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The most efficient critical vaccination coverage and its equivalence with maximizing the herd effect

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ABSTRACT

'Critical vaccination coverages' are vaccination allocations that result in an effective reproduction ratio of one. In a population with interacting subpopulations there are many different critical vaccination coverages. To find the most efficient critical vaccination coverage, we define the following optimization problem: minimize the required amount of vaccines to obtain an effective reproduction ratio of exactly one. We prove that this optimization problem is equivalent to the problem of maximizing the proportion of susceptibles that escape infection during an epidemic (i.e., maximizing the herd effect).

We propose an efficient general approach to solve these optimization problems based on Perron–Frobenius theory. We study two special cases that provide further insight into these optimization problems. First, we derive an efficient algorithm for the case of multiple populations that interact according to separable mixing. In this algorithm the subpopulations are ordered by their ratio of population size to reproduction ratio. Allocating vaccines based on this priority order results in an optimal allocation. Second, we derive an explicit analytic solution for the case of two interacting populations. We apply our solutions in a case study for pre-pandemic vaccination in the initial phase of an influenza pandemic where the entire population is susceptible to the new influenza virus. The results show that for the optimal allocation the critical vaccination coverage is achieved for a much smaller amount of vaccines as compared to allocations proposed previously.

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 that 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. 14]. 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., 22,42] or on the threshold criterion $R = 1$ [e.g., 7,26]. 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., 3,29,46] or simulation [e.g., 1,10,18] 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 [39] 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 [31]. 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 [2] 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 [2] shows that an epidemic occurs only for $R_0 > 1$, implying that the final size equation has an interior

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solution in that case. In case $R_0 \leq 1$ only the boundary solution exists, corresponding to no outbreak. We build upon [2] 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 that are protected from infection by vaccination, whereas the indirect herd effect is measured as the proportion of the people that 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 [28]. 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 previous work we already showed that this holds for a single population [17], we extend this in the current paper to interacting populations. The current paper differs from [17] in studying prepandemic vaccination with unlimited supply of vaccines, such that critical vaccination coverage is always attainable. In contrast, [17] 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 paper is that we gain insights in 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., 36,40] or enumerate all possibilities [e.g., 32,29]. (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 [14]. 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 [34].
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.

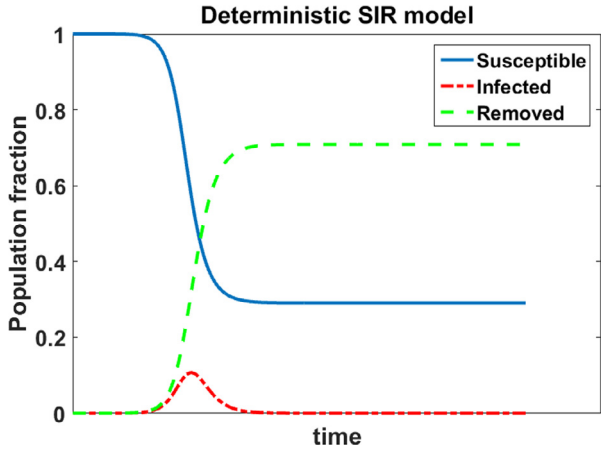

Fig. 1. Illustration of the deterministic *SIR* model for two populations with parameters $\gamma_j = 2.3$, $\beta_{jj} = 3$ for $j = 1, 2$ and $\beta_{jl} = 1$ for $j \neq l$. We introduce a minor infection of $i_j(0) = 10^{-6}$ for $j = 1, 2$ to analyze the time course of the epidemic. Because of symmetry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

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 paper is structured as follows. In Section 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 paper. Section 3 discusses the assumptions and some technical details that are needed for the analysis of the optimization problems. In Section 4 we prove that the two vaccine allocation problems are equivalent. Section 5 is dedicated to solving these problems. Section 6 contains an application of our solution method. We conclude the paper with a discussion in Section 7.

2. Problem formulation

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. 24]. 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 γ_j denote the recovery rate in population j and let β_{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:

$$\begin{aligned}
\frac{ds_j}{dt} &= -\sum_{l\in J} \beta_{jl} s_j i_l \quad \forall j \in J \\
\frac{di_j}{dt} &= \sum_{l\in J} \beta_{jl} s_j i_l - \gamma_j i_j \quad \forall j \in J \\
\frac{dr_j}{dt} &= \gamma_j i_j \quad \forall j \in J
\end{aligned} \tag{1}$$

Fig. 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.,