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Optimal Control of Infectious Diseases in a Population with Heterogeneous Dynamic Immunity *

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Abstract

Exposure to infectious agents triggers immune responses in individual hosts. Heterogeneity of immune responses of the individual hosts and the host population affects the transmission dynamics of the infectious agent. We extend a previously developed epidemiological modelling approach where heterogeneity of individual-specific immunity was incorporated and explore optimal control problems associated with the corresponding control strategies. This allows for the study of dynamic intervention scenarios. We focus on vaccination leading to perfect or imperfect immunity as well as treatment and/or chemoprophylaxis interventions depending on the modelling scenario. The objective of the control strategy we explore within the context of an epidemic is to minimise the number of infected individuals and medical costs. We investigate steady states, bifurcation points and make connections to known properties of simple homogeneous SI-models with respect to critical vaccination thresholds. Analytical results show that the number of infected persons in an endemic steady state is predominantly determined by the dynamics of immunity. Our findings show that the level of vaccination needed to protect the population against an epidemic is similar to that of homogeneous models. For imperfect vaccines the critical vaccination threshold is higher. The versatility of our model can be shown when combining the cases where vaccination grants immunity for some and partial protection by immune boosting for others. The use of chemoprophylaxis and treatment has the strongest effect when chemoprophylaxis is used for the susceptible population early on and widely. The incorporation of population immunity heterogeneities in epidemic modelling shows how immune response can influence the dynamics of epidemics and can provide insight into the within host and host population interactions.

Keywords: mathematical epidemiology, heterogeneous SI-models, optimal control, size-structured systems, immunoepidemiology, treatment, vaccination

1 Introduction

The immune system of an individual is a key factor in the transmission of infectious agents. Immune responses play a crucial role in the process of an individual becoming infected or not. Previous immunity as well as the speed and efficiency by which immune responses are mounted determine the course of the infection within a host, leading to a faster recovery at the individual level and it results in a decreased chance of infecting other individuals at the population level having a profound public health benefit. Susceptibility and immune status, response of the individual host and the host population affected, and

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infectivity of the infectious agent influence the outcome of an epidemic. This has lead to the study of immunoepidemiological models that combine the within-host immune responses with the between-host transmission of the infectious agent.
One line of research, which we will follow here, deals with immune systems that undergo a dynamic change, in particular a waning and boosting of the immune level of an individual. For example, in [1] an SIS-model for a microparasite infection is developed, and in [2] an SIR-model is presented suitable to model tuberculosis or various sexually transmitted diseases. In this paper we take as a starting point the SIS-model developed in [3] to model the transmission of airborne infectious agents in a heterogeneous population and we exemplify it in the case of the transmission of the influenza virus.

In [4] it is noted that there exists a large literature on mathematical modelling of infectious diseases but only a small amount of these papers deal with the topic of controlling epidemics and very few do so by using optimal control theory. General forms of control strategies include vaccination, treatment, quarantine or health promotion campaigns. The resulting models are mathematically challenging and consequently only few analytic results are available. In line with this, the present work also focuses on numerical analysis of the considered models. However, we identify and describe some interesting qualitative features of the modelling approach too.

It is stated in [5] that one of the largest contributions of mathematical models of vaccination strategies is the evaluation of the necessary vaccination coverage in order to eradicate the epidemic. Therefore, this will be one of our main concerns. Here, we first consider the case of perfect vaccination that results, at least temporarily, in immunity of the vaccinated individual towards the disease. However, for diseases like influenza it has been argued in [6, 7] that vaccination may not lead to perfect immunity and the efficacy can vary depending on age and immune status. We therefore also consider the case of imperfect immunity in a model where vaccination may lead to just an increased immune level of the vaccinated individual.
As an alternative intervention we will consider treatment of infected individuals and/or chemoprophylaxis of susceptibles as a preventive measure. We also consider a combination of these two types of intervention and compare the effects of each of these choices.

In our numerical analysis we consider optimal control problems of epidemiological models, where the aim is to minimise the impact of a disease outbreak while keeping the cost for the intervention as low as possible. Using this approach we cannot only consider interventions that are constant over the considered time horizon (such as e.g. in [8, 9]), but also interventions that are dynamic. This allows to intervention effort to be increased according to the development of the outbreak, see e.g. [6, 10, 11] and the references therein for the application of optimal control theory in epidemiology.

The paper is organised as follows. In Section 2 we introduce the SI-model developed in [3] which will be the basis of our explorations. Furthermore, we present some results concerning the steady states of this system of partial differential equations (PDEs) for a specific set of parameters. In Section 3 we consider vaccination of the population and calculate the necessary coverage to prevent disease outbreaks. In Section 4 we analyse the dynamics of a single outbreak with treatment of the infected population and preventive chemoprophylaxis of the susceptible population, and compare the effects of these two strategies. In Section 5 we consider the case where a vaccine does not confer full immunity all the time. Some of the vaccinated individuals are only partially protected from a boost of their respective immune state.

2 The heterogeneous SI model

As a starting point we use the following model developed in [3]:

$$\begin{aligned}\frac{\partial}{\partial t}S(t,\omega)+\frac{\partial}{\partial \omega}(d(\omega)S(t,\omega))&=-\sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\,\mathrm{d}\xi S(t,\omega)+\delta(\omega)I(t,\omega),\\ \frac{\partial}{\partial t}I(t,\omega)+\frac{\partial}{\partial \omega}(e(\omega)I(t,\omega))&=\sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\,\mathrm{d}\xi S(t,\omega)-\delta(\omega)I(t,\omega).\end{aligned} \tag{1}$$

Here, the parameter ω describes the immune level of an individual. The functions $d(\omega)\leq 0$ and $e(\omega)\geq 0$ describe the dynamic change of the immune level of an individual during his period of susceptibility or infectiousness. The functions $p(\omega)$ and $q(\omega)$ denote the susceptibility and infectiousness of an individual with immune level ω, respectively. The recovery rate is given by $\delta(\omega)$ and σ denotes the contact rate.

