Impact of imperfect vaccine, vaccine trade-off and population turnover on infectious disease dynamics

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Abstract

Vaccination is an essential tool for the management of infectious diseases. However, many vaccines are imperfect having only a partial protective effect in decreasing disease transmission and/or favouring recovery of infected individuals, and possibly exhibiting trade-off between these two properties. Furthermore, the success of vaccination depends also on the population turnover, the rate of entry to and exit from the population. We here investigate by mean of a mathematical model the interplay between these factors to predict optimal vaccination strategies. We first compute the basic reproduction number and study the global stability of the equilibria. We then assess the most influential parameters determining the total number of infected over time using a sensitivity analysis. We derive conditions for the vaccination coverage and efficiency to achieve disease eradication assuming different intensity of the population turnover (weak and strong), vaccine properties (transmission and/or recovery) and trade-off between the latter. We show that the minimum vaccination coverage increases with lower population turnover, decreases with higher vaccine efficiency (transmission or recovery), and is increased/decreased by up to 15% depending on the vaccine trade-off. We conclude that the coverage target for vaccination campaigns should be evaluated based on the interplay between these factors.

Keywords: Imperfect vaccine; Vaccine trade-off; Population turnover; Mathematical model; Global stability; Sensibility analysis.

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1. Introduction

Vaccination is one of the most effective public health policies for protecting humans and animals from infectious diseases. Global vaccination campaigns have helped eradicate diseases such as smallpox, measles, poliomyelitis, rinderpest in most parts of the world, ultimately saving the lives of millions of humans and animals. By definition, a perfect vaccine would keep vaccinated individuals from becoming infected when exposed to the pathogen. An imperfect vaccine, however, does not prevent vaccinated individuals from becoming infected upon pathogen exposure but may still be beneficial in various ways (Anderson and May 1992). For example, imperfect vaccines may provide benefits such as preventing infection, limiting parasite within-host growth and thus reducing the damage done to the host (Vale et al. 2014), or preventing transmission by infected hosts (Gandon et al. 2003). As we have seen recently with the epidemic of Covid-19, imperfect vaccines can be used to reduce the number of infected individuals and also to protect individuals at risk of developing the more lethal form of the infection. The use of imperfect vaccine may be advantageous when the vaccination efficiency is volatile and decreases due to the appearance of new variants of the virus (Hwang et al. 2021, Ioannidis 2021, Dagan et al. 2021).

The effectiveness of a given vaccine is determined not only by its biochemical and immunological properties, but also by how the vaccine is deployed and what other health management (biosecurity) measures are in place. Maintaining herd immunity during a disease outbreak, for example, has been promoted as a highly effective disease control strategy (Djatcha et al. 2017, Ashby and Best 2021, Mancuso et al. 2021). However, a continuous influx of new susceptible, possibly unvaccinated individuals contributes to the long-term persistence of the disease in the population (Scherer and McLean 2002, Pulliam et al. 2007). The frequent introduction of pathogens into a partially immune population (with an intermediate level of population immunity) can lead to longer lasting epidemics and/or a higher total number of infectious individuals than the introduction into a naive population (Pulliam et al. 2007). This phenomenon is named as "epidemic enhancement" (Pulliam et al. 2007). More generally, the population turnover rate, that is the rate at which individuals can enter and exit the considered population, may affect the effectiveness of control strategies (Booth et al. 2013, Knight et al. 2020, Nuismer et al. 2022). In human but also domesticated animals, population turnover takes the form of immigration and emigration in and out of the population, as well as birth and death of individuals. The turnover is an often neglected factor in epidemiology when generalizing predictions of disease modelling from human to domesticated and wild animal populations.

Moreover, a second parameter of importance in studying the efficiency of vaccination strategies, is the existence of biological trade-offs in the epidemiology of infectious diseases. The prime exam-

ple, is the trade-off between parasite virulence and transmission rate which raises challenges for vaccine manufacturing. Indeed, in the seminal paper by (Gandon et al. 2003), vaccines affecting disease transmission are predicted to possibly lead to a decrease of parasite virulence, while other types of vaccines (reducing within-host growth rate) may lead to an increase of parasite virulence, and thus the counter-effect of a worst epidemiological outcome. Interestingly, much work has been devoted to generate precise predictions for virulence evolution in known parasite species by incorporating empirical characterizations of vaccine effects into models capturing the epidemiological details of a given system (Gandon and Day 2008, Alizon et al. 2009, Cressler et al. 2016). In contrast, the biochemical and immunological trade-offs of the vaccine itself have received little attention. We specifically mean here that vaccination can affect several aspects of the disease dynamics, such as within-host growth and transmission, with possible trade-offs between these characteristics. For example, a vaccine reducing within-host growth may be more or less effective in reducing disease transmission. We therefore consider the definition of imperfect vaccines as i) providing partial protection (non-maximal efficiency) against infection (decreasing transmission), and ii) partially enhancing the recovery of infected individuals. We are interested in the possible trade-off between these two properties. There has been remarkably little work done to generally assess how the interplay between different vaccine properties, trade-offs, and vaccination strategies influences the burden of the epidemic in an heterogeneous community/population with imperfect vaccination.

The aim of this study is therefore to assess, through mathematical modelling, whether the use of vaccines decreasing the infection rate is more efficient to eradicate the disease in an heterogeneous community than a vaccine that both reduces the infection and favours recovery, or a vaccine reducing the infection rate but favouring recovery. We also want to assess whether these results depend on the effect of population turnover, in order to generalize our results to animal populations.

The paper is organized as follows. First, the model is formulated in Section 2. We then compute the basic properties of the steady state solutions as well as the existence of a local and global stability of the equilibria of the model (Section 3). We then perform a numerical sensitivity analysis of the model and study examples of numerical analyses for different parameter values to describe the interaction between population turnover and vaccine trade-offs on the epidemiological outcome. We conclude by providing predictions on the applicability of these results to vaccination strategies in human populations but also domesticated (and wild) animal species for which turnover rates represent different end of a continuum.

2. Model formulation

The formulation of the model is based on compartmental modeling (Anderson 2013), which consists in creating virtual reservoirs called compartments. A compartment is a kinetically homogeneous structure. This means that any individual who enters a compartment is identical, from the epidemiological point of view, to any other already present in that compartment. A mathematical model therefore consists of describing the flow of individuals between the various compartments.

To study the dynamic of an infectious disease during and after the vaccination campaign, we modify the model formulated in (Gandon et al. 2003) by adding a recovered compartment and we consider a frequency-dependent disease transmission (incidence rate). The model takes in to account only host-to-host transmission of the disease. Since many vaccines do not guaranty a perfect immunity, we consider an heterogeneous host community/population with two types of hosts: fully susceptible to the disease, or partially resistant to infection due to the imperfect vaccination. The fully susceptible hosts consist of uninfected (S_1) and infected (I_1) individuals. Among the partially resistant hosts, there are uninfected (S_2) and infected (I_2) individuals. All infected individuals (fully susceptible or partially resistant) can become recovered (R), and all recovered individuals are fully immune to reinfection (Gandon and Day 2007). Thus, the total population at time t, $N(t)$ is given by

$$N(t) = S_1(t) + S_2(t) + I_1(t) + I_2(t) + R(t).$$

We assume the parasite population to be monomorphic (having only one type or genotype). We also assume that new uninfected hosts arise through birth and immigration at constant rate, $\theta \geq 0$. Among these new uninfected, a proportion, $0 \leq p \leq 1$, is partially immune due to the vaccination, while the remaining proportion $1 - p$ is susceptible (completely vulnerable to the parasite). Uninfected, infected and recovered hosts die naturally at a rate $\mu \geq 0$, and infected hosts suffer additional mortality due to the virulence of the parasite. Since host resistance due to vaccination may reduce the impact of the parasite within-host growth (Gandon et al. 2003), we assume the virulence of the parasite on fully susceptible hosts, $d_1 \geq 0$, to be greater than that on partially resistant hosts, $d_2 \geq 0$. Uninfected hosts become infected with the forces of infection $\lambda_1(t) = \beta_{11}\dfrac{I_1(t)}{N(t)} + \beta_{12}\dfrac{I_2(t)}{N(t)}$ and $\lambda_2(t) = \beta_{21}\dfrac{I_1(t)}{N(t)} + \beta_{22}\dfrac{I_2(t)}{N(t)}$ when they are fully susceptible or partially resistant, respectively. The rates of transmisison are $\beta_{11} \geq 0$ (respectively $\beta_{21} \geq 0$) from infected, I_1, to susceptible individuals S_1 (respectively S_2), while $\beta_{12} \geq 0$ (respectively $\beta_{22} \geq 0$) is the transmission rate from infected, I_2, to susceptible individuals S_1 (respectively S_2). And since the resistance can decrease the probability of becoming infected (Gandon et al. 2003), we generally assume $\beta_{21} \leq \beta_{11}$ and $\beta_{22} \leq \beta_{12}$. Recovery rates may differ between the fully susceptible $\gamma_1 \geq 0$, and the partially resistant host, $\gamma_2 \geq 0$. The schematic diagram of the model is as shown in Figure 1.

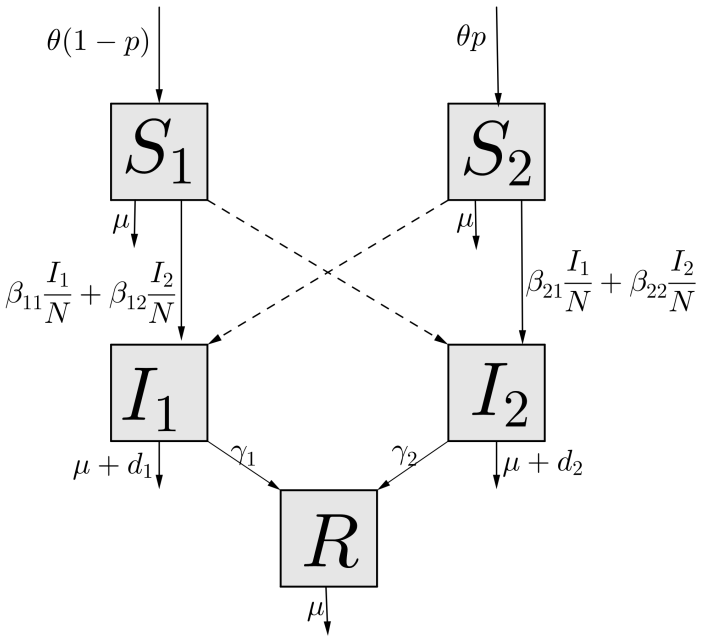


Figure 1: Schematic diagram of the epidemiological model with imperfect vaccination.

