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ON THE TIME-OPTIMAL VACCINATION CONTROL FOR AN SEIR EPIDEMIC MODEL WITH EVENTUAL MODELLING ERRORS

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Abstract. *This paper presents a time-optimal vaccination control for an SEIR (susceptible-exposed-infectious-recovered by immunity, or immune, subpopulations) epidemic model under a bang-bang vaccination control. The model can eventually include generic uncertainties with parameterization errors and unmodeled dynamics. The designed bang-bang control operates with two design "a priori" vaccination control levels and chooses the switching time instants between both of them. Both values are chosen being compatible with the positivity and global stability of the epidemic model. The two constant vaccination controls define two possible disease-free equilibrium points in the absence of switching actions which are stable if the disease transmission rate lies below a certain critical value. It is assumed that the disease transmission rate is below such a critical value so that the resulting disease-free equilibrium point under any constant vaccination control, or, in general, if the vaccination is time-varying but it converges to a constant value, is asymptotically stable. The time-optimal vaccination control is generated from a design chosen constant value plus an incremental value which is generated by the minimization of the Hamiltonian associated with the minimal-time loss function. The targeted state final value is defined as a certain closed ball around some point being a reasonable approximate measure of both existing disease-free equilibrium points associated with the two vaccination levels used for the time-optimal control. Numerical examples are discussed to evaluate the proposed optimization method.*
Keywords: Epidemic model, SEIR epidemic model, Vaccination control, Bang-bang control, Time-optimal control, Hamiltonian

1. **Introduction.** Epidemic models are receiving important attention in the last years mainly because of their inherent interest in their potential application related to health care issues and also because of their interest in the fields of differential and difference equations because of their nonlinear inherent nature and positivity solutions requirement [20], and the fact they lead to typical nonlinear dynamic effects like, for instance, existence of multiple equilibrium points, unforced and forced oscillatory behaviors, bifurcations and chaos problems appearance [8-11] and populations fluctuations [24]. See, for instance, [1,2] for a general view. There is extensive literature available about local stability around the equilibrium points and global stability of epidemic models. See, for instance, [25-28] and

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some of the cited literature therein. It is well-known that, in the absence of vaccination controls, or under constant vaccination controls, there are usually at least two equilibrium points, the so-called disease-free one and the endemic one and that, in typical situations, both of them are not jointly stable or unstable and when the disease-free equilibrium pointy is stable the endemic one does not exist and when the endemic equilibrium exists it is stable while the disease-free equilibrium point is unstable. There are critical values of the disease transmission rates which define which of both equilibrium points is relevant for asymptotic stability, the disease-free one being relevant for small values of such a disease transmission rate while the endemic one is relevant for large values over the critical value. This property is equivalent to the evaluation of so-called reproduction number with biological meaning to be less than one (the disease is removed as time increases) or greater than one (the disease-free spreads with time), respectively [1,2]. On the other hand, the optimization is an important tool in generating optimal controls which minimize a suitable loss function related to alternative choices of the controls or suboptimal controls. See, for instance, [3-7], for a general optimization framework, and [12-16] and [21-23] for some related applications on epidemic models. The main objective of this paper is to focus the optimization problem on the time-optimal controls of an SEIR epidemic model to reach a prescribed neighborhood around a disease-free equilibrium point or a certain region surrounding two possible equilibrium points being reachable under two respective constant vaccination controls. Since the equilibrium points depend on both the disease parameterization and the controller gains, it is possible to drive the solution trajectories towards a suitable equilibrium point within a prescribed region in a suboptimal minimum time through the appropriate synthesis of the controller gains. So the minimal time-optimal control strategies through the paper are really suboptimal ones because of the model simplifications and the practical objectives relaxing. This feature is the main novelty of this paper in the context of optimization of epidemic models related to the available background literature. This strategy is adopted since it is a sufficient tool to guarantee prescribed small levels of infection in a reasonably small finite time. The bang-bang vaccination control law is designed by choosing two possible primary vaccination controls which respect the model stability and positivity required constraints. The rest of the paper is organized as follows. Section 2 is devoted to the description of the model under vaccination controls and with eventual presence of uncertainties. Some positivity, stability and characterization of the properties of the equilibrium points are analyzed and discussed. Section 3 relies on the formulation of the time-optimal control problem to drive the state trajectory solution to a prescribed closed neighborhood around a targeted point of interest which can be either an equilibrium point or some point describing closely two equilibrium points corresponding to the two distinct constant vaccination controls which are used as the min/max values for bang-bang controls. The basic idea is to decrease the effective disease effects in a minimum time with a prescribed accuracy margin. Some simulated examples are described in Section 4 for a time-optimal control strategy driving the state-trajectory solution towards a neighborhood surrounding the achievable disease-free equilibrium points under design constant vaccination controls which define the bang-bang strategy. Finally, conclusions end the paper.

Notation

- $\boldsymbol{R}_+ = \boldsymbol{R}_{0+} \cup \{0\}$, $\boldsymbol{R}_{0+} = \{z \in \boldsymbol{R} : z \geq 0\}$,
- $\boldsymbol{Z}_+ = \boldsymbol{Z}_{0+} \cup \{0\}$, $\boldsymbol{Z}_{0+} = \{z \in \boldsymbol{Z} : z \geq 0\}$,
- the symbol $\wedge$ denotes the logic conjunction "AND",
- the symbol $\vee$ denotes the logic disjunction "OR",
- the symbol $\oplus$ denotes the logic exclusive disjunction "XOR",

- $Q \succ 0$ (respectively, $Q \succeq 0$) denotes positive definiteness (respectively, positive semi-definiteness) of the matrix Q,

- the disease-free and endemic equilibrium points are denoted without specific related subscripts unless confusion could be expected in order to keep a simple notation. They are denoted with the respective subscripts "df" and "end" when necessary to avoid a potential confusion,

- the equilibrium points are denoted with the superscript "star" and the optimal values of costates, state trajectory solutions, optimal controls and Hamiltonians are denoted with the superscript "o",

- $B(x^*, r)$ and $\overline{B}(x^*, r)$ are the open and closed balls centred at $x^* \in \boldsymbol{R}^n$ of radius r. Thus, $\overline{\boldsymbol{R}}_{0+}$ is the closed nonnegative real semi-axis, i.e., $\overline{\boldsymbol{R}}_{0+} = \boldsymbol{R}_{0+} \cup \{+\infty\}$,

- e_n^T is the n-th canonical unity vector in $\boldsymbol{R}^4$ for $n \in \overline{4}$,

- $\boldsymbol{I}_n$ is the n-th identity matrix.

∂P and P^0 denote, respectively, the boundary and the interior of the set P. For discontinuous functions at t, $f(t) = f(t^+) = \lim_{\tau \downarrow t} f(\tau)$ and $f(t^-) = \lim_{\tau \uparrow t} f(\tau)$.

2. **Problem Statement.** Consider the SEIR epidemic model:

$$\dot{S}(t) = \mu - \mu S(t) - \beta I(t) S(t) + S_u(t) - V(t); \quad S(0) = S_0 \tag{1}$$

$$\dot{E}(t) = -(\mu + \sigma) E(t) + \beta I(t) S(t) + E_u(t); \quad E(0) = E_0 \tag{2}$$

$$\dot{I}(t) = -(\mu + \gamma) I(t) + \sigma E(t) + I_u(t); \quad I(0) = I_0 \tag{3}$$

$$\dot{R}(t) = \gamma I(t) - \mu R(t) + R_u(t) + V(t); \quad R(0) = R_0 \tag{4}$$

where S, E, I and R, denote respectively, the susceptible, exposed, infectious and recovered subpopulations, V is the vaccination control, physically, the number of vaccinated in the time interval dt, and the admissible initial conditions satisfy $\min(S_0, E_0, I_0, R_0) \geq 0$. Nominal dynamics is the one defined by structured explicit functions in the model. Non-nominal contributions to the dynamics in the model are the ones which have not described through structured functions in (1)-(4). The non-nominal dynamics contributions describing the deviations from the nominal behavior are referred to in the notation with subscripts "u". The parameters are:

- μ is the natural mortality rate which is supposed to be equal to the recruitment rate. Its inverse is the natural host lifespan,

- β is the disease transmission rate,

- σ is the disease latency rate. Its inverse is the average latent period,

- γ is the removal or recovery rate. Its inverse is the average infectious period.

The assumption that the natural mortality equalizes the recruitment rate facilitates the presentation while it can be directly extended at the expenses of some slightly more involved calculations to the case that both parameters are distinct. See, for instance, some of the classical models described in [2] and, more recently, in [17-19]. A simple physical and reasonable interpretation is that the population of newborns and immigrates are recruited at the same rate as the joined deaths and out-migrates.

By summing-up both sides of the above equation, one gets that the total population $N(t) = S(t) + E(t) + I(t) + R(t)$; $\forall t \in \boldsymbol{R}_{0+}$ is described by the following dynamics:

$$\dot{N}(t) = \mu - \mu N(t) + N_u(t); \quad N(0) = N_0 = S_0 + E_0 + I_0 + R_0 \tag{5}$$

where $N_u(t) = S_u(t) + E_u(t) + I_u(t) + R_u(t)$; $\forall t \in \boldsymbol{R}_{0+}$. The nominal epidemic model (1)-(4) is defined for the case $N_u(t) = S_u(t) = E_u(t) = I_u(t) = R_u(t) \equiv 0$. The non-nominal contributions can include uncertain dynamics associated, for instance, to higher-order dynamics, unmodeled delayed dynamics or influences of parametrical uncertainties

in the dynamics which are neglected in the nominal description. Note from (1) and (4) that the vaccination just adds population to the immune which is removed from the susceptible. This causes directly that epidemic models are not controllable by vaccination since these two components of the state vector cannot be prefixed to arbitrary values separately. The vaccination effort can be constant along time, impulsive (operating in practice by concentrated effort in very short period of time) or by feedback rules by taking information from the subpopulations of interest modulated through control gains. In the third section of this paper, we focus on optimal vaccination control of minimum time to reach an equilibrium or a ball of the state space surrounding some approximate equilibrium zone of the state space. It is well-known that minimum time-optimal control is of bang-bang type. To adapt this particular feature to our current problem, we operate the bang-bang action on an incremental vaccination control with respect to an average constant value. It turns out that the bang-bang incremental vaccinating effort can be generated via feedback from the costate time-evolution from the minimum time (i.e., optimal) corresponding Hamiltonian.

Assume that, for any $t \in \boldsymbol{R}_{0+}$, the following assumptions hold.

Assumption 2.1. *Assume that the non-nominal contribution functions to the dynamics are of the forms:*

$S_u(t) = S_u\left(S\left(h_{SS}(t)\right), I\left(h_{IS}(t)\right), g_S\left(\hat{x}\left(t, \overline{h}_{SS}(t), \overline{h}_{IS}(t)\right)\right), t\right)$

$E_u(t) = E_u\left(E\left(h_{EE}(t)\right), S\left(h_{SE}(t)\right), I\left(h_{IE}(t)\right), g_E\left(\hat{x}\left(t, \overline{h}_{EE}(t), \overline{h}_{SE}(t), \overline{h}_{IE}(t)\right)\right), t\right)$

$I_u(t) = I_u\left(I\left(h_{II}(t)\right), E\left(h_{EI}(t)\right), g_I\left(\hat{x}\left(t, \overline{h}_{II}(t), \overline{h}_{EI}(t)\right)\right), t\right)$

$R_u(t) = R_u\left(R\left(h_{RR}(t)\right), I\left(h_{IR}(t)\right), g_R\left(\hat{x}\left(t, \overline{h}_{RR}(t), \overline{h}_{IR}(t)\right)\right), t\right)$;

$\forall t \in \boldsymbol{R}_{0+}$, *and* $h_{zw} : \left[t - \overline{h}_{zw}(t), t\right] \times \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ *is a finite time-varying strip defining an eventual delay function from the subpopulation* z *to the subpopulation* w *at each time instant* t *whose finite maximum value is* $\overline{h}_{zw}(t) \geq 0$; $\forall t \in \boldsymbol{R}_{0+}$. *The functions* $g_{(.)}$ *describe eventual unmodeled dynamics which would make the real state vector* $\hat{x}(t)$ *to be of a higher dimension than the modelled state vector* $x(t) = (S(t), E(t), I(t), R(t))^T$.

Assumption 2.2. *The non-nominal contributions* $S_u(t)$, $E_u(t)$, $I_u(t)$ *and* $R_u(t)$ *are uniformly Lipschitz-continuous in all the subpopulations which take part of their respective arguments.*

Assumption 2.3.

$$(S(t) = 0) \Rightarrow (S_u(t) \geq V(t) - \mu)$$
$$(E(t) = 0) \Rightarrow (E_u(t) \geq V(t) - \mu - S_u(t))$$
$$(I(t) = 0) \Rightarrow (I_u(t) \geq -\sigma E(t))$$
$$(R(t) = 0) \Rightarrow (R_u(t) \geq -[\gamma I(t) + V(t)])$$

Note that if $\overline{h}_{zw}(t)$ is zero then there is no delay in the uncertainty coupling dynamics from the subpopulation z to the subpopulation w at each time instant t. The above assumptions can be reasonable in practice. For instance, it can be seen that Assumption 2.1 is reasonable since it is well-known that chronic individuals can be carriers of the disease which could be modelled by an extra state component as it happens in hepatitis B or herpes [1,2]. Another typical concern is that external migrating susceptible or infected individuals can contact the populations modelled in the considered epidemic model and can cause coupled dynamics contributions to such a model [29,30]. Such dynamics contributions are often subject to small delays as it can also be the case of the proper delayed dynamics of the populations considered in the model. For a general related context concerning the presence of delays and stability, see for instance, some references like [31-34].