A natural assumption on $d(\omega)$ and $e(\omega)$ is that $d(0)=e(1)=0$. This reflects the idea that the interval $[0,1]$ contains all possible immune levels. Note that by summing up the two equations in (1) and integrating from 0 to 1 we get

$$\frac{\mathrm{d}}{\mathrm{d}t}N(t)+d(1)S(t,1)+e(1)I(t,1)-d(0)S(t,0)-e(0)I(t,0)=0,$$

where $N(t)=\int_0^1 S(t,\omega)+I(t,\omega)\,\mathrm{d}\omega$ is the total number of individuals in the population. We will assume that the population is constant, i.e. $\frac{\mathrm{d}}{\mathrm{d}t}N(t)=0$. Using this, as well as our assumption on $d(\omega)$ and $e(\omega)$, this results for each $t\geq 0$ in

$$d(1)S(t,1)-e(0)I(t,0)=0.$$

We will therefore assume the boundary conditions

$$d(1)S(t,1)=0,\qquad e(0)I(t,0)=0,\quad t\geq 0. \tag{2}$$

2.1 Infected individual in the steady state

It was shown in Theorem 1 in [3] that if (1) has an endemic steady state $(S^*(\cdot),I^*(\cdot))$, then for any $\omega^*\in(0,1)$ there exists a $\theta^*>0$ such that the infected population is described by

$$I^*(\omega)=\frac{e^{-\int_{\omega^*}^{\omega}\frac{\sigma p(\xi)\theta^*}{d(\xi)}+\frac{\delta(\xi)+e'(\xi)}{e(\xi)}\mathrm{d}\xi}}{\int_0^1\left(1-\frac{e(\zeta)}{d(\zeta)}\right)e^{-\int_{\omega^*}^{\zeta}\frac{\sigma p(\xi)\theta^*}{d(\xi)}+\frac{\delta(\xi)+e'(\xi)}{e(\xi)}\mathrm{d}\xi}\mathrm{d}\zeta}.$$

From this we can deduce the following.

Theorem 1 *If $\frac{e(\omega)}{d(\omega)}=c$ is constant, then the number of infected individuals in the steady state is given by*

$$\int_0^1 I^*(\omega)\,\mathrm{d}\omega=\frac{1}{1-c}.$$

In particular, this number is independent of all other parameters.

Proof

$$\int_0^1 I^*(\omega)\mathrm{d}\omega=\frac{\int_0^1 e^{-\int_{\omega^*}^{\omega}\frac{\sigma p(\xi)\theta^*}{d(\xi)}+\frac{\delta(\xi)+e'(\xi)}{e(\xi)}\mathrm{d}\xi}\,\mathrm{d}\omega}{\int_0^1\left(1-\frac{e(\omega)}{d(\omega)}\right)e^{-\int_{\omega^*}^{\omega}\frac{\sigma p(\xi)\theta^*}{d(\xi)}+\frac{\delta(\xi)+e'(\xi)}{e(\xi)}\mathrm{d}\xi}\mathrm{d}\omega}=\frac{1}{\left(1-\frac{e(\omega)}{d(\omega)}\right)}=\frac{1}{1-c}.$$

□

The statement of Theorem 1 is somewhat surprising, as it tells us that the number of infected persons in an endemic steady state is entirely determined by in-host processes, in particular by the dynamics of the immunity. We also note that, if there should be multiple steady states, they only differ in the immune state distribution but not in the number of infected individuals (which is of course the more relevant property).

2.2 Existence of steady states

We also want to show that for special shapes of the parameters (used in our computations later on) an endemic steady state always exists . Assume the following functional forms of the parameters:

$$\begin{aligned} d(\omega) &= (\omega^2 - \omega)d, \\ e(\omega) &= -(\omega^2 - \omega)e, \\ \delta(\omega) &= \omega\delta, \\ p(\omega) &= 1 - \omega, \\ q(\omega) &= 2p(\omega), \end{aligned}$$

for $d, e, \delta > 0$. In [3] it was shown that the existence of an endemic steady state of this system is equivalent to the existence of a root of the function $r(\theta)$ given by

$$r(\theta) = \int_0^1 \left(\left(1 - \frac{e(\omega)}{d(\omega)} \right) \theta - q(\omega) \right) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\xi)\theta^*}{d(\xi)} + \frac{\delta(\xi) + e'(\xi)}{e(\xi)} \mathrm{d}\xi} \mathrm{d}\omega,$$

where ω^* is an arbitrary number in the interval $(0, 1)$. For our choice of parameters this turns into

$$r(\theta) = \int_0^1 \left(\left(1 + \frac{e}{d} \right) \theta - q(\omega) \right) \left(\frac{\omega}{\omega^*} \right)^{\frac{\sigma\theta - d}{d}} \left(\frac{1 - \omega}{1 - \omega^*} \right)^{\frac{\delta - e}{e}} \mathrm{d}\omega.$$

It is therefore finite if $\frac{\sigma\theta}{d} - 1 > -1$ and $\frac{\delta}{e} - 1 > -1$, which is fulfilled whenever $\theta > 0$. The function is then obviously continuous for $\theta \in (0, \infty)$. Furthermore, it can be seen that for θ sufficiently close to zero $r(\theta)$ is smaller than zero, and if θ is sufficiently large then $r(\theta)$ is positive. Therefore a root always exists and so does an endemic steady state.

2.3 Optimal control

We aim to place the system (1) and extensions thereof in an optimal control setting, in order to be able to calculate the optimal intervention strategies in the following sections. We therefore consider the following optimal control problem

$$\max_{u \in \mathcal{U}} \int_0^T \int_0^1 h(t, \omega, x(t, \omega), y(t), u(t, \omega)) \mathrm{d}\omega \mathrm{d}t + \int_0^1 k(\omega, x(T, \omega), y(T)) \mathrm{d}\omega, \tag{3}$$

with state equations

$$\begin{aligned} \frac{\partial}{\partial t} x(t, \omega) + \frac{\partial}{\partial \omega} A(t, \omega) x(t, \omega) &= f(t, \omega, x(t, \omega), y(t), u(t, \omega)), \\ y(t) &= \int_0^1 g(t, \omega, x(t, \omega), u(t, \omega)) \mathrm{d}\omega, \\ x(0, \omega) &= x_0(\omega), \end{aligned}$$

where $x(t,\omega) \in \mathbb{R}^n$, $y(t) \in \mathbb{R}^m$, and $\mathcal{U}$ is closed convex subset of $L^\infty([0,T] \times [0,1], \mathbb{R}^l)$. In [12, chap. 7] a version of Pontryagin's maximum principle for this kind of problem has been developed under assumptions which will be met in the examples we consider here. Using this maximum principle one can use gradient projection algorithms to numerically calculate the optimal control u. This is a standard approach in optimal control theory (see e.g. [13]).

In the present context, the state equations are obviously given by the dynamics of the disease. The function (3) to be maximised represents the aim to minimise the impact of the disease on the population as cost-effective as possible.

