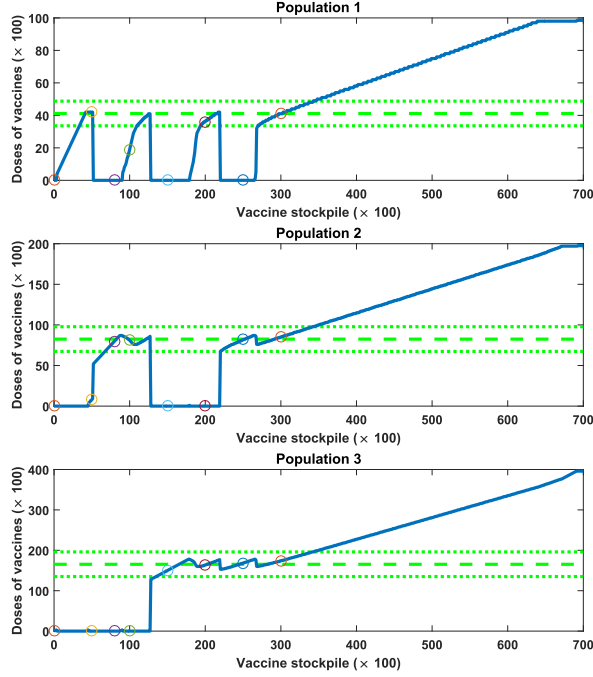
populations. Numerical analysis of the optimal vaccine allocation (e.g., by Keeling and Shattock (2012)) shows switch points where a small increase in vaccine stockpile results in a completely different allocation. Our analysis explains these switch points: they are related to a change in the subset of populations to approach the dose-optimal vaccination fraction.

The structure of the optimal allocation is illustrated in Figure 3.7, 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:  $\tau = 0$ ,  $\sigma_j = 2$  for  $j = 1, 2, 3$  and initial states  $(s_0^1, i_0^1) = (0.985, 0.015)$ ,  $(s_0^2, i_0^2) = (0.988, 0.012)$  and  $(s_0^3, i_0^3) = (0.990, 0.010)$ . In Figure 3.7, we indeed observe that the vaccinated populations receive a number of allocated vaccines that is close to  $\tilde{V}_j$ .

To relate Figure 3.7 to the description of the optimal allocation in Theorem 3.4, we explain the optimal allocation for two vaccine stockpile sizes:  $V = 5000$  and  $V = 10000$ . For  $V = 5000$ , the optimal strategy is roughly to allocate 4200 vaccines to population 1 and the remaining 800 to population 2. We thus see all three vaccination possibilities of Theorem 3.4 present: (i) population 1 gets the regular fraction, (ii) population 2 the exceptional fraction and (iii) population 3 is not vaccinated at all. For  $V = 10000$ , we see the roles of population 1 and 2 reversed with population 1 getting 1900 vaccines and population 2 receiving the remaining 8100. We can calculate that  $\tilde{V}_1 = \tilde{f}_1 N_1 = 3963$ ,  $\tilde{V}_2 = \tilde{f}_2 N_2 = 8173$  and  $\tilde{V}_3 = \tilde{f}_3 N_3 = 16702$ . The two examples for  $V$ , as well as the optimal allocations in Table 3.1 and Figure 3.7, illustrate that vaccines in the optimal allocation are allocated such that the vaccination fractions in the vaccinated populations are always close to the dose-optimal fraction and that at most one population has a substantial lower vaccination fraction.

We use our explanation of the optimal allocation in terms of the dose-optimal vaccination fraction to derive a guideline for the vaccine allocation problem (3.2). This simple heuristic does not find the optimal solution, but it does capture an important structure of the optimal solution: as many populations as possible are vaccinated with their dose-optimal vaccination fraction  $\tilde{f}_j$ .

1. We order populations based on the benefits per dose of vaccine such that  $D_1(\tilde{f}_1) \geq \dots \geq D_n(\tilde{f}_n)$ , where the function  $D(f)$  is defined in (3.4).
2. Following the order of step 1, we vaccinate as many populations as possible with their dose-optimal vaccination fraction until the vaccine stockpile is insufficient



**Figure 3.7:** 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  $\tilde{V}_j = \tilde{f}_j N_j$ , the upper dotted line equals  $V_j^* = f_j^* N_j$  and the lower dotted line equals  $\bar{V}_j = \bar{f}_j N_j$ . The circles indicate the values from Table 3.1.

to reach dose-optimal coverage for the next population (case 1) or until dose-optimal coverage is reached for all populations (case 2).

3. We allocate the remaining vaccines. In case 1, these vaccines are allocated to the unvaccinated population in which these vaccines are most beneficial (i.e., the population for which allocating the remaining vaccines would result in the highest  $D_j(f_j)$ ). In case 2, we allocate the remaining vaccines pro rata over all populations.

We evaluate the performance of the heuristic as well as the gains of using the optimal allocation and compare to the equitable allocation in Table 3.3. Since the direct effect of vaccination is not affected by the allocation, we focus only on the herd effect. In particular, we look at the additional herd effect which leaves out the herd effect that is already achieved without any vaccination:

$$\text{additional herd effect} = \sum_{j \in J} N_j (G_j(f_j) - G_j(0)) \quad (3.5)$$

The table shows that the optimal allocation is significantly more effective in harnessing the herd effect than the pro rata allocation. We also observe that the allocation heuristic performs close to optimal. It captures the same structure as the optimal solution, which results in a good performance.

To investigate the impact of heterogeneous  $\sigma$  we have performed an additional experiment in which the disease parameters of the populations change to  $\sigma_1 = 1.5, \sigma_2 = 2, \sigma_3 = 2.5$ . The relative improvement of the optimal allocation over the pro rata allocation increases from 0-21% to 5-72% in that case. We have also investigated an algorithm based on minimizing  $R_0$ . However, the performance of this algorithm was poor and the corresponding results are therefore not reported.

Vaccine stockpile	Equitable allocation	Heuristic allocation	Optimal allocation	Relative improvement optimal over equitable allocation
2000	671	762	762	+ 13.56%
5000	1742	2037	2037	+ 16.93%
8000	2893	3235	3511	+ 21.36%
10000	3707	4274	4274	+ 15.30%
15000	5912	6265	6702	+ 13.36%
20000	8350	8842	8910	+ 6.71%
25000	10930	11032	11170	+ 2.20%
30000	13255	13226	13264	+ 0.07%

**Table 3.3:** The additional herd effect (3.5) for three different allocation strategies for various vaccine stockpiles. The equitable allocation allocates pro rata over all populations, the heuristic allocation is determined via the heuristic described in Section 3.5.3 and the optimal allocation is specified in Table 3.1 and Figure 3.7. The population sizes are:  $N_1 = 10000$ ,  $N_2 = 20000$  and  $N_3 = 40000$ .

### 3.5.4 Interaction

Our model can be applied to geographically distant populations, and one might wonder how our insights are affected when these populations exhibit some interaction in the form of mutual infections. From a theoretical perspective, our results continue to hold for sufficiently weak interactions, while they are invalidated by sufficiently strong interactions. Indeed, for strong interaction sub-populations start to behave like a single large population, implying that pro rata allocation should perform well.

We determine at what level of interaction our results start to deteriorate by comparing the results derived for the non-interacting case with the structure of the optimal allocation for various levels of interaction. The *SIR* model with interaction is given by the following differential equations (Diekmann et al. 2013):

$$\begin{aligned}\frac{ds_j}{dt} &= - \sum_{k \in J} \beta_{jk} s_j i_k & \forall j \in J \\ \frac{di_j}{dt} &= \sum_{k \in J} \beta_{jk} s_j i_k - \gamma_j i_j & \forall j \in J \\ \frac{dr_j}{dt} &= \gamma_j i_j & \forall j \in J\end{aligned}\tag{3.6}$$

We consider an example with three populations with the population sizes and initial states being the same as in the non-interacting example presented in Section 3.5.3. We use the following parameters:  $\gamma_j = 1$  and  $\beta_{jj} = \beta = 2$  for all  $j \in J$ . The interaction is determined as follows:  $\beta_{jk} = c\beta \frac{N_k}{\sum_{m \neq j} N_m}$  for  $j, k \in J$  and  $j \neq k$ , such that  $\sum_{k \neq j} \beta_{jk} = c\beta$  for all  $j \in J$ , with  $c$  being the interaction factor: interaction between populations is a factor  $1/c$  weaker than interaction within populations.

The vaccination fractions  $\bar{f}_j$ ,  $\tilde{f}_j$  and  $f_j^*$  are computed by numerical evaluation of (3.6) fixing  $f_k = 0$  for  $k \neq j$ . Perhaps surprisingly, we still observe the convex-concave relation between the herd effect and the used vaccination fraction in that population. Numerical experiments in which we determine the optimal allocation via enumeration show that the insights for the non-interacting case carry over. Up to 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 lev-

els of interaction (0.01, 0.02, 0.05 and 0.1) the optimal allocation of small vaccine stockpiles remains unequitable, prioritizing initially only one population. Numerical results also show that ignoring interaction performs close to optimal and even outperforms the equitable allocation. We refer to Appendix 3.F for a graphical illustration of the numerical experiments mentioned in this section.

We assume that the interaction factor  $c$  is relatively small, which conforms to Wu et al. (2007) who note that individuals spend on average more than 97% of their time in their home regions. Also Sun et al. (2009) and Mamani et al. (2013) derive their results for sufficiently small between-country transmission rates. In the latter paper this is specified as the assumption that  $\beta_{ij}\beta_{jk} \approx 0$ . Our results indicate that vaccine allocation can benefit from increasing returns to scale also in case of larger interaction between populations. Hence, our structural results that characterize the optimal allocation apply for typical interacting models.

### 3.6 Discussion of assumptions

We briefly discuss the effect of modelling assumptions, extensions and the generality of the results. Our results continue to hold when several assumptions are relaxed as will be discussed here. We assume that the vaccine is completely effective and results in immunity directly. The effectiveness of a vaccine can be incorporated with an efficacy parameter that rescales the vaccination fraction (cf. Hill and Longini Jr 2003, Mylius et al. 2008). A delay in immunity can be approximated by using a slightly lower value for  $s(\tau)$  than at the vaccination moment. We also assume that it is possible to identify susceptible individuals. If this is not the case, some of the vaccines would be administered to infected or immune people. Under the condition that the vaccines are only effective for susceptible people, this implies that the proportion of people effectively vaccinated equals  $fs(\tau)$ . i.e., we can simply rescale a parameter to account for situations where susceptible people cannot be identified. All these small adjustments in the parameters do not change the structure of the herd effect and the optimal vaccine allocation. Thus, the structure described in the theorems and lemmas continues to hold. Finally, we assume that a single dose of vaccine is sufficient to achieve immunity. Our results cannot be directly applied to the situation where multiple doses of vaccine are given to an individual, particularly because there often needs to be a minimum time in between administering consecutive doses. As



the epidemic continues to spread in the meantime, this brings extra complexity to the problem (See Chapter 5).

The results in this chapter are established under the assumption that vaccination is the only intervention used. However, in practice vaccination is often combined with hygiene measures and 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 chapter carry over when multiple interventions are combined.

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. Note that the deterministic model considered in this chapter can be seen as the fluid approximation of a stochastic model. Unpublished numerical results by the authors indicate that the convex-concave pattern in the herd effect also holds for this stochastic *SIR* model. This is an indication that the insights of this chapter carry over, although proving convexity is even more difficult for the stochastic model. For populations with interaction we numerically illustrate in Section 3.5.4 and Appendix 3.F that the insights gained from the non-interacting case can still be applied, which is in line with the findings of Wu et al. (2007).

## 3.7 Conclusions

In this chapter, 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 who escape infection. We find that vaccination can have a secondary effect in addition to the primary one, which causes a second dose of vaccine to have a bigger effect than the first. Based on this result we show that there is a unique vaccination fraction that results in the highest health benefit per dose of vaccine in a population and introduce the term *dose-optimal* for this fraction.

We discuss the qualitative difference between dose-optimal and critical vaccination coverage, where the latter aims at maximizing health benefits. We show that policy makers should stop vaccinating before the health benefits are maximized in order to achieve the most efficient allocation. When vaccines are scarce, the final doses needed to maximize health benefits in a population yield more in another population.

We characterize the solution of the vaccine allocation problem and we show the crucial importance of the dose-optimal vaccination fraction. A single dose of vaccine may be a drop in the ocean, but multiple doses together can save a population. Policy makers should therefore select a subset of populations to which the vaccines are allocated. By focusing on a limited number of populations, the available vaccine stockpile is used more efficiently than by allocating pro rata over all populations.

In the distribution of vaccines many logistical aspects play a role, ranging from transporting the vaccines from a central warehouse to health facilities, to setting up points of dispensing where people can be vaccinated. Allocating vaccines only to certain populations, might be easier from an logistical viewpoint than allocating to all populations. On the other hand, if vaccines are stockpiled locally, redistributing vaccines might lead to coordination problems (cf., Mamani et al. 2013). Further research could study the logistical consequences of vaccine allocation.

Vaccine allocation has an ethical dimension, unlike many other resource allocation problems where equity does not play a role. In this chapter, we distinguish between groups of people based on geography. Others use age groups or risk groups (e.g., Mylius et al. 2008, Medlock et al. 2009, Goldstein et al. 2009, 2012). Although prioritizing based on geography might seem unfair, geography might play a role in outbreaks of influenza, measles or in bioterror attacks. In the past, there have been outbreaks with large regional differences such as the 2009 H1N1 pandemic (Centers for Disease Control and Prevention 2009b). In situations with a large asymmetry between the regions, a geographic assymetric approach is perhaps more easily accepted. However, our results also show that sometimes asymmetric choices should be made in symmetric cases (e.g., two regions with the same parameters and disease progression). In those situations, our optimal allocation is less politically viable, and new ideas are needed to reconcile equity and efficiency in such cases.

Thus, the policy that we describe as optimal need not be the best policy if we also take equity considerations into account. The CDC for example uses ethical guidelines in decision making on influenza pandemics (Kinlaw and Levine 2007). These ethical guidelines are the result of an ethical debate on finding good vaccine allocations. The results derived in this chapter can be a valuable contribution to this ethical debate. Our optimal allocations 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. Next to that, policy makers can use strategies in which they balance between efficiency

and equity. For example, they can reserve part of the vaccine stockpile for pro rata allocation and allocate the remaining vaccines optimally (cf. Kaplan and Merson 2002, Wu et al. 2007). Another possibility is to add equity constraints that either set minimum levels for vaccination in each region or restrict the relative difference between populations (Teytelman and Larson 2013). Our relatively simple model, and the analytical results we obtained for it, could be a valuable starting point to test ideas on balancing equity, political viability, and effectiveness of vaccine allocations.

## Acknowledgements

The authors want to thank the senior editor and two anonymous reviewers for their valuable comments which significantly helped to improve the paper on which this chapter is based.

# Appendix

## 3.A The herd effect function

In this chapter, we study the herd effect of vaccination, denoted by the function  $G_j(f_j)$ . In Section 3.3.2 we have defined  $G_j(f_j)$  as the final fraction of people susceptible in population  $j$  after vaccinating a fraction  $f_j$  of the susceptible people at time  $\tau$ . More precisely, for  $f_j \in [0, s_j(\tau)]$

$$G_j(f_j) = \lim_{t \rightarrow \infty} s_j(t), \quad (3.7)$$

with  $s_j(t)$  evolving according to the differential equations of the *SIR* model (3.1) for  $t > \tau$ . In this appendix, we present and analyze an alternative formulation of the herd effect  $G_j(f_j)$ , which forms the basis of the structural analysis of the herd effect.

### 3.A.1 Implicit formulation of the herd effect

Based on the differential equations of the *SIR* model we derive an implicit expression for the herd effect. From (3.1) the following equation follows, which presents the

relation between  $i_j(t)$  and  $s_j(t)$  at any time  $t$  (Hethcote 1976):

$$i_j(t) = -s_j(t) + \frac{\log(s_j(t))}{\sigma_j} + s_{0,j} + i_{0,j} - \frac{\log(s_{0,j})}{\sigma_j} \quad (3.8)$$

Above relation characterizes the state of the system at any point in time, but prior to vaccination. Upon vaccination at time  $\tau$  the state of the system changes from state  $(s_j(\tau), i_j(\tau))$  to state  $(s_j(\tau) - f_j, i_j(\tau))$ . Hence, the state  $(s_j(\tau) - f_j, i_j(\tau))$  directly after vaccination can be seen as a new initial state, where  $i_j(\tau)$  can be obtained from (3.8).  $G_j(f_j)$  is then obtained from (3.8) by setting  $i_j(t) = 0$  and thus is the unique solution to:

$$\begin{aligned} 0 &= -G_j(f_j) + \frac{\log(G_j(f_j))}{\sigma_j} + s_j(\tau) - f_j + i_j(\tau) - \frac{\log(s_j(\tau) - f_j)}{\sigma_j} \\ \Leftrightarrow 0 &= -G_j(f_j) + \frac{\log(G_j(f_j))}{\sigma_j} + s_{0,j} + i_{0,j} - \frac{1}{\sigma_j} \log \left( s_{0,j} \left( 1 - \frac{f_j}{s_j(\tau)} \right) \right) - f_j \end{aligned} \quad (3.9)$$

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  $i_{0,j} = 0$ . (3.9) extends the *final size equation* to any initial state. The original final size equation can be recovered for  $f_j = 0$ ,  $s_{0,j} \rightarrow 1$  and  $i_{0,j} \rightarrow 0$  (see e.g., Kermack and McKendrick (1927), Ma and Earn (2006), Diekmann et al. (2013) and Keeling and Shattock (2012)). We refer to Appendix 3.E for an alternative expression of  $G_j(f_j)$  using the Lambert W function denoted by  $W(x)$  (cf. Corless et al. 1996, Ma and Earn 2006).

### 3.A.2 Derivatives of the herd effect

We present implicit equations for the first and second order derivative of the function  $G(f)$  with respect to  $f$  (we drop the subscript  $j$  for convenience). These derivatives will appear in the next sections to prove the structural characteristics of the herd effect  $G(f)$ . Denote by  $G'(f)$  and  $G''(f)$  respectively the first and second order derivative of the function  $G(f)$  with respect to  $f$  which can be derived from (3.9):

$$G'(f) \left[ 1 - \frac{1}{\sigma G(f)} \right] = \frac{1}{\sigma(s(\tau) - f)} - 1 \quad (3.10)$$

$$\begin{aligned}
G''(f) \left[ 1 - \frac{1}{\sigma G(f)} \right] &= \frac{1}{\sigma(s(\tau) - f)^2} - \frac{1}{\sigma} \left[ \frac{G'(f)}{G(f)} \right]^2 \\
\Leftrightarrow G''(f) &= \frac{G(f)^2 - [G'(f)(s(\tau) - f)]^2}{(\sigma G(f) - 1)G(f)(s(\tau) - f)^2}
\end{aligned} \tag{3.11}$$

## 3.B Analysis of the herd effect

This appendix consists of theorems that describe the characteristics of the function  $G(f)$ . The proofs for Theorem 3.1, Theorem 3.2 and Theorem 3.3 are presented as well as other results required for these proofs. This appendix is structured as follows. We start with deriving bounds on the herd effect in Section 3.B.1. Section 3.B.2 focuses on the structure of the function  $G(f)$ . In Section 3.B.3 we formally derive and study the dose-optimal vaccination fraction.

We need that the differential equations (3.1) 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.

### 3.B.1 Bounds on the herd effect

In the following three theorems we formally proof which values are feasible for  $G(f)$ .

**Theorem 3.B.1.** *It holds that  $G(f) > 0$  for all  $f \in [0, s(\tau))$  and  $\lim_{f \uparrow s(\tau)} G(f) = 0$ .*

*Proof.* Consider the characterization of  $G(f)$  in (3.28).

Note that  $W[0] = 0$  and  $W[x] < 0$  for  $\frac{-1}{e} \leq x < 0$  (Appendix 3.E). In our case  $x = -\sigma \exp\{-\sigma B(f, \sigma)\}$ , with  $\lim_{f \uparrow s(\tau)} B(f, \sigma) = +\infty$ . Thus,  $x < 0$  for  $f \in [0, s(\tau))$  and approaches 0 for  $f \uparrow s(\tau)$ . Therefore,  $W[x] < 0$  and  $G(f) > 0$  for  $f \in [0, s(\tau))$  and  $\lim_{f \uparrow s(\tau)} G(f) = 0$ .  $\square$

**Theorem 3.B.2.** *It holds that  $G(f) < \frac{1}{\sigma}$  for all  $f \in [0, s(\tau)]$  under the assumption that  $i_0 > 0$ .*

*Proof.* The differential equations in (3.1) 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.  $\square$

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

*Proof.* Upon vaccination the system changes from state  $(s(\tau), i(\tau))$  to state  $(s(\tau) - f, i(\tau))$ . By assumption we have that  $s(\tau) > 0$  and  $i(\tau) > 0$  for vaccination in an infected population. By the differential equations in (3.1) this implies that the derivative of  $s(t)$  directly after vaccination is negative. As  $G(f) = \lim_{t \rightarrow +\infty} s(t)$  (3.2) and  $s(t)$  is non-increasing over time, we have that  $G(f) < s(\tau + \epsilon) \leq s(\tau) - f$ .  $\square$

### 3.B.2 Analysis of the structure of the herd effect

This section is dedicated to deriving structural results on the herd effect  $G(f)$ . This is done by analyzing the derivatives of this function as presented in Section 3.A.2.

**Lemma 3.B.1.** *The function  $G(f)$  is twice differentiable for all  $f \in [0, s(\tau))$  in case of vaccination in an infected population ( $i_0 > 0$ ) and twice differentiable for all  $f \in [0, s(\tau))$  with  $f \neq s(\tau) - \frac{1}{\sigma}$  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  $f \in [0, s(\tau))$  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  $s(\tau) = s_0$ ) the function  $G(f)$  is indifferentiable if and only if  $f^* = s(\tau) - \frac{1}{\sigma}$  or  $f = s(\tau)$ .
- (iii). The function  $G(f)$  is twice differentiable for all  $f \in [0, s(\tau))$  in case of vaccination in an infected population.
- (iv). The function  $G(f)$  is twice differentiable for all  $f \in [0, s(\tau))$  except for  $f = f^* = s(\tau) - \frac{1}{\sigma}$  in case of vaccination in a completely susceptible population.

We start the proof:

- (i). Note that vaccination in an infected population means  $i(\tau) > 0$  and  $i_0 > 0$  which implies  $G(f) < \frac{1}{\sigma}$  by Theorem 3.B.2. For  $G(f) = \frac{1}{\sigma}$  the function  $G'(f)$  is not defined as can be seen in (3.10). However, this does not occur for vaccination in an infected population (Theorem 3.B.2). The function  $G(f) : [0, s(\tau)] \rightarrow \mathbb{R}$ . We therefore also analyze the existence of the derivative at the boundaries  $f = 0$  and  $f = s(\tau)$ . Because  $G(0) < \frac{1}{\sigma}$  by Theorem 3.B.2:

$$\lim_{f \downarrow 0} G'(f) = \frac{1}{\left[1 - \frac{1}{\sigma G(0)}\right]} \left( \frac{1}{\sigma s(\tau)} - 1 \right) \quad (3.12)$$

By Theorem 3.B.1 we have  $\lim_{f \uparrow s(\tau)} G(f) = 0 < \frac{1}{\sigma}$  and thus  $\lim_{f \uparrow s(\tau)} G'(f) < 0$ .

- (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 (3.28) and insert the parameter settings for vaccination in a completely susceptible population and the value for  $f^*$ :

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

By (i) the function  $G(f)$  is indifferentiable at  $f^*$ , because  $G(f^*) = \frac{1}{\sigma}$ . Part (i) also states that  $G(f)$  is indifferentiable at  $f = s(\tau)$ . 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  $y(f) = -\sigma(s(\tau) - f) \exp\{-\sigma(s(\tau) - f)\}$  for vaccination in a completely susceptible population (3.28). Clearly  $y(f) < 0$ , since  $f < s(\tau)$ . Thus, we only need to investigate for which  $f$  the function  $y(f) = -\exp\{-1\}$ . Note that this only holds for:  $\sigma(s(\tau) - f) = 1 \Leftrightarrow f = s(\tau) - \frac{1}{\sigma} = f^*$

- (iii). By (3.10) and (3.11)  $G(f)$  is twice differentiable unless one of the following conditions holds:  $G(f) = \frac{1}{\sigma}, f = s(\tau), G(f) = 0$ . In Theorem 3.B.1 we showed that  $G(f) > 0$  for all  $f \in [0, 1)$ . By Theorem 3.B.2 we know that  $G(f) < \frac{1}{\sigma}$  for

vaccination in an infected population and since  $\lim_{f \uparrow s(\tau)} G(f) = 0$ , 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 3.1.** *There is a unique vaccination fraction  $f^* = \max(s(\tau) - \frac{1}{\sigma}, 0)$  that maximizes the herd effect: the herd effect  $G(f)$  is increasing in  $f$  for all  $f < f^*$ , maximized for  $f = f^*$  and decreasing for  $f > f^*$ .*

*Proof.* By Theorem 3.B.1 the function  $G'(f)$  is not defined for  $f = s(\tau)$ , but we know that  $\lim_{f \uparrow s(\tau)} G(f) = 0$ . We analyze the derivative  $G'(f)$  (3.10). Because  $G(f) < \frac{1}{\sigma}$  for all  $f \in [0, s(\tau)]$  (Theorem 3.B.2), the function  $G(f)$  is maximized for  $f = f^* = s(\tau) - \frac{1}{\sigma}$ . It is increasing for  $f < f^*$  and decreasing for  $f > f^*$ . Note that for  $s(\tau) \leq \frac{1}{\sigma}$  we get  $f^* \leq 0$  and thus the function  $G(f)$  is only decreasing in that case. □

**Lemma 3.B.2.** *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  $G(f) = \frac{2}{\sigma} - (s(\tau) - f)$ .
- (ii).  $G''(f) > 0$  if and only if  $G(f) > \frac{2}{\sigma} - (s(\tau) - f)$ .
- (iii).  $G''(f) < 0$  for  $f \geq s(\tau) - \frac{1}{\sigma}$  and  $G''(f) < 0$  if and only if  $G(f) < \frac{2}{\sigma} - (s(\tau) - f)$  for  $f < s(\tau) - \frac{1}{\sigma}$ .

*Proof.* We analyze  $G''(f)$  which is presented in (3.11). Because  $\lim_{f \uparrow s(\tau)} G(f) = 0$  (Theorem 3.B.1), the function  $G''(f)$  is not defined for  $f = s(\tau)$ . We prove the three statements of the lemma:

- (i). We analyze  $G''(f) = 0$  and consider that  $G(f) < \frac{1}{\sigma}$  (Theorem 3.B.2):

$$\begin{aligned}
 G''(f) = 0 &\Leftrightarrow \frac{G(f)^2 - [G'(f)(s(\tau) - f)]^2}{(\sigma G(f) - 1)G(f)(s(\tau) - f)^2} = 0 \\
 &\Leftrightarrow G(f)^2 - [G'(f)(s(\tau) - f)]^2 = 0 \\
 &\Leftrightarrow G(f)^2 = \left[ \frac{[1 - \sigma(s(\tau) - f)]G(f)}{[\sigma G(f) - 1]} \right]^2 \\
 &\Leftrightarrow [1 - \sigma(s(\tau) - f)]^2 = [\sigma G(f) - 1]^2
 \end{aligned} \tag{3.13}$$



In the second step we use that  $(\sigma G(f) - 1)G(f)(s(\tau) - f)^2 \neq 0$ , which holds for all  $f < s(\tau)$  by Theorems 3.B.1 and 3.B.2. In the third step we substitute (3.10). Thus  $G''(f) = 0$  if and only if one of the following two relations holds:

$$\begin{aligned} 1 - \sigma(s(\tau) - f) = \sigma G(f) - 1 &\Leftrightarrow G(f) = \frac{2}{\sigma} - (s(\tau) - f) && \text{if } f < s(\tau) - \frac{1}{\sigma} \\ 1 - \sigma(s(\tau) - f) = 1 - \sigma G(f) &\Leftrightarrow G(f) = (s(\tau) - f) && \text{if } f > s(\tau) - \frac{1}{\sigma} \end{aligned}$$

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

- (ii). Consider the second expression in (3.11), by Theorems 3.B.1 and 3.B.2 we have:  
 $(\sigma G(f) - 1)G(f)(s(\tau) - f)^2 < 0$  for  $f < 1$  From (3.13) we derive:

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

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

$$\begin{aligned} 1 - \sigma(s(\tau) - f) < \sigma G(f) - 1 &\Leftrightarrow G(f) > \frac{2}{\sigma} - (s(\tau) - f) && \text{if } f < s(\tau) - \frac{1}{\sigma} \\ 1 - \sigma(s(\tau) - f) > 1 - \sigma G(f) &\Leftrightarrow G(f) > (s(\tau) - f) && \text{if } f \geq s(\tau) - \frac{1}{\sigma} \end{aligned}$$

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

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

$$\begin{aligned} 1 - \sigma(s(\tau) - f) > \sigma G(f) - 1 &\Leftrightarrow G(f) < \frac{2}{\sigma} - (s(\tau) - f) && \text{if } f < s(\tau) - \frac{1}{\sigma} \\ 1 - \sigma(s(\tau) - f) < 1 - \sigma G(f) &\Leftrightarrow G(f) < (s(\tau) - f) && \text{if } f \geq s(\tau) - \frac{1}{\sigma} \end{aligned}$$

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

□

**Theorem 3.B.4.** *The derivative of  $G(f)$  with respect to  $f$ , denoted by  $G'(f)$ , is bounded from above by 1, i.e.,  $G'(f) < 1 \quad \forall f \in [0, s(\tau)]$*

*Proof.* From (3.10) we have:

$$G'(f) \left[ 1 - \frac{1}{\sigma G(f)} \right] = \frac{1}{\sigma(s(\tau) - f)} - 1 \Leftrightarrow G'(f) = \frac{\sigma G(f)}{\sigma G(f) - 1} \cdot \frac{1 - \sigma(s(\tau) - f)}{\sigma(s(\tau) - f)} \quad (3.14)$$

From Lemma 3.B.2 we note that  $G'(f)$  has an extreme under the following condition:

$$G(f) = \frac{2}{\sigma} - (s(\tau) - f) \quad (3.15)$$

By contradiction we assume that there exists a vaccination fraction  $\bar{f}$  for which  $G'(\bar{f}) \geq 1$  and assume that  $\bar{f}$  meets condition (3.15), then:

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

We arrive at a contradiction, because by Theorem 3.1 we have that  $G'(f) < 0$  for all  $f > s(\tau) - \frac{1}{\sigma}$ . Thus,  $G'(f) < 1$  for all  $f$  that are an extreme for  $G'(f)$ . This completes the proof that  $G'(f) < 1$  for all  $f \in (0, s(\tau))$ . We consider the two boundary cases:  $f = 0$  and  $f = s(\tau)$ . From Lemma 3.B.1 we know that  $\lim_{f \uparrow s(\tau)} G'(f) < 0$  and thus the lemma is satisfied for  $f = s(\tau)$ . 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 1.
- (ii). if  $G''(0) > 0$ : then for a very small  $\epsilon > 0$  we have  $G'(\epsilon) > \lim_{f \downarrow 0} G'(f)$  and  $G'(f) < 1$  for all  $f \in (0, s(\tau)]$ . Thus also  $\lim_{f \downarrow 0} G'(f) < 1$ .

(iii). if  $G''(0) < 0$ : then from Lemma 3.B.2 we have that  $G(0) < \frac{2}{\sigma} - s(\tau)$ . By (3.12) we have:

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

Since  $G(f) < \frac{1}{\sigma}$  by Theorem 3.B.2, we have  $\lim_{f \downarrow 0} G'(f) < 0$  in case  $s(\tau) < \frac{1}{\sigma}$ . In that case the theorem is satisfied. For  $s(\tau) > \frac{1}{\sigma}$  we substitute  $G(0) < \frac{2}{\sigma} - s(\tau)$  in (3.12):

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

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

**Theorem 3.2.** *There exists a unique vaccination fraction  $\bar{f}$  with  $0 \leq \bar{f} \leq f^*$  such that  $G(f)$  is strictly convex ( $G''(f) > 0$ ) for all  $f < \bar{f}$  and strictly concave ( $G''(f) < 0$ ) for all  $f > \bar{f}$ .*

*Proof.* By (3.11) note that  $G''(f)$  is a continuous function for  $f < s(\tau)$ , because both  $G(f)$  and  $G'(f)$  are continuous by Lemma 3.B.1. Consider the function  $M(f) = G(f) - \frac{2}{\sigma} + (s(\tau) - f)$ . From Lemma 3.B.2 we have that  $\bar{f}$  must satisfy  $G(\bar{f}) = \frac{2}{\sigma} - (s(\tau) - \bar{f})$ , i.e.  $M(\bar{f}) = 0$ . Denote by  $M'(f)$  the derivative of  $M(f)$  with respect to  $f$ : By Theorem 3.B.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 3.B.2 we have  $G''(f) < 0$  for  $f \geq s(\tau) - \frac{1}{\sigma}$  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 3.B.2 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 3.B.3. By Lemma 3.B.2  $G(f)$  is concave for  $f \geq f^*$ , such that  $\bar{f} \leq f^*$ . This completes the proof of this theorem. □

**Lemma 3.B.3.** *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  $f^* = s(\tau) - \frac{1}{\sigma}$ .*

*Proof.* By Lemma 3.B.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 3.1), it holds that  $G(f) < \frac{1}{\sigma}$  for all  $f \neq f^*$ . In Lemma 3.B.2 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  $f \neq f^*$ .

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

Note that for  $f^*$  we have  $G(f^*) = \frac{1}{\sigma} = \frac{2}{\sigma} - (s(\tau) - f^*)$ . By Theorem 3.1 the function  $G(f)$  is decreasing for  $f > f^*$ , whereas the expression  $\frac{2}{\sigma} - (s(\tau) - f)$  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 3.B.4 the expression  $\frac{2}{\sigma} - (s(\tau) - f)$  increases with a faster rate than  $G(f)$ . This implies that  $G(f)$  is convex for all  $f < f^*$ . □

**Theorem 3.3.** *For the structure of  $G(f)$  we can distinguish three cases based on  $s(\tau)$ , the proportion of susceptibles at the moment of vaccination  $\tau$ :*

- (i)  $C < s(\tau) < 1$ : We have  $f^* > \bar{f} > 0$ . Thus  $G(f)$  is increasing and convex between 0 and  $\bar{f}$ , increasing and concave between  $\bar{f}$  and  $f^*$ , and decreasing and concave above  $f^*$ .
- (ii)  $1/\sigma < s(\tau) \leq C$ : We have  $f^* > 0$  and  $\bar{f} = 0$ . Thus  $G(f)$  is increasing and concave between 0 and  $f^*$ , and decreasing and concave above  $f^*$ .
- (iii)  $0 \leq s(\tau) < 1/\sigma$ : We have  $\bar{f} = f^* = 0$ . Thus  $G(f)$  is decreasing and concave everywhere.

*Proof.* From Theorem 3.2 it follows that  $\bar{f} \leq f^*$ . It therefore suffices to proof the following two steps:

- (a)  $f^* > 0$  if  $s(\tau) > 1/\sigma$  and  $f^* = 0$  otherwise.
- (b)  $\bar{f} > 0$  if  $s(\tau) > C$  and  $\bar{f} = 0$  otherwise.

The proof is given below:

- (a) This follows directly from Theorem 3.1:  $f^* = \max(s(\tau) - \frac{1}{\sigma}, 0)$ .

- (b) We start from deriving the value  $C$ . By Theorem 3.2 the function  $G(f)$  has a convex and a concave part for certain parameter settings. By Lemma 3.B.2 the following condition must hold for  $G(f)$  to be convex:  $G(f) > \frac{2}{\sigma} - (s(\tau) - f)$ . 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:

$$G(0) > \frac{2}{\sigma} - s(\tau) \quad (3.16)$$

We solve above inequality with equality to obtain the value  $C$ . By substituting in (3.9) this results in the following, where  $H(x) = -x + \frac{1}{\sigma} \log(x)$ :

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

We know that  $-1 < W[-\sigma \exp\{k\sigma\}] < 0$  (cf. Appendix 3.E) and thus  $\frac{1}{\sigma} < C < \frac{2}{\sigma}$ . Note that for  $s(\tau) \leq \frac{1}{\sigma}$  condition (3.16) is never met by Theorem 3.B.2. By Theorem 3.B.1 the condition is always met for  $s(\tau) \geq \frac{2}{\sigma}$ . Thus only for  $s(\tau) > C$  the function  $G(f)$  has a convex part and for  $s(\tau) = C$  we have  $\bar{f} = 0$ .