Assumption 2.2 is reasonable, since in general, the basic nonlinear dynamics contribution consists of terms of a quadratic nature involving products of the susceptible populations with the infectious ones. This profile is typical concerning the infection transmission governed by the transmission coefficient rate (See, for instance, Equations (1) and (2)). They also have the advantage, from a mathematical point of view, that they guarantee the existence and uniqueness of the solution of the differential system for any given initial conditions in the presence of those eventually non-linear terms as a result following from their Lipschitzian nature. To emphasize the reasonability of Assumption 2.3, note, for instance, that it is known that the dynamics of epidemic models is, in general, stable in a boundedness context, except in particular cases, if the system has non-negative solutions under non-negative initial conditions for a vaccination rule $V(t) \in [0, \mu]$. Such constraints also include the vaccination-free case. The epidemic models are required, by their own nature, to be positive in the sense that they have always non-negative solutions for all time within the closed real orthant of corresponding order to its dimension. Then, it suffices for $S_u(t)$ to exceed a non-negative minimum threshold to accomplish with the first constraint of Assumption 2.3. Similar considerations could be given for the remaining constraints included in Assumption 2.3. The following result holds concerning the positivity of the solution.

Theorem 2.1. *If Assumption 2.1 holds and $V : \boldsymbol{R}_{0+} \to [0, \mu]$ then the unique solution to the differential system (1)-(4) and the total population for each given admissible set of initial conditions is given by the following non-negative functions on $\boldsymbol{R}_{0+}$:*

$$S(t) = e^{-\left(\mu t + \beta \int_0^t I(\tau) d\tau\right)} S_0 + \int_0^t e^{-\int_\theta^t (\mu + \beta I(\tau)) d\tau} (\mu + S_u(\theta) - V(\theta)) d\theta \tag{6}$$

$$E(t) = e^{-(\mu+\sigma)t} E_0 + \int_0^t e^{-(\mu+\sigma)(t-\theta)} \left(\beta I(\theta) S(\theta) + E_u(\theta)\right) d\theta \tag{7}$$

$$I(t) = e^{-(\mu+\gamma)t} I_0 + \int_0^t e^{-(\mu+\gamma)(t-\theta)} \left(\sigma E(\theta) + I_u(\theta)\right) d\theta \tag{8}$$

$$R(t) = e^{-\mu t} R_0 + \int_0^t e^{-\mu(t-\theta)} (\gamma I(\theta) + R_u(\theta) + V(\theta)) d\theta \tag{9}$$

$$N(t) = e^{-\mu t} N_0 + \int_0^t e^{-\mu(t-\theta)} (\mu + N_u(\theta)) d\theta \tag{10}$$

The proof of Theorem 2.1 is given in Appendix A. □

Note that if $N_u(t) = S_u(t) = E_u(t) = I_u(t) = R_u(t) = 0$; $\forall t \in \boldsymbol{R}_{0+}$ and $V : \boldsymbol{R}_{0+} \to [0, \mu]$ then all the subpopulations and the total population are non-negative for each set of non-negative (i.e., admissible) initial conditions. So, the following conclusion is immediate from Theorem 2.1.

Corollary 2.1. *If $V : \boldsymbol{R}_{0+} \to [0, \mu]$ then the unique solution to the nominal differential system (1)-(4) and the corresponding total population are non-negative for all time for each given admissible set of initial conditions.*

Theorem 2.2. *Let Assumptions 2.1-2.3 hold and, furthermore, assume that*

1) $V : \boldsymbol{R}_{0+} \to [0, \mu]$,

2) $V(t) \to V^*$ as $t \to \infty$,

3) the limits $S_u(t) \to S_u^*$ $(\geq V^* - \mu)$, $R_u(t) \to R_u^*$ $(\geq -V^*)$ as $t \to \infty$ and

$$\lim_{t \to \infty} \left(\int_0^t e^{\mu\theta} N_u(\theta) d\theta - \Psi e^{\mu t} \right) = 0$$

exist and are finite with $\Psi = S_u^* + R_u^*$, *and* $E_u(t) \to 0$, $I_u(t) \to 0$ *as* $t \to \infty$.

Then, there exists a unique disease-free equilibrium given by

$$x^* = (S^*, E^*, I^*, R^*)^T = \left(1 + \frac{S_u^* - V^*}{\mu}, 0, 0, \frac{R_u^* + V^*}{\mu}\right)^T \tag{11}$$

such that $E_u^* = I_u^* = 0$ *with* $N^* = 1 + \frac{R_u^* + S_u^*}{\mu}$.

The proof of Theorem 2.2 is given in Appendix B. □

The vaccination limits can be relaxed if the non-nominal dynamics terms are known as addressed in the next result whose proof is direct from Theorem 2.2.

Corollary 2.2. *Let Assumptions 2.1-2.3 hold and, furthermore, assume that*

1) $V : \boldsymbol{R}_{0+} \to [0, \mu + S_u(t)] \cap [-R_u(t), \infty)$,

2) $V(t) \to V^*$ *as* $t \to \infty$,

3) the limits $S_u(t) \to S_u^*$ $(\geq V^* - \mu)$, $R_u(t) \to R_u^*$ $(\geq -V^*)$ *as* $t \to \infty$ *and*

$$\lim_{t \to \infty} \left(\int_0^t e^{\mu\theta} N_u(\theta) d\theta - \Psi e^{\mu t} \right) = 0$$

exist and are finite with $\Psi = S_u^* + R_u^*$, *and* $E_u(t) \to 0$, $I_u(t) \to 0$ *as* $t \to \infty$.

Then, there exists a unique disease-free equilibrium point given by Equation (11).

Remark 2.1. *Note that the vaccination limit under Corollary 2.2 is* $V^* \in [0, \mu + S_u^*] \cap [-R_u^*, \infty)$ *and that the non-negativity of any trajectory solution under non-negative initial conditions still hold if Theorem 2.1 is relaxed to the vaccination constraint* $V : \boldsymbol{R}_{0+} \to [0, \mu + S_u(t)] \cap [-R_u(t), \infty)$.

The following result is concerned with the existence of the endemic equilibrium point if the disease transmission rate exceeds a certain threshold.

Theorem 2.3. *Consider the epidemic models (1)-(4) under Assumption 2.1 and the following further assumptions.*

1) The non-nominal contributions are given by $S_u(t) = K_{Su}(t)S(t)$, $E_u(t) = K_{Eu}(t)E(t)$, $I_u(t) = K_{Iu}(t)I(t)$ *and* $R_u(t) = K_{Ru}(t)R(t)$ *with some functions* K_{Su}, K_{Eu}, K_{Iu}, K_{Ru}: $\boldsymbol{R}_{0+} \to \boldsymbol{R}$ *such that* $K_{Su}(t) \to K_{Su}^*$, $K_{Eu}(t) \to K_{Eu}^*$, $K_{Iu}(t) \to K_{Iu}^*$ *and* $K_{Ru}(t) \to K_{Ru}^*$ *as* $t \to \infty$ *and that the values of those limits are independent of the particular disease-free or endemic equilibrium point.*

2) The vaccination control law is of the form:

$$V(t) = K_V(t)S(t) + \mu_V(t) = K_R(t)R(t); \quad \forall t \in \boldsymbol{R}_{0+} \tag{12}$$

for some control gains K_V, K_R, $\mu_V : \boldsymbol{R}_{0+} \to \boldsymbol{R}$ *which converge asymptotically so that* $K_V(t) \to K_V^*$, $K_R(t) \to K_R^*$, *and* $\mu_V(t) \to \mu_V^*$ $(= K_{Su}^* - K_V^*)$ *as* $t \to \infty$ *such that the following constraint holds:*

$$K_V^* + K_R^* = K_{Su}^* - K_{Ru}^* + (\overline{\gamma} - \gamma)/K_{RI}^* \tag{13}$$

where $K_{RI}^* = R^*/I^*$ *are positive real constants.*

3) $K_{Iu}^* \neq \mu + \gamma$

Then, the endemic equilibrium point is given by the steady-state subpopulations:

$$S^* = \frac{(\overline{\mu} + \overline{\gamma})(\overline{\mu} + \overline{\sigma})}{\beta\overline{\sigma}} = \frac{1}{\overline{R}_0}, \quad E^* = \frac{\overline{\mu}(\overline{\mu} + \overline{\gamma})}{\beta\overline{\sigma}}\left(\overline{R}_0 - 1\right) \tag{14a}$$

$$I^* = \frac{\overline{\mu}}{\beta}\left(\overline{R}_0 - 1\right), \quad R^* = \frac{\overline{\gamma}}{\beta}\left(\overline{R}_0 - 1\right) \tag{14b}$$

and it exists and it is unique provided that the reproduction number $\overline{R}_0 > 1$ *or, equivalently, that the disease transmission rate is large enough to satisfy the constraint*

$$\begin{aligned}\beta > \beta_{ec} &= \frac{(\overline{\mu}+\overline{\gamma})(\overline{\mu}+\overline{\sigma})}{\overline{\sigma}} \\ &= \frac{(\mu+\gamma-K_{Iu}^*+\sigma^{-1}(\mu+\gamma-K_{Iu}^*)(K_{Su}^*-K_V^*-K_{Eu}^*))(\mu+\sigma-K_{Eu}^*)}{\sigma+K_{Su}^*-K_V^*-K_{Eu}^*}\end{aligned}$$

where:

$$\begin{aligned}\overline{\mu} &= \mu-\mu_V^* = \mu+K_V^*-K_{Su}^* = \mu^*+K_V^* \\ \overline{\sigma} &= \sigma+\mu_V^*-K_{Eu}^* = \sigma+K_{Su}^*-K_V^*-K_{Eu}^* = \sigma^*-K_V^* \\ \overline{\gamma} &= \gamma+\mu_V^*-K_{Iu}^*+(\overline{\sigma}-\sigma)/K_{IE}^* \\ &= \gamma+K_{Su}^*-K_V^*-K_{Iu}^*+(\overline{\sigma}-\sigma)/K_{IE}^* = \gamma^*-K_V^*+(\overline{\sigma}-\sigma)/K_{IE}^*\end{aligned} \tag{15a}$$

$$\begin{aligned}\mu^* &= \mu-K_{Su}^* \\ \sigma^* &= \sigma+K_{Su}^*-K_{Eu}^* \\ \gamma^* &= \gamma+K_{Su}^*-K_{Iu}^* \\ K_{IE}^* &= I^*/E^*\end{aligned} \tag{15b}$$

are positive.

The proof of Theorem 2.3 is given in Appendix C. □

Note that the gain limits of Theorem 2.3 (i) characterizing the uncertainties of the endemic equilibrium points and the controller gains can be distinct of those corresponding ones to their disease-free equilibrium counterparts. However, the mentioned independence of the equilibrium point is simply made so as to make less involved the presentation.

Remark 2.2. *Note that Theorem 2.1, Theorem 2.2 and Corollary 2.2 guarantee the non-negativity of any solution defined by non-negative initial conditions which converges to an existing disease-free equilibrium point which depends on the limit if the vaccination control provided that the non-nominal disturbance dynamics contributions converge asymptotically. If any of the limits* S_u^* *or* R_u^* *is negative, null or positive, it means that the susceptible or recovered subpopulations as time tends to infinity have lower, identical or higher numbers than those corresponding to the perfectly modelled situation.*

Remark 2.3. *Note that the endemic critical disease transmission rate in the perfectly modelled case is*

$$\beta_{ec0} = \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma-K_V^*}\left(1-\sigma^{-1}K_V^*\right) = \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma} \tag{16}$$

which cannot be increased by the design of the limit vaccination gains. However, if the constraint $\mu_V^* = -K_V^*$ *of Theorem 2.3 for the perfectly modelled situation is modified as* $\mu_V^* = -\lambda K_V^*$ *for some* $\lambda \in (0,1)$ *then* $\beta_{ec0} = \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma-K_V^*}(1-\sigma^{-1}\lambda K_V^*)$ *and* $\frac{d\beta_{ec0}}{dK_V^*} > 0$ *for any* $K_V^* > 0$ *so that such a gain improves with the vaccination.*

Remark 2.4. *Note that, although not all the conditions are necessary for each part of the corresponding implication, we have:*

1) $K_{Su}^* = K_{Eu}^* = K_{Iu}^* = 0 \Rightarrow \mu^* = \mu$, $\sigma^* = \sigma$, $\gamma^* = \gamma$.

