

On a generalized SVEIR epidemic model under regular and adaptive impulsive vaccination*

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Abstract. A model for a generic disease with incubation and recovered stages is proposed. It incorporates a vaccinated subpopulation which presents a partial immunity to the disease. We study the stability, periodic solutions and impulsive vaccination design in the generalized modeled system for the dynamics and spreading of the disease under impulsive and non-impulsive vaccination. First, the effect of a regular impulsive vaccination on the evolution of the subpopulations is studied. Later a non-regular impulsive vaccination strategy is introduced based on an adaptive control law for the frequency and quantity of applied vaccines. We show the later strategy improves drastically the efficiency of the vaccines and reduce the infectious subpopulation more rapidly over time compared to a regular impulsive vaccination with constant values for both the frequency and vaccines quantity.

Keywords: epidemic model, SVEIR, stability, vaccination, adaptive control, simulation.

1 Introduction

There is a network of interactions that define the spreading of any infectious disease. It usually involves different types of susceptible and infectious subpopulations [1–5] as well as the transitions between them. These transitions and the system dynamics derived from them strongly depend on the type of disease and the circumstances in which it is

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transmitted, such as the number of different hosts susceptible to the infection and the development of the infectious disease in each of those subpopulations [6]. Infectious disease have been modeled and described in many papers both in the absence of vaccination and with different vaccination strategies. In this paper, we have chosen a disease model inspired in a previous work [7], but changing some attributes related to the vaccinated subpopulation. We consider, in particular, the use of impulsive vaccination and provide several design methods to adjust both the inter-vaccination time period and the fraction of vaccinated population. Also, a reproduction number is provided to describe the stability of the periodic regime. Consequently, the mathematical model resulting introduces two types of susceptible subpopulation with different incidence rates of contagion: the susceptible and the vaccinated subpopulation [8–10]. Moreover, there are two classes of infected subpopulations since the infectious process is divided in two stages. The primary stage assumes that the infectious agent is already inside the host but remains latent and non-infectious. At the secondary stage the host develops the disease and becomes symptomatic and infectious [11, 12]. Finally, the host recovers from the disease and becomes immune to the disease for a certain time after becoming susceptible again. When only a regular non-impulsive vaccination is applied the dynamics of the SVEIR model asymptotically leads the state variables of the system (subpopulations) to either a disease-free equilibrium (DFE) regime or an endemic one. The reached final state depends on the model parameters, i.e., the propagated disease. We focus our study when the disease-free equilibrium point is unstable and a regular impulsive vaccination is added to the regular non-impulsive one in order to avoid the permanence of the infectious subpopulation. In this way, the state can be maintained oscillating around the disease-free equilibrium point and, given this context, we study the induced periodicity. Furthermore, non-regular impulsive vaccination strategies will be developed in order to improve the disease removal when the disease-free equilibrium point is unstable or, if it is stable, when the disease prevalence decreases slowly. Consequently, a regime where the infectious subpopulation tends to zero is obtained. Such vaccination strategies are based on adaptive control techniques since the rules for generating the impulses are updated based on those used formerly for signal adaptation [13–19], but whose application in disease control and vaccination is novel. In this sense, a closed loop control system governs the vaccination impulses, each one characterized by a vaccination rate θ , that involves the fraction of vaccinated population at such impulsive vaccination instant, and an inter-vaccination period t_v until the next impulse is applied. In this paper, we first present the possible outcomes of a disease-free population from a set of constants θ and t_v . Then, we define a set of adaptive sampling laws with the obtained results, namely we set at each vaccination action θ or t_v to a certain range of values based on the available data of susceptible and infectious subpopulation measures [20–23].

Furthermore, after applying the two proposed different adaptive sampling laws, one adjusting the θ while t_v remains constant and the other adjusting t_v while θ is constant, we compare the efficiency of this research with that obtained when a regular impulsive vaccination is applied, where the parameters θ and t_v are set constant. We find a relevant increase of the efficiency of the vaccination when adaptive rules for t_v or θ are applied.

In this sense, various laws for updating t_v or θ and their capabilities to lead the system to the desired state will be presented and discussed.

The paper is organized as follows. In Section 2, the disease model is presented with the significance of all the parameters included in it. Section 3 studies the equilibrium points of the dynamics without impulsive vaccination and establishes the stability of such points by defining a reproduction number. The stability of the disease-free state with a regular impulsive vaccination is discussed in Section 4 and all the preceding theoretical results are verified through simulations in Section 5. First, a simulation for a regular non-impulsive vaccination system, and then simulations for a set of regular impulsive systems are developed. Section 6 introduces the adaptive laws involving a constant inter-vaccination time interval t_v while the vaccination rate θ is updated. On the contrary, in Section 7, t_v is adjusted in real time while the vaccination rate θ remains constant. The efficiency of the previous adaptive sampling laws with respect to the regular impulsive vaccination will be compared in Section 8, and in Section 9, the SVEIR model will be used to describe a possible outbreak of pertussis and the evolution of the disease applying different vaccination strategies. Final conclusions will be presented in Section 10.

2 The SVEIR model

2.1 Notation

Our model is described in the following terms:

Subpopulations

- $S(t)$ subpopulation susceptible to the disease
- $V(t)$ subpopulation which has been vaccinated
- $E(t)$ subpopulation exposed to the disease, although not sick or infectious yet
- $I(t)$ subpopulation which fully develops the disease and is able to infect others
- $R(t)$ subpopulation immune due to vaccination or being recovered from the disease
- $N(t)$ total population which is the sum of all the subpopulations

Parameters

Here we present all the parameters involving the epidemic model. Observe that all the parameters are non-negative.

- b_1, b_3 birth rates of the population, a constant one (b_1) and a population-dependent one (b_3)
- b_2 natural death rate of any subpopulation
- γ, γ_1 ratio of transition to recovered from infected ($I \rightarrow R$) and vaccinated ($V \rightarrow R$) subpopulations, respectively
- α extra death rate caused by the disease in the infected (I) subpopulation
- τ average time of transition from exposed to infected ($E \rightarrow I$) subpopulations
- ω average time of transition from immune to susceptible subpopulations ($R \rightarrow S$)
- β disease transmission constant
- η constant saturation related to the transmission of the disease which defines the incidence rate

δ	a diminishing factor related to the disease transmission in the vaccinated subpopulation in contrast to that corresponding to the susceptible one
V_c	fraction of the population which is vaccinated since birth ($V_c \in [0, 1]$)
t_v	time intervals between two consecutive impulsive vaccinations
θ	vaccination rate or the fraction of the susceptible subpopulation affected by the impulsive vaccination

Vaccination strategies

Three different vaccination strategies can be applied to the SVEIR model:

- Regular non-impulsive vaccination: This vaccination strategy is applied at all time instants to a fraction V_c of the arriving (newborn) susceptible subpopulation. This strategy can be applied alone or complementary to the other two.
- Regular impulsive vaccination: This vaccination strategy is applied to a constant fraction θ of the susceptible subpopulation at uniformly distributed time instants, i.e., at time instant nt_v with $n \in \mathbb{N}$ and a constant $t_v > 0$.
- Non-regular impulsive vaccination: This vaccination strategy is applied to a time-varying fraction $\theta(t_i)$ of the susceptible subpopulation at non-uniformly distributed time instants t_i with $i \in \mathbb{N}$.

2.2 The model

We propose a generic model of five subpopulations with two delays for the spreading of diseases based on a previous model [7] where the full immunity acquired by vaccination has been replaced with the same temporal immune response derived from experiencing the disease. This model is, in turn, based on simpler SIR and SVEIR epidemic models [4, 12, 24–26]. We call ω to the delay from the moment one individual recovers and acquires the immunity to the moment such an individual becomes susceptible to the disease again (susceptible subpopulation). The second delay τ is defined from the time instant when the host becomes infected to that when it becomes infective to others. We call this apparent healthy, non-infectious subpopulation, exposed subpopulation. Also, we assume that the recovered subpopulation presents an immunity to the disease obtained through two different ways: either it is acquired after recovering from the disease or it is induced by vaccination. This vaccination is administered regularly to a fraction of newborn individuals that depend on the total population and, at specific moments in time, to a fraction of the susceptible subpopulation by means of an impulsive vaccination strategy. Both transitions, from vaccinated and infectious subpopulations to the recovered one, lead to an immunity indistinguishable from each other. The natural death rate b_2 is the inverse of the life expectancy, and the rates γ and γ_1 are the inverse of the average times of transition from infectious to immune and from vaccinated to immune subpopulations, respectively.

