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AN EPIDEMIOLOGY MODEL THAT INCLUDES A LEAKY VACCINE WITH A GENERAL WANING FUNCTION

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Abstract. Vaccination that gives partial protection for both newborns and susceptibles is included in a transmission model for a disease that confers no immunity. A general form of the vaccine waning function is assumed, and the interplay of this together with the vaccine efficacy and vaccination rates is discussed. The integro-differential system describing the model is studied for a constant vaccine waning rate, in which case it reduces to an ODE system, and for a constant waning period, in which case it reduces to a system of delay differential equations. For some parameter values, the model is shown to exhibit a backward bifurcation, leading to the existence of subthreshold endemic equilibria. Numerical examples are presented that demonstrate the consequence of this bifurcation in terms of epidemic control. The model can alternatively be interpreted as one consisting of two social groups, with education playing the role of vaccination.

1. **Introduction.** A classical SIS epidemic model for a disease that confers no immunity has only a disease free equilibrium (DFE) when parameters render the *basic reproduction number* $\mathcal{R}_0 < 1$, and has one endemic stable equilibrium for parameters making $\mathcal{R}_0 > 1$. Thus the disease dies out if $\mathcal{R}_0 < 1$. By definition (see *e.g.*, Anderson and May [1]), $\mathcal{R}_0$ is "the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual". A precise definition of $\mathcal{R}_0$ for an ODE model can be given as the spectral radius of the next generation matrix, see, *e.g.*, [4, 25]. In terms of stability, $\mathcal{R}_0$ is a threshold parameter, such that if $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable, and unstable if $\mathcal{R}_0 > 1$. In the latter case, the disease can go to an endemic level and control strategies are usually implemented to eradicate the disease or at least

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to lower its prevalence to reasonable levels. Such strategies include treatment to cure or increase the life expectancy of infected individuals, and vaccination as a prophylactic measure to prevent infection. In modeling such strategies, the aim is to determine the necessary amount of treatment or vaccination (usually modeled as number of individuals treated or vaccinated per unit time) so that the disease dies out. However, treatment and vaccination are not completely efficient. Vaccines may have low efficacy and be "leaky" (*i.e.*, successfully vaccinated individuals may have only partial protection from infection). Data support the fact that a vaccine usually wanes, thus providing only temporary protection (*i.e.*, after a certain time vaccinated individuals become susceptible again). Different ways in which a vaccine can fail are discussed by McLean and Blower [20] and references therein.

Kribs-Zaleta and Velasco-Hernández introduced in [18] a model of infectious disease transmission for a disease that confers no immunity in which the susceptible population is vaccinated at a rate ϕ but the vaccine gives only partial protection. This SIS with vaccination model is appropriate for diseases such as pertussis, tuberculosis [18], and hepatitis B [17]. They showed that under certain parameter conditions this quite simple ODE model [18] admits a backward bifurcation. To show the dependence of the basic reproduction number with vaccination on the vaccination rate, they denoted it $\mathcal{R}(\phi)$, with $\mathcal{R}(0) = \mathcal{R}_0$. For certain parameter values, there exists a critical value $\mathcal{R}_c$ such that for $\mathcal{R}_c < \mathcal{R}(\phi) < 1$ a hysteresis effect may arise with multiple endemic equilibria. In this case, there are three equilibria for the system: a stable trivial one (corresponding to the DFE), an unstable endemic equilibrium and a larger stable endemic equilibrium. This result has important consequences for the vaccination strategy, and the aim of the campaign must be to reduce $\mathcal{R}(\phi)$ below $\mathcal{R}_c$, not merely below one. For values of $\mathcal{R}(\phi)$ such that $\mathcal{R}_c < \mathcal{R}(\phi) < 1$, the success or failure of the strategy depends on the number of individuals who are initially infected. The range of parameter values for which backward bifurcation is possible in this model is not negligible [18]. A backward bifurcation is also found when this ODE model is extended to include a recovered class [2].

Backward bifurcation has also been observed in some other ODE epidemic models, including HIV/AIDS models [5, 7, 16] and multigroup models [8, 9], in which the backward bifurcation is connected to asymmetries between the different groups. Greenhalgh et al [6] used an SISI model with vaccination for animal infections with incomplete immunity (e.g., bovine respiratory syncytial virus, pseudorabies virus in pigs) and found that a backward bifurcation can occur. This phenomenon is also found in a simple SIS model, but with a nonconstant contact rate [24].

Other models with vaccination have been considered in the literature. For example, Hethcote and Yorke [15, Section 4.5] formulated an SIS core/noncore ODE model for gonorrhea and examined the effectiveness of two vaccination strategies. If a vaccine for gonorrhea becomes available, they predicted that it is likely to give only temporary immunity [15, p. 45] and they assumed that such a vaccine would be totally effective. Their model with vaccination of individuals chosen at random from the population at risk shows that such a strategy would be very effective in controlling gonorrhea. Multigroup models that include totally effective vaccination of newborns and susceptibles have also been considered (see, *e.g.*, [11, 13]). In [8, 9] models for two social groups "normal" and "educated" were formulated. The educated group can be regarded as a vaccinated group having a lower transmission rate for the disease. Individuals can move back and forth between the two groups,

according to such changes as educational status, public health policies. The SIS models studied in [8] and [9, Equation(6)] are similar to the ODE model that we analyze in Section 3.