2) $K_V^* = K_{Su}^*$; $K_{Eu}^* = K_{Iu}^* = 0 \Rightarrow \overline{\mu} = \mu$, $\overline{\sigma} = \sigma$, $\overline{\gamma} = \gamma$.

3) $K_V^* = K_{Su}^* = 0 \Rightarrow \overline{\mu} = \mu^*$, $\overline{\sigma} = \sigma^*$, $\overline{\gamma} = \gamma^*$.

4) $K_V^* = K_{Su}^* = K_{Eu}^* = K_{Iu}^* = 0 \Rightarrow \overline{\mu} = \mu^* = \mu$, $\overline{\sigma} = \sigma^* = \sigma$, $\overline{\gamma} = \gamma^* = \gamma$.

5) The critical threshold β_c *guaranteeing the existence of the endemic equilibrium, so equivalently the basic reproduction number, depends on the non-modelled effects and the*

vaccination gains. If the vaccination gains converge asymptotically to zero and if the model (1)-(4) is perfectly modelled then $\overline{\mu} = \mu$, $\overline{\sigma} = \sigma$ *and* $\overline{\gamma} = \gamma$. *On the other hand, note from (15) that the critical disease transmission rate threshold for the existence of endemic equilibrium for the nominal model is*

$$\beta_{co} = \frac{\left(\mu + \gamma - K_{IEo}^{*-1} K_V^*\right)(\mu + \sigma)}{\sigma - K_V^*} = \frac{(\mu + \gamma - \sigma^{-1}(\mu + \gamma) K_V^*)(\mu + \sigma)}{\sigma - K_V^*} \tag{17}$$

since $K_{Su}^* = K_{Iu}^* = K_{Eu}^* = 0$ *and* $K_{IEo}^* = \frac{\sigma}{\mu + \gamma}$.

Theorem 2.4. *The following properties hold:*

Assume that all the conditions of Corollary 2.2 and that there exists some non-negative real constant M *such that* $\limsup_{t \to \infty} \left(\int_0^t e^{\mu\theta} N_u(\theta) d\theta - M e^{\mu t} \right) \leq 0$. *Then, the following properties hold:*

(i) *Assume that the conditions of Theorem 2.3 hold. Then, the Jacobian matrices about the disease-free and endemic equilibrium points, which define the dynamics of the corresponding asymptotic linearized systems, are the following ones:*

$$A_{df}^* = \begin{bmatrix} -\left(\mu + K_V^* - K_{Su}^*\right) & 0 & -\beta S_{df}^* & 0 \\ 0 & -\left(\mu + \sigma - K_{Eu}^*\right) & \beta S_{df}^* & 0 \\ 0 & \sigma & -\left(\mu + \gamma - K_{Iu}^*\right) & 0 \\ K_V^* & 0 & \gamma & -\left(\mu - K_{Ru}^*\right) \end{bmatrix} \tag{18}$$

$$\begin{aligned} A_{end}^* &= A_{end}^*\left(\overline{R}_0\right) \\ &= \begin{bmatrix} -\left(\mu + \beta I_{end}^* \delta\left(\overline{R}_0\right)\right) & 0 & -\beta S_{end}^* \delta\left(\overline{R}_0\right) & 0 \\ \beta I_{end}^* \delta\left(\overline{R}_0\right) & -\left(\mu + \sigma - K_{Eu}^*\right) & \beta S_{end}^* \delta\left(\overline{R}_0\right) & 0 \\ 0 & \sigma & -\left(\mu + \gamma - K_{Iu}^*\right) & 0 \\ K_V^* & 0 & \gamma & -\left(\mu - K_{Ru}^*\right) \end{bmatrix} \end{aligned} \tag{19}$$

where the parameterization (15) defines the endemic equilibrium point linearized dynamics, and

$$\delta\left(\overline{R}_0\right) = \begin{cases} 0 & \text{if } \beta \leq \beta_{ec} \\ 1 & \text{if } \beta > \beta_{ec} \end{cases} \tag{20}$$

(ii) *The disease-free equilibrium point is locally asymptotically stable if* $\mu_V^* \in [0, \mu)$ *and* $\beta \in [\beta_{dc0}, \beta_{dc1}]$, *where*

$$\beta_{dc0} = \frac{\max\left[0, \max\left(\left|K_{Eu}^* - K_{Su}^*\right|, \left|K_{Ru}^* - K_{Su}^*\right|\right) - \left|K_{Iu}^* - K_{Su}^*\right|\right]}{\sqrt{2} S_{df}^*} \tag{21a}$$

$$\beta_{dc1} = \frac{\mu + \min\left(K_V^* - K_{Su}^*, \sigma - K_{Eu}^*, \gamma - K_{Iu}^*, -K_{Su}^*\right)}{\sqrt{2} S_{df}^*}$$

provided that $\beta_{dc1} \geq \beta_{dc0}$, *or if* $\beta \in [0, \beta_{dc2}]$, *where*

$$\begin{aligned} \beta_{dc2} = &\frac{\mu + \min\left(K_V^* - K_{Su}^*, \sigma - K_{Eu}^*, \gamma - K_{Iu}^*, -K_{Su}^*\right)}{\sqrt{2} S_{df}^*} \\ &- \frac{\left(\left|K_{Iu}^* - K_{Su}^*\right| + \left|K_{Eu}^* - K_{Su}^*\right| + \left|K_{Ru}^* - K_{Su}^*\right|\right)}{\sqrt{2} S_{df}^*} \end{aligned} \tag{21b}$$

provided that

$$\mu > \left(|K^*_{Iu} - K^*_{Su}| + |K^*_{Eu} - K^*_{Su}| + |K^*_{Ru} - K^*_{Su}|\right) - \min\left(K^*_V - K^*_{Su}, \sigma - K^*_{Eu}, \gamma - K^*_{Iu}, -K^*_{Su}\right).$$

The endemic equilibrium point exists and it is locally asymptotically stable if:

$$\beta > \beta_{ec} = \frac{(\overline{\mu} + \overline{\gamma})(\overline{\mu} + \overline{\sigma})}{\overline{\sigma}} \tag{22}$$

provided that $\max\left(|K^*_{Iu} - K^*_{Su}|, |K^*_{Eu} - K^*_{Su}|, |K^*_{Ru} - K^*_{Su}|\right) \leq \beta_{ec} S^*_{df}$.

(iii) *The epidemic model is globally stable, i.e., the solutions of all the subpopulations are bounded for any finite non-negative initial conditions and any disease transmission rates. Furthermore, the model has no stable limit cycle and then the two equilibrium points are not jointly either locally asymptotically stable or unstable.*

The proof of Theorem 2.4 is given in Appendix D. □

3. **Time-Optimal Control.** In this section, we simplify Assumption 2.1 to the absence of delays, i.e., $\overline{h}_{zw} \equiv 0$, and unmodeled dynamics in current model and the dynamics of the discrepancies in-between the current. In the next section, we will give also a numerical example to discuss the robustness in the presence of small uncertainties in the model. The non-nominal model is described by the real vector function:

$$\begin{aligned}\overline{E}(t) &= K(t, x(t))x(t) = (E_{Su}(t), E_{Eu}(t), E_{Iu}(t), E_{Ru}(t))^T \\ &= (K_{Su}(t, s(t))S(t), K_{Eu}(t, s(t))E(t), K_{Iu}(t, s(t))E(t), K_{Ru}(t, s(t))R(t))^T\end{aligned}$$

where $K : \boldsymbol{R}_{0+} \times \boldsymbol{R}^4_{0+} \to \boldsymbol{R}^{4\times 4}_{0+}$ is piecewise-continuous and bounded everywhere in its definition domain. The system (1)-(4), subject to the above constraint, can be rewritten equivalently as:

$$\dot{x}(t) = Ax(t) + (\beta g(t, x(t))d + K(t, x(t))x(t) + c + b(V_0 + u(t))), \quad x(0) = x_0 \geq 0 \tag{23}$$

("$\geq$" stands here for the non-negativity of all the vector components) where the disease-free linearized matrix of dynamics A^*_{df0} of (18) and (D2) of Appendix D has been re-denoted by A, where

$$b = (-1, 0, 0, 1)^T, \quad c = (\mu, 0, 0, 0)^T, \quad d = (-1, 1, 0, 0)^T \tag{24}$$

and the vaccination control law $V(t) = (V_0 + u(t)) \in [0, \mu]$ where $V_0 \in \boldsymbol{R}_{0+}$ is a constant value chosen "a priori", $u(t)$ is a scalar incremental control to be generated from the optimization problem and $u(t) \in [-V_0, \mu - V_0]$; $\forall t \in \boldsymbol{R}_{0+}$ is the feasible constrained control in order to accomplish with the positivity constraint $V(t) \in [0, \mu]$; $\forall t \in \boldsymbol{R}_{0+}$, [8-11]. The optimization problem will be formulated based on Pontryagin's Principle under the following solvability hypotheses.

H1) Let the assumptions of Theorem 2.4 and the conditions of Theorem 2.4(ii) hold with $\beta < \min(\beta_{dc}, \beta_{ec})$ so that the disease-free equilibrium point is globally asymptotically stable, or instead:

H1') Assumption H1 holds except that $\beta < \beta_{dc}$.

H2) The loss function to be minimized is $J = J(T) = \int_0^T dt$ with $T < \infty$ and its associate Hamiltonian is:

$$\begin{aligned}H &= 1 + p^T(t)\left[Ax(t) + (\beta g(t, x(t))d + K(t, x(t))x(t) + c + b(V_0 + u(t)))\right] \\ &= 1 + p^T(t)\left[Ax(t) + \left(\beta e_1^T x(t) G x(t) + K(t, x(t))x(t) + c + b(V_0 + u(t))\right)\right]\end{aligned} \tag{25}$$

where $g(x(t))e_1^T x(t) = S(t)I(t)$, $e_i \in \boldsymbol{R}^4$ is the ith canonical Euclidean unity vector, $p(t)$ is the co-state of the state $x(t)$ and the optimal incremental control law $u^o(t) \in U \subseteq$

$[-V_0, \mu - V_0]$; $\forall t \in \boldsymbol{R}_{0+}$ has to be found which makes minimum the Hamiltonian H and $G = (G_{ij}) \in \boldsymbol{R}^{4\times 4}$ is a sparse matrix defined by $G_{23} = -G_{13} = 0$ and $G_{ij} = 0$ for $i(\neq 1, 2) \in \overline{4}$, $j(\neq 3) \in \overline{4}$.

H3) For any given $x_0 \in P \not\in \partial P$ (∂P being the boundary of P), find a final targeted point v^o

$$x^o(T^o) = v^o, \quad v^o(\neq 0) \in \partial P \tag{26}$$

where $V_0 \in \boldsymbol{R}_{0+}$ is a constant value being chosen "a priori", $u^o(t)$ is a scalar incremental optimal control to be generated from the optimization problem:

$$u^o = u^o(t, V_0, \lambda, \rho) \in [\lambda\mu - V_0, \rho\mu - V_0] \subseteq [-V_0, \mu - V_0]; \quad \forall t \in \boldsymbol{R}_{0+} \tag{27}$$

for some design prefixed real constants $\rho(> \lambda)$, $\lambda \in [0, 1]$.

H4) The target state $x^0(T^0)$ is at the boundary ∂P of a prescribed neighborhood of center $x^* = x_1^* \oplus x_2^*$ ("$\oplus$" standing for the logic exclusive disjunction XOR), where:

$$\begin{aligned} P &= P\,(x^*, Q, r) \\ &= \left\{x \in \boldsymbol{R}^4 : \left(x^T - x^{*^T}\right) Q(x - x^*) \leq r^2, Q = Q^T \left(\in \boldsymbol{R}^{4\times 4}\right) \succeq 0, r > 0\right\} \end{aligned} \tag{28}$$

$$x_1^* = x_1^*(\lambda) = \left(1 - \lambda + \frac{S_u^*}{\mu}, 0, 0, \lambda + \frac{R_u^*}{\mu}\right)^T \tag{29}$$

$$x_2^* = x_2^*(\rho) = \left(1 - \rho + \frac{S_u^*}{\mu}, 0, 0, \rho + \frac{R_u^*}{\mu}\right)^T \tag{30}$$

Note that it is the feasible constrained optimal incremental control accomplishes with the positivity constraint $V(t) \in [\lambda\mu, \rho\mu] \subseteq [0, \mu]$; $\forall t \in \boldsymbol{R}_{0+}$.

Note also that $x^* = \left(1 + \frac{S_u^* - V^*}{\mu}, 0, 0, \frac{R_u^* + V^*}{\mu}\right)^T$ is the disease-free equilibrium point if $V(t) \to V^*$ as $t \to \infty$ and that (29) and (30) are the disease-free equilibrium points for $V^* = \lambda\mu$ and $V^* = \rho\mu$, respectively.

