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Decision Support

The benefits of combining early aspecific vaccination with later specific vaccination

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ABSTRACT

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

We model disease progression using the seminal *SIR* model, and consider a decision maker who allocates her budget over two vaccine types: an early aspecific vaccine and a later specific vaccine. We analytically characterize the switching curve separating the parameter space region where the late specific vaccine is preferred from the region where the early aspecific type is preferred. More importantly, we show that the decision maker should not only consider *pure* strategies, i.e., strategies which spend the entire budget on one of the types. Instead, she should invest in both vaccine types to benefit both from an early response and from an effective vaccine. We prove that at the switching curve, such a *hybrid* strategy is strictly better than either of the pure strategies due to the non-linear dynamics of epidemics. Our numerical experiments show that a hybrid strategy can reduce the number of infections by more than 50% compared to the best pure strategy. Such experiments also substantiate our restriction to two vaccine types.

1. Introduction

One of the crucial aspects of successful vaccination is timing. As an infectious disease can spread quickly through a population, the earlier people can be immunized, the better. However, an effective response strategy cannot always be started directly, either because the characteristics of the outbreak are not yet known, or because it takes time to produce and distribute the right vaccines. Thus, policy makers face a trade-off between vaccination timing and an effective response strategy. The effectiveness of the response is related to the *efficacy* of a vaccine, which is a measure of relative risk in a vaccinated group compared to an unvaccinated control group. The higher the efficacy of a vaccine, the better the vaccine is able to achieve immunity in the vaccinee.

There are numerous practical situations where policy makers must make a trade-off between vaccination timing and an effective response strategy. Here are three examples of decisions that need to be made in vaccine delivery where this trade-off plays a role:

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

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

3. For some vaccines a single dose only results in limited protection. To benefit fully from the vaccine, you need multiple doses, a number of days apart. When a certain number of doses of vaccine is available, policy makers must decide how this vaccine stockpile should be allocated: they can either give a single dose to a large number of people, or two doses to half of the group (Matrajt, Britton, Halloran, & Longini, 2015). Practitioners also confirmed the practical relevance of studying this decision problem (private communication, Wallinga, 2016). For example, it played a role in the 2009 H1N1 influenza pandemic. In case of a pandemic, it is advised to administer two doses of vaccine. For seasonal influenza, a single dose is sufficient because most people have been infected with the same influenza subtype before. In 2009 it was unclear whether one or two doses were necessary because the H1N1 subtype had been circulating for a longer time, but the virus causing the outbreak was very different. In such a case it is likely that a single dose protects relatively well, but two doses protect better.

   It may not be obvious how timing of vaccination plays a role in this example. However, the fact that there is a fixed time in between two doses implies that the epidemic can spread between the first and the second dose. A one-dose strategy thus corresponds to a quick response, whereas a two-dose strategy has a higher efficacy, revealing the same generic trade-off as for the other two types of decisions. However, this third decision problem has a few aspects that would need to be captured by making the following two additional assumptions. Firstly, the amount of vaccines allocated for the second dose cannot be larger than the amount of vaccines allocated for the first dose. Secondly, it is no longer possible to vaccinate people randomly with the second dose, because to benefit from the higher efficacy these people should have already received the first dose.

In this paper, we synthesize these decision problems and formulate a general problem that encapsulates all three examples. We formulate this general problem in terms of example 2, but the other examples can analogously be analyzed, although example 3 requires some additional assumptions. We therefore leave it for future research to study how our results can be translated to example 3. In this article, we consider a policy maker who has a limited budget to fight an outbreak of an infectious disease. The budget can be spent on multiple vaccine types that differ in time of availability and in their efficacy. Most of our research focuses on a simple example with two vaccine types. Type 1 is an early aspecific vaccine with low efficacy and type 2 is a late specific vaccine with high efficacy. We analyze for which combinations of parameters (moment of availability, efficacy) type 1 is preferred over type 2. We first prove a rather intuitive result: the existence of a switching curve which separates the region in the parameter space where the late specific vaccine is preferred from the region where the early aspecific type is preferred. In this paper, we give an analytical expression characterizing this curve.

More importantly, we show that the decision maker should not only consider spending her entire budget on one of the vaccine types. Instead, she should invest in both vaccine types to benefit both from the early response and from the effective vaccine. Such a *hybrid strategy* has received little attention in the literature, although some national pandemic response plans propose a similar strategy by emphasizing the importance of investing in stockpiles of vaccines for known virus types as well as expanding the vaccine manufacturing capacity for the production of pandemic vaccines tailored to a specific virus (Homeland Security Council, 2006; U.S. Department of Health & Human Services, 2005).

Our main contribution in this paper is to formally propose and analyze such hybrid strategies. We characterize the areas in the parameter space where either of the two pure strategies or the hybrid strategy is optimal. We prove that there is an area around the switching curve where hybrid strategies are superior to pure strategies. We argue that this is due to the non-linear dynamics of an epidemic. By using both vaccine types, the early vaccine can be used to reduce the initial growth in infections, while the more effective vaccine is used to control the epidemic. Our numerical results show that a hybrid strategy can reduce the number of infections by more than 50% compared to the best pure strategy. Our analysis of hybrid strategies contributes to three streams of literature (see Section 2). This is because our formulation generalizes examples 1–3 above.

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

In this paper, we focus on the most interesting case of hybrid strategies, namely those with two vaccine types. Our numerical results show that this choice is not restrictive, as hybrid strategies with more than two vaccine types are not beneficial. Moreover, our results can also be applied to vaccines that become available in batches instead of instantaneously.

The remainder of the paper is structured as follows. We start with a literature review in Section 2, in which we also discuss various epidemic models. In Section 3 we formally define the