Mathematically, the model is as follows:

$$\begin{cases} \dfrac{\mathrm{d}S_1}{\mathrm{d}t} &= \theta(1-p) - \lambda_1(t)S_1(t) - \mu S_1(t), \\ \dfrac{\mathrm{d}S_2}{\mathrm{d}t} &= \theta p - \lambda_2(t)S_2(t) - \mu S_2(t), \\ \dfrac{\mathrm{d}I_1}{\mathrm{d}t} &= \lambda_1(t)S_1(t) - (\mu+\gamma_1+d_1)I_1(t), \\ \dfrac{\mathrm{d}I_2}{\mathrm{d}t} &= \lambda_2(t)S_2(t) - (\mu+\gamma_2+d_2)I_2(t), \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} &= \gamma_1 I_1(t) + \gamma_2 I_2(t) - \mu R(t). \end{cases} \tag{1}$$

A summary of the biological significance of the model parameters (1) is given in Table 1.

Table 1: Description and value of the model parameters.

Parameter	Description	Units	Value	Source
θ	Recruitment rate	$person.day^{-1}$	variable	Assumed
μ	Natural mortality rate	day^{-1}	variable	Assumed
p	Proportion of new hosts vaccinated	-	variable	Assumed
β_{11}	Transmission rate from I_1 to S_1	day^{-1}	variable	Assumed
β_{12}	Transmission rate from I_2 to S_1	day^{-1}	variable	Assumed
β_{21}	Transmission rate from I_1 to S_2	day^{-1}	variable	Assumed
β_{22}	Transmission rate from I_2 to S_2	day^{-1}	variable	Assumed
d_1	Mortality rate due to infection of S_1	day^{-1}	0.0008	(Mancuso et al. 2021)
d_2	Mortality rate due to infection of S_2	day^{-1}	0.0001	(Mancuso et al. 2021)
γ_1	Recovery rate of I_1	day^{-1}	0.1	(Mancuso et al. 2021)
γ_2	Recovery rate of I_2	day^{-1}	0.13	(Mancuso et al. 2021)

3. Mathematical analysis

3.1. Basic properties

First, we study the basic characteristics of the system solutions: the existence, non-negativity and boundedness of solutions. These are 1) essential to make sure that the model (1) is well defined mathematically and epidemiologically, and 2) useful for the proofs of the stability results.

3.1.1. Positive invariance of the nonegative orthant

For any associated Cauchy problem, the system (1) which is a C^∞-differentiable system, has a unique maximal solution.

Lemma 3.1. *The following result corresponds to Proposition B.7, Appendix B in (Smith and Waltman 1995). Let D be an open subset of $\mathbb{R}^n$, $f : \mathbb{R} \times D \to \mathbb{R}^n$, be a vector-valued function, $f = (f_1, f_2, \cdots, f_n)$. Consider a system of ODEs of the form*

$$x' = f(t, x). \tag{2}$$

Suppose that f in eq. (2) has the property that solutions of initial value problems $x(t_0) = x_0 \geq 0$ are unique and for all i $f_i(t, x) \geq 0$ whenever $x \geq 0$ satisfies $x_i = 0$. Then $x(t) \geq 0$ for all $t \geq t_0$ for which it is defined, provided $x(t_0) \geq 0$.

Theorem 3.2. *If the initial conditions of system (1) are such that $S_1(0) \geq 0$, $S_2(0) \geq 0$, $I_1(0) \geq 0$, $I_2(0) \geq 0$ and $R(0) \geq 0$, then the solution $(S_1(t), S_2(t), I_1(t), I_2(t), R(t))$ of the system equation is non-negative for all $t \geq 0$.*

Proof. Consider the model (1). We have

$$\frac{\mathrm{d}S_1}{\mathrm{d}t}\Big|_{S_1=0} = \theta(1-p) \geq 0,$$

$$\frac{\mathrm{d}S_2}{\mathrm{d}t}\Big|_{S_2=0} = \theta p \geq 0,$$

$$\frac{\mathrm{d}I_1}{\mathrm{d}t}\Big|_{I_1=0} = \beta_{11}\frac{I_1(t)}{N(t)}S_1(t) \geq 0,$$

$$\frac{\mathrm{d}I_2}{\mathrm{d}t}\Big|_{I_2=0} = \beta_{21}\frac{I_1(t)}{N(t)}S_2(t) \geq 0,$$

$$\frac{\mathrm{d}R}{\mathrm{d}t}\Big|_{R=0} = \gamma_1 I_1(t) + \gamma_2 I_2(t) \geq 0,$$

for all $S_1, S_2, I_1, I_2, R \geq 0$. By using Lemma 3.1, we conclude that the solution $(S_1(t), S_2(t), I_1(t), I_2(t), R(t))$ of the system equation is non-negative for all $t \geq 0$. □

Thus, solutions of the system (1) with non-negative initial conditions will be non-negative for all $t \geq 0$.

3.1.2. Boundedness of solutions

Since the variables of model (1) are non-negative and we are dealing with the dynamic of a number of individuals, it is important and biologically realistic that the total number of individuals does not explode (that is, it is bounded).

Lemma 3.3. *The closed set*

$$\Omega = \left\{(S_1(t), S_2(t), I_1(t), I_2(t), R(t)) \in \mathbb{R}^5 : S_1(t) \geq 0, S_2(t) \geq 0, I_1(t) \geq 0, I_2(t) \geq 0, R(t) \geq 0, \;\; N(t) \leqslant \frac{\theta}{\mu}\right\}$$

is positively invariant and attracting for the system (1).

Proof. Using the system (1), the dynamics of the total human population satisfies:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \theta - \mu N - d_1 I_1 - d_2 I_2 \leqslant \theta - \mu N.$$

Integrating both sides of the expression above, we deduce that

$$N(t) \leqslant \frac{\theta}{\mu} + \left(N(0) - \frac{\theta}{\mu}\right)e^{-\mu t}, \quad \forall t \geqslant 0, \tag{3}$$

where $N(0)$ is the value of $N(t)$ at time zero. We deduce that if $N(0) \leqslant \frac{\theta}{\mu}$, then $0 \leqslant N(t) \leqslant \frac{\theta}{\mu}$, $\forall t \geqslant 0$ and Ω is positively invariant. If $N(0) \geqslant \frac{\theta}{\mu}$, then from eq. (3) the total population decreases and the solutions of the system (1) enter Ω. Hence $N(t)$ is bounded as $t \to \infty$, which means that Ω is attracting. □

Remark 3.1. We know from Theorem 13 in (Lambert 1976) that every maximal solution of the Cauchy problem (2) that is bounded is global, that is it is exists for all $t \geq 0$. Then, every maximal solution of the system (1) is well defined for all $t \geq 0$.

The system (1) is epidemiologically and mathematically well posed in Ω since its state variables are non-negative and the size of the total population is bounded. The maximum value of N represents the size of the total population under the ideal situation without infection.

3.2. Disease-free equilibrium and its stability

For the analysis of the spread of an infection, we define the disease-free equilibrium (DFE) which is a state of the population without infection. The disease-free equilibrium is deduced from the resolution of the system (1) by taking $I_1 = 0$ and $I_2 = 0$. Thus, the disease-free equilibrium satisfies the following system of equations:

$$\begin{cases} \theta(1-p) - \mu S_1^0 = 0, \\ \theta p - \mu S_2^0 = 0. \end{cases} \tag{4}$$

Solving the system of equations (4) yields the disease-free equilibrium point:

$$Q^0 = (S_1^0, S_2^0, 0, 0, 0),$$

where $S_1^0 = \frac{\theta(1-p)}{\mu}$, $S_2^0 = \frac{\theta p}{\mu}$ and $N^0 = S_1^0 + S_2^0 = \frac{\theta}{\mu}$.

The linear stability of Q^0 depends on the well known reproduction number $\mathcal{R}_0$, which is defined as the average number of secondary cases caused by an infected individual, during its infectious period, when introduced into a population of susceptible individuals. We study the stability of the equilibrium through the next generation operator (Jacquez and Simon 1993, van den Driessche and Watmough 2002). Recalling the notations in (van den Driessche and Watmough 2002) for system (1), the matrices $\mathcal{F}$ of the new infection and $\mathcal{V}$ of the remaining transfer terms are respectively given by

$$\mathcal{F} = \begin{bmatrix} \beta_{11}\frac{S_1 I_1}{N} + \beta_{12}\frac{S_1 I_2}{N} \\ \\ \beta_{21}\frac{S_2 I_1}{N} + \beta_{22}\frac{S_2 I_2}{N} \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} (\mu + \gamma_1 + d_1) I_1 \\ \\ (\mu + \gamma_2 + d_2) I_2 \end{bmatrix}.$$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at Q^0 are respectively,

$$F = \begin{bmatrix} \beta_{11}\dfrac{S_1^0}{N^0} & \beta_{12}\dfrac{S_1^0}{N^0} \\ \\ \beta_{21}\dfrac{S_2^0}{N^0} & \beta_{22}\dfrac{S_2^0}{N^0} \end{bmatrix} \text{ and } V = \begin{bmatrix} \mu+\gamma_1+d_1 & 0 \\ \\ 0 & \mu+\gamma_2+d_2 \end{bmatrix}. \tag{5}$$

Then,

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta_{11}S_1^0}{N^0(\mu+\gamma_1+d_1)} & \dfrac{\beta_{12}S_1^0}{N^0(\mu+\gamma_2+d_2)} \\ \\ \dfrac{\beta_{21}S_2^0}{N^0(\mu+\gamma_1+d_1)} & \dfrac{\beta_{22}S_2^0}{N^0(\mu+\gamma_2+d_2)} \end{bmatrix},$$

and the reproduction number of model system (1) is

$$\begin{aligned} \mathcal{R}_0 = \rho(FV^{-1}) =& \frac{1}{2}\Big[\frac{S_1^0}{N^0}\mathcal{R}_{0,11} + \frac{S_2^0}{N^0}\mathcal{R}_{0,22} + \sqrt{\Big(\frac{S_1^0}{N^0}\mathcal{R}_{0,11} - \frac{S_2^0}{N^0}\mathcal{R}_{0,22}\Big)^2 + 4\frac{S_1^0}{N^0}\frac{S_2^0}{N^0}\mathcal{R}_{0,12}\mathcal{R}_{0,21}}\Big], \\ \mathcal{R}_0 =& \frac{1}{2}\Big[(1-p)\mathcal{R}_{0,11} + p\mathcal{R}_{0,22} + \sqrt{\Big((1-p)\mathcal{R}_{0,11} - p\mathcal{R}_{0,22}\Big)^2 + 4p(1-p)\mathcal{R}_{0,12}\mathcal{R}_{0,21}}\Big], \end{aligned} \tag{6}$$

where $\dfrac{S_1^0}{N^0} = 1-p$ (respectively $\dfrac{S_2^0}{N^0} = p$) is the proportion of susceptible individuals that have not been vaccinated (respectively have been vaccinated) at the DFE Q^0. Similarly, we define $\mathcal{R}_{0,11} = \dfrac{\beta_{11}}{\mu+\gamma_1+d_1}$ as the average number of secondary cases generated by an unvaccinated infected individual during its infectious period through the interaction with the unvaccinated population. Furthermore $\mathcal{R}_{0,12} = \dfrac{\beta_{12}}{\mu+\gamma_1+d_1}$ represents the average number of secondary cases generated by a vaccinated infected in the unvaccinated part of the population, $\mathcal{R}_{0,21} = \dfrac{\beta_{21}}{\mu+\gamma_2+d_2}$ is the average number of secondary cases generated by an unvaccinated infected in the vaccinated part of the population, and $\mathcal{R}_{0,22} = \dfrac{\beta_{22}}{\mu+\gamma_2+d_2}$ represents the average number of secondary cases generated by an infected vaccinated individual in the vaccinated part of the population. Further, $\rho(FV^{-1})$ is the spectral radius of FV^{-1}.