3 Vaccination

3.1 The model

We extend system (1) by introducing a control $u(t)$ which describes the rate over time with which the susceptible population is vaccinated. Furthermore, the fraction of the population k which is already vaccinated at time $t = 0$ can be controlled as well. We consider the simple case of perfect vaccination, i.e. every vaccinated person becomes completely immune against the disease. Vaccinated individuals, denoted by $V(\cdot)$, loose their immunity with rate γ. We assume that an individual that was vaccinated and looses its immunity becomes susceptible with immune status ω with probability $P(\omega)$, where $\int_0^1 P(\omega)\mathrm{d}\omega = 1$. The resulting equations are:

$$\begin{aligned}
\frac{\partial}{\partial t}S(t,\omega) + \frac{\partial}{\partial \omega}(d(\omega)S(t,\omega)) &= -\sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\mathrm{d}\xi S(t,\omega) + \delta(\omega)I(t,\omega) - u(t)S(t,\omega) + \gamma V(t)P(\omega),\\
\frac{\partial}{\partial t}I(t,\omega) + \frac{\partial}{\partial \omega}(e(\omega)I(t,\omega)) &= \sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\mathrm{d}\xi S(t,\omega) - \delta(\omega)I(t,\omega),\\
\frac{\mathrm{d}}{\mathrm{d}t}V(t) &= u(t)\int_0^1 S(t,\omega)\mathrm{d}\omega - \gamma V(t),\\
S(0,\omega) = S_0(\omega), \quad I(0,\omega) &= I_0(\omega), \quad V(0) = V_0,\\
u(t) &\in U.
\end{aligned} \tag{4}$$

The goal is to maximize the following objective function

$$\min_u \int_0^T \int_0^1 c_u u(t)^2 + c_I I(t,\omega)\mathrm{d}\omega\mathrm{d}t + c_T \int_0^1 I(T,\omega)\mathrm{d}\omega - c_V V(T). \tag{5}$$

Here, $c_u u(t)^2$ is the cost of vaccinating a fraction $u(t)$ of the susceptible population. The running costs of infected individuals are given by $c_I I(t,\omega)$, while the term $c_T \int_0^1 I(T,\omega)\mathrm{d}\omega$ determines their terminal cost. We also include the negative cost $-c_V V(T)$ to account for the fact that it may be desirable to have an immune subpopulation at the end of our calculations. The choice of the cost function as linear in the number of infected and quadratic in the control is customary, see [6, 10, 11, 14] as well as the references therein.

3.2 Numerical results

In our numerical calculations we use, similar to [3], the following parameter values:

$$\delta(\omega) = \frac{1}{2}\omega, \quad p(\omega) = 1-\omega, \quad q(\omega) = 2p(\omega), \quad \gamma = 0.02, \quad d(\omega) = -0.015\omega(1-\omega), \quad e(\omega) = 0.15\omega(1-\omega).$$

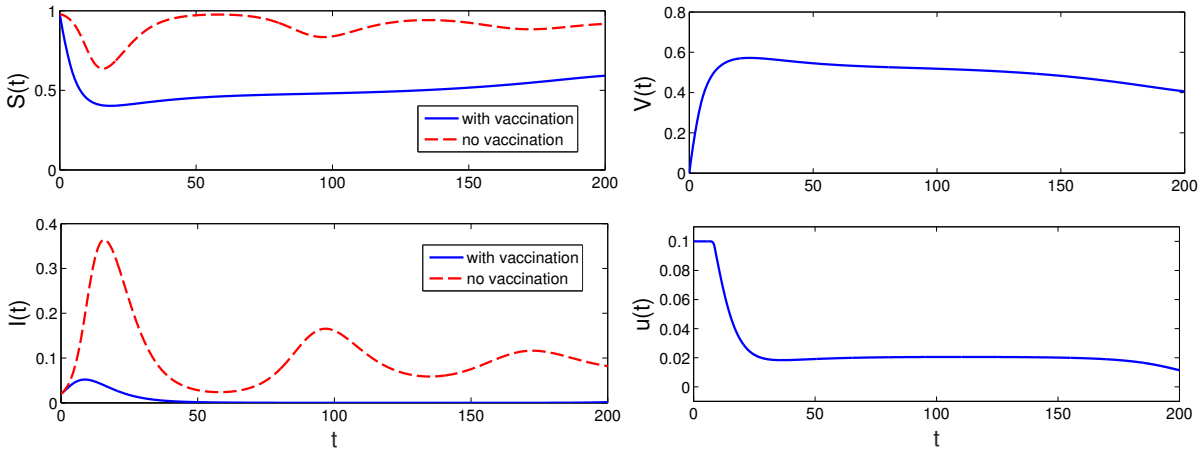

Figure 1: We illustrate the evolution of the aggregated subpopulations which solve the optimal control problem (5). Furthermore we compare them to the uncontrolled case in which the vaccinated population and the control are obviously identically zero. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $V(0) = 0$, $U = [0, 0.1]$, $c_u = 10$, $C_I = 1$, $c_T = 4$, $c_V = 0.2$, $P(\omega) = 168\omega^5(1-\omega)^2$.

As the initial immune state distribution is unknown, we use a generic symmetric polynomial $I_0(\omega) = S_0(\omega) = \omega^4 - 2\omega^3 + \omega^2$ normalized in such a way that $\int I_0(\omega)\mathrm{d}\omega = 0.02$, which marks the identification of the epidemic. The initial number of susceptibles is therefore $\int S_0(\omega)\mathrm{d}\omega = 0.98$ if $V(0) = 0$, and $\int S_0(\omega)\mathrm{d}\omega = 0.98 - V_0$ in the case of pre-epidemic vaccination, such that the entire population adds up to 1. Note that the population again remains constant in this model.

Even though the perfect immunity of vaccinated individual wanes over time they are assumed to have a slightly higher immune state when re-entering the class of susceptibles marked by $P(\omega) = \omega^5(1-\omega)^2$, which exhibits a peak towards 1. The cost terms for the objective function are assumed to be: $c_u = 10$, $C_I = 1$, $c_T = 4$, and $c_V = 0.2$. We first consider the case without previous vaccination.

Numerical results show that the system exhibits an interesting oscillatory behaviour in the uncontrolled case, which is caused by the waning immunity of the population when the prevalence is low, see Figure 1. Furthermore, the solution of the minimization problem (5) suggests that it is best to vaccinate as early as possible and to keep vaccination coverage high enough in order to eradicate the disease and prevent a new outbreak. See again Figure 1 for how the optimal control steers the trajectory towards the disease-free equilibrium.

