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# Population dynamics of live-attenuated virus vaccines

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ABSTRACT

Viruses contained in live-attenuated virus vaccines (LAVV) can be transmitted between individuals, resulting in secondary or *contact vaccinations*. This fact has been exploited successfully in the use of the Oral Polio Vaccine (OPV) to better control wild-type polio viruses. In this work we analyze general LAVV vaccination models for infections that confer lifelong immunity. We consider both standard (continuous) vaccination strategies and pulse vaccination programs (where mass vaccination is carried out at regular intervals). For continuous vaccination, we provide a complete global analysis of a very general compartmental ordinary differential equation LAVV model. We find that the threshold vaccination level required for the eradication of wild-type virus depends on the basic reproduction numbers of both the wild-type and vaccine viruses, but is otherwise independent of the distributions of the durations in each of the sequence of stages of disease progression (e.g., latent, infectious, *etc.*). Furthermore, even for vaccine viruses with reproduction numbers below one, which would naturally fade from the population upon cessation of vaccination, there can be a significant reduction in the threshold vaccination level. The dependence of the threshold vaccination level on the virus reproduction numbers largely generalizes to the pulse vaccination model. For shorter pulsing periods there is negligible difference in threshold vaccination level as compared to continuous vaccination campaigns. Thus, we conclude that current policy in many countries to employ annual pulsed OPV vaccination does not significantly diminish the benefits of contact vaccination.



## 1. Introduction

Both currently and historically live-attenuated virus vaccines (LAVV) have been employed against a wide range of viral diseases. Examples include the smallpox vaccine, the Oral Polio Vaccine (OPV), measles vaccine, and HIV vaccines currently under development (Blower et al., 2001; Woodrow and Levine, 1990).

Unlike an inactivated vaccine, a LAVV is a functioning, replicating virus that has been significantly reduced in virulence and transmissibility through the attenuation process. Typically this attenuation is achieved by passing the virus through a sequence of animal host tissues where there is selective pressure for mutations that reduce its virulence (Woodrow and Levine, 1990).

The transmission of LAVVs, so-called inadvertent or *contact vaccinations* is the focus of this work. Although the transmissibility of LAVVs is significantly reduced compared with native or virulent forms, it has long been recognized that LAVV transmission can be sufficient to have an important effect on the epidemiological dynamics at the population level. The World Health Organization (WHO) has cited contact vaccination as one of the five primary reasons for the use of OPV in the developing world (Hull et al., 1994; John, 2004). In this case it is seen as a benefit, as the transmission of vaccine virus lowers the proportion of the population that must be directly vaccinated to control the spread of the wild-type virus.

Contact vaccination may have played an important role in leading to the eradication of smallpox in the 1970s. However, observed smallpox contact vaccination (Neff et al., 2002) is currently viewed negatively because it implies a risk of serious allergic reaction in individuals who have not chosen to be vaccinated. In addition, as for any LAVV, the smallpox vaccine virus has the potential to mutate and thereby revert to the original wild-type form (Woodrow and Levine, 1990). The potential to re-introduce an eradicated pathogen makes contact vaccination a very dangerous risk in this case.

We focus our attention specifically on LAVV vaccination for infectious diseases that generally confer lengthy or lifelong immunity to the infecting pathogen. These include not only polio and smallpox, but also childhood infectious diseases such as measles, mumps, rubella and pertussis. We investigate the significance of the role of contact vaccination in decreasing the required vaccination coverage to control pathogenic wild-type virus spread, specifically deriving analytical expressions for the critical

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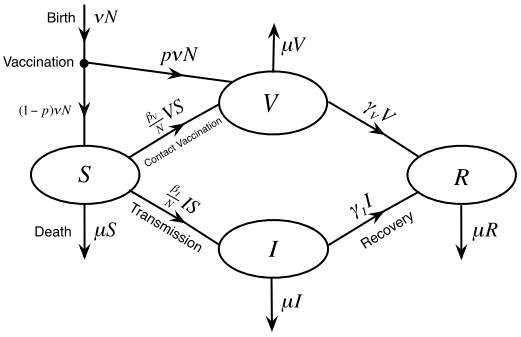


**Fig. 1.** Flow diagram for the SIVR model, the simplest LAVV model. The population size is $N$. The ODE formulation of this model is given, in terms of *proportions* of the population, by system (1).

vaccination coverage levels in terms of epidemiologically measurable quantities.

The first part of our analysis deals with LAVV programs in which vaccination takes place continuously. We begin by presenting the simplest LAVV models, which are variants of the standard Susceptible-Infected-Removed (SIR) and Susceptible-Exposed-Infectious-Removed (SEIR) models; we then proceed to expand the results to a very general staged progression model, which among other things allows us to examine more realistically distributed latent and infectious periods for both the wild-type and vaccine viruses.

The second part of our analysis deals with pulse vaccination LAVV programs. In such programs mass vaccinations are performed at regular time intervals. This analysis has particular relevance to polio, as some form of annual pulse OPV campaign is currently in use in 55 countries around the globe (Anon, 2008).

Throughout this work we make the simplifying assumption that the vaccine virus cannot undergo reversion (a return to its virulent form via mutation). While this ignores a potentially critical biological process, we have previously shown that reversion is likely to contribute significantly to the population dynamics of the pathogen only if cessation of vaccination is planned within a few years (Wagner and Earn, 2008). Since we do not consider this "endgame" in this paper, ignoring reversion does not represent a significant approximation.

Some previous mathematical modelling of LAVV transmission has been carried out for HIV (Blower et al., 2001) and OPV (Eichner and Hadeler, 1995). In the case of HIV, LAVV transmission was investigated in the context of an imperfectly attenuated vaccine, which – in addition to having limited efficacy – had the potential to cause the disease itself, irrespective of reversion. In the case of OPV, a simple LAVV model was formulated and a partial local analysis performed (Eichner and Hadeler, 1995); a full global analysis of this OPV model is a special case of the general results we derive in the following sections.

A list of symbols used in this article is presented in Table 1.

## 2. LAVV models

The simplest LAVV model is based on the standard SIR model (Anderson and May, 1991; Hethcote, 2000) and can be represented as a flow chart (Fig. 1) or as a set of coupled ordinary differential equations (ODEs),

$$\frac{dS}{dt} = (1-p)\nu - \beta_I IS - \beta_V VS - \nu S \tag{1a}$$

$$\frac{dI}{dt} = \beta_I IS - (\nu + \gamma_I)I \tag{1b}$$

$$\frac{dV}{dt} = p\nu + \beta_V VS - (\nu + \gamma_V)V \tag{1c}$$

$$\frac{dR}{dt} = \gamma_I I + \gamma_V V - \nu R. \tag{1d}$$

The host population is split into homogeneous classes representing the proportions of individuals who are susceptible ($S$), infectious with wild-type virus ($I$), infectious with attenuated vaccine virus ($V$) or immune ($R$). The parameters $\beta_I$, $\beta_V$, $\frac{1}{\gamma_I}$ and $\frac{1}{\gamma_I}$ represent the transmission rates and mean infectious periods for the wild-type and vaccine viruses, respectively. In the flow chart, both birth (at *per capita* rate $\nu$) and natural death (at *per capita* rate $\mu$) are shown. However, because Eq. (1) is written in terms of proportions rather than numbers of individuals in each compartment, only $\nu$ appears in the ODEs (He and Earn, 2007; Wagner and Earn, 2008). Also notice that with the assumption of standard incidence (Hethcote, 2000) ($\frac{\beta}{N}$ in Fig. 1), the proportional model is independent of the population size $N$.

The parameter $p$ is the proportion of individuals who are vaccinated before entering the susceptible class (in practice, there is often a substantial delay between birth and vaccination so that maternally-acquired immunity has had a chance to wane). These vaccinated individuals then enter the attenuated virus infectious class ($V$) and are able to pass the vaccine virus to susceptible individuals, resulting in contact vaccinations. The model (1) assumes that there is no disease-specific mortality, that vaccination – whether direct or inadvertent – confers lifelong immunity, and that the vaccine virus does not evolve (and hence cannot revert to the virulent form). The assumption of lifelong and complete immunity is particularly valid in the case of LAVVs for childhood diseases, as they provide an active immune response very similar to natural infection (Kew et al., 2004; Woodrow and Levine, 1990).

We denote the basic reproduction numbers of the wild-type and vaccine viruses as $\mathcal{R}_0$ and $\mathcal{R}_V$, respectively. The basic reproduction number is defined in the standard manner as the average number of secondary infections (or secondary immunizations) caused by a single infectious individual in a fully susceptible population. As the vaccine virus is attenuated, substantially reducing both transmissibility as well as virulence, we impose the condition $\mathcal{R}_V < \mathcal{R}_0$. Furthermore we assume $\mathcal{R}_0 > 1$ as otherwise the virus would fade out from the population naturally without vaccination.

The ODE system (1) was originally proposed by Eichner and Hadeler (1995) to model polio dynamics when vaccinating with Oral Polio Vaccine (OPV). They showed that system (1) exhibits a *disease free equilibrium* (DFE), which is (locally) asymptotically stable, whenever

$$p \geq p_{\text{crit}}\left(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}\right), \tag{2}$$

where $p_{\text{crit}}$ is the minimum proportion of the population that must be vaccinated to eradicate a disease with a vaccine that is not transmissible, i.e.,

$$p_{\text{crit}} = 1 - \frac{1}{\mathcal{R}_0}. \tag{3}$$

It is important to note that contact vaccination leads to a significant reduction in the threshold vaccination proportion (2) even for $\mathcal{R}_V < 1$, in which case we expect the vaccine virus to fade from the population upon cessation of vaccination. This reduction of critical proportion is demonstrated in Fig. 2, which compares the critical proportion under contact vaccination to $p_{\text{crit}}$ (standard vaccination) for various fixed $\mathcal{R}_V$ values across a range of $\mathcal{R}_0$ values.

Below the threshold (2), system (1) has a biologically meaningful endemic equilibrium. We demonstrate below that the DFE is, in fact, *globally* asymptotically stable if condition (2) holds and that the endemic equilibrium is globally asymptotically stable otherwise. These conclusions are also valid for models that incorporate

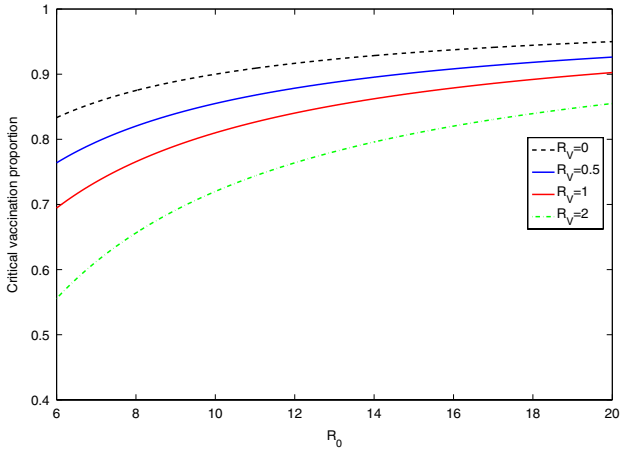


**Fig. 2.** Critical vaccination proportion (2) as a function of wild-type virus basic reproduction number $\mathcal{R}_0$ for fixed values of vaccine virus basic reproduction number $\mathcal{R}_V$. Also shown is the standard critical vaccination level $p_{\text{crit}}$ (dashed black line) corresponding to $\mathcal{R}_V = 0$. Contact vaccination leads to a significant reduction in the critical vaccination proportion even for $\mathcal{R}_V < 1$ and relatively high $\mathcal{R}_0$ values.

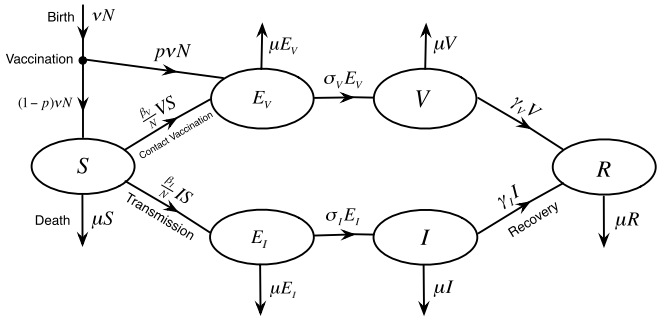


**Fig. 3.** Flow diagram for the SEIVR model. The compartments $E_V$ and $E_I$ represent exposed classes of individuals who have been infected, respectively, by the vaccine and wild-type virus but are not yet infectious. The mean latent periods for the vaccine and wild-type virus are given by $\frac{1}{\sigma_V}$, $\frac{1}{\sigma_I}$ and $N$ represents the total population size.

latent periods (delays between the time of infection or vaccination and the onset of infectiousness); see the SEIVR model depicted in Fig. 3. Much more generally, we show in this paper that these global stability results are valid for any staged progression LAVV model (depicted generically in Fig. 4).

### 2.1. Global stability of generalized LAVV models

We show that for the very general class of LAVV models depicted in Fig. 4, there is always a unique DFE and a critical vaccination threshold that is always given by Eq. (2). If $p \geq p_{\text{crit}}(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0})$ then the DFE is globally asymptotically stable, while if $p < p_{\text{crit}}(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0})$ there exists a unique globally asymptotically stable *endemic equilibrium*. An important feature of the general staged progression model that we consider is that any of the stages of infection can have durations that are distributed realistically (as opposed to exponentially). Mathematically, each stage is Erlang distributed with an arbitrary shape parameter (see Wagner and Earn (2008) Section 4.3.1 for mathematical details).