The infectious incidence rate in the susceptible subpopulation is proportional to β and depends on $I(t)$ and $S(t)$. Due to the effects of the impulsive vaccination, there is a great variation in the number of the susceptible individuals, so a saturation factor, similar to some other previous true mass action-type models [3,27], is introduced in order

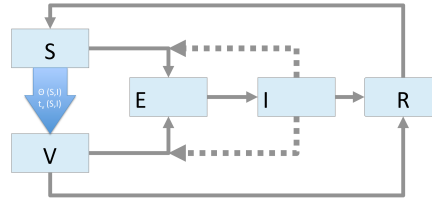


Fig. 1. A block diagram of the SVEIR model.

to maintain a reasonable infection rate irrespective of the value of $S(t)$ is high or low. This saturation factor is proportional to $1/(1 + \eta S(t))$ with $\eta \in \mathbb{R}$, $\eta > 0$. A similar incidence rate occurs in the vaccinated subpopulation with the parameter β reduced by a diminishing factor $\delta \in [0, 1)$, which implies the reduced possibility of a successful contagion to the disease in this subpopulation, and a saturation factor analogous to that of the susceptible subpopulation given by $1/(1 + \eta V(t))$. The SVEIR model with delays is described by the following equations:

$$\begin{aligned} \dot{S}(t) = & b_1 - b_2 S(t) - \frac{\beta S(t)I(t)}{1 + \eta S(t)} + e^{-b_2 \omega} (\gamma I(t - \omega) + \gamma_1 V(t - \omega)) \\ & + b_3(1 - V_c)N(t), \end{aligned} \quad (1)$$

$$\dot{V}(t) = -\delta \frac{\beta V(t)I(t)}{1 + \eta V(t)} - \gamma_1 V(t) - b_2 V(t) + b_3 V_c N(t), \quad (2)$$

$$\begin{aligned} \dot{E}(t) = & \beta \left[\frac{S(t)I(t)}{1 + \eta S(t)} + \delta \frac{V(t)I(t)}{1 + \eta V(t)} \right. \\ & \left. - e^{-b_2 \tau} \left(\frac{S(t - \tau)I(t - \tau)}{1 + \eta S(t - \tau)} + \delta \frac{V(t - \tau)I(t - \tau)}{1 + \eta V(t - \tau)} \right) \right] - b_2 E(t), \end{aligned} \quad (3)$$

$$\dot{I}(t) = \beta e^{-b_2 \tau} \left(\frac{S(t - \tau)I(t - \tau)}{1 + \eta S(t - \tau)} + \delta \frac{V(t - \tau)I(t - \tau)}{1 + \eta V(t - \tau)} \right) - (b_2 + \alpha + \gamma)I(t), \quad (4)$$

$$\dot{R}(t) = \gamma_1 V(t) + \gamma I(t) - b_2 R(t) - (\gamma I(t - \omega) + \gamma_1 V(t - \omega))e^{-b_2 \omega}, \quad (5)$$

$$\begin{aligned} S(t^+) = & (1 - \theta)S(t), & V(t^+) = & V(t) + \theta S(t), \\ E(t^+) = & E(t), & I(t^+) = & I(t), & R(t^+) = & R(t) \end{aligned} \quad (6)$$

if $t = nt_v$ ($n = 1, 2, 3, \dots$), $\theta \in [0, 1]$ with $N(t) = S(t) + V(t) + E(t) + I(t) + R(t)$ being the total population. Equation (6) is an impulsive function representing a vaccination campaign acting periodically on a fraction ($0 \leq \theta \leq 1$) of the susceptible subpopulation, which is converted into vaccinated subpopulation. A visual representation of the model structure can be seen at Fig. 1 where all the transition between subpopulations are represented through arrows, and the influence of the disease on those transitions is depicted by dashed arrows. Through the paper the notation for the left limit at the impulse time instants nt_v^- will be simply denoted by nt_v . The parameters ω and τ are the internal delays at (1), (5) and (3), (4), respectively. The above model is different from other models [3]

not only due to the distinct growth and death rates involved, but also because an additional population-dependent birth rate is considered and vaccination is administered to a fraction of the newborn. Furthermore, note that the presence of delays is often relevant in dynamic systems [12, 23, 26], and the migrations from vaccinated and infectious to the susceptible subpopulation (through the temporary immune recovered subpopulation) are taken into account.

3 Disease-free equilibrium point with no impulsive vaccination

In order to study the equilibrium points, first we will consider the SVEIR model with regular non-impulsive vaccination, i.e., $\theta = 0$ in (6), and a constant vaccination rate V_c is applied. Let S^* , V^* , E^* , I^* , R^* be the respective subpopulations at the eventual equilibrium points, i.e., $\lim_{t \rightarrow \infty} (S(t), V(t), E(t), I(t), R(t))^T = (S^*, V^*, E^*, I^*, R^*)^T$. Since the values of the subpopulations at an equilibrium point are constant, delay-dependency disappears at the equilibrium so that $\lim_{t \rightarrow \infty} I(t - \tau) = \lim_{t \rightarrow \infty} I(t - \omega) = \lim_{t \rightarrow \infty} I(t) = I^*$ and $\lim_{t \rightarrow \infty} E(t - \tau) = \lim_{t \rightarrow \infty} E(t) = E^*$. The model equations (1)–(5) lead to

$$\begin{aligned} b_1 - b_2 S^* - \frac{\beta S^* I^*}{1 + \eta S^*} + (\gamma I^* + \gamma_1 V^*) e^{-b_2 \omega} + b_3 (1 - V_c) N^* &= 0, \\ -\delta \frac{\beta V^* I^*}{1 + \eta V^*} - \gamma_1 V^* - b_2 V^* + b_3 V_c N^* &= 0, \\ (1 - e^{-b_2 \tau}) \beta \left(\frac{S^*}{1 + \eta S^*} + \delta \frac{V^*}{1 + \eta V^*} \right) I^* - b_2 E^* &= 0, \\ e^{-b_2 \tau} \beta \left(\frac{S^*}{1 + \eta S^*} + \delta \frac{V^*}{1 + \eta V^*} \right) I^* - (b_2 + \alpha + \gamma) I^* &= 0, \\ (1 - e^{-b_2 \omega}) (\gamma_1 V^* + \gamma I^*) - b_2 R^* &= 0, \\ \dot{S}^* + \dot{V}^* + \dot{E}^* + \dot{I}^* + \dot{R}^* = b_1 - (b_2 - b_3) N^* - \alpha I^* &= 0 \end{aligned} \quad (7)$$

for the purpose of obtaining the respective subpopulations at the equilibrium points. By assuming the condition of non-negativity for all subpopulations, i.e., $(S^*, V^*, E^*, I^*, R^*)^T \geq 0$, the solution of equation (7) reveals a set of points at which the equilibrium is reached. A solution of (7) such that $I^* \neq 0$ is defined as an endemic equilibrium point and, if $I^* = 0$, then we say it is a disease-free equilibrium point. The model discussed here presents only one disease-free equilibrium (DFE) point, where $I^* = 0$ and $E^* = 0$. The values of the susceptible, vaccinated and recovered subpopulation as well as the total population at such a DFE point are obtained from the equations in (7) by introducing $I^* = E^* = 0$. In this way,

$$N^* = \frac{b_1}{b_2 - b_3}, \quad (8)$$

$$S^*(\omega) = \frac{b_1}{b_2} \left[1 + \frac{b_3}{b_2 - b_3} \left(1 + V_c \left(\frac{e^{-b_2 \omega} \gamma_1}{b_2 + \gamma_1} - 1 \right) \right) \right], \quad (9)$$

$$V^* = V_c \frac{b_3 b_1}{(\gamma_1 + b_2)(b_2 - b_3)}, \quad (10)$$

$$R^*(\omega) = \frac{1 - e^{-b_2 \omega}}{b_2} \gamma_1 V^* = V_c \frac{b_1}{b_2} \frac{b_3 \gamma_1 (1 - e^{-b_2 \omega})}{(\gamma_1 + b_2)(b_2 - b_3)}. \quad (11)$$

Observe that the susceptible and recovered subpopulation depend on the ω delay.

3.1 Linearization

Proposition 1. *The following properties hold:*

- (i) *The DFE point $(S^*(\omega), V^*, 0, 0, R^*(\omega))^T$ of system (1)–(5) is locally asymptotically stable for any delays $\tau' \in (\tau - \Delta\tau, \tau + \Delta\tau)$ and $\omega' \in (\omega - \Delta\omega, \omega + \Delta\omega)$ for $\Delta\tau \in [0, \Delta\tau^*)$, $\Delta\omega \in [0, \Delta\omega^*)$ with sufficiently small $\Delta\tau^*$ and $\Delta\omega^*$ if $b_2 > b_3$ and $\alpha + \gamma_1 + b_2 > \beta e^{-b_2 \tau} (S^*(\omega)/(1 + \eta S^*(\omega)) + \delta V^*/(1 + \eta V^*))$.*
- (ii) *The DFE point $(S^*(0), V^*, 0, 0, R^*(0))^T$ of system (1)–(5) is locally asymptotically stable for any delays $\tau \in [0, \tau^*)$ and $\omega \in [0, \omega^*)$ with small enough τ^* and ω^* if $b_2 > b_3$ and $\alpha + \gamma_1 + b_2 > \beta (S^*(0)/(1 + \eta S^*(0)) + \delta V^*/(1 + \eta V^*))$.*

Proof. First, we linearize the dynamic equations (1)–(5) around the DFE point by means of the associated Jacobi matrix $\mathbf{J} = [J_{ij}] = [\partial \dot{x}_i / \partial x_j]$ for $i, j \in \{1, 2, \dots, 5\}$ with $x_1 \equiv S$, $x_2 \equiv V$, $x_3 \equiv E$, $x_4 \equiv I$ and $x_5 \equiv R$ evaluated at the DFE point. The eigenvalues of this matrix are obtained by calculating the roots of the characteristic equation

$$\text{Det}(\lambda I - \mathbf{J}) = 0. \quad (12)$$

Such eigenvalues are given by

$$\lambda_i = \left\{ -b_2, -b_2, -b_2 - \gamma_1, -b_2 + b_3, \beta e^{-b_2 \tau} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right) - (b_2 + \alpha + \gamma) \right\}, \quad (13)$$

where $S^*(\omega)$ and V^* at the DFE point are given in (9) and (10), respectively. The real part of all the eigenvalues of the Jacobi matrix must be less than zero so that the linearized model around the DFE point is asymptotically stable, which means that this point is locally stable in the non-linear model.