Remark 3.2. From the expression of the reproduction number $\mathcal{R}_0$ in eq. 6, we deduce that $\mathcal{R}_0 \geq \max\{(1-p)\mathcal{R}_{0,11}; p\mathcal{R}_{0,22}\}$. Moreover using (6) for $p = 0$ (all new hosts are unvaccinated), $\mathcal{R}_0 = \mathcal{R}_{0,11}$. Further if $p = 1$ (all new hosts are vaccinated), then $\mathcal{R}_0 = \mathcal{R}_{0,22}$.

The importance of the reproduction number is due to the result given in the next lemma derived from Theorem 2 in (van den Driessche and Watmough 2002).

Lemma 3.4. *The disease-free equilibrium Q^0 of the system (1) is locally asymptotically stable in Ω if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The biological meaning of Lemma 3.4 is that a sufficiently small number of infected hosts does not induce an epidemic unless the reproduction number $\mathcal{R}_0$, is greater than unity. That is, the disease

rapidly dies out (when $\mathcal{R}_0 < 1$) if the initial number of infected hosts is in the basin of attraction of the DFE, Q^0. Global asymptotic stability of the DFE is required to better control the disease. In addition, analysing the expansion of the basin of attraction of Q^0 is a more challenging task for the model under consideration, involving a fairly new result. For this purpose, we use Theorems 2.1 and 2.2 in (Shuai and van den Driessche 2013).

Theorem 3.5. *If $\mathcal{R}_0 \leqslant 1$, the disease-free equilibrium Q^0 of system (1) is globally asymptotic stable in Ω. If $\mathcal{R}_0 > 1$, Q^0 is unstable, the system (1) is uniformly persistent and there exists at least one endemic equilibrium in the interior of Ω.*

Proof. See Appendix A. □

As a consequence of the meaning of Theorem 3.5 and Remark 3.2, we can confidently deduce that the disease can be eradicated from the host community if the value of $\mathcal{R}_0$ is reduced to less than the unity, independently of whether individuals introduced in the population are all vaccinated or not.

3.3. Endemic equilibrium and its stability

Let $Q^* = (S_1^*, S_2^*, I_1^*, I_2^*, R^*)$ be the positive endemic equilibrium (EE) of model system (1). Then, the positive endemic equilibrium can be obtained by setting the right hand side of all equations in model system (1) to zero, giving:

$$\begin{cases} \theta(1-p) - \beta_{11}\dfrac{S_1^* I_1^*}{N^*} - \beta_{12}\dfrac{S_1^* I_2^*}{N^*} - \mu S_1^* = 0, \\ \theta p - \beta_{21}\dfrac{S_2^* I_1^*}{N^*} - \beta_{22}\dfrac{S_2^* I_2^*}{N^*} - \mu S_2^* = 0, \\ \beta_{11}\dfrac{S_1^* I_1^*}{N^*} + \beta_{12}\dfrac{S_1^* I_2^*}{N^*} - (\mu + \gamma_1 + d_1) I_1^* = 0, \\ \beta_{21}\dfrac{S_2^* I_1^*}{N^*} + \beta_{22}\dfrac{S_2^* I_2^*}{N^*} - (\mu + \gamma_2 + d_2) I_2^* = 0, \\ \gamma_1 I_1^* + \gamma_2 I_2^* - \mu R^* = 0. \end{cases} \tag{7}$$

Given the complexity of the system (7), we are not determining an explicit formula for the endemic equilibrium point Q^*. Note that determining Q^* is often very difficult to be carried out when the system is complex and has a large size. However, to prove the existence of Q^*, we can rewrite the system (7) as a fixed point problem and use Theorem 2.1 in (Hethcote and Thieme 1985). To do this, we solve the system (7). After algebraic manipulations, we obtain:

$$R^* = \frac{\gamma_1 I_1^* + \gamma_2 I_2^*}{\mu},\ S_1^* = \frac{\theta(1-p)N^*}{\beta_{11}I_1^* + \beta_{12}I_2^* + \mu N^*}, \quad S_2^* = \frac{\theta p N^*}{\beta_{21}I_1^* + \beta_{22}I_2^* - d_1 I_1^* - d_2 I_2^* + \theta},$$

$$I_1^* = \frac{\theta(1-p)(\beta_{11}I_1^* + \beta_{12}I_2^*)}{(\mu+\gamma_1+d_1)(\beta_{11}I_1^* + \beta_{12}I_2^* - d_1 I_1^* - d_2 I_2^* + \theta)} = H_1(I^*) \text{ and}$$

$$I_2^* = \frac{\theta p(\beta_{21}I_1^* + \beta_{22}I_2^*)}{(\mu+\gamma_2+d_2)(\beta_{21}I_1^* + \beta_{22}I_2^* - d_1 I_1^* - d_2 I_2^* + \theta)} = H_2(I^*) \text{ with } I^* = (I_1^*, I_2^*).$$

Then, the endemic equilibrium are the fixed points of H given by $I = H(I)$ where $I = (I_1, I_2)$. By definition, H is continuous, monotonously non decreasing and strictly sublinear. H is also a bounded function which maps the non negative orthant Ω into itself. Morever, $H(0) = 0$ by definition and the jacobian of H at the zero, $H^{'}(0)$, exists and is irreducible since

$$H^{'}(0) = \begin{bmatrix} \beta_{11}a_1 & \beta_{12}a_1 \\ \\ \beta_{21}a_2 & \beta_{22}a_2 \end{bmatrix} = FV^{-1},$$

where $a_1 = \dfrac{1-p}{\mu+\gamma_1+d_1}$ and $a_2 = \dfrac{p}{\mu+\gamma_2+d_2}$.

We deduce that the spectral radius $\rho(H^{'}(0))$ of the matrix $H^{'}(0)$ is $\mathcal{R}_0$. Then, the existence and the uniqueness of a non-negative fixed point occurs if and only if $\mathcal{R}_0 > 1$.

Proposition 3.1. The system (1) has only one endemic equilibrium whenever $\mathcal{R}_0 > 1$.

We establish the following result to analyze the stability of Q^*.

Theorem 3.6. *If $\mathcal{R}_0 > 1$, the endemic equilibrium Q^* is globally asymptotic stable in Ω.*

Proof. Consider the following Lyapunov candidate function:

$$L = L_1 + L_2 + L_3 + L_4,$$

where $L_1 = S_1 - S_1^* - S_1^* \log\left(\dfrac{S_1}{S_1^*}\right)$, $L_2 = S_2 - S_2^* - S_2^* \log\left(\dfrac{S_2}{S_2^*}\right)$, $L_3 = I_1 - I_1^* - I_1^* \log\left(\dfrac{I_1}{I_1^*}\right)$ and $L_4 = I_2 - I_2^* - I_2^* \log\left(\dfrac{I_2}{I_2^*}\right)$.

Using the inequality $1 - z + \log(z) \leqslant 0$ for $z > 0$ with equality if and only if $z = 1$, differentiation and using the EE values give

$$L^{'} = L_1^{'} + L_2^{'} + L_3^{'} + L_4^{'},$$

where

$$
\begin{aligned}
L_1^{'} &= \left(1-\frac{S_1^*}{S_1}\right)\frac{\mathrm{d}S_1}{\mathrm{d}t} \\
&= \left(1-\frac{S_1^*}{S_1}\right)\left[\beta_{11}\frac{S_1^*I_1^*}{N^*}-\beta_{11}\frac{S_1I_1}{N}+\beta_{12}\frac{S_1^*I_2^*}{N^*}-\beta_{12}\frac{S_1I_2}{N}-\mu S_1+\mu S_1^*\right] \\
&= -\frac{\mu(S_1-S_1^*)^2}{S_1}+\beta_{11}\frac{S_1^*I_1^*}{N^*}\left[1-\frac{S_1^*}{S_1}-\frac{S_1I_1N^*}{S_1^*I_1^*N}+\frac{I_1N^*}{I_1^*N}\right]+\beta_{12}\frac{S_1^*I_2^*}{N^*}\left[1-\frac{S_1^*}{S_1}-\frac{S_1I_2N^*}{S_1^*I_2^*N}+\frac{I_2N^*}{I_2^*N}\right].
\end{aligned}
$$

$$
\begin{aligned}
\text{Then}\quad L_1^{'} \leqslant\ & \beta_{11}\frac{S_1^*I_1^*}{N^*}\left[\frac{I_1N^*}{I_1^*N}-\log\left(\frac{I_1N^*}{I_1^*N}\right)-\frac{S_1I_1N^*}{S_1^*I_1^*N}+\log\left(\frac{S_1I_1N^*}{S_1^*I_1^*N}\right)\right] \\
&+\beta_{12}\frac{S_1^*I_2^*}{N^*}\left[\frac{I_2N^*}{I_2^*N}-\log\left(\frac{I_2N^*}{I_2^*N}\right)-\frac{S_1I_2N^*}{S_1^*I_2^*N}+\log\left(\frac{S_1I_2N^*}{S_1^*I_2^*N}\right)\right].
\end{aligned} \tag{8}
$$

We can also deduce in an analogous way:

$$
\begin{aligned}
L_2^{'} \ \leqslant\ & \beta_{22}\frac{S_2^*I_2^*}{N^*}\left[\frac{I_2N^*}{I_2^*N}-\log\left(\frac{I_2N^*}{I_2^*N}\right)-\frac{S_2I_2N^*}{S_2^*I_2^*N}+\log\left(\frac{S_2I_2N^*}{S_2^*I_2^*N}\right)\right] \\
&+\beta_{21}\frac{S_2^*I_1^*}{N^*}\left[\frac{I_1N^*}{I_1^*N}-\log\left(\frac{I_1N^*}{I_1^*N}\right)-\frac{S_2I_1N^*}{S_2^*I_1^*N}+\log\left(\frac{S_2I_1N^*}{S_2^*I_1^*N}\right)\right].
\end{aligned} \tag{9}
$$