This completes the proof of this theorem.  $\square$

### 3.B.3 The dose-optimal vaccination fraction

We present the dose-optimal vaccination fraction  $\tilde{f}$  and relate it to the vaccination fractions  $f^*$  and  $\bar{f}$  as defined in Theorem 3.1 and Theorem 3.2 respectively.

**Corollary 3.4.** *The function  $D(f)$  as defined by (3.4) is maximized by the unique vaccination fraction  $\tilde{f}$  for which  $G'(\tilde{f}) = D(\tilde{f})$ . 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:  $D(f) = \frac{1}{f} [G(f) - G(0)]$ .

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

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 limit definition of the one-sided derivative. For parameter settings for which the function  $G(f)$  does not have a convex part, the function  $D(f)$  is maximized for  $f = 0$ . Namely, in that case  $G(f)$  is concave, meaning that the slope of  $G(f)$  is decreasing in  $f$ . The average slope on the interval  $[0, f]$ , measured by  $D(f)$ , is then also decreasing. Analogously,  $D(f)$  is increasing as long as  $G(f)$  is convex. 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:

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

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 3.5.** *Consider the following three vaccination fractions:  $f^*$  as defined in Theorem 3.1,  $\bar{f}$  as defined in Theorem 3.2 and  $\tilde{f}$  as defined in Corollary 3.1. The following relation holds:  $\bar{f} \leq \tilde{f} \leq f^*$*

*Proof.* By Lemma 3.B.2 we know that  $G''(f) \leq 0 \Leftrightarrow G(f) \leq \frac{2}{\sigma} - (s(\tau) - f)$ . Filling in the expression for  $f^* = s(\tau) - \frac{1}{\sigma}$  results in  $G(f^*) \leq \frac{1}{\sigma}$ . This clearly holds by Theorem 3.B.2 and thus  $\bar{f} \leq f^*$ , due to Theorem 3.2. 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  $\lim_{f \downarrow 0} D(f) = 0$  and  $\tilde{f}$  maximizes  $D(f)$ . This implies that  $G'(\tilde{f}) \geq 0$  and thus  $\tilde{f} \leq f^*$  by Theorem 3.1. By argument we showed in Corollary 3.1 that  $\tilde{f}$  cannot be in the convex domain of the function  $G(f)$ , such that  $\bar{f} \leq \tilde{f}$ . This completes the proof of this lemma.  $\square$

**Lemma 3.B.4.** *For increasing  $\sigma$  the dose-optimal vaccine fraction  $\tilde{f}$  converges to  $f^*$ .*

*Proof.* The basic reproduction ratio is denoted by  $\sigma$ . By Lemma 3.2 it suffices to show that  $\lim_{\sigma \uparrow +\infty} f^* - \bar{f} = 0$ . By definition we have  $\lim_{\sigma \uparrow +\infty} f^* = \lim_{\sigma \uparrow +\infty} s(\tau) - \frac{1}{\sigma} = s(\tau)$ . Clearly, for  $\sigma \uparrow +\infty$  and  $\bar{f} = s(\tau)$  the condition  $G(\bar{f}) = \frac{2}{\sigma} - (s(\tau) - \bar{f})$  is satisfied, as  $\lim_{f \uparrow s(\tau)} G(f) = 0$  by Theorem 3.B.1. This completes the proof.  $\square$

**Lemma 3.B.5.** *In case of vaccination in a completely susceptible population  $\bar{f} = \tilde{f} = f^*$ .*

*Proof.* This result follows directly from Lemma 3.2 and Lemma 3.B.3.  $\square$

### 3.B.4 The best vaccination moment

In Section 3.4.5 we state that it is optimal to vaccinate as early as possible in an ideal world. We prove this in the following lemma.

**Lemma 3.B.6.** *The herd effect  $G(f)$  is increasing in  $s(\tau)$ .*

*Proof.* Let  $G'_{s(\tau)}(f, s(\tau))$  be the derivative of  $G(f, s(\tau))$  with respect to  $s(\tau)$ :

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

Observe that the objective function is increasing in  $s(\tau)$ , because  $G(f, s(\tau)) < \frac{1}{\sigma}$  by Theorem 3.B.2. Therefore, to maximize the herd effect one should vaccinate as soon as possible, i.e., when  $s(\tau)$  is as high as possible.  $\square$

## 3.C 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  $k = 1, \dots, n$ . Interpretation dictates that  $s(t) + \sum_{k=1}^n i_k(t) + r(t) = 1$  for all  $t$ . Let  $\beta_k$  and  $\gamma_k$  denote respectively the transmission rate and recovery rate in infectious stage  $k$ . The differential equations for the  $SI^nR$  model are:

$$\begin{aligned} \frac{ds}{dt} &= -s \sum_{k=1}^n \beta_k i_k \\ \frac{di_1}{dt} &= s \sum_{k=1}^n \beta_k i_k - \gamma_1 i_1 \\ \frac{di_k}{dt} &= \gamma_{k-1} i_{k-1} - \gamma_k i_k \quad k = 2, \dots, n \\ \frac{dr}{dt} &= \gamma_n i_n \end{aligned} \tag{3.17}$$

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

**Theorem 3.C.1.** *Up to a constant, the expression for  $G(f)$  given in (3.9) 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 (3.17), using  $\sigma = \sum_{k=1}^n \frac{\beta_k}{\gamma_k}$ . Analogous to Ma and Earn (2006) we define  $G_k(t) = \sum_{j=k+1}^n i_j(t) + r(t)$ ,  $G_n(t) = r(t)$ . From (3.17) this implies that  $\frac{d}{dt} G_k(t) = \gamma_k i_k$ .

$$\begin{aligned} \int_0^\infty \frac{1}{s(t)} ds &= - \sum_{k=1}^n \beta_k \int_0^\infty i_k(t) dt \Leftrightarrow \\ \log(s(t)) - \log(s(0)) &= - \sum_{k=1}^n \frac{\beta_k}{\gamma_k} [G_k(t) - G_k(0)] \\ &= \sigma \left[ s(t) + \sum_{k=1}^n i_k(t) \right] - \sigma \left[ s(0) + \sum_{k=1}^n i_k(0) \right] \\ &\quad - \sum_{k=1}^n \frac{\beta_k}{\gamma_k} \left[ \sum_{m=k+1}^n i_m(t) - i_m(0) \right] \end{aligned} \tag{3.18}$$



We let  $t \rightarrow \infty$  and use that  $i_k(\infty) = 0$  for  $k = 1, \dots, n$ . This results in the following expression, which is equal to the expression for the  $SIR$  (3.9) model up to a constant:

$$0 = -s(\infty) + \frac{1}{\sigma} \log(s(\infty)) - \frac{1}{\sigma} \log(s(0)) + s(0) + \sum_{k=1}^n i_k(0) - \frac{1}{\sigma} \sum_{k=1}^n \frac{\beta_k}{\gamma_k} \sum_{m=k+1}^n i_m(0) \quad (3.19)$$

We vaccinate a fraction  $f$  of the population at time  $\tau$ . Analogous to the analysis of the  $SIR$  model, we let  $(s(\tau) - f, i_1(\tau), \dots, i_n(\tau))$  be a new initial state and define the value  $s(\infty)$  according to (3.19). The values for  $i_k(\tau)$  for  $k = 1, \dots, n$  can be calculated according to (3.18). We define  $G(f) = \lim_{t \rightarrow \infty} s(t)$ , where  $s(t)$  follows (3.17) for  $t > \tau$ . This results in the following:

$$\begin{aligned} 0 = & -G(f) + \frac{1}{\sigma} \log(G(f)) - \frac{1}{\sigma} \log \left( s(0) \left( 1 - \frac{f}{s(\tau)} \right) \right) + s(0) + \sum_{k=1}^n i_k(0) \\ & - f - \frac{1}{\sigma} \sum_{k=1}^n \frac{\beta_k}{\gamma_k} \sum_{m=k+1}^n i_m(0) \end{aligned} \quad (3.20)$$

Above expression equals the expression for the  $SIR$  model (3.9) up to the final term, which is a constant.  $\square$

**Lemma 3.6.** *The results of Theorem 3.1, Theorem 3.2, Theorem 3.3 and Corollary 3.1 also apply to the  $SI^nR$  model with  $\sigma = \sum_{k=1}^n \frac{\beta_k}{\gamma_k}$ . In particular, for each  $SI^nR$  model with given initial conditions there exist vaccination fractions  $\bar{f}, \tilde{f}$  and  $f^*$  that together characterize the convex-concave and increasing-decreasing shape of the herd effect.*

*Proof.* By Theorem 3.C.1 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.  $\square$

## 3.D Optimal vaccine allocation

In this appendix, we characterize the optimal solution to the vaccine allocation problem of Section 3.3.3. We first derive a basic result in Section 3.D.1: that it is subop-

timal to leave vaccines unused. The main derivation of the optimality conditions is presented in Section 3.D.2.

### 3.D.1 The total effect of vaccination

We formally show that it is optimal to use the entire available vaccine stockpile. Thereto we define the function  $F_j(f_j)$  as the total effect of vaccinating with a fraction  $f_j$  in population  $j$ :

$$F_j(f_j) = G_j(f_j) + f_j \quad (3.21)$$

Observe that the dose-optimal vaccination fraction  $\tilde{f}$  as defined by Corollary 3.1 does not only result in the highest additional herd effect per dose of vaccine, but also in the highest additional *total effect* per dose of vaccine. Formally,  $\tilde{f}$  also maximizes the average slope of the total effect  $F(f)$  on the interval  $[0, f]$ , calculated as  $[F(f) - F(0)]/f$ . As vaccinating with the fraction  $\tilde{f}$  is very efficient per dose of vaccine, the optimal allocation tries to allocate as close as possible to  $\tilde{f}$  in a subset of all the populations as can be seen in Theorem 3.5.

**Theorem 3.D.1.** *The fraction of people not infected during the epidemic,  $F_j(f_j) = G_j(f_j) + f_j$ , is increasing in  $f_j$  for all  $f_j \in [0, s_j(\tau))$ .*

*Proof.* We prove this theorem for a single population and therefore drop the subscript  $j$  in the proof. Let  $F'(f)$  denote the derivative of  $F(f)$  with respect to  $f$ :  $F'(f) = \frac{d}{df} F(f) = G'(f) + 1$ . By Theorem 3.1  $G'(f) > 0$  for all  $f < s(\tau) - \frac{1}{\sigma}$  and  $G'(f) < 0$  for all  $f > s(\tau) - \frac{1}{\sigma}$ . Hence, the function  $F(f)$  is increasing for all  $f < s(\tau) - \frac{1}{\sigma}$ .  $F(f)$  is increasing under the following condition:

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

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

Because the functions  $F_j(f_j)$  are all non-decreasing there always exists an optimal solution for which all available vaccines are used:

**Lemma 3.D.1.** *The vaccine allocation problem always has an optimal solution for which  $\sum_{j \in J} f_j N_j = V$ .*

*Proof.* Let  $x_j$  for all  $j \in J$  be a solution of the vaccine allocation problem and assume that  $\sum_{j \in J} x_j N_j < V$ . 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  $\sum_{j \in J} y_j N_j = V$ . By Lemma 3.D.1 the functions  $F_j(f)$  are non-decreasing and thus  $F_j(y_j) \geq F_j(x_j)$  for all  $j \in J$ . This implies that:  $\sum_{j \in J} N_j F_j(y_j) \geq \sum_{j \in J} N_j F_j(x_j)$ . Hence, the proposed solution  $y_j$  for all  $j \in J$  for which  $\sum_{j \in J} y_j N_j = V$  is also an optimal solution.  $\square$

### 3.D.2 Optimality conditions

Theorem 3.2 establishes that resource allocation Problem (3.2) is a knapsack problem with  $S$ -shaped return functions: 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  $\delta$  be the KKT multiplier for the capacity constraint,  $\lambda_j$  for the non-negativity constraint  $f_j \geq 0$  for all  $j \in J$  and  $\mu_j$  for the constraint  $f_j \leq s_j(\tau)$  for all  $j \in J$ . Denote by  $\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}$  the vectors with the variables  $f_j, \lambda_j$  and  $\mu_j$  respectively. Let  $\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \delta)$  denote the Lagrange function of the maximization problem. The KKT conditions for this problem are given in (3.22). Observe that the *marginal efficiency*  $\omega$ , as introduced in Section 3.5.1, follows from the KKT condition that the partial derivative of  $\mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \delta)$  with respect to  $f_j$  equals 0 for all  $j \in J$ .

$$\begin{aligned}
 \mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \delta) &= \sum_{j \in J} N_j F_j(f_j) - \delta \left( \sum_{j \in J} f_j N_j - V \right) - \sum_{j \in J} (\mu_j (f_j - s_j(\tau)) - \lambda_j f_j) \\
 \frac{\partial}{\partial f_j} \mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \delta) &= 0 \quad \forall j \in J \\
 \delta \left( \sum_{j \in J} f_j N_j - V \right) &= 0 \quad \delta \geq 0 \\
 \lambda_j f_j &= 0 \quad \forall j \in J \quad \lambda_j \geq 0 \quad \forall j \in J \\
 \mu_j (f_j - s_j(\tau)) &= 0 \quad \forall j \in J \quad \mu_j \geq 0 \quad \forall j \in J
 \end{aligned} \tag{3.22}$$

We analyze the solution to (3.2) using the KKT conditions. We first present the solution to the general problem in Theorem 3.D.2. In Lemma 3.D.2 and Lemma 3.D.3 we discuss two simplifications. These enable us to proof the Central Insight in Theorem 3.4.

**Theorem 3.D.2.** *For every optimal solution to (3.2) there exist  $J' \subseteq J$ ,  $k \in J'$  and  $\omega \geq 0$  such that:*

- (i). *For all  $j \in J' \setminus \{k\}$ ,  $f_j$  is the unique solution to  $G'_j(f_j) = \omega$  for which  $f_j \geq \bar{f}_j$ .*
- (ii).  *$G'_k(f_k) = \omega$ , 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  $f_j = s_j(\tau)$  for every  $j \in J \setminus J'$ .*

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

- (a). Let  $J' \subseteq J$  such that  $0 < f_j < s_j(\tau)$  for all  $j \in J'$ . We prove that  $G'_j(f_j) = \omega$  for all  $j \in J'$ .
- (b). We prove that for at most one population there is a strictly positive vaccination fraction in the strictly convex domain, i.e.  $0 < f_k < \bar{f}_k$  for at most one  $k \in J'$ .

We proof the two steps consecutively:

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

$$\begin{aligned} \frac{\partial}{\partial f_j} \mathcal{L}(\mathbf{f}, \boldsymbol{\lambda}, \boldsymbol{\mu}, \delta) &= N_j F'_j(f_j) - \delta N_j - \mu_j + \lambda_j \\ &= N_j [F'_j(f_j) - \delta] = 0 \Leftrightarrow F'_j(f_j) = G'_j(f_j) + 1 = \delta \end{aligned}$$

Hence,  $G'_j(f_j) = \omega$ , with  $\omega = \delta - 1$ .

- (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  $f_2$ . Choose an  $0 < \epsilon < \min \left\{ f_1, f_2 \frac{N_2}{N_1}, \bar{f}_1 - f_1, (\bar{f}_2 - f_2) \frac{N_2}{N_1} \right\}$  and let  $\delta = \epsilon \frac{N_1}{N_2}$  such that:

$$f_1 N_1 + f_2 N_2 = (f_1 + \epsilon) N_1 + (f_2 - \delta) N_2$$

By the KKT conditions  $F'_1(f_1) = F'_2(f_2)$  and by convexity of  $F_1(f_1)$  and  $F_2(f_2)$  the following can be derived:

$$\begin{aligned} N_1 F_1(f_1 + \epsilon) + N_2 F_2(f_2 - \delta) &> N_1 F_1(f_1) + N_2 F_2(f_2) + \epsilon N_1 [F'_1(f_1) - F'_2(f_2)] \\ &= N_1 F_1(f_1) + N_2 F_2(f_2) \end{aligned}$$

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 3.D.2.** *If  $s_j(\tau) > \frac{1}{\sigma_j}$  for all  $j \in J$ , then there is no optimal solution to (3.2) for which  $f_j = 0$  and  $f_k = s_k(\tau)$  for two populations  $j, k \in J$ . This implies that (iii) of Theorem 3.D.2 changes into: Either  $f_j = 0$  for all  $j \in J \setminus \{J' \cup \{k\}\}$  or  $f_j = s_j(\tau)$  for all  $j \in J \setminus \{J' \cup \{k\}\}$ .*

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

$$f_1 N_1 + f_2 N_2 = (f_1 + \epsilon) N_1 + (f_2 - \delta) N_2$$

The following holds:

$$\begin{aligned} &N_1 F_1(\epsilon) + N_2 F_2(s_2(\tau) - \delta) - N_1 F_1(0) - N_2 F_2(s_2(\tau)) \\ &= N_1 [G_1(\epsilon) - G_1(0)] + N_2 [G_2(s_2(\tau) - \delta) - G_2(s_2(\tau))] > 0 \end{aligned}$$

For  $s_j(\tau) > \frac{1}{\sigma_j}$  the function  $G_j(f)$  is initially increasing by Theorem 3.1, implying that  $G_1(\epsilon) > G_1(0)$ . Furthermore, by Theorem 3.B.1  $G_j(f_j) > 0$  for all  $0 \leq f_j < s_j(\tau)$  and  $\lim_{f_j \uparrow s_j(\tau)} G_j(f_j) = 0$ . This implies that  $G_2(s_2(\tau) - \delta) > G_2(s_2(\tau))$ . Thus, a small change in allocation can improve the solution. We arrive at a contradiction which completes the proof of this lemma. □

**Lemma 3.D.3.** *If  $s_j(\tau) > \frac{1}{\sigma_j}$  for all  $j \in J$  and  $V \leq \sum_{j \in J} N_j f_j^*$  then there is no optimal solution to (3.2) with  $f_j = s_j(\tau)$  for some  $j \in J$ . This implies that (iii) of Theorem 3.D.2 changes into:  $f_j = 0$  for all  $j \in J \setminus \{J' \cup \{k\}\}$ .*

*Proof.* By contradiction assume that there is a population  $k \in J$  for which  $f_k = s_k(\tau)$  in the optimal solution. Since  $s_k(\tau) > \frac{1}{\sigma_k}$  this implies that  $f_k > f_k^* = s_k(\tau) - \frac{1}{\sigma_k}$ . Because  $V \leq \sum_{j \in J} N_j f_j^*$  there must also be a population  $l$  for which  $f_l < f_l^*$  in the optimal allocation. Let  $\epsilon > 0$  be sufficiently small such that  $f_l + \epsilon < f_l^*$  and  $f_k - \epsilon \frac{N_l}{N_k} > f_k^*$ . Then the following holds, where the inequality follows from Theorem 3.1:

$$N_l F_l(f_l + \epsilon) + N_k F_k\left(s_k(\tau) - \epsilon \frac{N_l}{N_k}\right) - N_l F_l(f_l) - N_k F_k(s_k(\tau)) \\ N_l [G_l(f_l + \epsilon) - G_l(f_l)] + N_k \left[ G_k(s_k(\tau)) - G_k\left(s_k(\tau) - \epsilon \frac{N_l}{N_k}\right) \right] > 0$$

A small change in allocation can improve the solution. Hence, there cannot be an optimal solution with  $f_j = s_j(\tau)$  for some  $j \in J$ . We arrive at a contradiction which proves the first part of this lemma. The implication then directly follows from Lemma 3.D.2.  $\square$

**Theorem 3.4** (Central Insight). *Every optimal solution to (3.2) can be characterized as follows:*

- (i). *A subset of populations  $J' \subseteq J$  is vaccinated with the regular fraction that corresponds to marginal efficiency  $\omega$ .*
- (ii). *Possibly another population  $k$  is also vaccinated with marginal efficiency  $\omega$ , but with the exceptional fraction for which  $f_k < \bar{f}_k$ .*
- (iii). *The remaining populations are not vaccinated at all.*

*Proof.* This theorem can be reformulated more analytically as follows: For every optimal solution to (3.2) there exist  $J' \subseteq J$ ,  $k \in J'$  and  $\omega \geq 0$  such that:

- (i). For all  $j \in J' \setminus \{k\}$ ,  $f_j$  is the unique solution to  $G'_j(f_j) = \omega$  for which  $f_j \geq \bar{f}_j$ .
- (ii).  $G'_k(f_k) = \omega$ , 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).  $f_j = 0$  for all  $j \in J \setminus J'$ .

The proof then follows directly from Theorem 3.D.2, Lemma 3.D.2 and Lemma 3.D.3.  $\square$

**Theorem 3.5.** *Consider a set of populations  $J$  with  $\forall j: G_j(f) = G(f)$  and a total available amount of resources equal to  $V$ . Let  $|J| = n$  and order the populations such that  $N_1 \leq \dots \leq N_n$ . The optimal allocation for particular cases is as follows:*

- (a). *if  $V < \tilde{f}N_1$ , then allocate only to the smallest population. Set  $f_1 = V/N_1$  and  $f_j = 0$  for  $j = 2, \dots, n$ .*
- (b). *if  $V = \sum_{j \in K} \tilde{f}N_j$  for a subset  $K \subseteq J$ , then set  $f_j = \tilde{f}$  for  $j \in K$  and  $f_j = 0$  for  $j \notin K$ .*
- (c). *if  $V > \sum_{j \in J} \tilde{f}N_j$ , then allocate pro rata over all the populations:  $f_j = \frac{V}{\sum_{j \in J} N_j}$  for all  $j \in J$ .*

*Proof.* This proof uses ideas that are also used in the proof of Proposition 1 of Ginsberg (1974).

- (a). Step (b) in the proof of Theorem 3.D.2 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  $G(\cdot)$  for all  $f < \tilde{f} < \bar{f}$ .
- (b). The proposed allocation results in the maximum attainable value for the objective function for  $V$  available vaccines and is thus optimal.
- (c). We prove the optimality of the proposed allocation using the items of Theorem 3.D.2. More precisely, regarding item (iii) we show that  $f_j = s(\tau)$  cannot occur for any  $j \in J'$  and we analyze the two types of strategies that remain. Consider item (iii): for the special case of identical parameters it holds that  $s_j(\tau) := s(\tau)$  for all  $j \in J$ . We can show that an allocation with  $f_j = s(\tau)$  and  $f_k < s(\tau)$  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 inequality follows because of the structure of the function  $F(\cdot)$ . Thus, it is not optimal to set  $f_j = s(\tau)$  for some  $j \in J$ . Using this result, there are two possible allocations remaining by Theorem 3.D.2:

- (i) Either the amount  $V$  is allocated pro rata over the populations in  $K \subseteq J$ .  
i.e.,  $f_j = \frac{V}{\sum_{j \in K} N_j} = \hat{x}$  and  $f_j = 0$  for all  $j \notin K$ .
- (ii) Or an amount  $\xi$  is allocated to one population  $k$  and the remaining  $(V - \xi)$  is allocated pro rata over all populations in  $I \subseteq J \setminus \{k\}$ . i.e.,  $f_k = \xi/N_k$ ,  
 $f_j = \frac{V - \xi}{\sum_{j \in I} N_j} = \hat{y}$  for  $j \in I$  and  $f_j = 0$  for all  $j \notin I \cup \{k\}$ .

First we consider scheme (i) and prove that it is optimal to allocate pro rata over all populations, i.e., we show that it is optimal to let  $K$  equal  $J$ . Let  $z_j$  and  $x_j$  respectively denote the pro rata allocation over  $K \subset J$  and over  $J$ , such that  $z_j = \hat{z} = \frac{V}{\sum_{j \in K} N_j}$  for all  $j \in K$  and  $x_j = \hat{x} = \frac{V}{\sum_{j \in J} N_j}$  for all  $j \in J$ . Note that  $\hat{z} > \hat{x} > \bar{f}$ , because  $V > \sum_{j \in J} N_j \bar{f}$  by assumption. This implies the following inequality by Corollary 3.1:

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

The first equivalence follows by substituting the definitions of  $\hat{x}$  and  $\hat{z}$  and the second equivalence follows by rearranging terms. The last inequality shows precisely that allocating pro rata over all populations gives a higher objective value than allocating pro rata over  $K \subset J$ .

Second, we now consider allocation scheme (ii), in which an amount of  $\xi$  is allocated to population  $k$  and the remaining  $V - \xi$  is allocated pro rata over  $I \subseteq J \setminus \{k\}$  to reach a vaccination fraction  $\hat{y}$ . We will show that allocation scheme (ii) will never be superior to allocation scheme (i), in which the latter allocates pro rata over all populations to reach a vaccination fraction  $\hat{x}$ . By contradiction we assume that allocation (ii) is optimal and thus better than allocation (i).

We first show that the vaccination fraction  $\hat{x}$  in allocation (i) is smaller than the vaccination fraction  $\hat{y}$  in allocation (ii). By Theorem 3.D.2  $\xi/N_k$  lies in the convex domain of  $F(\cdot)$ , which implies  $\xi/N_k < \bar{f} < \hat{f}$ . We also know that



$\tilde{f} < \hat{x} \leq \frac{1}{N_k}(\sum_{j \in J} N_j - \sum_{j \in I} N_j)\hat{x}$ , where the first inequality follows because  $\hat{x} > \tilde{f}$  by  $V > \sum_{j \in J} N_j \tilde{f}$  and the second inequality because  $I \subseteq J \setminus \{k\}$ . By combining the inequalities, we have that:

$$\begin{aligned} \xi/N_k &< \frac{1}{N_k}(\sum_{j \in J} N_j - \sum_{j \in I} N_j)\hat{x} \\ \Leftrightarrow \quad \xi \sum_{j \in J} N_j &< V \sum_{j \in J} N_j - \sum_{j \in I} N_j \\ \Leftrightarrow \quad \frac{V}{\sum_{j \in J} N_j} &< \frac{V - \xi}{\sum_{j \in I} N_j} \end{aligned}$$

The first equivalence follows from  $\hat{x} = \frac{V}{\sum_{j \in J} N_j}$  and in the second equivalence we rewrite terms. Note that the last inequality is precisely  $\hat{x} < \hat{y}$ .

We now compare allocation (i) and (ii). Under the assumption that (ii) is better than (i), the following must hold:

$$\begin{aligned} N_k F(\xi/N_k) + \sum_{j \in I} N_j F(\hat{y}) + \sum_{j \notin I \cup \{k\}} N_j F(0) &> \sum_{j \in J} N_j F(\hat{x}) \\ \Leftrightarrow N_k G(\xi/N_k) + \sum_{j \in I} N_j G(\hat{y}) + \sum_{j \notin I \cup \{k\}} N_j G(0) &> \sum_{j \in J} N_j G(\hat{x}) \end{aligned} \quad (3.23)$$

The equivalence above follows from the fact that both allocations allocate the same amount of vaccines, i.e., the direct effect is the same. Hence, it suffices to consider the herd effect instead of the total effect. (3.23) implies the following:

$$\begin{aligned} N_k G\left(\frac{\xi}{N_k}\right) + \sum_{j \in I} N_j \left[ \int_0^{\hat{y}} G'(f) df + G(0) \right] + \sum_{j \notin I \cup \{k\}} N_j G(0) &> \sum_{j \in J} N_j \left[ \int_0^{\hat{x}} G'(f) df + G(0) \right] \\ \Leftrightarrow N_k G\left(\frac{\xi}{N_k}\right) + \sum_{j \in I} N_j \int_0^{\hat{y}} G'(f) df &> \sum_{j \in J} \left[ N_j \int_0^{\hat{x}} G'(f) df \right] + N_k G(0) \\ \Leftrightarrow \sum_{j \in I} N_j \left[ \int_0^{\hat{y}} G'(f) df - \int_0^{\hat{x}} G'(f) df \right] &> \sum_{j \notin I} \left[ N_j \int_0^{\hat{x}} G'(f) df \right] - N_k \left[ G\left(\frac{\xi}{N_k}\right) - G(0) \right] \\ \Leftrightarrow \sum_{j \in I} N_j \int_{\hat{x}}^{\hat{y}} G'(f) df &> \sum_{j \notin I} N_j [G(\hat{x}) - G(0)] - N_k \left[ G\left(\frac{\xi}{N_k}\right) - G(0) \right] \end{aligned} \quad (3.24)$$

The equivalences above follow from rearranging, cancelling and recombining terms. By Lemma 3.2  $\tilde{f}$  is in the concave domain, which also holds for all  $f > \tilde{f}$ . Since  $\hat{y} > \hat{x} > \tilde{f}$  it holds that  $G''(\hat{y}) < 0$  and  $G''(\hat{x}) < 0$ . This implies that  $(\hat{y} - \hat{x})G'(\hat{x}) > \int_{\hat{x}}^{\hat{y}} G'(f)df$ . We thus have the following:

$$\begin{aligned} \sum_{j \in I} N_j [(\hat{y} - \hat{x})G'(\hat{x})] &> \sum_{j \in I} N_j \int_{\hat{x}}^{\hat{y}} G'(f)df \\ &> \sum_{j \notin I} N_j [G(\hat{x}) - G(0)] - N_k [G(\xi/N_k) - G(0)] \quad (3.25) \\ &> \sum_{j \notin I} N_j G'(\hat{x})\hat{x} - N_k [G(\xi/N_k) - G(0)] \end{aligned}$$

The second inequality follows from (3.24) and in the last inequality we use that  $[G(f) - G(0)]/f > G'(f)$  for all  $f > \tilde{f}$  by Corollary 3.1. The three inequalities in (3.25) together establish that:

$$\begin{aligned} \sum_{j \in I} N_j (\hat{y} - \hat{x})G'(\hat{x}) &> \sum_{j \notin I} N_j G'(\hat{x})\hat{x} - N_k [G(\xi/N_k) - G(0)] \\ \Leftrightarrow G'(\hat{x}) \left[ \sum_{j \in I} N_j (\hat{y} - \hat{x}) - \sum_{j \notin I} N_j \hat{x} \right] &> -N_k [G(\xi/N_k) - G(0)] \\ \Leftrightarrow -\xi G'(\hat{x}) &> -N_k [G(\xi/N_k) - G(0)] \\ \Leftrightarrow G'(\hat{x}) &< [G(\xi/N_k) - G(0)]/(\xi/N_k) \end{aligned} \quad (3.26)$$

The first equivalence follows from rearranging terms and the second by definition of  $\hat{x}$  and  $\hat{y}$ . The third equivalence follows from multiplying both sides of the inequality with  $-1/\xi$ .

We will now show that the last inequality in (3.26) will lead to a contradiction. Because the function  $G(\cdot)$  is convex at  $\xi/N_k$  we have that  $[G(\xi/N_k) - G(0)]/(\xi/N_k) < G'(\xi/N_k)$ . Thus, under the assumption that (ii) is optimal it must hold that  $G'(\hat{x}) < G'(\xi/N_k)$  by the last inequality of (3.26). If allocation (ii) is optimal we also have that  $G'(\xi/N_k) = G'(\hat{y})$  by Theorem 3.D.2, and thus that  $G'(\hat{x}) < G'(\hat{y})$ . However, because  $\hat{x} < \hat{y}$  and both fractions are in the concave domain of the function  $G(\cdot)$  it holds that  $G'(\hat{x}) > G'(\hat{y})$ . We thus arrive at a contradiction, which implies that allocation scheme (ii) can never

be better than allocation scheme (i) for  $V > \sum_{j \in J} N_j \tilde{f}$ . Thus, the optimal allocation for  $V > \sum_{j \in J} N_j \tilde{f}$  is allocation (i): i.e., the pro rata allocation over all populations in  $J$ . This completes the proof of part (c) of this theorem.  $\square$

### 3.E The Lambert W function

This appendix considers the Lambert W function, or product log function (cf. Corless et al. (1996)). This function is denoted by  $W(x)$  and solves:

$$x = W(x)e^{W(x)} \quad (3.27)$$

The herd effect  $G(f)$  can be expressed using the Lambert W function:

$$G(f) = \frac{-1}{\sigma} W(-\sigma \exp\{-\sigma B(f)\})$$

$$\text{with } B(f) = s_0 + i_0 - \frac{1}{\sigma} \log \left( s_0 \left( 1 - \frac{f}{s(\tau)} \right) \right) - f \quad (3.28)$$

which can be verified by substituting (3.28) into (3.27), which leads to (3.9). 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  $W_p(x)$ .

Let  $G(f) = \frac{-1}{\sigma} W[y(f)]$ , with  $y(f) = -\sigma s_0 \left( 1 - \frac{f}{s(\tau)} \right) \exp\{-\sigma(s_0 + i_0 - f)\}$  (3.28). 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 3.E.1.**  $-\frac{1}{e} \leq y(f) \leq 0$

*Proof.* We can easily see that  $y(f) \leq 0$ , because  $\sigma > 0$ ,  $s_0 > 0$  and  $f \leq s(\tau)$ . Analyze the extreme values of  $y(f)$ :

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

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

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

By (3.8) above relation holds, because  $i(\tau) \geq 0$ . □

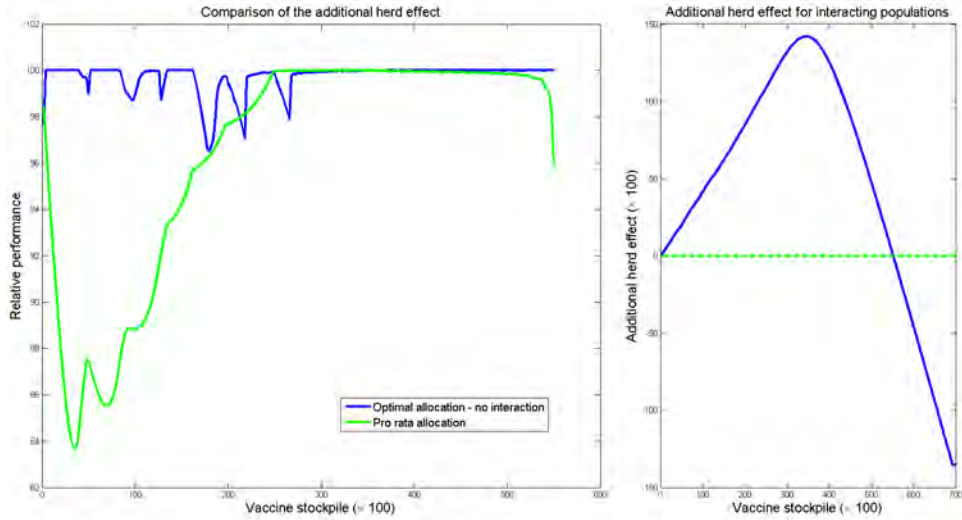
By Theorem 3.B.2 we know that  $G(f) < \frac{1}{\sigma}$  and thus  $-1 < W(-\sigma \exp\{-\sigma B(f, \sigma)\}) < 0$ . By Theorem 3.E.1 only the principal branch  $W_0(x)$  is needed when using the Lambert W function for  $G(f)$  in (3.28).

### 3.F Interacting populations

In Section 3.5.4, the optimal allocation is analyzed for geographically distant populations that interact with each other. We use the same initial states and population sizes as in Section 3.5.3.

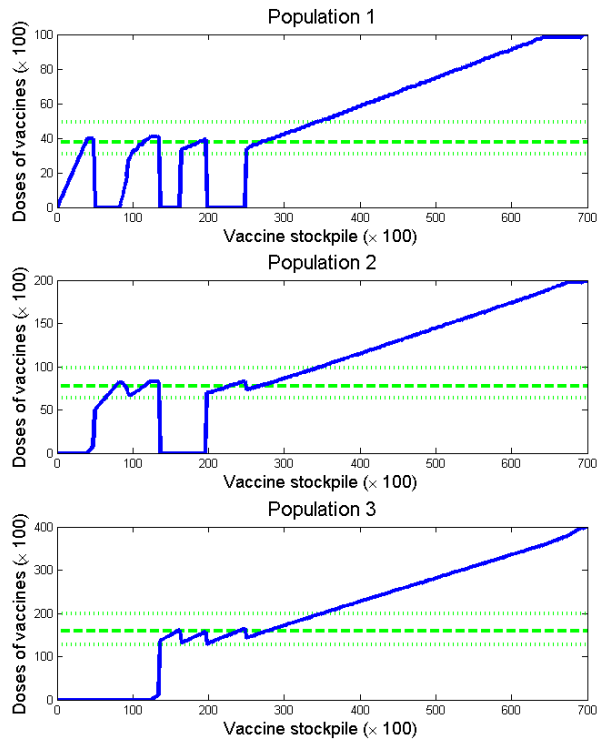
In this appendix, we study the relative performance of ignoring interaction by either using the optimal allocation for non-interacting populations or by using the equitable allocation, which allocates pro rata over all populations. In Figure 3.8 we illustrate the performance of these two solutions relative to the optimal allocation for the interacting case. We evaluate the additional herd effect and observe that the non-interacting solution performs close to optimal and outperforms the equitable 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.