Remark 3.1. *The combined differential system associated to the Hamiltonian (25) is given by:*

$$\dot{x} = \frac{\partial H}{\partial p} = Ax(t) + (\beta g(x(t))d + K(t, x(t))x(t) + c + b(V_0 + u(t))) \tag{31a}$$

$$\begin{aligned} \dot{p} = -\frac{\partial H}{\partial x} = &-\left[A^T + \beta\left(G^T x^T(t) e_1 + G x(t) e_1^T\right) + K^T(t, x(t))\right. \\ &\left. + \nabla_x K(t, x(t))x(t)\right] p(t) \end{aligned} \tag{31b}$$

$$H(T) = H(x(T), p(T), u(T), T, V_0, r) = 0 \tag{31c}$$

Note that the system dynamics (31a) prior to the particular optimal control solutions is identical to (23) as expected.

Remark 3.2. *The non-unique incremental control gains which guarantee the generation of the optimal incremental control $u^o(t) \in [\lambda\mu - V_0, \rho\mu - V_0]$ satisfy the subsequent constraints for any $t \in \boldsymbol{R}_{0+}$:*

$$K_V^o(t) \in \left[-\frac{V_0 + \mu_V^o(t)}{S(t)}, \frac{\mu - V_0 - \mu_V^o(t)}{S(t)}\right] \text{ if } S(t) \neq 0 \tag{32a}$$

$$\mu_V^o(t) = u^o(t) \in [\lambda\mu - V_0, \rho\mu - V_0], \quad K_V^o(t) \text{ arbitrary if } S(t) = 0. \tag{32b}$$

The following result is related to the time-optimal vaccination.

Theorem 3.1. *Assume that the hypotheses H1 (or H1') to H4 hold with* $r \le r_0 < \infty$ *and* r_0 *being of free-choice under H1, or* $r < r_0$ *for some* $r_0 = r_0(\min(\beta_{dc}, \beta_{ec}))$ *under H1'. Then, the following properties hold.*

(i) *For each given quintuple* $(V_0, x_0, v^o, \lambda, \rho)$ *being defined for prefixed design constants* λ, $\rho(>\lambda) \in [0,1]$, *there exists a minimum time (time-optimal)* T^o *and a corresponding time-optimal incremental control* $u^o(t) \in [\lambda\mu - V_0, \rho\mu - V_0] \subseteq [-V_0, \mu - V_0]$; $\forall t \in [0, T^o]$ *such that its associated optimal vaccination control:*

$$V^o(t) = V^o(V_0, t) = (V_0 + u^o(t)) \in [\lambda\mu, \rho\mu] \subseteq [0, \mu], \quad \forall t \in [0, T^o] \tag{33}$$

minimizes the Hamiltonian (25) to a value:

$$\begin{aligned} H^o(t) &= H^o\left(x^o(t), p^o(t), u^o(t), t, \lambda, \rho, r\right) \\ &= 1 + p^{o^T}(t)\big[Ax^o(t) + \big(\beta e_1^T x^o(t) G x^o(t) \\ &\quad + K(t, x^o(t))x^o(t) + c + b(V_0 + u^o(t))\big)\big]; \quad \forall t \in [0, T^o) \end{aligned} \tag{34a}$$

$$H^o(T^o) = H^o\left(x^o(T^o), p^o(T^o), u^o(T^o, \lambda, \rho), T^o, V_0, r\right) = 0 \tag{34b}$$

(ii) *If Assumptions 2.1-2.3 hold in the absence of any delays then a unique time-optimal vaccination control with a minimum number of control switches exists with a unique associated time-optimal Hamiltonian.*

Proof: Under the given conditions the disease-free equilibrium point is globally asymptotically stable for any $V(t) \to V^* \in [0, \mu)$ as $t \to \infty$. In particular, if $V^* = \lambda\mu \vee \rho\mu$ (with "$\vee$" and "$\wedge$" standing for the logic disjunction "OR" and conjunction "AND", respectively). According to the dynamic Equations (31), associated with the Hamiltonian (25), it follows that the optimal incremental control is:

$$u^o(t) = \begin{cases} \lambda\mu - V_0 & \text{if } \left[p^{o^T}(t^-)b > 0 (\Leftrightarrow p_4^0(t^-) > p_1^0(t^-)) \wedge p^{o^T}(t)b \ge 0 (\Leftrightarrow p_4^0(t) \ge p_1^0(t))\right] \\ \rho\mu - V_0 & \text{if } \left[p^{o^T}(t^-)b < 0 (\Leftrightarrow p_4^0(t^-) < p_1^0(t^-)) \wedge p^{o^T}(t)b \le 0 (\Leftrightarrow p_4^0(t) \le p_1^0(t))\right] \end{cases}; \tag{35}$$

$\forall t \in [0, T]$ (so that it is not arbitrary within any time interval on nonzero measure for which $p^{o^T}(t)b \equiv 0$) which gives a corresponding vaccination optimal control:

$$V^o(t) = V_0 + u^o(t) \tag{36}$$

$\forall t \in [0, T]$ while being unique within any time interval of nonzero measure for which $p^{o^T}(t)b \equiv 0$, which avoids, from (35) in (36), eventual non-uniquely defined singular controls, where (32a) and (32b) satisfy respective initial and final conditions $x(0) = x_0$ and

$$\begin{aligned} &p^{o^T}(T^o)\left[Ax^o(T^o) + \left(\beta e_1^T x^o(T^o) G x^o(T^o)\right.\right. \\ &\left.\left. + K\left(t, x^o(T^o)\right) x^o(T^o) + c + b\left(V_0 + u^o(T^o)\right)\right)\right] = -1 \end{aligned} \tag{37}$$

since the final time instant is free. Note that along the optimal trajectory:

$$\begin{aligned} &H\left(x^o(t), p^o(t), u^o(t), t, \lambda, \rho, r\right) \\ &\le \min_{u^o(t) \in [\lambda\mu - V_0, \rho\mu - V_0]} H(x(t), p(t), u(t), t, \lambda, \rho, r); \quad \forall t \in [0, T] \end{aligned} \tag{38}$$

for a minimum final time $T = T^0$ satisfying (34b) so that the optimal Hamiltonian is independent of V_0 since $V^0(t)$ is independent of V_0. Property (i) has been proved. Property (ii) is proved in Appendix E. □

Remark 3.3. *The condition* $\overline{B}(x_1^*, r_0) \cap \overline{B}(x_2^*, r_0) = \emptyset$ *(with* $\overline{B}(.)$ *standing for the closure of the ball* $B(.)$*) of Case b in the proof of Theorem 3.1 (ii) is not very relevant since it can be sufficient in practice an arbitrary choice between the two values of the vaccination controls to target points in a prefixed target ball around any of the disease-free equilibrium points.*

Remark 3.4. *The time-optimal control* $V^o(t)$ *can be formulated as a classical* ± 1 *bang-bang control by the choice* $\rho = \lambda + \frac{2}{\mu}$ *which leads to* $V_0 = 1 + \lambda\mu = \rho\mu - 1$ *and* $u^o(t) = -sgn\left(p^{o^T}(t)b\right)$ *for any* $t \in \boldsymbol{R}_{0+}$ *such that* $p^{o^T}(t)b \neq 0$ *since*

$$u^o(t) = \lambda\mu - V_0 = -1 = -sgn\left(p^{o^T}(t)b\right) \text{ if } p^{o^T}(t)b > 0, \tag{39}$$

$$u^o(t) = \rho\mu - V_0 = 1 = sgn\left(p^{o^T}(t)b\right) \text{ if } p^{o^T}(t)\, b < 0. \tag{40}$$

Theorem 3.1 has a clear subsequent version for the linearized system around the disease-free equilibrium point since the final conditions for the co-state can be computed from the final targeted state so that the whole optimal trajectory solution problem becomes an initial condition problem.

Theorem 3.2. *The time-optimal incremental control (and then the time-optimal associated vaccination control) is unique and it steers a unique extremal state-trajectory solution in a minimum finite-time* T^o *to* ∂P *for any given initial conditions under the subsequent assumptions.*

A.1. Assumptions 2.1-2.3 hold and, furthermore, assume that the limits $S_u(t) \to S_u^*$ $(\geq -\mu)$, $R_u(t) \to R_u^*(\geq -V^*)$ *as* $t \to \infty$ *and* $\lim_{t\to\infty}\left(\int_0^t e^{\mu\theta}N_u(\theta)d\theta - \Psi e^{\mu t}\right) = 0$ *exist and are finite with* $\Psi = S_u^* + R_u^*$*, and* $E_u(t) \to 0$, $I_u(t) \to 0$ *as* $t \to \infty$.

A.2. The disease transmission rate β *is small enough so that the linearized dynamics about the disease-free unforced (i.e., vaccination-free) equilibrium point* $x^* = \left(1 + \frac{S_u^*}{\mu}, 0, 0, \frac{R_u^*}{\mu}\right)^T$*, which is globally asymptotically Lyapunov's stable, is given by the stability matrix:*

$$A = \begin{bmatrix} -\overline{\mu} & 0 & -\beta\left(1 + \frac{S_u^*}{\mu}\right) & 0 \\ 0 & -(\overline{\mu} + \overline{\sigma}^*) & \beta\left(1 + \frac{S_u^*}{\mu}\right) & 0 \\ 0 & \overline{\sigma}^* & -(\overline{\mu} + \overline{\gamma}^*) & 0 \\ 0 & 0 & \overline{\gamma}^* & -\overline{\mu} \end{bmatrix} \tag{41}$$

A.3. The hypotheses H2-H4 hold with the change $x^* = \left(1 + \frac{S_u^*}{\mu}, 0, 0, \frac{R_u^*}{\mu}\right)^T$ *to redefine* P *in (28), where the searched time-optimal control satisfies (27) with* $\rho = \lambda + \frac{2}{\mu}$ *with* $q = g^T\hat{Q}g\,(\in \boldsymbol{R}_+)$*, where* $g = e_1$*, or* $g = e_4$*,* $\hat{Q} = \hat{Q}^T \succ 0$*, where "*$\succ$*" stands for positive definiteness, and* P *in (28) is replaced with*

$$\begin{aligned} P_S &= P(S^*, Q, r) \\ &= \left\{S \in \boldsymbol{R} : q(S - S^*)^2 \leq r^2, q = g^T\hat{Q}g > 0, \hat{Q} = \hat{Q}^T\left(\in \boldsymbol{R}^{4\times 4}\right) \succ 0, r > 0\right\} \end{aligned} \tag{42}$$

if $g = e_1$*, or*

$$\begin{aligned} P_R &= P(R^*, Q, r) \\ &= \left\{R \in \boldsymbol{R} : q(R - R^*)^2 \leq r^2, q = g^T\hat{Q}g > 0, \hat{Q} = \hat{Q}^T\left(\in \boldsymbol{R}^{4\times 4}\right) \succ 0, r > 0\right\} \end{aligned} \tag{43}$$

if $g = e_4$.

A.4. The matrix $\hat{Q} = \hat{Q}^T$ $(\in \boldsymbol{R}^{4\times 4}) \succ 0$ *is such that* $\tilde{x}^T(t)\hat{Q}\tilde{x}(t)$ *is a Lyapunov function for the incremental unforced linearized system* $\dot{\tilde{x}}(t) = A\tilde{x}(t)$ *subject to* $\tilde{x}(0) = \tilde{x}_0 \in \boldsymbol{R}^4_{0+}$, *where* $\tilde{x}(t) = x(t) - x^*$, *about the vaccination-free disease-free equilibrium point.*

The proof of Theorem 3.2 is given in Appendix F. □

4. **Simulation Examples.** This section contains some simulation examples illustrating the behaviour of the time-optimal control developed in Section 3. Initially we will consider the uncertainty-free SEIR model described by the following parameters $\mu^{-1} = 20$ days^{-1}, $\sigma^{-1} = 21$ days^{-1}, $\sigma = \gamma$ and $\beta = 0.1826$ days. The initial conditions are given by $S(0) = 0.9$, $E(0) = 0.05$, $I(0) = 0.01$ and $R(0) = 0.04$ for a total initial population summing up unity. The interpretation of these numerical values relies on the use of a normalized initial population to one while the sum of all the initial subpopulations equalizes to unity. This implies that the particular subpopulations values are easily interpreted as percentages after multiplication by 100. The numerical discussion in terms of percentages or per/unity populations is a common operation procedure in the background literature when discussing the epidemic models versus time. On the other hand, the particular numbers taken for each initial subpopulation keep a reasonable assumption for certain epidemic diseases like, for instance, influenza that most of the population is susceptible (90%) while the initial infection starts with very low numbers of exposed and infectious and the number of initial recovered (or immune) is also typically caused by small numbers.

Now we can define two disease-free equilibrium points given by $V_1^* = 0.0014$ and $V_2^* = 0.0016$ which corresponds to two equilibrium points $P_1 = (0.32, 0, 0, 0.68)$ and $P_2 = (0.25, 0, 0, 0.75)$, respectively. Those disease-free equilibrium points are reachable by the above two given different levels of constant vaccination. From these two equilibrium points, we can define the closed ball for the suitable levels of susceptible subpopulation given by $[S_a, S_b] = [0.22, 0.35]$. The subsequent time-optimal control problem design is formulated as the calculation of the incremental control command necessary to steer the susceptible within this ball in the minimum time interval. That is, we perform the subsequent basic two steps.