We also have

$$
\begin{aligned}
L_3^{'} &= \left(1-\frac{I_1^*}{I_1}\right)\frac{\mathrm{d}I_1}{\mathrm{d}t} \\
&= \left(1-\frac{I_1^*}{I_1}\right)\left[\beta_{11}\frac{S_1I_1}{N}+\beta_{12}\frac{S_1I_2}{N}-(\mu+\gamma_1+d_1)I_1\right] \\
&= \left(1-\frac{I_1^*}{I_1}\right)\left[\beta_{11}\frac{S_1I_1}{N}+\beta_{12}\frac{S_1I_2}{N}-\beta_{11}\frac{S_1^*I_1}{N^*}+\beta_{12}\frac{S_1^*I_2^*I_1}{N^*I_1^*}\right] \\
&= \beta_{11}\frac{S_1^*I_1^*}{N^*}\left[\frac{S_1I_1N^*}{S_1^*I_1^*N}-\frac{S_1N^*}{S_1^*N}-\frac{I_1}{I_1^*}+1\right]+\beta_{12}\frac{S_1^*I_2^*}{N^*}\left[\frac{S_1I_2N^*}{S_1^*I_2^*N}-\frac{S_1I_1^*I_2N^*}{S_1^*I_1I_2^*N}-\frac{I_1}{I_1^*}+1\right],
\end{aligned}
\tag{10}
$$

$$
\begin{aligned}
L_3^{'} &\leqslant \beta_{11}\frac{S_1^*I_1^*}{N^*}\left[\frac{S_1I_1N^*}{S_1^*I_1^*N}-\log\left(\frac{S_1I_1N^*}{S_1^*I_1^*N}\right)-\frac{I_1}{I_1^*}+\log\left(\frac{I_1}{I_1^*}\right)\right] \\
&+\beta_{12}\frac{S_1^*I_2^*}{N^*}\left[\frac{S_1I_2N^*}{S_1^*I_2^*N}-\log\left(\frac{S_1I_2N^*}{S_1^*I_2^*N}\right)-\frac{I_1}{I_1^*}+\log\left(\frac{I_1}{I_1^*}\right)\right].
\end{aligned}
$$

Similarly, we obtain

$$
\begin{aligned}
L_4^{'} &\leqslant \beta_{22}\frac{S_2^*I_2^*}{N^*}\left[\frac{S_2I_2N^*}{S_2^*I_2^*N}-\log\left(\frac{S_2I_2N^*}{S_2^*I_2^*N}\right)-\frac{I_2}{I_2^*}+\log\left(\frac{I_2}{I_2^*}\right)\right] \\
&+\beta_{21}\frac{S_2^*I_1^*}{N^*}\left[\frac{S_2I_1N^*}{S_2^*I_1^*N}-\log\left(\frac{S_2I_1N^*}{S_2^*I_1^*N}\right)-\frac{I_2}{I_2^*}+\log\left(\frac{I_2}{I_2^*}\right)\right].
\end{aligned}
\tag{11}
$$

Therefore, by adding (8), (9), (10) and (11) we deduce

$$
\begin{aligned}
L^{'} \leqslant & \left(-\frac{I_1N^*}{I_1^*N}+\log\left(\frac{I_1N^*}{I_1^*N}\right)\right)\left(-\beta_{11}\frac{S_1^*I_1^*}{N^*}-\beta_{21}\frac{S_2^*I_1^*}{N^*}\right) \\
&+\left(-\frac{I_2N^*}{I_2^*N}+\log\left(\frac{I_2N^*}{I_2^*N}\right)\right)\left(-\beta_{12}\frac{S_1^*I_2^*}{N^*}-\beta_{22}\frac{S_2^*I_2^*}{N^*}\right) \\
&+\left(-\frac{I_1}{I_1^*}+\log\left(\frac{I_1}{I_1^*}\right)\right)\left(\beta_{11}\frac{S_1^*I_1^*}{N^*}+\beta_{12}\frac{S_1^*I_2^*}{N^*}\right) \\
&+\left(-\frac{I_2}{I_2^*}+\log\left(\frac{I_2}{I_2^*}\right)\right)\left(\beta_{22}\frac{S_2^*I_2^*}{N^*}+\beta_{21}\frac{S_2^*I_1^*}{N^*}\right).
\end{aligned}
$$

Then $L^{'} \leqslant 0$, since $-z+\log(z) \leqslant -1$, $\forall z>0$.

Since $\{Q^*\}$ is the only invariant subset in Ω where $L=0$, therefore by La Salle's invariance principle (La Salle 1976), Q^* is globally global asymptotic stable in Ω. □

The epidemiological consequence of this theorem is that the disease persists as endemic in the host population as soon as $\mathcal{R}_0 > 1$.

3.4. Herd immunity threshold

Herd immunity is a form of indirect protection from infectious disease that occurs when a sufficient percentage of a population has become immune to an infection, whether through previous infections or vaccination, and thereby reducing the likelihood of infection for individuals lacking immunity. This is due to the fact that immune individuals are unlikely to contribute to disease transmission, disrupting chains of infection, which stops or slows down the spread of disease. To compute the herd immunity threshold associated with the system (1), we set the reproduction number, $\mathcal{R}_0$ to one and solve for $p = \dfrac{S_2^0}{N^0}$ which is the proportion of susceptible individuals which have been vaccinated at the DFE, Q^0. Then we have,

$$\begin{aligned}\mathcal{R}_0 = 1 &\Longleftrightarrow \big[2 - \mathcal{R}_{0,11} + (\mathcal{R}_{0,11} - \mathcal{R}_{0,22})p\big]^2 = \big[\mathcal{R}_{0,11} - (\mathcal{R}_{0,11} + \mathcal{R}_{0,11})p\big]^2 + 4p(1-p)\mathcal{R}_{0,12}\mathcal{R}_{0,21} \\ &\Longleftrightarrow \big[(\mathcal{R}_{0,11} - \mathcal{R}_{0,22})^2 - (\mathcal{R}_{0,11} + \mathcal{R}_{0,22})^2 + 4\mathcal{R}_{0,12}\mathcal{R}_{0,21}\big]p^2 + \big[2(2 - \mathcal{R}_{0,11})(\mathcal{R}_{0,11} - \mathcal{R}_{0,22}) \\ &\quad + 2\mathcal{R}_{0,11}(\mathcal{R}_{0,11} + \mathcal{R}_{0,22}) - 4\mathcal{R}_{0,12}\mathcal{R}_{0,21}\big]p + (2 - \mathcal{R}_{0,11})^2 - \mathcal{R}_{0,11}^2 = 0.\end{aligned}$$

Thus solving $\mathcal{R}_0 = 1$ is equivalent to finding the roots of polynomial $Q(p)$ given by:

$$Q(p) = Ap^2 + Bp + C, \tag{12}$$

where $A = 4\mathcal{R}_{0,12}\mathcal{R}_{0,21} - 4\mathcal{R}_{0,11}\mathcal{R}_{0,22}$, $B = 4\mathcal{R}_{0,11}(1 + \mathcal{R}_{0,22}) - 4(\mathcal{R}_{0,22} + \mathcal{R}_{0,12}\mathcal{R}_{0,21})$ and $C = 4(1 - \mathcal{R}_{0,11})$.

Noting that negative thresholds are biologically meaningless (in our case), the conditions for $Q(p)$ to have positive real roots are determined below. For this purpose, we perform a case analysis to determine the positive real zeros of Q.

Let $\Delta = B^2 - 4AC$ be the discriminant of the equation $Q(p) = 0$.

Case 1 Suppose $A = 0$. Then

$$p_c = -\frac{C}{B}$$

is the only real root of Q. In addition $p_c > 0$ if and only if B and C have opposite signs and $B \neq 0$.

Case 2 Suppose $A \neq 0$ and $\Delta = 0$. Then

$$p_{c_0} = -\frac{B}{2A}$$

is the only real root of Q. Further $p_{c_0} > 0$ if and only if A and B have opposite signs.

Case 3 Suppose $A \neq 0$ and $\Delta > 0$. Then

$$p_{c_1} = \frac{-B - \sqrt{\Delta}}{2A} \text{ and } p_{c_2} = \frac{-B + \sqrt{\Delta}}{2A}$$

are the real roots of Q.

Moreover, if $A > 0$, then

$$\begin{cases} p_{c_1} > 0 \text{ if and only if } \sqrt{\Delta} < -B, \\ p_{c_2} > 0 \text{ if and only if } \sqrt{\Delta} > B. \end{cases}$$

Therefore, Q has two positive real roots if $A > 0$, $B < 0$, $C > 0$ and $\Delta > 0$. In addition, it has one positive real root if ($A > 0$, $B < 0$, $C < 0$ and $\Delta > 0$) or ($A > 0$, $B > 0$ and $C < 0$ and $\Delta > 0$).

Finally if $A < 0$, then

$$\begin{cases} p_{c_1} > 0 \text{ if and only if } \sqrt{\Delta} > -B, \\ p_{c_2} > 0 \text{ if and only if } \sqrt{\Delta} < B. \end{cases}$$

Therefore, Q has two positive real roots if $A < 0$, $B > 0$, $C < 0$ and $\Delta > 0$. It has one positive real root if ($A < 0$, $B > 0$, $C > 0$ and $\Delta > 0$) or ($A < 0$, $B < 0$, $C > 0$ and $\Delta > 0$).

Theorem 3.5 and Theorem 3.6 can be combined to give the following result:

Corollary 3.1. An imperfect vaccine can lead to the elimination of the disease if $Q(p) > 0$ (*i.e.* $\mathcal{R}_0 < 1$). If $Q(p) < 0$ (*i.e.* $\mathcal{R}_0 > 1$), then the disease persists in the population.

The implication of Corolloary 3.1 is that the use of an imperfect vaccine can lead to the elimination of the disease in the host population, if the proportion of vaccinated individuals satisfies one of the following conditions:

1. $p > p_c$, if $A = 0$, $B > 0$ and $C < 0$;
2. $p \in [0, p_c[$, if $A = 0$, $B > 0$ and $C > 0$;
3. $p \neq p_{c_0}$, if $A > 0$, $\Delta = 0$ and $B < 0$;
4. $p \in [0, p_{c_1}[$ or $p > p_{c_2}$, if $A > 0$, $\Delta > 0$, $B < 0$ and $C > 0$;
5. $p > p_{c_1}$ or $p > p_{c_2}$, if ($A > 0$, $\Delta > 0$, $B < 0$ and $C < 0$) or ($A > 0$, $\Delta > 0$, $B > 0$ and $C < 0$);
6. $p \in]p_{c_2}, p_{c_1}[$, if $A < 0$, $\Delta > 0$, $B > 0$ and $C < 0$;
7. $p \in [0, p_{c_1}[$ or $p \in [0, p_{c_2}[$, if ($A < 0$, $\Delta > 0$, $B > 0$ and $C > 0$) or ($A < 0$, $\Delta > 0$, $B < 0$ and $C > 0$).