In the SIS model with vaccination formulated in [18], the vaccine is assumed to wane exponentially. In Section 2, we assume a more general form of the waning function in formulating an SIS model with vaccination of the population at risk and a fraction of the newborns. Our aim is to demonstrate the interplay between vaccine efficacy, vaccination rates and vaccine waning on the dynamics of a disease that confers no immunity. As noted in [18], the limiting case of no recovery leads to an SI model that is more appropriate for fatal diseases with vaccination or education. In Section 3, we specialize to the case in which the vaccine wanes exponentially and in Section 4 we specialize to the case in which the vaccine waning time is a constant. We take parameters relevant for some human diseases and use a combination of analytical and numerical techniques to consider ranges of the vaccination rates for which backward bifurcation can occur. This shows that subthreshold endemic equilibria are possible, which may be important when it comes to designing vaccination strategies.

2. **Formulation of the model.** Our model has the transfer diagram shown in Figure 1. There are three classes S, I and V, corresponding respectively to *susceptible*, *infective* and *vaccinated* individuals, with numbers in each class given by $S(t)$, $I(t)$, $V(t)$, respectively. As noted in the introduction, $V(t)$ may alternatively correspond to an educated class, but we continue to refer to it as vaccinated. Individuals move from one class to the other as their status with respect to the disease evolves. New individuals are born with a birth rate $d > 0$, and as we do not account for vertical transmission or immigration of infectives, this inflow does not enter the I class. All individuals, whatever their status, are subject to death, which occurs with the rate d. Since it is assumed that the disease does not cause death, the total population $N = S + I + V$ is constant. We assume that a proportion $\alpha \in [0, 1)$ of newborns are vaccinated at birth; thus αdN enter the V class, and the remainder $(1 - \alpha)dN$ enter the S class. Susceptible individuals (regardless of whether they have been previously vaccinated) are further vaccinated at the rate ϕ.

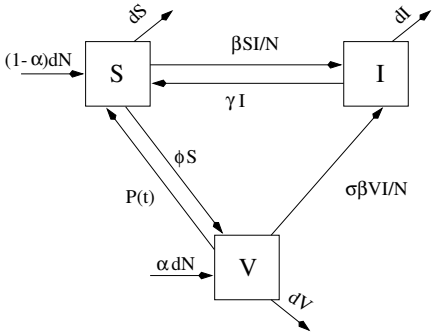

FIGURE 1. The flow diagram for the general model.

Disease transmission is assumed to be of *standard incidence* type (see [19] for a recent discussion of transmission terms), so that the number of infectives produced by random contacts between I infective and S susceptible individuals is given by

$\beta IS/N$, where $\beta > 0$ is the transmission coefficient, representing the number of adequate contacts per individual per time unit. Disease immunity is induced by vaccination, but those successfully vaccinated may be only partially protected from infection, resulting in infected individuals coming from the vaccinated class. The number $1 - \sigma$ is the degree of vaccine efficacy, with $\sigma \in [0, 1]$. If $0 < \sigma < 1$, then the vaccine is leaky. If $\sigma = 0$, then the vaccine is totally effective. If $\sigma = 1$, then the vaccine is useless, the V and S classes are identical and the model reduces to a classical SIS model. Henceforth we consider $0 \leq \sigma < 1$. The number of infectives produced by random contact between I infective and V vaccinated individuals is given by $\sigma\beta IV/N$. The parameter σ can be interpreted as the factor by which vaccination reduces disease transmission. For simplicity, it is assumed that if an individual in the V class is infected, then that individual is equally as infectious as an individual infected from the S class.

The vaccinated individuals can then either

- die (at the natural death rate d),
- or become infective if the vaccine is leaky (*i.e.*, $\sigma > 0$),
- or have the vaccine protection wear off, that is, reenter the S class.

This last point is one of interest here. In [18] it is supposed that the vaccine wanes exponentially but here we assume a more general waning function $P(t)$ for the vaccine. We suppose that there is a fraction $P(t)$ of the vaccinated individuals who are still under protection of the vaccine t units after being vaccinated. We suppose that $P(t)$ is a nonnegative and nonincreasing function with $P(0^+) = 1$, and such that $\int_0^\infty P(u)du$ is positive and finite. Two special forms of $P(t)$, namely a negative exponential and a step function are considered in Sections 3 and 4, respectively.

Finally, we suppose that any infective individuals can be cured: members of the I class can return to the susceptible class (with no immunity), and do so at a rate $\gamma \geq 0$ (the *recovery* rate). The effect of vaccination is assumed to disappear after an infection: there is no recovery to the V class.

Since the total population remains constant, it is more convenient to use proportions in each class. Hereafter, we use $I(t)$ and $V(t)$ to denote the proportion of infective and vaccinated individuals, respectively, with $S(t) = 1 - I(t) - V(t)$, the proportion of susceptibles. Let the initial susceptible and infective proportions be $S(0) > 0, I(0) > 0$ and let $V_0(t)$ be the proportion of individuals who are initially in the vaccinated class and for whom the vaccine is still effective at time t. An expression for $V_0(t)$ is obtained from the vaccination class-age derivation, see (4) below.