Step 1: The basic control command levels define two potential suitable equilibrium points. This part of the design can be performed through the tools of Section 2.

Step 2: We define a suitable ball surrounding those points and then we calculate an incremental bang-bang control which allows to reach the ball in a minimum time. This part of the design can be performed through the tools of Section 3 through Equations (31)-(35) that will be used. The performed various numerical experiments are now described.

Firstly, Figures 1 and 2 show the evolution of the system in the absence of vaccination. Note that, for a whole disease cycle the susceptible subpopulation evolves to the total population through time while exposed, infectious and recovered asymptotically vanish.

Figure 3 shows the evolution of the system when the optimal control law is used with $V_1^* = 0.0014 = \lambda\mu$ and $V_2^* = 0.0016 = \rho\mu$ implying $\lambda = 0.68$ and $\rho = 0.75$. $V(t) = 0$ when $p^T b = 0$ and $p(0)^T = \begin{bmatrix} 10 & -200 & -200 & 10 \end{bmatrix}$. Compared with Figures 1 and 2, note that in the presence of vaccination the final values of the susceptible and immune together equalize the total population while the infected sup-populations still asymptotically vanish. Remember that, in the absence of vaccination, the total population has become asymptotically susceptible. In addition, Figure 4 shows the optimal control command obtained from (36) where it can be seen that there are two switches leading to the minimal time. On the other hand, Figure 5 displays the trajectory of the susceptible for different vaccination functions. In that figure, we can observe that the optimal control drives the

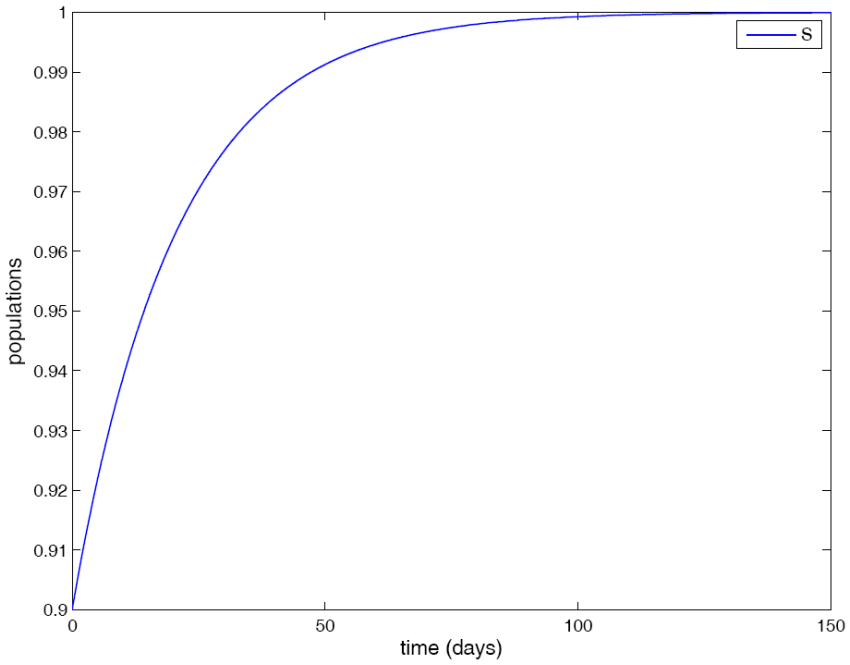

FIGURE 1. Evolution of the susceptible in the absence of vaccination

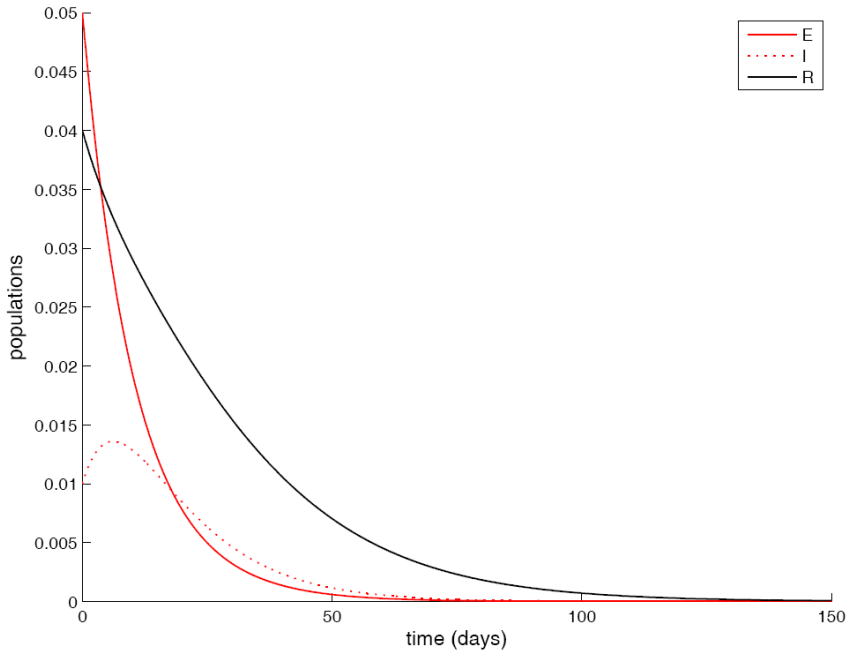

FIGURE 2. Evolution of the infective, infectious and immune in the absence of vaccination

susceptible within the prescribed ball in a minimum time given by 37.42 days. The co-state of the time-optimal trajectory satisfies the constraint $H(T) = 0 = 1 - p_1(T) + p_4(T)$ for a finite positive target time T, or equivalently, $p_1(T) - p_4(T) = 1$. From the numerical simulation we obtained that $p_1(37.42) - p_4(37.42) \approx 1.01$, satisfying the optimality constraint. It has to be pointed out that the so-called minimum time-optimal controls are really approximately optimal, i.e., suboptimal but with an acceptable closeness to the optimal situation, because of the model approximations and the fact that a final ball

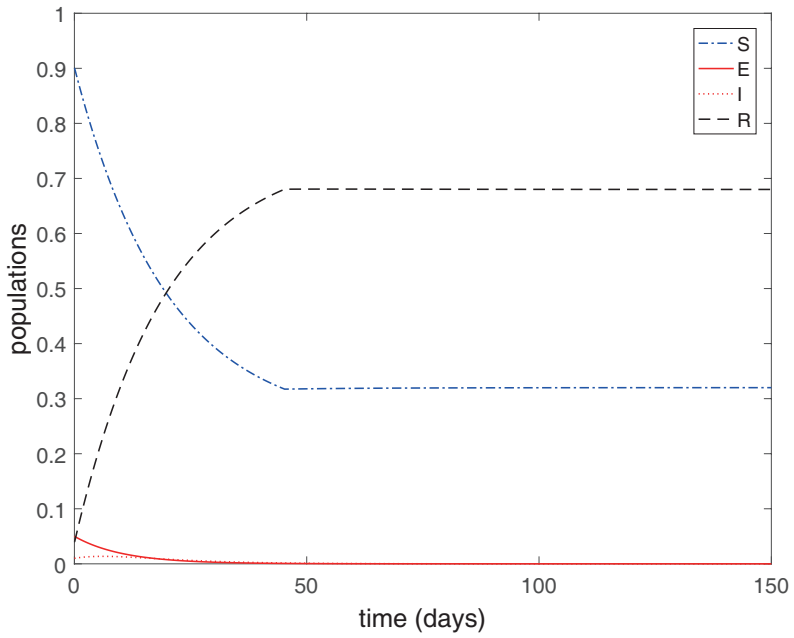

FIGURE 3. Evolution of the system with the bang-bang type vaccination control

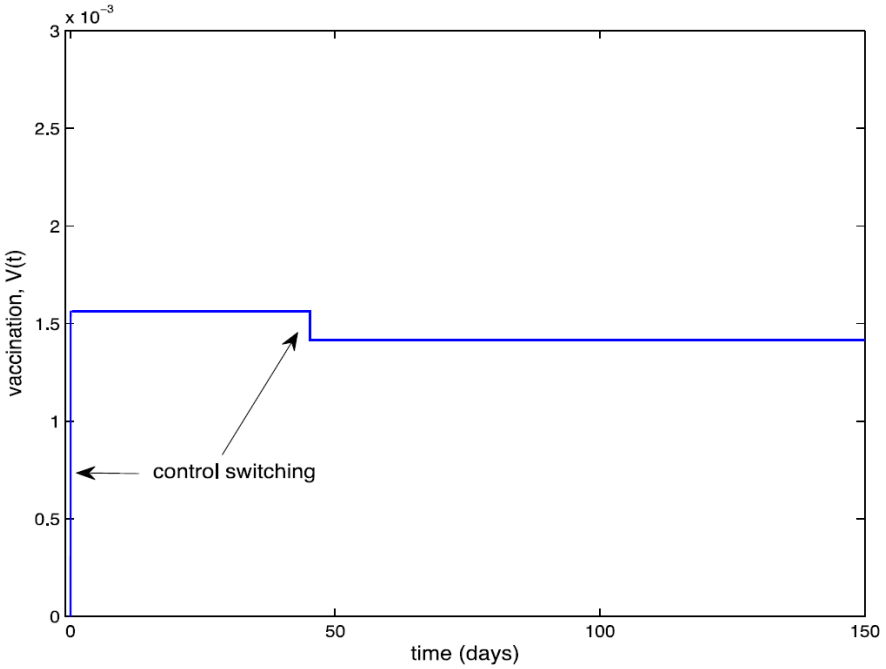

FIGURE 4. Bang-bang type vaccination control

around an equilibrium point or that some final targeted ball including several potential equilibrium points is targeted as an acceptable practical objective.

We may now define a general ball involving all the subpopulations described by:

$$[S_a, S_b] \times [E_a, E_b] \times [I_a, I_b] \times [R_a, R_b] = [0.22, 0.35] \times [0, 0.03] \times [0, 0.03] \times [0.67, 0.75]$$

so that the minimum time will be attained when all the subpopulations lie within their corresponding intervals. In this case, the time needed to make all the subpopulations reach the defined ball is given by the immune, R, as Figure 6 depicts, which is of 42.58 days.

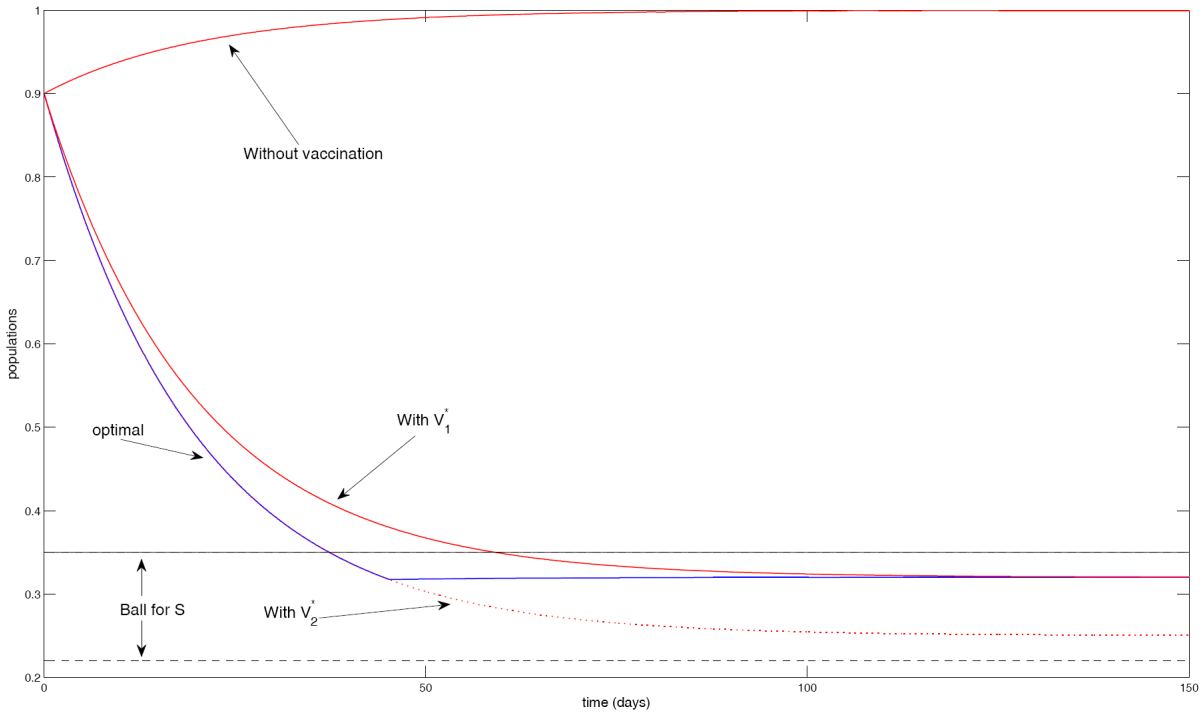

FIGURE 5. Time employed by the system in reaching the closed ball of the susceptible for different control commands

