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Finding optimal vaccination strategies under parameter uncertainty using stochastic programming

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ABSTRACT

We present a stochastic programming framework for finding the optimal vaccination policy for controlling infectious disease epidemics under parameter uncertainty. Stochastic programming is a popular framework for including the effects of parameter uncertainty in a mathematical optimization model. The problem is initially formulated to find the minimum cost vaccination policy under a chance-constraint. The chance-constraint requires that the probability that $R_* \leqslant 1$ be greater than some parameter α, where R_* is the post-vaccination reproduction number. We also show how to formulate the problem in two additional cases: (a) finding the optimal vaccination policy when vaccine supply is limited and (b) a cost–benefit scenario. The class of epidemic models for which this method can be used is described and we present an example formulation for which the resulting problem is a mixed-integer program. A short numerical example based on plausible parameter values and distributions is given to illustrate how including parameter uncertainty improves the robustness of the optimal strategy at the cost of higher coverage of the population. Results derived from a stochastic programming analysis can also help to guide decisions about how much effort and resources to focus on collecting data needed to provide better estimates of key parameters.

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1. Introduction

Vaccination is one of the primary strategies used by public health authorities to control human infectious diseases. Mathematical models have long played a major role in identifying and evaluating strategies to allocate resources in order to guarantee maximum effectiveness of vaccination in controlling infectious disease outbreaks. Three primary modeling approaches have been used in this effort – deterministic analytical models, stochastic analytical models, and computer simulations. The determination of optimal vaccination strategies may be sensitive to changes in model parameter values, however, so there is a need for new methods that can take parameter uncertainty into account in order to find more robust vaccination policies. We present here a description of one such method, stochastic programming, and illustrate how this method can improve our ability to find optimal vaccination strategies.

The goal of most deterministic and stochastic epidemiological models addressing vaccination strategies is to derive appropriate strategies analytically. Deterministic models focused on identifying reasonable vaccination strategies for the control of infectious diseases date back to at least the 1960s [early papers include, for example, [11,23,36,40]]. In general, deterministic vaccination models fall into two major groups. The majority of these models are used to evaluate predetermined vaccination strategies to see which of the proposed strategies may be most effective. Analysis of most of these models generally involves exploration of the steady state behavior of the model system and determination of an epidemic threshold. The effectiveness of different proposed vaccination strategies in reducing the susceptible population below the epidemic threshold for the minimum cost is then evaluated. In some of the recent more complex models, computer simulation is used to assess the effectiveness of different strategies. Models of this type have been developed for a number of infectious diseases, including tuberculosis [11,40], measles [1,3,20,37], rubella [2,13,19,27], pertussis [18,21,22,24], and respiratory illnesses [34].

The second group of deterministic vaccination models do not start with predetermined strategies; rather, they center on the use of optimization methods in combination with deterministic epidemic models to identify the optimal vaccination strategy. Optimization methods have been used both in a theoretical framework [23] and to guide the development of vaccination policies for specific diseases, including tuberculosis [36], influenza [28], and smallpox [16].

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A number of stochastic models have also been developed to determine optimal vaccination strategies. For example, Ball et al. [4] develop an SIR epidemic model[1] with both local mixing at the household level and global mixing at the community level. They introduce the notation, R_*, to represent the threshold parameter for a community of households. They analyze the case of a perfect vaccine and show that under this condition, a strategy that allocates vaccines to those households with the largest number of unvaccinated individuals is best for reducing R_* to a level that will control an epidemic. Becker and Starczak [9] study vaccination policies in a stochastic SIR model divided into a community of households. They derive a closed form equation for the post-vaccination reproductive number, R_*, then formulate and numerically solve a linear program to find the minimum vaccination coverage under the constraint $R_* \leqslant 1$. This constraint ensures that the disease will tend to die out. (Becker and Starczak [9] use the notation R_{HV} rather than R_*, but the concepts are equivalent.) Drawing upon the earlier work of Ball et al. [4], Ball and Lyne [6] consider the case of an all-or-nothing vaccine where a person is either totally immune following vaccination or the vaccine does not work at all. They show that if the sequence $\{n\mu_n\}$ is convex, where μ_n is the mean size of a local outbreak within a household of size n, then the optimal solution to the linear programming problem formulation of Becker and Starczak [9] can be characterized explicitly. Ball et al. [5] use the model described by Ball and Lyne [6] to address the question of optimal allocation of vaccines. They show that an explicit characterization of the optimal vaccination strategy is only possible in certain special cases, such as proportionate mixing. Müller [32] uses an SIRS epidemic model to derive optimal vaccination strategies in an age structured population and compares the conditions needed for optimal vaccination coverage of individuals as opposed to entire populations. Hill and Longini [25] use a general framework that could apply to several epidemic situations (e.g., diseases with permanent immunity (SIR models), incorporation of latent periods (SEIR models), or no immunity (SIS models) with and without vital dynamics). They develop a method to derive optimal vaccination strategies for populations divided into m heterogenous subgroups and fully examine the use of the model in populations with two subgroups and proportionate mixing.