Conversely, the disease persists in the population if the proportion of individuals vaccinated satisfies one of these conditions:

1. $p \in [0, p_c[$, if $A = 0$, $B > 0$ and $C < 0$;
2. $p > p_c$, if $A = 0$, $B > 0$ and $C > 0$;
3. $p \neq p_{c_0}$, if $A < 0$, $\Delta = 0$ and $B > 0$;
4. $p \in]p_{c_1}, p_{c_2}[$, if $A > 0$, $\Delta > 0$, $B < 0$ and $C > 0$;
5. $p \in [0, p_{c_1}[$ or $p \in [0, p_{c_2}[$, if ($A > 0$, $\Delta > 0$, $B < 0$ and $C < 0$) or ($A > 0$, $\Delta > 0$, $B > 0$ and $C < 0$);

6. $p \in [0, p_{c_2}[$ or $p > p_{c_1}$, if $A < 0$, $\Delta > 0$, $B > 0$ and $C < 0$;

7. $p > p_{c_1}$ or $p > p_{c_2}$, if ($A < 0$, $\Delta > 0$, $B > 0$ and $C > 0$) or ($A < 0$, $\Delta > 0$, $B < 0$ and $C > 0$).

We conclude the analytical part of our study by stating that the eradication of a disease is conditioned by the proportion of vaccinated individuals, this threshold for vaccination coverage is called the critical vaccination proportion (p_c). In some cases, there is one critical proportion which determines whether the basic reproduction number,$\mathcal{R}_0$, is less than one or not. In other cases, two critical proportions are found defining the occurrence of three different possible dynamics: disease eradication when $\mathcal{R}_0 < 1$, endemic disease dynamics when $\mathcal{R}_0 > 1$ with presence or absence of epidemiological oscillations of the number of infected individuals. In the latter case of two thresholds, the analytical results derived above do not allow to predict the epidemiological dynamics and the vaccination proportions. We therefore provide numerical simulations in the follow up section.

4. Numerical simulations

We refine the above analytical results by numerical simulations to assess the influence of the various model parameters and the impact of population turnover and trade-offs in vaccination efficiency, on the epidemiological dynamics (*i.e.* the number of infected individuals, and $\mathcal{R}_0$). To illustrate the behaviour of our model (1), we use parameter values for the mortality rates, d_1, d_2, and the recovery rates, γ_1, γ_2, measured for Covid-19 as an example of a highly transmissible disease (based on data from the United States (Mancuso et al. 2021)). In order to assess the influence of the various parameters of the model on the epidemiological outcome, we vary their values as described in Table 1. Note that we do not attempt here to model precisely the Covid-19 epidemics, but we focus on highly transmissible diseases relevant for public health. We indeed aim to go beyond applicability to a particular diseases (Covid-19) and to provide a generalized overview of the influence of vaccination trade-offs on epidemics.

4.1. Global sensitivity analysis

Uncertainty / sensitivity analyses are first used to determine which model input parameters have the greatest impact on the epidemiological outcome (Marino et al. 2008). The sensitivity analysis of the model parameters is carried out to measure the correlation between the model parameters and 1) the total number of infected individuals ($I_1 + I_2$), and 2) the threshold parameter $\mathcal{R}_0$. The analysis is performed by using the Latin Hypercube Sampling (LHS) technique and partial rank correlation coefficients (PRCCs) (Marino et al. 2008). In our analysis, 1,000 model simulations are performed by running the model for 200 time steps (equivalent to 200 days) and number of infected are recorded at time points 50, 100 and 200. To perform the sensitivity analysis, each parameter has a parameter range defines by the

Table 2: Summary of the influence of parameters on the total numbers of infected at different time points.

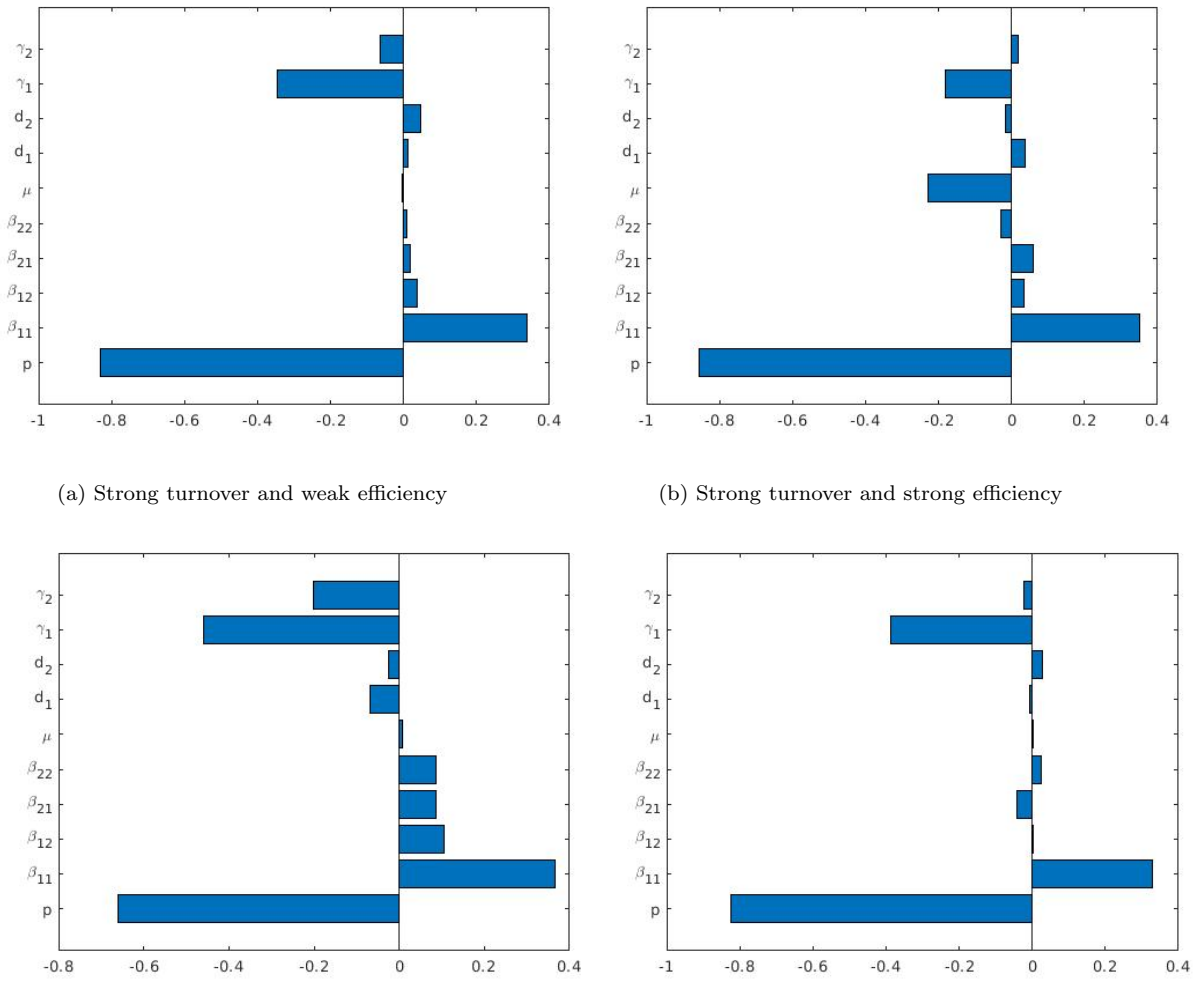
Scenarios	Total Infected: $I_1 + I_2$		
	$t = 50$ days	$t = 100$ days	$t = 200$ days
Strong turnover and weak efficiency	$\theta(+)$, $\beta_{11}(+)$, $\mu(-)$,$\gamma_1(-)$	$\theta(+)$, $\beta_{11}(+)$, $\mu(-)$,$\gamma_1(-)$	$\theta(+)$, $\beta_{11}(+)$, $\mu(-)$,$\gamma_1(-)$
Strong turnover and strong efficiency	$\theta(+)$, $\beta_{11}(+)$,$\mu(-)$,$\gamma_1(-)$	$\theta(+)$, $\beta_{11}(+)$, $\mu(-)$,$\gamma_1(-)$	$\theta(+)$, $\beta_{11}(+)$, $\mu(-)$,$\gamma_1(-)$
Weak turnover and weak efficiency	$\beta_{11}(-)$,$\beta_{21}(-)$, $\beta_{22}(-)$	$\beta_{21}(-)$, $\beta_{22}(-)$,$\gamma_1(+)$,$\gamma_2(+)$	$\theta(+)$, $\beta_{21}(-)$,$\gamma_1(+)$
Weak turnover and strong efficiency	$\theta(+)$, $\beta_{11}(-)$,$\beta_{21}(-)$,$\gamma_1(-)$	$\beta_{21}(-)$,$\mu(-)$,$\gamma_1(+)$	$\theta(+)$, $\beta_{21}(-)$,$\mu(-)$,$\gamma_1(+)$

maximum (respectively the minimum) being 50% greater (respectively less) than its baseline (values in Table C.3, C.4, C.5, C.6). We then divide each parameter range into 1,000 equally large sub-intervals, and draw a value per parameter within that interval using a Uniform draw. By this mean we obtain a uniform distribution of 1,000 parameter values for each parameter. The parameter space (or LHS matrix) has dimension of length 11 with each dimension specifying an uncertain parameter vector of length 1,000. The base parameter values are chosen to define several scenarios of interest regarding the intensity of the turnover (weak and strong) and efficiency of the vaccine (weak and strong). In PRCC analysis, the parameters with the larger positive or negative PRCC values (> 0.5 or < -0.5) and with corresponding small p-values (< 0.05) are deemed the most influential in determining the outcome of the model. A positive (negative) correlation coefficient corresponds to an increasing (decreasing) monotonic trend between the chosen response function and the parameter under consideration. The results of the PRCC analyses are found in Tables C.3, C.4, C.5, C.6 in Appendix C.

Based on the results from Tables C.3, C.4, C.5, C.6, we provide in table 2 a summary of the the parameters that significantly affect the number of infected. Overall, it appears that the recruitment rate, θ and the recovery rate of the infected who have not been vaccinated, γ_1, are the two main parameters driving the number of infected. This suggests that an effective control strategy should aim to limit significantly the immigration of new hosts in the population (to decrease θ) and improve the treatment of infected individuals (to increase γ_1). We then proceed to a similar analysis with $\mathcal{R}_0$, and summarize the sensitivity analysis of the LHS and PRCC techniques in Figure 2. We find, perhaps unsurprisingly, that the proportion of new hosts vaccinated, p, is the most significant parameter explaining the change in $\mathcal{R}_0$, along with the transmission rate from unvaccinated infected to unvaccinated susceptibles, β_{11} and the recovery rate of the infected who have not been vaccinated, γ_1 (Table 2).