With the above assumptions, we obtain the following integro-differential system.

$$\frac{dI(t)}{dt} = \beta(S(t) + \sigma V(t))I(t) - (d + \gamma)I(t) \tag{1a}$$

$$V(t) = V_0(t) + \int_0^t (\phi S(u) + \alpha d)P(t - u)e^{-d(t-u)}e^{-\sigma\beta\int_u^t I(x)dx}du \tag{1b}$$

In the integral term in (1b), αd is the proportion of vaccinated newborns, $\phi S(u)$ is the proportion of vaccinated susceptibles, $P(t-u)$ is the fraction of the proportion vaccinated still in the V class $t - u$ time units after going in (*i.e.*, not returned to S), $e^{-d(t-u)}$ is the fraction of the proportion vaccinated not dead due to natural causes, and $e^{-\sigma\beta\int_u^t I(x)dx}$ is the fraction of the proportion vaccinated not gone to

the infective class. Thus the integral in (1b) sums the proportion of those who were vaccinated at time u and remain in the V class at time t.

For easy reference, the parameters are collected below.

- $d > 0$: natural death rate.
- $\gamma \geq 0$: recovery rate.
- $\beta > 0$: disease infectivity.
- $\phi \geq 0$: vaccination rate of susceptibles.
- $\alpha \in [0, 1)$: fraction of newborns vaccinated.
- $0 < 1 - \sigma \leq 1$: degree of vaccine efficacy.

A method to obtain (1b) and an expression for $V_0(t)$ is to formulate the model with vaccination class-age τ. Consider the equation for $v(t, \tau)$, the density with respect to vaccination class-age τ of the proportion of individuals in vaccination class-age τ who are still vaccinated at time t,

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) v(t, \tau) = -(\sigma\beta I(t) + d + \eta(\tau))v(t, \tau) \tag{2}$$

where $V(t) = \int_0^\infty v(t, \tau)d\tau$. Here $\eta(\tau)$ is the vaccine waning rate coefficient, with the proportion still in the V class at vaccination class-age τ being $P(\tau) = e^{-\int_0^\tau \eta(q)dq}$, which is assumed to satisfy the previous assumptions on the general waning function. The inflow at vaccination class-age zero is $v(t, 0) = \phi S(t) + \alpha d$, and $v(0, \tau) \geq 0$ is specified. Integrating along characteristics yields

$$\begin{aligned} v(t, \tau) &= v(t - \tau, 0)e^{-\int_{t-\tau}^t (\sigma\beta I(q)+d)dq - \int_0^\tau \eta(q)dq} \\ &\qquad \text{for } 0 \leq \tau \leq t \\ v(t, \tau) &= v(0, \tau - t)e^{-\int_0^t (\sigma\beta I(q)+d)dq - \int_{\tau-t}^\tau \eta(q)dq} \\ &\qquad \text{for } t \leq \tau \leq \infty \end{aligned}$$

Dividing the integral for $V(t)$ at t, substituting in the solutions, and changing integration variables gives

$$\begin{aligned} V(t) = &\int_0^t (\phi S(u) + \alpha d)P(t - u)e^{-\int_u^t (\sigma\beta I(x)+d)dx} du \\ &+ e^{-\int_0^t (\sigma\beta I(x)+d)dx} \int_0^\infty v(0, u)\frac{P(t + u)}{P(u)} du \end{aligned} \tag{3}$$

where the above definitions of $v(t, 0)$ and $P(\tau)$ have been used. This is equivalent to (1b) with

$$V_0(t) = e^{-\int_0^t (\sigma\beta I(x)+d)dx} \int_0^\infty v(0, u)\frac{P(t + u)}{P(u)} du \tag{4}$$

The ratio $P(t + u)/P(u) = e^{-\int_u^{t+u} \eta(q)dq}$ is well defined for $t + u \geq u \geq 0$ and bounded above by 1. Since $V(0)$ is finite, the integral in (3) and (4) converges. Thus $V_0(t)$ is nonnegative, nonincreasing and $\lim_{t\to\infty} V_0(t) = 0$. This vaccination class-age approach (similar to that used for an infection class-age in [14]) gives an explicit expression for $V_0(t)$.

To begin analysis of the model, define the subset $\mathcal{D}$ of the nonnegative orthant by

$$\mathcal{D} = \{(S, I, V); S \geq 0, I \geq 0, V \geq 0, S + I + V = 1\}$$

To ensure that the model is well posed, and thus biologically meaningful, we need to verify that solutions remain in $\mathcal{D}$.

THEOREM 2.1. *The set $\mathcal{D}$ is positively invariant under the flow of (1) with $I(0) > 0, S(0) > 0$.*

Proof. From (1a), and the initial condition $I(0) > 0$,

$$I(t) = I(0)e^{\int_0^t (\beta(S(u)+\sigma V(u))-(d+\gamma)du} > 0$$

for all $t \geq 0$. Note that $I(t)$ can approach zero as t approaches infinity.