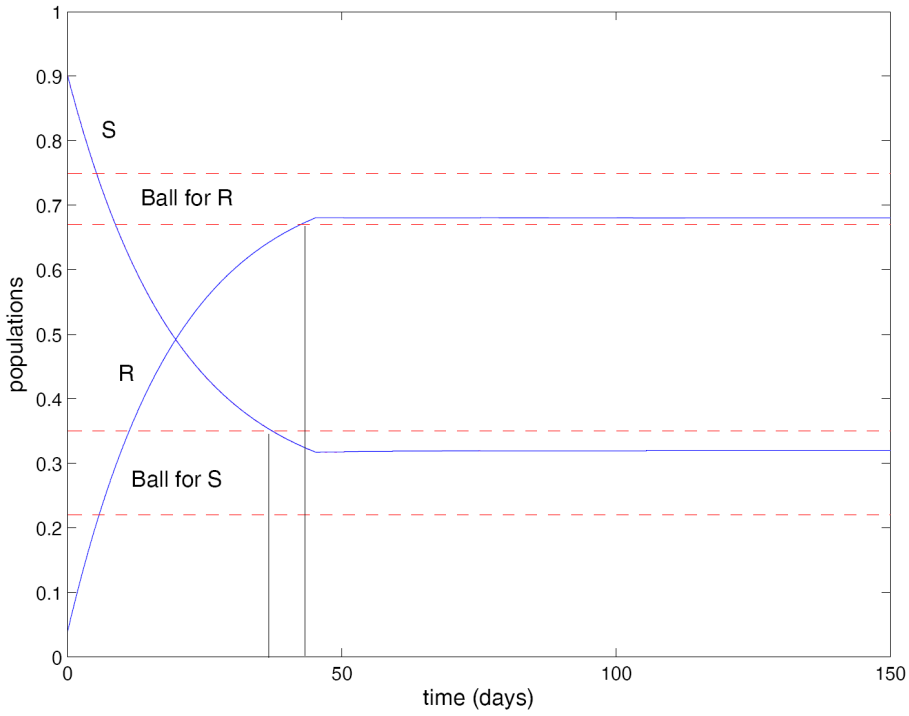

FIGURE 6. Time needed to reach the defined ball for the susceptible and immune subpopulations

Finally, we consider the case when the model suffers from parametric uncertainty. In this way, the actual parameters of the model are given as above but we perform the calculation of the control law as if they were 10% higher. The following Figure 7 displays the optimal control law obtained in this case while Figure 8 shows the evolution of the

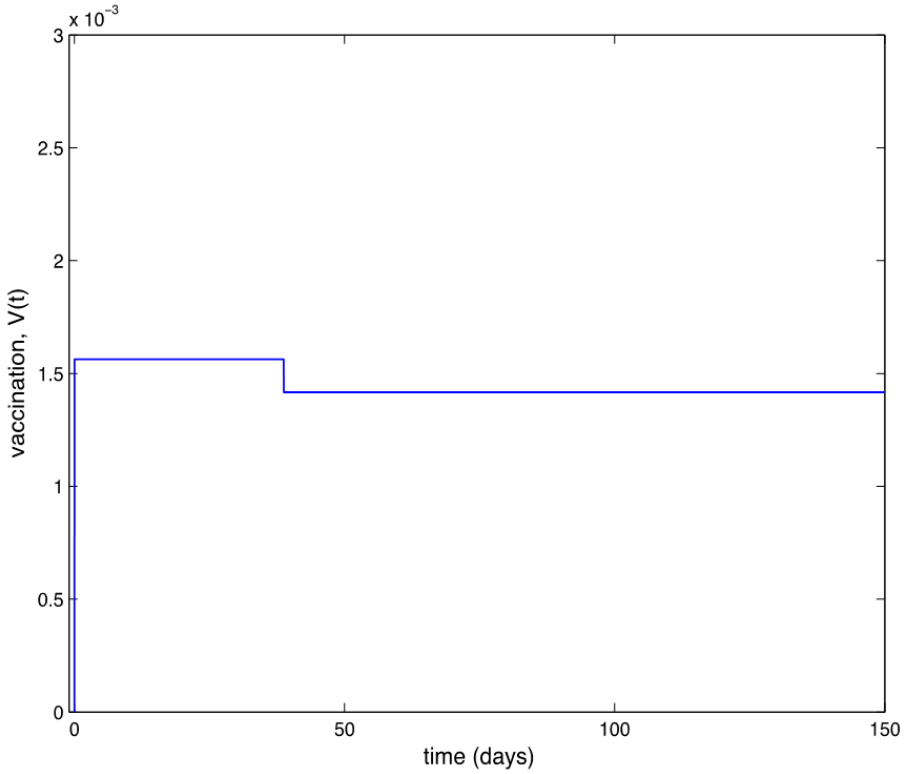

FIGURE 7. Vaccination control law in the presence of uncertainties

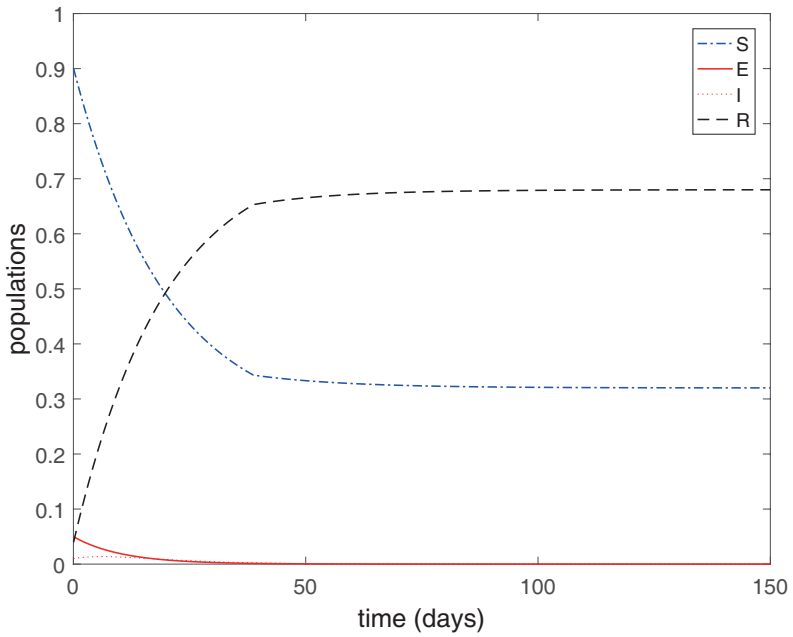

FIGURE 8. Evolution of the solution trajectories in the presence of uncertainties

system's solution trajectories. The time needed to steer the susceptible to the ball given by $[S_a, S_b] = [0.22, 0.35]$ is again of 37.42 days. It can be observed that the proposed optimal control law behaves robustly with respect to (relatively) small parametric uncertainties.

It can be commented that it is not difficult to implement the optimal controls in feedback for such, for instance, as (12), since the costate is related to the state through dynamic equations.

5. **Conclusions.** This paper discusses a time-optimal vaccination control strategy for an SEIR epidemic model with eventual parametrical uncertainties and unmodeled effects which is found to be of bang-bang type. The properties of positivity and stability of the solutions as well as the characterization of the equilibrium points and their stability properties are studied and discussed. The bang-bang vaccination control strategy is stated based on pre-defined design min/max vaccination control levels being compatible with the maintenance of the positivity property and they can be judiciously chosen so that the achievable disease-free equilibrium points under constant vaccination for both controls are found suitable in terms of susceptible and immune achievable equilibrium subpopulations. The time-optimal control objective is formulated in terms of achieving that the state-trajectory solution enters in a minimal time a closed ball of prescribed accuracy radius whose center is defined either by a suitable point joining the segment of both equilibrium points corresponding to the two constant vaccination levels used to define the limits of the optimal bang-bang control. Afterwards, a formulation of the time-optimal control problem is given to drive the state trajectory solution to a prescribed closed neighborhood around a targeted point of interest which can be either an equilibrium point or some point describing closely two equilibrium points corresponding to the two distinct constant vaccination efforts which are used as the min/max values for bang-bang controls. Both constant reference vaccination values are design values being compatible with the positivity of the model and each produces a suitable equilibrium point. The basic idea of the time-optimal control strategy is to minimize the effective disease effects in a minimum time with a prescribed accuracy margin. Some worked simulated examples are then described for the case when the disease transmission rate is small enough so that the disease-free equilibrium points are globally asymptotically stable.

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Appendix A. Proof of Theorem 2.1. Equations (6)-(10) follow directly from the differential systems (1)-(4) and (5). On the other hand, note that the solutions (6)-(10) are everywhere continuous and differentiable. If for some $t \in \boldsymbol{R}_{0+}$, $S(t) = 0$ then $S_u(t) \geq V(t) - \mu$ so that $\dot{S}(t) \geq 0$. As a result, $S : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ if $\min(S_0, I_0) \geq 0$. On the other hand, assume that $E(t) = 0$ and note from (1) and (2) and the first mean value theorem for definite integrals that:

$$\begin{aligned}
&S(t+\varsigma) + E(t+\varsigma) \\
&= e^{-\mu\varsigma}(S(t) + E(t)) + \int_t^{t+\varsigma} e^{-\mu(t+\varsigma-\theta)}(\mu + S_u(\theta) - V(\theta) - \sigma E(\theta) + E_u(\theta))d\theta \\
&\geq \int_t^{t+\varsigma} e^{-\mu(t+\varsigma-\theta)}(\mu + S_u(\theta) - V(\theta) - \sigma E(\theta) + E_u(\theta))d\theta \\
&= e^{-\mu\rho}(\mu + S_u(t+\rho) - V(t+\rho) - \sigma E(t+\rho) + E_u(t+\rho)) < 0
\end{aligned}$$

for some $\rho \in (0, \zeta)$, $\forall \varsigma (\geq t) \in \boldsymbol{R}_{0+}$ implies that, since $S : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$, $E(t+\zeta) < -S(t+\zeta) \leq 0$, $E_u(t+\rho) < V(t+\rho) - \mu - S_u(t+\rho) + \sigma E(t+\rho)$. By making $(\zeta - \rho) \to 0$ and by the continuity of the solution of (1)-(4), it follows that

$$E_u(t+\zeta) < V(t+\zeta) - \mu - S_u(t+\zeta) - \sigma|E(t+\zeta)| \leq V(t+\zeta) - \mu - S_u(t+\zeta).$$

By taking a small enough positive real ζ, we get a contradiction to the constraint $(E(t) = 0) \Rightarrow (E_u(t) \geq V(t) - \mu - S_u(t))$. As a result, $E : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ if $\min(S_0, E_0, I_0) \geq 0$. Now, note from (3) that $[(I(t) = 0) \wedge (I_u(t)) \geq -\sigma E(t)] \Rightarrow (\dot{I}(t) \geq 0)$ so that $I : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ if $\min(S_0, E_0, I_0) \geq 0$. Finally, note from (4) that $[(R(t) = 0) \wedge (R_u(t) \geq -[\gamma I(t) + V(t)])] \Rightarrow (\dot{R}(t) \geq 0)$ and thus $R : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ if $\min(S_0, E_0, I_0, R_0) \geq 0$. Finally, the solution to (5) satisfies $N : \boldsymbol{R}_{0+} \to \boldsymbol{R}_{0+}$ if $\min(S_0, E_0, I_0, R_0) \geq 0$ since all the subpopulations are non-negative for all time. □

Appendix B. Proof of Theorem 2.2. The nominal system is defined by (1)-(4) with total population given by (5) by zeroing the non-nominal contribution to the dynamics. On the other hand, the disease-free equilibrium is given by $x^* = (S^*, E^*, I^*, R^*)^T$ with $(E^* = I^* = 0) \Rightarrow (E_u^* = I_u^* = 0)$ by zeroing the time-derivatives in (2) and (3), where $E_u(t) \to E_u^*$, $I_u(t) = I_u^* \to 0$ as $t \to \infty$. On the other hand, the existence of the real number $\Psi = S_u^* + R_u^*$ of the third assumption implies from (5) that $N(t) \to N^* = 1 + \frac{S_u^* + R_u^*}{\mu}$ as $t \to \infty$ irrespective of the initial conditions. The non-negativity constraints $S_u^* \geq V^* - \mu$ and $R_u^* \geq -V^*$ guarantee that $N^* = S^* + R^* \geq 0$ with $\min(S^*, R^*) \geq 0$. □