4.2. Interplay between vaccine efficiency and population turnover

We now study the effect of population turn-over and vaccine efficiency on the epidemiological dynamics. Specifically, we use numerical simulations to find the vaccination coverage necessary to eradicate the



(a) Strong turnover and weak efficiency

(b) Strong turnover and strong efficiency

(c) Weak turnover and weak efficiency

(d) Weak turnover and strong efficiency

Figure 2: PRCCs describing the impact of model parameters on $\mathcal{R}_0$ of the model (1) with respect to some scenarios. The range of the parameters in (a) (respectively in (b), (c) and (d)) is the same as given on Table C.3(respectively on Table C.4, C.5, C.6).

disease in the community ($\mathcal{R}_0$ satisfying the corollary 3.1) under two population turnover rates (fixing the ratio θ/μ, we define strong turnover with $\theta = 1000$ and $\mu = 0.09$, and weak with $\theta = 10$ and $\mu = 0.0009$), when the efficiency of the vaccine only reduces transmission. The vaccine efficiency is set as weak ($\beta_{21} = (1-0.5)\beta_{11}$ and $\beta_{22} = (1-0.5)\beta_{12}$, defining an efficiency of 50%) or strong ($\beta_{21} = (1-0.9)\beta_{11}$ and $\beta_{22} = (1-0.9)\beta_{12}$, defining an efficiency of 90%).

4.2.1. Strong population turnover

The epidemiological dynamics in Figure3(b) under strong turnover and weak vaccine efficiency ($\mathcal{R}_0 = 1.2352$) shows that the dynamics reaches the endemic disease equilibrium. Furthermore if p takes value between 0 and p_1 (with $p_1 \approx 0.696$), the basic reproduction number is greater than 1, but if p is between

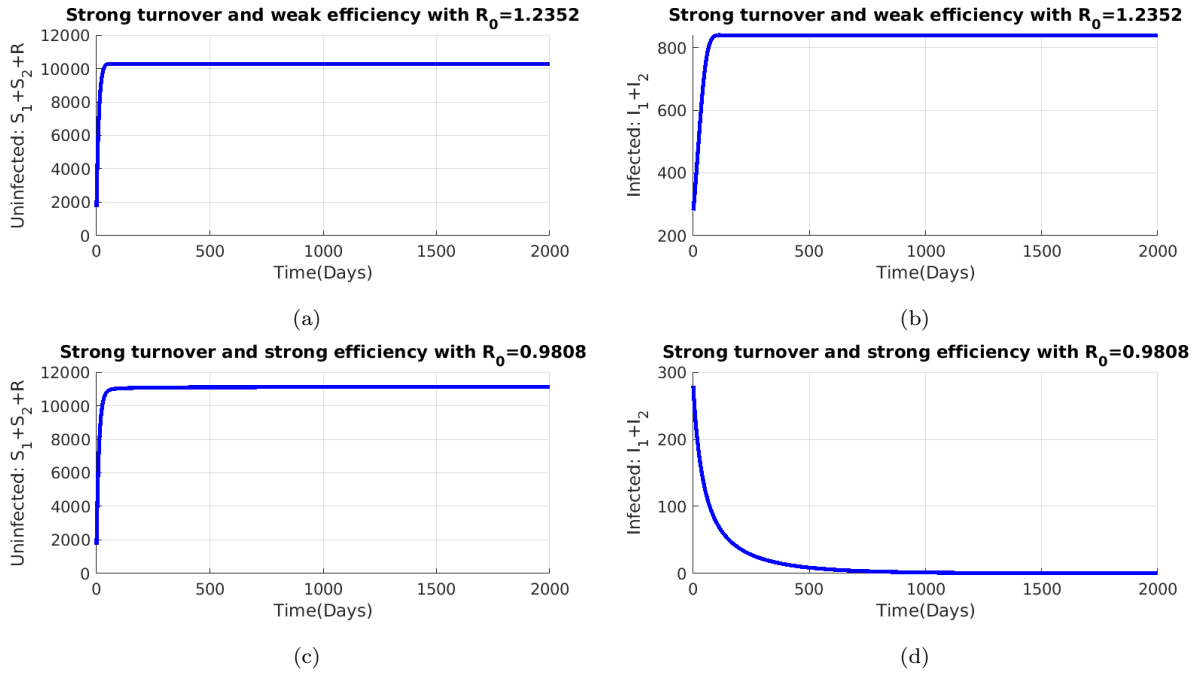


Figure 3: Epidemiological dynamics with the initial conditions $S_1(0) = 1000$, $S_2(0) = 700$, $I_1(0) = 200$, $I_2(0) = 80$, $R(0) = 20$ for various scenarios assuming the parameters $\beta_{11} = 0.35$, $\beta_{12} = 0.28$, $p = 0.5$ and strong population turnover ($\theta = 1000$, $\mu = 0.09$). We present under weak vaccine efficiency ($\beta_{21} = 0.175, \beta_{22} = 0.14$), the number of (a) uninfected and (b) infected individuals. We present under strong vaccine efficiency ($\beta_{21} = 0.035, \beta_{22} = 0.028$) the number of (c) uninfected and (d) infected individuals. Others parameters values are as in Table 1.

p_1 and 1, the basic reproduction number is less than 1 (as predicted in the analytical results in Corollary 3.1). So to eradicate the disease under strong population turnover and weak efficiency of the vaccine, a minimum vaccination rate is needed and defined by p_1. Under strong turnover and strong efficiency (Figure3(d), with $\mathcal{R}_0 = 0.9808$) the disease becomes extinct. Furthermore if the parameter p between 0 and p_2 with $p_2 \approx 0.489$, the basic reproduction number is greater than 1, while for p between p_2 and 1, the basic reproduction number is less than 1. So to eradicate the disease in this context of strong turnover and strong efficiency of the vaccine, there is a need to vaccinate more than 48.9% of the new host individuals.

4.2.2. Weak population turnover

To illustrate a weak population turnover, we consider the values $\theta = 10$ and $\mu = 0.0009$, noting that the ratio of θ/μ is the same as for the strong turnover investigated above. Under weak turnover, the epidemiological dynamics exhibits damped oscillations (recurring outbreaks) before stabilizing at the endemic state with disease persistence (Figure4(b) with $\mathcal{R}_0 = 2.2551$, Figure4(d) with $\mathcal{R}_0 = 1.8276$). These oscillations are due to the fact that individuals migrate rapidly in the recovered compartment, and a new outbreak only occurs when a sufficient number of susceptible are available from new recruit-

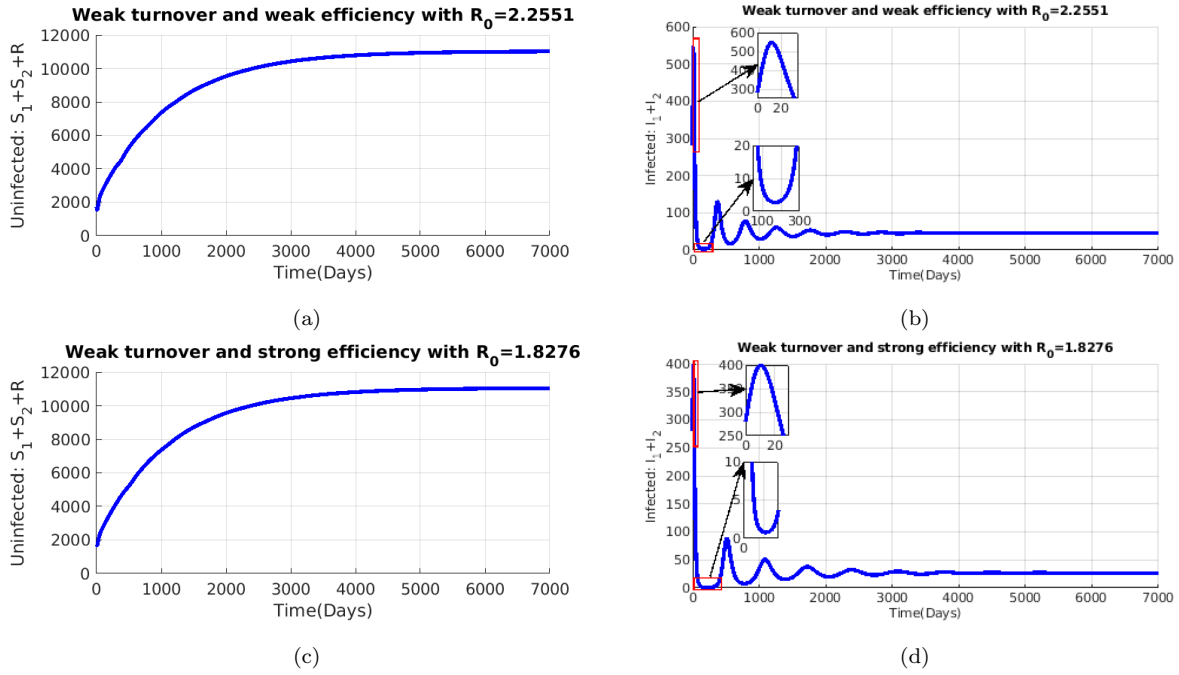


Figure 4: Simulation of model (1) at the initial conditions $S_1(0) = 1000$, $S_2(0) = 700$, $I_1(0) = 200$, $I_2(0) = 80$, $R(0) = 20$ when $\theta = 10$, $\beta_{11} = 0.35$, $\beta_{12} = 0.28$, $\beta_{21} = 0.175, \beta_{22} = 0.14$, $\mu = 0.0009$, $p = 0.5$, (a) Uninfected individuals in weak turnover and weak efficiency scenario and (b) Infected individuals in weak turnover and weak efficiency scenario. When $\theta = 10$, $\beta_{11} = 0.35$, $\beta_{12} = 0.28$, $\beta_{21} = 0.035, \beta_{22} = 0.028$, $\mu = 0.0009$, $p = 0.5$,(c) Uninfected individuals in weak turnover and strong efficiency scenario and (d) Infected individuals in weak turnover and strong efficiency scenario. Others parameters values are as in Table 1.

ment into the population and recovered individuals loosing their immunity (so-called waning immunity). This phenomenon was also described in (Ashby and Best 2021, Pulliam et al. 2007, Gumel et al. 2006, Scherer and McLean 2002), and the effect of turnover and waning immunity is specifically described in (Ashby and Best 2021, Pulliam et al. 2007).