We also study the optimal allocation for increasing levels of interaction. Figures 3.9, 3.10, 3.11 and 3.12 display the optimal allocation in case interaction between populations is respectively 0.01, 0.02, 0.05 and 0.1 times the interaction within a population. This corresponds to interaction between populations being a factor 100, 50, 20 or 10 times weaker than interaction within a population. The figures are discussed in Section 3.5.4.

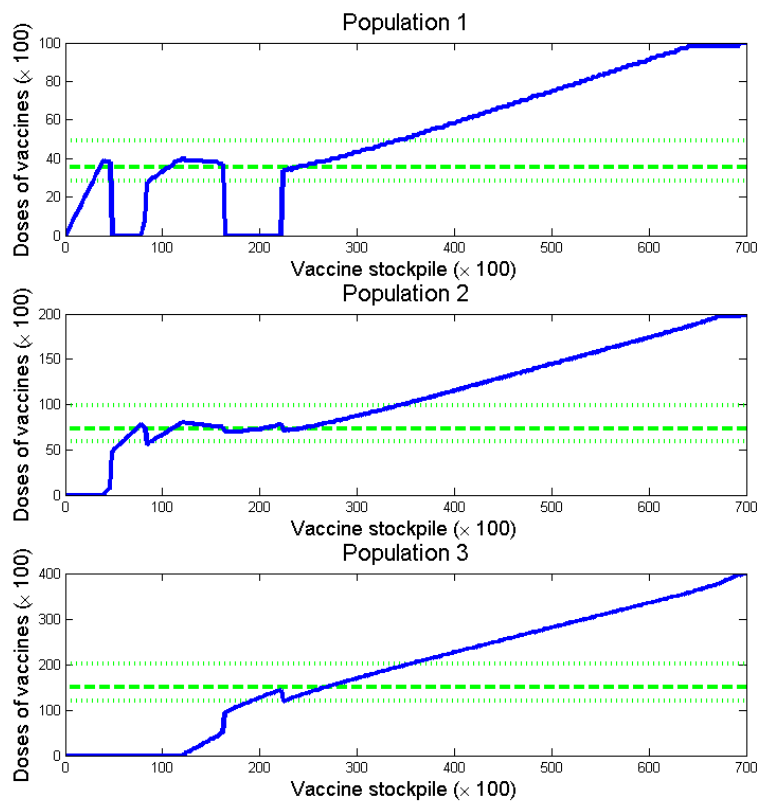


**Figure 3.8:** The left figure illustrates the relative performance of the optimal allocation for the non-interacting case (Figure 3.7) and the equitable pro rata allocation evaluated in the model as described in Section 3.5.4 with interactionfactor  $c = 0.01$ . We evaluate the additional herd effect for vaccine stockpiles up to size 550, because the right figure shows that for larger vaccine stockpiles the additional herd effect becomes negative.

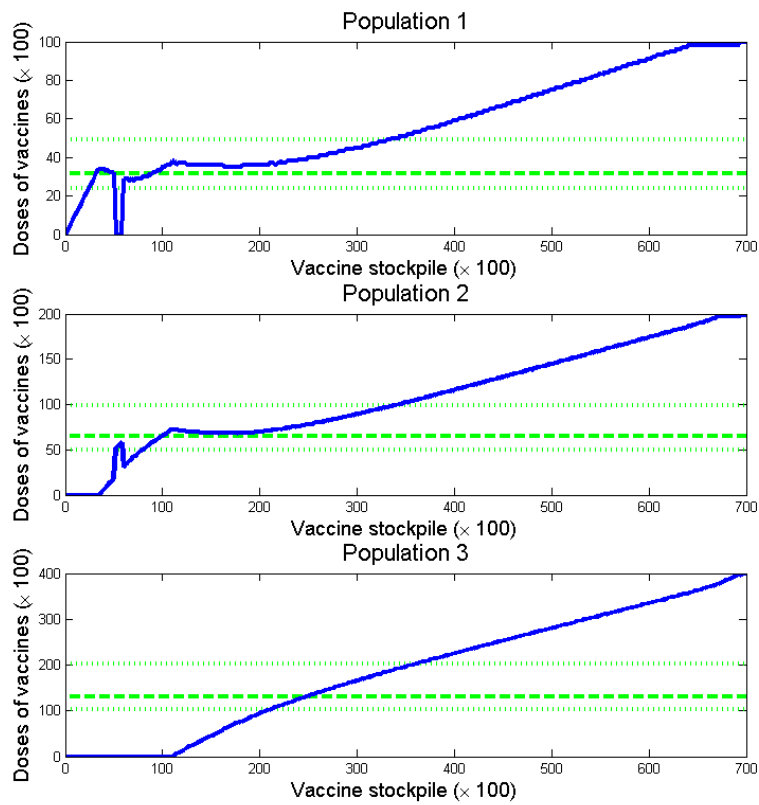
Each of the graphs present the optimal vaccine allocation (the solid lines) over three interacting populations for different sizes of vaccine stockpile. The dashed and dotted lines indicate the important vaccination fractions: the dashed line in the middle equals  $\tilde{V}_j = \tilde{f}_j N_j$ , the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



**Figure 3.9:** 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  $\tilde{V}_j = \tilde{f}_j N_j$ , the upper dotted line equals  $V_j^* = f_j^* N_j$  and the lower dotted line equals  $\bar{V}_j = \bar{f}_j N_j$ .

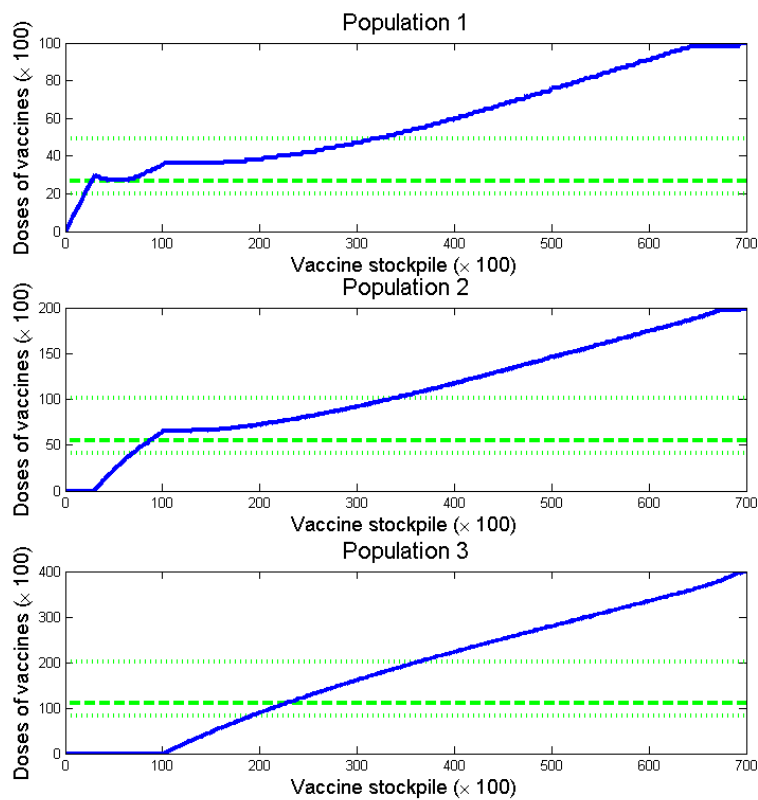


**Figure 3.10:** The optimal allocation in case interaction between populations is 0.02 times the interaction within a population.



**Figure 3.11:** The optimal allocation in case interaction between populations is 0.05 times the interaction within a population.





**Figure 3.12:** The optimal allocation in case interaction between populations is 0.1 times the interaction within a population.



## Chapter 4

# The most efficient critical vaccination coverage and its equivalence with maximizing the herd effect<sup>1</sup>

### 4.1 Introduction

In infectious disease epidemiology the potential of an infectious agent to cause an epidemic is often expressed in terms of the reproduction ratio and the final size. The final size is the eventual number of people who have become infected. The reproduction ratio, denoted by  $R$ , is considered to be one of the most important parameters in infectious disease epidemiology and has received considerable attention (cf. Diekmann et al. 2013). The effectiveness of a control strategy against the infectious agent is often expressed as the capability of the strategy to reduce the reproduction ratio or the final size. Several studies focus on the minimization of  $R$  under a capacity constraint on the available resources (e.g., Goldstein et al. 2009, Wallinga et al. 2010) or on the threshold criterion  $R = 1$  (e.g., Britton and Becker 2000, Hill and Longini Jr 2003).

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<sup>1</sup>This chapter is based on Duijzer et al. (2016).

$R$  is rather tractable and hence the above papers typically use analytical methods based on matrix algebra. In contrast, applying analytical methods to minimizing the final size is more difficult, as the final size is implicitly defined. Therefore, numerical evaluation (e.g., Arino et al. 2008, Keeling and Shattock 2012, Yuan et al. 2015) or simulation (e.g., Ferguson et al. 2005, Cooper et al. 2006, Andradóttir et al. 2014) are typically used to analyze the final size.

There is no obvious connection between minimization of the reproduction ratio  $R$  and minimization of the final size. It is not clear how an intervention that minimizes  $R$  affects the final size and vice versa. Tildesley and Keeling (2009) even show that the reproduction ratio within a population is a bad predictor for the final size when populations interact. The relation between  $R$  and the final size has been studied for a single population and a one-to-one relation can be derived (Ma and Earn 2006). However, this relation does not extend to multiple populations.

A first step in analyzing the relation between  $R$  and the final size for multiple populations is made by Andreasen (2011) for the case without infection control. The initial population is then completely susceptible and the reproduction ratio  $R$  equals the basic reproduction ratio  $R_0$ . Andreasen (2011) shows that an epidemic occurs only for  $R_0 > 1$ , implying that the final size equation has an interior solution in that case. In case  $R_0 \leq 1$  only the boundary solution exists, corresponding to no outbreak. We build upon Andreasen (2011) by including vaccination in a completely susceptible population and assuming that the disease is introduced after vaccination. In a vaccinated population the final size is determined by the direct effect of vaccination and the indirect effect. This latter effect is also known as the *herd effect*. The direct effect is measured as the proportion of the people who are protected from infection by vaccination, whereas the indirect herd effect is measured as the proportion of the people who are not exposed to infection and thus escape infection without being vaccinated. The herd effect can be influenced by the vaccine allocation and is therefore the most interesting.

We are interested in finding vaccine allocations that maximize the herd effect and we define the following optimization problem: maximize the overall herd effect. This problem is difficult to solve (Keeling and Ross 2015). We show that formulating the equivalent optimization problem in terms of  $R$  enables to solve the problem. We show analytically that the herd effect in a set of populations can only be maximized for a vaccination allocation that results in  $R = 1$ . In Chapter 3 we already showed that

this holds for a single population, we extend this in the current chapter to interacting populations. The current chapter differs from Chapter 3 in studying prepandemic vaccination with unlimited supply of vaccines, such that critical vaccination coverage is always attainable. In contrast, Chapter 3 focuses on *limited* vaccine stockpiles for sudden outbreaks, and it studies the intricate difficulties of allocating vaccines when critical coverage cannot be attained.

The main contribution of this chapter is that we gain insights into vaccine allocation problems by looking at them from the perspective of mathematical optimization. This enables us to formulate structured approaches to find the *optimal allocation*: the best possible allocation according to some well-defined criterion. Our approach differs from others in literature who either compare a few allocation schemes (e.g., Mylius et al. 2008, Tuite et al. 2010) or enumerate all possibilities (e.g., Medlock and Galvani 2009, Keeling and Shattock 2012). (Note that many aspects play a role in vaccine allocation [operational, ease of understanding et cetera]. So, our use of the word optimal should be seen relative: the solution is optimal insofar as our criterion for optimality is suitable.) Our contributions to vaccine allocation are summarized as follows.

1. We prove the equivalence between two interesting vaccine allocation problems: maximizing the herd effect and minimizing the required amount of vaccines to obtain  $R = 1$ .
2. We characterize the optimal allocation for two special cases and guarantee that no better allocation exists.
  - (a) We consider the case of separable mixing, which is often studied and assumes that upon transmission from one individual to another the two individuals involved influence transmission independently (Diekmann et al. 2013). We derive an algorithm that provides especially interesting insights: we show that vaccinating according to a very simple priority ordering based on population size and disease parameters results in the optimal allocation.
  - (b) For two populations we derive an explicit expression of the solution.
3. We present an efficient solution approach for general cases (i.e, cases with more than two populations and cases where separable mixing does not apply) based on Perron-Frobenius Theory (Meyer 2000).

4. Finally, we illustrate our approach to find the optimal allocation in a case study for pre-pandemic vaccination in the initial phase of an impending influenza pandemic. The results show that the amount of required vaccines to attain  $R = 1$  can differ substantially if we compare the optimal allocation with proposed allocations in literature.

The advantage of explicit solutions and an efficient solution approach is that optimal solutions can be derived even when parameters are uncertain. With explicit solutions one can directly see the effects of changes in parameters and the efficient solution approach makes it computationally easy to perform a sensitivity analysis.

The remainder of this chapter is structured as follows. In Section 4.2, we formulate the problem: The herd effect and the reproduction ratio  $R$  are presented and illustrated for the standard epidemiological *SIR* model. Next, we formulate the two vaccine allocation problems that are the main focus of the chapter. Section 4.3 discusses the assumptions and some technical details that are needed for the analysis of the optimization problems. In Section 4.4, we prove that the two vaccine allocation problems are equivalent. Section 4.5 is dedicated to solving these problems. Section 4.6 contains an application of our solution method. We conclude the chapter with a discussion in Section 4.7.

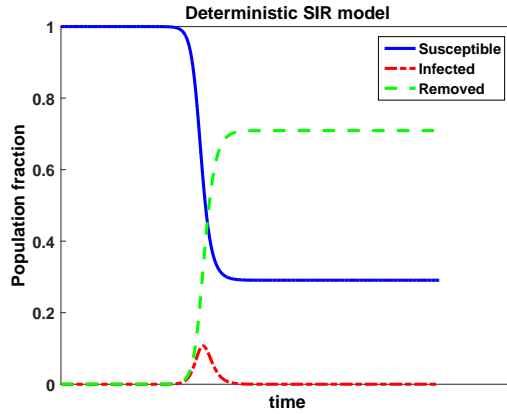
## 4.2 Problem formulation

### 4.2.1 The *SIR* model

We consider the standard epidemiological *SIR* model for a set  $J$  consisting of  $n$  interacting populations indexed by  $j$ , i.e.,  $|J| = n$ . Every population is divided into three compartments for which the evolution is tracked (cf. Hethcote 2000). Let  $s_j(t)$ ,  $i_j(t)$  and  $r_j(t)$  be the fractions of population  $j$  respectively susceptible, infected and removed at time  $t$ . Let  $\gamma_j$  denote the recovery rate in population  $j$  and let  $\beta_{jl}$  denote the transmission rate between susceptible people from population  $j$  and infected people from population  $l$ . The *SIR* model describes the time course of an epidemic and consists of the following system of differential equations:

$$\begin{aligned}
\frac{ds_j}{dt} &= - \sum_{l \in J} \beta_{jl} s_j i_l & \forall j \in J \\
\frac{di_j}{dt} &= \sum_{l \in J} \beta_{jl} s_j i_l - \gamma_j i_j & \forall j \in J \\
\frac{dr_j}{dt} &= \gamma_j i_j & \forall j \in J
\end{aligned} \tag{4.1}$$

Figure 4.1 illustrates the time course of an epidemic according to the *SIR* model. As time progresses the number of infected individuals will approach zero and the epidemic will die out, i.e.,  $\lim_{t \rightarrow +\infty} i_j(t) = 0$  for all  $j \in J$ . When the state of the system no longer changes, it is in a *disease free equilibrium* (DFE).



**Figure 4.1:** Illustration of the deterministic *SIR* model for two populations with parameters  $\gamma_j = 2.3$ ,  $\beta_{jj} = 3$  for  $j = 1, 2$  and  $\beta_{jl} = 1$  for  $j \neq l$ . We introduce a minor infection of  $i_j(0) = 10^{-6}$  for  $j = 1, 2$  to analyze the time course of the epidemic. Because of symmetry between populations the time course is presented for only one population.

We include vaccination in the *SIR* model at time  $t = 0$ . We assume that all individuals are vaccinated before the start of the epidemic and that the fractions of vaccinated individuals may differ between populations. Let  $f_j$  denote the fraction of people vaccinated in population  $j$ . We assume that one dose of vaccine suffices and that vaccination instantaneously leads to permanent immunity against infection. For a relaxation of the assumption of perfect vaccines we refer to Appendix 4.D.

Upon vaccination the system changes from state  $(s_j(0), i_j(0), r_j(0))$  to state  $((1 - f_j)s_j(0), i_j(0), r_j(0) + s_j(0)f_j)$  for all  $j \in J$ .

We are interested in the final state of an outbreak, i.e.,  $\lim_{t \rightarrow +\infty} s_j(t)$ , which depends on the initial state at time 0. In the remainder of this chapter we consider one specific initial state, namely the situation that vaccination takes place prior to an outbreak in a completely susceptible population. In the literature this type of vaccination is called *pre-pandemic vaccination*. Let  $\mathbf{s}_0, \mathbf{i}_0$  and  $\mathbf{r}_0$  respectively denote the vectors with initial fractions of people susceptible, infected and removed. For pre-pandemic vaccination it is assumed that  $\mathbf{s}_0 = \mathbf{1}$  and  $\mathbf{i}_0 = \mathbf{r}_0 = \mathbf{0}$ . Note that without infected individuals, the system in (4.1) is in equilibrium and no transmission can occur. To analyze an outbreak after pre-pandemic vaccination many studies therefore consider that the system is externally exposed to a ‘shock’ or that the disease is introduced after vaccination, meaning that an infinitesimal fraction of individuals gets infected. By Perron-Frobenius Theory the initial phase of an epidemic is uniquely determined (see Section 4.3.1) and it is therefore not necessary to specify the introduction of the disease in detail (cf. Diekmann 1977, Metz 1978).

### 4.2.2 Herd effect

Vaccination leads to people escaping infection in two ways: either directly or indirectly. The direct effect is measured as the proportion of individuals that are vaccinated themselves and hence immune. The indirect effect, also referred to as the herd effect (Fine 1993), is measured as the proportion of individuals that are unvaccinated and escape infection because of a reduction in force of infection due to vaccination. The individuals that escape infection without being vaccinated are still susceptible in the disease free equilibrium. Denote by  $G_j(\mathbf{f})$  the final fraction of people susceptible in population  $j$ , i.e., the herd effect in population  $j$ . Here  $\mathbf{f}$  denotes the vector with the vaccination fractions  $f_j$  for all populations  $j \in J$ . Then:

$$G_j(\mathbf{f}) = \lim_{t \rightarrow +\infty} s_j(t) \quad \forall j \in J \quad (4.2)$$

Note that this definition implies that there is a herd effect  $G_j(0) > 0$  even without any vaccination. Alternatively, one could compare the disease free equilibrium with and without vaccination and let  $H_j(\mathbf{f}) = G_j(\mathbf{f}) - G_j(0)$  denote the herd effect. But this definition has the disadvantage that the herd effect may become negative. In the



remainder of this chapter we will refer to  $G_j(\mathbf{f})$  as the herd effect, as this definition will be more convenient in demonstrating the relation between the herd effect and final size equation.

Let  $\sigma_j = \frac{\beta_{jj}}{\gamma_j}$ . From (4.1) we derive the functions  $G_j(\mathbf{f})$  for all  $j \in J$  using the initial conditions of pre-pandemic vaccination. We refer to Appendix 4.A.2 for the details on this derivation. We end up with the following implicit set of equations for the herd effect:

$$0 = -G_j(\mathbf{f}) + \frac{\log(G_j(\mathbf{f}))}{\sigma_j} - \frac{\log(1 - f_j)}{\sigma_j} + (1 - f_j) + \frac{1}{\sigma_j} \sum_{l \in J: l \neq j} \frac{\beta_{jl}}{\gamma_l} [1 - f_l - G_l(\mathbf{f})] \quad \forall j \in J \quad (4.3)$$

For the remainder of the chapter it is more convenient to reformulate (4.3) in matrix notation. Denote by  $\gamma$ ,  $\sigma$  and  $\mathbf{B}$  the following matrices, with  $\gamma$  and  $\sigma$  diagonal matrices:

$$\gamma = \begin{bmatrix} \frac{1}{\gamma_1} & & 0 \\ & \ddots & \\ 0 & & \frac{1}{\gamma_n} \end{bmatrix} \quad \sigma = \begin{bmatrix} \frac{1}{\sigma_1} & & 0 \\ & \ddots & \\ 0 & & \frac{1}{\sigma_n} \end{bmatrix} \quad \mathbf{B} = \begin{bmatrix} \beta_{11} & \cdots & \beta_{1n} \\ \vdots & \ddots & \vdots \\ \beta_{n1} & \cdots & \beta_{nn} \end{bmatrix} \quad (4.4)$$

Furthermore, let  $\mathbf{G}$  denote the vector  $[G_1(\mathbf{f}) \cdots G_n(\mathbf{f})]^T$ . Let  $\mathbf{1}$  denote the all ones vector of length  $n$ . Then (4.3) can be written as follows, with  $\log(\cdot)$  used element wise.

$$\sigma \log(\mathbf{G}) = \sigma \log(\mathbf{1} - \mathbf{f}) - \sigma \mathbf{B} \gamma [\mathbf{1} - \mathbf{f} - \mathbf{G}] \quad (4.5)$$

We used the *SIR* model to illustrate the implicit expression for the herd effect. Observe that for a single population with initial state  $(s_0, i_0, r_0) = (1 - f, 0, f)$  (4.5) collapses to the well-known final size formula. The implicit expression in (4.5) is therefore an extension of the final size formula, for which the generality is shown in Ma and Earn (2006). The final size of an outbreak equals the total number of people who have become infected and is therefore directly related to the number of people who have escaped infection, i.e., the total effect of vaccination. This total effect is the sum of the direct effect and the herd effect.

### 4.2.3 Reproduction ratio

The basic reproduction ratio, denoted by  $R_0$ , is defined as the number of new infections caused by a single infectious individual in a completely susceptible population.

In the initial phase of an epidemic there are very few infected individuals, so the population is almost completely susceptible.  $R_0$  is therefore related to the exponential initial growth rate of an epidemic (cf. Wallinga and Lipsitch 2007). For compartmental models,  $R_0$  can be determined from the differential equations (Diekmann et al. 2013).

After vaccination the population is no longer completely susceptible, so we can no longer use the basic reproduction ratio. In this chapter, we therefore consider the *effective reproduction ratio*. To formally define the effective reproduction ratio we introduce the following notation: Let  $\mathbf{S}(t)$  denote the diagonal matrix with entries  $s_j(t)$ , and let  $\mathbf{B}$  and  $\gamma$  be defined in accordance to (4.4).

**Definition 4.1.** *The effective reproduction ratio at time  $t$ , denoted by  $R_e(t)$ , is determined as follows:  $R_e(t) = \rho(\mathbf{S}(t)\mathbf{B}\gamma)$ , with  $\rho(\cdot)$  denoting the spectral radius, i.e., the largest eigenvalue.*

The matrix  $\mathbf{S}(t)\mathbf{B}\gamma$  is also referred to as the *next generation matrix* at time  $t$ . Hence, the effective reproduction ratio is the largest eigenvalue of the next generation matrix. Note that the effective reproduction ratio at time  $t$  only depends on the parameters and on the fractions of individuals susceptible. The fractions of infected individuals do not play a role. We denote by  $R_f = R_e(0)$  the effective reproduction ratio at time 0, directly after vaccination. At time  $t = 0$  it holds that  $s_j(0) = (1 - f_j)$  for all  $j \in J$ . This implies that  $R_f = \rho(\mathbf{F}\mathbf{B}\gamma)$ , with  $\mathbf{F}$  denoting the following diagonal matrix:

$$\mathbf{F} = \begin{bmatrix} (1 - f_1) & & 0 \\ & \ddots & \\ 0 & & (1 - f_n) \end{bmatrix} \quad (4.6)$$

Vaccination allocations  $\mathbf{f}$  that result in  $R_f = 1$  are referred to as ‘critical vaccination fractions’ or ‘critical vaccination coverages’. In a homogeneous population, or in a population where vaccine is allocated at random, such a critical vaccination coverage would be a single number. Here we deal with multiple interacting populations, where vaccine is not distributed at random, and hence we have multiple critical vaccination coverages, each of which is a vector with a vaccination fraction for every population. In Section 4.4, critical vaccination coverages and their importance for the herd effect are discussed further.

### 4.2.4 Vaccine allocation problems

Using the herd effect and the basic reproduction ratio we define two vaccine allocation problems. The herd effect relates to unvaccinated individuals benefitting from the vaccination of others. An efficient allocation thus makes the best possible use of the herd effect. We define the optimization problem of maximizing the herd effect:

$$\max \sum_{j \in J} N_j G_j(\mathbf{f}) \quad (4.7)$$

$$\text{s.t. } \mathbf{f} \in [0, 1]^n \quad (4.8)$$

In words, we maximize the number of susceptible individuals at the end of the epidemic, subject to the condition that the vaccine allocation  $\mathbf{f}$  consists of proper proportions between 0 and 1. The objective is to maximize the total herd effect (4.7), with  $N_j$  denoting the size of population  $j$ . The fact that the herd effect is implicitly defined (see (4.3)) significantly complicates the analysis of this optimization problem. Therefore, papers that focus on maximizing the herd effect, or relatedly on minimizing the final size under a capacity constraint, typically rely on numerical evaluation or enumeration to determine the optimal allocation (e.g., Arino et al. 2008, Keeling and Shattock 2012, Yuan et al. 2015). In contrast, in this chapter we propose an efficient approach to determine the optimal allocation. For specific cases of separable mixing and two populations we derive closed form solutions.

We also define a vaccine allocation problem based on the reproduction ratio, using the important threshold  $R_f = 1$ . For this threshold an outbreak will not lead to an increase in infected individuals (cf. Section 4.4). There are multiple critical vaccination coverages, i.e., vaccination allocations that result in  $R_f = 1$ . We are interested in finding the critical vaccination coverage that uses the least amount of vaccines, referred to as ‘the most efficient critical vaccination coverage’. This leads to the following optimization problem that minimizes the required amount of vaccines

such that  $R_f = 1$ :

$$\min \sum_{j \in J} N_j f_j \quad (4.9)$$

$$\text{s.t. } \rho(\mathbf{F}\mathbf{B}\boldsymbol{\gamma}) = 1 \quad (4.10)$$

$$\mathbf{f} \in [0, 1]^n \quad (4.11)$$

In words, we minimize the number of vaccinated individuals under the condition that the reproduction ratio is precisely one and the vaccine allocation  $\mathbf{f}$  is properly defined. Constraint (4.10) implies  $R_f = 1$ .

The problem of achieving critical coverage while minimizing the required vaccine stockpile, has been studied before in literature. Hill and Longini Jr (2003) consider the same model specifications as we do in this chapter and extensively study critical vaccination coverages. They also pay some attention to minimizing the number of allocated vaccines and propose to solve the problem using Lagrangian multipliers, which they acknowledge to be computationally inefficient. The authors present some ideas for another solution method and in this chapter we build upon those ideas to formulate our efficient solution approach. Under different model assumptions the problem simplifies. For example, for a stochastic epidemic spread and a population split up in households the problem can be approximated with a linear programming problem (Becker and Starczak 1997, Ball and Lyne 2002, Keeling and Ross 2015).

The remainder of this chapter is dedicated to analyzing the two vaccine allocation problems presented in this section. We prove their equivalence, propose a general solution approach and present explicit solutions for two special cases.

## 4.3 Preliminary analysis

In Section 4.3.1, we present some technical assumptions on the model and in Section 4.3.2 we derive a number of basic technical results. This groundwork is needed for the analysis of the optimization problems of Section 4.2.4.

### 4.3.1 Assumptions

We make the following assumptions with respect to the parameters:

**Assumption 4.2.** *The parameters  $\gamma_j$  and  $\beta_{jj}$  are strictly positive for all  $j \in J$  and  $\beta_{ij}$  are nonnegative for all  $i, j \in J$  with  $i \neq j$ .*

**Assumption 4.3.** *The matrix  $\mathbf{B}$  with elements  $\beta_{ij}$  is irreducible.*

The recovery rates  $\gamma_j$  are assumed to be strictly positive. If  $\gamma_j$  would equal 0 for some population  $j$  an infected individual in population  $j$  would remain infectious forever, which is unrealistic. The parameters  $\beta_{ij}$  represent the transmission rates from population  $j$  to population  $i$ . It is reasonable to assume that these rates are nonnegative. Note that  $\beta_{ij} = 0$  implies that there is no transmission between population  $i$  and  $j$ . This is for example the case when there is no direct contact between the two populations.

By Assumptions 4.2 and 4.3 the matrix  $\mathbf{B}$  and the product  $\mathbf{B}\gamma$  are nonnegative and irreducible which allows us to use Perron-Frobenius Theory (Meyer 2000). The irreducibility of the matrix ensures that all populations interact with each other. This interaction is either direct or indirect, i.e., via other populations. Excluding the unlikely possibility that the disease can be transmitted from population  $i$  to population  $j$  but not vice versa, the assumption that the matrix  $\mathbf{B}$  is irreducible does not restrict generality. Namely, if  $\mathbf{B}$  would be reducible, the problem can be decomposed into subproblems each consisting of a subset of populations with an irreducible transmission matrix.

By Perron-Frobenius Theory a nonnegative and irreducible matrix has a unique positive eigenvector corresponding to the largest eigenvalue. This eigenvector represents the distribution of infected individuals over the populations in the initial phase of the epidemic. Using this initial distribution the time course of the epidemic can be uniquely determined (Theorem 4.1).

### 4.3.2 Basic technical results

In this section, we derive a number of technical results to formally prove our equivalence results in Section 4.4. In Lemma 4.A.1 in Appendix 4.A, we formally prove that the differential equations in (4.1) behave in accordance to interpretation:  $s_j(t), i_j(t), r_j(t) \in [0, 1]$  and  $s_j(t) + i_j(t) + r_j(t) = 1$  for all  $j \in J$  and  $t \geq 0$ . Furthermore, the fraction of susceptible people is non-increasing over time and the fraction of removed people is non-decreasing over time. The next theorem formally shows that the differential equations of the *SIR* model have a unique solution.

**Theorem 4.1.** *Given the initial values  $s_j(0), i_j(0), r_j(0) \in [0, 1]$  such that  $s_j(0) + i_j(0) + r_j(0) = 1$  for all  $j \in J$  the differential equations in (4.1) have a unique solution at any time  $t$ .*

*Proof.* We prove that the differential equations in (4.1) are Lipschitz continuous (see Appendix 4.A). By the Picard-Lindelöf Theorem (Lindelöf 1894) there is a unique solution to the initial value problem.  $\square$

The following lemma establishes bounds on the herd effect  $G_j(\mathbf{f})$ , that is characterized in (4.3). We use these bounds in later sections.

**Lemma 4.4.** *For all  $j \in J$  the following holds:*

$$(i) \quad 0 \leq G_j(\mathbf{f}) \leq \min \left\{ (1 - f_j), \frac{1}{\sigma_j} \right\}$$

$$(ii) \quad G_j(\mathbf{f}) = 0 \text{ if and only if } f_j = 1.$$

*Proof.* See Appendix 4.A.  $\square$

## 4.4 Equivalence results

We are now able to analyze in detail the relation between the basic reproduction ratio and the herd effect. Section 4.4.1 relates  $R_f = \rho(\mathbf{FB}\gamma)$  to the solutions to the implicit expression of the herd effect in equation (4.5). Based on this relation we prove in Section 4.4.2 that the two optimization problems of Section 4.2.4 are equivalent.

### 4.4.1 The relation between $R_f$ and the herd effect

The stability of disease free equilibria and the relation with  $R_0$  has been investigated for different types of compartmental models (among others Van den Driessche and Watmough 2002, Andreasen 2011, Hu et al. 2012). Typically, the conclusion is that a disease free equilibrium (DFE) is stable for  $R_0 < 1$  and unstable for  $R_0 > 1$ . A DFE represents a solution to the final size equation, which is directly related to the herd effect as discussed before. The results in the literature focus on the case without interventions. In this section, we extend these results to pre-pandemic vaccination by deriving the relation between  $R_f$  and the herd effect. The pre-pandemic vaccination case can directly be translated to models without vaccination, by changing the initial

fraction of people susceptible  $s_j(0) := s_j(0)(1 - f_j)$ . Our definition of  $R_f$  is thus directly related to  $R_0$ . We confirm the critical role of  $R_f$  and the threshold  $R_f = 1$ .

The herd effect is defined according to the implicit set of equations (4.5). By Lemma 4.4 we know that any solution  $G_j(\mathbf{f})$  lies in the interval  $[0, (1 - f_j)]$  for all  $j \in J$ . By Theorem 4.1 the differential equations (4.1) have a unique solution at any point in time. This implies that there is also a unique solution for  $G_j(\mathbf{f})$ , which is a stable disease free equilibrium (DFE). Let  $\tilde{\mathbf{G}}$  denote the vector with elements  $G_j(\mathbf{f})/(1 - f_j)$ . We use  $\log(\cdot)$  element wise and rewrite (4.5) into:

$$0 = \log(\tilde{\mathbf{G}}) + B\gamma\mathbf{F}(1 - \tilde{\mathbf{G}}) \quad (4.12)$$

It can easily be verified that equation (4.12) always has the solution  $\tilde{\mathbf{G}} = \mathbf{1}$ , i.e.,  $G_j(\mathbf{f}) = (1 - f_j)$ . This solution will be referred to as the *trivial solution* in accordance to Andreasen (2011) and corresponds to the situation of no outbreak. Recall that directly after vaccination the fraction of people susceptible equals  $(1 - f_j)$  in population  $j$ . Hence, in the trivial solution all susceptible people will remain susceptible. Additionally, we consider solutions that do correspond to outbreaks. We use the term ‘interior solution’ to refer to a solution for which  $G_j(\mathbf{f}) \in (0, (1 - f_j))$  for all  $j \in J$ . We extend Lemma 1 of Andreasen (2011) to include vaccination and the case that  $R_f$  equals 1.

**Lemma 4.5.** *For  $R_f \leq 1$  equation (4.12) does not have an interior solution.*

*Proof.* By contradiction assume that there is an interior solution, denoted by  $\tilde{\mathbf{Y}}$ . Let  $\tilde{\mathbf{Y}}$  denote the vector with elements  $Y_j/(1 - f_j)$  which are all in  $(0, 1)$ . Recall that  $R_f = \rho(\mathbf{F}B\gamma)$  and let  $v$  be the left eigenvector corresponding to this largest eigenvalue. From Perron-Frobenius Theory (Meyer 2000) we know that we can choose  $v$  such that all elements are nonnegative and  $\|v\|_1 = 1$ . Left multiplication of (4.12) with  $v^T\mathbf{F}$  results in the following:

$$\begin{aligned} 0 &= v^T\mathbf{F} \log(\tilde{\mathbf{Y}}) + v^T\mathbf{F}B\gamma\mathbf{F}(1 - \tilde{\mathbf{Y}}) \\ &= v^T\mathbf{F} \log(\tilde{\mathbf{Y}}) + R_f v^T\mathbf{F}(1 - \tilde{\mathbf{Y}}) \\ &= v^T\mathbf{F} [\log(\tilde{\mathbf{Y}}) + (1 - \tilde{\mathbf{Y}})] + (R_f - 1) v^T\mathbf{F}(1 - \tilde{\mathbf{Y}}) \end{aligned} \quad (4.13)$$

Note that  $v^T \mathbf{F} \in (0, 1)^n$  and also  $(1 - \tilde{\mathbf{Y}}) \in (0, 1)^n$ . Furthermore, using that  $\log x < x - 1$  for  $x \neq 1$  we derive:

$$[\log(\tilde{\mathbf{Y}}) + (1 - \tilde{\mathbf{Y}})] < 0$$

Thus, the third line of (4.13) is the summation of a strictly negative and a nonpositive term for  $R_f \leq 1$  and is therefore strictly negative. We arrive at a contradiction, which completes the proof of this lemma.  $\square$

The interpretation of Lemma 4.5 is as follows: in case  $R_f \leq 1$  the system is in a stable disease free equilibrium. Introduction of a disease in the population will not lead to an outbreak in that case.