Differentiating (1b) gives

$$\frac{d}{dt}V(t) = \frac{d}{dt}V_0(t) + \phi S(t) + \alpha d - (d + \sigma\beta I(t))(V(t) - V_0(t)) + Q(t) \qquad (5)$$

where to simplify notation, we denote

$$Q(t) = \int_0^t (\phi S(u) + \alpha d) d_t(P(t-u)) e^{-d(t-u)} e^{-\sigma\beta \int_u^t I(x)dx} du$$

Suppose that $S(t) > 0$ until some finite time t_1, and that $S(t_1) = 0$. Then, using (1a) and (5),

$$\begin{aligned}\frac{d}{dt}(I+V)(t_1) &= -d(I(t_1)+V(t_1)) - \gamma I(t_1) + Q(t_1) + \alpha d \\ &\quad + \frac{d}{dt}V_0(t_1) + (d + \sigma\beta I(t_1))V_0(t_1)\end{aligned}$$

Since $S(t_1) = 0$, $I(t_1) + V(t_1) = 1$. From the hypotheses on $P(v)$, $d_t(P(t-u)) \leq 0$. So $Q(t_1) \leq 0$, since $S(t) \geq 0$ for $0 \leq t \leq t_1$. Therefore

$$\begin{aligned}-\frac{d}{dt}S(t_1) &= \frac{d}{dt}(I+V)(t_1) \\ &= -d(1-\alpha) - \gamma I(t_1) + Q(t_1) + \frac{d}{dt}V_0(t_1) + (d + \sigma\beta I(t_1))V_0(t_1) \\ &< 0\end{aligned}$$

since $d(1-\alpha) > 0$ and, by (4), $\frac{d}{dt}V_0(t_1) \leq -(d + \sigma\beta I(t_1))V_0(t_1)$. Thus $dS_1/dt > 0$, and so $S(t) \geq 0$ for all $t \geq 0$. This in turn implies that $Q(t) \leq 0$ for all $t \geq 0$. From (1b), since S and I as well as $P(v)$ are nonnegative, it follows directly that $V(t) \geq 0$ for all t. Since the three variables are nonnegative, it then follows from $I(t) + S(t) + V(t) = 1$ that each variable stays less than or equal to 1 for all t and thus the solutions remain in $\mathcal{D}$. □

With the assumed initial conditions in $\mathcal{D}$, it can be shown that the system defined by (1a) and (1b) is equivalent to the system defined by (1a) and (5). The equivalence of (5) with (1b) can be seen by using an integrating factor to write (5) as

$$\frac{d}{dt}\left[(V(t) - V_0(t))e^{\int_0^t (d+\sigma\beta I(x))dx}\right] = (\phi S(t) + \alpha d + Q(t))\, e^{\int_0^t (d+\sigma\beta I(x))dx}$$

and noting that the right hand side is

$$\frac{d}{dt}\left[\int_0^t (\phi S(u) + \alpha d) P(t-u) e^{\int_0^u (d+\sigma\beta I(x))dx} du\right]$$

The system defined by (1a) and (5) is of standard form, therefore results of Hale and Verduyn Lunel [10, p. 43] ensure the local existence, uniqueness and continuation of solutions of model (1).

Define the basic reproduction number with vaccination as

$$\mathcal{R}_{vac} = \mathcal{R}_0 \left[1 - \frac{(1-\sigma)(\phi + \alpha d)\tilde{P}}{1 + \phi\tilde{P}} \right] \tag{6}$$

in which

$$\mathcal{R}_0 = \frac{\beta}{d+\gamma}$$

is the basic reproduction number with no vaccination and

$$\tilde{P} = \lim_{t\to\infty} \int_0^t P(v) e^{-dv} dv$$

is the average length of time that an individual remains vaccinated before losing protection or dying. Note that $\tilde{P} < 1/d$. The number $\mathcal{R}_{vac}$, which depends on $\tilde{P}$, is the important quantity in the model with vaccination. When only one parameter varies in $\mathcal{R}_{vac}$, we sometimes make this dependence explicit, e.g., $\mathcal{R}_{vac}(\phi)$ indicates that ϕ is the bifurcation parameter that varies. Note that $\mathcal{R}_{vac} \leq \mathcal{R}_0$, and in the case of no vaccination, that is $\alpha = \phi = 0$, $\mathcal{R}_{vac} = \mathcal{R}_0$. From the values of S and V at the DFE (given in the proof of the following theorem), $\mathcal{R}_{vac}$ is equal to the product of the mean infective period $1/(d+\gamma)$ and the sum of the contact rate constant in each of the susceptible and vaccinated classes multiplied respectively by the proportion in that class at the DFE, namely $\beta S_{DFE} + \sigma\beta V_{DFE}$.

