Reducing vaccination level to eradicate a disease by means of a mixed control with isolation

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ABSTRACT

The present study has investigated mixed control strategy to reduce the required level of vaccination to eradicate a disease. It is well known that despite the advances on the development of new vaccines and control strategies to eradicate diseases, many diseases such as measles, tuberculosis and flu are still persistent. Any effort made to bring some light in this issue should be considered and developed. Here, we present a dynamic analysis of the SIR model to develop a simple but efficient strategy of control based on the simultaneously application of vaccination and isolation. We show how to significantly decrease the required level of vaccination to eradicate a disease. We have also found that a growth in population decreases the effects of isolation in the required time to eradicate a disease. Finally, we noticed that the effect of isolation for both fixed size population or variable population is more significant for lower levels of vaccination, which is particularly interesting in real life situations, where the high levels of vaccination are not undertaken. Numerical simulations are provided to show the effectiveness of the proposed technique.

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1. Introduction

Infectious diseases are one of the most important causes of morbidity and mortality in the world. Nevertheless, policies aimed at limiting their occurrence has been limited, particularly in developing countries [14]. One of the difficulties to achieve this task is the developing of effective vaccines. Even when there is a discovery of an effective vaccine the battle has not finished, as virus and bacteria evolve very fast, a phenomenon called drug resistance may occur. A recent and challenger example is the appearance of a drug-resistant Tuberculosis in China [20,39]. According to [39], 5.7% of the cases had multidrug-resistant Tuberculosis.

This situation becomes particularly severe when the number of eradicated diseases is analysed. Unfortunately, this number is still very little and although there is great reasons to celebrate the global eradication of smallpox, the same results are not yet achieved to many other diseases, such as measles, tuberculosis, and different types of influenza [13,14]. Among the main reasons that explain this failure, an efficient control strategy of the vaccines is certainly

one of them. The scientific community is aware of that and a myriad of papers on such issue is easily identified, such as [4,17,26,34,35].

One of the important scientific activities to help in eradicating diseases is the mathematical epidemiology. The author of [10] states in a concise way the reason of such studies: "The main reasons for studying mathematical models of disease spread is the hope that improved understanding of the transmission mechanism may lead to more effective control strategies". An example of such approach can be seen in [31], where mathematical analysis and numerical simulation are used to show the importance of CTL immune responses in eradication of the hepatitis B.

Among many mathematical strategies of modelling, the compartmental models [4,17], in general called SIR models, are usually considered one of the most important [8,9]. Although, it seems quite simple, the SIR model has been investigated in many aspects, such as nonlinear analysis of wave travelling of dispersal SIR epidemic model [36], variable population [1,37], on discrete time approach [3], HIV on micro-level population [11] and optimal control [2,6,12,15,16,41] to cite a few examples.

There are many works applying control theory on SIR and other compartmental models [2,5,15,25,27–29,37,41]. As pointed earlier, one of the most important goals of vaccinations campaigns is the eradication of the disease. There are many diseases that remain endemic and one of the reasons is that the levels of required vac-

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cines are sometimes very high. According to [14], only when the public coverage is above 93% in the measles case, does eradication occur. Although, a great effort has been done on strategies, particularly using optimal control [25,41], less attention has been observed in a mixed control to reduce the required level of vaccination to eradicate the disease. Mixed control is not a new method [7] it is currently using in many application situation, such as [23,40]. The authors of [19] use vaccination and isolation with the aim of reducing cost by means of an optimal control [16]. Another interesting paper is developed in [21], where the authors formulate by means of an optimal control a strategy to reduce the number of infected chronic hepatitis B individuals by means of isolation and vaccination. Similar works have been reported in [22] and [15], but focused in the outbreaks of hand, foot, and mouth disease in Taiwan and predicting and evaluating the epidemic rend of Ebola virus disease in West Africa, respectively. There also stochastic analysis of mixed control, particularly interesting for small populations, in the following works [24,30]. From a complex system perspective, an interesting work that applies mixed control can be seen in [38], where the authors deal with human contact networks that may change topologically from time to time.

This paper aims at contributing to present a procedure to calculate a threshold level of vaccination and isolation when these two control actions are present simultaneously. The theoretical investigation of epidemiological models with vaccination and isolation seems to be in its infancy, and is a thrilling area of future research [33]. The authors in [33] gives a detailed description of global analysis in SIRS epidemic model. Here, we further investigated this issue and show a possibility to use isolation, not only as replacing strategy, but as a way to decrease a level of vaccination required to eradicate a disease, as well as an effective way to reduce the settling time, that is, the time to reach the eradication. We also reported that the impact of isolation for each fixed size or variable population is extra sizeable for decrease ranges of vaccination, different from the numerical solutions found in [33], where the population is found fixed. In other words, situations that it feasible to have an expressive or maybe overall insurance of vaccination, the isolation is not so essential. However, for conditions, which may be effortlessly discovered in actual life, where the excessive levels of vaccination are not undertaken, a mixed control provides considerable help. We also describe in detail the difference of dynamical behaviour between vaccination and isolation.

A previous version of this work has been presented in [27].