#### 2.1.1. The general staged progression LAVV model

We begin by formulating the general staged progression LAVV model depicted in Fig. 4 as the following system of ODEs.

$$\frac{dS}{dt} = (1-p)\nu - \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S - \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S - \nu S \tag{4a}$$

$$\frac{dV_1}{dt} = p\nu + \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S - \left(\nu + \gamma_1^{\mathrm{V}}\right) V_1 \tag{4b}$$

$$\frac{dV_2}{dt} = \gamma_1^{\mathrm{V}} V_1 - \left(\nu + \gamma_2^{\mathrm{V}}\right) V_2 \tag{4c}$$

$$\vdots$$

$$\frac{dV_n}{dt} = \gamma_{n-1}^{\mathrm{V}} V_{n-1} - \left(\nu + \gamma_n^{\mathrm{V}}\right) V_n \tag{4d}$$

$$\frac{dI_1}{dt} = \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S - \left(\nu + \gamma_1^{\mathrm{I}}\right) I_1 \tag{4e}$$

$$\frac{dI_2}{dt} = \gamma_1^{\mathrm{I}} I_1 - \left(\nu + \gamma_2^{\mathrm{I}}\right) I_2 \tag{4f}$$

$$\vdots$$

$$\frac{dI_k}{dt} = \gamma_{k-1}^{\mathrm{I}} I_{k-1} - \left(\nu + \gamma_k^{\mathrm{I}}\right) I_k \tag{4g}$$

$$\frac{dR}{dt} = \gamma_k^{\mathrm{I}} I_k + \gamma_n^{\mathrm{V}} V_n - \nu R. \tag{4h}$$

In system (4), the variables $V_j$ represent infected stages (latent if the transmission rate $\beta_j^{\mathrm{V}} = 0$ and infectious if $\beta_j^{\mathrm{V}} > 0$). Similarly, the $I_j$ represent wild-type virus infected stages and $\beta_j^{\mathrm{I}}$ are the transmission rates in these stages. We denote the numbers of vaccine

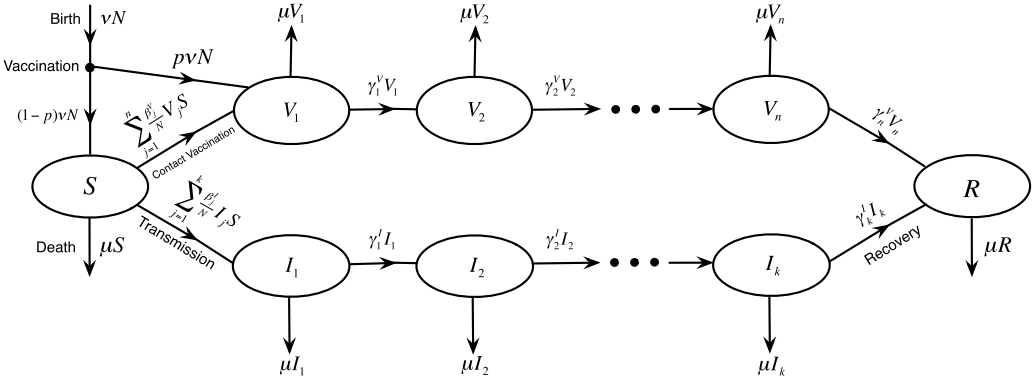


**Fig. 4.** Flow diagram for the general staged progression $SI_1I_2\cdots I_kV_1V_2\cdots V_n\mathrm{R}$ model, which includes an arbitrary number of stages of infection for both the wild-type and vaccine viruses.

virus and wild-type virus infected classes by $n$ and $k$, respectively. Without loss of generality, we assume $V_n$ and $I_k$ are the final vaccine and wild-type virus stages with nonzero infectivity (further classes with $\beta_j^{\mathrm{V}} = 0$ or $\beta_j^{\mathrm{I}} = 0$ could be absorbed into the removed class $R$). As in Eq. (1) the expanded model (4) is written in terms of proportions, so only the *per capita* birth rate $\nu$ appears and not the *per capita* death rate $\mu$. The parameters $\frac{1}{\gamma_j^{\mathrm{V}}}$ and $\frac{1}{\gamma_j^{\mathrm{I}}}$ represent the mean duration of the $j$th vaccine and wild-type virus infected stages respectively, and $p$ is the proportion of newborns that are successfully vaccinated (after maternal antibodies have waned).

### 2.1.2. Basic reproduction numbers

We calculate the basic reproduction numbers of the vaccine ($\mathcal{R}_{\mathrm{V}}$) and wild-type virus ($\mathcal{R}_0$), defined to be the number of secondary transmissions of a single infectious individual in an otherwise fully susceptible population. From the definition, we see that each virus must be considered independently. If considering the vaccine virus we fix all wild-type virus classes to zero, and vice versa, and set vaccination to zero. Applying the next generation method (Diekmann et al., 1990; van den Driessche and Watmough, 2002) to the resulting system yields the reproduction numbers,

$$\mathcal{R}_{\mathrm{V}} = \left( \frac{\beta_1^{\mathrm{V}}}{\left(\nu + \gamma_1^{\mathrm{V}}\right)} + \sum_{j=2}^{n} \frac{\beta_j^{\mathrm{V}}}{\left(\nu + \gamma_j^{\mathrm{V}}\right)} \left( \prod_{i=1}^{j-1} \frac{\gamma_i^{\mathrm{V}}}{\left(\nu + \gamma_i^{\mathrm{V}}\right)} \right) \right) \tag{5a}$$

$$\mathcal{R}_0 = \left( \frac{\beta_1^{\mathrm{I}}}{\left(\nu + \gamma_1^{\mathrm{I}}\right)} + \sum_{j=2}^{k} \frac{\beta_j^{\mathrm{I}}}{\left(\nu + \gamma_j^{\mathrm{I}}\right)} \left( \prod_{i=1}^{j-1} \frac{\gamma_i^{\mathrm{I}}}{\left(\nu + \gamma_i^{\mathrm{I}}\right)} \right) \right). \tag{5b}$$

The next generation method provides a straightforward algorithm to obtain reproduction numbers by examining the stability of the system at the DFE. For staged progression models, reproduction numbers are worked out explicitly in van den Driessche and Watmough (2002), along with a complete discussion of the method.

Eq. (5) can be also understood at a heuristic level. For example (for constant population) the term $\frac{\beta_j^{\mathrm{V}}}{\left(\nu+\gamma_j^{\mathrm{V}}\right)}$ can be understood as the average number of people infected (in a fully susceptible population) by an individual in the $j$th class, while the product term $\prod_{i=1}^{j-1} \frac{\gamma_i^{\mathrm{V}}}{\left(\nu+\gamma_i^{\mathrm{V}}\right)}$ represents the probability that an individual beginning in the first class will proceed to the $j$th class before dying. Summing over all classes gives the total average number of infections.

### 2.1.3. The disease free equilibrium

By definition, the DFE has $I_j^* = 0$ for all $j$, and at equilibrium we must have

$$V_j^* = \frac{\gamma_{j-1}^{\mathrm{V}}}{\left(\nu + \gamma_j^{\mathrm{V}}\right)} V_{j-1}^*, \quad j \geq 2. \tag{6}$$

Summing Eqs. (4a) and (4b) at equilibrium yields the relation

$$S^* = 1 - \frac{\left(\nu + \gamma_1^{\mathrm{V}}\right)}{\nu} V_1^*. \tag{7}$$

Expressing $V_j^*$ in terms of $V_1^*$ via Eqs. (6) and (5) and substituting (4a) into (4b) at equilibrium yields the quadratic equation

$$\frac{\left(\nu + \gamma_1^{\mathrm{V}}\right)}{\nu} V_1^{*2} - \left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right) V_1^* - \frac{p\nu}{\mathcal{R}_{\mathrm{V}}\left(\nu + \gamma_1^{\mathrm{V}}\right)} = 0. \tag{8}$$

We compute the unique positive solution of (8) yielding the DFE,

$$S^* = \left(1 - \frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right) - \sqrt{\left(\frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2 + \frac{p}{\mathcal{R}_{\mathrm{V}}}}\right) \tag{9a}$$

$$V_1^* = \frac{\nu}{\left(\nu + \gamma_1^{\mathrm{V}}\right)} \times \left(\frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right) + \sqrt{\left(\frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2 + \frac{p}{\mathcal{R}_{\mathrm{V}}}}\right) \tag{9b}$$

$$V_j^* = \frac{\nu}{\left(\nu + \gamma_1^{\mathrm{V}}\right)} \left( \prod_{i=2}^{j} \frac{\gamma_{i-1}^{\mathrm{V}}}{\left(\nu + \gamma_i^{\mathrm{V}}\right)} \right) \times \left(\frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right) + \sqrt{\left(\frac{1}{2}\left(1 - \frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2 + \frac{p}{\mathcal{R}_{\mathrm{V}}}}\right) \tag{9c}$$

$$I_j^* = 0. \tag{9d}$$

It should be noted that the equilibrium proportion of susceptibles, $S^*$, depends only on the reproduction numbers $\mathcal{R}_0$ and $\mathcal{R}_{\mathrm{V}}$, and not on the durations of any of the stages. The non-negativity of the equilibrium (see Appendix A of Wagner and Earn (2008)) implies that the equilibrium lies in the biologically meaningful set $= \{S, V_i, I_i : S, V_i, I_i \geq 0, S + \sum_{i=1}^{n} V_i + \sum_{i=1}^{k} I_i \leq 1\}$ by the arguments in Appendix A.2.

### 2.1.4. Endemic equilibrium

For $p < p_{\mathrm{crit}}(1 - \frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$ there exists a unique endemic equilibrium. To see this, we first note that (6) holds, as does the analogous relationship for the infected classes,

$$I_j^* = \frac{\gamma_{j-1}^{\mathrm{I}}}{\left(\nu + \gamma_j^{\mathrm{I}}\right)} {I_{j-1}}^*, \quad j \geq 2. \tag{10}$$

Applying (10) and (5) to (4e) at equilibrium yields

$$\left(\nu + \gamma_1^{\mathrm{I}}\right)\left(1 - \mathcal{R}_0 S^*\right) = 0, \tag{11}$$

which is equivalent to

$$S^* = \frac{1}{\mathcal{R}_0}. \tag{12}$$

Similarly, applying (6), (5) and (12) to Eq. (4b) yields

$$V_1^* = \frac{p\nu\mathcal{R}_0}{\left(\nu + \gamma_1^{\mathrm{I}}\right)\left(\mathcal{R}_0 - \mathcal{R}_{\mathrm{V}}\right)} \tag{13}$$

which is positive under the attenuation condition that $\mathcal{R}_{\mathrm{V}} < \mathcal{R}_0$. Substituting expression (13) into (4a) at equilibrium and again using (6), (5) and (10) yields

$$I_1{}^* = \frac{\nu}{\left(\nu + \gamma_1^{\mathrm{I}}\right)} \left( \left(1 - \frac{1}{\mathcal{R}_0}\right) - p\left(1 + \frac{\mathcal{R}_{\mathrm{V}}}{\left(\mathcal{R}_0 - \mathcal{R}_{\mathrm{V}}\right)}\right)\right). \tag{14}$$

We see that ${I_1}^* > 0$ if and only if $p < \left(1 - \frac{1}{\mathcal{R}_0}\right)\left(1 - \frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0}\right)$, and the *endemic equilibrium* may be expressed as

$$S^* = \frac{1}{\mathcal{R}_0} \tag{15a}$$

$$V_1^* = \left( \frac{p\nu\mathcal{R}_0}{\left(\nu + \gamma_1^{\mathrm{V}}\right)\left(\mathcal{R}_0 - \mathcal{R}_{\mathrm{V}}\right)} \right) \tag{15b}$$

$$V_j^* = \left( \frac{p\nu\mathcal{R}_0}{\left(\nu + \gamma_1^{\mathrm{V}}\right)\left(\mathcal{R}_0 - \mathcal{R}_{\mathrm{V}}\right)} \right) \left( \prod_{i=2}^{j} \frac{\gamma_{i-1}^{\mathrm{V}}}{\left(\nu + \gamma_i^{\mathrm{V}}\right)} \right)$$

$$j = 2, \ldots, n \tag{15c}$$

$$I_1^* = \left(\frac{\nu}{(\nu+\gamma_1^{\mathrm{I}})}\right)\left(\left(1-\frac{1}{\mathcal{R}_0}\right) - p\left(1+\frac{\mathcal{R}_{\mathrm{V}}}{(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}})}\right)\right) \tag{15d}$$

$$I_j^* = \left(\frac{\nu}{(\nu+\gamma_1^{\mathrm{I}})}\right)\left(\prod_{i=2}^{j}\frac{\gamma_{i-1}^{\mathrm{I}}}{(\nu+\gamma_i^{\mathrm{I}})}\right) \times \left(\left(1-\frac{1}{\mathcal{R}_0}\right) - p\left(1+\frac{\mathcal{R}_{\mathrm{V}}}{(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}})}\right)\right)$$

$$j = 2, \ldots, k. \tag{15e}$$

Again, the fact that the equilibrium is non-negative implies that it lies in the biologically meaningful state region $\mathcal{B}$.

### 2.2. Global stability conditions

We use Lyapunov's direct method (LaSalle and Lefschetz, 1961) to establish that the DFE is globally asymptotically stable if $p \geq p_{\mathrm{crit}}(1-\frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$ and that the endemic equilibrium is asymptotically stable if $p < p_{\mathrm{crit}}(1-\frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$.

The Lyapunov functions we construct are related to those used by Guo and Li (2006) to prove global stability in a standard epidemiological staged progression model. The Guo–Li functions are in turn generalizations of Lyapunov functions recently developed to prove global stability for a variety of epidemiological and ecological models (Freedman and So, 1985; Korobeinikov, 2004; Korobeinikov and Maini, 2004; Korobeinikov and Wake, 2002). The primary reason that these methods work for a wide range of high-dimensional ecological and epidemiological models is that they do not rely on explicit equilibrium expressions. Instead, we only require implicit relationships among the parameters and equilibria (which are straightforwardly derived directly from the differential equations) and the positive invariance of the positive cone with respect to the dynamical system.