With respect to the control of the disease, under weak vaccine efficiency, p can take any value between 0 and 1, the basic reproduction number is always greater than 1 (Figure4(b) with $\mathcal{R}_0 = 2.2551$). In contrast, when vaccine efficiency is strong, three cases occur Figure4(d) (with $\mathcal{R}_0 = 1.8276$). When p has a value between 0 and p_3 with $p_3 \approx 0.753$, the basic reproduction number is greater than 1 and we observe a damped periodicity of the number of infected individuals converging towards a stable endemic state. When p takes values between p_3 and p_4 (with $p_4 \approx 0.756$), the basic reproduction number, $\mathcal{R}_0$, is greater than 1 but no oscillations are observed. And for $p \in [p_4, 1]$, the basic reproduction number, $\mathcal{R}_0$, is less than 1, and disease becomes extinct. Note that between p_3 and p_4, the behavior can change very finely, but the resolution of our simulations does not allow us to decide on a very precise bound when oscillations occur or not. Therefore, to eradicate the disease in this context of weak population turnover and strong efficiency of the vaccine, a high vaccination coverage (more than 75.6% of the new host individuals) is

needed. Our results extend those in (Nuismer et al. 2016) showing that it is feasible to control disease by a weakly efficient vaccine acting on disease transmission, but that the required vaccination coverage depends on the population turnover. We note that the persistence of an endemic equilibrium is predicted by the condition $\mathcal{R}_0 > 1$, even if damped oscillations in the number of infected individuals occur. In other words, while the population turnover does not factor directly in the analytical expression of $\mathcal{R}_0$, it enters only indirectly by affecting the proportion of susceptible individuals available (eq. 6). The simulation results provide examples of the analytical expressions obtained in eq. 12 following the Corollary 3.1.

4.3. Interplay between types of vaccines and population turnover

We now assume that a vaccine has two potential mechanisms of action on the disease, namely blocking transmission and/or favouring the recovery of infected individuals. We investigate the effect of these vaccine types on the epidemiology depending on the population turnover. Specifically, model (1) is slightly modified to allow for the assessment of the efficiency of the vaccine regarding the probability of being infected and the recovery rate. This is achieved by simply rescaling the parameters as follows:

$$\beta_{21} = (1-\varepsilon)\beta_{11}, \beta_{22} = (1-\varepsilon)\beta_{12}, \text{ and } \gamma_1 = (1-\nu)\gamma_2, \tag{13}$$

where $0 \leq \varepsilon \leq 1$ represents the effect of the vaccine on disease transmission and $0 \leq \nu \leq 1$ represents the effect of the vaccine on recovery. Substituting the rescaled expressions in eq. 13 into the model (1), one deduces that the basic reproduction number the model (1) can be rewritten as:

$$\mathcal{R}_0 = \frac{1}{2}\Big[(1-p)\mathcal{R}_{0,11} + p\mathcal{R}_{0,22} + \sqrt{\Big((1-p)\mathcal{R}_{0,11} - p\mathcal{R}_{0,22}\Big)^2 + 4p(1-p)\mathcal{R}_{0,12}\mathcal{R}_{0,21}}\Big], \tag{14}$$

with $\mathcal{R}_{0,11} = \dfrac{\beta_{11}}{\mu + (1-\nu)\gamma_2 + d_1}$, $\mathcal{R}_{0,12} = \dfrac{\beta_{12}}{\mu + (1-\nu)\gamma_2 + d_1}$, $\mathcal{R}_{0,21} = \dfrac{(1-\varepsilon)\beta_{11}}{\mu + \gamma_2 + d_2}$ and $\mathcal{R}_{0,22} = \dfrac{(1-\varepsilon)\beta_{12}}{\mu + \gamma_2 + d_2}$. Simulations are carried out to assess the interplay of the type of vaccine and the population turnover.

Under a strong population turnover, as expected, the value of the reproduction number decreases as coverage and efficiency of the vaccine on the transmission increase (Figure 5(a)), and if the vaccine is designed to only decrease the transmission by 80% (*i.e.* $\varepsilon = 0.8$), the eradication of the disease in the host population can be achieved ($\mathcal{R}_0 < 1$) if at least 70% of the population is vaccinated (Figure 5(a)). On the other hand, the value of the reproduction number decreases as coverage increases and efficiency of the vaccine favoring recovery decreases (Figure 5(b)). With a vaccine designed to enhance recovery by 20% (*i.e.* $\nu = 0.2$), the eradication of the disease in the host population can be achieved ($\mathcal{R}_0 < 1$) if at least 68% of the population is vaccinated (Figure 5(b)). In Figure 5(c), we present the effect of the combined efficiency of the vaccine (decreasing transmission and favouring recovery) on the reproduction number at $p = 0.5$. The eradication of the disease can be achieved ($\mathcal{R}_0 < 1$) if the vaccine has a combined efficiency

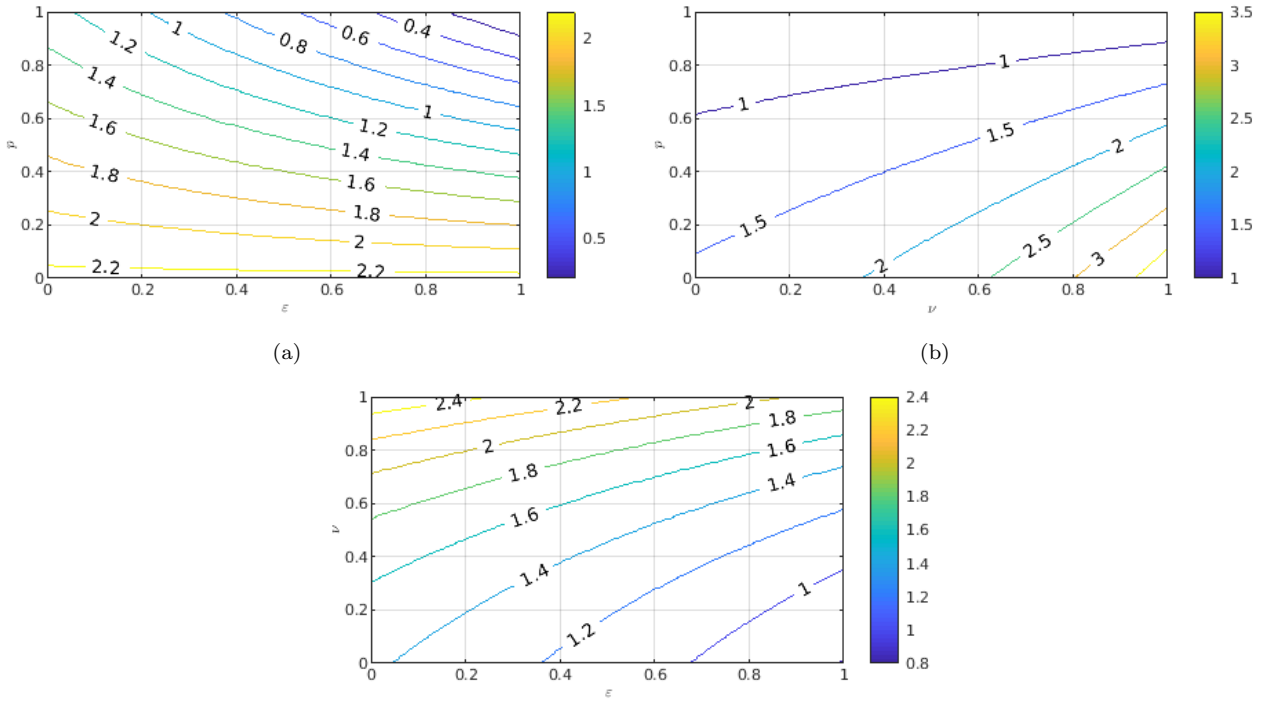


Figure 5: Contour plots of the basic reproduction number ($\mathcal{R}_0$) of the model (1) with a strong population turnover as a function of (a) vaccination coverage, p, and vaccine efficiency on disease transmission, ε (with fixed $\nu = 0.5$); (b) vaccination coverage, p, and vaccine efficiency on recovery, ν (with fixed $\varepsilon = 0.5$); and (c) vaccine efficiency on recovery, ν, and vaccine efficiency on transmission, ε (with fixed $p = 0.5$). The parameters are $\theta = 1000$, $\beta_{11} = 0.35$, $\beta_{12} = 0.28$, $\beta_{21} = 0.175, \beta_{22} = 0.14$, $\mu = 0.09$, $d_1 = 0.0008$, $d_2 = 0.0001$, $\gamma_1 = 0.065$, $\gamma_2 = 0.13$.

of at least 85% against infection (and thus transmission) and at least 20% to enhance recovery (for a given vaccination coverage of $p = 0.5$). These figures represent subsets of the general results presented in Figure D.7, in which $\mathcal{R}_0$ is a function of ε, ν and p. The use of a vaccine with a combined efficiency (decreasing transmission and favouring recovery) can be associated to the vaccination coverage in order to achieve the elimination of the disease. For example, with a vaccination coverage of 20% ($p = 0.2$), it is not possible to eliminate the disease no matter the combined efficiency of the vaccine (Figure D.8), while at 80% coverage ($p = 0.8$), there are several combinations of vaccine types, decreasing transmission and favouring recovery, that can promote disease control (Figure D.8).

The above results change dramatically under a weak population turnover. As expected, the value of the reproduction number decreases as coverage and efficiency of the vaccine on the transmission increase (Figure D.9(a)), but a higher vaccination coverage is needed compared to the strong population turnover to achieve $\mathcal{R}_0 < 1$. Moreover, it is not possible to eradicate the disease if 1) the vaccine is only efficient to enhance recovery, no matter the vaccination coverage (Figure D.9(b)), or 2) if the efficiency of the vaccine

is combined but vaccination coverage is $p = 0.5$ (Figure D.10). The general results of $\mathcal{R}_0$ as a function of ε, ν and p demonstrate that under weak population turnover, disease eradication requires a very strong efficiency of the vaccine and a high coverage (Figure D.11).

4.4. Interplay between vaccine efficiency trade-off and population turnover

So far we have assumed that all parameters of vaccine efficiency can be independently chosen from one another. We study, here, the epidemiological dynamics when there exists a possible (and realistic) trade-off (relationship) between the vaccine efficiency on the transmission and on the recovery. We assume three possible trade-off curves: convex($\nu = \varepsilon^2$), concave($\nu = \sqrt{\varepsilon}$) or linear($\nu = \varepsilon$). Under a strong population turnover, assuming a vaccine of at least 60% of efficiency, disease eradication can be achieved ($\mathcal{R}_0 < 1$) if the coverage is at least 65% under a convex trade-off (Figure 6(a)), at least 80% under a concave trade-off (Figure 6(b)) and at least 75% under a linear trade-off (Figure 6(c)). Imposing vaccine trade-off affects therefore the shape of the $\mathcal{R}_0$ curves in Figure 6(a), 6(b), 6(c) compared to Figures 5(a) and 5(b), and may be important to predict the minimum vaccination coverage to be achieved. However under a weak population turnover, the disease persists no matter the vaccination coverage and whatever trade-off are assumed in the vaccine (Figures D.12(a), D.12(b) and D.12(c)).