Note that all parameters of the model are always defined as positive or zero for any infectious disease. Thus, the DFE point is locally asymptotically stable around some given delays τ and ω if

$$b_3 - b_2 < 0, \quad (14)$$

$$\beta e^{-b_2 \tau} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \frac{\delta V^*}{1 + \eta V^*} \right) - (b_2 + \alpha + \gamma) < 0. \quad (15)$$

Since the eigenvalues of the Jacobian matrix are continuous functions of all its entries, there are sufficiently small delay perturbations $\Delta\tau^*$ and $\Delta\omega^*$ which guarantee the local

stability of the DFE point for any delays $\tau' \in (\tau - \Delta\tau, \tau + \Delta\tau)$ and $\omega' \in (\omega - \Delta\omega, \omega + \Delta\omega)$ for all $\Delta\tau \in [0, \Delta\tau^*)$, $\Delta\omega \in [0, \Delta\omega^*)$. Hence Property (i).

In the same way, if $\omega = 0$ and $\tau = 0$, the stability conditions follow from a well known result in general theory of time-delay systems [19]. Just in this sense, the stability conditions of the equilibrium point for zero delays

$$\alpha + \gamma_1 + b_2 > \beta \left(\frac{S^*(0)}{1 + \eta S^*(0)} + \delta \frac{V^*}{1 + \eta V^*} \right), \quad b_2 > b_3, \quad (16)$$

directly guarantee the stability for small delays $\tau \in [0, \tau^*]$ and $\omega \in [0, \omega^*]$. Hence Property (ii). \square

Remark 1. If $\alpha + \gamma + b_2 < \beta(S^*(0)/(1 + \eta S^*(0)) + \delta V^*/(1 + \eta V^*))$, then the DFE point is unstable for zero and sufficient small delays $\tau \in [0, \tau^*]$ and $\omega \in [0, \omega^*]$ as it would happen if $b_2 < b_3$ which would also imply negative subpopulations. If $\alpha + \gamma + b_2 = \beta(S^*(0)/(1 + \eta S^*(0)) + \delta V^*/(1 + \eta V^*))$ and $b_2 > b_3$, then the linearized system around the DFE point is critically stable. Finally, if $b_2 = b_3$, then $I^* = b_1/\alpha \neq 0$ from (7). As a consequence, the system does not possess a DFE point.

Remark 2. Proposition 1(i) establishes the conditions to have a DFE point asymptotically locally stable for delays ω, τ . The first condition (14) implies that the population does not grow exponentially as the death rate is greater than the population-related birth rate. We can rearrange the parameters from the second condition (15) so we get

$$R_0 = \frac{\beta e^{-b_2\tau}}{b_2 + \alpha + \gamma} \left(\frac{S^*(\omega)}{1 + \eta S^*(\omega)} + \delta \frac{V^*}{1 + \eta V^*} \right), \quad (17)$$

where $S^*(\omega)$ and V^* at the DFE point are given in (9) and (10), respectively. The parameter R_0 defined through (17) is referred to the basic reproduction number, which is defined in epidemic research as the expected number of secondary infections derived per infected individual $\beta e^{-b_2\tau}(S^*(\omega)/(1 + \eta S^*(\omega)) + \delta V^*/(1 + \eta V^*))$ during the average course of the infectious phase of the disease $(b_2 + \gamma + \alpha)^{-1}$ [28–30]. Since $S^*(\omega) = S^*(V_c, b_1, b_2, b_3, \omega, \gamma_1)$ and $V^* = V^*(V_c, b_1, b_2, b_3, \gamma_1)$ the reproduction number will be $R_0(\beta, b_1, b_2, b_3, \delta, \eta, \alpha, \gamma, \gamma_1, \omega, \tau)$ and will give us information about the local stability around the DFE point as condition from (15) is equivalent to $R_0 < 1$. A consequence from Proposition 1 follows below.

Remark 3. If $R_0 > 1$, then the DFE point is locally unstable as it would happen if $b_2 < b_3$, which would also imply negative subpopulations. If $R_0 = 1$ and $b_2 > b_3$, then the linearized system around the DFE point is critically stable.

4 Regular impulsive vaccination around the disease-free equilibrium point

The behavior of the model under a regular impulsive vaccination is studied in this section. The main motivation is to mitigate and, potentially, eradicate the infection from the host

population when the DFE point is unstable under a regular non-impulsive vaccination strategy. The regular impulsive vaccination is characterized by a constant vaccination rate θ and a constant inter-vaccination time interval t_v . We will apply this vaccination strategy to an auxiliary model that we construct from the original model (1)–(6), in which there are not infected subpopulations: $E(t) = 0$ and $I(t) = 0$ for all $t \geq t_0$, being t_0 the hypothetical time instant at which the disease has been eradicated. The results we obtain in this auxiliary model would be analogous to our SVEIR model when it hypothetically tends to the disease-free state. The dynamic equations for this reduced model are

$$\begin{aligned}\dot{S}'(t) &= b_1 - b_2 S'(t) + b_3(1 - V_c)N'(t) + \gamma_1 V'(t - \omega)e^{-b_2 \omega}, \\ \dot{V}'(t) &= -\gamma_1 V'(t) - b_2 V'(t) + b_3 V_c N'(t), \\ \dot{R}'(t) &= \gamma_1 (V'(t) - V'(t - \omega)e^{-b_2 \omega}) - b_2 R'(t)\end{aligned}\quad (18)$$

for all $t \neq nt_v$ and

$$\begin{aligned}S'(t^+) &= (1 - \theta)S'(t), \\ V'(t^+) &= V'(t) + \theta S'(t), \\ R'(t^+) &= R'(t)\end{aligned}\quad (19)$$

for all $t = nt_v$ with $\theta \in [0, 1]$. The equation of the total population in such a disease-free situation is

$$\dot{N}'(t) = \dot{S}'(t) + \dot{V}'(t) + \dot{R}'(t) = b_1 - (b_2 - b_3)N'(t). \quad (20)$$

Such a total population presents a time evolution given by $N'(t) = N^* - (N^* - N_0) \times e^{-(b_2 - b_3)t}$, where N_0 denotes the initial value $N'(0) \geq 0$. By supposing that $b_2 > b_3$, it follows that $\lim_{t \rightarrow \infty} N'(t) = N^*$ and the system reaches the DFE state where the total population N^* is given by (8).

We will find the solution of these simplified equations (18)–(19) under a periodic impulsive vaccination showing that they exhibit a periodic steady regimen of period $T = T(m, \sigma) = mt_v + \sigma$ with $\sigma \in [0, t_v)$, $m \in \mathbb{N} \cup \{0\} \triangleq \mathbb{N}_0$. Furthermore, we will obtain the maximum values of the susceptible and vaccinated subpopulations within such a periodic regime. Proposition 2 establishes that the period $T(m, \sigma)$ of such a solution must be always a multiple of t_v , and that such a period is always t_v .

Proposition 2. *The following properties hold:*

- (i) *For a general periodic solution of (18)–(19) with a time period $T = T(m, \sigma) = mt_v + \sigma$, it is required that $\sigma = 0$.*
- (ii) *There is a unique general solution with time period $T(1, 0) = t_v$. This solution would be, from (i), that with the smallest time period.*

Proof. Assuming that the solutions of (18)–(19) exhibits a periodic behavior and that the period is given by $T(m, \sigma)$ with $\sigma \neq 0$, this would imply that, for any $n_1 \in \mathbb{N}$, $S(n_1 t_v) = S((n_1 + m)t_v + \sigma)$. However, while the susceptible subpopulation is required by the dynamic equation in (19) to show an impulse at $t = n_1 t_v$, this impulse is not

present at $t' = (n_1 + m)t_v + \sigma$ since $(n_1 + m)t_v < t' < (n_1 + m + 1)t_v$. Therefore, periodicity is not reached if $\sigma \neq 0$. Hence Property (i).

The demonstration of Property (ii) is omitted due to length constraints. The procedure for obtaining the proof is to find first the generic solution for $T(n, 0)$ and show then that this solution is unique and based on a superposition of $T(1, 0)$ solutions which, from Property (i), would be the solution with the smallest period. Hence Property (ii). \square

In order to simplify the notation, we redefine the variables for the vaccinated and susceptible subpopulations within the interval between two consecutive impulses after a large enough time so that they have reached the periodic regime and $\lim_{t \rightarrow \infty} N(t) = N^*$. In such a situation, the susceptible and vaccinated subpopulations can be denoted by

$$\begin{aligned} S_i(\tau) &\triangleq \lim_{r \rightarrow \infty} S'(\tau + (i+r)t_v), \\ V_i(\tau) &\triangleq \lim_{r \rightarrow \infty} V'(\tau + (i+r)t_v) \end{aligned} \quad (21)$$

for all $\{i, r\} \in \mathbb{N}_0$, $\tau \in [0, t_v)$, where (8) and (10) has been taken into account. Once we know that $S_i(\tau) = S_j(\tau)$, $V_i(\tau) = V_j(\tau)$ for all $i, j \in \mathbb{N}$, the equations in (18) at the periodic regime can be rearranged by using (21). In this way, the dynamics of the vaccinated subpopulation (2) is described by

$$\dot{V}_i(\tau) = (\gamma_1 + b_2)(V^* - V_i(\tau)). \quad (22)$$

On the other hand, the dynamics of the susceptible subpopulation (1) is rewritten as a two part equation due to the discontinuity derived from the delay $\omega = kt_v + xt_v$, being $k \in \mathbb{N}_0$ and $x \in [0, 1) \cap \mathbb{R}$, namely,