THEOREM 2.2. *For model (1) with a general waning function, there is always the DFE. If $\mathcal{R}_0 < 1$, then this is the only equilibrium, the disease dies out. If $\mathcal{R}_{vac} < 1$, the DFE is locally asymptotically stable (l.a.s.), if $\mathcal{R}_{vac} > 1$ it is unstable.*

Proof. Equation (1a) has $I = 0$ as an equilibrium and using $I = 0$ in equation (1b) gives

$$V(t) = V_0(t) + (\phi(1 - V(t)) + \alpha d) \int_0^t P(t-u) e^{-d(t-u)} du$$

In the limit $V_0(t) = 0$, therefore $V = (\phi(1-V) + \alpha d)\tilde{P}$ as $t \to \infty$, and the disease free equilibrium point

$$I_{DFE} = 0, \quad V_{DFE} = \frac{(\phi + \alpha d)\tilde{P}}{1 + \phi\tilde{P}}, \quad S_{DFE} = 1 - V_{DF} = \frac{(1 - \alpha d\tilde{P})}{1 + \phi\tilde{P}}$$

always exists. Since if $\mathcal{R}_0 < 1$ the only equilibrium of (1a) is $I_{DFE} = 0$, it follows from above that the DFE is the only equilibrium of system (1) when $\mathcal{R}_0 < 1$.

Suppose now that $\mathcal{R}_0 < 1$, *i.e.*, that $\beta < d + \gamma$. Then equation (1a) gives

$$\frac{dI}{dt} < (d+\gamma)\left((S + \sigma V) - 1\right) I$$

Since $I \geq 0$ and $S + \sigma V \leq S + V \leq 1$, this inequality implies that $dI/dt < 0$, and so $I(t) \to 0 = I_{DFE}$ as $t \to \infty$, for all initial conditions $I(0) > 0$.

Linearizing (1a) and (1b) about the DFE by setting $I(t) = q(t)$, $V(t) = V_{DFE} + r(t)$ gives the equations

$$\frac{dq(t)}{dt} = \left(\beta(S_{DFE} + \sigma V_{DFE}) - (d+\gamma)\right) q(t)$$

$$\begin{aligned} r(t) &= -\phi \int_0^t (r(u)+q(u))P(t-u)e^{-d(t-u)}du \\ &\quad -\sigma\beta \int_0^t (\phi(1-V_{DFE})+\alpha d)P(t-u)e^{-d(t-u)} \int_u^t q(x)dxdu. \end{aligned}$$

Letting $q(t) = C_1 e^{zt}$ and $r(t) = C_2 e^{zt}$, the above system becomes triangular and has a non trivial solution if and only if

$$z = \beta(S_{DFE} + \sigma V_{DFE}) - (d+\gamma) = (d+\gamma)(\mathcal{R}_{vac} - 1) \tag{7a}$$

or

$$1 = -\phi \int_0^\infty P(v)e^{-(d+z)v}dv \tag{7b}$$

as $t \to \infty$. These equations give the eigenvalues z at the DFE. Let $z = x + iy$ be a root of equation (7b). Then by the proof of Lemma 2 in [24], if $x \geq 0$, then $y = 0$. But since $\phi \geq 0$, equation (7b) has no nonnegative real root, thus all of its roots have negative real parts. Hence by (7a) the DFE is l.a.s if $\mathcal{R}_{vac} < 1$, and unstable if $\mathcal{R}_{vac} > 1$. □

3. **Case reducing to an ODE system.** If we assume that the vaccine waning rate is a constant $\theta > 0$, *i.e.*, $P(v) = e^{-\theta v}$, and $V_0(t) = V_0(0)e^{-(d+\theta)t}e^{-\int_0^t \sigma\beta I(x)dx}$ from (4), then (1a) and (5) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1-\sigma)V)I - (d+\gamma)I \tag{8a}$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma\beta IV - (d+\theta)V + \alpha d \tag{8b}$$

which with no newborn vaccination ($\alpha = 0$) is the model studied in [18]. From Theorem 2.2, the DFE with $I_{DFE} = 0$, $S_{DFE} = \frac{\theta + d(1-\alpha)}{d+\theta+\phi}$, $V_{DFE} = \frac{\phi + \alpha d}{d+\theta+\phi}$ always exists. Assume that $\mathcal{R}_0 > 1$, then endemic equilibria (positive I equilibria, denoted by I^*) can be obtained analytically from the quadratic equation

$$\mathcal{P}(I) = AI^2 + BI + C = 0$$

where

$$\begin{aligned} A &= -\sigma\beta \\ B &= \sigma(\beta - (d+\gamma)) - (d+\theta+\sigma\phi) \\ C &= (d+\gamma)(d+\theta+\phi)(\mathcal{R}_{vac} - 1)/\beta \end{aligned}$$

with

$$\mathcal{R}_{vac} = \mathcal{R}_0 \left(1 - \frac{(1-\sigma)(\phi + \alpha d)}{d+\theta+\phi}\right)$$

from (6). If I^* is a positive solution of $\mathcal{P}(I) = 0$, then (8a) implies that $V^* = (d + \gamma - \beta S^*)/(\sigma\beta)$. Substituting this value into the equation $d(I+V)/dt = 0$, shows that $S^* > 0$. Then (8b) gives $V^* > 0$. Thus all solutions with $I^* > 0$ lie in $\mathcal{D}$ and are biologically feasible. Note from (8a) that $I^* \leq 1 - 1/\mathcal{R}_0$.