2. The SIR model

Let the SIR model [17,27,28] be described as:

$$
\begin{aligned}
dS/dt &= \mu N(1-p) - \mu S - \beta IS/N, \\
dI/dt &= \beta IS/N - \gamma I - \mu I, \\
dR/dt &= \gamma I - \mu R + p\mu N,
\end{aligned}
\tag{1}
$$

where S, I and R are susceptible, infected and recovered individuals, respectively; p is a vaccination rate, N is the size of population, β is the transmission rate, μ is birth rate. We assume that population size is constant and $S(t) + I(t) + R(t) = N$. Following [15], the constant population size assumption is usual and is based on the hypothesis that the time scale of epidemic process is significantly faster than that of demographic rates. This strategy has been applied, for instance, in [15,18,33] and also reported in [17], where the author suggest its validity for some size population range and according to specific diseases. Finally, γ is recover rate. All the parameters of Eq. (1) are described in Table 1. The formulation of incidence in Eq. (1) is called standard incidence [17] and avoids the linear increasing of contact rate due to the size of population N.

Table 1
Variables and parameters of the SIR model.

Variable	Description	Unity
N	Size of population	individuals
S	Number of susceptible individuals	individuals
I	Number of infected individuals	individuals
R	Number of recovered individuals	individuals
μ	Birth rate	$time^{-1}$
p	Vaccination rate	$time^{-1}$
β	Average number of adequate contacts for transmission	$(individual \times time)^{-1}$
γ	Recover rate	$time^{-1}$

Eq. (1) may be simplified when it is divided by N and excluding R, since $R = N - S - I$. Thus, we have

$$
\begin{aligned}
ds/dt &= \mu(1-p) - \mu s - \beta is, \\
di/dt &= \beta is - \gamma i - \mu i.
\end{aligned}
\tag{2}
$$

When $p = 0$, (2) is the classic SIR model [17].

3. Stability analysis according to β

The stability of fixed points of the SIR model is analysed in function of β. The fixed points are given by

$$
\begin{aligned}
ds/dt &= f(s, i) = 0 \text{ and} \\
di/dt &= g(s, i) = 0,
\end{aligned}
\tag{3}
$$

which results in:

$$
P_1 = (s_1, i_1) = (1, 0) \text{ and}
\tag{4}
$$

$$
P_2 = (s_2, i_2) = \left(\frac{\gamma + \mu}{\beta}, \frac{\mu}{\gamma + \mu} - \frac{\mu}{\beta} \right).
\tag{5}
$$

The Jacobian matrix is given by

$$
J = \frac{\partial(f, g)}{\partial(s, i)} = \begin{bmatrix} \dfrac{\partial f}{\partial s} & \dfrac{\partial f}{\partial i} \\[2mm] \dfrac{\partial g}{\partial s} & \dfrac{\partial g}{\partial i} \end{bmatrix}
\tag{6}
$$

$$
= \begin{bmatrix} -\mu - \beta i & -\beta s \\ \beta i & \beta s - (\gamma + \mu) \end{bmatrix}.
$$

Evaluating the Jacobian matrix on P_1 and P_2 we have:

$$
J_{P_1} = \begin{bmatrix} -\mu & -\beta \\ 0 & \beta - (\gamma + \mu) \end{bmatrix} \text{ and}
\tag{7}
$$

$$
J_{P_2} = \begin{bmatrix} -\dfrac{\mu\beta}{\gamma + \mu} & -(\gamma + \mu) \\[3mm] -\dfrac{\mu\beta}{\gamma + \mu} - \mu & 0 \end{bmatrix}.
\tag{8}
$$

The eigenvalues associated to P_1 and P_2 are the roots of

$$
\rho_1^2 - T_1 \rho_1 + \Delta_1 = 0 \text{ and}
\tag{9}
$$

$$
\rho_2^2 - T_2 \rho_2 + \Delta_2 = 0,
\tag{10}
$$

where $T_{1,2}$ and $\Delta_{1,2}$ are the trace and determinant of matrix $J_{P_{1,2}}$:

$$
T_1 = \beta - \gamma - 2\mu
\tag{11}
$$

$$
\Delta_1 = -\mu\beta + \mu(\gamma + \mu)
\tag{12}
$$

$$
T_2 = -\frac{\beta\mu}{\gamma + \mu}
\tag{13}
$$

$$
\Delta_2 = \beta\mu - \mu(\gamma + \mu).
\tag{14}
$$

We summarize some types of fixed point by comparison of the parameters Δ and T such as:

- If $\Delta < 0$, then $\rho_{1,2}$ are real with different signs and the fixed point is called saddle, which is unstable.
- If $\Delta > 0$ and $T^2 - 4\Delta > 0$, then $\rho_{1,2}$ are real with same signal. Moreover, if $T > 0$ then the fixed point is an unstable node or if $T < 0$ then it is a asymptotically stable node.
- If $\Delta > 0$ and $T^2 - 4\Delta < 0$, then $\rho_{1,2}$ are complex conjugated, such as if $T > 0$ then fixed point is a spiral source; if $T < 0$ then the fixed point is spiral source and $T = 0$ is a centre

Applying this previous analysis we have the following results for P_1:

- $\Delta_1 < 0 \therefore \beta > \gamma + \mu$: in this range of values P_1 is a saddle, and thus, unstable. This is equivalent to the well known result $R_0 = \beta/(\gamma + \mu) > 1$ [17].
- $\Delta_1 > 0 \therefore \beta < (\gamma + \mu)$ and $T_1^2 - 4\Delta_1 > 0 \therefore \beta \neq \gamma$: since $\beta < (\gamma + \mu)$, we have $T_1 < 0$, which means that P_1 is a asymptotically stable node.
- $\Delta_1 > 0 \therefore \beta < (\gamma + \mu)$ and $T_1^2 - 4\Delta_1 = 0 \therefore \beta = \gamma$. In this case, the system has two equivalent eigenvalues. When $\beta = \gamma$, we gave $T_1 = \beta - \gamma - 2\mu < 0$, resulting in a degenerated stable node.