$$\dot{S}_i(\tau) = \begin{cases} b_2(S^*(\omega) - S_i(\tau)) + \gamma_1(V_i(0^+) - V^*)e^{-b_2\omega - (b_2 + \gamma_1)(\tau - (1-x)t_v)}, & 0 \leq \tau < xt_v, \\ b_2(S^*(\omega) - S_i(\tau)) + \gamma_1(V_i(0^+) - V^*)e^{-b_2\omega - (b_2 + \gamma_1)(\tau - xt_v)}, & xt_v \leq \tau < t_v, \end{cases} \quad (23)$$

where V^* and $S^*(\omega)$ are the values of the susceptible and vaccinated subpopulation from (9) and (10), respectively. It can be seen from these equations that in the periodic regime $\dot{S}_i(\tau) > 0$ and $\dot{V}_i(\tau) < 0$ if $S_i(\tau) < S^*$ and $V_i(\tau) > V^*$ for all $\tau \in (0, t_v)$. This means that the susceptible subpopulations is continuously increasing, while the vaccinated subpopulation is continuously decreasing within the time interval $[jt_v, (j+1)t_v)$ for any $j \in \mathbb{N}$ and large enough such that the model dynamics has reached the stationary periodic regime. Therefore, we know the maximum values of both subpopulations:

$$\begin{aligned} \max_{0 \leq \tau < t_v} \{S_i(\tau)\} &= S_i(t_v) = \frac{S_i(0^+)}{1 - \theta}, \\ \max_{0 \leq \tau < t_v} \{V_i(\tau)\} &= V_i(0^+), \end{aligned} \quad (24)$$

where the values for $V_i(0^+)$, $S_i(0^+)$ are defined as

$$\begin{aligned} S_i(0^+) &= S_0 = \frac{s_1(1-\theta)}{s_2 - e^{b_2(xt_v - \omega)}\theta s_3}, \\ V_i(0^+) &= V^* + \frac{s_1\theta}{(s_2 - e^{b_2(xt_v - \omega)}\theta s_3)(1 - e^{-(b_2 + \gamma_1)t_v})} \end{aligned} \quad (25)$$

with s_1 , s_2 and s_3 given by

$$\begin{aligned} s_1 &= (e^{b_2 t_v} - 1)(e^{(b_2 + \gamma_1)t_v} - 1)S^*(\omega), \\ s_2 &= (e^{(b_2 + \gamma_1)t_v} - 1)(e^{b_2 t_v} - (1 - \theta)), \\ s_3 &= e^{\gamma_1 x t_v} + e^{(b_2 + \gamma_1)t_v} - e^{(b_2 + \gamma_1)x t_v} - 1. \end{aligned} \quad (26)$$

Since the subpopulations $S'(t)$ and $V'(t)$ in the auxiliary model will be, respectively, above the values $S(t)$ and $V(t)$ of the original SVEIR model (the demonstration of this is omitted due to the constraints of the length of the paper) when the disease is permanent, i.e., $\lim_{t \rightarrow \infty} \inf\{S'(t) - S(t)\} \geq 0$ and $\lim_{t \rightarrow \infty} \inf\{V'(t) - V(t)\} \geq 0$ if $I(t) > 0$ and $E(t) > 0$, we use the values from the auxiliary model in (24) to define the impulsive reproduction number $R(\theta, t_v)$ as

$$R(\theta, t_v) = \frac{\beta e^{-b_2 \tau}}{\gamma + b_2 + \alpha} \left(\max_{0 \leq t < t_v} \left\{ \frac{S_i(t)}{1 + \eta S_i(t)} \right\} + \max_{0 \leq t < t_v} \left\{ \delta \frac{V_i(t)}{1 + \eta V_i(t)} \right\} \right), \quad (27)$$

$$R(\theta, t_v) = \frac{\beta e^{-b_2 \tau}}{\gamma + b_2 + \alpha} \left(\frac{S_i(t_v)}{1 + \eta S_i(t_v)} + \delta \frac{V_i(0^+)}{1 + \eta V_i(0^+)} \right). \quad (28)$$

Now we take the dynamic equation for the infectious subpopulation from (4). For a sufficiently large time $t \geq t' = n_0 t_v$, $n_0 \in \mathbb{N}$, so that (21) is fulfilled, we can establish an upper-bound for the growth of the infectious subpopulation, namely,

$$\begin{aligned} \dot{I}(t) &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S(t)}{1 + \eta S(t)} + \frac{\delta V(t)}{1 + \eta V(t)} \right\} \right) \\ &\quad \times I(t - \tau) - (\gamma + b_2 + \alpha)I(t) \\ &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S(t)}{1 + \eta S(t)} \right\} + \max_{t' \leq t < t' + t_v} \left\{ \frac{\delta V(t)}{1 + \eta V(t)} \right\} \right) \\ &\quad \times I(t - \tau) - (\gamma + b_2 + \alpha)I(t) \\ &\leq \beta e^{-b_2 \tau} \left(\max_{t' \leq t < t' + t_v} \left\{ \frac{S'(t)}{1 + \eta S'(t)} \right\} + \max_{t' \leq t < t' + t_v} \left\{ \frac{\delta V'(t)}{1 + \eta V'(t)} \right\} \right) \\ &\quad \times I(t - \tau) - (\gamma + b_2 + \alpha)I(t) \\ &\leq \beta e^{-b_2 \tau} \left(\max_{0 \leq t < t_v} \left\{ \frac{S_i(t)}{1 + \eta S_i(t)} \right\} + \max_{0 \leq t < t_v} \left\{ \frac{\delta V_i(t)}{1 + \eta V_i(t)} \right\} \right) \\ &\quad \times I(t - \tau) - (\gamma + b_2 + \alpha)I(t), \\ &\leq (\gamma + b_2 + \alpha)(R(\theta, t_v)I(t - \tau) - I(t)). \end{aligned} \quad (29)$$

The interpretation given to the impulsive reproduction number $R(\theta, t_v)$ is intuitively analogous to the standard reproduction number R_0 from (17), but under a more complex regular impulsive vaccination instead of only a regular non-impulsive vaccination V_c . It leads to the identification of the parameters which make the model presents a stable oscillation around the DFE point under an impulsive vaccination strategy when $R_0 > 1$, i.e., when the DFE point is unstable with the application of only a regular non-impulsive vaccination V_c .

The following result in Proposition 3 is addressed to give conditions for guaranteeing that the infectious subpopulation converge asymptotically to zero provided that $R(\theta, t_v) < 1$.

Proposition 3. *If $R(\theta, t_v) < 1$, then $I(t) \rightarrow 0$ as $t \rightarrow \infty$.*

Proof. For all $t > 0$, we know from (4) that

$$\dot{I}(t) = aI(t) + b(t)I(t - \tau) \quad (30)$$

being $a = -(\alpha + b_2 + \gamma)$ and $b(t) = \beta e^{-b_2 \tau} S(t - \tau) / (1 + \eta S(t - \tau)) + \delta \beta e^{-b_2 \tau} V(t - \tau) / (1 + \eta V(t - \tau))$. At a sufficient large t , we know from (28) that

$$\frac{|b(t)|}{|a|} \leq R(\theta, t_v) < 1 \quad (31)$$

and then $\lim_{t \rightarrow \infty} I(t) = 0$ is obtained from [19]. \square

Proposition 4. *If $\theta = 0$ (i.e., in the absence of impulsive vaccination), then the impulsive reproduction number $R(0, t_v)$ becomes the standard, non-impulsive, reproduction number, i.e., $R(0, t_v) = R_0$, and implies that the stability at the DFE point when $R_0 < 1$ is not only local, but also globally asymptotically stable.*

Proof. As $\theta = 0$, $R(0, t_v) = (\beta e^{-b_2 \tau} / (\gamma + b_2 + \alpha))(S^*(\omega) / (1 + \eta S^*(\omega)) + \delta V^* / (1 + \eta V^*)) = R_0 < 1$. Then, from Proposition 3, we get that $\lim_{t \rightarrow \infty} I(t) = 0$. The dynamic for the exposed subpopulation from (3) becomes $\dot{E}(t) \rightarrow -b_2 E(t)$, so that $\lim_{t \rightarrow \infty} E(t) = 0$ since $b_2 > 0$. Then, the susceptible, vaccinated and recovered subpopulations reach their values in (9)–(11) at the DFE point. \square

5 Numerical simulations with regular impulsive vaccination

Parameter settings

In order to check if the reproduction number R_0 is equally valid in the periodic stationary regime of the non linear SVEIR model, we run a simulation of the dynamics of the disease for a given set of initial conditions during a sufficient time to obtain a stationary regime, and study the result. We have decided to use a student version of MATLAB ©7.11.0 (R2010b) Language for setting different values for the model parameters, displaying the solution data, and performing the technical computing, while the Simulink block-module

environment from Matlab resolves the dynamics of the SVEIR model (1)–(5). We design the Simulink system using such equations, plus the following restriction that guarantee the non-negativity of the subpopulations:

$$X_i(t_0) < 0 \Rightarrow X_i(t_0) = 0 \quad \forall t_0. \quad (32)$$

The proposed SVEIR model is now tested numerically for a given parameterization. A real case study for pertussis is later on discussed in Section 9. The average life span is established as 70 years, so $b_2^{-1} = 70$ years. We set $b_3 < b_2$ as the population would grow exponentially otherwise, and choose $b_1^{-1} = b_3^{-1} = 140$ years in order to have a disease-free total population equal to 1 ($N^* = b_1/(b_2 - b_3) = 1$). The vaccination parameters are set $V_c = 1$ and $\delta = 0.2$ while the saturation constant $\eta = 0.18$. For the transition rate from vaccinated to recovered subpopulation, we will pick five months of partial immunity before getting a total one in the recovered state, so $\gamma_1^{-1} = 150/365$ years. The extra death rate for the infected is 0.5 months^{-1} , so $\alpha^{-1} = 2/12$ years. About the parameters τ , ω and γ , we will take a range of possible values from the data available [31–36] in order to study further the dynamics of the epidemic:

- $\tau = 0.04\text{--}4$ years (15–1500 days), $\omega = 1\text{--}100$ years, $\gamma = 12.2\text{--}2.4 \text{ years}^{-1}$.