3.3 Bifurcation between endemic and disease-free steady state

For simple homogeneous models it is a well established fact that the critical level of vaccination V_C needed to ensure that the disease free steady state is asymptotically stable, and that the introduction of the disease into the population will not lead to a large outbreak, is given by $V_C = 1 - \frac{1}{R_0}$, where R_0 is the basic reproduction number, see e.g. [15]. Since we do not have an analytical expression for R_0 we numerically derive a similar description of V_C using a function $R(\sigma)$ depending the contact rate σ.

For varying, but constant, controls u we numerically calculate the value u^* such that the system converges to an endemic steady state for $u < u^*$ and to the disease free steady state for $u > u^*$. This investigation is done for different values of σ and leads to a functional dependence $u^*(\sigma)$. As

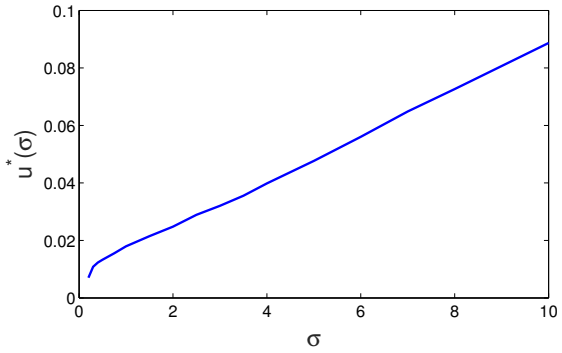

Figure 2: The numerically computed, critical vaccination rate u^* which is needed in order to eradicate the disease in dependence of σ. An affine dependence is demonstrated. Parameter values are: $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1-\omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $V(0) = 0$, $P(\omega) = 168\omega^5(1-\omega)^2$.

expected, the necessary vaccination rate, and therefore the percentage of the population vaccinated, increase with the contact rate. Furthermore, as it can be seen in Figure 2, the dependence between σ and u^* is approximately affine. We therefore assume the existence of two constant $b, m \in \mathbb{R}$ such that $u^*(\sigma) \approx m\sigma + b$.

As a measure for V_C we use the percentage V^* of the population that is vaccinated in the steady state when using the value u^*. V^* can be computed from the differential equation for V in a steady state. By denoting with $S^*(\cdot)$ the susceptible population in a steady state, and recalling that for u^* the steady state is disease free, we get from (4)

$$\begin{aligned} & 0 = u^* \int_0^1 S^*(\omega)\mathrm{d}\omega - \gamma V^* \\ \iff \quad & 0 = u^*(1 - V^*) - \gamma V^* \\ \iff \quad & V^* = \frac{u^*}{\gamma + u^*}. \end{aligned} \tag{6}$$

By defining

$$R(\sigma) := 1 + \frac{m}{\gamma}\sigma + \frac{b}{\gamma},$$

and combining (6) with the affine dependence of $u^*(\sigma) \approx m\sigma + b$ we get

$$V^*(\sigma) \approx \frac{m\sigma + b}{\gamma + m\sigma + b} = 1 - \frac{\gamma}{\gamma + m\sigma + b} = 1 - \frac{1}{R(\sigma)}, \tag{7}$$

which is of the desired form. In Figure 3 we can see a comparison between numerically computed values of V^* and what is suggested by the approximation (7).

Note that the function $R(\sigma)$, which is our proxy for the basic reproduction number, is greater than one for every $\sigma > 0$. This is consistent with the results in Section 2.2, where it was shown that for our choice of parameter functions an endemic steady state always exists. This is usually indicated by the basic reproduction being greater than one.

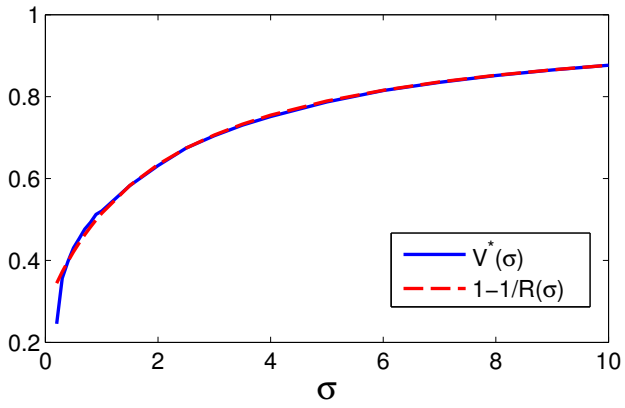

Figure 3: A comparison of the numerically computed critical vaccination threshold V^* and the value predicted by $1 - \frac{1}{R(\sigma)}$. The two curves are almost identical, except for very low values of σ, where the system exhibits a highly oscillatory behaviour, which may influence the result. Parameter values are: $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $V(0) = 0$, $P(\omega) = 168\omega^5(1-\omega)^2$.

3.4 Comparison to pre-epidemic vaccination

In the case of pre-epidemic vaccination we assume that $\gamma = 0$. This captures the notion that vaccinated individuals are granted immunity for a duration significantly longer than the time scale of a disease outbreak. If the duration of the effect of vaccination is short, then pre-emptively vaccinated individuals are potentially again susceptible at the time of a disease outbreak. Since this is obviously a wasteful strategy, we restrict ourselves here to long-lasting vaccination duration, where pre-emptive action is a viable strategy.

Under this assumption there is no re-entry to the susceptible population with a higher immune state. This additional effect of vaccination only happens in the case of vaccinating during the outbreak at a constant rate. This contributes to the difference in the levels required to ensure the convergence to the disease-free steady state, see Figure 4.

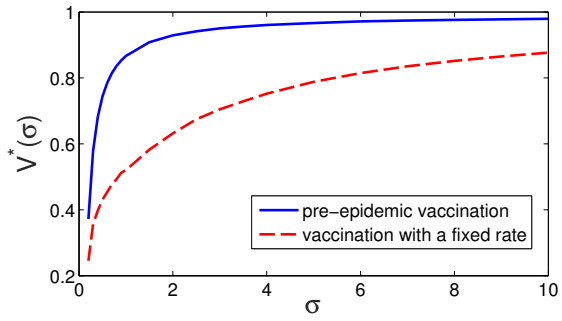

Figure 4: A comparison of the vaccination levels required to achieve herd immunity for pre-epidemic vaccination and vaccinating with a constant rate during the outbreak. Due to the additional effect on the immune state, critical vaccination coverage is lower when vaccinating continuously during the outbreak. Parameter values are: $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1-\omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $I_0(\omega) = 0.02\cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $P(\omega) = 168\omega^5(1-\omega)^2$. $V(0)$ is zero in the case of vaccination with a fixed rate; in the pre-epidemic case it is given by $V^*(\sigma)$. $S_0(\omega) = (0.98 - V(0))\cdot 30(\omega^4 - 2\omega^3 + \omega^2)$.