To analyze the case that  $R_f > 1$  we use a variable transformation and introduce the variable vector  $\mathbf{x}(\mathbf{f})$  with elements  $x_j(\mathbf{f}) = 1 - \frac{G_j(\mathbf{f})}{1-f_j}$ . We rewrite (4.5) into:

$$\mathbf{x}(\mathbf{f}) = 1 - \exp \left\{ - [\mathbf{B}\gamma \mathbf{F} \mathbf{x}(\mathbf{f})]_j \right\} \quad (4.14)$$

From (4.14) and Lemma 4.4 we can derive that the variables  $x_j(\mathbf{f})$  lie in the interval  $[0, 1)$  for all  $j \in J$ .

**Theorem 4.2.** *For  $R_f > 1$  equation (4.12) has a unique interior solution.*

*Proof.* This theorem is equivalent to the statement that (4.14) has a unique positive solution in case  $R_f > 1$ . Equation (4.14) has a positive solution if and only if  $\rho(\mathbf{B}\gamma \mathbf{F}) > 1$  (Theorem 1 of Chan 2013). Note that  $\mathbf{F}$  is an invertible matrix, which implies that the matrices  $\mathbf{B}\gamma \mathbf{F}$  and  $\mathbf{F}\mathbf{B}\gamma$  are similar and have the same eigenvalues. Hence,  $R_f := \rho(\mathbf{F}\mathbf{B}\gamma) = \rho(\mathbf{B}\gamma \mathbf{F})$ . This completes the proof of this theorem.  $\square$

Recall that the herd effect expression is directly related to the final size equation. Theorem 4.2 therefore coincides with Diekmann and Heesterbeek (2000) who claim (in exercise 6.19) that the final size equation has a unique non-trivial (i.e., non-zero) solution in case  $R_0 > 1$ .

#### 4.4.2 Equivalence of the two problems

The results in the previous section are minor extensions of known results in the literature. However, based on these results we are now able to prove one of the main



contributions of this chapter: the equivalence of the two vaccine allocation problems that were discussed before.

**Theorem 4.3.** *The overall herd effect,  $\sum_{j \in J} N_j G_j(\mathbf{f})$ , is maximized for a vaccine allocation  $\mathbf{f}$  that results in  $R_f = 1$ .*

*Proof.* We will prove this lemma by contradiction in two steps. First we show that the overall herd effect cannot be maximized for a vaccine allocation that results in  $R_f < 1$  and in the second step we will exclude the possibility that an allocation with  $R_f > 1$  maximizes the overall herd effect.

Step 1: by contradiction assume that there is a vaccine allocation  $\mathbf{x}$  resulting in  $R_f < 1$ , which maximizes the overall herd effect. Denote by  $\mathbf{X}$  the diagonal matrix with entries  $(1 - x_j)$ . Furthermore, define the function  $g(t) = \rho[(t\mathbf{I} + (1 - t)\mathbf{X})\mathbf{B}\gamma]$  for  $t \in [0, 1]$ . By construction  $g(0) = \rho(\mathbf{X}\mathbf{B}\gamma) < 1$  and to avoid triviality we can assume that  $g(1) = \rho(\mathbf{B}\gamma) > 1$ . By Lemma 4.B.1, which is formulated and proven in Appendix 4.B, the function  $g(t)$  is continuous in  $t$ . Hence, there exists a  $t^* \in (0, 1)$  for which  $g(t^*) = 1$  by the intermediate value theorem. Let  $\mathbf{Y} := t^*\mathbf{I} + (1 - t^*)\mathbf{X}$ . Note that  $\mathbf{Y}$  is also a diagonal matrix and let the vector  $\mathbf{y}$  be such that  $(1 - y_j)$  for all  $j \in J$  are the diagonal elements of  $\mathbf{Y}$ . We compare the vaccine allocation vectors  $\mathbf{y}$  and  $\mathbf{x}$ : It holds that  $y_i \leq x_i$  for all  $i \in J$  and a strict inequality for at least one population by the fact that  $t^* \in (0, 1)$ . By Lemma 4.5 the trivial solution holds for both  $\mathbf{x}$  and  $\mathbf{y}$ , because  $\rho(\mathbf{X}\mathbf{B}\gamma) < 1$  and  $\rho(\mathbf{Y}\mathbf{B}\gamma) = 1$ . Hence,

$$\sum_{j \in J} N_j G_j(\mathbf{y}) = \sum_{j \in J} N_j (1 - y_j) > \sum_{j \in J} N_j (1 - x_j) = \sum_{j \in J} N_j G_j(\mathbf{x})$$

We arrive at a contradiction:  $\mathbf{x}$  cannot maximize the overall herd effect. Thus, we conclude that the overall herd effect is maximized for a vaccination fraction that results in  $R_f \geq 1$ .

Step 2: by contradiction assume that there is a vaccine allocation  $\mathbf{z}$  resulting in  $R_f > 1$ , which maximizes the overall herd effect. By definition of  $R_f$  we have that  $R_e(0) > 1$  which implies by Lemma 4.B.6 (see Appendix 4.B) that  $\lim_{t \rightarrow +\infty} R_e(t) < 1$ . We know that  $R_e(t)$  is continuous in  $t$  (Lemma 4.B.4 in Appendix 4.B) and hence by the intermediate value theorem there exists a time  $\tau > 0$  at which  $R_e(\tau) = 1$ . Since  $\lim_{t \rightarrow +\infty} R_e(t) < R_e(\tau)$  and  $R_e(t)$  can only decrease by a decrease in the

fraction of people susceptible, the following holds:

$$\sum_{j \in J} N_j G_j(\mathbf{z}) = \lim_{t \rightarrow +\infty} \sum_{j \in J} N_j s_j(t) < \sum_{j \in J} N_j s_j(\tau) \quad (4.15)$$

Let us now consider an alternative vaccination allocation denoted by  $\mathbf{y}$ , such that  $y_j = (1 - s_j(\tau))$  for all  $j \in J$ . The definition of  $R_e(\tau)$  does not depend on the fraction of people infected at time  $\tau$ . By construction we thus have that  $\mathbf{y}$  results in  $R_f = 1$ . From Lemma 4.5 we conclude the following:

$$\sum_{j \in J} N_j G_j(\mathbf{y}) = \sum_{j \in J} N_j (1 - y_j) = \sum_{j \in J} N_j s_j(\tau) > \sum_{j \in J} N_j G_j(\mathbf{z}),$$

where the inequality follows from (4.15). We arrive at a contradiction:  $\mathbf{z}$  cannot maximize the overall herd effect.

We conclude that the vaccine allocation  $\mathbf{f}$  that maximizes the overall herd effect cannot result in  $R_f > 1$  nor in  $R_f < 1$ . Thus,  $R_f$  must equal 1, which completes the proof of this lemma.  $\square$

We are now able to prove the main result of this section:

**Theorem 4.4.** *Problem (4.7) - (4.8) and Problem (4.9) - (4.11) are equivalent.*

*Proof.* We conclude the following:

$$\begin{array}{|c|} \hline \max \quad \sum_{j \in J} N_j G_j(\mathbf{f}) \\ \text{s.t.} \\ \mathbf{f} \in [0, 1]^n \\ \hline \end{array} \Leftrightarrow \begin{array}{|c|} \hline \max \quad \sum_{j \in J} N_j G_j(\mathbf{f}) \\ \text{s.t.} \\ R_f = 1 \\ \mathbf{f} \in [0, 1]^n \\ \hline \end{array} \Leftrightarrow \begin{array}{|c|} \hline \max \quad \sum_{j \in J} N_j (1 - f_j) \\ \text{s.t.} \\ R_f = 1 \\ \mathbf{f} \in [0, 1]^n \\ \hline \end{array} \Leftrightarrow \begin{array}{|c|} \hline \min \quad \sum_{j \in J} N_j f_j \\ \text{s.t.} \\ R_f = 1 \\ \mathbf{f} \in [0, 1]^n \\ \hline \end{array}$$

The first implication follows from Theorem 4.3. For the second implication we apply Lemma 4.5 which states that  $G_j(\mathbf{f}) = (1 - f_j)$  for all  $j \in J$  in case  $R_f = 1$ .  $\square$

By Theorem 4.4 the two optimization problems presented in Section 4.2.4 are equivalent. The intuitive explanation of this result is that the problem of minimizing the number of vaccines to attain  $R_f = 1$  requires a very efficient allocation of vaccines. Maximizing the herd effect thus leads to the most efficient allocation of vaccines.

## 4.5 Solving the problems

Optimization problem (4.9) - (4.11) has a simple linear objective function. The main difficulty of this problem is the constraint  $R_f = 1$ , which is not in general convex (or concave) (c.f. Hill and Longini Jr 2003). We have shown in Theorem 4.4 that Problem (4.7) - (4.8) can also be formulated as an optimization problem with a linear objective function and the constraint  $R_f = 1$ . In this section, we show that this constraint simplifies for two special cases. This simplification has important consequences, as it enables us to solve the vaccine allocation problem to optimality for these two special cases. In Section 4.5.1, we assume a special structure on the contact matrix  $\mathbf{B}\gamma$ : separable mixing. Section 4.5.2 studies the important special case of two populations. Finally, in Section 4.5.3 we present a novel solution method that is able to solve the vaccine allocation problems for the general case, without additional assumptions on the contact matrices or the number of populations.

### 4.5.1 Separable mixing

For notational convenience we will use  $k_{ij}$  to denote the elements of the matrix  $\mathbf{B}\gamma$ . We consider a special structure on the matrix  $\mathbf{B}\gamma$ , where  $k_{ij} = a_i b_j$ . This structure is called *separable mixing* and means that population  $j$  is equally susceptible to all other populations and population  $i$  is equally infectious to all other populations (Diekmann et al. 2013). The special case that  $a$  is proportional to  $b$ , i.e.,  $a_i = \delta b_i$  for all  $i \in J$ , is called *proportionate mixing*. Separable and proportionate mixing are often studied (e.g., Hethcote and Van Ark 1987, Cairns 1989, Ross and Black 2015). For separable mixing,  $R_f$  can explicitly be determined. Denote by  $\text{Tr}(\cdot)$  the trace of a matrix and let  $\sigma_j = \frac{\beta_{jj}}{\gamma_j}$ . By definition  $\sigma_j$  can be seen as an internal reproduction ratio in population  $j$ . For separable mixing  $R_f$  is defined as follows:

$$R_f = \text{Tr}(\mathbf{F}\mathbf{B}\gamma) = \sum_{j \in J} \frac{\beta_{jj}}{\gamma_j} (1 - f_j) = \sum_{j \in J} \sigma_j (1 - f_j)$$

By Lemma 4.5 and Lemma 4.B.3 any solution for which  $R_f < 1$  can never be optimal. Hence, the solution to Problem (4.9) - (4.11) does not change if we relax the constraint  $R_f = 1$  to  $R_f \leq 1$ . The linear definition of  $R_f$  for separable mixing significantly

simplifies the optimization problems of Section 4.2.4 which now become:

$$\max \quad \sum_{j \in J} N_j(1 - f_j) \quad (4.16)$$

$$\text{s.t.} \quad \sum_{j \in J} \sigma_j(1 - f_j) \leq 1 \quad (4.17)$$

$$\mathbf{f} \in [0, 1]^n \quad (4.18)$$

In words, we maximize the herd effect subject to the constraint that  $R_f \leq 1$  and properly defined vaccination fractions.

Based on the relaxation we are able to derive a solution method for the problem. Observe that Problem (4.16) - (4.18) is the linear programming (LP) relaxation of a knapsack problem, one of the basic problems in combinatorial optimization. This LP relaxation can be solved to optimality by a simple *greedy* algorithm (Dantzig 1957). A *greedy* algorithm is a procedure that consecutively makes decisions that are locally optimal. For the LP relaxation of a knapsack problem such a procedure also results in the global optimum. We propose the greedy algorithm in Algorithm 1 to solve Problem (4.16) - (4.18) to optimality.

---

**Algorithm 1** The greedy algorithm for solving Problem (4.16) - (4.18)

---

```

1: procedure GREEDY ALGORITHM
2:   reorder the populations such that  $\frac{N_1}{\sigma_1} \leq \dots \leq \frac{N_n}{\sigma_n}$ 
3:    $f_j \leftarrow 0$  for all  $j \in J$  ▷ Initialize the solution
4:    $k \leftarrow 1$ 
5:   while  $\sum_{j=k+1}^n \sigma_j(1 - f_j) > 1$  do
6:      $f_k \leftarrow 1$ 
7:      $k \leftarrow k + 1$ 
8:   end while
9:    $f_k = 1 - \frac{1}{\sigma_k} \left[ 1 - \sum_{j=k+1}^n \sigma_j(1 - f_j) \right]$ 
10:   $\mathbf{f} = [f_j]_j$ 
11:  return  $\mathbf{f}$  ▷ Return the optimal solution
12: end procedure
```

---

The ordering of the populations in line 2 can be done without loss of generality. The allocation resulting from Algorithm 1 prioritizes small populations and populations with a high  $\sigma_j$ . Vaccinating these populations costs relatively few vaccines, but has a large impact on lowering the reproduction ratio  $R_f$ . Note that population  $j$

has a high  $\sigma_j$  either because this population has a high transmission rate or a long infectious period (and therefore a low recovery rate). i.e., either  $\beta_{jj}$  is high or  $\gamma_j$  is low. Because of the structure of separable mixing, a population with a high internal transmission rate also plays an important role in the transmission between itself and other populations. Thus, the prioritized populations either contribute heavily to the transmission or have a long infectious period. The algorithm uses these simple characteristics to derive the vaccination allocation that results in the highest overall herd effect (and equivalently, the most efficient critical vaccination coverage).

The optimal order in the greedy algorithm is identical to the optimal order reported for a related problem studied by Cairns (1989), who considers vaccination with a fixed rate during a time interval and the objective of minimizing the effective reproduction ratio at a certain time. The authors prove that for separable mixing it is optimal to allocate all vaccination effort to one population during a specific time interval. During consecutive time intervals the populations are vaccinated in order of increasing activity, which is exactly the order used in our greedy algorithm. Although the problem studied by Cairns (1989) differs in many respects from the problem in this chapter, it is interesting to observe that under the assumption of separable mixing the same optimal population ordering is found.

### 4.5.2 Two populations

For two populations an explicit expression for the condition  $R_f = 1$  is derived in Section 4.5.2. Based on this expression we are able solve the optimization problem explicitly. In Section 4.5.2 we present this explicit solution.

#### Explicit expression for $R_f = 1$

Recall that  $R_f = \rho(\mathbf{FB}\gamma)$ . Denote by  $\sigma_1 = \frac{\beta_{11}}{\gamma_1}$ , by  $\sigma_2 = \frac{\beta_{22}}{\gamma_2}$ . Denote by  $c = \frac{\beta_{12}\beta_{21}}{\beta_{11}\beta_{22}}$ . We use  $\det(\cdot)$  and  $\text{Tr}(\cdot)$  to denote respectively the determinant and trace of a matrix. From the definition of the largest eigenvalue for a  $2 \times 2$  matrix we derive that any vaccination allocation  $f_1, f_2$  for which  $R_f = 1$  satisfies the following condition:

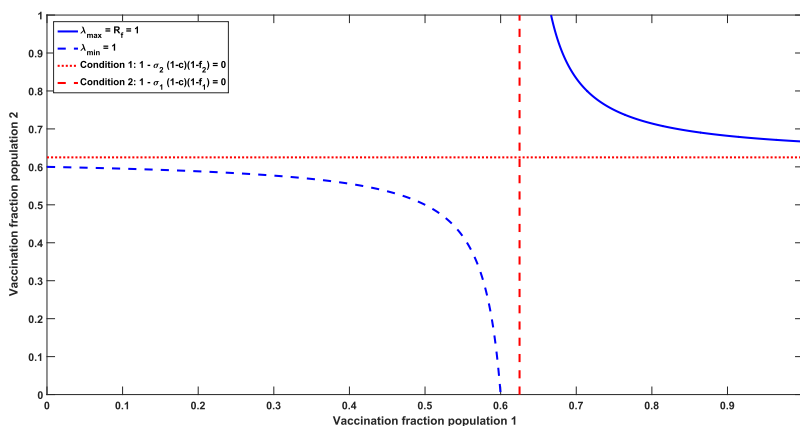
$$\det(\mathbf{FB}\gamma) - \text{Tr}(\mathbf{FB}\gamma) + 1 = 0$$

Furthermore, we use that  $\text{Tr}(\mathbf{FB}\gamma) = \text{Tr}(\mathbf{B}\gamma) - \sigma_1 f_1 - \sigma_2 f_2$  and  $\det(\mathbf{FB}\gamma) = (1 - f_1)(1 - f_2) \det(\mathbf{B}\gamma)$ . After substituting  $\text{Tr}(\mathbf{B}\gamma) = \sigma_1 + \sigma_2$  and  $\det(\mathbf{B}\gamma) = \sigma_1 \sigma_2 (1 - c)$

we obtain that the critical vaccination fractions satisfy the following equation:

$$(1 - f_1)(1 - f_2)\sigma_1\sigma_2(1 - c) - \sigma_1(1 - f_1) - \sigma_2(1 - f_2) + 1 = 0 \quad (4.19)$$

Not *all* solutions to (4.19) are critical vaccination coverages. In fact, (4.19) is a hyperbola and all critical vaccination coverages lie on one branch of the hyperbola (cf. Hill and Longini Jr 2003). The part of the correct branch of the hyperbola that contains the critical vaccination coverages is characterized in Lemma 4.6. This lemma is also illustrated in Figure 4.2.



**Figure 4.2:** Illustration of the hyperbola with parameters  $\beta_{jj} = 3, \gamma_j = 1$  for  $j = 1, 2$  and  $\beta_{ij} = 1$  for  $i \neq j$ . The lower branch results in the smallest eigenvalue, denoted by  $\lambda_{min}$ , being equal to 1. The upper branch is the correct branch, and results in a largest eigenvalue, denoted by  $\lambda_{max} = R_f$ , equal to 1.

**Lemma 4.6.** *Let  $D$  denote the feasible region for the vaccination fractions:*

$$D = \{(f_1, f_1) | f_1, f_1 \in [0, 1]\}.$$

*The part of the hyperbola for which  $R_f = 1$  is described by  $(f_1, f_2) \in D$  and the condition  $1 - \sigma_1(1 - c)(1 - f_1) > 0$  (equivalently the very same part of the hyperbola may also be characterized by  $(f_1, f_2) \in D$  and the condition  $1 - \sigma_2(1 - c)(1 - f_2) > 0$ ).*

*Proof.* We first show that the condition  $1 - \sigma_1(1 - c)(1 - f_1) > 0$  results in the correct branch of the hyperbola. The condition  $(f_1, f_2) \in D$  stipulates that the vaccination fractions are properly defined. Secondly, we show that the other condition can be derived analogously. Rewriting (4.19) gives:

$$(1 - f_2) = \frac{1 - \sigma_1(1 - c)(1 - f_1)}{\sigma_2[1 - \sigma_1(1 - c)(1 - f_1)]} \quad (4.20)$$

From (4.20) we derive that the hyperbola has an asymptote for  $1 - \sigma_1(1 - c)(1 - f_1) = 0$ . Distinguish between the following two cases: (i)  $c < 1$  and (ii)  $c \geq 1$ . First we analyze case (i): For  $R_f = 1$  we have  $G_j(\mathbf{f}) = (1 - f_j)$  and by Lemma 4.4 we know that  $G_j(\mathbf{f}) < \frac{1}{\sigma_j}$ . This implies the following:

$$(1 - f_1) < \frac{1}{\sigma_1} < \frac{1}{\sigma_1(1 - c)}$$

Thus, vaccination fractions that result in  $R_f = 1$  can only occur in the branch of the hyperbola for which  $1 - \sigma_1(1 - c)(1 - f_1) > 0$ . Consider case (ii): For  $c \geq 1$  the asymptote lies outside the feasible region and therefore it is not needed to specify a single branch. However, the condition  $1 - \sigma_1(1 - c)(1 - f_1) > 0$  is always satisfied for  $(f_1, f_2) \in D$ . It can thus be added without changing the solution space.

In the same way the condition on  $f_2$  can be derived by noting that (4.20) can be rewritten as follows:

$$(1 - f_1) = \frac{1 - \sigma_2(1 - c)(1 - f_2)}{\sigma_1[1 - \sigma_2(1 - c)(1 - f_2)]}$$

Using the same argument, we can show that the correct branch of the hyperbola is described by  $1 - \sigma_2(1 - c)(1 - f_2) > 0$ . Hence, the symmetry between the two populations is still retained.  $\square$

## Solution

The conditions derived in Lemma 4.6 to specify the part of the hyperbola that contains the critical vaccination coverages can replace the constraint  $R_f = 1$  in the vaccine allocation problem:

$$\max \quad N_1(1 - f_1) + N_2(1 - f_2) \quad (4.21)$$

$$\text{s.t.} \quad (1 - f_1)(1 - f_2)\sigma_1\sigma_2(1 - c) - \sigma_1(1 - f_1) - \sigma_2(1 - f_2) + 1 = 0 \quad (4.22)$$

$$1 - \sigma_2(1 - c)(1 - f_2) > 0 \quad (4.23)$$

$$f_j \in [0, 1] \quad j = 1, 2 \quad (4.24)$$

Constraints (4.22) and (4.23) stipulate that  $R_f = 1$ . It suffices to use only one of the equivalent conditions of Lemma 4.6.

In Theorem 4.5 we will present the solution to Problem (4.21) - (4.24). This solution contains a list of at most three candidate solutions: two boundary solutions (with  $f_j \in \{0, 1\}$  for  $j = 1$  or  $j = 2$ ) and possibly one interior solution (with  $\mathbf{f} \in (0, 1)^2$ ). The interior solution can be derived by substituting  $(1 - f_2)$  in the objective function using equality constraint (4.22). By setting the derivative of the objective function with respect to  $f_1$  equal to zero we obtain a solution, which is presented in Theorem 4.5. However, it is possible that this solution does not satisfy (4.23) - (4.24). In that case, we will show that the optimal solution to (4.21) - (4.24) must be a *boundary solution*: i.e., a solution  $(f_1, f_2)$  that satisfies (4.22) - (4.23) for which  $f_1 \in \{0, 1\}$  and/or  $f_2 \in \{0, 1\}$ . In Lemma 4.7 we therefore present an exhaustive list of all possible boundary solutions:

**Lemma 4.7.** *There are always precisely two boundary solutions to Problem (4.21) - (4.24). The first solution depends on  $\sigma_1$ :*

$$\begin{aligned} (i) \quad & f_1 = 0 & f_2 = 1 - \frac{1}{\sigma_2} \left[ \frac{1 - \sigma_1}{1 - \sigma_1(1 - c)} \right] & \text{if } \sigma_1 \leq 1 \\ (ii) \quad & f_1 = 1 - \frac{1}{\sigma_1} & f_2 = 1 & \text{if } \sigma_1 > 1 \end{aligned}$$



The second solution depends on  $\sigma_2$ :

$$\begin{aligned} (iii) \quad f_1 &= 1 - \frac{1}{\sigma_1} \left[ \frac{1 - \sigma_2}{1 - \sigma_2(1 - c)} \right] & f_2 &= 0 & \text{if } \sigma_2 \leq 1 \\ (iv) \quad f_1 &= 1 & f_2 &= 1 - \frac{1}{\sigma_2} & \text{if } \sigma_2 > 1 \end{aligned}$$

*Proof.* To derive the four boundary solutions we use that  $f_j \in [0, 1]$  for  $j = 1, 2$  by (4.24). We fix the vaccination fractions per population to the two boundary values 0 and 1. Condition (4.22) is used to derive the expression for the other vaccination fraction. This gives us the four boundary solutions that are presented in the lemma. In the remainder of the proof we analyze the feasibility of the boundary solutions with respect to constraints (4.23) - (4.24) for the different ranges of  $\sigma_1$  and  $\sigma_2$ .

Note that solutions (i) and (ii) are identical in case  $\sigma_1 = 1$ . The same holds for solutions (iii) and (iv) in case  $\sigma_2 = 1$ . To investigate the feasibility of solution (i) we substitute the value  $f_1 = 0$  in constraint (4.23) and obtain that  $1 - \sigma_1(1 - c) > 0$ . If we now consider the expression for  $f_2$  in solution (i), we see that we need  $\sigma \leq 1$  to have  $f_2 \leq 1$ . Thus solution (i) can only satisfy constraints (4.23) and (4.24) at the same time if  $\sigma_1 \leq 1$ . Equivalently, solution (iii) can only satisfy both constraints (4.23) and (4.24) if  $\sigma_2 \leq 1$ . Using constraint (4.24) we can easily verify that solution (ii) is only feasible in case  $\sigma_1 > 1$ , because that prevents negative  $f_1$ . Equivalently,  $\sigma_2 > 1$  renders solution (iv) feasible.

Based on these conclusions we proved which of the boundary solutions are feasible for which values for  $\sigma_1$  and  $\sigma_2$ . This completes the proof of this lemma.  $\square$

**Theorem 4.5.** *The optimal solution to Problem (4.21) - (4.24) can be found among the boundary solutions given in Lemma 4.7 and the following solution:*

$$f_1 = 1 - \frac{1}{\sigma_1} \left[ \frac{1 - \sqrt{\frac{c\sigma_1 N_2}{\sigma_2 N_1}}}{1 - c} \right] \quad \text{and} \quad f_2 = 1 - \frac{1}{\sigma_2} \left[ \frac{1 - \sqrt{\frac{c\sigma_2 N_1}{\sigma_1 N_2}}}{1 - c} \right]$$

For  $c \geq 1$  only the boundary solutions need to be considered.

The proof of Theorem 4.5 can be found in Appendix 4.E. Observe that the vaccination fractions in Theorem 4.5 are closely related to  $f_j = 1 - \frac{1}{\sigma_j}$  for  $j = 1, 2$  with a correction factor for the interaction. Without interaction, i.e., when  $c = 0$ , the vaccination fractions boil down to  $f_j = 1 - \frac{1}{\sigma_j}$  for  $j = 1, 2$ .

### 4.5.3 The general case

In this section, we present a general solution approach for the vaccine allocation problems. Thereto we reformulate the optimization problems using Perron-Frobenius theory (Meyer 2000).  $R_f$  is the largest eigenvalue of the nonnegative and irreducible matrix  $\mathbf{FB}\gamma$  by Assumptions 4.2 and 4.3.

Perron-Frobenius theory states that a nonnegative and irreducible matrix has exactly one right eigenvector, the so-called *Perron vector* which is normalized and strictly positive. This eigenvector corresponds to the largest eigenvalue and has the following epidemiological interpretation: the Perron vector is the frequency distribution over the populations of the number of cases in the initial phase of an epidemic. The Perron vector can be used to reformulate the optimization problem of Section 4.2.4 (cf. Hill and Longini Jr 2003). Hill and Longini Jr (2003) also speculate that a solution approach based on Perron-Frobenius theory might be an interesting research direction. To the best of our knowledge we are the first to derive such a solution approach.

Let  $\mathbf{v}$  denote the right eigenvector that corresponds to  $R_f = 1$ . The following holds:

$$\mathbf{FB}\gamma\mathbf{v} = \mathbf{v} \Rightarrow \sum_{j \in J} (1 - f_i) \frac{\beta_{ij}}{\gamma_j} v_j = v_i$$

We normalize the vector  $\mathbf{v}$  such that  $\|\mathbf{v}\| = 1$ , using the  $\ell_1$ -norm. The optimization problems of Section 4.2.4 are then equivalent to the following problem:

$$\max \quad \sum_{j \in J} N_j (1 - f_j) \tag{4.25}$$

$$\text{s.t.} \quad (1 - f_i) \sum_{j \in J} \frac{\beta_{ij}}{\gamma_j} v_j = v_i \quad i \in J \tag{4.26}$$

$$\sum_{j \in J} v_j = 1 \tag{4.27}$$

$$v_j > 0 \quad j \in J \tag{4.28}$$

$$(1 - f_j) \in [0, 1] \quad j \in J \tag{4.29}$$

Given the objective function and the nonnegativity of the parameters  $\beta_{ij}$  and  $\gamma_j$ , constraints (4.26) can be relaxed to:

$$(1 - f_i) \sum_{j \in J} \frac{\beta_{ij}}{\gamma_j} v_j \leq v_i \quad i \in J \quad (4.30)$$

**Lemma 4.8.** *For any solution to Problem (4.25) - (4.29) we have  $f_i \geq 1 - \frac{\gamma_i}{\beta_{ii}}$ .*

By constraints (4.29) we have that  $f_j \in [0, 1]$ . In case  $\frac{\beta_{ii}}{\gamma_i} > 1$  the lower bound derived in Lemma 4.8 is stronger than the bound  $f_i \geq 0$ . For  $\frac{\beta_{ii}}{\gamma_i} \leq 1$  the lower bound of Lemma 4.8 is already satisfied by the nonnegativity of  $f_i$ . Observe that Lemma 4.8 implies that the reproduction number within every population is less than or equal to 1 in the optimal solution.

**Lemma 4.9.** *The feasible region of Problem (4.25) - (4.29) is not convex.*

The proofs of Lemma 4.8 and Lemma 4.9 can be found in Appendix 4.C.

Problem (4.25) - (4.29) contains two classes of variables:  $(1 - f_j)$  and  $v_j$  for all  $j \in J$ . The objective function (4.25) and the constraints (4.27) - (4.29) are all linear in these variables. Constraints (4.26) are quadratic in the two classes of variables, which makes this problem a quadratically constrained programming problem (QCP). The quadratic constraints (4.26) are not convex.

The lack of convexity makes it difficult to solve Problem (4.25) - (4.29) to optimality. We therefore propose a solution approach that cannot guarantee global optimality, but works well in our numerical experiments. We implement the formulation of our solution approach in Matlab and use the built-in function `fmincon`. This function is able to minimize nonlinear programming problems with different types of constraints: linear (in)equality constraints, bounds on the variables and nonlinear (in)equality constraints. It is therefore suitable to solve the QCP formulation (4.25) - (4.29). The problem formulation can easily be transformed into a minimization problem by multiplying the objective function with -1. The solution approach of `fmincon` is based on interior point methods and barrier functions (c.f. Waltz et al. 2006). Global optimality cannot be guaranteed, because constraints (4.26) are not convex. To reduce the likelihood of ending up in a local optimum, we propose to use a multi start approach where we solve the problem multiple times for random start solutions. In our numerical experiments we compare the outcome of the solution approach to

the optimal solutions derived in the previous sections for randomly generated cases with separable mixing or two populations. Note that the problem for two populations can either be convex or concave (Hill and Longini Jr 2003). Next to these special cases, we also compared the solution to the example in Hill and Longini Jr (2003) with five age groups and no separable mixing. For all of these problem instances our proposed solution approach is able to find the optimal solution within seconds.

Generating a random start solution that is feasible with respect to constraints (4.26) - (4.29) is not trivial, as the feasible region is not convex by Lemma 4.9. We propose the following approach to generate start solutions that satisfy most constraints. We can easily generate a random unit vector in  $(0,1)$ , that satisfies constraints (4.27) - (4.28). We then determine  $f_i$  with constraint (4.26) and set  $f_i = 0$  in case this results in a negative vaccination fraction. This guarantees (4.29) and possibly also constraints (4.26) for some  $i \in J$ .

## 4.6 Practical application

In this section, we present a practical application to illustrate our results. We apply our optimization model to a case study using the model and parameter values of Wallinga et al. (2010). Section 4.6.1 describes this case study and in Section 4.6.2 we present the results.

### 4.6.1 Case study - case description

We now present a case study for which the parameters are taken from the literature (Wallinga et al. 2010). An age-structured population is considered with six age groups: 0-5, 6-12, 13-19, 20-39, 40-59 and 60+. The population sizes  $N_j$  and contact parameters, denoted by  $\delta_{ij}$  are presented respectively in Table 4.1 and Table 4.2.

Age group	0-5	6-12	13-19	20-39	40-59	60+	total
Population ( $\times 10^3$ )	1060	1265	1642	4857	3312	2477	14613

**Table 4.1:** The population sizes of the different age groups.

The spread of the disease is modeled with a heterogeneous *SIR* model, see Section 4.2.1. The transmission rates  $\beta_{ij}$  as presented in this chapter can be calculated

$\delta_{ij}$ ( $10^{-7}$ day $^{-1}$ )	0-5	6-12	13-19	20-39	40-59	60+
0-5	1.393	0.259	0.146	0.284	0.130	0.094
6-12	0.259	2.261	0.266	0.287	0.170	0.095
13-19	0.146	0.266	1.847	0.418	0.309	0.123
20-39	0.284	0.287	0.418	0.623	0.407	0.207
40-59	0.130	0.170	0.309	0.407	0.504	0.272
60+	0.094	0.095	0.123	0.207	0.272	0.447

**Table 4.2:** The age-specific contact matrix.

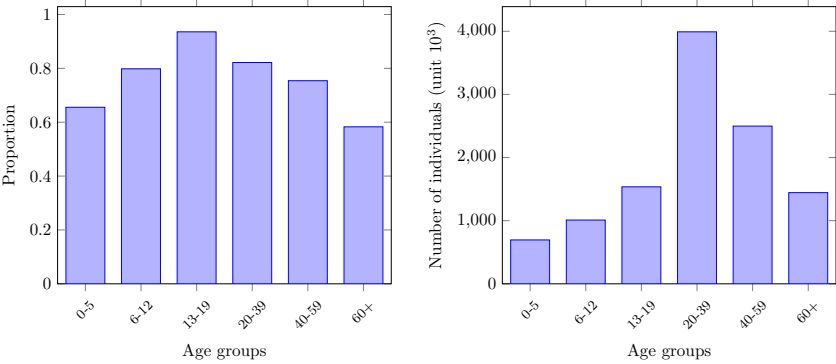
as follows:  $\beta_{ij} = \delta_{ij}N_j$ , with  $\delta_{ij}$  being the proportion of age group  $i$  contacted by an infected individual in age group  $j$  per unit of time. The recovery rate is assumed to be the same for every age group:  $\gamma_j = 0.286$  for all  $j \in J$ . This results in an expected duration in the infected compartment (i.e., the *generation interval*) of 3.5. The reproduction ratio without vaccination is equal to  $\rho(\mathbf{B}\gamma) = 2.1$ . The parameter values for both the generation interval and the reproduction ratio are in line with other studies in literature (Boëlle et al. 2011, Vink et al. 2014).

### 4.6.2 Case study - solution

We solve our optimization problems to determine the optimal vaccine allocation. The resulting optimal allocation is compared to the following four allocation schemes:

- **Random allocation** - The vaccines are allocated at random (i.e., pro rata) over the age groups.
- **Greedy allocation** - The age groups are prioritized in accordance to the priority order presented in Algorithm 1.
- **High-infection scheme 1** - The age groups are prioritized based on the final size as a fraction of the age group size, which results in the following order: 13-19, 20-39, 6-12, 40-59, 0-5, 60+.
- **High-infection scheme 2** - The prioritization is determined based on the absolute final sizes (i.e., fractional final size weighted by age group size). This leads to the following priority order: 20-39, 40-59, 13-19, 60+, 6-12, 0-5.

A high-infection risk scheme is also studied by Mylius et al. (2008). To determine the priority order in these allocation schemes we determine for every age group the expected final size (i.e., infection attack rate) without vaccination. These final sizes are presented in Figure 4.3.



**Figure 4.3:** The final size without vaccination for the different age groups in fractions of the age group size (left) and in absolute numbers (right).

For the greedy allocation and the high-infection schemes we vaccinate according to the priority order until we achieve the threshold  $R_f = 1$  in a similar way as in Algorithm 1. The resulting vaccine allocations are presented in Table 4.3.