Proceeding similarly, we have for P_2:

- $\Delta_2 < 0 \therefore \beta < \gamma + \mu$: P_2 is a saddle, which means that there is a endemic equilibrium.
- $\Delta_2 > 0 \therefore \beta > (\gamma + \mu)$ e $T_1^2 - 4\Delta_1 > 0 \therefore \beta_1 > \beta > \beta_2$, where:

$$\beta_1 = 2\frac{(\gamma + \mu)}{\mu}\left((\gamma + \mu) - \sqrt{\gamma^2 + \mu\gamma}\right) \text{ and} \tag{15}$$

$$\beta_2 = 2\frac{(\gamma + \mu)}{\mu}\left((\gamma + \mu) + \sqrt{\gamma^2 + \mu\gamma}\right). \tag{16}$$

As $T_2 < 0, \forall\beta$, in this range of values P_2 is a stable asymptotically node. Furthermore, $\beta_2 > \beta_1 > \gamma + \mu$, as:

$$2\frac{(\gamma + \mu)}{\mu}((\gamma + \mu)\sqrt{\gamma^2 + \mu\gamma}) > \gamma + \mu$$

and

$$(\gamma + \mu)\sqrt{\gamma^2 + \mu\gamma} > \frac{\mu}{2}$$
$$\gamma + \frac{\mu}{2} > \sqrt{\gamma^2 + \mu\gamma}$$
$$\left(\gamma + \frac{\mu}{2}\right)^2 > \left(\sqrt{\gamma^2 + \mu\gamma}\right)^2$$
$$\gamma^2 + \gamma\mu + \frac{\mu^2}{4} > \gamma^2 + \mu\gamma$$
$$\frac{\mu^2}{4} > 0.$$

- $\Delta_2 > 0 \therefore \beta > (\gamma + \mu)$ e $T_1^2 - 4\Delta_1 < 0 \therefore \beta_1 < \beta < \beta_2$: P_2 is a sink node.
- $\Delta_2 > 0 \therefore \beta > (\gamma + \mu)$ and $T_1^2 - 4\Delta_1 = 0 \therefore \beta = \beta_1 = \beta_2$: P_2 is also stable node.

Note that for $\beta = \gamma + \mu$, the system presents a *transcritical bifurcation* because there is an exchange of stability between fixed points. For this value of β, $P_1 = P_2$ is a *elliptical stable node*, for $T_{1,2} < 0$. At this point, there is only one negative eigenvalue. Epidemiologically, $\beta > \gamma + \mu$ means that the rate of infected transmission is

Table 2
Stability analysis of P_1.

Case	Description	Parameters of model SIR
I	Asymptotically stable node	$\beta < (\gamma + \mu)$ and $\beta \neq \gamma$
II	Degenerated stable node	$\beta < (\gamma + \mu)$ and $\beta = \gamma$
III	Elliptical stable node $P_1 = P_2$	$\beta = (\gamma + \mu)$
IV	Saddle	$\beta > (\gamma + \mu)$

Table 3
Stability analysis of P_2.

Case	Description	Parameters of model SIR
V	Saddle	$\beta < (\gamma + \mu)$
VI	Asymptotically stable node	$\beta > (\gamma + \mu)$ and $\beta_1 > \beta > \beta_2$
VII	Sink node	$\beta > (\gamma + \mu)$ and $\beta_1 < \beta < \beta_2$
VIII	Degenerated stable node	$\beta > (\gamma + \mu)$ and $\beta = \beta_1$ or $\beta = \beta_2$

sufficiently high to maintain the population infected above zero. On the other hand, for $\beta < \gamma + \mu$ the rate of newly infected individuals is lower than the mortality of infected individuals causing at a certain moment, the reduction of population of infected individuals to zero.

Tables 2 and 3 summarises the main cases of stability for the fixed points P_1 and P_2, respectively. In Fig. 1, we show the main cases of the stability analysis in the phase plane si for the SIR.

3.1. Performance index

In this subsection, we present a performance index used in this work to evaluate the proposed method. As our focus is to eradicate the disease, it sounds naturally to measure the time, in which the number of infected is reduced to zero. In some sense, this is a settling time, T_s, for a free-disease system [32]. Thus, T_s is the time required for the output (number of infected individuals) to settle within a certain percent of its final outcome, which is a free-disease situation. As we are working with a continuous and normalised population, we must define a threshold to extract T_s. Considering an arbitrary population of N individuals, the T_s is the time required to the infected reaches

$$i(T_s) < \frac{1}{N} \tag{17}$$

Here, we adopt $N = 100,000$, which means $i(T_s) < 10^{-5}$.