4 Treatment

In this section we extend the basic model (1) in a different direction. We now assume that treatment against the infection is possible in two different ways: preventive treatment that reduces the probability of susceptible individuals to become infected, and treatment of infected people which decreases their infectivity and increases the chance of recovery.

4.1 The model

Antiviral treatment is given to the infected population at rate $v(t)$ which moves them to a new compartment $I_T(\cdot)$ in which their infectivity q is lowered by a factor r_q when in contact with a susceptible individual and they experience faster recovery δ by a factor r_δ. The immune state, however, is for simplicity assumed to remain unchanged during this process. Being moved to the new class their immune state then is assumed to increase in the same way as it does for infected individuals not receiving treatment. Chemoprophylaxis is also given to the susceptible population as a preventive measure at rate $u(t)$ which moves them into a new compartment S_P. The effect of this prevention is twofold. First, it reduces their susceptibility p by a factor r_p when in contact with an infected individual and by a factor $r_{p,q}$ if this person is already receiving treatment. Additionally, susceptible individuals which received chemoprophylaxis

and still become infected move directly to the class I_T. The resulting equation are:

$$\begin{aligned}
\frac{\partial}{\partial t}S(t,\omega) + \frac{\partial}{\partial \omega}(d(\omega)S(t,\omega)) =& -\sigma p(\omega)\int_0^1 q(\xi)(I(t,\xi) + r_q I_T(t,\xi))\mathrm{d}\xi S(t,\omega) - u(t)S(t,\omega),\\
\frac{\partial}{\partial t}S_P(t,\omega) + \frac{\partial}{\partial \omega}(d(\omega)S_P(t,\omega)) =& -\sigma p(\omega)\int_0^1 q(\xi)(r_p I(t,\xi) + r_{p,q} I_T(t,\xi))\mathrm{d}\xi S_P(t,\omega) + u(t)S(t,\omega),\\
\frac{\partial}{\partial t}I(t,\omega) + \frac{\partial}{\partial \omega}(e(\omega)I(t,\omega)) =& \sigma p(\omega)\int_0^1 q(\xi)(I(t,\xi) + r_q I_T(t,\xi))\mathrm{d}\xi S(t,\omega)\\
&- \delta(\omega)I(t,\omega) - v(t)I(t,\omega),\\
\frac{\partial}{\partial t}I_T(t,\omega) + \frac{\partial}{\partial \omega}(e(\omega)I_T(t,\omega)) =& \sigma p(\omega)\int_0^1 q(\xi)(r_p I(t,\xi) + r_{p,q} I_T(t,\xi))\mathrm{d}\xi S_P(t,\omega)\\
&+ v(t)I(t,\omega) - r_\delta \delta(\omega)I_T(t,\omega),\\
\frac{\mathrm{d}}{\mathrm{d}t}R(t) =& \int_0^1 \delta(\omega)(I(t,\omega) + r_\delta I_T(t,\omega))\mathrm{d}\omega,\\
u(t) \in& U, \quad v(t) \in V.
\end{aligned}$$

Similar to the vaccination case in Section 3 we try to minimise the total cost, given by

$$\int_0^T \int_0^1 c_u u^2(t) + c_v v^2(t) + I(t,\omega) + I_T(t,\omega)\mathrm{d}\omega. \tag{8}$$

Due to the fact that the epidemic always dies out in an SIR-model, no scrap value is needed.

4.2 Numerical Results

In our numerical calculations we assume that the parameter values for the objective function are equal $c_u = c_v = 5$, as both controls represent the administration of the same antiviral drug. The epidemiological paramters are altered through the administration of antiviral drugs according to the epidemic case in [9]. The susceptibility of an individual that received chemoprophylaxis is dramatically reduced by $r_p = 0.33$ and even more when encountering an infected person receiving treatment $r_{p,q} = 0.1$. The infectivity of a treated infected individual when in contact with a susceptible is reduced by the factor $r_q = 0.67$. The speed of recovery, however, is not drastically increased $r_\delta = 1.33$.

We consider three different strategies on how to administer antiviral treatment in order to dampen the outbreak. Similar to what is done in [9] we look at treatment of only the infected individuals, chemoprophylaxis for susceptible persons, and a combination of both. The rate at which treatment is given in each of these scenarios is determined by the corresponding optimal control problem (8).

Single measure

First, we look at a strategy consisting of giving chemoprophylaxis only to the susceptible population, as a preventive measure. The optimal rate at which this chemoprophylaxis should be administered can be seen in Figure 5. As can be expected, drug administering is high during the initial outbreak and declines quickly afterwards. The severity of the outbreak is drastically decreased, resulting in a reduction from $\sim$77% to $\sim$29% from the number of people becoming infected during the outbreak.

In comparison, when distributing antiviral treatment only among infected individuals, the reduction in the severity of the outbreak is only from $\sim$ 77% to $\sim$ 76%. In Figure 8 the difference in the effects of the measures can be seen. The optimal choice of the rate of treatment $v(t)$ is shown in Figure 6.

The larger impact of preventive measures is due to the fact that the effect of prevention is twofold. First, individuals in the class S_P are less likely to become infected as their susceptibility is reduced, and second, when becoming infected they experience the same benefit as infected treated patients.