	Age groups					
	0-5	6-12	13-19	20-39	40-59	60+
Optimal allocation	0.000	0.515	0.862	0.791	0.000	0.000
Random allocation	0.530	0.530	0.530	0.530	0.530	0.530
Greedy allocation	1.000	1.000	1.000	0.635	0.000	0.000
High-infection scheme 1	0.000	0.124	1.000	1.000	0.000	0.000
High-infection scheme 2	0.000	0.022	1.000	1.000	1.000	1.000

**Table 4.3:** The vaccination fractions in every age group for the different allocation schemes.

We compare the vaccine allocation schemes in terms of the herd effect and the required vaccine stockpile to achieve the threshold  $R_f = 1$ . The differences between the different allocations can be substantial, as can be seen in Table 4.4.

The results in Table 4.4 show that the optimal allocation significantly outperforms the other allocation schemes. High-infection scheme 1 results in the second best performance, but nevertheless achieves a herd effect of approximately 9% below the optimum. High-infection scheme 2 results by far in the lowest herd effect (and

	Herd effect	Required vaccine stockpile
<b>Optimal allocation</b>	8.705	5.908
<b>Random allocation</b>	6.867	7.746
<b>Greedy allocation</b>	7.563	7.050
<b>High-infection scheme 1</b>	7.957	6.656
<b>High-infection scheme 2</b>	2.297	12.316

**Table 4.4:** The herd effect and required vaccine stockpile to attain  $R_f = 1$  for different allocation schemes (unit  $10^6$ ).

equivalently in the largest required vaccine stockpile). Even when we disregard this worst performing allocation scheme, the optimal allocation still increases the herd effect with 9 to 26%.

We analyzed the robustness of our optimal allocation for different values of  $\gamma$ . The analysis shows that the optimal allocation only changes minimally, for example for  $\gamma = 0.30$  the optimal allocation for the consecutive age groups is as follows:  $\mathbf{f} = [0, 0.4905, 0.8545, 0.7297, 0, 0]$ .

## 4.7 Discussion

In this chapter, we analyze the impact of vaccine allocation on the reproduction ratio and the herd effect. We prove the equivalence of two vaccine allocation problems: finding the optimal allocation that results in a critical coverage and finding the optimal allocation that maximizes the herd effect. We use this equivalence to propose solution methods for finding optimal allocations. The solution methods depend on the transmission of infection within and between subpopulations. For the general case, an efficient solution approach is presented based on Perron-Frobenius theory. For two special cases, we can characterize the optimal solution completely: we provide an exact algorithm for the case where the population contact structure follows separable mixing, we derive an explicit solution for the case where the population consists of two subpopulations.

Our contribution to the existing literature on vaccine allocation derives from our application of mathematical optimization techniques. The meaning of the phrase ‘optimal allocation’ differs slightly in the existing literature. In the epidemiological literature an ‘optimal allocation’ often refers to an allocation that is the best out of

the numerically evaluated allocation schemes, where the schemes are selected (e.g., Mylius et al. 2008, Tuite et al. 2010) or obtained in an exhaustive search of all possible alternatives (e.g., Medlock and Galvani 2009, Keeling and Shattock 2012). In contrast, we rely on mathematical optimization where the focus is on finding and characterizing the best possible solution according to a given objective (optimization criterion). The main practical benefit of mathematical optimization is that, once the optimal solution is found, we can evaluate it numerically with standard software, often this allows for an efficient sensitivity analysis with arbitrary precision. From our perspective, an even larger benefit is that we know what the optimal allocation looks like and that we can guarantee that there is no better allocation. To the best of our knowledge we are the first to solve the considered vaccine allocation problems to optimality.

Our results on optimal allocation schemes come with a guarantee of being optimal. In this, they are qualitatively different from other allocation schemes that have been put forward in the existing literature that might perform well, but do not guarantee that there is no better allocation possible. Some of our results confirm existing findings. For example, for separable mixing we found that a simple allocation scheme does guarantee optimality. Some of our results significantly improve over existing allocation schemes. For example, in the case study in Section 4.6 we show that the optimal allocation significantly outperforms other allocation schemes. The allocation schemes, whether obtained through enumeration or mathematical optimization, are primarily intended to inform public health policy makers. The actual decisions may rely on other aspects than optimality alone, and could include ethical and operational considerations.

In our approach, we assume that transmission parameters within and between subpopulations remain constant and are known. In practice it is not possible to determine these contact parameters exactly. For infections that are transmitted through close contacts, studies often rely on proxy measures derived from social contacts (e.g., Wallinga et al. 2006, Mossong et al. 2008, Hens et al. 2009). Building upon this work others such as Goeyvaerts et al. (2010) and Fumanelli et al. (2012) use serological and socio-economic data respectively to estimate the structure of the transmission matrix. In order to apply our results in practice, these methods represent a valuable direction of research for obtaining increasingly precise estimates of the transmis-



sion parameters that we require in our models. We stress that even without precise knowledge of parameters our findings are meaningful. Using numerical analysis we show that increasing parameter estimation errors results in worse performance for all allocation schemes, and the allocation that is optimal for the parameter estimates continues to perform well. Our optimal allocation is therefore robust for errors in estimating the transmission parameters.

Other assumptions include the use of a deterministic transmission model, the unlimited availability of vaccines and the irreducibility of the transmission matrix. To derive our results, we made use of the deterministic *SIR* compartmental model. The final size equation and the reproduction ratio for this model are valid for a broader class of models (Ma and Earn 2006, Van den Driessche and Watmough 2002, Diekmann et al. 2013). The deterministic assumption is only valid in case of a large population. Our results do not apply to small populations where stochastic effects cannot be neglected. The assumption of an unlimited stockpile enables to achieve the threshold  $R_f = 1$ . The solutions are relevant for stockpiles large enough to achieve this threshold, but not for smaller stockpiles. For small stockpiles the problem of maximizing the herd effect becomes more complex (see Chapter 3). In order to use Perron-Frobenius theory, we assume that the transmission matrix  $\mathbf{FB}\gamma$  is irreducible. Although irreducibility is technically lost in case  $f_k = 1$  for some  $k \in J$ , this does not affect our solution method. In that case, a reduced matrix can be constructed which is nonnegative and irreducible (cf. Section 7.2 of Diekmann et al. 2013).

To conclude, we have applied mathematical optimization in vaccine allocation problems. Our results bring two interesting insights to the field of vaccine allocation. First, we show that in some cases optimizing different criteria results in the same allocation. This is the case for the optimization of the short term reproduction ratio and optimizing the long term herd effect. Secondly, we have demonstrated that vaccine allocation problems are susceptible to mathematical optimization. If the objective can properly be defined, it is expected that one can also derive the corresponding optimal allocation. Future research on vaccine allocation could therefore focus on exactly specifying the objective of vaccination. It is worthwhile to investigate to what extent optimization in vaccine allocation can be applied with other transmission models or objectives.

## Acknowledgements

The authors want to thank Prof. Odo Diekmann for his useful input.

## Appendix

### 4.A Analysis of the *SIR* model

We start with proving some technical results on the differential equations of the *SIR* model in Section 4.A.1. In Section 4.A.2 we explain the derivation of the implicit herd effect definition and prove the bounds on the herd effect.

#### 4.A.1 Differential equations

**Lemma 4.A.1.** *For initial values  $s_j(0), i_j(0), r_j(0) \in [0, 1]$  and  $s_j(0) + i_j(0) + r_j(0) = 1$  for all  $j \in J$ , the solution  $(s_j(t), i_j(t), r_j(t))$  to (4.1) satisfies the following conditions:*

- (i)  $s_j(t) + i_j(t) + r_j(t) = 1$  for all  $j \in J$  and at any time  $t \geq 0$
- (ii)  $s_j(t), i_j(t), r_j(t) \in [0, 1]$  for all  $j \in J$  and at any time  $t \geq 0$
- (iii)  $s_j(t)$  is non-increasing over time and  $r_j(t)$  is non-decreasing over time for all  $j \in J$

*Proof.* We prove the statements consecutively.

(i) Immediate from  $\frac{ds_j}{dt} + \frac{di_j}{dt} + \frac{dr_j}{dt} = 0$ .

(ii) By item (i) it suffices to prove that  $s_j(t), i_j(t), r_j(t)$  are nonnegative for all  $j \in J$ . Note that the differential equations in (4.1) are continuous. Assume by contradiction that  $s_j(t_2) < 0$  at  $t_2 > 0$ . Due to the continuity of the differential equations there must be a time  $0 < t_1 < t_2$  at which  $s_j(t_1) = 0$ . However, by (4.1) we then have  $\frac{ds_j}{dt} = 0$ , implying that  $s_j(t)$  must then stay 0. We arrive at a contradiction: it is not possible for  $s_j(t)$  to become negative. Analogous we can prove that  $i_j(t)$  is nonnegative, since  $\frac{di_j}{dt} \geq 0$  when  $i_j(t_3) = 0$  for some  $t_3 > 0$ . Finally,  $i_j(t)$  being nonnegative implies that  $r_j(t)$  is non-decreasing and thus  $r_j(t)$  is also nonnegative. We proved the lemma for a single population  $j$ , but the proof applies to all  $j \in J$ .

- (iii) The result follows directly from the differential equations in (4.1) and the non-negativity of  $s_j(t)$  and  $i_j(t)$  for all  $j \in J$  and for any time  $t$  proven in item (ii).

□

**Theorem 4.1.** *Given the initial values  $s_j(0), i_j(0), r_j(0) \in [0, 1]$  such that  $s_j(0) + i_j(0) + r_j(0) = 1$  for all  $j \in J$  the differential equations in (4.1) have a unique solution at any time  $t$ .*

*Proof.* To prove this theorem we will show that the differential equations are Lipschitz continuous: a function  $f(\mathbf{x}) : \mathbb{R}^n \rightarrow \mathbb{R}$  is Lipschitz continuous if and only if there is a bounded nonnegative constant  $K$  and a norm such that:

$$|f(\mathbf{x}_1) - f(\mathbf{x}_2)| \leq K \|\mathbf{x}_1 - \mathbf{x}_2\|$$

We prove Lipschitz continuity for one population, but the proof applies to all populations  $j \in J$ . Denote by  $\mathbf{x} = [s_1(t), \dots, s_n(t), i_1(t), \dots, i_n(t)]$  and define the functions  $f_1(\mathbf{x}) = \frac{ds_j(t)}{dt}$ ,  $f_2(\mathbf{x}) = \frac{di_j(t)}{dt}$ ,  $f_3(\mathbf{x}) = \frac{dr_j(t)}{dt}$ . By Lemma 4.A.1 we have  $0 \leq \mathbf{x} \leq 1$  element wise. We derive the following, using the  $\ell_1$ -norm:

$$\begin{aligned} |f_1(\mathbf{x}_1) - f_1(\mathbf{x}_2)| &= \left| -\sum_{l \in J} \beta_{jl} s_j^1 i_l^1 + \sum_{l \in J} \beta_{jl} s_j^2 i_l^2 \right| \\ &= \left| (s_j^2 - s_j^1) \sum_{l \in J} \beta_{jl} i_l^1 + s_j^2 \sum_{l \in J} \beta_{jl} (i_l^2 - i_l^1) \right| \\ &\leq \sum_{l \in J} \beta_{jl} \left( |(s_j^2 - s_j^1)| + \left| \sum_{l \in J} (i_l^2 - i_l^1) \right| \right) \\ &\leq \sum_{l \in J} \beta_{jl} \|\mathbf{x}_1 - \mathbf{x}_2\|_1 \end{aligned}$$

For  $f_2(\mathbf{x})$  we derive that:

$$\begin{aligned}
 |f_2(\mathbf{x}_1) - f_2(\mathbf{x}_2)| &= \left| \sum_{l \in J} \beta_{jl} s_j^1 i_l^1 - \gamma_j i_j^1 - \sum_{l \in J} \beta_{jl} s_j^2 i_l^2 + \gamma_j i_j^2 \right| \\
 &= \left| (s_j^1 - s_j^2) \sum_{l \in J} \beta_{jl} i_l^1 + s_j^2 \sum_{l \in J: l \neq j} \beta_{jl} (i_l^1 - i_l^2) + (s_j^2 \beta_{jj} - \gamma_j) (i_j^1 - i_j^2) \right| \\
 &\leq \left( \gamma_j + \sum_{l \in J} \beta_{jl} \right) \left( |(s_j^1 - s_j^2)| + \left| \sum_{l \in J: l \neq j} (i_l^1 - i_l^2) \right| + |(i_j^1 - i_j^2)| \right) \\
 &\leq \left( \gamma_j + \sum_{l \in J} \beta_{jl} \right) \|\mathbf{x}_1 - \mathbf{x}_2\|_1
 \end{aligned}$$

Finally, we also conclude that  $f_3(\mathbf{x})$  is Lipschitz continuous:

$$|f_3(\mathbf{x}_1) - f_3(\mathbf{x}_2)| = |\gamma_j i_j^1 - \gamma_j i_j^2| \leq \gamma_j \|\mathbf{x}_1 - \mathbf{x}_2\|_1$$

Given the initial value and the Lipschitz continuous differential equations, we can apply the Picard-Lindelöf Theorem (Lindelöf 1894). This theorem states that there is a unique solution to the differential equations for any point in time, which completes the proof.  $\square$

#### 4.A.2 The herd effect

In this chapter, we make extensive use of the herd effect, which is implicitly defined in (4.3). We will shortly explain in this section how (4.3) can be derived. Based on the differential equations in (4.1) we can derive the following relation by inserting the expression for  $\frac{dr_l}{dt}$  into the expression for  $\frac{ds_j}{dt}$ :

$$s_j(t) = s_j(0) \exp \left\{ - \sum_{l \in J} \frac{\beta_{jl}}{\gamma_l} [r_l(t) - r_l(0)] \right\}$$

Considering that  $s_j(t) + i_j(t) + r_j(t) = 1$  for all  $t$  and for all  $j \in J$  and denoting by  $\sigma_j = \frac{\beta_{jj}}{\gamma_j}$ :

$$\begin{aligned} s_j(t) &= s_j(0) \exp \left\{ - \sum_{l \in J} \frac{\beta_{jl}}{\gamma_l} [s_l(0) + i_l(0) - s_l(t) - i_l(t)] \right\} \\ i_j(t) &= -s_j(t) + \frac{1}{\sigma_j} \log(s_j(t)) + s_j(0) + i_j(0) - \frac{1}{\sigma_j} \log(s_j(0)) \\ &\quad + \frac{1}{\sigma_j} \sum_{l \in J: l \neq j} \frac{\beta_{jl}}{\gamma_l} [s_l(0) + i_l(0) - s_l(t) - i_l(t)] \end{aligned}$$

Equation (4.A.2) holds for every  $t$ , so also for  $t \rightarrow +\infty$ . By the definition in (4.2) we have that  $G_j(\mathbf{f}) = \lim_{t \rightarrow +\infty} s_j(t)$  for all  $j \in J$ . We also know that  $i_j(+\infty) = 0$  for all  $j \in J$ . Inserting the expressions for  $t \rightarrow +\infty$  results in the implicit herd effect definition in (4.3).

**Lemma 4.10.** *For all  $j \in J$  the following holds:*

- (i)  $0 \leq G_j(\mathbf{f}) \leq \min \left\{ (1 - f_j), \frac{1}{\sigma_j} \right\}$
- (ii)  $G_j(\mathbf{f}) = 0$  if and only if  $f_j = 1$ .

*Proof.* We can rewrite (4.3) using the Lambert W function (cf. Corless et al. 1996, Ma and Earn 2006):

$$G_j(\mathbf{f}) = \frac{-1}{\sigma_j} W \left[ -\sigma_j (1 - f_j) \exp \left\{ -\sigma_j \left( (1 - f_j) + \frac{1}{\sigma_j} \sum_{l \in J: l \neq j} \frac{\beta_{jl}}{\gamma_l} [1 - f_l - G_l(\mathbf{f})] \right) \right\} \right]$$

Denote by  $B_j(\mathbf{f})$  the following function, such that  $G_j(\mathbf{f}) = \frac{-1}{\sigma_j} W [B_j(\mathbf{f})]$ :

$$B_j(\mathbf{f}) = -\sigma_j (1 - f_j) \exp \left\{ -\sigma_j \left( (1 - f_j) + \frac{1}{\sigma_j} \sum_{l \in J: l \neq j} \frac{\beta_{jl}}{\gamma_l} [1 - f_l - G_l(\mathbf{f})] \right) \right\}$$

Note that  $\sigma_j > 0$  for all  $j \in J$  by Assumption 4.2. By definition of the Lambert W function  $W(0) = 0$  and  $W(x) \in [-1, 0)$  for  $x \in [-\frac{1}{e}, 0)$ . To complete the proof of this lemma, it therefore suffices to show that  $B_j(\mathbf{f}) \in [-\frac{1}{e}, 0]$  and  $B_j(\mathbf{f}) = 0$  if and only if  $f_j = 1$ . From the nonnegativity of the exponential function, it follows directly that  $B_j(\mathbf{f}) \leq 0$  and  $B_j(\mathbf{f}) = 0$  if and only if  $f_j = 1$ . Using that  $G_j(\mathbf{f}) \leq (1 - f_j)$  and that

the function  $f(y) = \frac{-y}{e^y}$  is minimized for  $y = 1$ , the following holds:

$$\begin{aligned} B_j(\mathbf{f}) &= -\sigma_j(1 - f_j) \exp \left\{ -\sigma_j \left( (1 - f_j) + \frac{1}{\sigma_j} \sum_{l \in J: l \neq j} \frac{\beta_{jl}}{\gamma_l} [1 - f_l - G_l(\mathbf{f})] \right) \right\} \\ &\geq -\sigma_j(1 - f_j) \exp \{-\sigma_j(1 - f_j)\} \geq \frac{-1}{e} \end{aligned}$$

We showed that  $0 \leq G_j(\mathbf{f}) \leq \frac{1}{\sigma_j}$  and that  $G_j(\mathbf{f}) = 0$  if and only if  $f_j = 1$ . By Lemma 4.4 we also know that  $G_j(\mathbf{f}) \leq (1 - f_j)$ , which completes the proof of this lemma.  $\square$

## 4.B Theoretical results on $R_f$

**Lemma 4.B.1.** *The largest eigenvalue of a matrix  $A$ , denoted by  $\rho(A)$ , is a continuous function of  $A$ .*

*Proof.* The eigenvalues of a matrix  $A$  are equal to the roots of the characteristic polynomial of  $A$ . By Naulin and Pabst (1994) the roots of a polynomial depend continuously on the coefficients of the polynomial. That implies that the eigenvalues of  $A$  are continuous in the matrix  $A$ . Let  $A$  be a  $n \times n$  matrix. Denote by  $\mathbf{a}$  and  $\mathbf{b}$  the vectors with elements  $a_i$  and  $b_i$  for  $i = 1, \dots, n$ , i.e., the vectors with the eigenvalues of the matrices  $A$  and  $B$  respectively. This implies that  $\rho(A) = \max_i |a_i|$  and  $\rho(B) = \max_i |b_i|$ . For every  $i$  the following holds:

$$\begin{aligned} |a_i| &\leq |b_i| + |a_i - b_i| && \text{by the triangle inequality} \\ &\leq \rho(B) + \|a - b\|_\infty \end{aligned}$$

This implies that  $\rho(A) \leq \rho(B) + \|a - b\|_\infty$  and by symmetry also  $\rho(B) \leq \rho(A) + \|a - b\|_\infty$ . Thus,  $|\rho(A) - \rho(B)| \leq \|a - b\|_\infty$ , meaning that the largest eigenvalue of a matrix continuously depends on the eigenvalues. Since the eigenvalues are continuously dependent on the matrix, the largest eigenvalue is a continuous function of the matrix. This completes the proof of this lemma.  $\square$

The largest eigenvalue of a matrix can be defined with Gelfand's formula, which holds for any norm:

$$\rho(A) = \lim_{k \rightarrow +\infty} \|A^k\|^{\frac{1}{k}} \quad (4.31)$$

Using Gelfand's formula we derive the following result:

**Corollary 4.B.2.** *Let  $A$  and  $B$  be two nonnegative matrices with  $A \leq B$  element wise. If the inequality between  $A$  and  $B$  is strict for at least one element, then  $\rho(A) < \rho(B)$ . Otherwise,  $\rho(A) \leq \rho(B)$ .*

*Proof.* This proof is based on Meyer (2000) (Example 7.10.2). The Frobenius norm is defined as follows:

$$\|A\|_F = \sqrt{\sum_i \sum_j |a_{ij}|^2}$$

Note that the following holds:

$$A \leq B \Rightarrow A^k \leq B^k \Rightarrow \|A^k\|_F \leq \|B^k\|_F$$

The proof can easily be completed using (4.31):

$$\|A^k\|_F \leq \|B^k\|_F \Rightarrow \|A^k\|_F^{\frac{1}{k}} \leq \|B^k\|_F^{\frac{1}{k}} \Rightarrow \lim_{k \rightarrow +\infty} \|A^k\|_F^{\frac{1}{k}} \leq \lim_{k \rightarrow +\infty} \|B^k\|_F^{\frac{1}{k}}$$

Above result implies that  $\rho(A) \leq \rho(B)$ . Using the Frobenius norm we establish that  $\|A^k\|_F < \|B^k\|_F$  when  $A$  is strictly smaller than  $B$  for at least one element. In that case we thus have  $\rho(A) < \rho(B)$ . This completes the proof.  $\square$

From Corollary 4.B.2 we can derive the following result:

**Lemma 4.B.3.** *Let  $\mathbf{f}^i$  denote a vector of vaccination fractions with corresponding reproduction ratio  $R_f(\mathbf{f}^i)$  for  $i = 1, 2$ . If  $\mathbf{f}^2 \geq \mathbf{f}^1$  for all elements and  $\mathbf{f}^1 \neq \mathbf{f}^2$ , then  $R_f(\mathbf{f}^2) < R_f(\mathbf{f}^1)$ .*

*Proof.* Denote by  $\mathbf{F}_1$  and  $\mathbf{F}_2$  the matrices with on the diagonal respectively the elements of  $(1 - \mathbf{f}^1)$  and  $(1 - \mathbf{f}^2)$ . It holds that  $R_f(\mathbf{f}^2) = \rho(\mathbf{F}_2 B \gamma)$  and  $R_f(\mathbf{f}^1) = \rho(\mathbf{F}_1 B \gamma)$ . We also have that  $\mathbf{F}_2 \leq \mathbf{F}_1$  with at least one element strict, because  $\mathbf{f}^1 \neq \mathbf{f}^2$ . We can apply Corollary 4.B.2:

$$R_f(\mathbf{f}^2) = \rho(\mathbf{F}_2 B \gamma) < \rho(\mathbf{F}_1 B \gamma) = R_f(\mathbf{f}^1)$$

$\square$

**Lemma 4.B.4.**  $R_e(t)$  is continuous in  $t$ .

*Proof.* In Lemma 4.B.1 we show that the largest eigenvalue of a matrix  $A$ , denoted by  $\rho(A)$ , is a continuous function of  $A$ . From the differential equations (4.1) we conclude that  $s_j(t)$  is a continuous function for all  $j \in J$ . By Definition 4.1 this implies that  $R_e(t)$  is continuous in  $t$ , which completes the proof.  $\square$

**Corollary 4.B.5.**  $R_e(t)$  is monotonically non-increasing in  $t$ , i.e.,  $R_e(t+\epsilon) \leq R_e(t)$  for any  $\delta > 0$ .

*Proof.* By Lemma 4.A.1  $s_j(t)$  is non-increasing and thus  $\mathbf{S}(t+\delta) \leq \mathbf{S}(t)$ . By Corollary 4.B.2 this implies:  $R_e(t+\delta) = \rho(\mathbf{S}(t+\delta)\mathbf{B}\gamma) \leq \rho(\mathbf{S}(t)\mathbf{B}\gamma) = R_e(t)$ .  $\square$

**Lemma 4.B.6.** If  $R_f > 1$  then  $\lim_{t \rightarrow +\infty} R_e(t) < 1$ . [Theorem 2 in Chan (2013)]

## 4.C Optimization problems

**Lemma 4.11.** For any solution to Problem (4.25) - (4.29) we have  $f_i \geq 1 - \frac{\gamma_i}{\beta_{ii}}$ .

*Proof.* Let  $k \in \arg \min_{j \in J \setminus \{i\}} \left\{ \frac{\beta_{ij}}{\gamma_j} \right\}$ . We derive the following relation for  $f_i$  using (4.26) - (4.28):

$$f_i = 1 - \frac{v_i}{\sum_{j \in J} \frac{\beta_{ij}}{\gamma_j} v_j} \geq 1 - \frac{v_i}{\frac{\beta_{ik}}{\gamma_k}(1 - v_i) + \frac{\beta_{ii}}{\gamma_i} v_i}$$

To derive a lower bound on  $f_i$  we maximize above expression with respect to  $v_i$ :

$$\frac{d}{dv_i} \left[ 1 - \frac{v_i}{\frac{\beta_{ik}}{\gamma_k}(1 - v_i) + \frac{\beta_{ii}}{\gamma_i} v_i} \right] = \frac{\frac{\beta_{ik}}{\gamma_k}}{\left[ \frac{\beta_{ik}}{\gamma_k}(1 - v_i) + \frac{\beta_{ii}}{\gamma_i} v_i \right]^2} \geq 0$$

By Assumption 4.2 the derivative is nonnegative and the expression is thus maximized for  $v_i = 1$ . This proves the lower bound on  $f_i$ :  $f_i \geq 1 - \frac{\gamma_i}{\beta_{ii}}$ .  $\square$

**Lemma 4.12.** The feasible region of Problem (4.25) - (4.29) is not convex.

*Proof.* It suffices to give a counter example. Consider the case that  $|J| = 2$  and define the matrix  $B\gamma$  and the variable vector  $\mathbf{x}$ :

$$B\gamma = \begin{bmatrix} 1 & 3 \\ 3 & 1 \end{bmatrix} \quad \mathbf{x} = [(1 - f_1), (1 - f_2), v_1, v_2]$$



One can easily check that the following two vectors are feasible with respect to constraints (4.26) - (4.29):  $\mathbf{x}_1 = [0.25 \ 0.25 \ 0.5 \ 0.5]$  and  $\mathbf{x}_2 = [0.1 \ 0.5 \ 0.25 \ 0.75]$ . Take the convex combination  $\mathbf{x}_3 = \alpha \mathbf{x}_1 + (1 - \alpha) \mathbf{x}_2$  with  $\alpha = 0.5$ , that results in  $\mathbf{x}_3 = [0.175 \ 0.375 \ 0.375 \ 0.675]$ . Constraints (4.27) - (4.29) are clearly satisfied by  $\mathbf{x}_3$ . However,  $\mathbf{x}_3$  is not feasible with respect to constraint (4.26) nor to the relaxation in (4.30):

$$0.175 \times [1 \times 0.375 + 3 \times 0.675] \approx 0.3937 > 0.375$$

$$0.375 \times [3 \times 0.375 + 1 \times 0.675] \approx 0.6563 \neq 0.675$$

This completes the proof.  $\square$

## 4.D Vaccine efficacy

In this chapter, we assumed that a vaccine is completely effective and leads to complete immunity. In literature this assumption is often relaxed by including a vaccine efficacy parameter (cf. Hill and Longini Jr 2003). In this section, we study the effects of such a relaxation. Let  $\psi_j$  denote the vaccine efficacy rate in population  $j$ . Vaccination then implies a shift from state  $(s_j(0) = 1, i_j(0) = 0, r_j(0) = 0)$  to state  $((1 - \psi_j f_j), 0, \psi_j f_j)$  for all  $j \in J$ . Introducing a vaccine efficacy parameter is simply a rescaling of the vaccination fraction  $f_j$ . However, this rescaling has consequences for the equivalence of the two optimization problems defined in Section 4.4.2. As a result of reduced vaccine efficacy, the number of allocated vaccines is no longer equal to the number of effective vaccines. The total herd effect attained when  $R_f = 1$  is now equal to  $\sum_{j \in J} N_j (1 - \psi_j f_j)$ , whereas the number of allocated vaccines still equals  $\sum_{j \in J} N_j f_j$ . Thus, the last implication in the proof of Theorem 4.4 no longer holds. Only for the special case that  $\psi_j = \psi$  for all  $j \in J$  the equivalence still holds.

Without equivalence the two problems can still be solved with the solution approach of Section 4.5.3. The quadratic equality constraint in (4.26) can be reformulated as follows:

$$(1 - \psi_i f_i) \sum_{j \in J} \frac{\beta_{ij}}{\gamma_j} v_j = v_i \Leftrightarrow f_i = \frac{1}{\psi_i} \left[ 1 - \frac{v_i}{\sum_{j \in J} \frac{\beta_{ij}}{\gamma_j} v_j} \right] \quad i \in J \quad (4.32)$$

The objective function and the other constraints of Problem (4.25) - (4.29) remain valid for the problem of minimizing the required amount of vaccines to achieve  $R_f = 1$ . For maximizing the herd effect the objective function must be changed to  $\max \sum_{j \in J} (1 - \psi_j f_j) N_j$ .

## 4.E Proof for $n = 2$

**Theorem 4.5.** *The optimal solution to Problem (4.21) - (4.24) can be found among the boundary solutions given in Lemma 4.7 and the following solution:*

$$f_1 = 1 - \frac{1}{\sigma_1} \left[ \frac{1 - \sqrt{\frac{c\sigma_1 N_2}{\sigma_2 N_1}}}{1 - c} \right] \quad \text{and} \quad f_2 = 1 - \frac{1}{\sigma_2} \left[ \frac{1 - \sqrt{\frac{c\sigma_2 N_1}{\sigma_1 N_2}}}{1 - c} \right]$$

For  $c \geq 1$  only the boundary solutions need to be considered.

*Proof.* By (4.20) we rewrite the objective function of Problem (4.21) - (4.24) into:

$$O(f_1) = N_1(1 - f_1) + N_2 \left[ \frac{1 - \sigma_1(1 - f_1)}{\sigma_2[1 - \sigma_1(1 - c)(1 - f_1)]} \right]$$

We analyze the extrema of this function by setting the derivative of  $O(f_1)$  with respect to  $f_1$  equal to 0:

$$\begin{aligned} \frac{d}{df_1} O(f_1) &= -N_1 + \frac{c\sigma_1 N_2}{\sigma_2[1 - \sigma_1(1 - c)(1 - f_1)]^2} = 0 \\ \Leftrightarrow [1 - \sigma_1(1 - c)(1 - f_1)]^2 &= \frac{c\sigma_1 N_2}{\sigma_2 N_1} \\ \Leftrightarrow f_1 &= 1 - \frac{1}{\sigma_1} \left[ \frac{1 - \sqrt{\frac{c\sigma_1 N_2}{\sigma_2 N_1}}}{1 - c} \right] \end{aligned}$$

In the third step we use (4.23). The objective function  $O(f_1)$  thus has a unique extreme:

$$f_1 = 1 - \frac{1}{\sigma_1} \left[ \frac{1 - \sqrt{\frac{c\sigma_1 N_2}{\sigma_2 N_1}}}{1 - c} \right] \quad \text{and} \quad f_2 = 1 - \frac{1}{\sigma_2} \left[ \frac{1 - \sqrt{\frac{c\sigma_2 N_1}{\sigma_1 N_2}}}{1 - c} \right] \quad (4.33)$$

where  $f_2$  is derived by substituting the expression for  $f_1$  in (4.20). To verify whether this extreme is a minimum or a maximum, we analyze the second order derivative of  $O(f_1)$ :

$$\frac{d^2}{d(f_1)^2}O(f_1) = \frac{-2\sigma_1^2 c(1-c)N_2}{\sigma_2[1 - \sigma_1(1-c)(1-f_1)]^3}$$

Note that the denominator is positive by constraint (4.23). We distinguish between the following three cases: (a)  $c = 1$ , (b)  $c > 1$  and (c)  $c < 1$ . In case (a) the function  $O(f_1)$  is linear. For case (b) the second order derivative is positive, implying that the extreme in (4.33) is a minimum. For both case (a) and (b) the function  $O(f_1)$  is thus maximized in one of the boundary points. In case (c) the second order derivative is positive.

Thus, for  $c \geq 1$  the optimal solution can be found among the two boundary solutions that are feasible according to Lemma 4.7. For  $c < 1$  the solution in (4.33) is a candidate for the optimal solution. However, this candidate possibly results in  $f_1, f_2$  that violate constraints (4.23) or (4.24), rendering the candidate solution infeasible. Therefore, also the feasible boundary solutions must be compared. This completes the proof of this theorem.  $\square$



## Chapter 5

# The benefits of combining early aspecific vaccination with later specific vaccination<sup>1</sup>

### 5.1 Introduction

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

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<sup>1</sup>This chapter is based on Duijzer et al. (2017a).

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

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

In this chapter, we synthesize these different decision problems and formulate a general problem that encapsulates all three examples. We formulate this general

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

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

Our main contribution in this chapter is formally proposing and analyzing such hybrid strategies. We characterize the areas in the parameter space where either of the two pure strategies or the hybrid strategy is optimal. We prove that there is an area around the switching curve where hybrid strategies are superior to pure strategies. We argue that this is due to the nonlinear dynamics of an epidemic: By using both vaccine types the early vaccine can be used to reduce the initial growth in infections, while the better vaccine is used to control the epidemic. Our numerical results show that a hybrid strategy can reduce the number of infections by more than 50% compared to the best pure strategy. We note that, because our formulation generalizes examples 1-3 above, our analysis of hybrid strategies contributes to three streams of literature (see Section 5.2).

In this chapter, we focus on the most interesting case of hybrid strategies, namely those with two vaccine types. Our numerical results show that this choice is not

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

The remainder of the chapter is structured as follows. We start with a literature review in Section 5.2. In Section 5.3, we formally define the vaccination problem. This problem is analyzed in Section 5.4: we compare the two vaccine types and analyze hybrid strategies. In Section 5.5, we derive our numerical results. We close with a discussion and conclusions in Sections 5.6 and 5.7.

## 5.2 Literature

Extant literature considers the trade-off between timing of vaccination and vaccine efficacy in three separate practical settings. We now first discuss literature in the setting of the annual influenza vaccine, then literature on the effects of timing of vaccination and finally literature on the number of doses to use. Timing of vaccination is part of a much broader stream of literature on vaccine logistics. An overview can be found in Chapter 2.

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

Wu et al. (2005) discuss the ‘follow policy’, where the forecasted epidemic strain is included in the annual vaccine. The authors investigate whether this policy can be improved by including information on the strains to which the individual has been exposed in the past. The results show that the follow policy is only slightly suboptimal and is therefore recommended to be continued. Kornish and Keeney (2008) study when it is beneficial to defer the decision on the vaccine composition in order to buy time to gather more information about the coming influenza season. Deferring reduces uncertainty and could lead to better decisions on which strains to include



in the vaccine. However, waiting too long reduces the available time for production, potentially leading to higher production costs. The authors assume that they can estimate the number of cases during the outbreak, based on the information at the current time. The authors formulate a commit-or-defer model and derive conditions on the optimal decision using dynamic programming. When discussing their model assumptions, the authors mention the disadvantage of waiting with production while gathering information on one of the strains that are included in the vaccine. They suggest a solution in which production of the other strains could start earlier and the new strain is only added to the vaccines subsequently produced. This solution can be seen as some kind of hybrid strategy, but the strategy is not formally analyzed by the authors.

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

**Timing of vaccination** The second example of a trade-off between timing and efficacy is the selection among multiple vaccine types with different delivery times. Matrajt and Longini Jr (2010) study a related problem and compare multiple moments of vaccination and different available stockpiles. Their results show how the vaccine stockpile size and the moment at which this stockpile becomes available af-

fect the optimal allocation over the different age groups and risk-groups. A similar setting is studied by Matrajt et al. (2013), who focus on a network of cities connected by an airline network instead of a single population. Motivated by practical considerations, they shortly discuss the case of vaccines that arrive in two batches, with fixed amounts of vaccines per batch. This is a form of hybrid strategy and results show that the optimal allocation almost coincides with the pro rata allocation over children in the different cities. Yarmand et al. (2014) study a two-phase allocation problem with minimum required vaccination levels in each phase, where the required level for a region in the second phase only applies if the epidemic in that region is not yet contained after phase 1. They formulate a stochastic programming problem and show how the optimal allocation depends on the minimum required levels. Nguyen and Carlson (2016) compare different vaccination strategies which differ in when and how much vaccines become available. Deterministic and stochastic models are used and the optimal allocation for two coupled populations is determined numerically. All vaccines are assumed to be available at one time. The authors present contour plots that indicate which combinations of the vaccination fraction and the timing of vaccination result in the same final size. We extend this work by analytically describing the shape of these contour curves as well as by analyzing hybrid strategies where people can be vaccinated at multiple moments in time.