5. Discussion and Conclusion

When a large proportion of a population becomes immune to a virus, it becomes harder for the disease to spread. This is the core concept underlying the concept of herd immunity (Djatcha et al. 2017, Ashby and Best 2021, Mancuso et al. 2021). However, there are numerous individuals who refuse to be vaccinated because of various reasons (health concerns, lack of information, systemic mistrust, see (Muller et al. 2022)), and some vaccines provide only partial protection from disease or can be only efficient against few disease variants (see the recent Covid-19 epidemics and the vaccine efficiency and waning of immunity against different variants). Therefore, it is rather common that pathogens face an heterogeneous population of vaccinated and unvaccinated hosts (Muller et al. 2022), and this has consequences for the evolution of the disease itself (Gandon et al. 2003, Alizon et al. 2009, Gandon and Day 2007). In this study, we used mathematical modelling approaches (analysis and numerical simulations) to assess the potential population-level impact of the using different types of imperfect vaccines to control the burden of a disease in a community. In a first part, we provide a theoretical analysis of the model, including the basic reproduction number $\mathcal{R}_0$ and conditions for the stability of the equilibria. We derive the condition to be satisfied regarding the proportion of vaccinated individuals at steady state in order to attain herd immunity. We express this condition as the critical coverage to be achieved for $\mathcal{R}_0 < 1$.

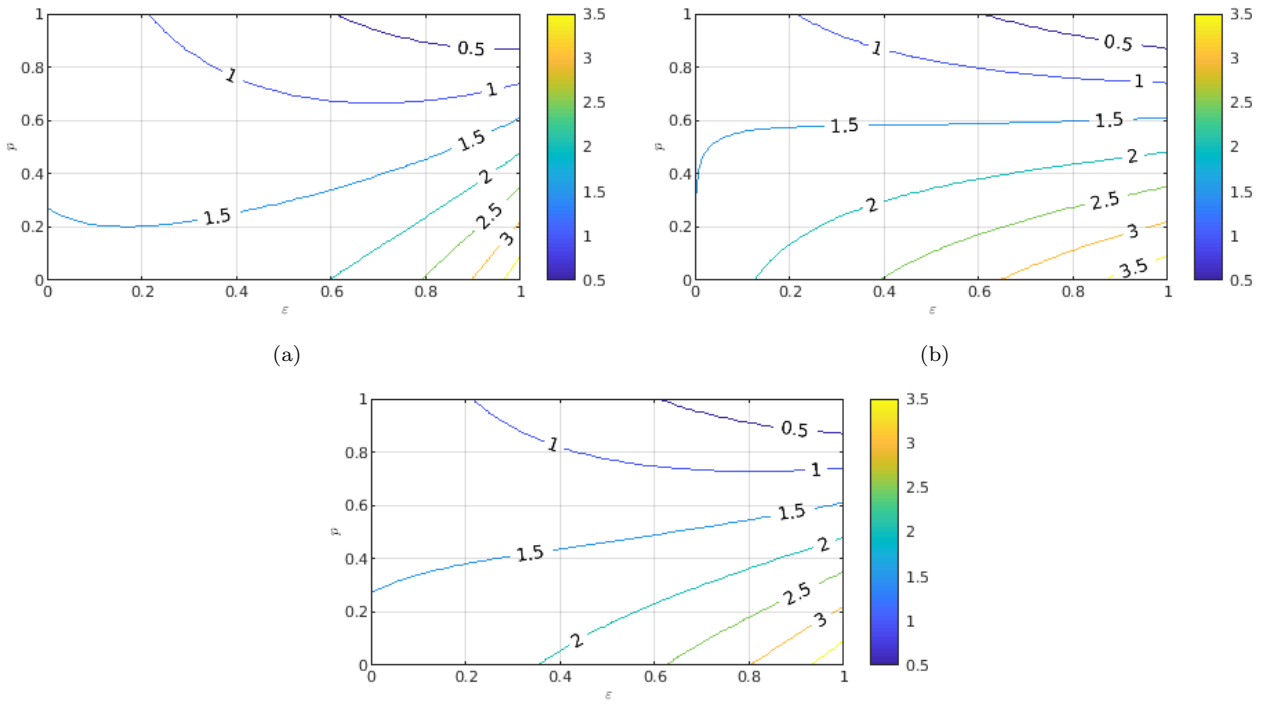


Figure 6: Contour plots of the basic reproduction number ($\mathcal{R}_0$) of the model (1) with a strong population turnover as a function of vaccine coverage, p, and vaccine efficiency on the transmission, ε when: (a) $\nu = \varepsilon^2$ (convex relationship); (b) $\nu = \sqrt{\varepsilon}$ (concave relationship); (c)$\nu = \varepsilon$ (linear relationship). The parameters are $\theta = 1000$, $\beta_{11} = 0.35$, $\beta_{12} = 0.28$, $\beta_{21} = 0.175, \beta_{22} = 0.14$, $\mu = 0.09$, $d_1 = 0.0008$, $d_2 = 0.0001$, $\gamma_1 = 0.065$, $\gamma_2 = 0.13$.

When the vaccine is developed to prevent infection and stop transmission, our results show that it is possible to eliminate the disease with a strong population turnover if the vaccination coverage is greater than 69.6% (respectively 48.9%) with a weak (respectively strong) efficiency of the vaccine. However, when population turnover is weak, we observe damped oscillations and eradication is possible with a vaccine with high efficiency and a coverage greater than 75.6%. Otherwise, the disease persists and becomes endemic in the community. We highlight here the effect of population turnover as an important first factor in deciding the effectiveness of vaccination campaigns (as suggested in (Scherer and McLean 2002, Pulliam et al. 2007, Knight et al. 2020)). For example with respect to application to a human population, the turnover can be consider as migration in and out of the community since the birth and death rate are usually small and fairly constant. Our results suggest that for a community with strong migration (strong turnover), we can vaccinate individuals coming in, in order to reduce the basic reproduction number. However, if there is a weak migration (weak turnover) as for example when flights and travel are restricted, the vaccination strategy should be improved by undertaking a mass vaccination campaign and using a high efficiency vaccine. A similar reasoning applies to domesticated animals (livestocks) with

the migration of (potentially vaccinated) individuals between farms influencing the epidemic.

We then analyse more finely the effect of the type of vaccine and its efficiency on disease dynamics. The vaccine can decrease transmission and/or favour recovery of infected individuals. Disease eradication is possible if the vaccine decreases transmission by 82%, enhances recovery by at least 25% and a vaccination coverage of 82% is achieved under a strong population turnover. Under weak turnover, maximum vaccine efficiency and coverage are required. Therefore, there is also an interplay between the strength of population turnover and the efficiency of the vaccine (and the property of the vaccine). Finally, we explore the importance of vaccine design if trade-off between the vaccine efficiency to stop transmission (infection) and disease recovery are expected. We use three trade-off curves, and show that the convex ($\nu = \varepsilon^2$) function is the most desirable, when the efficiency of the vaccine is at least 60% under a strong turnover of population. However, under a weak population turnover, the disease cannot be easily eradicated no matter the vaccination coverage and the efficiency of a combined vaccine. Furthermore, we notice that a smaller vaccination coverage and/or efficiency is needed when using a vaccine designed with a convex trade-off between the above two properties (decrease transmission and favour recovery) than other vaccines (different trade-offs or no trade-off).

Our model has some limitations and advantages compared to previous work in the literature, as we intend here to study the overall behaviour of our model under different schematic scenarios. First, we use, for illustrative purpose, Covid-19 parameters to exemplify expected threshold for vaccination coverage for a highly transmissible disease. We thus caution here against building precise recommendations (for Covid-19 vaccination) based on our results. Second, our model does not explicitly account for a continuous vaccination (or a large vaccination campaigns) of individuals in a community. Vaccination is linked in our model to the population turnover, explaining the appearance of periodic oscillations in disease incidence (the honey moon periods, (Ashby and Best 2021, Pulliam et al. 2007, Gumel et al. 2006, Scherer and McLean 2002)). Such periodic epidemics occur and are predicted for Covid-19, and may likely be due to immunity waning of the various vaccines against new variants (Mancuso et al. 2021). Third, we use a frequency-dependent transmission which allows us to derive analytical results in more depth than some previous models, but may underestimate the spread of disease and speed of disease dynamics. Thus to obtain precise predictions regarding vaccination efficiency and campaigns for a given disease, the ad hoc parameters of our models need to be correctly adjusted.

This model contains some general conclusions which are not only applicable to human populations, but also domesticated (livestocks) and wild animals or even crops. Domesticated animals also require vaccinations (*e.g* (Gulbudak and Martcheva 2014, Bitsouni et al. 2019)), and our study draws recommendations on the importance of turnover and migration rates in and out of the population. Our results

also suggest that in livestocks, the type of vaccine can be adjusted depending on the disease, especially if it is desirable that infected animals recover well, rather than attempting to prevent any transmission (*e.g* (Gulbudak and Martcheva 2014, Bitsouni et al. 2019)). Our results may be also be relevant to consider for vaccination campaigns of wild endangered animals (Barnett and Civitello 2020). In addition, we also suggest that the principles of the model apply to plant (crop) immunization. To protect plants against invasion of pathogens or pests, one can use different biotic and synthetic chemicals to induce immunity in the plant (Dyakov et al. 2007) or protect plants by spraying fungicides (Parnell et al. 2006). In a field, or among fields, some plants will be more resistant than others for a certain period of time. The spray is equivalent to the vaccination, and is in that case decoupled from the population turnover which is the planting/renewal and harvesting/removal of plants. Plant epidemiology modelling has been used to predict the efficiency of imperfect fungicide treatments on the epidemics and on yield (Rock et al. 2014, Parnell et al. 2006), with results mirroring our own.

In summary, we show that it is possible to achieve disease control by vaccination in a population with strong turnover, even if we use a weak imperfect vaccine designed to reduce only transmission. However, a higher vaccination coverage and a strong efficiency vaccine are necessary to control the disease under weak population turnover. Besides, a vaccine with convex trade-off between the efficiency to reduce transmission and to enhance recovery is recommendable along with a high vaccination coverage.

Authors contributions

Conception and design: HLNB, OMP, AT; Formal investigation: HLNB, OMP; Numerical simulations: HLNB; Writing first draft: HLNB; Supervision: OMP, AT, JMN; Revision of draft: AT, OMP, JMN.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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