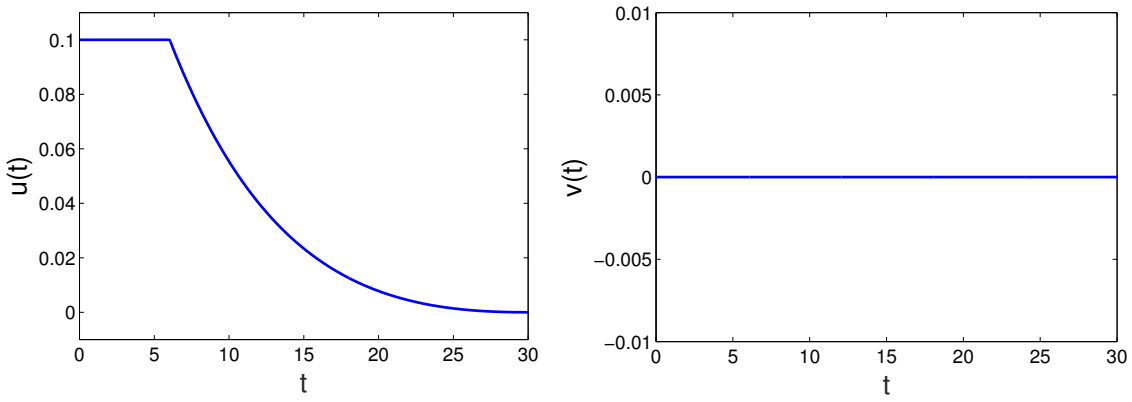

Figure 5: Optimal control variables in the case where antiviral drugs are only given to the susceptible population as a preventive measure. Consequently the rate of vaccination is zero over the whole time interval. The policy is computed by solving the maximum principle of the corresponding minimisation problem as described in Section 2.3. This intervention policy is very effective and results in a significant decrease of the severity of the epidemic: the percentage of the population that are affected by the disease during the considered time period decreases from $\sim$77% to $\sim$29%. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $S_P(0,\omega) \equiv 0$, $I_T(0,\omega) \equiv 0$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $U = [0, 0.1]$, $V = [0, 0]$, $c_u = c_v = 5$, $r_p = 0.33$, $r_q = 0.67$, $r_{p,q} = 0.1$, $r_\delta = 1.33$.

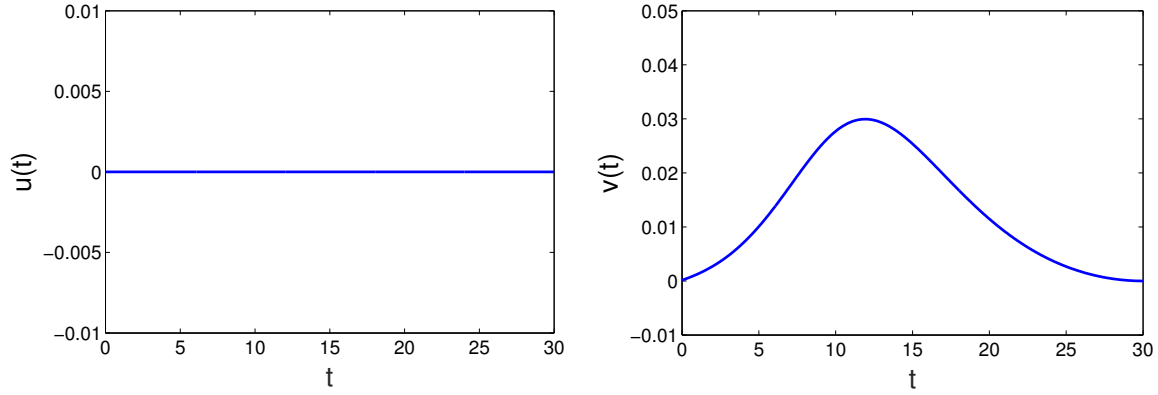

Figure 6: Optimal control variables in the case where only treatment of the infected subpopulation is present. Consequently the rate of preventive treatment is zero. The policy is computed by solving the maximum principle of the according minimisation problem as described in Section 2.3. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $S_P(0,\omega) \equiv 0$, $I_T(0,\omega) \equiv 0$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $U = [0, 0]$, $V = [0, 0.1]$, $c_u = c_v = 5$, $r_p = 0.33$, $r_q = 0.67$, $r_{p,q} = 0.1$, $r_\delta = 1.33$.

Combined measures

The optimal drug administration policy when using both intervention measures can be seen in Figure 7. Much more effort is put into the more effective preventive measures. The optimal rate at which

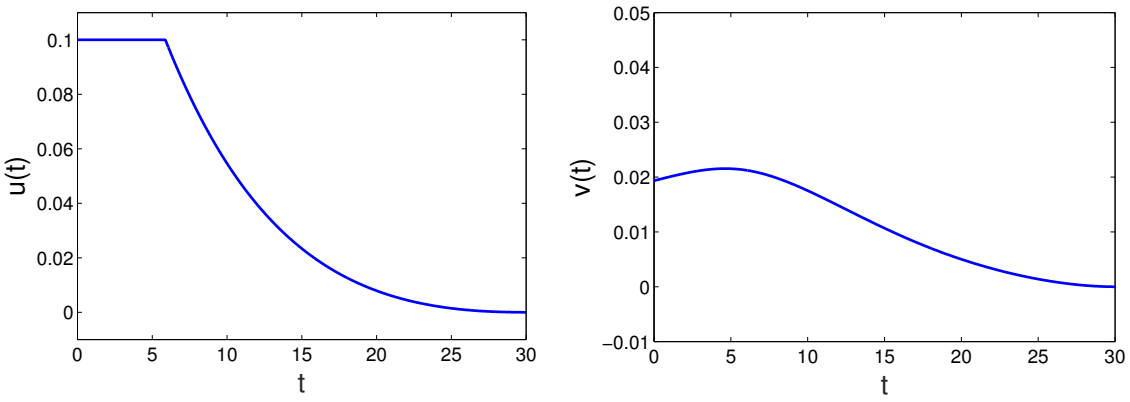

Figure 7: Optimal control variables for the combined strategy of prevention and treatment. The policy is computed by solving the maximum principle of the according minimisation problem as described in Section 2.3. Note that the profile for the preventive measures (which were shown to be very effective) is very similar to the case without treatment, while the optimal choice of the rate of treatment changes noticeably. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $S_P(0,\omega) \equiv 0$, $I_T(0,\omega) \equiv 0$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $U = [0, 0.1]$, $V = [0, 0.1]$, $c_u = c_v = 5$, $r_p = 0.33$, $r_q = 0.67$, $r_{p,q} = 0.1$, $r_\delta = 1.33$.

chemoprophylaxis is given to the susceptible population in the combined strategy is almost unchanged compared to pure prevention strategy (see Figure 5 and Figure 7) whereas a difference in the treatment policy is evident due to the different course of the epidemic. Due to the peak of the epidemic occurring at a later point in time, treatment too scales up towards this point and then decreases with the number of infected individuals.

In Figure 8 we see the effect on the outbreak of the combined strategy. Most of the benefit is due to the preventive measures, whereas including treatment of infected individuals only marginally increases the effect of the intervention.

4.3 Effect on the final size of the epidemic

The effect of giving preventive antiviral treatment at a constant rate to the susceptible population on the percentage of people who became infected can be seen in Figure 9. For low rates the dependence seems to be linear but becomes more convex for higher rates. This makes sense as a doubling in the rate only leaves less than twice as many people with chemoprophylaxis. These findings are in line with [9] where it is shown that preventive treatment can drastically reduce the severity of an epidemic.