#### 2.2.1. Global stability of the disease free equilibrium

To establish the global asymptotic stability of the DFE (9) when $p \geq p_{\mathrm{crit}}(1-\frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$ we first note that this condition is equivalent to the condition $S^* \leq \frac{1}{\mathcal{R}_0}$ (Appendix C). We then proceed to construct a Lyapunov function of the form

$$L_{\mathrm{DFE}} = L_{\mathrm{DFE}}^1 + L_{\mathrm{DFE}}^2 \tag{16a}$$

$$L_{\mathrm{DFE}}^1 = I_1 + \sum_{j=2}^{k} a_j I_j \tag{16b}$$

$$L_{\mathrm{DFE}}^2 = \left(S - S^*\ln(S)\right) + \left(V_1 - V_1^*\ln(V_1)\right) + \sum_{j=2}^{n} b_j\left(V_j - V_j^*\ln\left(V_j\right)\right) \tag{16c}$$

where $a_j, b_j$ are appropriately chosen positive coefficients and $*$ denotes the equilibrium value at the DFE. We note that $L_{\mathrm{DFE}}$ has a global minimum (with respect to the positive cone) located at the DFE which we denote as $\mathbf{X}^0 = (S^*, V_1^* \ldots V_k^*, 0, \ldots 0)$ and furthermore that for any variable $P$,

$$\frac{\partial}{\partial P}\left(P - P^*\ln(P)\right) = 1 - \frac{P^*}{P}. \tag{17}$$

#### 2.2.2. Construction of $L_{\mathrm{DFE}}^1$

We observe that Eqs. (4e)–(4g) can be written in the form

$$\frac{d}{dt}\begin{pmatrix} I_1 \\ I_2 \\ \vdots \\ I_k \end{pmatrix} = \begin{pmatrix} \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S \\ 0 \\ \vdots \\ 0 \end{pmatrix} - \mathcal{V}\begin{pmatrix} I_1 \\ I_2 \\ \vdots \\ I_k \end{pmatrix}, \tag{18}$$

where the $k \times k$ matrix $\mathcal{V}$ is given by

$$\mathcal{V} = \begin{pmatrix} -(\nu+\gamma_1^{\mathrm{I}}) & & & & \\ \gamma_1^{\mathrm{I}} & -(\nu+\gamma_2^{\mathrm{I}}) & & & \\ & \gamma_2^{\mathrm{I}} & -(\nu+\gamma_3^{\mathrm{I}}) & & \\ & & \ddots & \ddots & \\ & & & \gamma_{k-1}^{\mathrm{I}} & -(\nu+\gamma_k^{\mathrm{I}}) \end{pmatrix}. \tag{19}$$

The matrix $\mathcal{V}$ has a non-negative inverse which can be computed directly as

$$\mathcal{V}^{-1} = \begin{pmatrix} \frac{1}{(\nu+\gamma_1^{\mathrm{I}})} & & & \\ \frac{\gamma_1^{\mathrm{I}}}{(\nu+\gamma_1^{\mathrm{I}})(\nu+\gamma_2^{\mathrm{I}})} & \frac{1}{(\nu+\gamma_2^{\mathrm{I}})} & & \\ \frac{\gamma_1^{\mathrm{I}}\gamma_2^{\mathrm{I}}}{(\mu+\gamma_1^{\mathrm{I}})(\nu+\gamma_2^{\mathrm{I}})(\nu+\gamma_3^{\mathrm{I}})} & \frac{\gamma_2^{\mathrm{I}}}{(\nu+\gamma_2^{\mathrm{I}})(\nu+\gamma_3^{\mathrm{I}})} & \frac{1}{(\nu+\gamma_3^{\mathrm{I}})} & \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix}. \tag{20}$$

Furthermore, $\mathcal{R}_0$ can be expressed in a straightforward manner (Diekmann et al., 1990; van den Driessche and Watmough, 2002) in terms of $\mathcal{V}$ as

$$\mathcal{R}_0 = \begin{pmatrix}\beta_1^{\mathrm{I}} & \beta_2^{\mathrm{I}} & \ldots & \beta_k^{\mathrm{I}}\end{pmatrix}\mathcal{V}^{-1}\begin{pmatrix}1\\0\\\vdots\\0\end{pmatrix}. \tag{21}$$

Motivated by (18) and (21), we choose the coefficients $a_j$ as

$$\begin{pmatrix}1 & a_2 & \ldots & a_k\end{pmatrix} = \frac{1}{\mathcal{R}_0}\begin{pmatrix}\beta_1^{\mathrm{I}} & \beta_2^{\mathrm{I}} & \ldots & \beta_k^{\mathrm{I}}\end{pmatrix}\mathcal{V}^{-1}, \tag{22}$$

where we note that the leading coefficient is equal to 1 by construction (Eq. (21)).

It then follows from (16b), (18), (21) and (22) that

$$\frac{d}{dt}L_{\mathrm{DFE}}^1 = \begin{pmatrix}1 & a_2 & \ldots & a_k\end{pmatrix}\frac{d}{dt}\begin{pmatrix} I_1 \\ I_2 \\ \vdots \\ I_k \end{pmatrix} = \left(S - \frac{1}{\mathcal{R}_0}\right)\sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j. \tag{23}$$

#### 2.2.3. Construction of $L_{\mathrm{DFE}}^2$

We first write obtain the required implicit equilibrium expressions among the state variables at $S$ and $V_1, \ldots, V_n$, namely

$$(1-p)\nu = \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^* + \nu S^* \tag{24a}$$

$$\sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* = (\gamma_1^{\mathrm{V}} + \nu)V_1^* - p\nu \tag{24b}$$

$$\frac{\gamma_{j-1}^{\mathrm{V}} V_{j-1}^*}{\left(\nu+\gamma_j^{\mathrm{V}}\right)} = V_j^*\,, \quad j=2,\ldots,n. \tag{24c}$$

From expressions (16c) and (17) we see that

$$\frac{d}{dt}L_{\mathrm{DFE}}^2 = \left(1-\frac{S^*}{S}\right)\frac{dS}{dt} + \left(1-\frac{V_1^*}{V_1}\right)\frac{dV_1}{dt} + \sum_{j=2}^{n} b_j\left(1-\frac{V_j^*}{V_j}\right)\frac{dV_j}{dt}\,. \tag{25}$$

We select the coefficients $b_j$ using the same inductive algorithm presented by Guo and Li (2006), which yields

$$b_n = \frac{\beta_n^{\mathrm{V}} S^*}{\left(\nu+\gamma_n^{\mathrm{V}}\right)} \tag{26a}$$

$$b_j = \frac{b_{j+1}\gamma_j^{\mathrm{V}} + \beta_j^{\mathrm{V}} S^*}{\left(\nu+\gamma_j^{\mathrm{V}}\right)}\,, \qquad j=2,\ldots,n-1\,. \tag{26b}$$

We note that the definition as $V_n$ as the final class with nonzero vaccine virus infectivity, $\beta_n^{\mathrm{V}} > 0$, ensures that $b_j > 0$ for all $j$, and that recurrence relation (26) can be straightforwardly solved (Guo and Li, 2006) to yield

$$b_j = \frac{\sum_{i=j}^{n} \beta_i^{\mathrm{V}} V_i^* S^*}{\left(\nu+\gamma_j^{\mathrm{V}}\right) V_j^*}\,, \qquad j=2,\ldots,n\,. \tag{27}$$

We compute the first term of (25) as

$$\begin{aligned}
\left(1-\frac{S}{S^*}\right)\frac{dS}{dt} &= (1-p)\nu - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S - \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S - \nu S \\
&\quad -(1-p)\nu\frac{S^*}{S} + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S^* + \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* + \nu S^* \\
&= \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^* + \nu S^* - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S - \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S - \nu S \\
&\quad - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^*\frac{S^{*2}}{S} - \nu\frac{S^{*2}}{S} + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S^* + \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* + \nu S^* \\
&= \nu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right) - \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S + \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* \\
&\quad - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S^* + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^* - \sum_{j=1}^{n}\beta_j^{\mathrm{V}}\frac{S^{*2}}{S} \\
&\le -\sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S + \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S^* \\
&\quad + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^* - \sum_{j=1}^{n}\beta_j^{\mathrm{V}}\frac{S^{*2}}{S}.
\end{aligned} \tag{28}$$

In Eq. (28) we substitute for $(1-p)\nu$ using (24a) and in the final inequality we use the fact that $\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right) \le 0$ with equality only if $S = S^*$. This inequality is just a corollary of the fact that the arithmetic mean is always greater than or equal to the geometric mean (Appendix B).

Computing the second term of (25), using (4) and (24b), we find

$$\begin{aligned}
\left(1-\frac{V_1^*}{V_1}\right)\frac{d}{dt}V_1 &= p\nu - p\nu\frac{V_1^*}{V_1} + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S - \left(\nu+\gamma_1^{\mathrm{V}}\right)V_1 \\
&\quad - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S\frac{V_1^*}{V_1} + \left(\nu+\gamma_1^{\mathrm{V}}\right)V_1^* \\
&= 2p\nu - p\nu\frac{V_1^*}{V_1} + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S - \left(\nu+\gamma_1^{\mathrm{V}}\right)V_1 \\
&\quad - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S\frac{V_1^*}{V_1} + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^*\,.
\end{aligned} \tag{29}$$

Now we proceed as in Guo and Li (2006) to make the inductive choice of the coefficients $b_j$ clear. For $j \ge 2$,

$$\begin{aligned}
b_j\left(1-\frac{V_j^*}{V_j}\right)\frac{d}{dt}V_j &= b_j\gamma_{j-1}^{\mathrm{V}} V_{j-1} - b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)V_j \\
&\quad - b_j\gamma_{j-1}^{\mathrm{V}} V_{j-1}\frac{V_j^*}{V_j} + b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)V_j^*\,.
\end{aligned} \tag{30}$$

Using the choice of the coefficients $b_j$ (26), we find

$$\begin{aligned}
&\sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S^* - \left(\nu+\gamma_1^{\mathrm{V}}\right)V_1 + \sum_{j=2}^{n} b_j\gamma_{j-1}^{\mathrm{V}} V_{j-1} - b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)V_j \\
&\quad = \left(\beta_1^{\mathrm{V}} S^* - \left(\nu+\gamma_1^{\mathrm{V}}\right) + b_2\gamma_1^{\mathrm{V}}\right)V_1 + \left(\beta_n^{\mathrm{V}} S^* - b_n\left(\nu+\gamma_n^{\mathrm{V}}\right)\right)V_n \\
&\qquad + \sum_{j=2}^{n-1}\left(\beta_j^{\mathrm{V}} S^* + b_{j+1}\gamma_j^{\mathrm{V}} - b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)\right)V_j \\
&\quad = \left(\beta_1^{\mathrm{V}} S^* - \left(\nu+\gamma_1^{\mathrm{V}}\right) + b_2\gamma_1^{\mathrm{V}}\right)V_1.
\end{aligned} \tag{31}$$

Eq. (31) may be further simplified by substituting from Eq. (27) for $b_2$ and employing (24b) and (24c). In this way we find

$$\begin{aligned}
&\left(\beta_1^{\mathrm{V}} S^* - \left(\nu+\gamma_1^{\mathrm{V}}\right) + b_2\gamma_1^{\mathrm{V}}\right)V_1 \\
&\quad = \left(\beta_1^{\mathrm{V}} S^* - \left(\nu+\gamma_1^{\mathrm{V}}\right) + \frac{\sum_{j=2}^{n}\beta_j^{\mathrm{V}} V_j^* S^*}{\left(\nu+\gamma_2^{\mathrm{V}}\right)V_2^*}\gamma_1^{\mathrm{V}}\right)V_1 \\
&\quad = \left(-\left(\nu+\gamma_1^{\mathrm{V}}\right)V_1^* + \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^*\right)\frac{V_1}{V_1^*} \quad = -p\nu\frac{V_1}{V_1^*}\,.
\end{aligned} \tag{32}$$

Therefore, collecting terms from (31), (32), (29) and (25), we see that

$$\begin{aligned}
\frac{d}{dt}L_{\mathrm{DFE}}^2 &\le \left(\sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* - \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S\right) + p\nu\left(2-\frac{V_1^*}{V_1}-\frac{V_1}{V_1^*}\right) \\
&\quad + \left(-\sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^*\frac{S^{*2}}{S} - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S\frac{V_1^*}{V_1} - \sum_{j=2}^{n}\frac{b_j\gamma_{j-1}^{\mathrm{V}} V_{j-1} V_j^*}{V_j}\right) \\
&\quad + \left(\sum_{j=2}^{n} b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)V_j^* + 2\sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^* S^*\right) \\
&\le \underbrace{\left(\sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S^* - \sum_{j=1}^{k}\beta_j^{\mathrm{I}} I_j S\right)}_{F} \\
&\quad + \underbrace{\left(-\sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j^*\frac{S^{*2}}{S} - \sum_{j=1}^{n}\beta_j^{\mathrm{V}} V_j S\frac{V_1^*}{V_1} - \sum_{j=2}^{n}\frac{b_j\gamma_{j-1}^{\mathrm{V}} V_{j-1} V_j^*}{V_j}\right)}_{G} \\
&\quad + \underbrace{\left(\sum_{j=1}^{n} b_j\left(\nu+\gamma_j^{\mathrm{V}}\right)V_j^* + 2\sum_{j=2}^{n}\beta_j^{\mathrm{V}} V_j^* S^*\right)}_{H}\,,
\end{aligned} \tag{33}$$

with equality if and only if $S = S^*$ and $V_1 = V_1^*$. The terms $G$ and $H$ may be simplified to show $G + H \leq 0$, precisely as in Guo and Li (2006). We include the argument here for the sake of completeness. Using the solution of the inductive relationship for the terms $b_j\left(\nu + \gamma_j^{\mathrm{V}}\right) V_j^*$ (27) yields

$$H = \sum_{j=2}^{n} b_j\left(\nu + \gamma_j^{\mathrm{V}}\right) V_j^* + 2\sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* S^* = \sum_{j=1}^{n} (j+1)\beta_j^{\mathrm{V}} V_j^* S^*. \tag{34}$$

Substituting for $b_j$ in terms of (27), applying the equilibrium relationship (24c) and exchanging the order of summation, yields

$$\sum_{j=2}^{n} \frac{b_j \gamma_{j-1}^{\mathrm{V}} V_{j-1} V_j^*}{V_j} = \sum_{j=2}^{n}\sum_{r=j}^{n} \beta_r^{\mathrm{V}} V_r^* S^* \frac{\gamma_{j-1}^{\mathrm{V}} V_{j-1}}{\left(\nu + \gamma_j^{\mathrm{V}}\right) V_j} = \sum_{j=2}^{n}\sum_{r=j}^{n} \beta_r^{\mathrm{V}} V_r^* S^* \frac{V_j^* V_{j-1}}{V_j V_{j-1}^*} = \sum_{j=2}^{n} \beta_j^{\mathrm{V}} V_j^* S^* \sum_{r=2}^{j} \frac{V_r^* V_{r-1}^*}{V_r V_{r-1}^*}. \tag{35}$$

Using (27) and (35) yields the desired result

$$G + H = \beta_1^{\mathrm{V}} V_1^* S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) + \sum_{j=2}^{n} \beta_j^{\mathrm{V}} V_j^* S^*\left((j+1) - \frac{S^*}{S} - \frac{S V_j V_1^*}{S^* V_j^* V_1} - \sum_{r=2}^{j} \frac{V_r^* V_{r-1}}{V_r V_{r-1}^*}\right) \leq 0, \tag{36}$$

with equality if and only if $S = S^*, V_1 = V_1^*, \ldots, V_j = V_j^*$, since the arithmetic mean is always greater than the geometric mean (Appendix B).