Backward bifurcation leading to two endemic equilibria occurs for $\sigma > 0$ (*i.e.*, a leaky vaccine) if $\mathcal{P}'(0) = B > 0$, $\mathcal{P}(0) = C < 0$ and $B^2 > 4AC$. On an $(\mathcal{R}_{vac}(\phi), I)$ bifurcation diagram (see Figure 2), this occurs for $\mathcal{R}_c(\phi) < \mathcal{R}_{vac}(\phi) < 1$, where $\mathcal{R}_c(\phi)$ is the value of $\mathcal{R}_{vac}(\phi)$ at the saddle node bifurcation point where the two values of I coincide, *i.e.*, $I = I_c = B/(-2A)$. For $\mathcal{R}_{vac}(\phi) < \mathcal{R}_c(\phi)$, there is no

endemic equilibrium (EEP). For $\mathcal{R}_{vac}(\phi) > 1$, the constant term $C > 0$, and there is a unique EEP. Note that if the vaccine is totally effective ($\sigma = 0$), there is no endemic equilibrium for $\mathcal{R}_{vac}(\phi) \leq 1$, and no backward bifurcation occurs.

By standard planar ODE arguments (see *e.g.*, [21]), the following behavior can be shown, for which a sketch of the proof is given.

THEOREM 3.1. *For the ODE system (8) with $V(0) \geq 0$, $I(0) > 0$,*

(i) if $\mathcal{R}_{vac} < \mathcal{R}_c$, then the disease dies out,

(ii) if $\mathcal{R}_c < \mathcal{R}_{vac} < 1$, then the EEP with larger I is l.a.s., and the EEP with smaller I is unstable, and

(iii) if $\mathcal{R}_{vac} > 1$, then the unique EEP is globally asymptotically stable in $\mathcal{D} - \{I = 0\}$.

Proof. The Jacobian matrix J of the linearized system at an endemic equilibrium I^* has $tr(J) < 0$ and $det(J) = 2\sigma\beta^2 I^*(I^* - I_c)$. If $\mathcal{R}_c < \mathcal{R}_{vac} < 1$, then two EEP exist, with $det(J) > 0$ for $I^* > I_c$, giving linear stability for the larger I^* value, whereas $det(J) < 0$ for $I^* < I_c$, giving instability at the smaller I^* value. This proves (ii). With $1/(IV)$ as a multiplier, the Bendixson-Dulac criterion [21, p. 265] rules out periodic solutions in the interior of $\mathcal{D}$. The global results in (i) and (iii) are completed by using the Poincaré Bendixson theorem [21, p. 245]. □

Using [25, Theorem 4] the nature of the bifurcation at $\mathcal{R}_{vac} = 1$ is determined by $sgn(a)$ where

$$a = \gamma - \beta S_{DF} - \theta - \sigma\phi - \sigma^2\beta V_{DF} \tag{9}$$

at $\mathcal{R}_{vac} = 1$. If $sgn(a) < 0$ then the bifurcation is forward; whereas if $sgn(a) > 0$ the bifurcation is backward.

We illustrate the backward bifurcation with a numerical bifurcation diagram (Figure 2) using parameters appropriate for a human disease, e.g., pertussis (see, *e.g.*, [3]), with a 3 week average disease duration ($\gamma = 0.04762$) taking the time unit as one day. Average lifetime is assumed to be 75 years ($d = 3.6530E - 05$), and the average number of adequate contacts per infective per day is estimated at 0.4 ($\beta = 0.4$). Assume that most babies are vaccinated in the first few months of life, and that the vaccine is effective, thus that $\alpha = 0.9$ (90% of newborns vaccinated) and $\sigma = 0.1$ (90% protection). Pertussis vaccine begins to wane after about 3 years [3, p. 378], and the average waning time of the vaccine $1/\theta$ is assumed to be 5 years, giving $\theta = 5.4794E - 04$. With these parameter values, there is backward bifurcation for a range of ϕ values given by $0.0254 \leq \phi \leq 0.1506$ (*i.e.*, vaccination of susceptibles on average every 1 to 8 weeks).

With the above parameter values, $\mathcal{R}_0 = 8.3936$ and $\mathcal{R}_{vac} = 0.8807$ for $\phi = 0.1$, which is in the range of backward bifurcation since the critical value $\mathcal{R}_c = 0.8669 < \mathcal{R}_{vac} < 1$, see Figure 2. In the backward bifurcation range, the value of $\mathcal{R}_{vac}(\phi)$ must be decreased below $\mathcal{R}_c$ to ensure that the disease is controlled, *i.e.*, $I \to 0$; otherwise, if I is above the unstable EEP, then I tends to the stable endemic value. Note that from Figure 2, values of this endemic equilibrium mean that between 50% and 80% of the population is infective for most of the backward bifurcation range.