**Optimal vaccine dosage** There are some studies on determining the optimal dose for vaccines against pandemic influenza. Riley et al. (2007) show that a lower vaccine dose may be preferred, because it increases coverage levels. Similar results are found by Wood et al. (2009), who find that the lowest dose results in the smallest attack rate. Matrajt et al. (2015) compare the effects of a one-dose and a two-dose strategy for influenza vaccination and use a more analytical approach. The authors prove that there is a threshold in the level of protection that is obtained after the first dose below which the two-dose strategy is the best. For pre-pandemic vaccination this threshold can analytically be characterized and for reactive vaccination numerical and simulation results are found. Our results contribute to this literature in two ways: we derive an analytical approach that also holds for the reactive case, but more importantly we propose hybrid strategies and show their benefits. These hybrid strategies translate to some people receiving one dose and others receiving two doses. Riley et al. (2007) briefly mention the possibility to give health care workers a higher

dosage than the remainder of the population, but this strategy is not analyzed. This strategy can be seen as a hybrid strategy which is advocated in this chapter.

**Model** We now relate our modelling choices to current literature. We make use of the *SIR* model, which is a seminal model in epidemiology proposed by Kermack and McKendrick (1927). As our problem incorporates the effect of timing of vaccination, we allow for vaccination during an outbreak (see also Meyers et al. 2009, Chowell et al. 2009, Matrajt and Longini Jr 2010, Tuite et al. 2010). Alternatively, there are studies that focus on pre-pandemic vaccination, assuming that all vaccines are available prior to the outbreak (e.g. Wu et al. 2007, Keeling and Shattock 2012, Duijzer et al. 2016). To evaluate the effects of different vaccination strategies we focus on minimizing the *final size*, i.e., the proportion of people infected during the outbreak (e.g., Wu et al. 2007, Wang et al. 2009, Keeling and Shattock 2012, Lee et al. 2015b). An alternative performance criterion is the reproduction ratio  $R$ , which is related to the initial growth of infections (Diekmann et al. 2013). There are studies that focus on minimizing the reproduction ratio (Goldstein et al. 2009, Wallinga et al. 2010) or on reaching a certain threshold value of the reproduction ratio (e.g., Tanner et al. 2008, Gittings and Matson 2016). The reproduction ratio differs from the final size by focusing on the short term, whereas the final size takes into account the entire time course of the epidemic. However, in Chapter 4 we show that under certain conditions optimization problems involving these two performance criteria are equivalent.

## 5.3 Problem formulation

We evaluate the effects of different vaccination strategies and make use of the deterministic *SIR* model to model the time course of the epidemic. This model is explained in Section 5.3.1. In Section 5.3.2, we describe the effect of vaccination on the epidemic and the considered decision problem. We formalize this in Section 5.3.3. In Section 5.3.4, we formulate the optimization problem that is studied in this chapter.

### 5.3.1 The *SIR* model

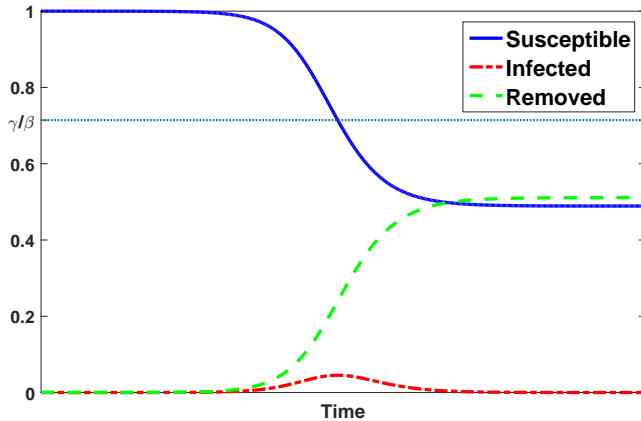
The *SIR* model is a seminal model in epidemiology proposed by Kermack and McKendrick (1927). The population is divided into three compartments for which the time course is tracked (cf. Hethcote 2000). Let  $s(t)$ ,  $i(t)$  and  $r(t)$  be the fractions of the population respectively susceptible, infected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

$$\begin{aligned}\frac{ds}{dt} &= -\beta si \\ \frac{di}{dt} &= \beta si - \gamma i \\ \frac{dr}{dt} &= \gamma i\end{aligned}\tag{5.1}$$

We assume that boundary conditions  $s(0) = s_0$ ,  $i(0) = i_0$  and  $r(0) = r_0$  are given, with  $i_0 > 0$  and  $s_0 + i_0 + r_0 = 1$ . Figure 5.1 illustrates the time course for an epidemic that evolves according to the *SIR* model. This figure is made using the Runge-Kutta method (Greenbaum and Chartier 2012). The figure shows that not everybody gets infected during the outbreak. Around 50% of the population is still susceptible when the epidemic has died out, so they have escaped infection. We also observe in the figure that the fraction of infected individuals initially increases until it reaches a certain peak value. After the peak, the epidemic starts to die out. From the differential equations we can derive that this peak occurs when  $s(t) = \frac{\gamma}{\beta}$ . We therefore refer to an epidemic being controlled when  $s(t)$  is below the threshold  $\frac{\gamma}{\beta}$ . Although the number of infected people in a controlled epidemic can still be substantial, there are more recoveries than new infections per time unit so that the proportion of infected people is decreasing.

### 5.3.2 Problem description

Vaccination reduces the fraction of susceptible individuals, in order to control the epidemic at an earlier point in time and to avoid or reduce an increase in the fraction



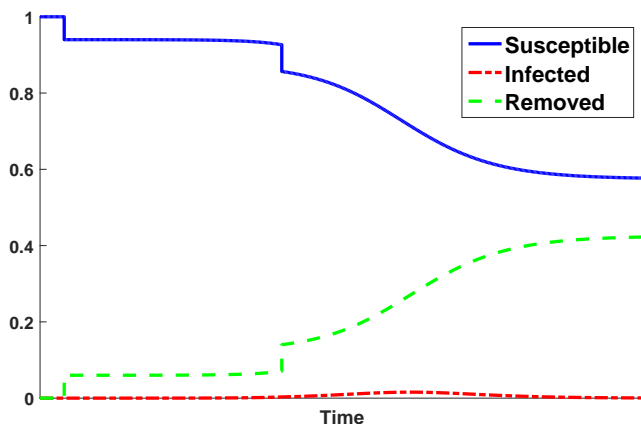
**Figure 5.1:** Illustration of the deterministic *SIR* model with parameters  $\gamma = 0.25$ ,  $\beta = 0.35$ ,  $i_0 = 10^{-6}$  and  $s_0 = 1 - i_0$ .

of infected individuals. The effect of vaccination is twofold. The people who directly benefit from vaccination are the vaccinees, because they acquire (partial) immunity due to vaccination. Indirectly also unvaccinated people benefit from the vaccination of others, as it reduces their disease exposure. This indirect effect of vaccination is known as the *herd effect* (Fine 1993).

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

The effect of vaccination on the epidemic is illustrated in Figure 5.2. In this figure we consider a population of  $10^6$  individuals where 150 000 people are vaccinated at time 10 with a vaccine that has efficacy 0.4 and another 100 000 people are vaccinated at time 100 with a vaccine that has efficacy 0.7. This means that effectively  $150\,000 \times$

$0.4 + 100\,000 \times 0.7 = 130\,000$  people have become immune through vaccination. If we compare Figure 5.1 and Figure 5.2, we see that vaccination lowers the peak in infected individuals. In addition, more people have escaped infection when vaccination is used: the proportion of people still susceptible when the epidemic has died out (i.e., the herd effect) has increased from 50% to almost 60%.



**Figure 5.2:** Illustration of vaccination in the deterministic *SIR* model with vaccination, with parameters as in Figure 5.1.

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

### 5.3.3 Vaccination

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

We also assume that vaccination takes no time, meaning that vaccination results in immunity immediately. We refer to Section 5.6 for a discussion of these assumptions. Under our assumptions vaccination causes a shift at time  $\tau_j$  from state  $(s(\tau_j), i(\tau_j))$  to state  $(s(\tau_j) - f_j, i(\tau_j))$ . This implies that  $r(\tau_j)$  shifts to  $r(\tau_j) + f_j$ . This is a common way of modelling vaccination (e.g., Hill and Longini Jr 2003, Bansal et al. 2006, Mylius et al. 2008).

To compare different vaccination strategies we consider the state of the system when  $t \rightarrow \infty$ . This state is also referred to as ‘disease-free equilibrium’, because  $\lim_{t \rightarrow \infty} i(t) = 0$  which can be derived from the differential equations (5.1). For notational convenience, we define  $\mathbf{f} = (f_1, \dots, f_n)$  and  $\tau = (\tau_1, \dots, \tau_n)$ . Let  $G(\mathbf{f}, \tau)$  denote the final fraction of people susceptible in the disease-free equilibrium. More precisely, for  $f_j \in [0, \phi_j s(\tau_j)]$  and for all  $j \in J$

$$G(\mathbf{f}, \tau) = \lim_{t \rightarrow \infty} s(t), \quad (5.2)$$

with  $s(t)$  evolving according to (5.1) in between two consecutive vaccination moments and after the last vaccination moment. We determine  $G(\mathbf{f}, \tau)$  with an implicit relation called the *final size equation*, details are in Appendix 5.A.  $G(\mathbf{f}, \tau)$  quantifies the so-called *herd effect*, which is the indirect effect of vaccination where unvaccinated people benefit from the vaccination of others. We refer to Chapter 3 for a more extensive analysis of the herd effect and the function  $G(\mathbf{f}, \tau)$  for a single vaccination moment. In the remainder of this chapter we focus on the *final size*, i.e., the proportion of the population that has been infected during the outbreak. The final size is denoted by  $Z(\mathbf{f}, \tau)$  and can be calculated as follows:

$$Z(\mathbf{f}, \tau) = s_0 - G(\mathbf{f}, \tau) - \sum_{j \in J} f_j + i_0 \quad (5.3)$$

Observe that the part  $s_0 - G(\mathbf{f}, \tau)$  in above equation determines the proportion of people who were susceptible at the beginning of the outbreak, but are no longer susceptible at the end. These people have either become infected or have become immune because of vaccination. By correcting for those that are vaccinated ( $\sum_{j \in J} f_j$ ), we remain with the number of infections during the outbreak. We add the initial infections ( $i_0$ ) to determine the final size of the outbreak. For a more detailed discussion of modelling vaccination in the *SIR* model we refer to Chapter 3.

### 5.3.4 Optimization problem

In this section, we formally define our decision problem. Recall that we consider a decision maker with a total budget  $B$  to spend on the vaccine types in  $J$  in order to minimize the final size of the outbreak. Using the notation that is introduced in Section 5.3.3, the optimization problem can be formulated as follows:

$$\begin{aligned}
 \min \quad & Z(\mathbf{f}, \tau) \\
 \text{s.t.} \quad & N \sum_{j \in J} \frac{f_j}{\varphi_j} \leq B \\
 & f_j \geq 0 \quad \forall j \in J
 \end{aligned} \tag{5.4}$$

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

## 5.4 Analytical results

In this section, we study Problem (5.4) and compare different vaccination strategies. In Section 5.4.1, we start with showing that a hybrid vaccination strategy can equivalently be summarized as a vaccination strategy with a single vaccination moment. The characterization of this single moment strategy enables us to analyze hybrid strategies in the following sections. In Section 5.4.2, we focus on comparing two vaccination strategies. We analyze pure strategies in which the entire budget is spent on one vaccine type, and we consider hybrid strategies where the budget is divided over the two vaccine types. Section 5.4.3 is dedicated to the analysis of two vaccine types that arrive in batches, such that vaccination does not take place at a single moment, but during a vaccination campaign.

### 5.4.1 Characterizing hybrid vaccination strategies

Hybrid vaccination strategies are difficult to compare, because they differ both in the times at which people are vaccinated and in the proportion of the population vaccinated at those times. To simplify the comparison, we show how to construct for each hybrid strategy a single moment strategy, *such* that the hybrid strategy and



the single moment strategy have the same final size. Note that this single moment strategy differs from the pure strategies described earlier, because the vaccination moment for the single moment strategy need not, and typically is not, one of the moments at which vaccination is possible for the hybrid strategy.

The formal result is presented in the following theorem. The proof can be found in Appendix 5.B. In this theorem  $s_{(i)}(t)$  and  $s_{(ii)}(t)$  respectively denote the proportion of people susceptible at time  $t$  in the hybrid strategy (i) and the single moment strategy (ii).

**Theorem 5.1.** *We consider an initial state denoted by  $(s_0, i_0)$  and use the SIR model to evaluate the epidemic. A hybrid vaccination strategy (i) with  $n$  vaccination moments at times  $\tau_1, \dots, \tau_n$  and corresponding vaccination fractions  $f_1, \dots, f_n$  results in the same final size as a single moment vaccination strategy (ii) with one vaccination moment at time  $\tau^T$  and a vaccination fraction  $f^T = \sum_{j=1}^n f_j$  if and only if  $\tau^T$  satisfies the following condition:*

$$1 - \frac{f^T}{s_{(ii)}(\tau^T)} = \prod_{j \in J} \left( 1 - \frac{f_j}{s_{(i)}(\tau_j)} \right) \quad (5.5)$$

*There is always exactly one  $\tau^T \in [\tau_1, \tau_n]$  satisfying (5.5).*

The interpretation of Theorem 5.1 is as follows. Effectively vaccinating a certain number of people divided over  $n$  moments in the time interval  $[\tau_1, \tau_n]$  results in the same final size as effectively vaccinating this same number of people at once at some time  $\tau^T$ . Although the existence of  $\tau^T$  may be intuitive, its characterization in (5.5) is not trivial. The contribution of Theorem 5.1 is therefore that we characterize the single moment vaccination strategy: we describe the vaccination fraction and the time at which vaccination should take place.

The condition (5.5) that characterizes  $s_{(ii)}(\tau^T)$  has the following interpretation. Upon vaccination at time  $\tau_j$  in strategy (i) the susceptible population reduces from  $s_{(i)}(\tau_j)$  to  $s_{(i)}(\tau_j) - f_j = s_{(i)}(\tau_j) \left( 1 - \frac{f_j}{s_{(i)}(\tau_j)} \right)$ , i.e.,  $s_{(i)}(\tau_j)$  is multiplied with the factor  $\left( 1 - \frac{f_j}{s_{(i)}(\tau_j)} \right)$ . The time  $\tau^T$  is *such* that multiplying  $s_{(ii)}(\tau^T)$  with the product of all these factors for  $j = 1, \dots, n$  results in a reduction of  $f^T$ . The characterization of  $\tau^T$  allows us to compare different hybrid strategies with each other and with pure strategies. To compute the actual value for  $\tau^T$ , we numerically evaluate of the

differential equations in (5.1) to determine at which time the proportion of susceptible people equals  $s_{(ii)}(\tau^T)$ .

In Appendix 5.C, we show that the result of Theorem 5.1 also holds for a more general epidemic model, namely the  $SI^nR$  model with  $n$  consecutive infectious stages. The  $SI^nR$  model can also take into account a latent period or multiple levels of infectivity. Since the characterization of  $s(\tau^T)$  in Theorem 5.1 underlies the other results in this chapter, we conjecture that these results also extend to this more general epidemic model. If this conjecture is true, our choice for the simple  $SIR$  model is not restrictive.

### 5.4.2 Comparison of vaccination strategies

In this section, we focus on comparing vaccination strategies in which two vaccine types can be used, i.e.,  $|J| = 2$ . Consider a policy maker that has a certain budget available to spend on these two vaccine types. We start with considering strategies in which all budget is spent on one vaccine type. We refer to these vaccination strategies as ‘pure strategies’. Next, we extend these results to hybrid strategies in which the budget may be divided over the two types.

#### Pure strategies

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

If the vaccines of type 2 are available very early, i.e., just after  $\tau_1$ , hardly any new infections will occur in the interval  $[\tau_1, \tau_2]$ . The higher efficacy per dollar of type 2 outweighs the delayed availability, because it allows to effectively vaccinate more people and possibly even to control the epidemic directly at  $\tau_2$ . On the other hand, if the vaccines of type 2 are available when the epidemic is already declining, they are of little use. In a declining epidemic the risk of becoming infected is low and you

would almost only vaccinate people who would not have become infected anyways. Thus, when type 2 is available very late, we prefer type 1 vaccines because they are available in time to reduce the growth in infections and lower the risk of infection for unvaccinated people.

We thus see that type 1 is preferred when type 2 is available very late, but also that type 2 is preferred if this type is available early. This implies that there is a specific time for the availability of type 2 at which the two pure strategies are equally good. Theorem 5.2 derives a formal result along these lines and characterizes the curve where the pure strategies are equally good. In this theorem  $\tau_2$  is implicitly defined through  $s_2(\tau_2)$ , with  $s_j(t)$  denoting the proportion of people susceptible in strategy  $j$  at time  $t$ .

**Theorem 5.2.** *The pure strategies 1 and 2 result in the same final size under the following condition:*

$$s_2(\tau_2) = \frac{s_1(\tau_1)\varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)(\varphi_2 - \varphi_1)} \quad (5.6)$$

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

Recall that the proportion of people susceptible is decreasing over time, such that a lower  $s_2(\tau_2)$  implies a later availability (i.e., a higher  $\tau_2$ ). Thus, Theorem 5.2 confirms our finding that strategy 2 is worse if the vaccines of this type are available late, but better if they are available early. We can derive the following managerial implications from Theorem 5.2. First, we observe that if the two vaccine types have the same efficacy per dollar, the best vaccine is the one that is available at the earliest time. Secondly, if the two vaccine types are available at the same time such that  $s_1(\tau_1) = s_2(\tau_2)$ , the vaccine with the highest efficacy per dollar results in the lowest final size. In short, vaccinating early is better and vaccines with a higher efficacy per dollar are better. These conclusions also imply that later available vaccine types with a lower efficacy per dollar are always dominated by vaccine types that are available at an earlier time and have a higher efficacy. This confirms our choice to consider vaccine types for which  $\tau_1 < \tau_2$  and  $\varphi_1 < \varphi_2$ .

If the epidemic can be controlled with only vaccines of type 1, then there are not many new infections after  $\tau_1$  and  $G(f_1, \tau_1)$  is only slightly smaller than  $\left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)$ . By (5.6) in that case vaccines of type 2 can only be preferred if  $\tau_2$  is very close to  $\tau_1$ .

In condition (5.6) the two parameters that characterize type 2 appear: the availability and the efficacy per dollar. For strategy 1 and 2 to be equally good, there is a trade-off between those two parameters. Delaying should be compensated by a higher efficacy per dollar. Though if the availability is too far delayed, there is no compensation possible.

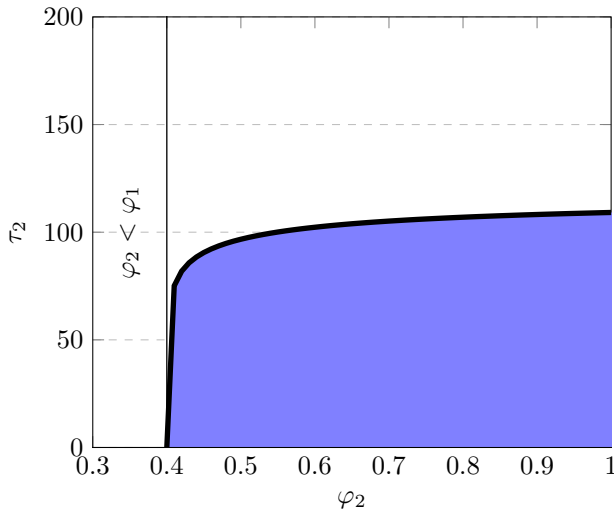
**Corollary 5.1.** *The value for  $\tau_2$  that satisfies (5.6) is increasing in  $\varphi_2$ .*

We illustrate the switching curve for two vaccination strategies in Figure 5.3. We can compute  $\tau_2$  easily from (5.6) by numerical evaluation of the differential equations (5.1). The parameters for this figure are as follows:  $B/N = 0.5$  and  $\beta = 0.35, \gamma = 0.24$ . Both vaccines have a price of 1 dollar per dose. Vaccines of type 1 have efficacy per dollar  $\varphi_1 = 0.4$  and are available at time 0 when  $i_0 = 10^{-6}$  and  $s_0 = 1 - i_0$ . To construct the figure, we use (5.6) to determine the relation between  $s_2(\tau_2)$  and  $\varphi_2$  and we evaluate the differential equations to derive  $\tau_2$  from  $s_2(\tau_2)$ . The figure shows the same structure as described before. We also see that vaccines which become available very late are never preferred, regardless of their efficacy per dollar.

## Hybrid strategies

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

To investigate when hybrid strategies can be optimal, we take the efficacy per dollar of type 2 as fixed and vary the time at which these vaccines become available. We start with  $\tau_2$  high, such that it is best to spend the entire budget on vaccines of type 1. By advancing the availability of type 2, we will reach a point at which these vaccines are so attractive, that it is no longer optimal to spend the entire budget on vaccines of type 1. The following theorem shows under which condition this happens. To derive this condition, we make use of Theorem 5.1 which provides a useful characterization of the hybrid strategy.



**Figure 5.3:** Illustration of the switching curve. In the white area strategy 1 results in the lowest final size and is therefore the best and in the dark area this holds for strategy 2.

**Theorem 5.3.** *Consider the pure strategy where all vaccines are of type 1. It is better to shift  $\epsilon$  vaccines to type 2, with  $\epsilon > 0$  small, under the following condition:*

$$\frac{\varphi_2}{\varphi_1} > \frac{[s_1(\tau_1^v) - G(f_1, \tau_1)] / s_1(\tau_1^v)}{[s_1(\tau_2) - G(f_1, \tau_1)] / s_1(\tau_2)}, \quad (5.7)$$

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

By spending some of the budget on vaccines of type 1 and some on vaccines of type 2, the population can benefit from the advantages of both vaccine types. The early vaccination with type 1 reduces the initial growth in infections and with the high efficacy per dollar of type 2 many people can achieve immunity due to vaccination. Such a hybrid strategy is only beneficial if the epidemic is still ongoing when the vaccines of type 2 become available and if the efficacy per dollar of type 2 is high enough. This can also be seen if we analyze the condition in Theorem 5.3. The term on the right-hand side represents the proportion of the total number of infections after  $\tau_1$  that occurs while waiting for the vaccines of type 2, i.e., in the interval

$[\tau_1, \tau_2]$ . This proportion is an indication of the additional infections experienced if the decision maker decides to wait for vaccines of type 2. It is beneficial to wait if the gain in efficacy per dollar, captured by the ratio  $\frac{\varphi_2}{\varphi_1}$ , outweighs the additional infections during this waiting time.

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

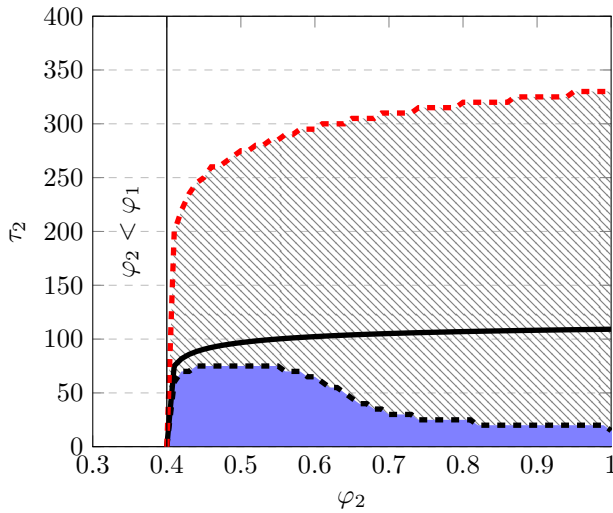
One could argue that if the decision maker should shift  $\epsilon$  vaccines from type 1 to type 2, why not spend the entire budget on vaccines of type 2? There are two main reasons why this would not result in a good strategy. Firstly, the vaccines of type 2 are available at a later point in time.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

**Lemma 5.2.** *At the indifference curve, when the two pure strategies are equally good, the hybrid strategy is strictly better and results in a lower final size.*

**Lemma 5.3.** *If the two pure strategies are equally good for vaccines of type 2 that become available at time  $T$ , then there exists a  $T^* > T$  such that it is optimal to shift  $\epsilon$  vaccines to type 2 when the vaccines of type 2 become available at time  $T^*$ .*

The interpretation of Lemma 5.3 is that while advancing the availability of type 2, you will first reach the point where it is optimal to shift a little bit of the budget to type 2 before you reach the switching curve. Thus, even if the pure strategy with only

type 2 is worse than the pure strategy with only type 1, it can be beneficial to use vaccines of type 2 in a hybrid strategy. Lemma 5.2 confirms that the hybrid strategy is optimal around the switching curve. The structure described by these two lemmas is also illustrated in Figure 5.4, which is determined with enumeration. We observe that the solid switching curve lies in the dashed region where hybrid strategies are optimal. The parameters for this figure are the same as in Section 5.4.2.



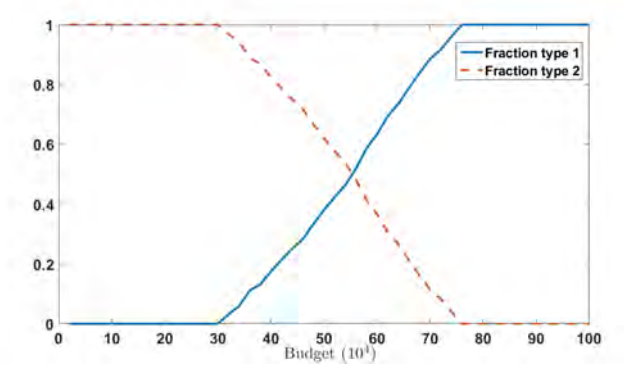
**Figure 5.4:** This figure illustrates the optimal strategy. In the white area strategy 1 results in the lowest final size and is therefore the best and in the dark area this holds for strategy 2. The dashed area between the two dashed lines is a sketch of the region in which a hybrid strategy is optimal. The solid curve represents the switching curve from Figure 5.3.

We observe the following in Figure 5.4. If pure strategy 1 is optimal for some  $\tau_2$ , it is also optimal when the vaccines of type 2 are available even later. Delaying the availability of type 2 results in even more infections while waiting for this type which are not outweighed by the gain in efficacy per dollar. Analogously, pure strategy 2 remains optimal if  $\tau_2$  is reduced. The reduced waiting time results in less infections, so the gain in efficacy per dollar will surely compensate that. Next to that, if  $\tau_2$  is smaller there are still more people susceptible when the vaccines of type 2 become available, such that more vaccines are needed to control the epidemic at  $\tau_2$ . This

implies that there is no incentive to reduce the vaccination fraction at  $\tau_2$  by shifting some vaccines to type 1. We also see that by increasing  $\varphi_2$  we can move from a region where pure strategy 2 is optimal to a region where the hybrid strategy is optimal. For these higher values of  $\varphi_2$ , pure strategy 2 is no longer optimal, because the type 2 vaccines became so efficacious that spending the entire budget on these vaccines would lead to vaccinating people who would not have become infected in the first place.

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

As a final part of this section, we analyze the effects of an increasing budget in Figure 5.5. The figure shows that for small budgets, the optimal strategy is to order only the vaccines with the highest efficacy per dollar. In those cases the budget is insufficient to control the epidemic, so it is best to effectively vaccinate as many people as possible. However, when the budget increases, it becomes beneficial to use a hybrid strategy. For a sufficiently large budget the epidemic can already be controlled at  $\tau_1$  and the optimal strategy is to use only the vaccines of type 1.



**Figure 5.5:** Optimal division of the budget over the two vaccine types with the following characteristics:  $\tau_1 = 0$ ,  $\varphi_1 = 0.4$ ,  $\tau_2 = 90$  and  $\varphi_2 = 0.7$ .



The results in Sections 5.4.2 and 5.4.2 are derived for a homogeneous population. In the discussion in Section 5.6, we discuss how our results are expected to carry over to heterogeneous populations, for example populations with multiple age groups.

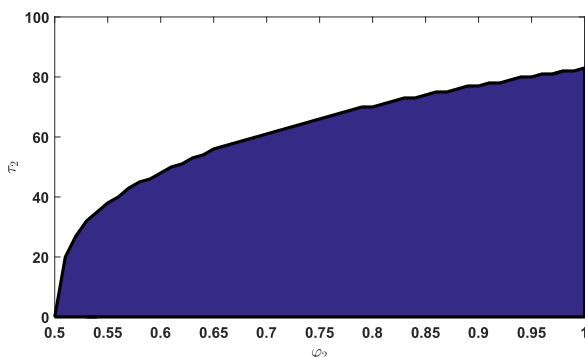
### 5.4.3 Two vaccination campaigns

In this section, we present one more result that follows from Theorem 5.1. This result is an extension of our results on pure strategies in Section 5.4.2. Instead of considering vaccines that are all allocated at once, we consider vaccines that are allocated in a vaccination campaign consisting of multiple vaccination moments. There are multiple reasons why a single vaccination moment might not be possible. Logistical considerations may play a role, which render it practically infeasible to allocate all vaccines at the same time (e.g., Rachaniotis et al. 2012, Ramirez-Nafarrate et al. 2015). Next to that, the production of vaccine is a complex process, amongst others characterized by random yields (cf., Adida et al. 2013, Eskandarzadeh et al. 2016). Together with capacity constraints, this can result in production processes or technologies that produce vaccines in batches, such that the vaccines become available over time. In this section, we extend some of our results to the case of vaccination campaigns.

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

$$1 - \frac{(\varphi_2 - \varphi_1)B}{NG(\varphi_1, \tau_1)} - \prod_{j=1}^n \left( \frac{s_j^1}{s_j^2} \right) \left( \frac{nNs_j^2 - \varphi_2 B}{nNs_j^1 - \varphi_1 B} \right) = 0 \quad (5.8)$$

If the left-hand side is positive (negative), strategy 1 is better (worse). The derivation of this condition can be found in Appendix 5.D.3 and makes use of Theorem 5.1. Note that condition 5.8 implicitly defines the relation between  $\tau_2$  and  $\varphi_2$ , as  $s_j^2$  for all  $j$  depend on  $\tau_2$ . We can compute this relation through numerical analysis. Figure 5.6 illustrates the relation for the parameters  $\varphi_1 = 0.5$ ,  $\tau_1 = 0$ ,  $n = 4$ ,  $T = 30$  and  $B = 0.2N$ . As expected, we see that campaign 2 is better than campaign 1 if either campaign 2 does not start too late, or if the corresponding vaccines have a high efficacy. Again, we see that for  $\tau_2$  above a certain threshold, around 80 in this case, vaccines of campaign 2 are too late to be optimal. Since a campaign with multiple moments is already some kind of hybrid strategy in itself, we do not consider partially investing in two campaigns.



**Figure 5.6:** The switching curve for the two vaccination campaigns. In the white area campaign 1 is optimal and in the dark area campaign 2. The initial state and disease parameters are the same as in Figure 5.3.

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

## 5.5 Numerical experiments

In this section, we perform some numerical experiments. Our analytical results in Section 5.4 show theoretically that hybrid strategies can outperform pure strategies

for two vaccine types. The objective of our numerical experiments in this section is twofold: firstly, we want to know how many infections can actually be saved by using a hybrid strategy and secondly we investigate whether it is beneficial to use a hybrid strategy with more than two vaccine types.

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

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

We study all subsets of three vaccine types in which no vaccine type(s) is/are dominated by others. This means that we do not consider those subsets which include two vaccine types that have the same time at which the vaccines become available or the same efficacy per dollar. For example, if a decision maker has to choose between vaccines of type 4 and 5, she will always prefer the vaccines of type 4 because they are available earlier and have the same efficacy per dollar. Analogously, type 6 will always be preferred if one has to choose between type 5 and 6, because both vaccine types are available at the same time, but type 6 has a higher efficacy per dollar. Taking these considerations into account, we find 14 subsets consisting of three vaccine types each. For these subsets we analyze the best pure strategy, the best hybrid strategy with at most 2 types and the best hybrid strategy with at most 3 types. Note that the pure strategies are also included in the hybrid strategies. For the hybrid strategies we use enumeration and a stepsize of  $1000 = 10^{-3}N$  vaccines. The results are reported in Table 5.1. In this table, the final size for the pure strategies is reported as a population fraction. For the hybrid strategies the relative performance

compared to the best pure strategy is presented. Recall that our goal is to minimize the final size. Hence, if the reported value in the table is below 100, it means that the hybrid strategy is better and results in a lower final size than the pure strategy.

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

**Table 5.1:** Table with the final sizes achieved with the different vaccination strategies. In brackets the optimal allocation over the three considered types with a step size  $10^3$  doses of vaccine. \* the allocations for hybrid strategies with at most two and at most three vaccine types are the same.

We start with discussing the column on hybrid strategies with at most two vaccine types in Table 5.1. The results show that in most cases a hybrid strategy is preferred. We see that the hybrid strategy often combines the earliest available vaccine with the vaccine that has the highest efficacy per dose. By using a hybrid strategy the final size can be reduced with even more than 60% for vaccine types 1,2,7 and 1,3,7. Only for a few vaccine type combinations the final size of the best hybrid strategy is the same as the final size of the best pure strategy, which implies that the pure strategy is optimal in those cases. We conclude from Table 5.1 that using a hybrid strategy can result in a substantially lower final size and is therefore worth investigating.

The second goal of this section is to investigate hybrid strategies with more than two vaccine types. Interestingly, if we analyze Table 5.1 and compare hybrid strategies with at most two types with hybrid strategies with at most three vaccine types, the final sizes are the same for all subsets of vaccine types. The additional freedom

that is introduced by allowing to divide the budget over three vaccine types does not result in further reductions of the final size. Additional experiments not reported here have also supported the conclusion that hybrid strategies with more than two vaccine types typically give no or very little additional benefits

In this section, we do not analyze hybrid strategies with more than three vaccine types. Nevertheless we can draw conclusions for those situations. Consider a hybrid vaccination strategy with  $n$  vaccine types. By applying Theorem 5.1 to types 3, ...,  $n$  and summarizing them in one moment, the strategy with  $n$  vaccine types is equivalent to a vaccination strategy with three vaccine types. In our numerical results we do not find situations where a hybrid vaccination strategy with three vaccine types is better than a hybrid strategy with at most two vaccine types. It is therefore unlikely that hybrid strategies with more than three vaccine types are optimal.

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

## 5.6 Discussion

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

The results in this chapter are established under some assumptions. We model vaccination as an immediate transition of people from the susceptible compartment to the removed compartment. This assumption could be relaxed to studying the case where vaccination takes more time, which can be modelled as a vaccination campaign (cf., Section 5.4.3). In our analysis we assume that the vaccine efficacy is known for every vaccine type. Further research is needed to extend the analysis to environments where efficacy is uncertain, e.g., situations where the delayed availability is caused by a vaccine development phase with unknown outcome. Furthermore, we base our analysis on the  $SIR$  model, but show in Appendix 5.C how some results extend to the more general  $SI^nR$  model. In the  $SIR$  model we consider a homogeneous population. Alternatively, a model for a heterogeneous population could be used, for

example a population that is subdivided in multiple age groups (e.g., Medlock et al. 2009, Teytelman and Larson 2012). In a heterogeneous population the final size is the result of an optimization problem that is used to determine which allocation over the age groups is best. We conjecture that a switching curve result similar to Theorem 5.2 can be derived in the case of a heterogeneous population, i.e., that there exists a curve separating the region where a pure type 1 strategy is optimal from the region where a pure type 2 strategy is optimal. Making the vaccines of type 2 more attractive by increasing their efficacy, reducing their price or by advancing their availability will reduce the final size, as the original allocation is still feasible. Another interesting research direction is incorporating high-risk and high-transmission groups (e.g., Samii et al. 2012, Lee et al. 2015b).

## 5.7 Conclusions

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

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

pressure to respond quickly and the aim to spend the budget on the best possible vaccine.

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

## Acknowledgements

The authors want to thank Prof. Jacco Wallinga of the National Institute for Public Health and the Environment for his help in defining the problem.