4. Dynamics according to vaccination

This section presents the effect of vaccination on the dynamics of the SIR model. Solving the system of equations (3), and considering $p \neq 0$, we obtain the following fixed points for the SIR model:

$$P_1 = (s_1, i_1) = (1 - p, 0) \tag{18}$$

and

$$P_2 = (s_2, i_2) = \left(\frac{\gamma + \mu}{\beta}, \frac{\mu(1 - p)}{\gamma + \mu} - \frac{\mu}{\beta}\right). \tag{19}$$

The Jacobian matrix evaluated at fixed points P_1 and P_2 is:

$$J_{P_1} = \begin{bmatrix} -\mu & -\beta(1 - p) \\ 0 & \beta(1 - p) - (\gamma + \mu) \end{bmatrix} \tag{20}$$

$$J_{P_2} = \begin{bmatrix} -\frac{\mu\beta(1 - p)}{\gamma + \mu} & -\gamma - \mu \\ -\frac{\mu\beta(1 - p)}{\gamma + \mu} - \mu & 0 \end{bmatrix}. \tag{21}$$

The values of $T_{1,2}$ and $\Delta_{1,2}$ are:

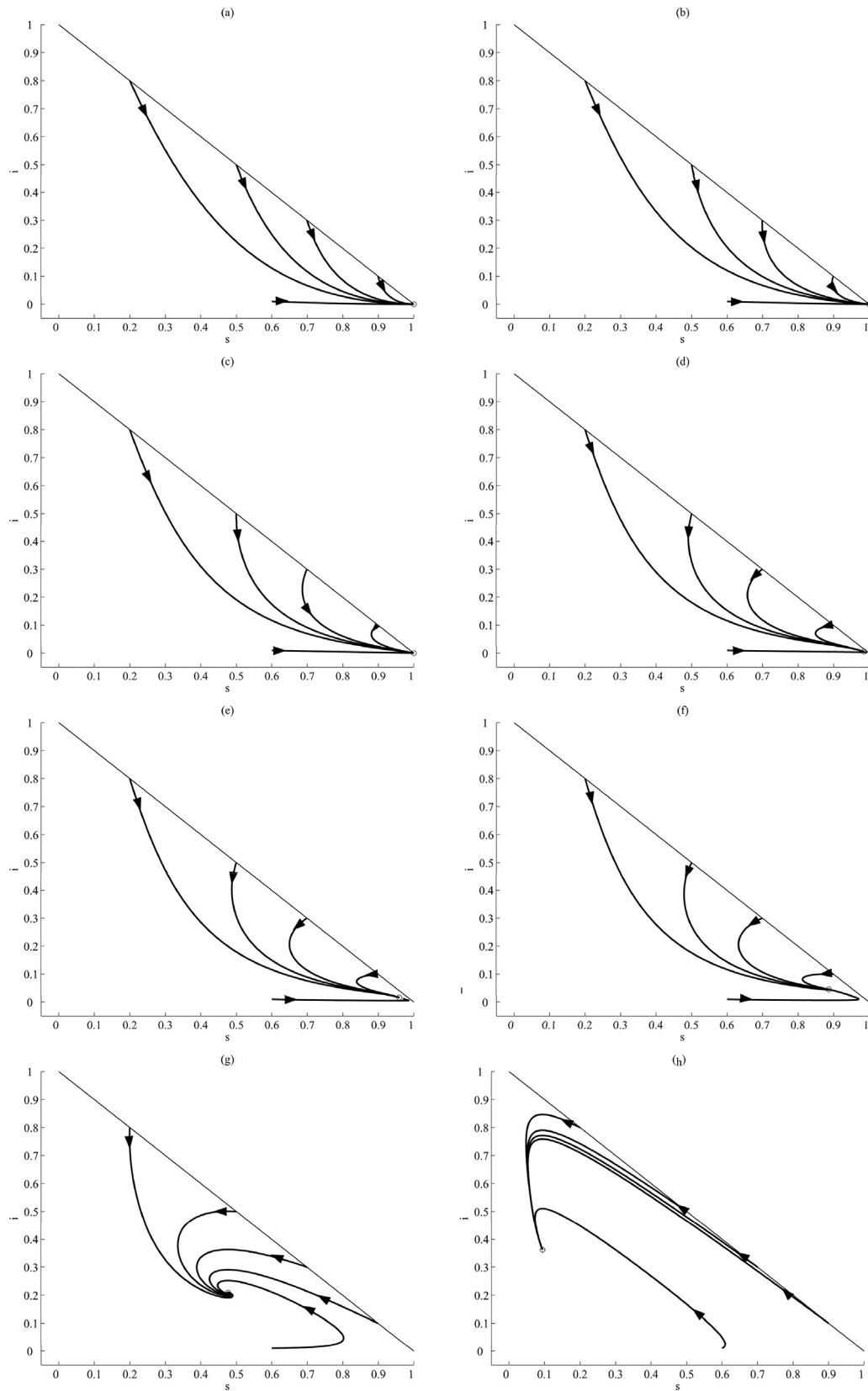$$T_1 = \beta(1 - p) - \gamma - 2\mu \tag{22}$$