This backward bifurcation persists (with the other parameter values fixed as above) even in the case in which the vaccine does not wane ($\theta = 0$, giving $\mathcal{R}_{vac}(\phi) = 0.8396$ and a critical value $\mathcal{R}_c(\phi) = 0.7599$). Varying one parameter, but keeping the other parameters fixed as above, the backward bifurcation persists for all $\alpha \in [0, 1)$, but not for the case in which only newborns are vaccinated ($\phi = 0$). If

there is no recovery (*i.e.*, $\gamma = 0$), it can be seen from (9) that there is no backward bifurcation in this ODE model. However, for a corresponding ODE model with disease induced mortality (*i.e.*, nonconstant population) and no newborn vaccination, backward bifurcation is possible for $\gamma = 0$ (see Figure 4 [18]). This case may be relevant for HIV/AIDS, since there is currently great effort to find a vaccine for this disease, and such a vaccine is unlikely to give complete protection.

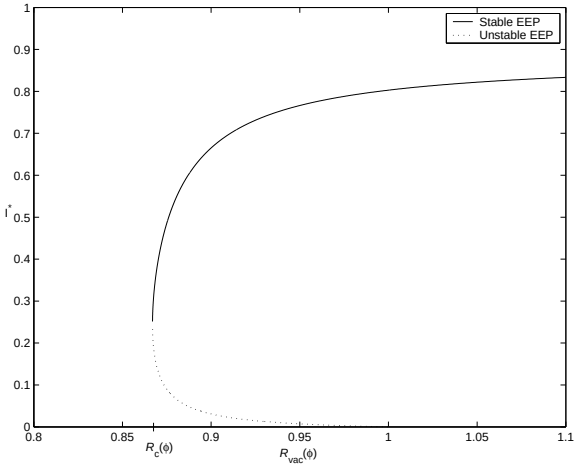

FIGURE 2. Backward bifurcation in the ODE vaccination model, obtained by varying ϕ in $[0.01, 0.2]$ with other parameters as given in the text. Here and in other bifurcation diagrams, only the endemic equilibria are shown (the solid curve is the locally stable EEP, the dashed curve is the unstable EEP).

4. **Step function (delay) case.** Suppose that the vaccine waning period is constant and equal to ω, that is the function $P(v)$ takes the form of a step function on a finite interval:

$$P(v) = \begin{cases} 1 \text{ if } v \in [0, \omega] \\ 0 \text{ otherwise} \end{cases}$$

Since $V_0(t) = 0$ for $t > \omega$, with $S = 1 - I - V$ the integral equation (1b) becomes, for $t > \omega$

$$V(t) = \int_{t-\omega}^{t} (\phi(1 - I(u) - V(u)) + \alpha d) e^{-d(t-u)} e^{-\sigma\beta \int_u^t I(x)dx} du \tag{10}$$

Differentiating this last expression (see equation (5)) gives the delay differential equation (DDE) model as the two dimensional system, for $t > \omega$

$$\frac{d}{dt} I(t) = \beta(1 - I(t) - (1-\sigma)V(t))I(t) - (d+\gamma)I(t) \tag{11a}$$

$$\begin{aligned} \frac{d}{dt} V(t) =& \phi(1 - I(t) - V(t)) \\ & - \phi(1 - I(t-\omega) - V(t-\omega)) e^{-d\omega} e^{-\sigma\beta \int_{t-\omega}^t I(x)dx} \\ & - \sigma\beta IV - dV + \alpha d \left(1 - e^{-d\omega} e^{-\sigma\beta \int_{t-\omega}^t I(x)dx}\right) \end{aligned} \tag{11b}$$

Hereafter, we shift time by ω so that these equations hold for $t > 0$.

The well posedness of the problem follows from Theorem 2.1 and from the fact that solutions of (1) exist and are unique. For a constant waning period, the basic reproduction number with vaccination from (6) is

$$\mathcal{R}_{vac} = \mathcal{R}_0 \left(1 - \frac{(1-\sigma)(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})}\right) \tag{12}$$

With $I_{DFE} = 0$, from Theorem 2.2

$$S_{DFE} = \frac{d - \alpha d(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})},\ V_{DFE} = \frac{(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \tag{13}$$

From nullclines, there exists one (or more) (EEP) iff there exists $0 < I^* \leq 1$ such that

$$V^* = f(I^*) = g(I^*) \tag{14}$$

where

$$f(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} \tag{15}$$

for $\sigma < 1$, and

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I} \tag{16}$$

This seems hard, if not impossible, to solve explicitly. It is however possible to tackle the problem numerically as described in the following subsections.

4.1. **Visualising and locating the bifurcation.** From the nullcline equations, an EEP exists iff there exists an $I^* \in (0, 1]$ such that equation (14) holds. So we study the zeros of

$$H(I) = f(I) - g(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} - \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I}$$

To state the problem in a formal way, with fixed d, let $\mathcal{A} = \{\alpha, \beta, \gamma, \omega, \phi, \sigma\}$ be the set of parameters of interest, and denote

$$H(I, \mathcal{A}) = f(I) - g(I) \tag{17}$$

to show the dependence on these parameters. We proceed as follows.