Combining (23), (33) and (36) yields

$$\frac{d}{dt} L_{\mathrm{DFE}} = \frac{d}{dt} L_{\mathrm{DFE}}^1 + \frac{d}{dt} L_{\mathrm{DFE}}^2 \leq \left(S^* - \frac{1}{\mathcal{R}_0}\right) \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S. \tag{37}$$

Applying the result of Appendix C, which states

$$S^* \leq \frac{1}{\mathcal{R}_0} \iff p \geq p_{\mathrm{crit}}\left(1 - \frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0}\right), \tag{38}$$

we obtain the desired result

$$p \geq p_{\mathrm{crit}}\left(1 - \frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0}\right) \Longrightarrow \frac{d}{dt} L_{\mathrm{DFE}} \leq 0, \tag{39}$$

with equality in Eq. (39) along a subset of $\mathcal{K} = \{(S, V_1, \ldots, V_n, I_1, \ldots, I_k) : S = S^*, V_1 = V_1^*, \ldots, V_j = V_j^*\}$, containing the first $n+1$ coordinates of the DFE, $\mathbf{X}^0$. Notice that if $S^* = \frac{1}{\mathcal{R}_0}$ then equality in (39) holds everywhere in $\mathcal{K}$. However, it is evident from (4) that $\mathbf{X}^0$ is the only invariant subset of $\mathcal{K}$. Hence, the LaSalle Invariance Principle (LaSalle and Lefschetz, 1961; LaSalle, 1976) guarantees that $\mathbf{X}^0$ is globally asymptotically stable, completing the proof.

### 2.2.4. Global stability of the endemic equilibrium

We employ a Lyapunov function of the standard form to prove that the endemic equilibrium (15) is globally asymptotically stable whenever it exists, i.e., if $p < p_{\mathrm{crit}}(1 - \frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$. The Lyapunov function is

$$L_{\mathrm{EE}} = \left(S - S^* \ln(S)\right) + \left(I_1 - I_1{}^* \ln(I_1)\right) + \left(V_1 - V_1^* \ln(V_1)\right) + \sum_{j=2}^{n} c_j\left(V_j - V_j^* \ln(V_j)\right) + \sum_{j=2}^{k} d_j\left(I_j - I_j{}^* \ln(I_j)\right), \tag{40}$$

where $*$ denotes the value at the endemic equilibrium (15). Again we choose the $a_j$, $b_j$ by the inductive algorithm presented in Guo and Li (2006), such that

$$c_n = \frac{\beta_n^{\mathrm{V}} S^*}{\left(\nu + \gamma_n^{\mathrm{V}}\right)} \tag{41a}$$

$$c_j = \frac{c_{j+1}\gamma_j^{\mathrm{V}} + \beta_j^{\mathrm{V}} S^*}{\left(\nu + \gamma_j^{\mathrm{V}}\right)} \quad j = 2 \ldots n-1 \tag{41b}$$

$$d_k = \frac{\beta_k^{\mathrm{I}} S^*}{\left(\nu + \gamma_k^{\mathrm{I}}\right)} \tag{41c}$$

$$d_j = \frac{d_{j+1}\gamma_j^{\mathrm{I}} + \beta_j^{\mathrm{I}} S^*}{\left(\nu + \gamma_j^{\mathrm{I}}\right)} \quad j = 2 \ldots k-1. \tag{41d}$$

Much of the analysis is identical to that of Section 2.2.1 of this paper and Section 5 of Guo and Li (2006), so we highlight only the differences.

The equilibrium relationships, (24b) and (24c), still hold for the endemic equilibrium as they did for the DFE. However, Eq. (24a) is now replaced by the expression

$$(1-p)\nu = \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* S^* + \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* S^* + \nu S^* \tag{42}$$

and we now have the equilibrium relationships

$$\sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* S^* = \left(\nu + \gamma_1^{\mathrm{I}}\right) I_1{}^* \tag{43a}$$

$$\frac{\gamma_{j-1}^{\mathrm{I}} I_{j-1}{}^*}{\left(\nu + \gamma_j^{\mathrm{I}}\right)} = I_j{}^*. \tag{43b}$$

We compute the first term of $\frac{d}{dt} L_{\mathrm{EE}}$ analogously to (25), employing (42).

$$\begin{aligned}
\frac{\partial L_{\mathrm{EE}}}{\partial S}\frac{d}{dt}S &= \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} \\
&= \nu S^*\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) \\
&\quad + \left(-\sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S + \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S^* + \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* S^* - \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* \frac{S^{*2}}{S}\right) \\
&\quad + \left(-\sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S + \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S^* + \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* S^* - \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* \frac{S^{*2}}{S}\right) \\
&\leq \underbrace{\left(-\sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S + \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j S^* + \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* S^* - \sum_{j=1}^{n} \beta_j^{\mathrm{V}} V_j^* \frac{S^{*2}}{S}\right)}_{A_{\mathrm{V}}} \\
&\quad + \underbrace{\left(-\sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S + \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j S^* + \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* S^* - \sum_{j=1}^{k} \beta_j^{\mathrm{I}} I_j{}^* \frac{S^{*2}}{S}\right)}_{A_{\mathrm{I}}}
\end{aligned} \tag{44}$$

with equality only when $S = S^*$. We now can split our calculations into

$$\frac{d}{dt} L_{\mathrm{EE}} \leq \left(A_{\mathrm{V}} + \left(1 - \frac{V_1^*}{V_1}\right)\frac{d}{dt}V_1 + \sum_{j=2}^{n} c_j\left(1 - \frac{V_j}{V_j^*}\right)\frac{d}{dt}V_j\right) + \left(A_{\mathrm{I}} + \left(1 - \frac{I_1^*}{I_1}\right)\frac{d}{dt}I_1 + \sum_{j=2}^{k} d_j\left(1 - \frac{I_j}{I_j^*}\right)\frac{d}{dt}I_j\right). \tag{45}$$

The first term of (45) is exactly that computed in Eqs. (28)–(32), while the second term is exactly that computed in Eqs. (25)–(33) of Guo and Li (2006). We therefore conclude that

$$\frac{d}{dt}L_{\mathrm{END}} \leq 0\,, \tag{46}$$

with equality if and only if $S = S^*, V_1 = V_1^*, \ldots, V_j = V_j^*, I_1 = I_1{}^*, \ldots, I_j = I_j{}^*$. This confirms that the endemic equilibrium (15) is globally asymptotically stable when it exists.

### 2.3. Disease- and vaccine-induced mortality

The model (4) does not take into account the effects of disease- or vaccine-induced mortality. Using a related model, we take these factors into account. We demonstrate that inclusion of these effects does not change the qualitative results (stability thresholds). The staged progression model we consider may be phrased in the following manner,

$$\frac{dS}{dt} = (1-p)B - \sum_{j=1}^{n}\beta_j^{\mathrm{V}}V_jS - \sum_{j=1}^{k}\beta_j^{\mathrm{I}}I_jS - \mu S \tag{47a}$$

$$\frac{dV_1}{dt} = pB + \sum_{j=1}^{n}\beta_j^{\mathrm{V}}V_jS - \left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)V_1 \tag{47b}$$

$$\frac{dV_2}{dt} = \gamma_1^{\mathrm{V}}V_1 - \left(\mu+\gamma_2^{\mathrm{V}}+\varepsilon_2^{\mathrm{V}}\right)V_2 \tag{47c}$$

$$\vdots$$

$$\frac{dV_n}{dt} = \gamma_{n-1}^{\mathrm{V}}V_{n-1} - \left(\mu+\gamma_n^{\mathrm{V}}+\varepsilon_n^{\mathrm{V}}\right)V_n \tag{47d}$$

$$\frac{dI_1}{dt} = \sum_{j=1}^{k}\beta_j^{\mathrm{I}}I_jS - \left(\mu+\gamma_1^{\mathrm{I}}+\varepsilon_1^{\mathrm{I}}\right)I_1 \tag{47e}$$

$$\frac{dI_2}{dt} = \gamma_1^{\mathrm{I}}I_1 - \left(\mu+\gamma_2^{\mathrm{I}}+\varepsilon_2^{\mathrm{I}}\right)I_2 \tag{47f}$$

$$\vdots$$

$$\frac{dI_k}{dt} = \gamma_{k-1}^{\mathrm{I}}I_{k-1} - \left(\mu+\gamma_k^{\mathrm{I}}+\varepsilon_k^{\mathrm{I}}\right)I_k \tag{47g}$$

$$\frac{dR}{dt} = \gamma_k^{\mathrm{I}}I_k + \gamma_n^{\mathrm{V}}V_n - \mu R. \tag{47h}$$

In contrast to (4) the system (47) is phrased in terms of total population $N$ rather than proportions. The total birth rate is given by $B$, $\varepsilon_j^{\mathrm{V}}$ and $\varepsilon_j^{\mathrm{I}}$ represent the vaccine- and wild-type virus-induced death rates in each stage, while $\mu$ is the *per capita* natural death rate. The terms $\beta_j^{\mathrm{V}}, \beta_j^{\mathrm{I}}$ represent the total transmission rate of vaccine and wild-type virus in each stage. Note that this model assumes pseudo-mass action incidence $\beta$ as opposed to standard incidence $\frac{\beta}{N}$. The previous LAVV models considered assumed standard incidence. Other parameters are as defined in (4).

The motivation for our departure from using proportional models is mathematical in nature. As demonstrated in He and Earn (2007) for the proportional version of the standard SIR model with disease-induced mortality, inclusion of disease-induced mortality results in quadratic terms not present in the original proportional model. Due to this fact, the form of Lyapunov functions used to show stability in the absence of vaccine- and disease-induced mortality cannot be straightforwardly employed. However, assuming a constant birth rate, the Lyapunov functions can be straightforwardly applied to the model written in terms of total population (47). In the absence of vaccine- and disease-induced mortality there is no difference between the models (47) and (4) after the latter is expressed in proportions.

Since the total birth rate is fixed, the model (47) will be valid over time periods for which the total birth rate is relatively stable. As previously noted the model (4) employs pseudo-mass action mixing as opposed to standard mass action mixing. This assumption is not biologically unrealistic, as pseudo-mass action mixing has been shown to successfully predict transitions in dynamics of childhood diseases (Bauch and Earn, 2003; Earn et al., 2000).

For system (47) the basic reproduction numbers of the wild-type and vaccine virus are (Guo and Li, 2006; van den Driessche and Watmough, 2002)

$$\mathcal{R}_{\mathrm{V}} = \frac{B}{\mu}\left(\frac{\beta_1^{\mathrm{V}}}{\left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)} + \sum_{j=2}^{n}\frac{\beta_j^{\mathrm{V}}}{\left(\mu+\gamma_j^{\mathrm{V}}+\varepsilon_j^{\mathrm{V}}\right)} \times\left(\prod_{i=1}^{j-1}\frac{\gamma_i^{\mathrm{V}}}{\left(\mu+\gamma_i^{\mathrm{V}}+\varepsilon_i^{\mathrm{V}}\right)}\right)\right) \tag{48a}$$

$$\mathcal{R}_0 = \frac{B}{\mu}\left(\frac{\beta_1^{\mathrm{I}}}{\left(\mu+\gamma_1^{\mathrm{I}}+\varepsilon_1^{\mathrm{I}}\right)} + \sum_{j=2}^{k}\frac{\beta_j^{\mathrm{I}}}{\left(\mu+\gamma_j^{\mathrm{I}}+\varepsilon_j^{\mathrm{I}}\right)} \times\left(\prod_{i=1}^{j-1}\frac{\gamma_i^{\mathrm{I}}}{\left(\mu+\gamma_i^{\mathrm{I}}+\varepsilon_i^{\mathrm{I}}\right)}\right)\right). \tag{48b}$$

Straightforward computation establishes that system (47) has a unique DFE given by

$$S^* = \frac{B}{\mu}\left(1-\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)-\sqrt{\left(\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2+\frac{p}{\mathcal{R}_{\mathrm{V}}}}\right) \tag{49a}$$

$$V_1^* = \frac{B}{\left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)} \times\left(\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)+\sqrt{\left(\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2+\frac{p}{\mathcal{R}_{\mathrm{V}}}}\right) \tag{49b}$$

$$V_j^* = \frac{B}{\left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)}\left(\prod_{i=2}^{j}\frac{\gamma_{i-1}^{\mathrm{V}}}{\left(\mu+\gamma_i^{\mathrm{V}}+\varepsilon_i^{\mathrm{V}}\right)}\right) \times\left(\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)+\sqrt{\left(\frac{1}{2}\left(1-\frac{1}{\mathcal{R}_{\mathrm{V}}}\right)\right)^2+\frac{p}{\mathcal{R}_{\mathrm{V}}}}\right), \tag{49c}$$

$$I_j^* = 0 \tag{49d}$$

and a unique *endemic equilibrium* given by

$$S^* = \frac{B}{\mu\mathcal{R}_0} \tag{50a}$$

$$V_1^* = \left(\frac{pB\mathcal{R}_0}{\left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)\left(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}}\right)}\right) \tag{50b}$$

$$V_j^* = \left(\frac{pB\mathcal{R}_0}{\left(\mu+\gamma_1^{\mathrm{V}}+\varepsilon_1^{\mathrm{V}}\right)\left(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}}\right)}\right)\left(\prod_{i=2}^{j}\frac{\gamma_{i-1}^{\mathrm{V}}}{\left(\mu+\gamma_i^{\mathrm{V}}+\varepsilon_i^{\mathrm{V}}\right)}\right) \quad j=2,\ldots,n \tag{50c}$$

$$I_1{}^* = \left(\frac{B}{\left(\mu+\gamma_1^{\mathrm{I}}+\varepsilon_1^{\mathrm{I}}\right)}\right) \times\left(\left(1-\frac{1}{\mathcal{R}_0}\right)-p\left(1+\frac{\mathcal{R}_{\mathrm{V}}}{\left(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}}\right)}\right)\right) \tag{50d}$$

$$I_j^* = \left(\frac{B}{(\mu+\gamma_1^{\mathrm{I}}+\varepsilon_1^{\mathrm{I}})}\right)\left(\prod_{i=2}^{j}\frac{\gamma_{i-1}^{\mathrm{I}}}{(\mu+\gamma_i^{\mathrm{I}}+\varepsilon_i^{\mathrm{I}})}\right) \times\left(\left(1-\frac{1}{\mathcal{R}_0}\right)-p\left(1+\frac{\mathcal{R}_{\mathrm{V}}}{(\mathcal{R}_0-\mathcal{R}_{\mathrm{V}})}\right)\right)$$

$$j=2,\ldots,k. \tag{50e}$$

By employing Lyapunov functions analogous to those used to show global stability of the DFE and EE for the LAVV model (4), it is seen that the EE is globally asymptotically stable whenever $p < p_{\mathrm{crit}}(1-\frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$ while the DFE is globally asymptotically stable whenever $p \geq p_{\mathrm{crit}}(1-\frac{\mathcal{R}_{\mathrm{V}}}{\mathcal{R}_0})$. The computations follow exactly from the stability proofs for system (4), therefore we do not repeat them here.