## Appendix

### 5.A *SIR* model

In this chapter, we use the final size to compare the severity of different vaccination strategies. In Section 5.3.3, we show that the herd effect, denoted by the function  $G(\mathbf{f}, \tau)$ , is an important determinant in the final size. The herd effect is defined as the final fraction of people susceptible after a vaccination strategy characterized by vaccination fractions  $\mathbf{f}$  and times  $\tau$ . More precisely, for  $f_j \in [0, \varphi_j s_j(\tau)]$

$$G(\mathbf{f}, \tau) = \lim_{t \rightarrow \infty} s(t), \tag{5.9}$$

with  $s(t)$  evolving according to (5.1) for  $t > \tau_n$ . In this appendix, we present and analyze an alternative formulation of the herd effect, which forms the basis of the structural analysis of the herd effect.

Based on the differential equations of the *SIR* model, we derive an implicit expression for the herd effect. From (5.1) the following equation follows, which presents the relation between  $i(t)$  and  $s(t)$  at any time  $t$  (Hethcote 1976):

$$\begin{aligned} i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s_0 + i_0 - \frac{\log(s_0)}{\sigma} \\ \Leftrightarrow s(t) &= s_0 \exp\{-\sigma(s_0 + i_0 - s(t) - i(t))\} \end{aligned} \quad (5.10)$$

Above relation characterizes the state of the system at any point in time, but prior to vaccination. In Theorem 5.1 we show that for any vaccination strategy with multiple vaccination moments, there is a single-moment strategy resulting in the same final size. In this single-moment strategy a fraction  $f^T$  of the population is vaccinated at time  $\tau^T$ . In the remainder of this section we will use the parameters of the single-moment vaccination strategy to analyze  $G(\mathbf{f}, \tau)$ .

Upon vaccination at time  $\tau^T$  the state of the system changes from state  $(s(\tau^T), i(\tau^T))$  to state  $(s(\tau^T) - f^T, i(\tau^T))$ . Hence, the state  $(s(\tau^T) - f^T, i(\tau^T))$  directly after vaccination can be seen as a new initial state, where  $i(\tau^T)$  can be obtained from (5.10). Since  $\lim_{t \rightarrow \infty} i(t) = 0$ , the function  $G(\mathbf{f}, \tau)$  can be derived from (5.10) by setting  $i(t) = 0$  and thus is the unique solution to:

$$\begin{aligned} 0 &= -G(\mathbf{f}, \tau) + \frac{\log(G(\mathbf{f}, \tau))}{\sigma} + s(\tau^T) - f^T + i(\tau^T) - \frac{\log(s(\tau^T) - f^T)}{\sigma} \\ \Leftrightarrow 0 &= -G(\mathbf{f}, \tau) + \frac{\log(G(\mathbf{f}, \tau))}{\sigma} + s_0 + i_0 - \frac{1}{\sigma} \log\left(s_0 \left(1 - \frac{f^T}{s(\tau^T)}\right)\right) - f^T \end{aligned} \quad (5.11)$$

Above equation holds for all  $i_0 > 0$ . Denote by  $Z(\mathbf{f}, \tau)$  the final size according to (5.3). Rewriting (5.11) gives the following:

$$G(\mathbf{f}, \tau) = s_0 \left(1 - \frac{f^T}{s(\tau^T)}\right) \exp\{-\sigma Z(\mathbf{f}, \tau)\} \quad (5.12)$$



Observe that (5.11) and (5.12) are implicit definitions of the herd effect. Alternatively, we can derive a definition based on the Lambert W function (Corless et al. 1996, Ma and Earn 2006). This definition can be used to calculate the herd effect:

$$G(\mathbf{f}, \tau) = \frac{-1}{\sigma} W \left[ -s_0 \left( 1 - \frac{f^T}{s(\tau^T)} \right) \exp\{-\sigma(s_0 + i_0 - f^T)\} \right] \quad (5.13)$$

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

**Lemma 5.A.1.** *For fixed  $f^T$ , the herd effect  $G(\mathbf{f}, \tau)$  is increasing in  $s(\tau^T)$  and the final size  $Z(\mathbf{f}, \tau)$  is decreasing in  $s(\tau^T)$ .*

*Proof.* See Section 3.4.5 in Chapter 3. □

## 5.B Multiple vaccination moments

In this Appendix, we prove Theorem 5.1. Thereto we first present two supporting results: a result on the dynamics of an epidemic in Lemma 5.B.1 and a technical result in Lemma 5.B.2.

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

**Lemma 5.B.1.** *For all  $k = 1, \dots, n$  we consider the following two systems, that both follow the dynamics of the SIR model. Note that (i) is a system with vaccination and (ii) a system without vaccination:*

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

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

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

*Proof.* This theorem will be proven by induction. We start with proving that it holds for  $k = 1$ . Consider system (i) and note that the relation between  $i(\tau_1)$  and  $s(\tau_1)$  just prior to vaccination at time  $\tau_1$  can be described by (5.10) as follows:

$$i(\tau_1) = -s(\tau_1) + \frac{\log(s(\tau_1))}{\sigma} + s_0 + i_0 - \frac{\log(s_0)}{\sigma} \quad (5.14)$$

On the interval  $t \in [\tau_1, \tau_2)$  we can see system (i) as a system that starts at time  $\tau_1$  with initial state  $[(s(\tau_1) - f_1), i(\tau_1)]$ . We can use (5.10) again to derive the relation between  $i(t)$  and  $s(t)$  for  $t \in [\tau_1, \tau_2)$ :

$$\begin{aligned} i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s(\tau_1) - f_1 + i(\tau_1) - \frac{\log(s(\tau_1) - f_1)}{\sigma} \\ \Leftrightarrow i(t) &= -s(t) + \frac{\log(s(t))}{\sigma} + s_0 + i_0 - f_1 - \frac{1}{\sigma} \log \left( 1 - \frac{f_1}{s(\tau_1)} \right) - \frac{\log(s_0)}{\sigma} \quad (5.15) \\ \Leftrightarrow s(t) &= s(0) \left( 1 - \frac{f_1}{s(\tau_1)} \right) \exp\{\sigma f_1\} \exp\{-\sigma[s_0 + i_0 - s(t) - i(t)]\} \end{aligned}$$

In the second line of above derivation we substitute  $s(\tau_1)$  and  $i(\tau_1)$  from (5.14) and in the third line we take the exponent. We can verify with (5.10) that the states  $(s(t), i(t))$  for  $t \in [\tau_1, \tau_2)$  that satisfy (5.15) are also part of the time course of system (ii) for  $k = 1$  by substituting in (5.10) the following initial state for system (ii):  $s^1(0) = s_0^1 := s_0 \cdot \left( 1 - \frac{f_1}{s(\tau_1)} \right) \exp\{\sigma f_1\}$  and  $s_0^1 + i_0^1 := s_0 + i_0$ . Let  $t_1^*$  denote the time at which system (ii) is in the state  $(s(\tau_1) - f_1, i(\tau_1))$ . Such time  $t_1^*$  must exist, because the state  $(s(\tau_1) - f_1, i(\tau_1))$  is part of the time course of system (ii). Then the time course of system (i) on the interval  $(\tau_1, \tau_2)$  is equivalent to that of system (ii) on the interval  $(t_1^*, t_1^* + \tau_2 - \tau_1)$ . This completes the base case of the proof by induction.

We perform the inductive step and assume that the theorem holds for  $k$ . In that case we can determine the state of systems (i) and (ii) at time  $\tau_{k+1}$  with (5.10) as

follows, using that  $s_0^k + i_0^k = s_0 + i_0$  per definition:

$$\begin{aligned}
 s^k(\tau_{k+1} + t_k^* - \tau_k) &= s_0^k \exp \left\{ -\sigma[s_0^k + i_0^k - s^k(\tau_{k+1} + t_k^* - \tau_k) - i^k(\tau_{k+1} + t_k^* - \tau_k)] \right\} \\
 \text{by induction } \iff s(\tau_{k+1}) &= s_0^k \exp \left\{ -\sigma[s_0^k + i_0^k - s(\tau_{k+1}) - i(\tau_{k+1})] \right\} \\
 &= s_0 \prod_{j=1}^k \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right] \exp \left\{ -\sigma[s_0 + i_0 - s(\tau_{k+1}) - i(\tau_{k+1})] \right\}
 \end{aligned} \tag{5.16}$$

We now prove that above relation implies that the theorem also holds for  $k + 1$ . Thereto, we analyse system (i) for  $t \in (\tau_{k+1}, \tau_{k+2})$ . We make use of (5.10) and take the state at time  $\tau_{k+1}$  just after vaccination,  $(s(\tau_{k+1} - f_{k+1}), i(\tau_{k+1}))$ , as the initial state. Then the following holds for  $t \in (\tau_{k+1}, \tau_{k+2})$ :

$$\begin{aligned}
 s(t) &= (s(\tau_{k+1}) - f_{k+1}) \exp \left\{ -\sigma[s(\tau_{k+1}) - f_{k+1} + i(\tau_{k+1}) - s(t) - i(t)] \right\} \\
 &= s_0 \prod_{j=1}^{k+1} \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right] \exp \left\{ -\sigma[s_0 + i_0 - s(t) - i(t)] \right\}
 \end{aligned} \tag{5.17}$$

In the second step we use (5.16) to substitute  $s(\tau_{k+1})$  and  $i(\tau_{k+1})$ . We can again verify with (5.10) that the states  $(s(t), i(t))$  for  $t \in (\tau_{k+1}, \tau_{k+2})$  that satisfy (5.17) are part of the time course of system (ii) for  $k + 1$ , as before for the case  $k = 1$ . Let  $t_{k+1}^*$  denote the time at which system (ii) is in the state  $(s(\tau_{k+1}) - f_{k+1}, i(\tau_{k+1}))$ , then the time course of system (i) on the interval  $(\tau_{k+1}, \tau_{k+2})$  is equivalent to that of system (ii) on the interval  $(t_{k+1}^*, t_{k+1}^* + \tau_{k+2} - \tau_{k+1})$ . This completes the proof of this theorem.  $\square$

**Lemma 5.B.2.** *The following relation holds for all  $n \geq 1$ , where we define  $\prod_{k=1}^{j-1} (1 - x_k) = 1$  for  $j = 1$ :*

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

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

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

□

**Theorem 5.1.** *We consider an initial state denoted by  $(s_0, i_0)$  and use the SIR model to evaluate the epidemic. A hybrid vaccination strategy (i) with  $n$  vaccination moments at times  $\tau_1, \dots, \tau_n$  and corresponding vaccination fractions  $f_1, \dots, f_n$  results in the same final size as a single moment vaccination strategy (ii) with one vaccination moment at time  $\tau^T$  and a vaccination fraction  $f^T = \sum_{j=1}^n f_j$  if and only if  $\tau^T$  satisfies the following condition:*

$$1 - \frac{f^T}{s_{(ii)}(\tau^T)} = \prod_{j \in J} \left( 1 - \frac{f_j}{s_{(i)}(\tau_j)} \right) \quad (5.5)$$

There is always exactly one  $\tau^T \in [\tau_1, \tau_n]$  satisfying (5.5).

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

Denote by  $s_1(\infty)$  and  $s_2(\infty)$  the final fraction of people susceptible in system (i) and (ii) respectively. Note that for  $t \rightarrow +\infty$  the fraction of infected individuals goes to zero. From Lemma 5.B.1 and the fact that  $i_1(\infty) = 0$  we derive that  $s_1(\infty)$  follows from the following expression:

$$s_1(\infty) = s_0 \prod_{j=1}^n \left[ \left( 1 - \frac{f_j}{s(\tau_j)} \right) \exp\{\sigma f_j\} \right] \exp \left\{ -\frac{\beta}{\gamma} [s_0 + i_0 - s_1(\infty)] \right\} \quad (5.18)$$

In case of a single vaccination moment we can use the final line of (5.15):

$$s_2(\infty) = s(0) \left(1 - \frac{f^T}{s(\tau^T)}\right) \exp\{\sigma f^T\} \exp\left\{-\frac{\beta}{\gamma}[s_0 + i_0 - s_2(\infty)]\right\} \quad (5.19)$$

For  $f^T = \sum_{i=1}^n f_i$  and  $\frac{f^T}{s(\tau^T)} = 1 - \prod_{i=1}^n \left(1 - \frac{f_i}{s(\tau_i)}\right)$  it holds that (5.18) and (5.19) are equal to each other, which implies that  $s_1(\infty) = s_2(\infty)$ . With the equal herd effects and the same amount of effectively allocated vaccines, the final sizes of the two strategies are equal.

It remains to show that  $\tau^T \in [\tau_1, \tau_n]$ . We prove this in the following two steps:

(i) we show that  $s_1(\tau_n) < s(\tau^T) < s(\tau_1)$  and (ii) we show that  $\tau_1 < \tau^T < \tau_n$ .

(i) Observe that  $s_1(\tau_j) < s_1(\tau_{j-1}) - f_{j-1}$  for  $j = 2, \dots, n$ , which also implies that  $s_1(\tau_j) < s_1(\tau_1) \prod_{k=1}^{j-1} \left(1 - \frac{f_k}{s_1(\tau_k)}\right)$  for  $j = 2, \dots, n$ . We can derive the following, using Lemma 5.B.2:

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

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

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

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

(ii) Given that  $s(t)$  is decreasing over time,  $s(\tau^T) < s_1(\tau_1)$  implies that  $\tau^T > \tau_1$ . Furthermore, by Lemma 5.B.1 strategies (i) and (ii) are equivalent for time  $t > \tau_n$ . This implies that  $\tau^T < \tau_n$  and hence,  $\tau^T \in [\tau_1, \tau_n]$ .

This completes the proof of this theorem.  $\square$

## 5.C Generality of Theorem 5.1

One of the extensions to the standard *SIR* compartmental model, is the *SI<sup>n</sup>R* model with  $n$  different consecutive infectious stages. Let  $s(t)$  and  $r(t)$  denote the fraction of people respectively susceptible and removed at time  $t$ . The fractions of people infected in every state are given by  $i_k(t)$  for  $k = 1, \dots, n$ . Interpretation dictates that  $s(t) + \sum_{k=1}^n i_k(t) + r(t) = 1$  for all  $t$ . Let  $\beta_k$  and  $\gamma_k$  denote respectively the transmission rate and recovery rate in infectious stage  $k$ . The differential equations for the *SI<sup>n</sup>R* model are:

$$\begin{aligned}\frac{ds}{dt} &= -s \sum_{k=1}^n \beta_k i_k \\ \frac{di_1}{dt} &= s \sum_{k=1}^n \beta_k i_k - \gamma_1 i_1 \\ \frac{di_k}{dt} &= \gamma_{k-1} i_{k-1} - \gamma_k i_k \quad k = 2, \dots, n \\ \frac{dr}{dt} &= \gamma_n i_n\end{aligned}\tag{5.20}$$

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

In (5.10) we present a relation between  $s(t)$  and  $i(t)$ . A similar relation can be derived for the *SI<sup>n</sup>R* model (See Appendix 3.C):

$$\begin{aligned}\log(s(t)) - \log(s(0)) &= \sigma \left[ s(t) + \sum_{k=1}^n i_k(t) \right] - \sigma \left[ s(0) + \sum_{k=1}^n i_k(0) \right] \\ &\quad - \sum_{k=1}^n \frac{\beta_k}{\gamma_k} \left[ \sum_{m=k+1}^n i_m(t) - i_m(0) \right]\end{aligned}\tag{5.21}$$

Using (5.21) we can derive that the result of Theorem 5.1 also holds for the *SI<sup>n</sup>R* model. The proof is identical, we only need to use an adjusted version of Lemma 5.B.1. Next, we show how the result of this latter theorem carries over to the more general *SI<sup>n</sup>R* epidemic model.

**Lemma 5.C.1.** *For all  $k = 1, \dots, m$  we consider the following two systems, that both follow the dynamics of the  $SI^nR$  model. Note that (i) is a system with vaccination and (ii) a system without vaccination:*

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

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

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

*Proof.* The proof is analogous to the proof of Theorem 5.1, now only using the relation between  $s(t)$  and  $i_1(t), \dots, i_n(t)$  from (5.21) instead of the relation for the  $SIR$  model (5.10).  $\square$

## 5.D Analytical results

### 5.D.1 Pure strategies

In this section, we derive the switching curve which is presented in Theorem 5.2. To prove this theorem, we propose a function that can be used to compare the two pure vaccination strategies. In the supporting result of Lemma 5.D.1 we show how this function can be used to determine which strategy is best, i.e., which strategy results in the lowest final size. We define this function  $H(f_1, f_2, s_1, s_2)$  as follows:

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

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

**Lemma 5.D.1.** *The sign of the function  $H(f_1, f_2, s_1, s_2)$  determines which strategy is best: if the function value equals zero, the two strategies are equally good and if the function value is positive (negative) strategy 1 is better (worse).*

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

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

The proof is as follows:

(i)

$$\begin{aligned}
 & Z(f_1, \tau_1) - Z(f_2, \tau_2) &&= 0 \\
 \Leftrightarrow & G(f_1, \tau_1) + f_1 - G(f_2, \tau_2) - f_2 &&= 0 \quad \text{substitute (5.3)} \\
 \Leftrightarrow & s_0 \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) \exp\{-\sigma Z(f_1, \tau_1)\} + f_1 - f_2 &&= 0 \quad \text{substitute (5.12) and} \\
 & && \text{use } Z(f_1, \tau_1) = Z(f_2, \tau_2) \\
 \Leftrightarrow & \left( \frac{f_2}{s_2} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) [f_1 - f_2] &&= 0 \quad \text{substitute (5.12)}
 \end{aligned}$$

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

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

By Lemma 5.A.1 we know that the final size  $Z(f, \tau)$  is monotonically decreasing in  $s(\tau)$ . Hence, if  $s_2$  is slightly lower than the expression above, then  $Z(f_2, \tau_2) > Z(f_1, \tau_1)$ .

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

- (iii) Analogous to (ii).

□



**Theorem 5.2.** *The pure strategies 1 and 2 result in the same final size under the following condition:*

$$s_2(\tau_2) = \frac{s_1(\tau_1)\varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{B\varphi_1}{N}\right)(\varphi_2 - \varphi_1)} \quad (5.6)$$

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

*Proof.* The results follows directly from Lemma 5.D.1. □

**Corollary 5.4.** *The value for  $\tau_2$  that satisfies (5.6) is increasing in  $\varphi_2$ .*

*Proof.* We proof this result by taking the derivative of the switching curve (5.6) with respect to  $\varphi_2$ :

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

Above expression is negative, if  $G(f_1, \tau_1) < \left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right)$  which means that the final fraction of people susceptible is smaller than the fraction of people susceptible just after vaccination. This holds, because the proportion of people susceptible is decreasing over time. Hence,  $s_2(\tau_2)$  is decreasing in  $\varphi_2$ . By the same argument this means that the value for  $\tau_2$  that satisfies (5.6) is increasing in  $\varphi_2$ . This completes the proof. □

## 5.D.2 The hybrid strategy

In this section, we analyze the hybrid strategy that consists of an early aspecific vaccine and a late specific vaccine. We respectively denote by strategy 1 and 2 the two pure strategies for the considered vaccine types. We start this section with Theorem 5.3 in which we derive under which condition the hybrid strategy outperforms strategy 1. We know that strategy 1 and 2 are equally good at the switching curve. Hence, if the condition derived in Theorem 5.3 holds at the switching curve, then the hybrid strategy is better than both pure strategies at the switching curve. We show in Lemma 5.2 that this is indeed the case. Before we prove this lemma, we first

present two auxiliary results on the dynamics of the *SIR* model in Lemma 5.D.2 and Lemma 5.D.3.

In this section, we use the following notation: strategy 3 denotes the hybrid strategy with  $V_1$  vaccines of type 1 and  $V - V_1$  vaccines of type 2, with  $V_1 \in (0, V)$ . In Table 5.2 we summarize the three strategies, and formulate the hybrid strategy in terms of a pure strategy by applying Theorem 5.1. We denote by  $s_i(t)$  the proportion of people susceptible at time  $t$  in strategy  $i = 1, 2, 3$ .

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

**Table 5.2:** This table describes the three vaccination strategies. The last two columns with  $f_i, s_i$  characterize the vaccination strategy by Theorem 5.1 with only one vaccination moment and the same final size.

**Theorem 5.3.** *Consider the pure strategy where all vaccines are of type 1. It is better to shift  $\epsilon$  vaccines to type 2, with  $\epsilon > 0$  small, under the following condition:*

$$\frac{\varphi_2}{\varphi_1} > \frac{[s_1(\tau_1^v) - G(f_1, \tau_1)] / s_1(\tau_1^v)}{[s_1(\tau_2) - G(f_1, \tau_1)] / s_1(\tau_2)}, \quad (5.7)$$

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

*Proof.* In this proof, we compare strategy 1 and strategy 3 of Table 5.2. These strategies are identical, and therefore equally good, in case  $V_1 = V$ . By Lemma 5.D.1 the following condition holds if these strategies are equally good:

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

We evaluate the derivative of  $H(f_1, f_3, s_1, s_3)$  with respect to  $V_1$  at the point  $V_1 = V$ . If this derivative is positive, then decreasing  $V_1$  results in a decrease of  $H(f_1, f_3, s_1, s_3)$ , rendering it negative and implying that  $\exists \epsilon > 0$  such that strategy 3 with  $V_1 = V - \epsilon$  is better than strategy 1 by Lemma 5.D.1.

We now investigate this derivative with respect to  $V_1$ . Note that  $V_1$  only plays a role in strategy 3, such that  $s_1, f_1$  and  $G_1(f_1, \tau_1)$  are not affected by changes in  $V_1$ . We use the following notation:  $s'_3(t) = \frac{\partial}{\partial V_1} s_3(t)$ .

$$\begin{aligned}
& \frac{\partial}{\partial V_1} H(f_1, f_3, s_1, s_3) \\
&= \frac{\partial}{\partial V_1} \left\{ \left( \frac{f_3}{s_3} - \frac{f_1}{s_1} \right) G(f_1, \tau_1) + \left( 1 - \frac{f_1}{s_1} \right) [f_1 - f_3] \right\} \\
&= G(f_1, \tau_1) \frac{\partial}{\partial V_1} \frac{f_3}{s_3} - \left( 1 - \frac{f_1}{s_1} \right) \frac{\partial}{\partial V_1} f_3 \\
&= G(f_1, \tau_1) \frac{\partial}{\partial V_1} \left( \frac{V_1 \varphi_1}{N s_1} + \left( 1 - \frac{V_1 \varphi_1}{N s_1} \right) \left( \frac{(V - V_1) \varphi_2}{N s_3(\tau_2)} \right) \right) - \left( 1 - \frac{f_1}{s_1} \right) \frac{\partial}{\partial V_1} \frac{V_1 \varphi_1 + (V - V_1) \varphi_2}{N} \\
&= G(f_1, \tau_1) \left( \left( 1 - \frac{V_1 \varphi_1}{N s_1} \right) \left( \frac{(V - V_1) \varphi_2 N s'_3(\tau_2) - N s_3(\tau_2) \varphi_2}{N^2 s_3(\tau_2)^2} \right) + \frac{\varphi_1}{N s_1} \left( 1 - \frac{(V - V_1) \varphi_2}{N s_3(\tau_2)} \right) \right) \\
&\quad - \left( 1 - \frac{f_1}{s_1} \right) \frac{\varphi_1 - \varphi_2}{N}
\end{aligned}$$

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

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

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

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

This completes the proof of this theorem.  $\square$

**Lemma 5.D.2.** *Consider two systems  $s_j(t)$  and  $i_j(t)$  for  $j = 1, 2$  and assume that they both follow the dynamics of the deterministic SIR model. If  $s_1(0) = (1 - f_1)s_2(0)$  and  $i_1(0) = i_2(0)$ , then  $s_1(t) > (1 - f_1)s_2(t)$  for all  $t > 0$ .*

*Proof.* We proof this lemma as follows:

- At time 0 it holds that  $i_1(0) = i_2(0)$  and  $s_1(0) = (1 - f_1)s_2(0)$ .
- As long as  $s_1(t) < s_2(t)$  we can show that also  $i_1(t) < i_2(t)$  and that  $s_1(t) > (1 - f_1)s_2(t)$ .
- When  $s_1(t) \geq s_2(t)$  the lemma clearly holds.
- By Lemma 5.D.3 the curves  $s_1(t)$  and  $s_2(t)$  intersect at most once. This proves the lemma for all  $t > 0$ .

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

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

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

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

**Lemma 5.D.3.** *Consider two different initial states  $(s_0^j, i_0^j)$  for  $j = 1, 2$  and assume that  $s_j(t)$  and  $i_j(t)$  follow the dynamics of the deterministic SIR model. Then  $s_1(t) = s_2(t)$  for at most one  $t \in [0, \infty)$ . i.e., the curves for the proportion of people susceptible intersect at most once.*

*Proof.* Define the function  $H(x) = -x + \frac{1}{\sigma} \log(x)$ . Then the following can be derived from (5.10):

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

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

$$i_1(t) - i_2(t) = i_0^1 - i_0^2 + H(s_0^2) - H(s_0^1) \quad (5.22)$$

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

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

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

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

If above condition is satisfied, the constant at the right-hand side of (5.22) must be positive. Now consider the intersection at  $t_2$ , where we need the following:

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

This condition can only be satisfied if the right-hand side of (5.22) is negative. Since this right-hand side is a constant, it cannot be positive and negative at the same time. Hence, it is not possible to have two intersections. We arrive at a contradiction and conclude that the curves  $s_1(t)$  and  $s_2(t)$  can intersect at most once, which completes the proof of this lemma.  $\square$

**Lemma 5.5.** *At the indifference curve, when the two pure strategies are equally good, the hybrid strategy is strictly better and results in a lower final size.*

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

- We use Lemma 5.D.1 to find an expression for  $G(f_1, \tau_1)$  making use of the fact that the two pure strategies, strategy 1 and 2, are equally good.

- This expression for  $G(f_1, \tau_1)$  is substituted in the condition of Theorem 5.3 and we show that the resulting expression is positive.

By Lemma 5.D.1 the following condition holds if strategy 1 and 2 are equally good:

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

We insert above expression for  $G(f_1, \tau_1)$  the second to last condition of Theorem 5.3 to show that the hybrid strategy is better.

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

In the second step we substitute the expression for  $G(f_1, \tau_1)$ . To show that above condition holds, we apply Lemma 5.D.2 and note that until  $\tau_1$  the two epidemics follow the same time course. Hence, the hybrid strategy with  $V_1 = V - \epsilon$  is better than the pure strategies. This completes the proof of this theorem.  $\square$

**Lemma 5.6.** *If the two pure strategies are equally good for vaccines of type 2 that become available at time  $T$ , then there exists a  $T^* > T$  such that it is optimal to shift  $\epsilon$  vaccines to type 2 when the vaccines of type 2 become available at time  $T^*$ .*

*Proof.* Observe that  $T$  and  $T^*$  are respectively characterized by (5.6) and (5.7). In both expressions the time is implicitly characterized via  $s_2(T)$  or  $s_1(T^*)$ . In condition (5.7) we used the following notation  $s_1(\tau_1^v)$  is the proportion of people susceptible just after vaccination at time  $\tau_1$ . i.e.,  $s_1(\tau_1^v) = \left( s_1(\tau_1) - \frac{V\varphi_1}{N} \right)$ . Substituting this

expression in (5.7) and rewriting gives the following:

$$s_1(T^*) = \frac{\left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right) \varphi_2 G(f_1, \tau_1)}{\varphi_1 G(f_1, \tau_1) + \left(s_1(\tau_1) - \frac{V\varphi_1}{N}\right) (\varphi_2 - \varphi_1)} = s_2(T) \left(1 - \frac{V\varphi_1}{Ns_1(\tau_1)}\right) \quad (5.23)$$

The second equation is derived from (5.6). Note that  $s_1(\tau_1^v) = s_1(\tau_1) \left(1 - \frac{V\varphi_1}{s_1(\tau_1)N}\right)$  and  $s_2(\tau_1) = s_1(\tau_1)$ . By Lemma 5.D.2 at time  $T$  the following holds:

$$s_1(T) > s_2(T) \left(1 - \frac{V\varphi_1}{Ns_1(\tau_1)}\right).$$

Since the proportion of people susceptible is decreasing over time, this implies that  $T < T^*$ , which completes the proof.  $\square$

### 5.D.3 Two vaccination campaigns

In Section 5.4.3, we describe two technologies that can be used for the production of vaccines for a vaccination campaign. The resulting vaccination campaigns have each  $n$  vaccination moments. To analyze the campaigns and the corresponding final sizes, we apply the result of Lemma 5.B.1. Using the notation of that theorem, we have that  $f_i^T = \frac{\varphi_i B}{N}$  and  $1 - \frac{f_i^T}{s_i(\tau_i^T)} = \prod_{j=1}^n \left(1 - \frac{\varphi_i B}{s_j^i nN}\right)$  for  $i = 1, 2$ . We make use of expression (5.6) to derive the switching curve that compares two single-moment vaccination strategies. We use that  $f_j^i = \frac{\varphi_i B}{nN}$  for  $i = 1, \dots, n$ .

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

In the second step, we substitute the expression for  $s_2(\tau_2^T)$ . The derivation above leads to condition (5.8), which is presented in Section 5.4.3.





## Chapter 6

# Summary and conclusions

This dissertation focuses on the allocation of scarce health resources to fight infectious disease outbreaks. In particular, we look at vaccination, which is a very effective way to reduce the number of infections. Our extensive literature review in Chapter 2 shows which decision problems play a role in the vaccine supply chain. Chapters 3 - 5 focus on a specific part of the vaccine supply chain, namely vaccine allocation. In these chapters, we analyze three vaccine allocation problems. Our results show the benefits of using an analytical optimization perspective: we provide new insights into complex decision problems that increase understanding of the nonlinear dynamics of infectious diseases and their effect on optimal solutions. In doing so, we aim to help decision makers and contribute to the debate on good vaccine allocations.

In Chapter 2 we conducted a literature review in the Operations Research/Operations Management field on decision problems related to the vaccine supply chain. We structured this literature by proposing a supply chain framework. We defined the following four components in the vaccine supply chain: product, production, allocation and distribution. The vaccine supply chain has some unique characteristics, including high uncertainty in supply and demand and asymmetry between the involved parties. We emphasized the importance of further research on sudden outbreaks and the supply chain in developing countries. Our review shows the valuable contribution that the OR/OM community has already made to solving logistical problems in vaccination and highlights promising directions for future research. These research directions include incorporating technological developments that affect the decision

problems in the vaccine supply chain and integrating the consecutive stages of the supply chain in the analysis to achieve overall improvement.

In Chapter 3, 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 who escape infection. We find that vaccination can have a secondary effect in addition to the primary one, which surprisingly causes a second dose of vaccine in a population to have a bigger effect than the first. Based on this result we show that there is a unique vaccination fraction that results in the highest health benefit per dose of vaccine and we introduce the term *dose-optimal* for this fraction. We characterize the solution of the vaccine allocation problem and we show the crucial importance of the dose-optimal vaccination fraction. A single dose of vaccine may be a drop in the ocean, but multiple doses together can save a population. From this perspective, it may therefore be attractive to select a subset of populations to which the vaccines are allocated. By focusing on a limited number of populations, the available vaccine stockpile is used more efficiently than by allocating pro rata across all populations. In practice, unequitable allocations are currently often applied when vaccines are divided over age groups, not over different regions. Our analysis provides a theoretical explanation for the efficiency of a geographical allocation and thereby contributes to the understanding of vaccine allocation.

Chapter 4 studies the impact of vaccination on the effective reproduction ratio,  $R_f$ , and the herd effect. The effective reproduction ratio is related to the initial growth rate of infections. A compartmental model for disease progression is used to model the outbreak and we prove that a vaccine allocation maximizes the overall herd effect if and only if  $R_f = 1$ . In Chapter 4, we formulate two optimization problems: finding a vaccine allocation that minimizes the number of vaccines needed to attain  $R_f = 1$  and finding a vaccine allocation that maximizes the herd effect. We show that these two problems are equivalent and established a connection between two seemingly unrelated parts of literature. Based on this equivalence result, we propose solution methods. In two special cases the optimal solution can be characterized completely. For separable mixing, we provide an optimal greedy algorithm and for two populations we derive an explicit solution. For the general case, an efficient solution approach is presented based on Perron-Frobenius theory. We illustrate this solution approach in a case study in which we compare our optimal allocation to

allocation heuristics proposed in literature. The results show that the herd effect can be increased by 9 to 26% by using the vaccine allocations we derived. Equivalently, using our optimal allocation, we are able to significantly reduce the required vaccine stockpile to attain  $R_f = 1$ .

In Chapter 5 we study the trade-off between the timing of vaccination and the effectiveness of the response. This trade-off plays a role in several vaccination problems, of which three examples are discussed in the introduction of the chapter. We focus on a problem with an early aspecific vaccine and a late specific vaccine. We demonstrate that it is not always optimal to spend the entire budget on one of the two vaccine types, but that a decision maker should consider using a *hybrid* strategy. By using a hybrid strategy, which divides the budget over the two vaccine types, the final size can be reduced by more than 50%. The derived insights are useful for decision makers who balance between the public pressure to respond quickly and the aim to spend the budget on the best possible vaccine. Extant literature mentions some practical considerations for using hybrid strategies. In Chapter 5 we provide an additional and more generally applicable motivation for the use of hybrid strategies, which supersedes the practical arguments used in literature or in the US national pandemic response plan.

In this dissertation, we use optimization methods to find solutions to complex decision problems. Our results show that this approach yields insights into the structure of the solutions that could not be obtained numerically. For example, in Chapter 3 and Chapter 5 we show that the nonlinearities in epidemics render a geographic approach and a hybrid vaccination strategy, respectively, to be efficient. Interestingly, until now in literature such strategies were mainly motivated by practical considerations. E.g., a geographic approach was advocated in situations with a large asymmetry between the regions. Hybrid strategies were mentioned in the production of influenza vaccine, where starting production earlier for some influenza strains allows sufficient time to produce vaccines against these strains while buying time to learn more about the other strains. In this dissertation, we give an important motivation for geographic and hybrid strategies, even in the absence of such practical considerations.

Vaccine allocation has an ethical dimension, unlike many other resource allocation problems where equity does not play a role. Equitable vaccine allocations are preferred, particularly within a country. The results in this dissertation show that optimality and equity are often far apart. For example, in Chapter 3 we show that prioritizing based on geography potentially reduces infections significantly. And in Chapter 4, we show that for a population divided into age groups, it is better to vaccinate some age groups completely and leave others unvaccinated. Prioritizing based on age groups is generally more accepted than distinguishing between groups of people based on geography. But even for age groups, the policy that we describe as optimal need not be the best policy if we also take equity considerations into account. Nevertheless, the results derived in this dissertation can be a valuable contribution to the ethical debate on finding good vaccine allocations. Our optimal allocations can be used as a benchmark to determine the effects on the final size of an epidemic if a suboptimal policy is selected that is motivated by fairness. In addition, policy makers can use strategies in which they balance between efficiency and equity. The simple models and analytical insights in this dissertation provide a valuable starting point for analyzing the efficiency of such strategies.

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# Nederlandse Samenvatting

## (Summary in Dutch)

Door de eeuwen heen hebben infectieziekten miljoenen doden veroorzaakt. Verschillende uitbraken van de pest kostten de levens van velen en ook griep epidemieën eisten hun slachtoffers. Vandaag de dag komen zulke immense aantallen van slachtoffers gelukkig nauwelijks meer voor en sommige ziekten zijn zelfs geëlimineerd. Niettemin kunnen uitbraken van een nieuw griepvirus of van ziekten als SARS, MERS of Ebola op de loer liggen, zoals we ook recent nog hebben gezien. Onderzoek naar de preventie van een epidemie, maar ook naar de juiste handelswijze in het geval van een uitbraak, heeft daarom hoge prioriteit. Een medische of epidemiologische insteek ligt hierin het meest voor de hand. Tegelijk komen er ook allerlei logistieke problemen om de hoek kijken (zie Hoofdstuk 2). Moeten er bijvoorbeeld voorraden aangelegd worden van vaccins? Zo ja, hoe groot moeten die voorraden zijn en waar moeten ze opgeslagen liggen? Wanneer de middelen beperkt zijn, brengt dat allocatieproblemen met zich mee: hoe kunnen de beschikbare gezondheidswerkers, medicijnen en vaccins het beste worden ingezet? Het zijn precies deze vragen waarbij de kennis en technieken van besliskunde van grote betekenis kunnen zijn.