Appendix C. Proof of Theorem 2.3. The critical disease transmission rate is given by

$$\begin{aligned}
\beta_{ec} = \frac{(\overline{\mu} + \overline{\gamma})(\overline{\mu} + \overline{\sigma})}{\overline{\sigma}} &= \frac{\left(\mu + \gamma - K_{Iu}^* + K_{IE}^{*-1}(\mu_V^* - K_{Eu}^*)\right)(\mu + \sigma - K_{Eu}^*)}{\sigma + \mu_V^* - K_{Eu}^*} \\
&= \frac{\left(\mu + \gamma - K_{Iu}^* + K_{IE}^{*-1}(K_{Su}^* - K_V^* - K_{Eu}^*)\right)(\mu + \sigma - K_{Eu}^*)}{\sigma + K_{Su}^* - K_V^* - K_{Eu}^*}
\end{aligned}$$

if $K_{IE}^* \neq 0$ which holds since the assumption $K_{Iu}^* \neq \mu + \gamma$ implies that $-\infty < K_{IE}^* = \frac{I^*}{E^*} = \frac{\sigma}{\mu + \gamma - K_{Iu}^*} < \infty$ from (2) and (3) at the endemic equilibrium point. Also, note that Equations (1)-(4) give the following additional constraints at the endemic equilibrium

point:

$$S^* = \frac{\mu - \mu_V^*}{\mu + \beta K_{IE}^* E^* + K_V^* - K_{Su}^*} = \frac{\mu + \sigma - K_{Eu}^*}{\beta K_{IE}^*} = \frac{(\mu + \sigma - K_{Eu}^*)(\mu + \gamma - K_{Iu}^*)}{\beta\sigma}$$
$$R^* = \frac{\gamma K_{IE}^* E^* + K_V^* S^* + \mu_V^*}{\mu - K_{Ru}^*}$$

Now, by zeroing the time-derivatives in (1)-(4) and taking account of the limit vaccination from (12), it follows under the given assumptions that

$$\begin{aligned}
&\mu - \mu_V^* - (\beta I^* + \mu - \mu_V^*) S^* = 0 \\
&- (\mu - \mu_V^* + \sigma + \mu_V^* - K_{Eu}^*) E^* + \beta I^* S^* = 0 \\
&- (\mu - \mu_V^* + \gamma + \mu_V^* - K_{Iu}^* + (\overline{\sigma} - \sigma)/K_{IE}^*) I^* + \overline{\sigma} E^* = 0 \\
&\overline{\gamma} I^* - (\mu - \mu_V^* + \mu_V^* - K_{Ru}^* - K_R^* + (\overline{\gamma} - \gamma)/K_{RI}^*) R^* = 0 \\
&V^* = K_V^* S^* + \mu_V^*
\end{aligned} \tag{C1}$$

The endemic equilibrium components for the perfectly modelled system in the absence of vaccination parameterized by μ, σ, γ and β are obtained in [2]. Thus, by redefining the model parameterization with the parametrical replacements $\mu \to \overline{\mu}$, $\sigma \to \overline{\sigma}$ and $\gamma \to \overline{\gamma}$, Equation (15), assumed to be positive, the effects of the limit non-nominal dynamics as well as the feedback vaccination control are re-absorbed in the standard SEIR model which has a unique endemic equilibrium (14) which exists if the basic reproduction number exceeds unity. Otherwise, it has some negative components and it does not exist if it is less than unity, or it is just the disease-free equilibrium point with null infection if it equalizes unity. □

Appendix D. Proof of Theorem 2.4. By convenience, we first prove Property (iii) since it is direct. Since $\limsup_{t\to\infty} \left(\int_0^t e^{\mu\theta} N_u(\theta) d\theta - M e^{\mu t} \right) \leq 0$, $0 \leq N(t) < +\infty$; $\forall t \in \boldsymbol{R}_{0+}$ for any finite initial conditions and from Remark 2.1 (see also Theorem 2.1), all the subpopulations are non-negative for all time under non-negative initial conditions and bounded since the total population is bounded for all time. So, the epidemic model is globally stable for any finite non-negative initial conditions and any disease transmission rates. Property (iii) has been proved.

On the other hand, for a constant vaccination control $V^* \in [0, \mu + S_u^*] \cap [-R_u^*, \infty)$ ($V* \in [0, \mu]$ if $S_u^* = R_u^*$), see Remark 2.1, the disease-free equilibrium point is $\left(\frac{\mu + S_u^* - V^*}{\mu}, 0, 0, \frac{R_u^* + V^*}{\mu} \right)^T$ according to (11). By inspection of the resulting Jacobian matrix with respect to the disease-free equilibrium point (1)-(4) and the use of (15), it follows directly that its matrix of dynamics is given by (18). Such a matrix can be rewritten equivalently by using (15) as follows

$$\begin{aligned}
A_{df}^* &= A_{df0}^* + \Delta_{df} = A_{df0}^* \left(\boldsymbol{I}_4 + A_{df0}^{*-1} \Delta_{df} \right) \\
&= \begin{bmatrix}
-(\mu^* + K_V^*) & 0 & -\beta S_{df}^* & 0 \\
0 & -(\mu^* + \sigma^*) & \beta S_{df}^* & 0 \\
0 & \sigma^* + K_{Eu}^* - K_{Su}^* & -(\mu^* + \gamma^*) & 0 \\
K_V^* & 0 & \gamma^* + K_{Iu}^* - K_{Su}^* & -(\mu^* + K_{Su}^* - K_{Ru}^*)
\end{bmatrix}
\end{aligned}$$

$$= \begin{bmatrix} -\overline{\mu} & 0 & -\beta S_{df}^* & 0 \\ 0 & -(\overline{\mu}+\overline{\sigma}) & \beta S_{df}^* & 0 \\ 0 & \begin{matrix}\overline{\sigma}+K_V^* \\ +K_{Eu}^*-K_{Su}^*\end{matrix} & \begin{matrix}-\left(\overline{\mu}+\overline{\gamma}+K_{IE}^{*-1}\left(K_V^*\right.\right. \\ \left.\left.+K_{Eu}^*-K_{Su}^*\right)\right)\end{matrix} & 0 \\ K_V^* & 0 & \begin{matrix}\overline{\gamma}+K_V^*+K_{Iu}^*-K_{Su}^* \\ +K_{IE}^{*-1}\left(K_V^*+K_{Eu}^*-K_{Su}^*\right)\end{matrix} & \begin{matrix}-(\overline{\mu}-K_V^* \\ +K_{Su}^*-K_{Ru}^*)\end{matrix} \end{bmatrix} \quad \text{(D1)}$$

$$A_{df}^* = \begin{bmatrix} -(\mu+K_V^*-K_{Su}^*) & 0 & -\beta S_{df}^* & 0 \\ 0 & -(\mu+\sigma-K_{Eu}^*) & \beta S_{df}^* & 0 \\ 0 & \sigma & -(\mu+\gamma-K_{Iu}^*) & 0 \\ K_V^* & 0 & \gamma & -(\mu-K_{Ru}^*) \end{bmatrix}$$

The matrix A_{df}^* is decomposable as a sum of a stability, then non-singular, lower triangular matrix A_{df0}^* with negative eigenvalues $-(\mu^*+K_V^*)$, $-(\mu^*+\sigma^*)$, $-(\mu^*+\gamma^*)$ and $-(\mu^*)$ plus a perturbation matrix Δ_{df}

$$A_{df0}^* = \begin{bmatrix} -(\mu^*+K_V^*) & 0 & 0 & 0 \\ 0 & -(\mu^*+\sigma^*) & 0 & 0 \\ 0 & \sigma^* & -(\mu^*+\gamma^*) & 0 \\ K_V^* & 0 & \gamma^* & -(\mu^*) \end{bmatrix} \quad \text{(D2)}$$

$$\Delta_{df} = \begin{bmatrix} 0 & 0 & -\beta S_{df}^* & 0 \\ 0 & 0 & \beta S_{df}^* & 0 \\ 0 & K_{Eu}^*-K_{Su}^* & 0 & 0 \\ 0 & 0 & K_{Iu}^*-K_{Su}^* & K_{Ru}^*-K_{Su}^* \end{bmatrix} \quad \text{(D3)}$$

Thus, one has that

$$A_{df}^* = A_{df0}^* + \Delta_{df} = A_{df0}^*\left(I + A_{df0}^{*^{-1}}\Delta_{df}\right) = \left(A_{df}^* - \Delta_{df}\right)\left(\boldsymbol{I}_4 + A_{df0}^{*^{-1}}\Delta_{df}\right) \quad \text{(D4)}$$

is non-singular, and thus a stability matrix, if the condition

$$\begin{aligned} 1 &> \frac{\max\left(\sqrt{2}\beta S_{df}^* + \left|K_{Iu}^*-K_{Su}^*\right|, \left|K_{Eu}^*-K_{Su}^*\right|, \left|K_{Ru}^*-K_{Su}^*\right|\right)}{\min\left(\mu^*, \mu^*+K_V^*, \mu^*+\sigma^*, \mu^*+\gamma^*\right)} \\ &\geq \max\left(\sqrt{2\beta^2 S_{df}^{*2}+\left(K_{Iu}^*-K_{Su}^*\right)^2}, \left|K_{Eu}^*-K_{Su}^*\right|, \left|K_{Ru}^*-K_{Su}^*\right|\right)\left\|A_{df0}^{*^{-1}}\right\|_2 \\ &\geq \left\|A_{df0}^{*^{-1}}\right\|_2 \|\Delta_{df}\|_2 \end{aligned} \quad \text{(D5)}$$

holds. Such a condition guarantees that it has no eigenvalue at the complex imaginary axis, then no eigenvalue exists on the positive real complex half-plane since the eigenvalues are continuous functions of the matrix entries. By using (15a), since $\mu > \max\left(K_V^*-K_{Su}^*, \sigma-K_{Eu}^*, \gamma-K_{Iu}^*, K_{Su}^*\right)$ the above condition holds if

$$1 > \frac{\max\left(\sqrt{2}\beta S_{df}^* + \left|K_{Iu}^*-K_{Su}^*\right|, \left|K_{Eu}^*-K_{Su}^*\right|, \left|K_{Ru}^*-K_{Su}^*\right|\right)}{\mu + \min\left(K_V^*-K_{Su}^*, \sigma-K_{Eu}^*, \gamma-K_{Iu}^*, -K_{Su}^*\right)} \quad \text{(D6)}$$

Such a condition is guaranteed if $\beta \in [\beta_{dc0}, \beta_{dc1}]$ under (21a) holds, or if $\beta \in [0, \beta_{dc2}]$ under (21b) holds since $S_u(t) = K_{Su}(t)S(t)$, $E_u(t) = K_{Eu}(t)E(t)$, $I_u(t) = K_{Iu}(t)I(t)$ and $R_u(t) = K_{Ru}(t)R(t)$ such that $K_{Su}(t) \to K_{Su}^*$, $K_{Eu}(t) \to K_{Eu}^*$, $K_{Iu}(t) \to K_{Iu}^*$ and $K_{Ru}(t) \to K_{Ru}^*$ as $t \to \infty$ together with the vaccination (12) with the given constrained

gain limits and (11) implies that $S_{df}^{*}=\frac{\mu-\mu_{V}^{*}}{\mu+K_{V}^{*}-K_{Su}^{*}}$. Then, (21) guarantees that the disease-free equilibrium point is locally asymptotically stable since its linearized version is locally asymptotically stable. For the linearization around the endemic equilibrium point, we define $\delta\left(\overline{R}_{0}\right)=\left\{\begin{array}{ll}0 & \text{if } \beta\leq\beta_{ec}\\ 1 & \text{if } \beta>\beta_{ec}\end{array}\right.$ from (20) since the endemic equilibrium point does not exist if $\beta\leq\beta_{ec}$ and $\overline{R}_{0}\leq 1$ while it exists if $\beta>\beta_{ec}$ (Theorem 2.3) so that we obtain the matrix of linearized dynamics (19). One gets from (18)-(20) that

$$A_{end}^{*}\left(\overline{R}_{0}\right)=A_{df}^{*}+\Delta_{end}\left(\overline{R}_{0}\right)=A_{df0}^{*}+\Delta_{end0}\left(\overline{R}_{0}\right) \tag{D7}$$

$$=A_{df}^{*}\left(\boldsymbol{I}_{4}+A_{df}^{*^{-1}}\Delta_{end}\left(\overline{R}_{0}\right)\right)=A_{df0}^{*}\left(\boldsymbol{I}_{4}+A_{df0}^{*^{-1}}\Delta_{end0}\left(\overline{R}_{0}\right)\right) \tag{D8}$$

where:

$$\Delta_{end}\left(\overline{R}_{0}\right)=\left[\begin{array}{cccc}-\beta I_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0 & -\beta\left(S_{end}^{*}\delta\left(\overline{R}_{0}\right)-S_{df}^{*}\right) & 0\\ \beta I_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0 & \beta\left(S_{end}^{*}\delta\left(\overline{R}_{0}\right)-S_{df}^{*}\right) & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\end{array}\right] \tag{D9}$$

$$\Delta_{end0}\left(\overline{R}_{0}\right)=\left[\begin{array}{cccc}-\beta I_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0 & -\beta S_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0\\ \beta I_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0 & \beta S_{end}^{*}\delta\left(\overline{R}_{0}\right) & 0\\ 0 & K_{Eu}^{*}-K_{Su}^{*} & 0 & 0\\ 0 & 0 & K_{Iu}^{*}-K_{Su}^{*} & K_{Su}^{*}-K_{Ru}^{*}\end{array}\right] \tag{D10}$$

If there is no non-nominal contribution in the model (1)-(4) then $\overline{\mu}=\mu$, $\overline{\sigma}=\sigma$, $\gamma=\overline{\gamma}$ and $\overline{R}_{0}=R_{0}=1$. Thus, if A_{df}^{*} is a stability matrix, then non-singular, one has that the asymptotic linearized dynamics about the endemic equilibrium point satisfying the constraints:

$$A_{end}^{*}(1)=A_{df}^{*}+\Delta_{end}(1)=A_{df}^{*}\left(I+A_{df}^{*^{-1}}\Delta_{end}(1)\right)=A_{df0}^{*}\left(I+A_{df0}^{*^{-1}}\Delta_{end0}(1)\right)$$

is non-singular and then stable since the eigenvalues are continuous functions of the matrix entries if $\beta>\beta_{ec}$ with $1>\sqrt{2}\beta S_{df}^{*}\left\|A_{df0}^{*^{-1}}\right\|_{2}$ and $\max\left(\left|K_{Iu}^{*}-K_{Su}^{*}\right|,\left|K_{Eu}^{*}-K_{Su}^{*}\right|,\left|K_{Ru}^{*}-K_{Su}^{*}\right|\right)\leq\beta_{ec}S_{df}^{*}$ since $1>\sqrt{2}\beta S_{df}^{*}\left\|A_{df0}^{*^{-1}}\right\|_{2}>\sqrt{2}\max\left(\left|K_{Iu}^{*}-K_{Su}^{*}\right|,\left|K_{Eu}^{*}-K_{Su}^{*}\right|,\left|K_{Ru}^{*}-K_{Su}^{*}\right|\right)\geq\left\|A_{df}^{*^{-1}}\right\|_{2}\left\|\Delta_{end}(1)\right\|_{2}$.