We see that incorporating vaccine- and wild-type virus-induced death rates, the stability threshold for wild-type virus eradication appears the same as Eq. (2), specified by the reproduction numbers of the vaccine and wild-type virus. Note, however, that the expressions for the reproduction numbers are different in the presence of disease- and/or vaccine-induced mortality.

## 3. Contact vaccination within a pulse vaccination campaign

Contact vaccination within a pulse vaccination campaign may be described by the following equations, where the time interval between vaccination pulses is $T$. The underlying structure is based upon the standard (SIR) model (Anderson and May, 1991), ignoring disease- and vaccine-induced mortality, and using proportions as state variables,

$$\frac{dS}{dt} = \nu - \beta^{\mathrm{I}}(t)IS - \beta^{\mathrm{V}}(t)VS - \nu S \tag{51a}$$

$$\frac{dV}{dt} = \beta^{\mathrm{V}}(t)VS - (\nu+\gamma^{\mathrm{V}})V \tag{51b}$$

$$\frac{dI}{dt} = \beta^{\mathrm{I}}(t)IS - (\nu+\gamma^{\mathrm{I}})I \tag{51c}$$

$$\frac{dR}{dt} = \gamma^{\mathrm{I}}I + \gamma^{\mathrm{V}}V - \nu R \tag{51d}$$

$$S(nT^+) = (1-p_{\mathrm{pulse}})S(nT^-) \quad n\in\mathbb{N} \tag{51e}$$

$$V(nT^+) = V(nT^-) + p_{\mathrm{pulse}}S(nT^-). \tag{51f}$$

The parameter $p_{\mathrm{pulse}}$ is the pulse vaccination proportion, i.e., the proportion of susceptibles who are vaccinated during each vaccination pulse. We use the notation

$$S(nT^-) = \lim_{\varepsilon\to 0^+} S(nT-\varepsilon), \tag{51g}$$

and, for the sake of generality, we allow the vaccine virus transmission rate $\beta^{\mathrm{V}}(t)$ and the wild-type virus transmission rate $\beta^{\mathrm{I}}(t)$ to be time dependent. However, we assume that the transmission rates are continuous functions of time and $T$-periodic,

$$\beta^{\mathrm{V}}(t+T) = \beta^{\mathrm{V}}(t)\,, \tag{51h}$$

$$\beta^{\mathrm{I}}(t+T) = \beta^{\mathrm{I}}(t)\,. \tag{51i}$$

In practice, the pulse interval $T$ will always be a multiple of one year, so we are including the possibility of any seasonal changes in transmission rates for any realistic pulse interval. Other quantities in (51) have the same meanings that they do in systems (1) and (4).

### 3.1. Existence of the disease free $T$-periodic solution

We prove that for the system given by (51) a biologically meaningful $T$-periodic *disease free solution* (DFS) always exists. The stability of this solution, and the existence of multiple $T$-periodic disease free solutions, will be discussed in subsequent subsections.

Existence is shown in the following manner. Firstly, we enforce the disease free condition, $I \equiv 0$, so Eq. (51c) is automatically satisfied and we are left with the reduced system

$$\frac{dS}{dt} = \nu - \beta^{\mathrm{V}}(t)VS - \nu S \tag{52a}$$

$$\frac{dV}{dt} = \beta^{\mathrm{V}}(t)VS - (\nu+\gamma^{\mathrm{V}})V \tag{52b}$$

$$S(nT^+) = (1-p_{\mathrm{pulse}})S(nT^-)\,, \quad n\in\mathbb{N}, \tag{52c}$$

$$V(nT^+) = V(nT^-) + p_{\mathrm{pulse}}S(nT^-)\,. \tag{52d}$$

Eq. (52) is two-dimensional and non-autonomous. Nevertheless, existence of a $T$-periodic solution may be shown by exploiting the theory of impulsive differential equations. We proceed by applying the methods described in Bainov and Simeonov (1993). The mathematical proofs as well as necessary definitions and theorems (as in Bainov and Simeonov (1993)) are presented in Appendix D.

### 3.2. Stability of the $T$-periodic disease free solution

#### 3.2.1. Necessary conditions

Having shown that a disease free $T$-periodic solution always exists, we now seek to discover under what conditions this solution is asymptotically stable. To this end we investigate the variational equation obtained from linearization of system (51) about the disease free $T$-periodic solution which we denote $\{S(t) = \widehat{S(t)},\ V(t) = \widehat{V(t)},\ I(t) = 0\}$. The variational equation that governs the growth and decay of perturbations $(s, v, i)$ about the DFS is given as follows, where $\dot{x}$ denotes the time derivative of $x$. For $t \neq kT$,

$$\begin{pmatrix}\dot{s}\\ \dot{v}\\ \dot{i}\end{pmatrix} = \begin{pmatrix}-\beta^{\mathrm{V}}(t)\widehat{V(t)}-\nu & -\beta^{\mathrm{V}}(t)\widehat{S(t)} & -\beta^{\mathrm{I}}(t)\widehat{S(t)}\\ \beta^{\mathrm{V}}(t)\widehat{V(t)} & \beta^{\mathrm{V}}(t)\widehat{S(t)}-(\nu+\gamma^{\mathrm{V}}) & 0\\ 0 & 0 & \beta^{\mathrm{I}}(t)\widehat{S(t)}-(\nu+\gamma^{\mathrm{I}})\end{pmatrix} \times\begin{pmatrix}s\\ v\\ i\end{pmatrix} \tag{53a}$$

while for $t = kT$,

$$\begin{pmatrix}s(kT)\\ v(kT)\\ i(kT)\end{pmatrix} = \begin{pmatrix}(1-p) & 0 & 0\\ p & 1 & 0\\ 0 & 0 & 1\end{pmatrix}\begin{pmatrix}s(kT^-)\\ v(kT^-)\\ i(kT^-)\end{pmatrix}. \tag{53b}$$

The fundamental matrix solution $\Psi(t)$ of (53) is defined to be

$$\Psi(t) = \begin{pmatrix}s_1 & s_2 & s_3\\ v_1 & v_2 & v_3\\ i_1 & i_2 & i_3\end{pmatrix} \tag{54a}$$

$$\Psi(0) = \mathbb{1} \tag{54b}$$

where each column of (54a) is a solution of (53). The stability of the $T$-periodic solution is determined by the eigenvalues of $\Psi(t)$ evaluated at time $t = T$. This result is explained by standard floquet theory (Perko, 1996). For any perturbation from the DFS which we denote $\varepsilon_S^0, \varepsilon_V^0, \varepsilon_I^0$, the growth of the perturbation is given as

$$\begin{pmatrix}\varepsilon_S(T)\\ \varepsilon_V(T)\\ \varepsilon_I(T)\end{pmatrix} = \Psi(T)\begin{pmatrix}\varepsilon_S^0\\ \varepsilon_V^0\\ \varepsilon_I^0\end{pmatrix} + \mathcal{O}((\varepsilon^0)^2). \tag{55}$$

if all eigenvalues of $\Psi(T)$ have magnitude less than one, sufficiently small perturbations will decay at least geometrically with every period $T$ and the DFS will be (locally) asymptotically stable.

Although there is no general method for constructing the fundamental matrix, much can still be said about it. It can be seen from (53) that the equation for the perturbation $i(t)$ is decoupled from the rest of the system and thus can be explicitly solved as

$$i(t) = i(0)e^{\int_0^t \beta^{\mathrm{I}}(r)\widetilde{S(r)} - (\nu+\gamma^{\mathrm{I}})\mathrm{d}r}. \tag{56}$$

As a result, we can slightly simplify the form of the fundamental matrix and write

$$\Psi(T) = \begin{pmatrix} \Psi_{11}(T) & \Psi_{12}(T) & \Psi_{13}(T) \\ \Psi_{21}(T) & \Psi_{22}(T) & \Psi_{23}(T) \\ 0 & 0 & e^{\int_0^T [\beta^{\mathrm{I}}(t)\widehat{S(t)} - (\nu+\gamma^{\mathrm{I}})]\,\mathrm{d}t} \end{pmatrix}. \tag{57}$$

Because the eigenvalues of block diagonal matrices are the eigenvalues of each of the blocks, the form of (57) implies that one of the eigenvalues of $\Psi(T)$ is

$$\lambda_3 = e^{[\int_0^T \beta^{\mathrm{I}}(t)\widehat{S(t)}\,\mathrm{d}t] - (\nu+\gamma^{\mathrm{I}})T}. \tag{58}$$

The $T$-periodic solution (DFS) will be local asymptotically stable if

$$\max_{i=1,2,3} |\lambda_i(\Psi(T))| < 1, \tag{59}$$

and only if

$$\max_{i=1,2,3} |\lambda_i(\Psi(T))| \le 1. \tag{60}$$

Inserting (58) in (60) gives a necessary condition for stability,

$$|\lambda_3| \le 1 \iff \int_0^T \beta^{\mathrm{I}}(t)\widehat{S(t)}\,\mathrm{d}t \le (\nu+\gamma^{\mathrm{I}})T. \tag{61}$$

A complete closed-form analytical expression for the $\Psi_{ij}$ cannot in general be computed, so we will be forced to complete the stability analysis numerically. If condition (61) is satisfied then the stability of the DFS will be determined by the eigenvalues of the smaller matrix

$$\Psi_{\text{reduced}}(T) = \begin{pmatrix} \Psi_{11}(T) & \Psi_{12}(T) \\ \Psi_{21}(T) & \Psi_{22}(T) \end{pmatrix}. \tag{62}$$

$\Psi_{\text{reduced}}(T)$ may be thought of as the fundamental matrix solution of the variational equation (53) restricted to the $(S, V)$ plane. In the following sections we will numerically investigate the eigenvalues of this matrix to determine the stability of the DFS.

It is enlightening to note that if the transmission rate $\beta^{\mathrm{I}}(t) = \beta^{\mathrm{I}}$, a constant, then expression (61) simplifies to the ubiquitous condition (d'Onofrio, 2002; Shulgin et al., 1998; Stone et al., 2000)

$$\frac{1}{T}\int_0^T \widehat{S(t)}\,\mathrm{d}t \le \frac{\gamma^{\mathrm{I}}+\nu}{\beta^{\mathrm{I}}} = \frac{1}{\mathcal{R}_0}, \tag{63}$$

which states that the average proportion of the population that is susceptible (over a pulse interval $T$) must be kept below the threshold level $\frac{1}{\mathcal{R}_0}$. The general necessary condition (61) is different only in that the average of $\widehat{S(t)}$ is weighted by the oscillation in transmission rate.

### 3.2.2. Sufficient conditions for stability

For the remainder of our analysis, we focus on the case of constant transmission: $\beta^{\mathrm{V}}(t) = \beta^{\mathrm{V}}$, $\beta^{\mathrm{I}}(t) = \beta^{\mathrm{I}}$. The $T$-periodic DFS will be asymptotically stable whenever

$$\frac{1}{T}\int_0^T \widehat{S(t)}\mathrm{d}t < \frac{1}{\mathcal{R}_0} \tag{64a}$$

$$\max_{i=1,2} |\lambda_i(\Psi_{\text{reduced}}(T))| < 1. \tag{64b}$$

In Eq. (64b) $\lambda_i$ denotes the Floquet multipliers, eigenvalues of $\Psi_{\text{reduced}}(T)$, where $\Psi_{\text{reduced}}(t)$ is fundamental matrix solution of the variational equation about the $T$-periodic DFS $(\widehat{S(t)}, \widehat{V(t)})$. The variational equation is given by

$$\begin{pmatrix} \dot{s} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -\beta^{\mathrm{V}}\widehat{V(t)} - \nu & -\beta^{\mathrm{V}}\widehat{S(t)} \\ \beta^{\mathrm{V}}\widehat{V(t)} & \beta^{\mathrm{V}}\widehat{S(t)} - (\nu+\gamma^{\mathrm{V}}) \end{pmatrix} \begin{pmatrix} s \\ v \end{pmatrix},$$

$$t \ne kT \tag{65a}$$

$$s(kT) = (1 - p_{\text{pulse}})\, s(kT^-) \tag{65b}$$

$$v(kT) = v(kT^-) + p_{\text{pulse}}\, s(kT^-) \tag{65c}$$

$$s(kT^-) = \lim_{\varepsilon \to 0^+} s(kT - \varepsilon). \tag{65d}$$

As there is no general analytical method for computing the fundamental matrix solution of the non-autonomous equation (65) we compute the eigenvalues of $\Psi_{\text{reduced}}(T)$ numerically. We define a non-linear map as the integration $\int_0^T$ of system (52) using a fourth-order Runge–Kutta scheme with stepsize of $\frac{1}{2}$ day. The $T$-periodic DFS is the fixed point of this map. Beginning from a known solution ($\mathcal{R}_{\mathrm{V}} = 0$) or one obtained numerically from successive integrations of the map, we use the bifurcation and continuation analysis software CONTENT 1.5 (Kuznetsov, 1998) to numerically continue the $T$-periodic DFS as a function of the system parameters and compute the floquet multipliers (64b). We subsequently investigate global stability via simulation in MATLAB, using a fourth-order adaptive stepsize routine.

So far, we have focused on the $T$-periodic DFS that we know exists. Our analysis does not rule out the possibility of multiple coexisting period-$T$ or period-$kT$ disease free solutions, or more complicated dynamics. We address these issues in our numerical analysis in the next subsection.

### 3.2.3. Uniqueness of disease free solutions

Pulse vaccination without transmission of vaccine virus ($\mathcal{R}_{\mathrm{V}} = 0$) has been well studied. In this case there exists a *unique* $T$-periodic DFS which can be computed straightforwardly. Furthermore, for a given vaccination proportion of susceptibles ($p_{\text{pulse}}$ in (51)) there exists a maximum pulsing period $T_{\max}$ for which this DFS is globally asymptotically stable (d'Onofrio, 2005; Stone et al., 2000; Shulgin et al., 1998). The fundamental idea that local stability of the $T$-periodic DFS in fact implies global stability has been extended to SEIR type models with Gamma distributed latent and infectious periods (d'Onofrio, 2002, 2004).

In the numerical analysis we now describe, we considered vaccine virus in the fairly large range $0 < \mathcal{R}_{\mathrm{V}} \le 7$. The birth rate was fixed at $\nu = 0.02\,\mathrm{yr}^{-1}$ and the vaccine virus infectious period was taken to be $\frac{1}{\gamma^{\mathrm{V}}} = 16$ days, roughly corresponding to wild-type poliovirus (Anderson and May, 1991). For $\mathcal{R}_{\mathrm{V}} \le 5$ and $T = 1, 2, 3$ years, the $T$-periodic DFS was computed via continuation in CONTENT 1.5, and found to be always locally stable in the $(S, V)$ plane (64b). Subsequent simulations indicated that the computed DFS is likely the unique stable DFS in this parameter range. For $T = 6$ years, the same results hold for $0 < \mathcal{R}_{\mathrm{V}} \le 4$, with a seemingly unique DFS that is locally asymptotically stable in the $(S, V)$ plane. (We note that in their continuous OPV vaccination models, Eichner and Hadeler (1995) considered $\mathcal{R}_0 = 12$ and $\mathcal{R}_{\mathrm{V}} = 3$.)