Finally, we choose a value of the disease transmission constant β so we can get the reproduction number higher than one, since as it is seen in (17), the reproduction number R_0 is directly proportional to β .

6 Non-regular impulsive vaccination strategy with adaptable vaccination rate θ

After proving the convenience of a regular impulsive vaccination, it is studied the implementation of a more sophisticated impulsive vaccination strategy. We introduce the concepts of vaccination cost (VC), directly related to the treatment and the number of consumed vaccines, and the disease cost (DC), related to the quantity of infected subpopulation over time. Our purpose is to guarantee the health of the population while minimizing both DC and VC costs.

A constant interval t_v between consecutive impulsive vaccination time instants is chosen, with a vaccination rate varying according to different rules within the range $\theta \in [0, 1]$. The notation for the time varying vaccination rate will be $\theta_i = \theta(it_v) = \theta(t_i)$. Also, the normalization of the infectious and susceptible subpopulation with respect to the total population N^* at the DFE point, i.e., $I'(t) = I(t)/N^*$, $S'(t) = S(t)/N^*$ are used for defining the rules which on-line adjust θ_i .

6.1 Vaccination rate updating rule based on infectious subpopulation quantity (VRIQ)

This strategy updates the impulsive vaccination rate θ_i by using a rule based on the quantity of infectious subpopulation. As $R(\theta, t_v)$ is a strictly decreasing function with

respect to $\theta \in [0, 1]$ i.e., $\partial R(\theta, t_v)/\partial \theta < 0$, there is only one value of θ corresponding to a given value of $R(\theta, t_v)$ with t_v being constant. Moreover, Proposition 3 establishes that if the impulsive reproduction number is smaller than 1, the disease is guaranteed to be eradicated, i.e., if $R(\theta, t_v) < 1$, then $\lim_{t \rightarrow \infty} I(t) = 0$. Such a result is used in the following way. Given a set of values for the SVEIR model parameters, a fixed value for t_v is chosen such that $R(0, t_v) \geq 1$ and $R(1, t_v) < 1$. Then a database of $R(\theta, t_v)$ for $\theta \in [\theta_{\min}, 1]$, where $\theta_{\min} = \arg\{\theta \in [0, 1] \mid R(\theta, t_v) = 1\}$, by taking into account (24), (25) and (28).

The aim of the VRIQ rule is to increment the impulsive vaccination rate if the infectious subpopulation exceeds a predefined size in order to reduce it. For such a purpose, the law used for updating such a vaccination rate at each vaccination time instant is given by

$$\theta_i = \arg\{\theta \mid R(\theta, t_v) = 1 + g_i(R(1, t_v) - 1)\}, \quad (33)$$

where g_i is an auxiliary value given by

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[I'(t_i)] > 0, \\ 1 - |\log_{10}[I'(t_i)]/C_I| & \text{if } \log_{10}[I'(t_i)] \in [-C_I, 0], \\ 0 & \text{if } \log_{10}[I'(t_i)] < -C_I \end{cases} \quad (34)$$

with $I'(t_i)$ being the normalized infectious subpopulation at the moment before the vaccination time instant t_i , and $C_I > 0$ a predefined constant. Note that the vaccination rate θ_i takes the minimum value θ_{\min} when the infectious subpopulation is very small, namely, $I'(t_i) < 10^{-C_I} \ll 1$ if C_I is large enough. In other words, $\theta_i = \theta_{\min}$ when the infection is near to be eradicated.

6.2 Vaccination rate updating rule based on susceptible subpopulation quantity (VRSQ)

We will use two different rules in order to update the value θ_i based on the susceptible subpopulation. The first one (VRSQ₁) is similar to the rule VRIQ in Section 6.1. The main difference between them is that the subpopulation accountable in the rule VRSQ₁ for setting the vaccination rate θ_i is not the infectious one, but the susceptible one. By taking into account that the contagion rate is directly proportional to the susceptible subpopulation from (1)–(5), the updating rule for θ_i has to maintain the susceptible subpopulation below a small upper-bound. For such a purpose, the law used to update the impulsive vaccination rate is given by

$$\theta_i = \arg\{\theta \mid R(\theta, t_v) = 1 + g_i(R(1, t_v) - 1)\}, \quad (35)$$

where the auxiliary value g_i is

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[S'(t_i)] > 0, \\ 1 - |\log_{10}[S'(t_i)]/C_S| & \text{if } \log_{10}[S'(t_i)] \in [-C_S, 0], \\ 0 & \text{if } \log_{10}[S'(t_i)] < -C_S \end{cases} \quad (36)$$

with a predefined constant $C_S > 0$ and $S'(t_i)$ the value of the normalized susceptible subpopulation at the moment before the impulsive vaccination time instant t_i . Note that θ_i takes the minimum value when $S'(t_i) < 10^{-C_S}$, i.e., when the susceptible subpopulation is very small if a suitable value for C_S is chosen.

In the second rule (VRSQ₂), the values θ_i are updated by using an explicit function of the susceptible subpopulation at the impulsive vaccination time instants

$$\theta_i = 1 - \frac{1}{1 + aS'(t_i)} \quad \text{with } a \geq 0. \quad (37)$$

6.3 Vaccination rate updating rule based on the infectious subpopulation growth (VRIG)

In this case, the impulsive vaccination rate θ_i is slightly increased or decreased from the previous value at each impulsive vaccination time instant with a function that depends on the growth of the infectious subpopulation, namely,

$$\begin{aligned} \bar{\theta}_{i+1} &= \theta_i + \Delta\theta_i, \quad \Delta\theta_i = \text{sgn}[\dot{I}'(t_i)] \frac{|\log_{10}[|\dot{I}'(t_i)|]|}{C_I}, \\ \theta_{i+1} &= \begin{cases} 0 & \text{if } \bar{\theta}_{i+1} < 0, \\ \bar{\theta}_{i+1} & \text{if } \bar{\theta}_{i+1} \in [0, 1], \\ 1 & \text{if } \bar{\theta}_{i+1} > 1 \end{cases} \end{aligned} \quad (38)$$

with a predefined constant $C_I > 0$. Here $\dot{I}'(t_i)$ can be estimated in practice in two ways, namely: a) $\dot{I}'(t_i)$ can be the growth of the normalized infectious subpopulation at the time of the impulse, or b) $\dot{I}'(t_i)$ can be replaced by $(I'(t_i) - I'(t_{i-1}))/t_v$, i.e., the difference between the normalized infectious subpopulation just before the current impulse time instant (t_i) and just before the previous one (t_{i-1}) divided by the constant inter-vaccination time interval (t_v). Such a measure can be used as a suitable approximation to the true growth $\dot{I}'(t_i)$.

6.4 Vaccination rate updating rule based on the susceptible subpopulation growth (VRSG)

The θ_i rate, like in the VRIG rule, is readjusted at each vaccination impulse time instant, but the purpose here is to react against the increase of the susceptible subpopulation with an increase of the impulsive vaccination rate, given that it indicates that the disease is still present:

$$\begin{aligned} \bar{\theta}_{i+1} &= \theta_i + \Delta\theta_i, \quad \Delta\theta_i = C_S \dot{S}'(t_i), \\ \theta_{i+1} &= \begin{cases} 0 & \text{if } \bar{\theta}_{i+1} < 0, \\ \bar{\theta}_{i+1} & \text{if } \bar{\theta}_{i+1} \in [0, 1], \\ 1 & \text{if } \bar{\theta}_{i+1} > 1 \end{cases} \end{aligned} \quad (39)$$

with a predefined constant $C_S > 0$. Here $\dot{S}'(t_i)$, as the $\dot{I}'(t_i)$ before, can be: a) the growth of the normalized susceptible subpopulation at the time of the impulse, or b) it can be replaced by $(S'(t_i) - S'(t_{i-1}))/t_v$, i.e., the difference between two data of the normalized susceptible subpopulation, one just before the current impulse time instant (t_i) and the other just before the previous impulse (t_{i-1}), divided by the constant inter-vaccination time interval (t_v).

7 Non-regular impulsive vaccination strategy with adaptable inter-vaccination time intervals

In our second approach, for obtaining an optimization of the vaccination and disease costs related to a disease, a set of rules for updating the time period $t_v(i)$ from the current vaccination time instant to the next one is developed while the impulsive vaccination rate θ remains constant. Again, the infectious and susceptible subpopulations are normalized with respect to the total population N^* at the DFE point. As the inter-vaccination time interval is time-varying, we define now the current vaccination time instant as the sum of all preceding inter-vaccination time intervals, namely, $t_i = \sum_{j=1}^i t_v(j)$, where $t_v(j) = t_j - t_{j-1}$ for $j \in \mathbb{N}$ and $t_v(1) = t_1 - t_0 = t_1$ since $t_0 = 0$, i.e., since the initial time instant is denoted by t_0 .