It is now proved that, furthermore, there is no limit cycle. Note the following features on the asymptotic version of (1)-(4) when all the control gains converge asymptotically.

1) A limit cycle can only surround a set of singular points if they have a net $PI=1$. If there is a limit cycle it cannot jointly surround both the disease-free equilibrium point and endemic equilibrium point since the net Poincaré index of both together would be either $PI=0$ if only one of them is saddle point while the other is not, $PI=-2$ if both of them are saddle points and $PI=2$ if none of them is a saddle point.

2) A limit cycle cannot surround the disease-free equilibrium point since it turns out from inspection in (1)-(4) that any existing oscillatory solution has to exist in any state component and it is impossible that this happens in the exposed and infected subpopulations around the disease-free equilibrium since negative values are not compatible art any time with the non-negativity property of the solution.

3) As a consequence of the above two features, it follows that any stable, unstable or semi-stable existing limit cycle could only surround the endemic equilibrium point. For $\beta\leq\beta_{ec}$ the endemic equilibrium does not exist. For $\beta>\beta_{c}$ the endemic equilibrium is locally asymptotically stable so that such a limit cycle, in case of existence, would

be unstable being only relevant to separate stability and instability regions. However, then, the disease-free equilibrium point should also be locally asymptotically stable and $\beta_{dc} \geq \beta_{ec}$, $\beta \in (\beta_c, \beta_{dc})$, where β_{dc} is the maximum threshold of the transmission rate guaranteeing the stability of the disease-free equilibrium, i.e., either β_{dc1} or β_{dc2} in (21b). This is impossible if $\beta \in (\beta_{dc}, \beta_{ec})$ and $\beta_{ec} \geq \beta_{dc}$. So, there is no limit cycle surrounding any of the two equilibrium points and they are not jointly locally unstable. The proof that they are not jointly locally asymptotically stable is developed in [3] for a model with delays and can be directly particularized to the current model. Properties (ii) and (iii) have been fully proved. □

Appendix E. Proof of Theorem 3.1 (ii). Again, under the given conditions, the disease-free equilibrium point is globally asymptotically stable for any $V(t) \to V^* \in [0, \mu)$ as $t \to \infty$. On the other hand, if $V^* = \lambda\mu$ then $x^*_{df} = x^*_1$ and if $V^* = \rho\mu$ then $x^*_{df} = x^*_2$.

To prove Property (ii), we discuss two possible cases which can arise, namely:

Case a) If $\overline{B}(x^*_1, r_0) \cap \overline{B}(x^*_2, r_0) \neq \emptyset$ then $x^* = x^*_1 \oplus x^*_2$. Thus, for any existing open time interval (t_1, t_2) of nonzero measure, if any, such that $(p^{o^T}(t)b = 0) \Leftrightarrow (p^o_1(t) = p^o_4(t))$ for all $t \in (t_1, t_2)$ with $p^o_1(t_1^-) \neq p^o_4(t_1^-)$ and $p^o_1(t_2) \neq p^o_4(t_2)$, there is no incremental control switch activated on $[t_1, t_2)$ so that $u^o(t) = u^o(t_1^-)$; $\forall t \in [t_1, t_2)$.

Case b) If $\overline{B}(x^*_1, r_0) \cap \overline{B}(x^*_2, r_0) = \emptyset$ and (t_1, t_2) is a time interval of nonzero measure as in Case a then there is no incremental control switch activated on (t_1, t_2), so that $u^o(t) = u^o(t_1)$; $\forall t \in (t_1, t_2)$ and there is a control switch at $t = t_1$ only if $x^* = x^*_1$, which is implied by $x^* = x^*_1 \oplus x^*_2$ and $\overline{B}(x^*_1, r_0) \cap \overline{B}(x^*_2, r_0) = \emptyset$ since $x^*_2 \notin \overline{B}(x^*_1, r_0) \cap \overline{B}(x^*_2, r_0)$, and $u^o(t_1^-) = u^0_2(t_1^-)$ or if $x^* = x^*_2$ and $u^o(t_1^-) = u^0_1(t_1^-)$ with $u^o_1(t) = \lambda\mu - V_0$ or $u^o_2(t) = \rho\mu - V_0$; $\forall t \in \boldsymbol{R}_{0+}$ since $u^o(t) \equiv u^o_1(t) \oplus u^o_2(t)$; $\forall t \in \boldsymbol{R}_{0+}$. That is, the last switch on $[0, t_2)$ happened at $t = t_1$ only in the case that in the absence of control switching the convergence to the disease-free equilibrium point was not possible.

As a result, the optimal-time incremental and vaccination controls with a (finite) minimum number of switches and its associated Hamiltonian are unique via (35) and (36) in both Case a and Case b and the optimal-time $T^o < +\infty$ to reach the compact and convex region P is unique for each given quintuple $(V_0, x_0, v^o, \lambda, \rho)$. □

Appendix F. Proof of Theorem 3.2. Since $\tilde{x}^T(t)\hat{Q}\tilde{x}(t)$ is a Lyapunov function then $\dot{\tilde{x}}^T(t)\hat{Q}\tilde{x}(t) = \tilde{x}^T(t)\hat{Q}A\tilde{x}(t) < 0$ for all nonzero $\tilde{x}(t) \in \boldsymbol{R}^4$ with $\hat{Q} = \hat{Q}^T \succ 0$. It is well-known that the linearized epidemic model is not controllable since the whole state cannot be steered in finite-time from any arbitrary given set of admissible initial conditions to a prefixed value as it becomes obvious since the controllability matrix is rank-defective. It is output-controllable if the output is defined as the susceptible subpopulation or the recovered subpopulation. It is well-known [4] that the state-trajectory solution of uncontrollable time-invariant systems cannot be reversed in time from final conditions to reduce the optimal solution of state and costate to an equivalent problem of initial conditions so that the problem is not so-called a normal problem. Consider with no loss of generality the situation with targeted final output (i.e., the susceptible subpopulation targeted value) in the set P_S (42), that is, $g = e_1$. Note that $v_a^T\hat{Q}v_a \geq v_a^T\hat{Q}v_b$ and $v_a^T v_a \geq v_a^T v_b$, and $S_a^T q S_a = S_b^T q S_b = qS_a^2 = qS_b^2 = r^2$ for any $S_a, S_b \in \partial P_S$ and $T^o \geq 0$ and $qS_aS_b \leq qS_b^2$ with the equality holding if and only if $S_a = S_b = \frac{r}{q} \in \partial P_S$ and $qS_aS_b < qS_b^2$, equivalently $S_b > S_a$, for any $S_b \in \partial P_S$ if $S_a \in P_S^0$. It is firstly proved by contradiction arguments that the extremal controls which steer any given admissible initial conditions to P_S are unique. It is well-known (see, for instance, [4]) that the optimal-time control of a time-invariant system satisfies $u(T-t) = -sgn\left(qb^T e^{A^T(T-t)}e_1 v\right)$ with

$v = x(T)$ for any $t \in [0,T]$ if $x(\tau = T - t = 0) = v(\neq 0)$ since from the problem normality $b^T e^{A^T(T-t)} e_1 v \neq 0$; $\forall t \in [0,T]$ and any $T \in \overline{\boldsymbol{R}}_{0+}$ $(= cl\boldsymbol{R}_{0+} = \boldsymbol{R}_{0+} \cup \{+\infty\})$. See also Remark 3.4 arguing that the choice of the control parameters according to $\rho = \lambda + \frac{2}{\mu}$ leads to a ± 1 bang-bang optimal incremental control. Assume that there exist two extremal incremental controls u_a^o, $u_b^o\,(\neq u_a^o)$ which steer the state from some given x_0 to a susceptible subpopulation $v_a \in \partial P_S$ at T_a^o and to $v_b \in \partial P_S$ at $T_b^o\,(\leq T_a^o)$. Then,

$$u_a^o(\tau) = -sgn\left(b^T e^{A^T(T_a^o - t)} e_1 S_a\right) = -sgn\left(qb^T e^{A^T(T_a^o - t)} e_1 S_a\right); \quad \forall t \in [0, T_a^o]$$

$$u_b^o(\tau) = -sgn\left(b^T e^{A^T\left(T_b^o - t\right)} e_1 S_b\right) = -sgn\left(qb^T e^{A^T\left(T_b^o - t\right)} e_1 S_b\right); \quad \forall t \in [0, T_b^o]$$

since, $q > 0$, and since $v_a^T e^{-AT_a^o} v_a \geq v_a^T e^{-AT_b^o} v_b$, then

$$e_1^T e^{-AT_a^o} e_1 S_a^2 - S_a \int_0^{T_a^o} e_1^T e^{-A\tau} b u_a^o(\tau) d\tau = e_1^T e^{-AT_b^o} e_1 S_a S_b - S_a \int_0^{T_b^o} e_1^T e^{-A\tau} b u_b^o(\tau) d\tau \quad \text{(F1)}$$

and, since $(-A)$ is antistable, this implies that

$$\begin{aligned} & - S_a \int_0^{T_a^o} e_1^T e^{-A\tau} b u_a^o(\tau) d\tau \\ = & - S_a \int_0^{T_b^o} e_1^T e^{-A\tau} b u_b^o(\tau) d\tau + e_1^T S_a e^{-AT_b^o} e_1 \left(S_b \boldsymbol{I}_4 - e^{A\left(T_b^o - T_a^o\right)} S_a\right) \\ \geq & - S_a \int_0^{T_b^o} e_1^T e^{-A\tau} b u_b^o(\tau) d\tau - \int_0^{T_a^o} q S_a e_1^T e^{-A\tau} b u_a^o(\tau) d\tau \\ \geq & - \int_0^{T_b^o} q S_a e_1^T e^{-A\tau} b u_b^o(\tau) d\tau \end{aligned} \quad \text{(F2)}$$

and hence

$$- \int_0^{T_a^o} q S_a e_1^T e^{A\left(T_a^0 - \tau\right)} b u_a^o(\tau) d\tau \geq - \int_0^{T_b^o} q S_a e_1^T e^{A\left(T_a^0 - \tau\right)} b u_b^o(\tau) d\tau \quad \text{(F3)}$$

since $T_b^o \leq T_a^o$, and

$$- \int_{T_b^o}^{T_a^o} q S_a e_1^T e^{A\left(T_a^0 - \tau\right)} b u_a^o(\tau) d\tau = \int_{T_b^o}^{T_a^o} q \left| S_a e_1^T e^{A\left(T_a^0 - \tau\right)} b \right| d\tau > 0 \quad \text{(F4)}$$

On the other hand, one gets from (F1) that

$$\begin{aligned} & q S_a^2 - \int_0^{T_a^o} q S_a e^{A\left(T_a^0 - \tau\right)} b u_a^o(\tau) d\tau - \int_0^{T_b^o} q S_a e^{A\left(T_a^0 - \tau\right)} b u_a^o(\tau) d\tau \\ & = q S_a S_b e^{A\left(T_a^o - T_b^o\right)} - \int_0^{T_b^o} q S_a e^{A\left(T_a^0 - \tau\right)} b u_b^o(\tau) d\tau \end{aligned} \quad \text{(F5)}$$

which contradicts $q S_a S_b \leq q S_b^2$, (F3) and (F4), unless $S^o = S_a = S_b \in \partial S$ and $T^o = T_a^o = T_b^o$. □