For higher $\mathcal{R}_{\mathrm{V}}$, holding $\mathcal{R}_{\mathrm{V}}$ fixed and varying the pulsing proportion ($0 \le p_{\text{pulse}} \le 1$) we observe a sequence of limit point bifurcations resulting in bistability and hysteresis. As a two-parameter bifurcation in $(p_{\text{pulse}}, \mathcal{R}_{\mathrm{V}})$ space, this is manifested as a cusp bifurcation starting at $\mathcal{R}_{\mathrm{V}} > 4$. Fig. 5 shows the coexisting stable and unstable DFS in $(S, V)$ space for $T = 6$, $\mathcal{R}_{\mathrm{V}} = 7$. The

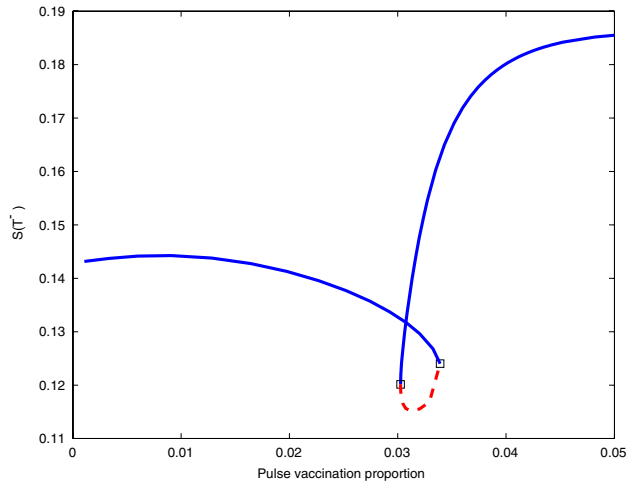


**Fig. 5.** Bifurcation diagram for the $T = 6$ periodic *disease free solution* in the $(S, V)$ plane ($\mathcal{R}_V = 7$, $1/\gamma V = 16$ days, $\nu = 0.02$). The bifurcation parameter is $p_{\text{pulse}}$, the pulse vaccination proportion, while the dependent parameter is $S(T^-)$, the proportion of susceptibles immediately before the vaccination pulse. The $(S, V)$ stable solution branches are shown with solid lines, unstable branches with dashed lines. Black rectangles indicate the location of the limit point bifurcations. The system exhibits bistability and hysteresis in the narrow range $0.030 < p_{\text{pulse}} < 0.035$.

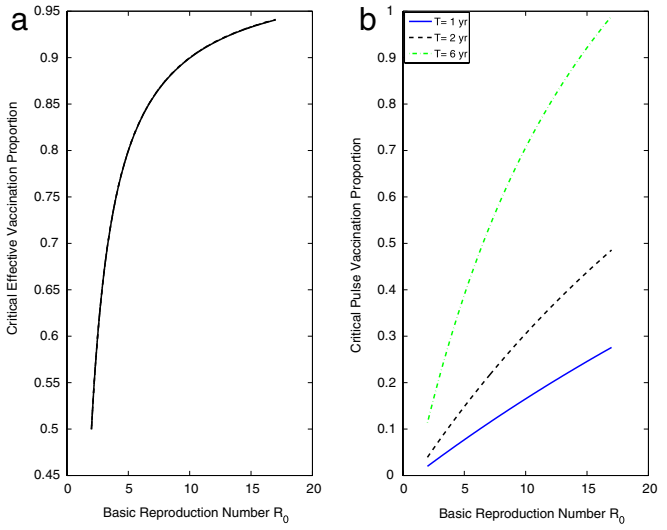


**Fig. 6.** (a) Critical effective vaccination proportion $p_{\text{eff,crit}}$ in the absence of contact vaccination ($\mathcal{R}_V = 0$) as a function of wild-type virus reproduction basic reproduction number $\mathcal{R}_0$. For continuous vaccination as well as pulse vaccination the curve is given by $p_{\text{eff,crit}} = p_{\text{crit}} = \left(1 - \frac{1}{\mathcal{R}_0}\right)$ independent of the pulsing period $T$. (b) Critical pulse vaccination proportion $p_{\text{pulse,crit}}$ in the absence of contact vaccination $\mathcal{R}_V = 0$ as a function of wild-type virus basic reproduction number $\mathcal{R}_0$. Pulsing periods of $T = 1, 2, 6$ years are considered. $p_{\text{pulse,crit}}$ increases non-linearly with $\mathcal{R}_0$. Note that higher $T$ and $\mathcal{R}_0$ values necessitate vaccination of nearly all susceptibles. However, for annual and biennial pulses $p_{\text{pulse,crit}}$ remains in a realistic range.

bifurcation parameter is the pulse vaccination proportion $p_{\text{pulse}}$ while the vertical axis gives the proportion of the susceptible population immediately before the vaccination pulse, which we denote $S(T^-)$. The solid line denotes stable solution branches in $(S, V)$ space, while the dashed lines denote unstable branches.

There are two coexisting $(S, V)$ stable DFSs in a narrow range of the proportion of susceptibles vaccinated ($0.030 \leq p_{\text{pulse}} \leq 0.035$). For smaller $\mathcal{R}_V$ this window is even narrower and closer to zero. The significance of the two coexisting DFSs is negligible in practice. These coexisting solutions are asymptotically stable in the $(S, V)$ plane; however, to be stable in the full $(S, V, I)$ space (51), condition (63) must also be satisfied. For the range of $p_{\text{pulse}}$ where there is bistability, computing the average level of susceptibles for each DFS over the pulsing period $T$, and enforcing the stability condition (63), we find numerically that

$$\frac{1}{T}\int_0^T \widehat{S(t)}\,\mathrm{d}t \leq \frac{1}{\mathcal{R}_0} \iff \mathcal{R}_V \approx \mathcal{R}_0. \tag{66}$$

So, the coexisting $(S, V)$ stable DFSs will be stable in the full $(S, V, I)$ space only if $\mathcal{R}_V \approx \mathcal{R}_0$. Result (66) may be intuitively obvious as the parameter range of bistability occurs when $p_{\text{pulse}}$ is very close to zero. For example, if a single vaccinated person were introduced into a population with no other vaccination, the wild-type virus could only be eradicated if $\mathcal{R}_V > \mathcal{R}_0$. This is to say that the vaccine virus must out-compete the wild-type virus. Similarly for only a small amount of vaccination, the vaccine virus must remain almost as competitive as the wild-type virus in order to achieve eradication.

The attenuation process results in vaccine virus reproduction numbers $\mathcal{R}_V$ that are significantly lower than the wild-type virus $\mathcal{R}_0$; hence, we expect the coexisting DFS to be unstable for all realistic parameters. Furthermore, no bifurcations – cusp or otherwise – were detected for $T = 1, 2, 3$ years. Thus, we find that for realistic epidemiological parameters the full epidemiological system exhibits at most one asymptotically stable DFS.

## 4. Control of wild virus spread

We now consider the control implications of the combination of pulse vaccination and contact vaccination, which we will abbreviate to "PC vaccination" for convenience. We analyze our model (51) with two comparisons in mind, both related to the ability of contact vaccination to help control wild-type virus spread.

### 4.1. Definitions and terminology

#### 4.1.1. PC versus standard pulse vaccination

Firstly, we wish to compare the efficacy of PC vaccination to that of standard pulse vaccination (i.e., pulse vaccination in the absence of vaccine virus transmission). This comparison may be achieved straightforwardly by examining $p_{\text{pulse,crit}}$, the threshold level of the pulse vaccination proportion $p_{\text{pulse}}$ required for asymptotic stability of the DFS (note that $p_{\text{pulse,crit}}$ depends on the pulse interval $T$).

For convenience, we define a normalized critical pulse proportion as

$$\widehat{p}_{\text{pulse,crit}}(\mathcal{R}_V, \mathcal{R}_0) = \frac{p_{\text{pulse,crit}}(\mathcal{R}_V, \mathcal{R}_0)}{p_{\text{pulse,crit}}(0, \mathcal{R}_0)}, \tag{67}$$

which represents the value of $p_{\text{pulse,crit}}$ normalized by the value of $p_{\text{pulse,crit}}$ in the absence of contact vaccination ($\mathcal{R}_V = 0$). Therefore, definition (67) gives the critical pulse vaccination proportion as a proportion of the critical value under standard pulse vaccination.

#### 4.1.2. PC versus CC vaccination

Secondly, we wish to answer whether – in the presence of contact vaccination – pulse vaccination campaigns (i.e., PC vaccination) will be more or less effective in controlling wild-type virus spread than continuous vaccination campaigns (i.e., CC vaccination). This second question is not as straightforward to answer, as there are many ways to compare the continuous (1) and pulse (51) vaccination models.

One relevant measure of comparison is the critical effective pulse vaccination proportion $p_{\text{eff,crit}}$ required to ensure stability of the DFS. We define the effective pulse vaccination proportion to

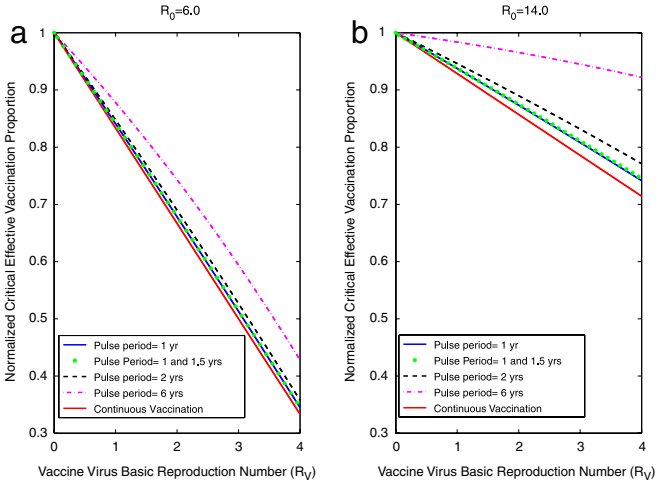


**Fig. 7.** Normalized critical effective vaccination proportion $\widehat{p}_{\text{eff,crit}}$ (70a) as a function of vaccine virus basic reproduction number $\mathcal{R}_V$ for pulse and continuous vaccination campaigns. (a) $\mathcal{R}_0 = 6$. (b) $\mathcal{R}_0 = 14$. Continuous vaccination is optimal in the sense of $\widehat{p}_{\text{eff,crit}}$ (and therefore $p_{\text{eff,crit}}$) given by Eq. (70a). As the period of vaccination $T$ and $\mathcal{R}_0$ are increased $\widehat{p}_{\text{eff,crit}}$ increases. For relatively long vaccination periods and high values of $\mathcal{R}_0$ there is little advantage as compared to standard vaccination; however for annual vaccine pulses there remains a significant advantage and negligible difference with the continuous vaccination curve. Alternating pulse intervals between one year and 1.5 years (green dotted curve) leads to results that are negligibly different from annual pulses (blue solid curve).(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be the number of successful vaccinations per pulsing period as a proportion of births over that same period,

$$p_{\text{eff}} = \frac{\text{vaccinations per pulse interval } T}{\nu T}. \tag{68}$$

Definition (68) is natural since in the case of continuous vaccination it reduces to the standard parameter $p$, the proportion of newborns vaccinated. Thus, for continuous vaccination $p_{\text{eff,crit}}$ can be computed analytically, while for pulse vaccination we compute it numerically. The critical values for continuous and pulse vaccination are given, respectively, by

$$\begin{aligned} p_{\text{eff,crit}}(\mathcal{R}_V, \mathcal{R}_0) &= p_{\text{crit}}\left(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}\right) \quad \text{(continuous)} \\ p_{\text{eff,crit}}(\mathcal{R}_V, \mathcal{R}_0) &= \frac{p_{\text{pulse,crit}}\, S(T^-)}{\nu T} \quad \text{(pulse)}. \end{aligned} \tag{69a}$$

In Eq. (69a), $S(T^-)$ is the proportion of the population that is susceptible immediately before the vaccination pulse (in the $T$-periodic DFS with $p_{\text{pulse}} = p_{\text{pulse,crit}}$).

In the absence of contact vaccination ($\mathcal{R}_V = 0$) the value of $p_{\text{eff,crit}}$ is in fact equivalent for both continuous and pulse vaccination, independent of the vaccination period $T$ (d'Onofrio, 2002; Shulgin et al., 1998). This fact is illustrated in Fig. 6a, which shows $p_{\text{eff,crit}}$ for $\mathcal{R}_V = 0$ as a function of $\mathcal{R}_0$ for pulsing periods of $T = 1, 2, 3, 6$ years. The result is a single curve $p_{\text{crit}} = \left(1 - \frac{1}{\mathcal{R}_0}\right)$ as predicted by Eq. (69a).

Due to this equality it is useful to define normalized quantities to compare CC and PC vaccination programs. We normalize by the value $p_{\text{crit}}$, the value of $p_{\text{eff,crit}}$ when $\mathcal{R}_V = 0$. We define $\widehat{p}_{\text{eff,crit}}$ to be the normalized critical effective vaccination proportion, which can be expressed for continuous and pulse vaccination programs respectively as

$$\begin{aligned} \widehat{p}_{\text{eff,crit}}(\mathcal{R}_V, \mathcal{R}_0) &= 1 - \frac{\mathcal{R}_V}{\mathcal{R}_0} \quad \text{(continuous)} \\ \widehat{p}_{\text{eff,crit}}(\mathcal{R}_V, \mathcal{R}_0) &= \frac{p_{\text{eff,crit}}(\mathcal{R}_V, \mathcal{R}_0)}{p_{\text{eff,crit}}(0, \mathcal{R}_0)} \quad \text{(pulse)} \\ p_{\text{eff,crit}}(0, \mathcal{R}_0) &= p_{\text{crit}}. \end{aligned} \tag{70a}$$

### 4.2. Numerical results

#### 4.2.1. PC versus CC

Figs. 7(a) and (b) show the normalized critical effective vaccination proportion $\widehat{p}_{\text{eff,crit}}$ as a function of $\mathcal{R}_V$ for wild-type viruses with $\mathcal{R}_0 = 6$ and 14. Vaccine virus reproduction numbers are considered in the range $0 \le \mathcal{R}_V \le 4$. The solid red line in each figure represents $\widehat{p}_{\text{eff,crit}}$ for continuous vaccination given by the analytical expression (70a).