7.1 Inter-vaccination time intervals updating rule based on infectious subpopulation quantity (IVIIQ)

The inter-vaccination time interval, as θ in the VRIQ rule, depends on the quantity of infectious subpopulation. Analogous to the previous methods, we create a database of $R(\theta, t_v)$ between a maximum and a minimum t_v . We will pick the more convenient time interval t_v within the range $t_v \in [t_v^{\min}, t_v^{\max}]$ with t_v^{\min} chosen such that $R(\theta, t_v^{\min}) < 1$ for a prefixed θ . We will take advantage from the fact that $R(\theta, t_v)$ decreases as the inter-vaccination time interval does, as $\partial R(\theta, t_v)/\partial t_v > 0$ for all t_v for a constant θ . Furthermore, from Proposition 3 an impulsive vaccination reproduction number $R(\theta, t_v) < 1$ will guarantee $\lim_{t \rightarrow \infty} I(t) = 0$, so in order to decrease the infectious subpopulation we will reduce the impulsive vaccination time intervals as the infectious subpopulation exceeds a predefined size. For such a purpose, we use the rule

$$t_v(i+1) = \arg\{t_v \in [t_v^{\min}, t_v^{\max}] \mid R(\theta, t_v) = 1 + g_i(R(\theta, t_v^{\min}) - 1)\}, \quad (40)$$

where the auxiliary function g_i is given by

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[I'(t_i)] > 0, \\ 1 - |\log_{10}[I'(t_i)]/C_I| & \text{if } \log_{10}[I'(t_i)] \in [-C_I, 0], \\ 0 & \text{if } \log_{10}[I'(t_i)] < -C_I \end{cases} \quad (41)$$

with a predefined constant $C_I > 0$, and where $I'(t_i)$ is the normalized infectious subpopulation at the moment before the vaccination time instant.

7.2 Inter-vaccination time intervals updating rule based on susceptible subpopulation quantity (IVISQ)

As in the previous VRSQ₁ and VRSQ₂ rules, we now propose two alternative ways to update the time interval between consecutive impulsive vaccinations. The first rule (IVISQ₁) is defined as the IVIIQ one in Section 7.1, with the difference that the subpopulation used for measuring the state of the disease propagation is not the infectious one, but the susceptible one. The aim is to reduce the susceptible subpopulation by vaccination so the following law is used for updating the inter-vaccination time intervals

$$t_v(i+1) = \arg\{t_v \in [t_v^{\min}, t_v^{\max}] \mid R(\theta, t_v) = 1 + g_i(R(\theta, t_v^{\min}) - 1)\}, \quad (42)$$

where g_i is given by

$$g_i = \begin{cases} 1 & \text{if } \log_{10}[S'(t_i)] > 0, \\ 1 - |\log_{10}[S'(t_i)]/C_S| & \text{if } \log_{10}[S'(t_i)] \in [-C_S, 0], \\ 0 & \text{if } \log_{10}[S'(t_i)] < -C_S \end{cases} \quad (43)$$

with a predefined constant $C_S > 0$, and $S'(t_i)$ being the value of the normalized susceptible subpopulation at the moment before the impulsive vaccination time instant. The second rule (IVISQ₂) used to update the inter-vaccination time intervals is

$$t_v(i+1) = t_v^{\min} + \frac{t_v^{\max} - t_v^{\min}}{1 + aS'(t_i)} \quad \text{with } a \geq 0. \quad (44)$$

7.3 inter-vaccination time intervals updating rule based on infectious subpopulation growth (IVIIG)

In this case, the inter-vaccination time interval $t_v(i+1)$ is slightly increased or decreased from the previous one at each impulsive vaccination time instant with a rule based on the growth of the infectious subpopulation. In this sense, the following adjusting law is proposed:

$$\bar{t}_v(i+1) = t_v(i) - \Delta t_v(i), \quad \Delta t_v(i) = \operatorname{sgn}[\dot{I}'(t_i)] \frac{|\log_{10}[|\dot{I}'(t_i)|]|}{C_I}, \quad (45)$$

$$t_v(i+1) = \begin{cases} t_v^{\min} & \text{if } \bar{t}_v(i+1) < t_v^{\min}, \\ \bar{t}_v(i+1) & \text{if } \bar{t}_v(i+1) \in [t_v^{\min}, t_v^{\max}], \\ t_v^{\max} & \text{if } \bar{t}_v(i+1) > t_v^{\max} \end{cases}$$

with $C_I > 0$ being a predefined constant. $\dot{I}'(t_i)$ can be a) the growth of the normalized infectious subpopulation at the time of the impulse, or b) $\dot{I}'(t_i)$ can be replaced by $(I'(t_i) - I'(t_{i-1}))/t_v(i)$, i.e., the difference between the normalized infectious subpopulation just before the current impulse time instant (t_i) and just before the previous one (t_{i-1}) divided by the inter-vaccination time interval ($t_v(i) = t_i - t_{i-1}$). Such a measure can be used as a suitable approximation to the true growth $\dot{I}'(t_i)$.

7.4 inter-vaccination time intervals updating rule based on susceptible subpopulation growth (IVISG)

Here $t_v(i)$, like in the IVIG rule of the previous section, is readjusted at each impulsive vaccination time instant, although the proposed adaptation law is based on the susceptible subpopulation instead of the infectious one. Now, an increase of the susceptible subpopulation gives place to a decrease of the time interval between impulsive vaccination time instants, namely,

$$\begin{aligned} \bar{t}_v(i+1) &= t_v(i) - \Delta t_v(i), \quad \Delta t_v(i) = C_S \dot{S}'(t_i), \\ t_v(i+1) &= \begin{cases} t_v^{\min} & \text{if } \bar{t}_v(i+1) < t_v^{\min}, \\ \bar{t}_v(i+1) & \text{if } \bar{t}_v(i+1) \in [t_v^{\min}, t_v^{\max}], \\ t_v^{\max} & \text{if } \bar{t}_v(i+1) > t_v^{\max} \end{cases} \end{aligned} \quad (46)$$

with $C_S > 0$ a predefined constant. $\dot{S}'(t_i)$ can be a) the growth of the normalized susceptible subpopulation at the time of the impulse, or b) replaced by $(S'(t_i) - S'(t_{i-1}))/t_v(i)$, i.e., the difference between two data points of the normalized susceptible subpopulation, one just before the current impulse time instant (t_i) and the other just before the previous impulse (t_{i-1}), divided by the inter-vaccination time interval ($t_v(i) = t_i - t_{i-1}$).

8 Efficient method for coherency in the comparison of non-regular impulsive vaccination strategies against regular ones

The impact of the different rules for updating the vaccination rate θ_i and the time interval $t_v(i)$ from Sections 6 and 7 is studied. For such a purpose, a simulation of an outbreak is run, beginning with initial conditions near the DFE point plus a small fraction of infectious subpopulation. We set a constant time interval $t_v = 1$ for the adaptive laws adjusting the time-varying rate θ_i in Section 6 and a constant vaccination rate $\theta = 0.05$ for the adaptive laws adjusting the time-varying inter-vaccination time intervals within a range of $t_v(i) \in (0.46, 1.50)$ in Section 7. The parameters of the system are set as those used in Section 5 giving place to a reproduction number $R_0 = 1.25$ associated to an unstable DFE point. The reproduction number R_0 is also small enough so the impulsive reproduction number $R(\theta, t_v)$ achieves values under 1 given the proposed range for θ and t_v . The disease cost is defined as $DC = A \int_0^{t_f} I(t) dt$, related to the value of the infectious subpopulation during the simulation time, and the vaccination cost is defined as $VC = V_1 + V_2$. The first part $V_1 = \int_0^{t_f} b_3 V_c N(t) dt$ is related to the amount of newborns vaccinated during the simulation from 0 to t_f and it is proportional to the constant vaccination rate V_c , while the second part $V_2 = \sum_{i=1}^n \theta_i S(t_i)$ is related to the total amount of vaccinated individuals by means of impulsive vaccination s with n being the number of impulsive vaccinations during the simulation.

After running the simulation and gathering information about the dynamics of the non-regular impulsive vaccination strategy and their DC and VC, we re-run the simulation again, now using a regular impulsive vaccination strategy with constant vaccination

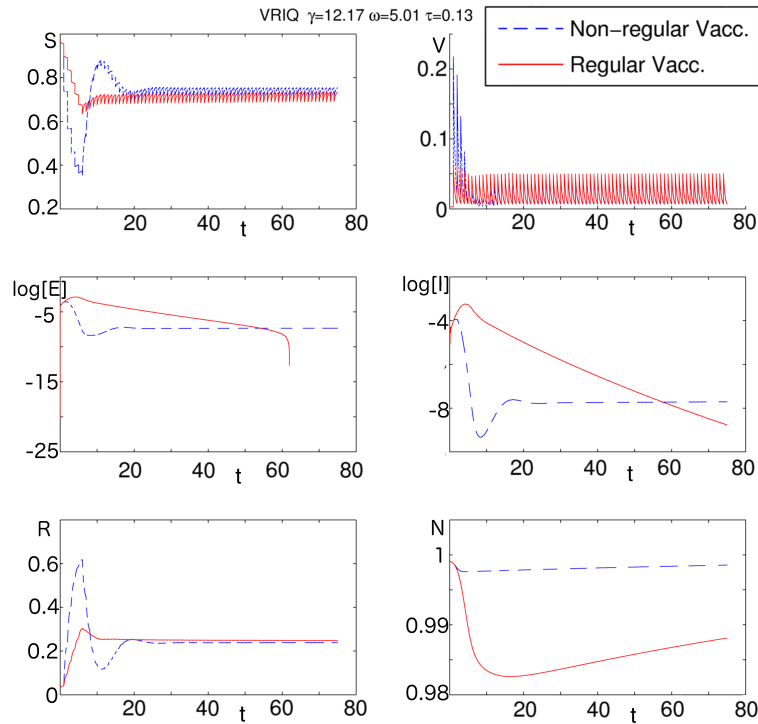


Fig. 2. A comparison between the model dynamics with a non-regular impulsive vaccination with a VRIQ strategy and a regular impulsive vaccination with the same vaccination cost.