Fig. 1. Phase plane *si* for SIR. The fixed point is represented in *o*. These plots have been built using a time range of 0 to 250 years and discretization step equals to 0.1. The initial conditions are $(s_0;i_0) = [(0.6;0.01),(0.9;0.1);(0.7;0.3),(0.5;0.5);(0.2;0.8)]$, while other parameters are $\gamma = 0.15$ and $\mu = 0.1$. The value of β is used according conditions of Table 2 and 3. (a) Case I: $\beta = 0.5\gamma < \gamma$. (b) Case II $\beta = \gamma$. (c) Case I: $\gamma < \beta = 0.5\mu + \gamma < \gamma + \mu$. (d) Case III: $\beta = \gamma + \mu$. (e) Case IV: $\gamma + \mu < \beta = \gamma + 1$, $1\mu < \beta_1$. (f) Case VIII: $\beta = \beta_1$. (g) Case VII: $\beta_1 > \beta = 1/8(7\beta_1 + \beta_2) > \beta_2$. (h) Case VI: $\beta = 1.2\beta_2 > \beta_2$.
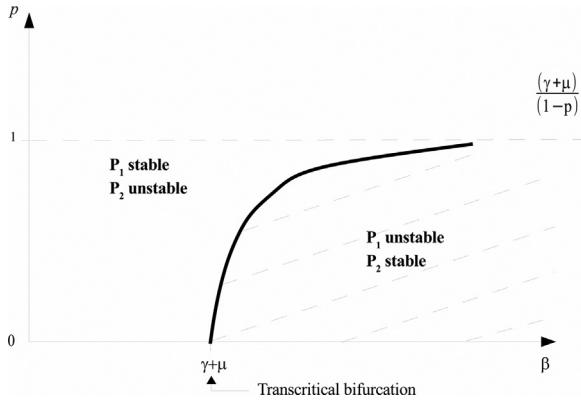
Fig. 2. Bifurcation diagram defined by vaccination. There are two areas, in which we observe a stability change on the fixed points P_1 and P_2. First we see that if $\beta < \frac{\gamma+\mu}{1-p}$ then P_1 is stable and P_2 is unstable. On the other hand, when $\beta > \frac{\gamma+\mu}{1-p}$, P_1 is unstable and P_2 is stable stable.

$$\Delta_1 = -\mu\beta(1-p) + \mu(\gamma+\mu) \tag{23}$$

$$T_2 = -\frac{\beta(1-p)\mu}{\gamma+\mu} \tag{24}$$

$$\Delta_2 = \beta(1-p)\mu - \mu(\gamma+\mu). \tag{25}$$

Let $\beta_p = \beta(p-1)$. Eqs. (22)–(25) by replacing β_p becomes equivalent to (11)–(14). There is now the following bifurcation point:

$$\begin{aligned} \beta_p &= \gamma+\mu \\ \beta(1-p) &= \gamma+\mu \\ \beta &= \frac{\gamma+\mu}{(1-p)}. \end{aligned} \tag{26}$$

Thus, the bifurcation point can be displaced $(\gamma+\mu)\to\infty$, as shown in Fig. 2. Whereas β depends on disease features and population conditions, vaccination allows eradication of the disease, while fixed point that has an endemic disease state pass to be unstable. The effect of vaccination on the temporal dynamics of the SIR model is illustrated in Fig. 3(a) and (b), in which it is possible to see a comparison of SIR model between a case where vaccination is insufficient to eradicate disease and another one where vaccination is sufficient. We used the T_s, as defined in Eq. (17), to check when an eradication has occurred. In this case, we found a settling time $T_s = 40.8$ s. Simulation details are on the legend of this figure.
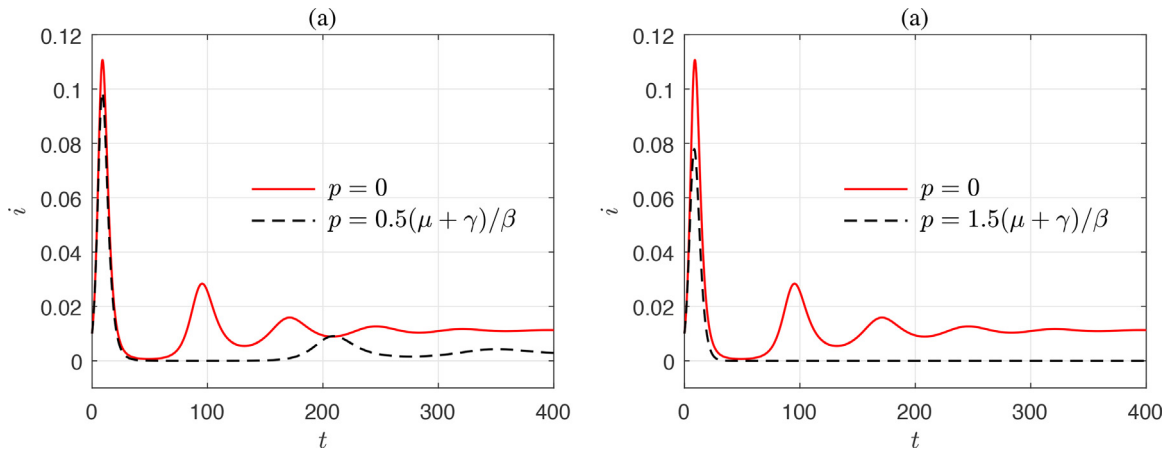
5. Dynamics of the isolation κ

Another way to ensure eradication of the disease is isolation (or segregation) of those infected. This is probably the most ancient practice that we know of. This section aims at analysing the dynamics of the SIR model due to isolation of infected individuals. The isolation of infected can be modelled with the compartment model such as:

$$\begin{aligned} ds/dt &= \mu - \mu s - \beta is, \\ di/dt &= \beta is - \gamma i - \mu i - \kappa i, \\ dr/dt &= \gamma i - \mu r, \\ di_s/dt &= \kappa i - \mu i_s, \end{aligned} \tag{27}$$

where κ corresponds to the isolation rate of infected, i_s the proportion of single individuals and $s + i + r + i_s = 1$. The result is a model called SIRI$_s$ (Susceptible – Infected – Recovered – Isolated).