Continuous vaccination gives a lower bound for $\widehat{p}_{\text{eff,crit}}$. For pulse vaccination strategies $\widehat{p}_{\text{eff,crit}}$ increases as both the pulsing period and $\mathcal{R}_0$ are increased. For sufficiently small periods the pulse vaccination results converge to those for continuous vaccination. For the parameter ranges considered, we see that even for annual pulsing, $\widehat{p}_{\text{eff,crit}}$ differs negligibly from the threshold (70a) for continuous vaccination. Additionally we see that for non-constant pulse intervals, demonstrated by the case of alternating pulse intervals of 1 and 1.5 years, the value of $\widehat{p}_{\text{eff,crit}}$ is strongly influenced by the minimum pulse interval. It will lie slightly above the value of $\widehat{p}_{\text{eff,crit}}$ when considering the minimum pulse interval alone (i.e., constant pulse interval case).

Continuous vaccination is – from the point of view of contact vaccination – an optimal strategy, in that removing susceptibles continuously maximizes the benefit of contact vaccination. We stress that we say optimal only in the sense of contact immunization, as there are a variety of other reasons why pulse vaccination as an overall strategy may be superior to continuous vaccination (Sabin, 1991; Wagner and Earn, 2008).

#### 4.2.2. PC versus standard pulse vaccination

It is useful to note that if $S(T^-)$ is independent of $\mathcal{R}_V$ then Eqs. (69) and (70) straightforwardly imply that $\widehat{p}_{\text{pulse,crit}} = \widehat{p}_{\text{eff,crit}}$. For the parameter values considered in this work, we have seen that $S(T^-)$ depends extremely weakly on $\mathcal{R}_V$. Consequently, graphs that we have drawn as a function of $\widehat{p}_{\text{eff,crit}}$ differ negligibly from the corresponding graphs as a function of $\widehat{p}_{\text{pulse,crit}}$; this equivalence is illustrated in Fig. 8 which shows $\widehat{p}_{\text{pulse,crit}}$ (Fig. 8(a)) and $\widehat{p}_{\text{eff,crit}}$ (Fig. 8(b)) as a function of $\mathcal{R}_V$ for $\mathcal{R}_0 = 12$. At the scales represented there is no detectable difference between the curves.

Since the behaviour of $\widehat{p}_{\text{eff,crit}}$ and $\widehat{p}_{\text{pulse,crit}}$ is practically equivalent, the discussion of Fig. 7 in Section 4.2.1 applies to $\widehat{p}_{\text{pulse,crit}}$. Hence, we see that for pulse vaccination the critical pulse vaccination proportion is bounded below by

$$p_{\text{pulse,crit}}(\mathcal{R}_V, \mathcal{R}_0) \ge p_{\text{pulse,crit}}(0, \mathcal{R}_0)\left(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}\right), \tag{71}$$

where $p_{\text{pulse,crit}}(0, \mathcal{R}_0)$ is the critical pulse vaccination proportion for standard pulse vaccination (no contact vaccination). Reiterating the statements of Section 4.2.1, there is little difference between the bounding curve and the curve for annual vaccination pulses, but the difference increases as the pulsing period $T$ is increased.

Values of $p_{\text{pulse,crit}}(0, \mathcal{R}_0)$ are shown in Fig. 6(b) for pulsing periods of 1, 2 and 6 years. Notice that for $T = 6$ and $\mathcal{R}_0 \approx 17$ in the absence of contact vaccination nearly 100% of the susceptible population must be vaccinated in every pulse, which is unrealistic. However, for biennial and shorter pulsing periods, $p_{\text{pulse,crit}}(0, \mathcal{R}_0)$ lies in a realistic range.

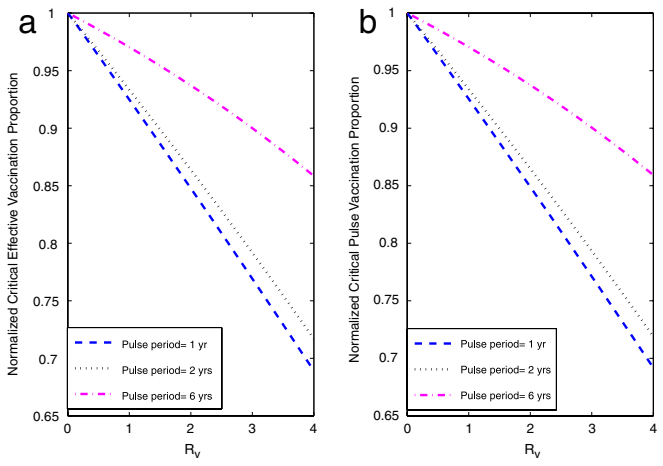


**Fig. 8.** Normalized critical effective vaccination proportion $\widehat{p}_{\text{eff,crit}}$ (70a) (a) and normalized critical pulse vaccination proportion $\widehat{p}_{\text{pulse,crit}}$ (67) (b) as a function of vaccine virus basic reproduction number ($\mathcal{R}_V$) for a wild-type virus of $\mathcal{R}_0 = 12$ and a range of pulsing periods. Notice $\widehat{p}_{\text{pulse,crit}} \approx \widehat{p}_{\text{eff,crit}}$. This approximate equality holds across the range of childhood diseases $0 < \mathcal{R}_0 \leq 30$ and is a direct result of the fact that $S(T^-)$, though strongly dependent on $\mathcal{R}_0$, depends very weakly on $\mathcal{R}_V$ (69a) (70a).

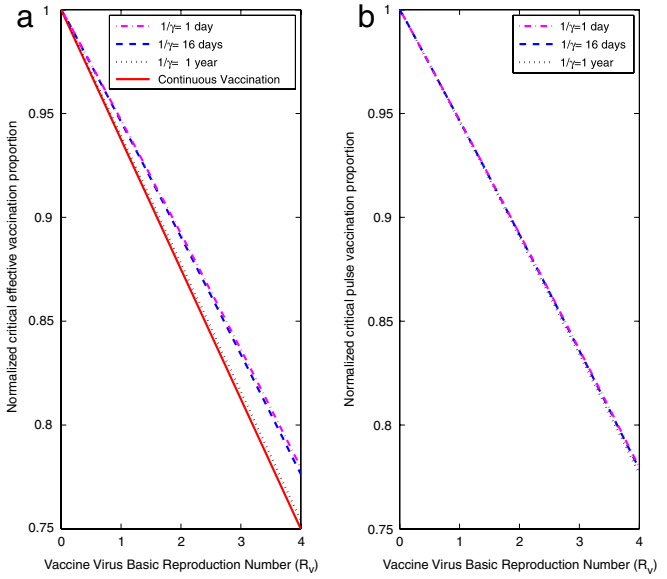


**Fig. 9.** (a) Normalized critical effective vaccination proportion $\widehat{p}_{\text{eff,crit}}$ (70) for an annual pulse vaccination campaign ($\mathcal{R}_0 = 16$) as a function of vaccine virus reproduction number $\mathcal{R}_V$. Curves show a range of vaccine virus infectious periods $1/\gamma V$ from 1 day to 1 year. The curves for vaccine virus infectious periods of 1 day and 16 days are indistinguishable, while for 1 year there is a slight decrease in $\widehat{p}_{\text{eff,crit}}$ differing negligibly with the continuous vaccination model (70a). (b) Normalized critical pulse vaccination proportion $\widehat{p}_{\text{pulse,crit}}$ for annual pulse vaccination campaigns as a function of vaccine virus reproduction numbers; parameter values as in (a). For vaccine virus mean infectious periods ranging from 1 day to 1 year there is negligible difference in $\widehat{p}_{\text{pulse,crit}}$. As well for mean vaccine virus infectious periods of 1 and 16 days the curves of $\widehat{p}_{\text{pulse,crit}}$ are negligibly different from the corresponding curves for $\widehat{p}_{\text{eff,crit}}$ in (a), as explained in Section 4.2.2.

#### 4.2.3. Dependence on infectious period

The previous numerical results assumed a vaccine virus mean infectious period of $\frac{1}{\gamma^V} = 16$ days, which corresponds approximately to the infectious period of wild-type poliovirus (Anderson and May, 1991). However, the results we have described are in fact valid much more generally, demonstrating only a very weak dependence on the length of the infectious period (for $\mathcal{R}_V$ fixed). Fig. 9 shows the normalized critical pulse vaccination proportion $\widehat{p}_{\text{pulse,crit}}$, and the normalized critical effective vaccination proportion $\widehat{p}_{\text{eff,crit}}$ as a function of $\mathcal{R}_V$ for annual pulse vaccination campaigns and vaccine virus infectious periods of $\frac{1}{\gamma^V} = 1$ day, 16 days and 1 year. The wild-type virus reproduction number is set at $\mathcal{R}_0 = 16$. The range of mean infectious periods up to a year includes all childhood infections, of which most have duration less than 1 month (Anderson and May, 1991).

In Fig. 9(b), $\widehat{p}_{\text{pulse,crit}}$ is indistinguishable for the three different mean infectious periods, again lying slightly above the line $1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}$. In Fig. 9(a), for the vaccine virus infectious periods of 1 day and 16 days, the $\widehat{p}_{\text{eff,crit}}$ values are indistinguishable from each other, as well as from the corresponding normalized curves $\widehat{p}_{\text{pulse,crit}}$ in Fig. 9(b). For the much larger vaccine virus infectious period of 1 year, there is a slight decrease ($<0.04$) in $\widehat{p}_{\text{eff,crit}}$, in fact differing negligibly from $\widehat{p}_{\text{eff,crit}}$ for the continuous vaccination model.

Biologically, this decrease in $\widehat{p}_{\text{eff,crit}}$ for longer vaccine virus mean infectious periods occurs because a longer infectious period yields a higher probability that vaccine infectiousness will persist until susceptibles have been replenished via births. This allows the infectious individual to cause a greater number of secondary transmissions. However, this effect is noticeable only for very long infectious periods (as long as the pulsing period itself). For childhood diseases, we conclude that the stability threshold has no significant dependence on the vaccine virus infectious period. Since the stability threshold (65) derived analytically is independent of the wild-type virus mean infectious period, we conclude that – like for continuous vaccination – for pulse vaccination the stability threshold depends in practice only on the reproduction numbers $\mathcal{R}_0$ and $\mathcal{R}_V$.

## 5. Discussion

The benefit of secondary or contact immunization arising from the use of live-attenuated virus vaccines has long been known by epidemiologists. Newly vaccinated individuals may pass on vaccine virus to their contacts resulting in (secondary) immunization. In fact, this benefit is cited as one of the five primary reasons for the use of the Oral Polio Vaccine (OPV) in the developing world (Hull et al., 1994; John, 2004). In this work, we have quantified this benefit, both for different types of vaccination strategies and for vaccine and wild-type pathogenic viruses with possibly very different epidemiological properties.

In the case where vaccinations are performed continuously in the population, we established that the necessary vaccination proportion to eradicate the wild-type pathogenic virus is given by a simple expression (2) that depends only on the *basic reproduction numbers* of the two viruses. Furthermore, eradication is achieved regardless of the composition of the population, in terms of susceptible and infected individuals when vaccination is initiated (mathematically, the disease free equilibrium is globally asymptotically stable if the vaccination level exceeds the threshold (2)). We showed that this result is valid regardless of how an individual's infectiousness varies over the course of his/her infection (from either wild-type or vaccine virus); an individual may progress through any number of distinct stages of infection, including latent stages, with the amount of time spent in each stage given probabilistically by an effectively arbitrary distribution.

Increasingly in the developing world, vaccination programs for childhood diseases incorporate some form of pulse vaccination whereby mass vaccinations are performed at regular intervals as opposed to continuously. Most notably, many countries in the developing world employ annual OPV vaccination (Anon, 2008). We compared the benefits of contact vaccination in pulse vaccination programs to the results derived for continuous vaccination, with

specific focus on the use of OPV. We showed that continuous vaccination maximizes the benefit of contact vaccination, in terms of reducing the critical vaccination level for wild-type virus eradication. This contrasts previous work (not considering the effects of contact immunization) which indicated that pulse and continuous vaccination strategies have the same critical vaccination level (in terms of vaccinations as a proportion of births over the same time period) (d'Onofrio, 2002; Shulgin et al., 1998).

For a given number of individuals vaccinated, the benefit of contact vaccination is lower for longer inter-pulse intervals and for larger wild-type virus basic reproduction numbers. This makes biological sense because, in addition to introducing new vaccine virus infectious individuals who can immunize others, vaccination reduces the pool of susceptible individuals who can become secondarily vaccinated. Consequently, spreading a given number of vaccinations evenly in time (continuous vaccination) maximizes the number of secondary vaccinations that can be achieved.

For OPV use, we found that although continuous vaccination always yields the lowest vaccination threshold, thresholds for *annual* OPV campaigns differ negligibly. However, for biennial and longer inter-pulse intervals, the differences become significant. The key point is that there is no significant decrease in the benefits of contact vaccination for current (annual) pulse OPV campaigns.

Compared to use of an inactivated (non-live) vaccine, even for low vaccine virus reproduction numbers ($\mathcal{R}_V < 1$), there is a significant reduction of threshold vaccination levels. Unfortunately, to assess the importance of contact vaccination quantitatively for a given pathogen, an estimate of $\mathcal{R}_V$ is required. Beyond anecdotal evidence and limited case studies (Neff et al., 2002), there has been no emphasis on the estimation of vaccine virus reproduction numbers. Such estimation is extremely difficult as, short of performing detailed serological studies, there is no way to distinguish immunity acquired from the wild-type or vaccine virus.

In this work we have assumed that vaccination (whether primary or contact) results in complete, lifelong immunity. This is generally a very good approximation for most childhood diseases (Woodrow and Levine, 1990). However, in the case where vaccination results in incomplete or waning immunity, contact vaccination may play an important role in boosting immunity of previously vaccinated individuals. The significance of contact immunization in boosting immunity will be investigated in future work.

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## Appendix A. Mathematical well-posedness

### A.1. Positive invariance of the biologically meaningful set

We denote the state of the system (4) as

$$\mathbf{X} = (S, V_1, V_2, \ldots, V_n, I_1, I_2, \ldots, I_k, R). \tag{72}$$

We show that the biologically meaningful set, defined as

$$\mathcal{B} = \left\{ \mathbf{X} : \mathbf{X}_i \geq 0,\ \sum_i \mathbf{X}_i = 1 \right\}, \tag{73}$$

is positively invariant with respect to Eq. (4). From the form of the equations it is straightforwardly seen that if all initial states are non-negative, they remain non-negative for all positive time. Furthermore summing Eqs. (4a)–(4h) yields the differential equation

$$\frac{d}{dt}\left(\sum_i \mathbf{X}_i\right) = \nu - \nu \sum_i \mathbf{X}_i \tag{74}$$

which has a single equilibrium at $\sum_i \mathbf{X}_i = 1$. Since by definition any initial condition in $\mathcal{B}$ satisfies $\sum_i \mathbf{X}_i(0) = 1$, (74) trivially implies that $\sum_i \mathbf{X}(t) = 1\,\forall t > 0$. Thus, $\mathbf{X}(t) \in \mathcal{B} \quad \forall t \geq 0$ and the model (4) is biologically well posed.