parameters θ and t_v . We will use the data from the non-regular impulsive vaccination strategy and get the most approximate vaccination parameters so the regular impulsive vaccination presents a VC comparable to the non-regular one. In this sense, a regular impulsive vaccination strategy of constants rates θ_m and inter-vaccination time intervals t_m will be applied, where θ_m and t_m are defined by the data registered from the vaccination rate θ_i and the inter-vaccination time intervals of the non-regular impulsive vaccination strategies of Sections 6 and 7, respectively. Namely,

$$\theta_m = \frac{\sum_{i=1}^n S(t_i)\theta_i}{\sum_{i=1}^n S(t_i)}, \quad t_m = \frac{1}{n} \sum_{i=1}^n t_v(i), \quad (47)$$

i.e., t_m is the average value of the inter-vaccination time intervals in the simulation corresponding to the strategies of Section 7 and θ_m is an average value of the vaccination rate corresponding to strategies of Section 6 pondered with the susceptible subpopulation at the impulsive instants. Our results show the differences over 70 years of simulation of the susceptible and the vaccinated subpopulations between the regular and the VRIQ strategy, as we can see at the 1st and 2nd graphic of Fig. 2. The change of rate between the vaccinated and susceptible subpopulations has a direct impact in the evolution of the re-

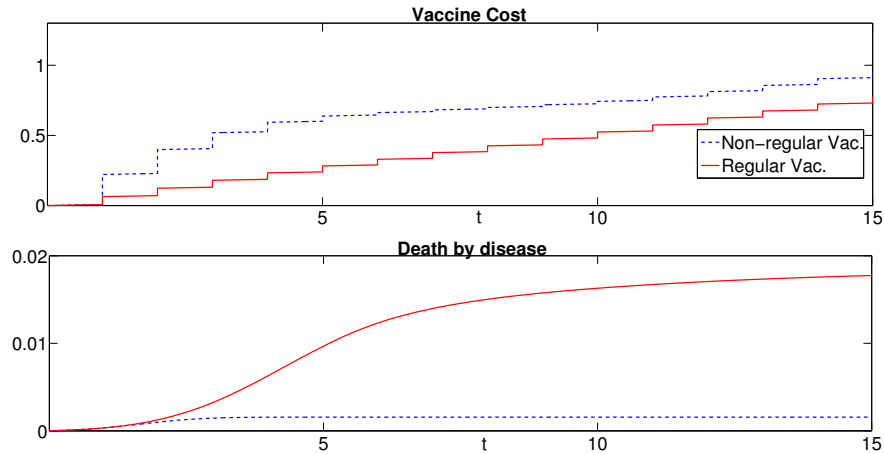


Fig. 3. Vaccination cost and number of deaths by infection versus time for a non-regular impulsive vaccination with VRIQ strategy and a regular impulsive vaccination.

covered and exposed subpopulations (3rd and 5th graphic) which subsequently, shapes the value of the infectious subpopulation as we see in the 4th graphic dropping to depreciable amounts at ($I < 10^{-7}$) so that the disease is considered effectively controlled. Finally, the value of the total population (6th graphic) is influenced by the extra death derived from the disease. The velocity of the disease decrement is also very important, as the disease cost DC can be too high if the infectious subpopulation presents high values for a long time. It is seen that the infectious subpopulation reaches an acceptable minimum level more rapidly when the VRIQ is applied instead of the regular impulsive vaccination. The death rate related to the disease is proportional to the number of infectious subpopulation, so the disease cost (DC) will give us also the total number of deaths caused by the disease after the simulation time, namely, $DC = A \int_0^{t_f} I(t) dt = A'[\text{death by disease}]$, where A and A' are some positive constants.

We see at Fig. 3 the consequences of the different dynamics induced in Fig. 2 for the regular impulsive vaccination and the non-regular impulsive one using the VRIQ rule. Both strategies have similar vaccination cost but they differ clearly in the disease cost. In this sense, the mortality by causes related to the infection is higher when a regular impulsive vaccination is used instead of a non-regular one with the VRIQ rule. In Table 2, we present the different death numbers after 70 years for each vaccination strategy against a regular impulsive vaccination with the same VC.

We can see in Table 2 that, with the exceptions of the IVIG₂ and the VRSG rules, the non-regular impulsive vaccination strategies are more effective and are able to control more rapidly an outbreak than the regular impulsive vaccination one. A better visualization of the costs of these strategies can be seen in Fig. 4. In these graphics, the vaccination and disease costs corresponding to different non-regular impulsive vaccination strategies are compared to the costs of several regular impulsive vaccination strategies. For such a purpose, two set of simulations are developed. The first set (discontinuous line) uses

Table 2. Deaths for different strategies.

Vacc. strategy	Deaths (non-regular)	Deaths (regular)
VRIQ — $C_I \in (4-12)$	$10^{-3}-8 \cdot 10^{-3}$	$9 \cdot 10^{-3}-13 \cdot 10^{-3}$
VRSQ ₁ — $C_S \in (0.04-0.12)$	$5 \cdot 10^{-4}-20 \cdot 10^{-4}$	$9 \cdot 10^{-3}-12 \cdot 10^{-3}$
VRSQ ₂ — $a \in (1.3-4)$	$5 \cdot 10^{-4}-6 \cdot 10^{-4}$	$7 \cdot 10^{-4}-10 \cdot 10^{-4}$
VRIG ₁ — $C_I \in (40-120) - \dot{I}'$	$\sim 5 \cdot 10^{-4}$	$5 \cdot 10^{-4}-50 \cdot 10^{-4}$
VRIG ₂ — $C_I \in (40-120) - \Delta I' / \Delta t$	$\sim 5 \cdot 10^{-4}$	$5 \cdot 10^{-4}-40 \cdot 10^{-4}$
VRSQ ₁ — $C_S \in (10-90) - \dot{S}'$	$5 \cdot 10^{-4}-28 \cdot 10^{-4}$	$5 \cdot 10^{-4}-14 \cdot 10^{-4}$
VRSQ ₂ — $C_S \in (10-90) - \Delta S' / \Delta t$	$5 \cdot 10^{-4}-15 \cdot 10^{-4}$	$5 \cdot 10^{-4}-14 \cdot 10^{-4}$
IVIIQ — $C_I \in (50-125)$	$3 \cdot 10^{-3}-3.5 \cdot 10^{-3}$	$4 \cdot 10^{-3}-6 \cdot 10^{-3}$
IVISQ ₁ — $C_S \in (2-6)$	$2.85 \cdot 10^{-3}-2.87 \cdot 10^{-3}$	$2.9 \cdot 10^{-3}-3.1 \cdot 10^{-3}$
IVISQ ₂ — $a \in (0.67-1.67)$	$2 \cdot 10^{-2}-6 \cdot 10^{-2}$	$2 \cdot 10^{-2}-6 \cdot 10^{-2}$
IVIIG ₁ — $C_I \in (25-62) - \dot{I}'$	$0.9 \cdot 10^{-2}-1.7 \cdot 10^{-2}$	$2.2 \cdot 10^{-2}-2.3 \cdot 10^{-2}$
IVIIG ₂ — $C_I \in (25-62) - \Delta I' / \Delta t$	$3 \cdot 10^{-3}-6 \cdot 10^{-3}$	$14 \cdot 10^{-3}-30 \cdot 10^{-3}$
IVISG ₁ — $C_S \in (0.67-1.67) - \dot{S}'$	$27 \cdot 10^{-3}-28 \cdot 10^{-3}$	$3.4 \cdot 10^{-3}-3.8 \cdot 10^{-3}$
IVISG ₂ — $C_S \in (0.67-1.67) - \Delta S' / \Delta t$	$2.9 \cdot 10^{-3}-3.1 \cdot 10^{-3}$	$2.82 \cdot 10^{-3}-2.85 \cdot 10^{-3}$

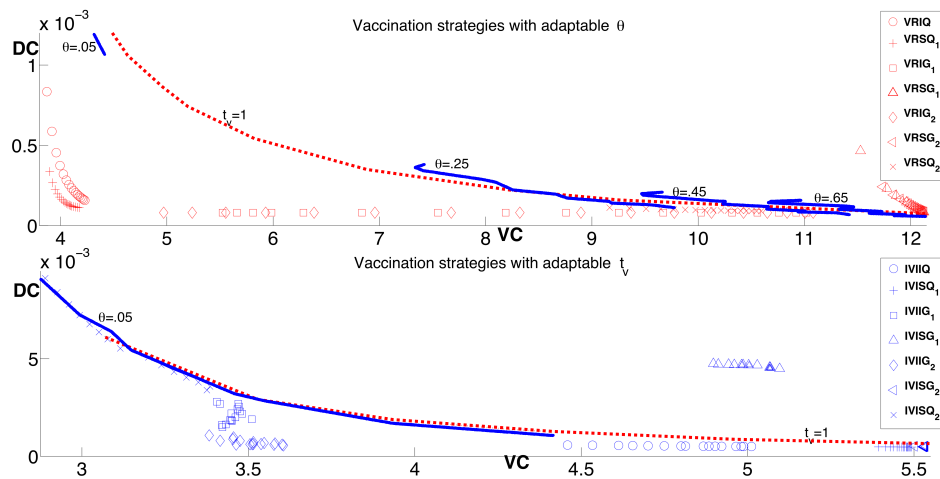


Fig. 4. A disposition of the different DC (assuming $A = 1$) and VC values for the vaccination strategies with the constants C_I and C_S from Table 2. The graphic of the top presents the vaccination strategies from Section 6, while the graphic of the bottom presents the strategies from Section 7. The discontinuous line in both graphics represents the DC/VC values of a regular impulsive vaccination with $t_v = 1$ for $\theta \in (0, 1)$, while the continuous lines represent the cost values associated to regular impulsive vaccination with different $t_v \in (0.4, 1.5)$ for a set of different values of $\theta = \{0.05, 0.25, 0.45, 0.65\}$.

the same value for the inter-vaccination time intervals ($t_v = 1$) and different constants values for θ , one value for each simulation. The second (continuous lines) uses a constant value for θ and different constant values for t_v within $t_v \in (0.4 - 1.5)$, one value of θ for each line ($\theta = \{0.05, 0.25, 0.45, 0.65\}$). The most adequate non-regular impulsive vaccination strategy can be identified in the graphic as the costs decreases in both axis. The non-regular impulsive vaccination rate strategies based on the VRIQ rules clearly present the minimum VC and the fastest decrement of the infectious subpopulation minimizing DC.