Very few of these analytical models include discussion of the effect of parameter uncertainty on the vaccination policies identified and/or evaluated but this uncertainty can have major consequences. For example, Longini et al. [28] show that the optimal allocation of vaccines derived from their influenza model is highly sensitive to both the epidemiological characteristics of the virus and to the choice of the objective function used in the optimization process. Similar conclusions about the sensitivity of model outcomes to epidemiological and structural uncertainty are reached by Bansal et al. [7], who use a contact network model to compare morbidity-based strategies that target high prevalence populations and mortality-based strategies that target high risk populations, Dushoff et al. [14] who use a very simple model to explore the consequences of different vaccine allocation strategies, and Clancy and Green [12] who use a Bayesian-decision theoretic approach and a general stochastic SIR model with a homogenous population under parameter uncertainty.

Computer simulation models within a fully stochastic framework have also been used to assess the effectiveness of various potential strategies to control infectious disease spread. Most of these papers focus on pure control strategies, such as antivirals, vaccines, quarantine, and travel restrictions, that are implemented over the entire population. The effect of these strategies used individually and in different combinations are analyzed through simulation (see, for example, [15,17,31]). As an example of a simulation model focused specifically on the identification of an optimal vaccination strategy, Patel et al. [33] use a genetic algorithm within the framework of a simulation of pandemic influenza. Their algorithm is a heuristic; in other words, it is designed to find feasible solutions to the problem but there is no guarantee for how close those solutions are to the true optimal solution. It is important to note that at the present time heuristic approaches are all that are available for this class of problems. Also, due to the large amount of computer time per simulation run, none of the simulation papers discussed here consider the effects of parameter uncertainty.

Both analytical models and simulation models have weaknesses that must be considered in light of the goals of a modeling project. A major criticism of analytical deterministic and stochastic vaccination models that allow closed form representations of R_* is that many assumptions are needed to have this property. These assumptions generally result in a model that is only a rough approximation of the actual spread of a disease through a population. Despite this weakness, analytical models can still be useful because they can give a clearer picture of the crucial parameters in a model [5]. For the task of identifying appropriate vaccination strategies, analytical models provide a good way to find mixed strategies that can provide insight into the groups that need to be particularly targeted by health authorities. Simulation models, which generally incorporate more realistic assumptions about population structure and disease transmission processes, are usually limited to pure or simple strategies because of the time required to run simulations given their complexity and the necessity of running them repeatedly because of their inherent randomness. Another important use of optimal strategies derived from analytical disease models is as a benchmark for strategies found via a heuristic on simulation models. The cost and effectiveness of the heuristic strategies can be checked against the optimal strategies of the analytical models to provide information on the quality of the heuristic strategies.

The complexity of human interactions means that parameter estimation for epidemiological models is notoriously difficult. Thus, vaccination policies found for any kind of model should be considered very carefully, especially if the uncertainty of the parameters is not taken into account. Policies derived from models with deterministic parameters may not be robust in the sense that even an optimal strategy might be highly suboptimal or even infeasible if parameters are changed slightly. Stochastic programming is a popular method for incorporating uncertainty in mathematical optimization problems by finding optimal decisions given that some parameter values are not deterministically known [10].

Using stochastic programming to include parameter uncertainty when finding optimal vaccination strategies can give several clear benefits. The stochastic programming framework allows for more robust vaccination strategies that are not as reliant on point estimates of parameter values. Stochastic programming can also help identify parameters to which optimal decisions are particularly sensitive, and so can provide guidance for allocation of resources for estimating parameters of the model.

The formulations presented in this paper include chance constraints to require $R_* \leqslant 1$ with at least a minimum probability, a random objective to minimize the probability that an epidemic will occur under resource constraints, and a cost-benefit formulation making the required probability for $R_* \leqslant 1$ a decision variable. The problem is formulated in a general framework that is valid for a wide class of epidemic models. We illustrate the stochastic

[1] Epidemiological models are often formulated as a series of compartments corresponding to different disease states, e.g. susceptible, exposed, infectious, recovered, etc. The models are then referred to by the series of capital letters that corresponds to the compartments within the basic model structure. For example, an SIR model considers individuals to be either susceptible (S), infectious (I), or recovered (R) and to progress through the stages in that order; an SIS model would consist of the stages susceptible – infectious – susceptible and would represent a disease for which there was no immunity.

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