To analyse the dynamic model (27), it is considered $r = 0$. This is a reasonable consideration since there are many diseases in which there is spontaneous recovery from infection, or the individual does not recover. Since $i_s = 1 - s - i$, we can neglect di_s/dt in (27), which yields the following equations for dynamic analysis of the effect of isolation:

$$\begin{aligned} ds/dt &= \mu - \mu s - \beta is, \\ di/dt &= \beta is - \mu i - \kappa i. \end{aligned} \tag{28}$$

Following the same steps as in Section 4, we find the fixed points P_1 and P_2:

$$P_1 = (s_1, i_1) = (1, 0) \tag{29}$$

$$P_2 = (s_2, i_2) = \left(\frac{\kappa+\mu}{\beta}, \frac{\mu}{\kappa+\mu} - \frac{\mu}{\beta}\right). \tag{30}$$

The Jacobian matrix evaluated on P_1 and P_2 are:

$$J_{P_1} = \begin{bmatrix} -\mu & -\beta \\ 0 & \beta - (\kappa+\mu) \end{bmatrix} \text{ and} \tag{31}$$

$$J_{P_2} = \begin{bmatrix} -\dfrac{\mu\beta}{\kappa+\mu} & -(\kappa+\mu) \\ \dfrac{\mu\beta}{\kappa+\mu} - \mu & 0 \end{bmatrix}. \tag{32}$$

The values of $T_{1,2}$ and $\Delta_{1,2}$ are:

$$T_1 = \beta - \kappa - 2\mu \tag{33}$$

Fig. 3. Effect of vaccination on the SIR model for infected i. The model parameters are: $\beta = 1.05$, $\mu = 1/60$, $\gamma = 0.6$. The models were simulated from 0 to 400 units of time. The initial conditions were $(s_0; i_0) = (0.99, 0.01)$. (a) Comparison of a situation without vaccination $(p = 0)$, and a situation where vaccination $p = 0.5(\mu + \gamma)/\beta$, *insufficient to eradicate the disease*. (b) Comparison between situation without vaccination $(p = 0)$, and a situation in which vaccination $p = 1.5(\mu + \gamma)/\beta$, *sufficient to eradicate disease*, with a settling time $T_s = 40.8$ s, according to Eq. (17).
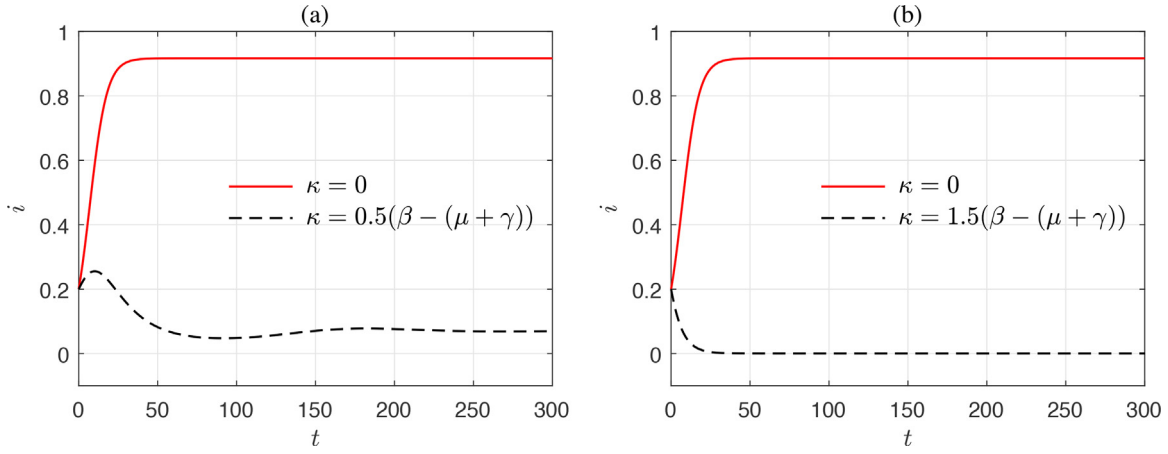
Fig. 4. Isolation effect on SIR model for the proportion of infected i. The model parameters are: $\beta = 0.2$, $\mu = 1/60$, $\gamma = 0$. The models were simulated in the time range 0 to 300 years with step 0.1 years of integration. The initial conditions were $(s_0; i_0) = (0.8, 0.2)$. (a) Comparison of a situation without isolation ($\kappa = 0$), and a situation in which the isolation $\kappa = 0.5(\beta - (\mu + \gamma))$, *insufficient* to eradicate disease. (b) Comparison between a situation without isolation ($\kappa = 0$) and a situation in which the isolation $\kappa = 1.5(\beta - (\mu + \gamma))$, *sufficient* to eradicate the disease, with a settling time $T_s = 72.4$ s, according to Eq. (17).
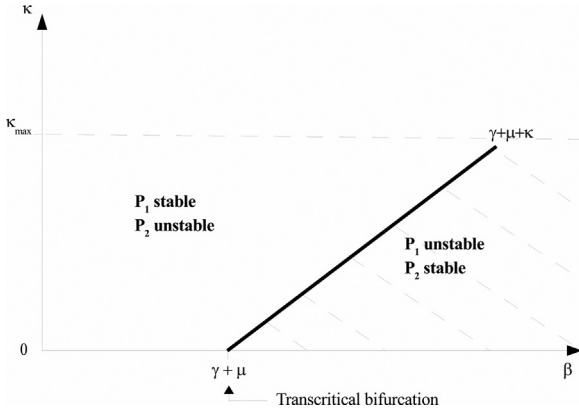