Note that since Eqs. (4a)–(4g) are independent of $R$, we need only deal *directly* with this subsystem, ignoring Eq. (4h). Thus, it is convenient to express $\mathcal{B}$ as

$$\mathcal{B} = \left\{ S, V_i, I_i : S, V_i, I_i \geq 0, \quad S + \sum_{i=1}^{n} V_i + \sum_{i=1}^{k} I_i \leq 1 \right\} \tag{75}$$

where it is understood that $R = 1 - S - \sum_{i=1}^{n} V_i - \sum_{i=1}^{k} I_i$.

### A.2. Location of equilibria

We show any equilibrium $\mathbf{X}^*$ of system (4) such that $S^* \geq 0$, $V_i^* \geq 0\,\forall i$ and $I_j^* \geq 0\,\forall j$ must in fact lie in the biologically meaningful set $\mathcal{B}$. To see this observe that at equilibrium Eq. (4h) implies

$$R^* = \frac{1}{\nu}\left(\gamma_n^V V_n^* + \gamma_k^I I_k^*\right). \tag{76}$$

The assumption that $V_n^*, I_k{}^*$ are non-negative then implies that $R^* \geq 0$, and thus all states are non-negative. As previously shown by (74) at *any* equilibrium we must have

$$\sum_i X_i^* = S^* + R^* + \sum_{i=1}^{n} V_i^* + \sum_{i=1}^{k} I_i^* = 1 \tag{77}$$

implying that $\mathbf{X}^* \in \mathcal{B}$. We make use of this result in the computation of the *disease free* and *endemic* equilibrium.

## Appendix B. Geometric and arithmetic means

A standard result is that for any set of positive real numbers

$$g_i > 0, \quad i = 1, \ldots, m, \tag{78}$$

the arithmetic mean is greater than or equal to the geometric mean, i.e.,

$$\frac{1}{m}\sum_{i=1}^{m} g_i \geq \left(\prod_{i=1}^{m} g_i\right)^{1/m}. \tag{79}$$

If $\prod_{i=1}^{m} g_i = 1$, then it follows immediately that

$$m - \sum_{i=1}^{m} g_i \leq 0, \tag{80}$$

with equality if and only if $g_i = 1$ for all $i$.

## Appendix C. Vaccination thresholds and the DFE

We show by a sequence of elementary arguments that for the *disease free equilibrium*,

$$S^* \leq \frac{1}{\mathcal{R}_0} \iff p \geq \left(1 - \frac{1}{\mathcal{R}_0}\right)\left(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}\right). \tag{81}$$

From (9a) we have

$$S^* = \frac{1}{2} + \frac{1}{2\mathcal{R}_V} - \sqrt{\frac{1}{4}\left(1 - \frac{1}{\mathcal{R}_0}\right)^2 + \frac{p}{\mathcal{R}_V}} \le \frac{1}{\mathcal{R}_0} \tag{82a}$$

$$\iff \frac{1}{2} + \frac{1}{2\mathcal{R}_V} - \frac{1}{\mathcal{R}_0} \le \sqrt{\frac{1}{4}\left(1 - \frac{1}{\mathcal{R}_0}\right)^2 + \frac{p}{\mathcal{R}_V}}. \tag{82b}$$

We note that since $\mathcal{R}_V < \mathcal{R}_0$ and $\mathcal{R}_0 > 1$ we have $\frac{1}{2} + \frac{1}{2\mathcal{R}_V} - \frac{1}{\mathcal{R}_0} > 0$. Therefore, we have

$$\left(\frac{1}{2} + \frac{1}{2\mathcal{R}_V} - \frac{1}{\mathcal{R}_0}\right)^2 \le \frac{1}{4}\left(1 - \frac{1}{\mathcal{R}_V}\right)^2 + \frac{p}{\mathcal{R}_V} \tag{83a}$$

$$\iff p \ge 1 - \frac{\mathcal{R}_V}{\mathcal{R}_0} + \frac{\mathcal{R}_V}{\mathcal{R}_0^2} - \frac{1}{\mathcal{R}_0} \tag{83b}$$

$$\iff p \ge \left(1 - \frac{1}{\mathcal{R}_0}\right) - \mathcal{R}_V\left(\frac{1}{\mathcal{R}_0} - \frac{1}{\mathcal{R}_0^2}\right) \tag{83c}$$

$$\iff p \ge \left(1 - \frac{1}{\mathcal{R}_0}\right)\left(1 - \frac{\mathcal{R}_V}{\mathcal{R}_0}\right). \tag{83d}$$

## Appendix D. Pulse vaccination and existence of periodic solutions

We establish the existence of a $T$-periodic DFS for the system (51), by analyzing the disease free subsystem (52). We begin by summarizing the necessary theorems from the theory of impulsive differential equations.

### D.1. Theory of impulsive differential equations

We utilize the following results proved in Bainov and Simeonov (1993). Consider a system

$$\frac{dx}{dt} = f(t,x), \quad t \ne \tau_k \tag{84}$$
$$\Delta x = L_k(x), \quad t = \tau_k$$

where $\Delta x = x(\tau_k^+) - x(\tau_k^-)$, and $t \in \mathbb{R}$, $k \in \mathbb{Z}$, $x \in \Omega \subset \mathbb{R}^n$.

The following conditions are also imposed:

1. $f(t+T,x) = f(t,x)$, $L_{k+q}(x) = L_k(x)$, $\tau_{k+q} = \tau_k + T$, $\exists q$ for some $\mathbb{N}$
2. The function $f : \mathbb{R} \times \Omega \to \mathbb{R}^n$ is continuous.
3. The functions $L_k(x)$ are continuous for $x \in \Omega$

Furthermore a set $\mathcal{D} \subset \Omega$ is defined to be *canonical* if it satisfies the following three properties:

4. the domain $\mathcal{D}$ is a bounded convex set
5. the closure of $\mathcal{D}$ can be expressed by a finite number of inequalities

$$\Phi_i(x) \le 0 \tag{85}$$

where $\Phi_i : \mathbb{R}^n \to \mathbb{R}$ are smooth functions.

6. if both $x \in \partial\mathcal{D}$ and $\Phi_i(x) = 0$ then the Jacobian matrix $\frac{\partial \Phi_i}{\partial x}(x) \ne 0$.

The primary result we apply may be stated as follows (Bainov and Simeonov, 1993):

**Theorem 1.** *Suppose conditions 1–3 are satisfied, the set $\mathcal{D}$ is canonical, $\Phi_i(x + L_k(x)) \le 0, \forall i, \forall x \in \mathcal{D}$ and the directional derivative of $\Phi$ along the flow at the boundary satisfies*

$$\frac{\partial \Phi_i}{\partial x}(x) f(t,x) \le 0 \quad (t \in \mathbb{R}, x \in \partial\mathcal{D}, i \in \alpha(x)), \tag{86}$$

*where $\alpha(x) = \{i : \Phi_i(x) = 0\}$. Then Eq. (84) has a $T$-periodic solution $y(t)$ which is contained in $\mathcal{D}$ for all $t \in \mathbb{R}$.*

It should be noted that conditions (86) combined with the condition $\Phi_i(x + L_k(x)) \le 0, \forall i, \forall x \in \mathcal{D}$, are equivalent to the property that the set $\mathcal{D}$ is positively invariant with respect to the system (84).

#### D.1.1. Existence of a $T$-periodic DFS

The system (52) can be rewritten in the form of Eq. (84) in Section D.1 as

$$\left.\begin{aligned} \frac{dS}{dt} &= \nu - \beta^V(t)VS - \nu S \\ \frac{dV}{dt} &= \beta^V(t)VS - (\nu + \gamma^V)V \end{aligned}\right\} = g(t,x), \quad t \ne kT \tag{87}$$
$$\begin{pmatrix}\Delta S \\ \Delta V\end{pmatrix} = (P - \mathbb{1})\begin{pmatrix}S \\ V\end{pmatrix}, \quad t = kT$$

where $\Delta X \equiv X(kT^+) - X(kT^-)$, $\mathbb{1}$ is the identity matrix and

$$P = \begin{pmatrix}1 - p_{\text{pulse}} & 0 \\ p_{\text{pulse}} & 1\end{pmatrix}. \tag{88}$$

As we are dealing with proportions of the population, the biologically meaningful set is $\mathcal{B} = \{(S,V) : S \ge 0, V \ge 0, S + V \le 1\}$.

By assumption, $\beta^V(t)$ in (87) is continuous. In addition, conditions 1 and 3 of Section D.1 are satisfied directly by Eqs. (87) and (88) with $\Omega = \mathcal{B}$. The set $\mathcal{B}$ is canonical in the sense of Section D.1: Firstly, $\mathcal{B}$ is compact (closed and bounded) and convex. Secondly, $\mathcal{B}$ is specified by three inequalities, which – together with their respective Jacobians – are

$$\Phi_1(x) = -S \le 0 \quad \frac{\partial \Phi_1}{\partial(S,V)} = \begin{bmatrix}-1, & 0\end{bmatrix} \tag{89a}$$

$$\Phi_2(x) = -V \le 0 \quad \frac{\partial \Phi_2}{\partial(S,V)} = \begin{bmatrix}0, & -1\end{bmatrix} \tag{89b}$$

$$\Phi_3(x) = S + V - 1 \le 0 \quad \frac{\partial \Phi_3}{\partial(S,V)} = \begin{bmatrix}1, & 1\end{bmatrix}. \tag{89c}$$

We next note that for $x \in \partial\mathcal{B}$

$$1 \in \alpha(x) \quad \text{if } S = 0 \tag{90a}$$
$$2 \in \alpha(x) \quad \text{if } V = 0 \tag{90b}$$
$$3 \in \alpha(x) \quad \text{if } S + V = 1 \tag{90c}$$

where $\alpha(x) = \{i : \Phi_i(x) = 0\}$, as defined in Section D.1. This implies that for $i \in \alpha(x)$ and $x \in \partial\mathcal{B}$

$$\frac{\partial \Phi_1}{\partial x}(x) g(t,x) = -\nu \tag{91a}$$

$$\frac{\partial \Phi_2}{\partial x}(x) g(t,x) = 0 \tag{91b}$$

$$\frac{\partial \Phi_3}{\partial x}(x) g(t,x) = -\gamma^V V \le 0. \tag{91c}$$

Additionally

$$\Phi_i\left(P\begin{pmatrix}S \\ V\end{pmatrix}\right) \le 0 \tag{92}$$

since $P$ is a linear function whose matrix representation has non-negative entries and column sums equal to one (88) (hence $P$ maps $\mathcal{B}$ to $\mathcal{B}$). From a biological perspective, $P$ moves individuals from the susceptible to the vaccinated class but does not result in a net change in the number of individuals, hence maintaining the positive invariance of $\mathcal{B}$.

Therefore, by Theorem 1 of Section D.1, the system (52) – and hence the original pulse vaccination system given by (51) – possesses a biologically meaningful $T$-periodic DFS.

**Table 1**
Table of notation.

| Symbol | Definition | Place defined |
|---|---|---|
| $p$ | (Continuous) vaccination proportion | Section 2 |
| $\beta^{\mathrm{I}}$ | Wild-type virus transmission rate | Section 2.1 |
| $\beta^{\mathrm{V}}$ | Vaccine virus transmission rate | Section 2.1 |
| $\gamma^{\mathrm{I}}$ | Wild-type virus recovery rate | Section 2.1 |
| $\gamma^{\mathrm{V}}$ | Vaccine virus recovery rate | Section 2.1 |
| $\varepsilon^{\mathrm{I}}$ | Wild-type virus specific death rate | Section 2.3 |
| $\varepsilon^{\mathrm{V}}$ | Vaccine virus specific death rate | Section 2.3 |
| $B$ | Total birth rate | Section 2.3 |
| $\mathcal{R}_0$ | Wild-type virus basic reproduction number | Sections 2 and 2.1.2 |
| $\mathcal{R}_{\mathrm{V}}$ | Vaccine virus basic reproduction number | Sections 2 and 2.1.2 |
| $p_{\mathrm{crit}}$ | Critical (continuous) vaccination proportion $\mathcal{R}_{\mathrm{V}} = 0$ | Section 2 |
| $S$ | Susceptible class | Section 2 |
| $E_{\mathrm{V}}$ | Vaccine virus latent class | Section 2 |
| $E_{\mathrm{I}}$ | Wild-type virus latent class | Section 2 |
| $V$ | Vaccine virus latent or infectious class | Section 2.1 |
| $I$ | Wild-type virus latent or infectious class | Section 2 |
| $R$ | Immune class | Section 2.1 |
| $N$ | Total population size | Section 2.1 |
| $\mathcal{B}$ | Biologically meaningful region of parameter space | Section 2.1.3 |
| $L_{\mathrm{DFE}}$ | Lyapunov function for the *disease free equilibrium* | Section 2.2.1 |
| $L_{\mathrm{EE}}$ | Lyapunov function for the *endemic equilibrium* | Section 2.2.1 |
| $\nu$ | *Per capita* birth rate | Section 3 |
| $\mu$ | *Per capita* natural death rate | Section 2 |
| $p_{\mathrm{pulse}}$ | Pulse vaccination proportion | Section 3 |
| $T$ | Time interval between vaccination pulses | Section 3 |
| $\Psi(t)$ | Fundamental matrix solution | Section 3.2 |
| $p_{\mathrm{eff}}$ | Effective vaccination proportion | Section 4.1.2 |
| $p_{\mathrm{eff,crit}}$ | Critical effective vaccination proportion | Section 4.1.2 |
| $\widehat{p}_{\mathrm{eff,crit}}$ | Normalized critical effective vaccination proportion | Section 4.1.2 |
| $S(T^-)$ | Proportion of susceptibles immediately before vaccination pulse | Section 4.1.2 |
| $p_{\mathrm{pulse,crit}}$ | Critical pulse vaccination proportion | Section 4.2.1 |
| $\widehat{p}_{\mathrm{pulse,crit}}$ | Normalized critical pulse vaccination proportion | Section 4.2.1 |
| $\mathcal{D}$ | Open set | Appendix D |

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