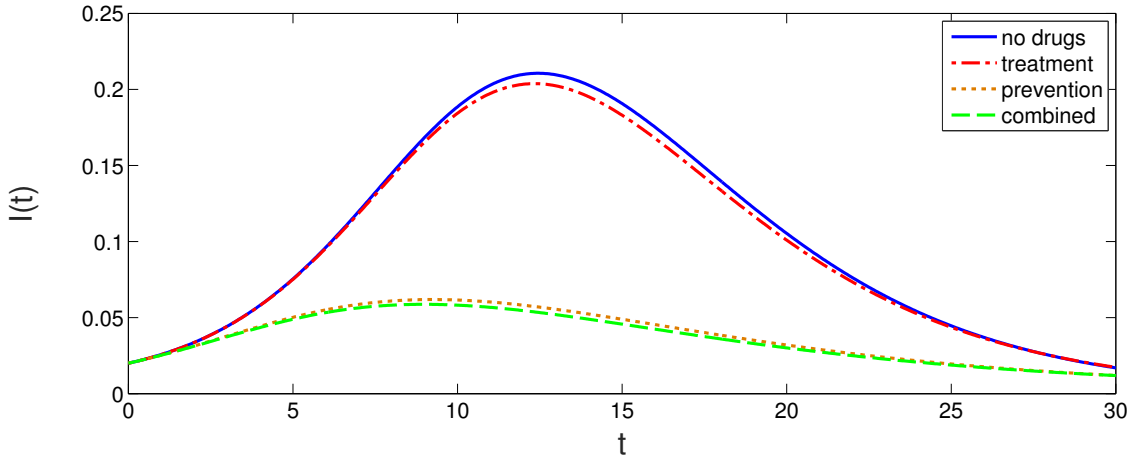

Figure 8: Percentage of infected individuals over the course of an epidemic. Administering antiviral drugs to susceptibles as a preventive measure is the most important aspect of intervention. Treating infected individuals only provides minor improvements. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $S_P(0,\omega) \equiv 0$, $I_T(0,\omega) \equiv 0$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $c_u = c_v = 5$, $r_p = 0.33$, $r_q = 0.67$, $r_{p,q} = 0.1$, $r_\delta = 1.33$. In the case where no drugs are administered at all both controls are zero $U = V = [0,0]$. Treatment only: $U = [0,0]$, $V = [0,0.1]$. Prevention only: $U = [0,0.1]$, $V = [0,0]$. The combined strategy allows both controls to be different from zero $U = [0,0.1]$, $V = [0,0.1]$.

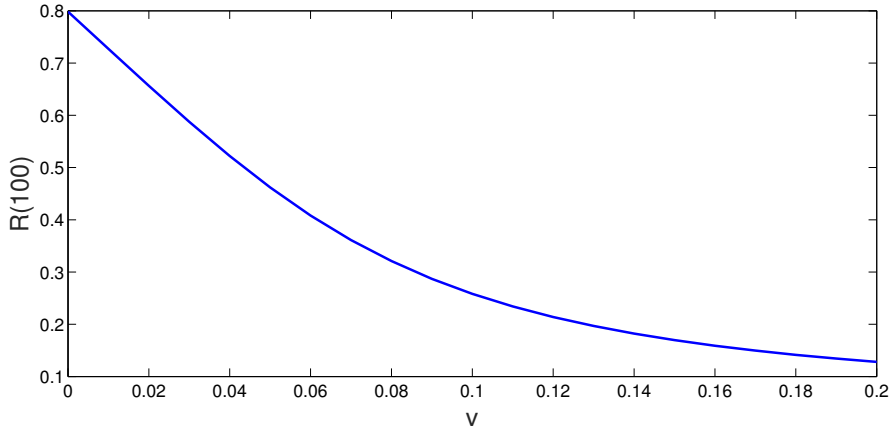

Figure 9: Final size of the epidemic (i.e. the number of people becoming infected during the outbreak) with respect to different constant rates at which chemoprophylaxis is given to the susceptible population. We can see diminishing returns for higher intervention rates. Parameter values are: $\sigma = 1$, $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1 - \omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $S_P(0,\omega) \equiv 0$, $I_T(0,\omega) \equiv 0$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $r_p = 0.33$, $r_q = 0.67$, $r_{p,q} = 0.1$, $r_\delta = 1.33$.

5 Imperfect vaccination

5.1 The model

This model includes the more realistic aspect of imperfect vaccination by assuming that a fraction of the vaccinated individuals do not become completely immune to the disease, but experience a boost in their respective immune state. Although remaining susceptible they are being moved to a new compartment V in order to keep track of who has been vaccinated. The immune state of the vaccinated population with imperfect immunity changes over time according to $f(\cdot) : [0,1] \to (-\infty, 0]$. Vaccinated individuals will move to the class V_P, in which they are granted perfect immunity, with probability $\Gamma(\omega)$ depending on their respective current immune state ω. The ones not gaining perfect immunity, but experiencing a boost in their current immune state ω will go to the higher immune state $\omega' \geq \omega$ with probability $b(\omega', \omega)$, similar to what is done in [16]. Reasonable assumptions on $\Gamma(\cdot)$ and $b(\cdot)$ include that $\Gamma(\xi) + \int_0^1 b(\omega, \xi)\mathrm{d}\omega = 1$, $\forall \xi \in [0,1]$ to ensure that the probability of being boosted to any immune state does in fact equal one and therefore keeps the population constant. At rate $\gamma \geq 0$ vaccinated people move back to the susceptible compartment so that they can be vaccinated again at some later point in time. Again as in Section 3 about perfect vaccination we use a re-entry distribution $P(\cdot)$. This model is an extension of model (4) as $\Gamma \equiv 1$, i.e. every vaccinated person moves to $V_P(\cdot)$, exactly gives the perfect immunity model. The resulting equation are:

$$\begin{aligned}
\frac{\partial}{\partial t}S(t,\omega) + \frac{\partial}{\partial \omega}(d(\omega)S(t,\omega)) &= -\sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\mathrm{d}\xi S(t,\omega) + \delta(\omega)I(t,\omega) - u(t)S(t,\omega) \\
&\quad + \gamma\left(V(t,\omega) + P(\omega)V_P(t)\right), \\
\frac{\partial}{\partial t}I(t,\omega) + \frac{\partial}{\partial \omega}(e(\omega)I(t,\omega)) &= \sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\mathrm{d}\xi(S(t,\omega) + V(t,\omega)) - \delta(\omega)I(t,\omega), \\
\frac{\partial}{\partial t}V(t,\omega) + \frac{\partial}{\partial \omega}(f(\omega)V(t,\omega)) &= -\sigma p(\omega)\int_0^1 q(\xi)I(t,\xi)\mathrm{d}\xi V(t,\omega) + u(t)\int_0^1 b(\omega,\xi)S(t,\xi)\mathrm{d}\xi - \gamma V(t,\omega), \\
\frac{\mathrm{d}}{\mathrm{d}t}V_P(t) &= u(t)\int_0^1 \Gamma(\omega)S(t,\omega)\mathrm{d}\omega - \gamma V_P(t).
\end{aligned}$$