Fig. 5. Change the bifurcation point because of the isolation. The insulation defines two regions where there is a change of stability of fixed points P_1 and P_2. For $\beta < \gamma + \mu + \kappa$, P_1 is stable and P_2 is unstable. For $\beta > \gamma + \mu + \kappa$, P_1 unstable and P_2 is stable.

$$\Delta_1 = -\mu\beta + \mu(\kappa + \mu) \tag{34}$$

$$T_2 = -\frac{\beta\mu}{\kappa + \mu} \tag{35}$$

$$\Delta_2 = \beta\mu - \mu(\kappa + \mu). \tag{36}$$

Let $\beta_q = \beta - \kappa$, and since $T_2 < 0 \ \forall \kappa$ and $\gamma = 0$, Eqs. (33)–(36) by replacement of β_q are equivalent to (11)–(14). The new bifurcation point is:

$$\beta_q = \gamma + \mu$$
$$\beta - \kappa = \gamma + \mu \tag{37}$$
$$\beta = \gamma + \mu + \kappa.$$

Similarly to vaccination, the bifurcation point may be shifted depending on the isolation rate. In this case, however, the bifurcation point can be varied from $(\gamma + \mu) \to \kappa_{max}$, where κ_{max} is the maximum rate of isolation of individuals infected, which in steady state is limited to $\beta s - \mu$. Fig. 5 shows the variation of the bifurcation point because of the isolation of infected individuals. In this figure, there are two regions where the fixed points P_1 and P_2 change stability. Fig. 4(a) and (b) show the effect of isolation in the temporal dynamics of the SIR model. The simulations were in such a way, as to allow comparison between the situation without intervention, $\kappa = 0$, with two situations, namely: the first κ is insufficient to erad-

icate the disease; the second κ is sufficient to eradicate the disease, with a settling time $T_s = 72.4$ s, according to Eq. (17). Simulation details are on the legend of this figure.

6. Mixed control

It is possible to apply both vaccination and isolation for the control of certain infectious diseases. To this end, in this section, the influence of vaccination and isolation in the dynamics is evaluated. The model ponders vaccination and isolation such as:

$$\begin{aligned} ds/dt &= \mu(1 - p) - \mu s - \beta is, \\ di/dt &= \beta is - \gamma i - \mu i - \kappa i. \end{aligned} \tag{38}$$

The fixed points for the model (38) are:

$$P_1 = (s_1, i_1) = (1 - p, 0) \text{ and} \tag{39}$$

$$P_2 = (s_2, i_2)$$
$$= \left(\frac{\gamma + \mu + \kappa}{\beta}, \frac{\mu(1 - p)}{\gamma + \mu + \kappa} - \frac{\mu}{\beta} \right). \tag{40}$$

The Jacobian Matrix of (38) is

$$\begin{aligned} J &= \frac{\partial(f, g)}{\partial(s, i)} = \begin{bmatrix} \dfrac{\partial f}{\partial s} & \dfrac{\partial f}{\partial i} \\ \dfrac{\partial g}{\partial s} & \dfrac{\partial g}{\partial i} \end{bmatrix} \\ &= \begin{bmatrix} -\mu - \beta i & -\beta s \\ \beta i & \beta s - (\gamma + \mu + \kappa) \end{bmatrix}. \end{aligned} \tag{41}$$

The Jacobian matrix evaluated at fixed points P_1 and P_2 are:

$$J_{P_1} = \begin{bmatrix} -\mu & -\beta(1 - p) \\ 0 & \beta(1 - p) - (\gamma + \mu + \kappa) \end{bmatrix} \tag{42}$$

$$J_{P_2} = \begin{bmatrix} -\dfrac{\mu\beta(1 - p)}{\gamma + \mu + \kappa} & -(\gamma + \mu + \kappa) \\ -\dfrac{\mu\beta(1 - p)}{\gamma + \mu + \kappa} - \mu & 0 \end{bmatrix}. \tag{43}$$

The values of $T_{1,2}$ and $\Delta_{1,2}$ are:

$$T_1 = \beta(1 - p) - \gamma - 2\mu - \kappa \tag{44}$$

$$\Delta_1 = -\mu\beta(1 - p) + \mu(\gamma + \mu + \kappa) \tag{45}$$

Table 4
Settling time for a combination of parameters of vaccination and isolation. The model parameters are: $\beta = 1.05$, $\mu = 1/60$, $\gamma = 0.6$. The models were simulated from 0 to 400 units of time. The initial conditions were $(s_0; i_0) = (0.99, 0.01)$. The parameters of vaccination tested are $p = [0.3; 0.5; 0.7; 0.9]$ and isolation $\kappa = [0.1; 0.2; 0.3; 0.4]$. For this case the required vaccination, according to Eq. (49) is $p_{min} = 0.41$. The cases where it not noticed eradication is indicated by the symbol '–'.