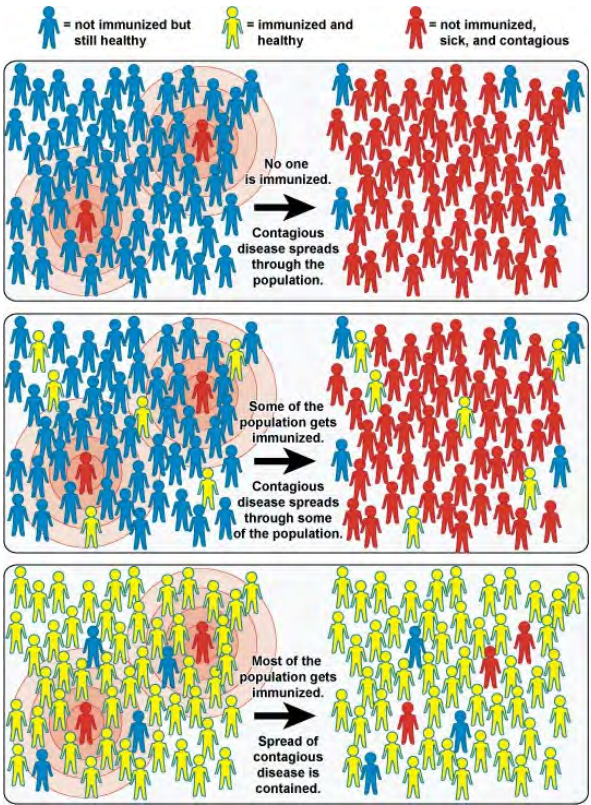
Eén van de meest effectieve manieren om een uitbraak van een infectieziekte te voorkomen, is door mensen te vaccineren. Vaccinatie leidt ertoe dat iemand (veel) minder vatbaar is voor de ziekte. Wanneer een deel van de bevolking is gevaccineerd, treden er dus minder besmettingen op. Hierdoor kan een infectieziekte zich minder snel verspreiden en wordt een uitbraak voorkomen of ingedamd. Echter, niet voor alle infectieziekten bestaat er een vaccin. Als er wel een vaccin is, is de beschikbare hoeveelheid bij een onverwachte uitbraak zelden toereikend om de gehele bevolking te

vaccineren. Dit brengt een allocatieprobleem met zich mee: hoe kunnen de beschikbare vaccins het best verdeeld worden? Wij bestuderen deze allocatie van vaccins over verschillende groepen in een totale bevolking. Deze bevolkingsgroepen noemen we populaties. Voorbeelden van populaties zijn verschillende steden en dorpen, maar ook de verschillende leeftijdsgroepen kunnen als populaties worden beschouwd.

In de literatuur is het vaccinatieallocatie probleem uitvoerig onderzocht. Veelal wordt met gedetailleerde simulatiemodellen bepaald wat het effect is van een vaccinatieallocatie. Verschillende allocaties worden vervolgens vergeleken en men trekt conclusies over de beste allocatie. Deze aanpak gebaseerd op scenario analyse is weliswaar informatief, maar resulteert niet in een duidelijk verklaring waarom bepaalde allocaties beter zijn dan andere. Dit levert vooral problemen op, aangezien de allocaties die goed blijken te zijn vaak tegenintuïtief en oneerlijk zijn (Keeling and Shattock 2012). Wij stellen daarom voor dit probleem vanuit de optimalisatie te benaderen en analytische methoden te gebruiken om inzichten te krijgen in de structuur van het probleem.

Om verschillende vaccinatieallocaties met elkaar te kunnen vergelijken, bekijken wij in ons onderzoek het effect van vaccinatie. Vaccinatie leidt tot een bepaald niveau van immuniteit, waardoor een gevaccineerd individu een kleinere kans heeft om geïnfecteerd te worden. Hierdoor zijn de gevaccineerde individuen beter beschermd, wat we het directe effect van vaccinatie noemen. Daarnaast heeft vaccinatie ook een indirect effect dat te maken heeft met het begrip groepsimmuniteit. Door vaccinatie wordt het niet-gevaccineerde deel van de bevolking omringd door gevaccineerde mensen die deels immuun zijn. Mensen die zelf niet gevaccineerd zijn, komen dus minder snel in aanraking met besmette mensen en hebben daardoor zelf ook een lagere kans op besmetting. Dit mechanisme noemen we groepsimmuniteit, wat wordt geïllustreerd in Figuur 6.1. Door vaccinatie worden dus twee groepen mensen beschermd tegen de infectieziekte: allereerst zij die zelf zijn gevaccineerd en daarnaast ook diegenen die indirect baat hebben bij de groepsimmuniteit.

Een effectieve vaccinatieallocatie maakt zo goed mogelijk gebruik van het indirecte effect. Op die manier krijg je het meeste waar voor je geld. In Hoofdstuk 3 zoeken we daarom naar die vaccinatieallocatie die het indirecte effect maximaliseert. Daarbij nemen we aan dat we een beperkte hoeveelheid vaccins tot onze beschikking hebben. Om dit indirecte effect te kwantificeren maken we gebruik van het bekende epidemiologische *SIR* model. Uit dit model leiden we een impliciete functie af voor



**Figuur 6.1:** Als een kritieke fractie van de bevolking immuun is voor een besmettelijke ziekte, zijn de meeste mensen in die bevolking beschermd. Dit verschijnsel heet ‘groepsimmunitet’ en is geïllustreerd in de onderste van de drie afbeeldingen. [Bron: National Institute of Allergy and Infectious Diseases (NIAID)]

het indirecte effect van vaccinatie. Een grondige analyse van deze impliciete functie levert een aantal interessante inzichten op. Zo kunnen we bijvoorbeeld aantonen dat er een unieke vaccinatiefractie is die resulteert in het grootste gemiddelde indirecte effect per vaccin. Deze vaccinatiefractie noemen we daarom de ‘dosis-optimale vaccinatiefractie’. De dosis-optimale vaccinatiefractie speelt een cruciale rol in de optimale allocatie. We kunnen deze optimale allocatie in grote lijnen als volgt karakteriseren: kies een aantal populaties en verdeel alle vaccins hierover zodanig dat de vaccinatiefractie in ieder van de gekozen populaties zo dicht mogelijk ligt bij de dosis-optimale

vaccinatiefractie van die populatie. Dit resulteert echter wel in allocaties die mogelijk de ene populatie hogere prioriteit geven dan de andere. Dit kan als volgt worden verklaard. Een kleine hoeveelheid vaccins is in een grote populatie wellicht een druppel op de gloeiende plaat. Dezelfde hoeveelheid kan echter in een kleine populatie het verschil maken tussen het explosief groeien en het direct uitdoven van een uitbraak. Hierdoor is het eerlijk verdelen van de vaccins over alle populaties in sommige gevallen een slecht idee, aangezien er dan in geen enkele populatie daadwerkelijk iets bereikt kan worden.

Waar we in Hoofdstuk 3 zijn uitgegaan van een beperkte hoeveelheid vaccins om daarmee een zo goed mogelijk resultaat te bereiken, keren we in Hoofdstuk 4 de vraag om: Hoeveel vaccines zijn er minimaal nodig om te voorkomen dat een uitbraak explosief kan groeien? Door op een slimme manier de vaccins te verdelen over de leeftijdsgroepen laten we zien dat we veel minder vaccins nodig hebben dan andere verdelingen die in de literatuur zijn voorgesteld. Het blijkt vooral belangrijk te zijn om die leeftijdsgroepen te vaccineren die een grote bijdrage leveren aan de verspreiding van de ziekte. Voor de Nederlandse bevolking zijn dit met name de leeftijdsgroepen 6-12, 13-19 en 20-39. Mensen in die leeftijdsgroepen hebben relatief veel contacten op school of werk en kunnen daarom veel nieuwe ziektegevallen veroorzaken. Door hen te vaccineren kan verspreiding voorkomen worden, waardoor ook de kwetsbare groepen als jonge kinderen en ouderen beschermd zijn.

Tot nu toe hebben we gekeken naar beslissingsproblemen met één vaccinatiemoment. In Hoofdstuk 5 bekijken we wat een goede strategie is als je op meerdere momenten zou kunnen vaccineren om de verspreiding van een bepaalde infectieziekte tegen te gaan. Om precies te zijn, bestuderen we twee vaccin types: het eerste type is snel beschikbaar, maar is niet zo effectief voor de infectieziekte die we bekijken. Het tweede type daarentegen is toegespitst op de betreffende ziekte en dus effectiever, maar komt pas later beschikbaar. We laten zien wanneer een beleidsmaker zou moeten investeren in welk type om ervoor te zorgen dat er zo min mogelijk mensen ziek worden. Verrassenderwijs laten onze resultaten zien dat het vaak een goed idee is om in beide vaccin types te investeren en het beschikbare budget over de twee types te verdelen. Hierdoor heb je op korte termijn een vaccin beschikbaar waarmee je direct een explosief groeiende uitbraak kunt voorkomen. Met de vaccins die later komen, kunnen dan vervolgens veel mensen effectief worden gevaccineerd.

De optimale oplossingen van de beslissingsproblemen rond vaccinatie die wij bekijken, zijn soms uiterst oneerlijk. Sommige populaties of leeftijdsgroepen krijgen wel vaccins, terwijl andere populaties of leeftijdsgroepen volledig ongevaccineerd blijven. Ook in eerder onderzoek, waarbij simulatiemodellen of numerieke analyses gebruikt zijn, kwamen dergelijke oneerlijke resultaten naar voren. Echter, vanuit zulke niet-analytische aanpakken is het lastig deze resultaten uit te leggen. De analytische benadering in ons onderzoek leidt tot nieuwe inzichten, waardoor we kunnen uitleggen hoe de oneerlijke, maar optimale allocaties tot stand komen.

In de praktijk spelen eerlijkheidsoverwegingen een belangrijke rol bij het opstellen van een vaccinatieallocatie. Het daarom niet mogelijk, of zelfs niet wenselijk, onze optimale allocaties direct te implementeren. Verschillende studies constateren hetzelfde probleem: optimaal en eerlijk liggen soms ver uit elkaar. Eén van de oplossingen die hiervoor wordt aangedragen is om de beschikbare hoeveelheid vaccins te splitsen in twee delen. Het eerste deel kan dan op een eerlijke manier verdeeld worden, terwijl het tweede deel gebruikt kan worden om een zo goed mogelijk resultaat te bereiken. Het onderzoek dat wij gedaan hebben, richt zich op deze tweede allocatie. Wij hopen dat onze analytische resultaten, die leiden tot meer inzicht in de effecten van vaccinatie, waardevol zijn in het opstellen van vaccinatieprogramma's. Bovendien laat ons onderzoek zien dat er, naast de klassieke logistieke problemen in de gezondheidszorg, zeker andere interessante terreinen zijn waar besliskunde en optimalisatie van toegevoegde waarde kunnen zijn.



# Curriculum Vitae



Evelot Duijzer (1989) obtained her Bachelor's degree (cum laude) in Econometrics and Management Science from Erasmus University Rotterdam in 2011. In 2013 she received her Master's degree (summa cum laude) in Management Science at the same university, with a specialization in Quantitative Logistics and Operations Research.

Evelot joined the Erasmus Research Institute of Management (ERIM) in September 2013 as a PhD student under the supervision of prof. dr. ir. Rommert Dekker and dr. Willem van Jaarsveld. She worked on resource allocation problems in infectious disease epidemiology, in particular on vaccine allocation. Her work has been published in Mathematical Biosciences and Omega. She has presented her research at various national and international conferences, including INFORMS Healthcare, Medical Decision Making and Vaccine. Her research interests include operations research, optimization and health care logistics.

During her PhD project she assisted in the courses Introduction to Statistics and Simulation and supervised several bachelor theses. In 2016 she obtained her University Teaching Qualification.





# Portfolio

## Publications

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### *Peer-reviewed journal articles:*

**Duijzer, Lotty E**, Willem van Jaarsveld, Jacco Wallinga and Rommert Dekker. (2016) The most efficient critical vaccination coverage and the relation with maximizing the herd effect. *Mathematical Biosciences*, 282: 68-81.

Vries, Harwin de and **Evelot Duijzer**. (2017) Incorporating driving range variability in network design for refueling facilities. *Omega* 69:102-114.

### *Non-peer-reviewed journal articles:*

**Duijzer, Lotty E**, Willem van Jaarsveld, Jacco Wallinga and Rommert Dekker. (2015) Vaccinatieallocatie en de kracht van optimalisatie. *STaTOR* 3: 4-8.

### *Working papers and reports:*

**Duijzer, Lotty E.**, Willem van Jaarsveld, Jacco Wallinga, Rommert Dekker. (2015) Dose-optimal vaccine allocation over multiple populations. *Econometric Institute Report EI 2015-29*.

**Duijzer, Lotty E.**, Willem van Jaarsveld, Rommert Dekker. (2017) Literature review - the vaccine supply chain. *Econometric Institute Report EI 2017-01*.

**Duijzer, Lotty E.**, Willem van Jaarsveld, Rommert Dekker. (2017) The benefits of combining early aspecific vaccination with later specific vaccination. *Econometric Institute Report EI 2017-03*.

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## Teaching

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### *Tutorial lecturer:*

Inleiding Statistiek (Introduction to Statistics), Erasmus School of Economics, Econometrics and Operations Research, 2013-2016.

Simulatie (Simulation), Erasmus School of Economics, Econometrics and Operations Research, 2013-2016.

### *Lecturer:*

Simulatie (Simulation), Erasmus School of Economics, Econometrics and Operations Research, 2016.

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## Additional activities

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### *Ad hoc reviewer for:*

European Journal of Operational Research

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## PhD courses

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Algorithms and Complexity

Markov Decision Processes

Noncooperative Games

Inventory Management in Supply Chains

Operations Research and Health Care

Advanced Topics in Stochastic Operations Research

Stochastic Programming

Multi-class Queues and Stochastic Networks

Networks and Polyhedra

Convex Analysis for Optimization

Epidemiology of Infectious Diseases

Scientific Integrity

Publishing Strategy

Teaching, presenting, and writing in English: CPE level

Crafting and publishing papers in Operations Research

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### **Conferences attended**

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OR 2013, Rotterdam, the Netherlands

Econometric Institute PhD Conference (EIPC) 2014, Rotterdam, the Netherlands

LNMB conference 2014, Lunteren, the Netherlands

ESE/iBMG - Technion workshop 2014, Rotterdam, the Netherlands

IFORS 2014, Barcelona, Spain

Econometric Institute PhD Conference (EIPC) 2015, Rotterdam, the Netherlands

LNMB conference 2015, Lunteren, the Netherlands

INFORMS Healthcare 2015, Nashville, Tennessee, USA

Econometric Institute PhD Conference (EIPC) 2016, Rotterdam, the Netherlands

LNMB conference 2016, Lunteren, the Netherlands

Society for Medical Decision Making - European Conference 2016, London, United Kingdom

Vaccine Congress 2016, Amsterdam, the Netherlands

Econometric Institute PhD Conference (EIPC) 2017, Rotterdam, the Netherlands

LNMB conference 2017, Lunteren, the Netherlands

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## **The ERIM PhD Series**

The ERIM PhD Series contains PhD dissertations in the field of Research in Management defended at Erasmus University Rotterdam and supervised by senior researchers affiliated to the Erasmus Research Institute of Management (ERIM). All dissertations in the ERIM PhD Series are available in full text through the ERIM Electronic Series Portal: <http://repub.eur.nl/pub>. ERIM is the joint research institute of the Rotterdam School of Management (RSM) and the Erasmus School of Economics at the Erasmus University Rotterdam (EUR).

### **Dissertations in the last five years**

Abbink, E.J., *Crew Management in Passenger Rail Transport*, Promotors: Prof. L.G. Kroon & Prof. A.P.M. Wagelmans, EPS-2014-325-LIS, <http://repub.eur.nl/pub/76927>

Acar, O.A., *Crowdsourcing for Innovation: Unpacking Motivational, Knowledge and Relational Mechanisms of Innovative Behavior in Crowdsourcing Platforms*, Promotor: Prof. J.C.M. van den Ende, EPS-2014-321-LIS, <http://repub.eur.nl/pub/76076>

Akemu, O., *Corporate Responses to Social Issues: Essays in Social Entrepreneurship and Corporate Social Responsibility*, Promotors: Prof. G.M. Whiteman & Dr S.P. Kennedy, EPS-2017-392-ORG, <https://repub.eur.nl/pub/95768>

Akin Ates, M., *Purchasing and Supply Management at the Purchase Category Level: Strategy, structure and performance*, Promotors: Prof. J.Y.F. Wynstra & Dr E.M. van Raaij, EPS-2014-300-LIS, <http://repub.eur.nl/pub/50283>

Akpinar, E., *Consumer Information Sharing*, Promotor: Prof. A. Smidts, EPS-2013-297-MKT, <http://repub.eur.nl/pub/50140>

Alexander, L., *People, Politics, and Innovation: A Process Perspective*, Promotors: Prof. H.G. Barkema & Prof. D.L. van Knippenberg, EPS-2014-331-S&E, <http://repub.eur.nl/pub/77209>

Alexiou, A. *Management of Emerging Technologies and the Learning Organization: Lessons from the Cloud and Serious Games Technology*, Promotors: Prof. S.J. Magala, Prof. M.C. Schippers and Dr I. Oshri, EPS-2016-404-ORG, <http://repub.eur.nl/pub/93818>

Almeida e Santos Nogueira, R.J. de, *Conditional Density Models Integrating Fuzzy and Probabilistic Representations of Uncertainty*, Promotors: Prof. U. Kaymak & Prof. J.M.C. Sousa, EPS-2014-310-LIS, <http://repub.eur.nl/pub/51560>

Bannouh, K., *Measuring and Forecasting Financial Market Volatility using High-frequency Data*, Promotor: Prof. D.J.C. van Dijk, EPS-2013-273-F&A, <http://repub.eur.nl/pub/38240>

Ben-Menahem, S.M., *Strategic Timing and Proactiveness of Organizations*, Promotors: Prof. H.W. Volberda & Prof. F.A.J. van den Bosch, EPS-2013-278-S&E, <http://repub.eur.nl/pub/39128>

Benschop, N., *Biases in Project Escalation: Names, frames & construal levels*, Promotors: Prof. K.I.M. Rhode, Prof. H.R. Commandeur, Prof. M. Keil & Dr A.L.P. Nuijten, EPS-2015-375-S&E, <http://repub.eur.nl/pub/79408>

Berg, W.E. van den, *Understanding Salesforce Behavior using Genetic Association Studies*, Promotor: Prof. W.J.M.I. Verbeke, EPS-2014-311-MKT, <http://repub.eur.nl/pub/51440>

Beusichem, H.C. van, *Firms and Financial Markets: Empirical Studies on the Informational Value of Dividends, Governance and Financial Reporting*, Promotors: Prof. A. de Jong & Dr G. Westerhuis, EPS-2016-378-F&A, <http://repub.eur.nl/pub/93079>

Blik, R. de, *Empirical Studies on the Economic Impact of Trust*, Promotor: Prof. J. Veenman & Prof. Ph.H.B.F. Franses, EPS-2015-324-ORG, <http://repub.eur.nl/pub/78159>

Boons, M., *Working Together Alone in the Online Crowd: The Effects of Social Motivations and Individual Knowledge Backgrounds on the Participation and Performance of Members of Online Crowdsourcing Platforms*, Promotors: Prof. H.G. Barkema & Dr D.A. Stam, EPS-2014-306-S&E, <http://repub.eur.nl/pub/50711>

Bouman, P., *Passengers, Crowding and Complexity: Models for Passenger Oriented Public Transport*, Prof. L.G. Kroon, Prof. A. Schöbel & Prof. P.H.M. Vervest, EPS-2017-420-LIS, <https://repub.eur.nl/>

Brazys, J., *Aggregated Macroeconomic News and Price Discovery*, Promotor: Prof. W.F.C. Verschoor, EPS-2015-351-F&A, <http://repub.eur.nl/pub/78243>

Byington, E., *Exploring Coworker Relationships: Antecedents and Dimensions of Interpersonal Fit, Coworker Satisfaction, and Relational Models*, Promotor: Prof. D.L. van Knippenberg, EPS-2013-292-ORG, <http://repub.eur.nl/pub/41508>

Cancurtaran, P., *Essays on Accelerated Product Development*, Promotors: Prof. F. Langerak & Prof. G.H. van Bruggen, EPS-2014-317-MKT, <http://repub.eur.nl/pub/76074>

Caron, E.A.M., *Explanation of Exceptional Values in Multi-dimensional Business Databases*, Promotors: Prof. H.A.M. Daniels & Prof. G.W.J. Hendrikse, EPS-2013-296-LIS, <http://repub.eur.nl/pub/50005>

Carvalho, L. de, *Knowledge Locations in Cities: Emergence and Development Dynamics*, Promotor: Prof. L. Berg, EPS-2013-274-S&E, <http://repub.eur.nl/pub/38449>

Chammas, G., *Portfolio concentration*, Promotor: Prof. J. Spronk, EPS-2017-410-F&E, <https://repub.eur.nl/pub/94975>

Cranenburgh, K.C. van, *Money or Ethics: Multinational corporations and religious organisations operating in an era of corporate responsibility*, Prof. L.C.P.M. Meijs, Prof. R.J.M. van Tulder & Dr D. Arenas, EPS-2016-385-ORG, <http://repub.eur.nl/pub/93104>

Consiglio, I., *Others: Essays on Interpersonal and Consumer Behavior*, Promotor: Prof. S.M.J. van Osselaer, EPS-2016-366-MKT, <http://repub.eur.nl/pub/79820>

Cox, R.H.G.M., *To Own, To Finance, and To Insure - Residential Real Estate Revealed*, Promotor: Prof. D. Brounen, EPS-2013-290-F&A, <http://repub.eur.nl/pub/40964>

Darnihamedani, P. *Individual Characteristics, Contextual Factors and Entrepreneurial Behavior*, Promotors: Prof. A.R. Thurik & S.J.A. Hessels, EPS-2016-360-S&E, <http://repub.eur.nl/pub/93280>

Dennerlein, T. *Empowering Leadership and Employees' Achievement Motivations: the Role of Self-Efficacy and Goal Orientations in the Empowering Leadership Process*, Promotors: Prof. D.L. van Knippenberg & Dr J. Dietz, EPS-2017-414-ORG, <https://repub.eur.nl/pub/98438>

Deng, W., *Social Capital and Diversification of Cooperatives*, Promotor: Prof. G.W.J. Hendrikse, EPS-2015-341-ORG, <http://repub.eur.nl/pub/77449>

Depecik, B.E., *Revitalizing brands and brand: Essays on Brand and Brand Portfolio Management Strategies*, Promotors: Prof. G.H. van Bruggen, Dr Y.M. van Everdingen and Dr M.B. Ataman, EPS-2016-406-MKT, <http://repub.eur.nl/pub/93507>

Dollevoet, T.A.B., *Delay Management and Dispatching in Railways*, Promotor: Prof. A.P.M. Wagelmans, EPS-2013-272-LIS, <http://repub.eur.nl/pub/38241>

Duyvesteyn, J.G. *Empirical Studies on Sovereign Fixed Income Markets*, Promotors: Prof. P. Verwijmeren & Prof. M.P.E. Martens, EPS-2015-361-F&A, <https://repub.eur.nl/pub/79033>

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Elemes, A, *Studies on Determinants and Consequences of Financial Reporting Quality*, Promotor: Prof. E. Peek, EPS-2015-354-F&A, <https://repub.eur.nl/pub/79037>

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Eskenazi, P.I., *The Accountable Animal*, Promotor: Prof. F.G.H. Hartmann, EPS-2015-355-F&A, <http://repub.eur.nl/pub/78300>

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Feng, Y., *The Effectiveness of Corporate Governance Mechanisms and Leadership Structure: Impacts on strategic change and firm performance*, Promotors: Prof. F.A.J. van den Bosch, Prof. H.W. Volberda & Dr J.S. Sidhu, EPS-2017-389-S&E, <https://repub.eur.nl/pub/98470>

Fernald, K., *The Waves of Biotechnological Innovation in Medicine: Interfirm Cooperation Effects and a Venture Capital Perspective*, Promotors: Prof. E. Claassen, Prof. H.P.G. Pennings & Prof. H.R. Commandeur, EPS-2015-371-S&E, <http://hdl.handle.net/1765/79120>

Fisch, C.O., *Patents and trademarks: Motivations, antecedents, and value in industrialized and emerging markets*, Promotors: Prof. J.H. Block, Prof. H.P.G. Pennings & Prof. A.R. Thurik, EPS-2016-397-S&E, <http://repub.eur.nl/pub/94036>

Fliers, P.T., *Essays on Financing and Performance: The role of firms, banks and board*, Promotor: Prof. A. de Jong & Prof. P.G.J. Roosenboom, EPS-2016-388-F&A, <http://repub.eur.nl/pub/93019>

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Hekimoglu, M., *Spare Parts Management of Aging Capital Products*, Promotor: Prof. R. Dekker, EPS-2015-368-LIS, <http://repub.eur.nl/pub/79092>

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Hogenboom, F.P., *Automated Detection of Financial Events in News Text*, Promotors: Prof. U. Kaymak & Prof. F.M.G. de Jong, EPS-2014-326-LIS, <http://repub.eur.nl/pub/77237>

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Hout, D.H. van, *Measuring Meaningful Differences: Sensory Testing Based Decision Making in an Industrial Context; Applications of Signal Detection Theory and Thurstonian Modelling*, Promotors: Prof. P.J.F. Groenen & Prof. G.B. Dijksterhuis, EPS-2014-304-MKT, <http://repub.eur.nl/pub/50387>

Houwelingen, G.G. van, *Something To Rely On*, Promotors: Prof. D. de Cremer & Prof. M.H. van Dijke, EPS-2014-335-ORG, <http://repub.eur.nl/pub/77320>

Hurk, E. van der, *Passengers, Information, and Disruptions*, Promotors: Prof. L.G. Kroon & Prof. P.H.M. Vervest, EPS-2015-345-LIS, <http://repub.eur.nl/pub/78275>

Iseger, P. den, *Fourier and Laplace Transform Inversion with Applications in Finance*, Promotor: Prof. R. Dekker, EPS-2014-322-LIS, <http://repub.eur.nl/pub/76954>

Jaarsveld, W.L. van, *Maintenance Centered Service Parts Inventory Control*, Promotor: Prof. R. Dekker, EPS-2013-288-LIS, <http://repub.eur.nl/pub/39933>

Khanagha, S., *Dynamic Capabilities for Managing Emerging Technologies*, Promotor: Prof. H.W. Volberda, EPS-2014-339-S&E, <http://repub.eur.nl/pub/77319>

Khattab, J., *Make Minorities Great Again: a contribution to workplace equity by identifying and addressing constraints and privileges*, Prof. D.L. van Knippenberg & Dr A. Nederveen Pieterse, EPS-2017-421-ORG, <https://repub.eur.nl/pub/99311>

Kil, J., *Acquisitions Through a Behavioral and Real Options Lens*, Promotor: Prof. H.T.J. Smit, EPS-2013-298-F&A, <http://repub.eur.nl/pub/50142>

Klooster, E. van't, *Travel to Learn: the Influence of Cultural Distance on Competence Development in Educational Travel*, Promoters: Prof. F.M. Go & Prof. P.J. van Baalen, EPS-2014-312-MKT, <http://repub.eur.nl/pub/51462>

Koendjibiharie, S.R., *The Information-Based View on Business Network Performance: Revealing the Performance of Interorganizational Networks*, Promoters: Prof. H.W.G.M. van Heck & Prof. P.H.M. Vervest, EPS-2014-315-LIS, <http://repub.eur.nl/pub/51751>

Koning, M., *The Financial Reporting Environment: The Role of the Media, Regulators and Auditors*, Promoters: Prof. G.M.H. Mertens & Prof. P.G.J. Roosenboom, EPS-2014-330-F&A, <http://repub.eur.nl/pub/77154>

Konter, D.J., *Crossing Borders with HRM: An Inquiry of the Influence of Contextual Differences in the Adoption and Effectiveness of HRM*, Promoters: Prof. J. Paauwe & Dr L.H. Hoeksema, EPS-2014-305-ORG, <http://repub.eur.nl/pub/50388>

Korkmaz, E., *Bridging Models and Business: Understanding Heterogeneity in Hidden Drivers of Customer Purchase Behavior*, Promoters: Prof. S.L. van de Velde & Prof. D. Fok, EPS-2014-316-LIS, <http://repub.eur.nl/pub/76008>

Krämer, R., *A license to mine? Community organizing against multinational corporations*, Promoters: Prof. R.J.M. van Tulder & Prof. G.M. Whiteman, EPS-2016-383-ORG, <http://repub.eur.nl/pub/94072>

Kroezen, J.J., *The Renewal of Mature Industries: An Examination of the Revival of the Dutch Beer Brewing Industry*, Promotor: Prof. P.P.M.A.R. Heugens, EPS-2014-333-S&E, <http://repub.eur.nl/pub/77042>

Kysucky, V., *Access to Finance in a Cross-Country Context*, Promotor: Prof. L. Norden, EPS-2015-350-F&A, <http://repub.eur.nl/pub/78225>

Lee, C.I.S.G., *Big Data in Management Research: Exploring New Avenues*, Promoters: Prof. S.J. Magala & Dr W.A. Felps, EPS-2016-365-ORG, <http://repub.eur.nl/pub/79818>

Legault-Tremblay, P.O., *Corporate Governance During Market Transition: Heterogeneous responses to Institution Tensions in China*, Promotor: Prof. B. Krug, EPS-2015-362-ORG, <http://repub.eur.nl/pub/78649>

Lenoir, A.S. *Are You Talking to Me? Addressing Consumers in a Globalised World*, Promoters: Prof. S. Puntoni & Prof. S.M.J. van Osselaer, EPS-2015-363-MKT, <http://repub.eur.nl/pub/79036>

Leunissen, J.M., *All Apologies: On the Willingness of Perpetrators to Apologize*, Promoters: Prof. D. de Cremer & Dr M. van Dijke, EPS-2014-301-ORG, <http://repub.eur.nl/pub/50318>

Li, D., *Supply Chain Contracting for After-sales Service and Product Support*, Promotor: Prof. M.B.M. de Koster, EPS-2015-347-LIS, <http://repub.eur.nl/pub/78526>

Li, Z., *Irrationality: What, Why and How*, Promotors: Prof. H. Bleichrodt, Prof. P.P. Wakker, & Prof. K.I.M. Rohde, EPS-2014-338-MKT, <http://repub.eur.nl/pub/77205>

Liu, N., *Behavioral Biases in Interpersonal Contexts*, Supervisors: Prof. A. Baillon & Prof. H. Bleichrodt, EPS-2017-408-MKT, <https://repub.eur.nl/pub/95487>

Liang, Q.X., *Governance, CEO Identity, and Quality Provision of Farmer Cooperatives*, Promotor: Prof. G.W.J. Hendrikse, EPS-2013-281-ORG, <http://repub.eur.nl/pub/39253>

Liket, K., *Why 'Doing Good' is not Good Enough: Essays on Social Impact Measurement*, Promotors: Prof. H.R. Commandeur & Dr K.E.H. Maas, EPS-2014-307-STR, <http://repub.eur.nl/pub/51130>

Loos, M.J.H.M. van der, *Molecular Genetics and Hormones: New Frontiers in Entrepreneurship Research*, Promotors: Prof. A.R. Thurik, Prof. P.J.F. Groenen, & Prof. A. Hofman, EPS-2013-287-S&E, <http://repub.eur.nl/pub/40081>

Lu, Y., *Data-Driven Decision Making in Auction Markets*, Promotors: Prof. H.W.G.M. van Heck & Prof. W. Ketter, EPS-2014-314-LIS, <http://repub.eur.nl/pub/51543>

Ma, Y., *The Use of Advanced Transportation Monitoring Data for Official Statistics*, Promotors: Prof. L.G. Kroon and Dr J. van Dalen, EPS-2016-391-LIS, <http://repub.eur.nl/pub/80174>

Manders, B., *Implementation and Impact of ISO 9001*, Promotor: Prof. K. Blind, EPS-2014-337-LIS, <http://repub.eur.nl/pub/77412>

Mell, J.N., *Connecting Minds: On The Role of Metaknowledge in Knowledge Coordination*, Promotor: Prof. D.L. van Knippenberg, EPS-2015-359-ORG, <http://hdl.handle.net/1765/78951>

Meulen, van der, D., *The Distance Dilemma: the effect of flexible working practices on performance in the digital workplace*, Promotors: Prof. H.W.G.M. van Heck & Prof. P.J. van Baalen, EPS-2016-403-LIS, <http://repub.eur.nl/pub/94033>

Micheli, M.R., *Business Model Innovation: A Journey across Managers' Attention and Inter-Organizational Networks*, Promotor: Prof. J.J.P. Jansen, EPS-2015-344-S&E, <http://repub.eur.nl/pub/78241>

Milea, V., *News Analytics for Financial Decision Support*, Promotor: Prof. U. Kaymak, EPS-2013-275-LIS, <http://repub.eur.nl/pub/38673>

Moniz, A., *Textual Analysis of Intangible Information*, Promotors: Prof. C.B.M. van Riel, Prof. F.M.G de Jong & Dr G.A.J.M. Berens, EPS-2016-393-ORG, <http://repub.eur.nl/pub/93001>

Mulder, J., *Network design and robust scheduling in liner shipping*, Promotors: Prof. R. Dekker & Dr W.L. van Jaarsveld, EPS-2016-384-LIS, <http://repub.eur.nl/pub/80258>

Naumovska, I., *Socially Situated Financial Markets: A Neo-Behavioral Perspective on Firms, Investors and Practices*, Promotors: Prof. P.P.M.A.R. Heugens & Prof. A. de Jong, EPS-2014-319-S&E, <http://repub.eur.nl/pub/76084>

Neerijnen, P., *The Adaptive Organization: the socio-cognitive antecedents of ambidexterity and individual exploration*, Promotors: Prof. J.J.P. Jansen, P.P.M.A.R. Heugens & Dr T.J.M. Mom, EPS-2016-358-S&E, <http://repub.eur.nl/pub/93274>

Okbay, A., *Essays on Genetics and the Social Sciences*, Promotors: Prof. A.R. Thurik, Prof. Ph.D. Koellinger & Prof. P.J.F. Groenen, EPS-2017-413-S&E, <https://repub.eur.nl/pub/95489>

Oord, J.A. van, *Essays on Momentum Strategies in Finance*, Promotor: Prof. H.K. van Dijk, EPS-2016-380-F&A, <http://repub.eur.nl/pub/80036>

Peng, X., *Innovation, Member Sorting, and Evaluation of Agricultural Cooperatives*, Promotor: Prof. G.W.J. Hendriks, EPS-2017-409-ORG, <https://repub.eur.nl/pub/94976>

Pennings, C.L.P., *Advancements in Demand Forecasting: Methods and Behavior*, Promotors: Prof. L.G. Kroon, Prof. H.W.G.M. van Heck & Dr J. van Dalen, EPS-2016-400-LIS, <http://repub.eur.nl/pub/94039>

Peters, M., *Machine Learning Algorithms for Smart Electricity Markets*, Promotor: Prof. W. Ketter, EPS-2014-332-LIS, <http://repub.eur.nl/pub/77413>

Pocock, M., *Status Inequalities in Business Exchange Relations in Luxury Markets*, Promotors: Prof. C.B.M. van Riel & Dr G.A.J.M. Berens, EPS-2017-346-ORG, <https://repub.eur.nl/pub/98647>

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Vaccination is one of the most effective ways to prevent an outbreak of an infectious disease. It results in immunity for the vaccinated individuals, but also reduces the infection pressure for unvaccinated people. In the past years, the Operations Research/Operations Management community has shown a growing interest in the logistical aspects of vaccination.

In this dissertation, we structure the literature on vaccine logics. Using a supply chain perspective, we identify the following four components in the vaccine supply chain: product, production, allocation and distribution. For each of the components, we describe the decision problems and we identify future research directions. In the remainder of this dissertation, we analyze three decision problems in the field of vaccine allocation: the allocation of a limited vaccine stockpile to fight a sudden outbreak, the allocation of prepandemic vaccines in an age-structured population and the allocation of a limited budget over multiple vaccine types. We use mathematical optimization to find solutions to these complex allocation problems.

We contribute by providing insights into the structure of the solutions that could not be obtained numerically. Our results show that optimality and equity are often far apart. Policy makers therefore need strategies in which they balance between efficiency and equity. The simple models and analytical insights in this dissertation provide a valuable starting point for analyzing such strategies.

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