For the computations we assume that the immune state of a vaccinated persons changes over time in the same way as it does for susceptibles $f(\cdot) = e(\cdot)$.

In line with [6, 7] where it is stated that the efficacy of influenza vaccination ranges from $80\% - 90\%$ in young healthy adults to $30\% - 40\%$ in the old and weak, we choose $\Gamma(\xi) = 0.2 + 0.8\xi$. As for the immune boosting we keep it simple as no precise information in known and make the assumption that vaccinated individual are boosted to any higher immune state with equal probability which gives $b(\omega, \xi) = \mathbb{1}_{[\omega \geq \xi]}\frac{1-\Gamma(\xi)}{1-\xi} \equiv 0.8$.

5.2 Bifurcation between endemic and disease-free steady state

Again, as in Section 3.3 we numerically find the switching point between the system converging to an endemic state or the disease free steady state, for varying, but constant, controls. The results are displayed in Figure 10. As can be expected, the critical vaccination threshold in the imperfect case is higher than the one for the perfect case at all times. Moreover the results are qualitatively in line with the ones from [15]. Two types of imperfect vaccines are discussed there. First, the case where vaccination has no effect at all in a fraction $p > 0$ of the cases and secondly, vaccines which leave people susceptible but with changed parameters, such as reduced transmission if the vaccinated person is infected and/or increased

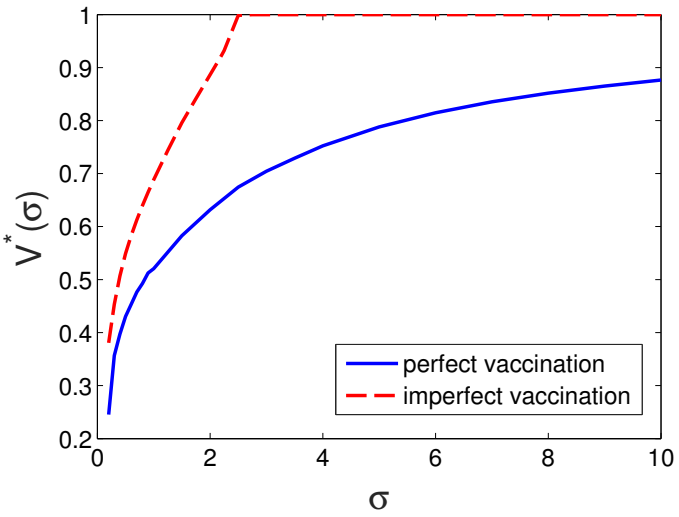

Figure 10: A comparison of the critical vaccination threshold V^* in dependence of the force of infection, for the case of perfect and imperfect vaccination. The necessary coverage needed in order to eradicate the disease is higher in the imperfect case for all σ. Parameter values are: $\delta(\omega) = \frac{1}{2}\omega$, $p(\omega) = 1-\omega$, $q(\omega) = 2p(\omega)$, $\gamma = 0.02$, $d(\omega) = -0.015\omega(1-\omega)$, $e(\omega) = 0.15\omega(1-\omega)$, $S_0(\omega) = 0.98 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $I_0(\omega) = 0.02 \cdot 30(\omega^4 - 2\omega^3 + \omega^2)$, $V(0,\omega) \equiv 0$, $V_P(0) = 0$, $P(\omega) = 168\omega^5(1-\omega)^2$, $\Gamma(\xi) = 0.2 + 0.8\xi$, $b(\omega,\xi) \equiv 0.8$.

recovery. The latter are called *leaky* vaccines. Our approach can be considered as a combination of perfect and leaky vaccination, leaving us with a very versatile model.

6 Discussion

In this paper we analyse the effects of different intervention strategies on an immunoepidemiological model. We consider perfect and imperfect vaccination, as well as treatment and chemoprophylaxis. By using optimal control theory we can also give more detailed information about the best possible strategies. Due to the mathematical complexity of the models under considerations, we restrict ourselves to a largely numerical analysis.

We calculate the level of vaccination needed to protect the population against a disease outbreak. We find that this level depends on the force of infection in line with the known formula $1 - \frac{1}{R_0}$ for standard homogeneous models.
With regard to intervening with antiviral treatment and chemoprophylaxis, we investigated different strategies of distributing the drugs. Treatment of infected individuals provided only small benefit in regards to the total size of the epidemic, independent of whether used in combination with chemoprophylaxis or not. However, numerical results suggest that giving treatment to the susceptible population as a preventive measure is an effective method and results in a drastic reduction in the size of the infected population.

Although we discuss several scenarios, there are of course numerous additional aspects of intervention strategies that are not considered here. For example, drug resistance could be taken into account, as done in [9] and suggested in [10].

A limitation of the considerations here is that the exact shapes of the parameter functions are not known. Obviously, they have a large influence on the behaviour of immunoepidemiological models, yet there is little information about them available. Identifying them is therefore of great importance for the application of such models.
Similarly, the difficulty of identifying the initial condition, which represents the immune state distribution of the population, is a difficult task. Some considerations have been made to make this problem more manageable (see [3]).
In our work we provide an approach where the source of population heterogeneity is considered in the immune status and immune responses of the population and immunity varies with time. This allows us to combine within-host with population host characteristics of an epidemic. Although our results are produced under several unknown conditions, such as the initial immunological status of the population at the beginning of the outbreak, we provide numerical results that can give insights into the effects differential immunity may have on the dynamics and control of epidemics. Explicit consideration of immunity and immune responses in epidemiological models may lead to better understanding of the complex dynamics that govern epidemics and facilitate the development of optimal control strategies. We conclude that the study of immunoepidemiological models still provides many important topics that could be subject to further research.

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