9 Vaccination strategies on a known disease: Pertussis

After proving the efficiency of the vaccination strategies in a generic disease, we apply our method to a specific disease so we can test our methods in a simulation of an actual disease. We have chosen pertussis (whooping cough) as it presents a temporary immunity while it still has a significant death ratio [35, 36] so all the parameters are suitable to the SVEIR model. According to the available data of pertussis, these model parameters are: $\tau = 8$ days, $\omega = 12$ years, $\gamma^{-1} = 15$ days, $\gamma_1^{-1} = 4$ days. A small mortality rate associated to the disease is given by $\alpha^{-1} = 3.8$ years, while the parameters independent of the disease, such as the characteristic growth and death rate of the population, the newborn vaccination rate and the saturation parameters for the vaccine and susceptible subpopulation remain the same as in the previous simulation ($b_2^{-1} = 70$ years, $b_1^{-1} = b_3^{-1} = 140$ years, $V_c = 1$, $\delta = 0.2$, $\eta = 0.18$). The disease transmission constant β is set so that the reproduction number is $R_0 = 1.5$.

Initial conditions are set near to the DFE ($S(0) = S^*$, $V(0) = V^*$ and $R(0) = R^*$) plus a small perturbation of infected subpopulation ($I(0) = 0.0001N^*$). We first compare the DC and VC (see Section 8) of a non-regular impulsive vaccination strategy with an adaptive vaccination rate θ_i to the DC and VC derived from a regular vaccination strategy given the same initial conditions. We choose the VRIQ strategy from Section 6.1, in which an impulse vaccination is administered annually ($t_v = 1$) to a fraction θ_i of the susceptible subpopulation, which can vary between 0 and 1.

It is seen in Fig. 5 that when the non-regular strategy is applied the DC, proportional to the deaths resulting from pertussis, is reduced substantially (56%), while the VC, derived from the number of vaccines administered, is only slightly increased (4%). Another comparison is made between a non-regular impulsive vaccination strategy with adaptive inter-vaccination time intervals and a regular impulsive vaccination strategy. We choose

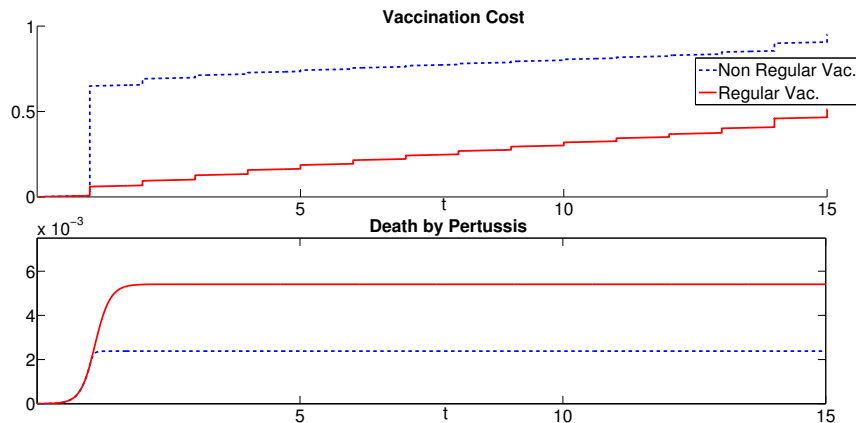


Fig. 5. Vaccination cost and number of deaths by infection versus time for a regular and a non-regular impulsive vaccination strategy (VRIQ).

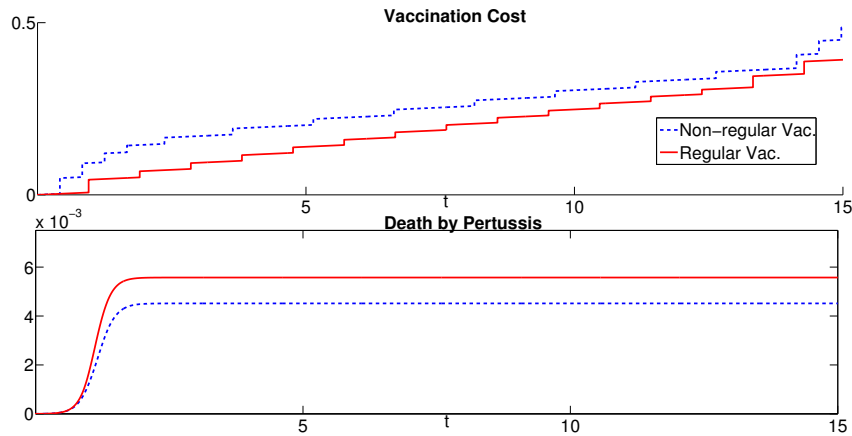


Fig. 6. Vaccination cost and number of deaths by infection versus time for a regular and a non-regular impulsive vaccination strategy (IVIIG).

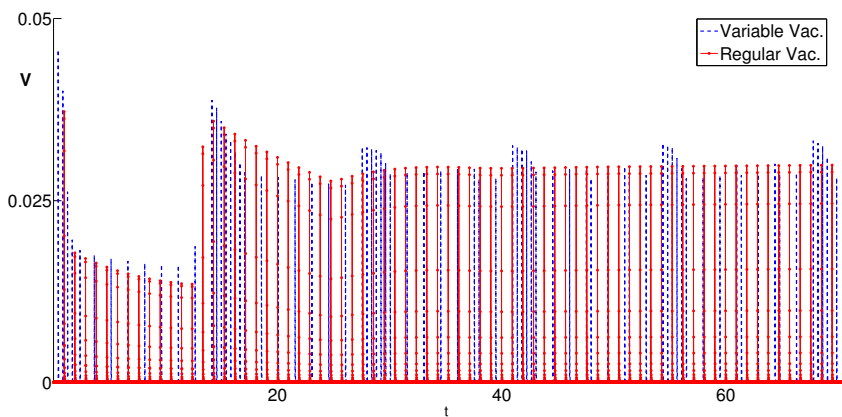


Fig. 7. Evolution over time (years) of vaccinated subpopulation from initial conditions near to DFE, given a regular and a non-regular impulsive vaccination strategy (IVIIG).

the IVIIG vaccination rule based on the infectious population growth from Section 7.3, in which an impulsive vaccination is administered at a constant rate to the susceptible subpopulation ($\theta = 0.05$) varying the interval between the impulses from 5 to 18 months ($t_v \in [0.41, 1.5]$), and compare the DC and VC to a regular vaccination strategy with the same vaccination rate and an inter-vaccination time interval which would be the average we get from the non-regular IVIIG strategy. We can see at Fig. 6 the result in terms of vaccines administered over time and extra deaths resulting from pertussis, which are proportional to the VC and DC, respectively. We can see that when the non-regular strategy is applied, the DC is reduced approximately to a 19% while the VC only increases a 5%.

The difference of the vaccinated subpopulation between the impulsive vaccination with adaptive time intervals and the regular one can be seen at Fig. 7. Observe that in the

case of the non-regular impulsive vaccination, a pattern of intensive vaccination emerges at intervals concurring with the average immunity time.

10 Conclusion

Theoretically valid impulsive vaccination strategies are presented and studied in order to eradicate an infectious disease. The impulsive reproduction number, related to the inter-vaccination time interval and the impulsive vaccination rate, gives us a first method for studying the stability of periodic solutions for subpopulations around the DFE point when such an equilibrium point is unstable with a regular non-impulsive vaccination strategy. It is the basis for controlling contagious diseases by means of prevention actions and for describing the model and the usefulness of the application of regular or non-regular (adaptive) impulsive vaccination strategies. The model may present an unstable disease-free equilibrium point under regular non-impulsive vaccination, but if a certain impulsive vaccination is applied, the system reaches a disease-free periodic state. Although the values of the subpopulations are constantly adjusted by impulsive vaccination, both the steady state oscillation reached under the regular impulsive vaccination and the DFE state have virtually eradicated the infected subpopulation. A non-regular adjustable vaccination strategy is proposed based on a set of rules that update the vaccination rate at each vaccination instant, which are uniformly distributed in time. Another set of rules maintain the vaccination rate constant and update the inter-vaccination time intervals. Both alternatives improve the result about the eradication of the disease compared with the results obtained with a regular impulsive vaccination. In the case of pertussis, the disease cost is reduced substantially at the expense of a small increase in the vaccination cost.

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