Vaccination	Fixed size population Isolation				Growth 10% Isolation				Growth 20% Isolation			
	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4
0.3	–	163.0	121.1	95.8	–	–	156.8	111.9	–	–	316.0	141.3
0.5	103.6	93.8	84.4	72.4	116.8	101.7	90.3	76.6	140.4	112.8	97.6	81.7
0.7	79.0	75.1	69.0	60.6	81.4	77.1	70.8	62.0	84.1	79.4	72.7	63.5
0.9	67.6	64.8	59.8	53.1	68.1	65.2	60.2	53.4	68.5	65.6	60.6	53.8

$$T_2 = -\frac{\beta(1-p)\mu}{\gamma + \mu + \kappa} \tag{46}$$

$$\Delta_2 = \beta(1-p)\mu - \mu(\gamma + \mu + \kappa). \tag{47}$$

Let $\beta_h = \beta(1-p) - \kappa$. Eqs. (22)–(25) with replacement of β_h are equivalent to (11)–(14), which yields the following bifurcation point:

$$\begin{aligned}
\beta_h &= \gamma + \mu \\
\beta(1-p) - \kappa &= \gamma + \mu \\
\beta &= \frac{\gamma + \mu + \kappa}{(1-p)}.
\end{aligned} \tag{48}$$

If one of the control variables is fixed, you can establish a minimum value of the other variable to guarantee stability. This can be obtained by isolating one of the variables κ or p in (48). Hence, by isolating p we have:

$$p = 1 - \frac{\gamma + \mu + \kappa}{\beta}. \tag{49}$$

Let $\gamma = 1/24$, $\mu = 1/24$, $\beta = 1.05$ and $\kappa = 0$. In this case, it would be necessary to vaccinate 95% of the population to eradicate the disease, in a situation that is not possible to isolate infected individuals. On the other hand, if it is possible to obtain $\kappa = 0.4$, it would be necessary to vaccinate only 57% of the population.

6.1. Effect of isolation on the settling time

In this section, we examine the effect of isolation on the settling time. As suggested in previous sections, isolation works in a way to reduce the required vaccination. In this, section we see this by means the following numerical simulation. The model parameters are: $\beta = 1.05$, $\mu = 1/60$, $\gamma = 0.6$. The models were simulated from 0 to 400 units of time. The initial conditions were $(s_0; i_0) = (0.99, 0.01)$. With these values, the minimum level vaccination to eradicate the disease is given by $p_{min} = 1 - (\gamma + \mu)/\beta = 0.41$. Using Eq. (49) and with $\kappa = 0.1$, p_{min} is reduced to 0.32. As it is possible to notice in Table 4, a mixed control with $p = 0.3$ and $\kappa = 0.1$ is not sufficient to eradicate the disease. Although, with $\kappa = [0.2; 0.3; 0.4]$ the eradication was possible, with $T_s = [163.0; 121.1; 95.8]$, respectively. Here we would like to point out other advantage of the mixed control. The isolation also plays an important rule to reduce the time in which the disease is eradicated. In order to check the mixed control in a situation of variable population, we also tested the proposed technique in two scenarios of growing population, that is, the rate of birth is greater than the rate of death. We tested with a growth of 10% and 20%. Three key important points should be noticed. First, a growth in the population reduces the effect of isolation. For instance, it was supposed to have free-disease with a mixed control of $p = 0.3$ and $\kappa = 0.2$, but with a growth in the population of 10% and 20%, this does not happen. Moreover, the T_s is substantially increased. For instance, with a mixed control of $p = 0.3$ and $\kappa = 0.3$ and fixed population, we find a $T_s = 121.1$, whereas for a growth of

20%, these values has been almost increased three times, changed into $T_s = 316.0$. The second point to be stressed is the fact the effect of a growing population can be overcome by an increase of isolation levels, that is, even with a lower vaccination level of $p = 0.3$, when acted together with an isolation level of $\kappa = 0.4$ it was possible to see eradication. Finally, Table 4 also makes clear that the effect of isolation for both fixed size population or variable population is more significant for lower levels of vaccination. In other words, situations that it possible to have an expressive or even total coverage of vaccination, the isolation is not so important. However, for situations, which can be easily found in real life, where the high levels of vaccination are not undertaken, a mixed control can be seen of a substantial help.

7. Conclusion

This paper presents a mixed control for a SIR epidemic model with isolation and vaccination. Our approach is based on the stability analysis of the fixed points related to the SIR epidemic model. We show that a hybrid approach reduces a required level of vaccination by means of application of an isolation procedure. This approach can be useful in many situations, which are difficult to vaccinate high levels of the population due economical or geographical reasons. A computational simulation of this mixed control shows a reduction from 95% to 57% of the level of the vaccination required to eradicate a disease. Additionally, we show in this paper, a qualitative difference of isolation and vaccination on the bifurcation point shifting. While an increment of vaccination presents a more substantial result for small values, in other cases, to eradicate a disease we must reach levels of vaccination closed to 100% of population, which is very difficult in practical situations, as we may see in Fig. 3. On the other hand, the behaviour of isolation seems quite linear regarding the shifting of bifurcation point, as seen in Fig. 4. This difference increases the potentiality of a mixed approach, when it is possible in practical situation, as low levels of isolation may be complementary for high levels of vaccination.

Two other aspects have been investigated. First, we show the importance of isolation in reducing the time required to observe eradication of a disease. After that, we have studied the impact of a variable population in the mixed control. The growth in population decreases the effect of isolation, which is an aspect that has not been reported in [33]. Although, we notice this in relatively high levels of population growth (10% and 20%), nevertheless the increasing of isolation levels is still able to reduce the vaccination rate required to eradicate a disease. Finally, we have noticed that the effect of isolation for both fixed size and variable population is more significant for lower levels of vaccination, which is particularly interesting in real life situations, where the high levels of vaccination are not undertaken.

In future works we intend to investigate the application of mixed control in specific and relevant diseases, such as Tuberculosis [23].

Acknowledgements

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