1. Choose a parameter $a_i \in \mathcal{A}$.
2. Fix all other a_j's ($j \neq i$).
3. Choose $a_{i,min}$, $a_{i,max}$ and Δa_i for a_i.
4. For all $a_{i,k} = a_{i,min} + k\Delta a_i$ (k such that $a_{i,k} \leq a_{i,max}$), compute I^* such that $H(I^*, a_{i,k}) = 0$.

Step 4 is carried out using the MatLab `fzero` function.

In the DDE case, analytically finding the point where (17) has a unique zero in $(0, 1]$ is impossible (compare $H(I)$ with the quadratic found for the ODE case in Section 3). It is however possible to obtain a better estimate than by mere observation of the numerically obtained bifurcation diagram, by making the following observations. It can be shown that

$$H(0) = \frac{\mathcal{R}_{vac} - 1}{(1 - \sigma)\mathcal{R}_0}$$

and that, for $\sigma < 1$

$$H(1) = -\frac{1}{(1 - \sigma)\mathcal{R}_0} - \frac{\alpha d(1 - e^{-d\omega - \sigma\beta\omega})}{\phi(1 - e^{-d\omega - \sigma\beta\omega}) + d + \sigma\beta} < 0$$

Therefore for $\mathcal{R}_{vac} < 1$, there are several possibilities, which are illustrated in Figure 3.

- If $\mathcal{R}_{vac} < \mathcal{R}_c$, then there is no EEP. $H(0)$ and $H(1)$ are strictly negative, and numerical simulations seem to indicate that H has no roots in $(0, 1]$ (*i.e.*, that $H < 0$ on this interval).
- If $\mathcal{R}_c < \mathcal{R}_{vac} < 1$, then there are endemic equilibria. Here, since $H(0)$ and $H(1)$ are strictly negative, the only possibility is thus to have an even number of zeros of H. Numerical simulations appear to indicate that the number of endemic equilibria is 2.

In between these two situations $\mathcal{R}_{vac} = \mathcal{R}_c$ and there is one endemic equilibrium I^*. Using the same procedure as for the visualisation of the bifurcation, it is possible to compute $\mathcal{R}_c$ by finding the value I^* such that $H(I^*, \mathcal{A}) = 0$ and $H'(I^*, \mathcal{A}) = 0$, for a given parameter $a_i \in \mathcal{A}$.

If $\mathcal{R}_{vac} > 1$ then $H(0) > 0$ and so there is an odd number of endemic equilibria. Numerical simulations indicate that there is a unique EEP, see Figure 3.

4.2. **Numerical simulations.** We use the same parameter values as in the ODE case of Section 3, except that the constant waning time (the delay) ω has to be substituted for θ. We take $\omega = 1767$, so the average length of time $\tilde{P}$ that an individual stays vaccinated is the same as in the ODE model of Section 3. These parameters give $\mathcal{R}_0 = 8.3936$ and $\mathcal{R}_{vac}(\phi) = 0.8808$, which is in the range of the backward bifurcation since (using the above method) $\mathcal{R}_c(\phi) = 0.8684$. The bifurcation diagram is very like that depicted in Figure 2. Numerical simulations of the DDE model indicate that there are no additional bifurcations; solutions either go to the DFE or to the (larger) EEP.

As a function of σ or β (rather than ϕ), the bifurcation has the shape shown on Figure 2, whereas for the other parameters, it appears "reversed" if plotted as a function of the parameter. Indeed, $\mathcal{R}_{vac}$ is an increasing function of σ and β, while it is a decreasing function of the other parameters for $\sigma < 1$, but changes very

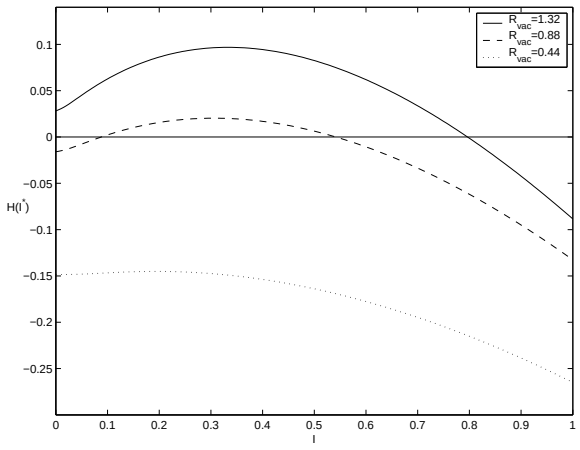

FIGURE 3. Value of the function $H(I)$, in three cases corresponding to three different values of β (from bottom to top): 0.2, 0.4 and 0.6. Other parameters as in Section 4.2. The corresponding values of $\mathcal{R}_{vac}$ are indicated as legend. In all three cases, $\mathcal{R}_0 > 1$.

little as α changes. Figure 4(a) shows the bifurcation for these parameter values as a function of ω. The situation is clearly different from that of Figure 2, since in Figure 4(a) every value of ω gives at least one endemic equilibrium.

It should be noted that this behavior is quite interesting in terms of epidemic control. Let ω_m be the value of ω determined by solving $\mathcal{R}_{vac}(\omega) = 1$ with $\mathcal{R}_{vac}$ given by (12). If all other parameters are fixed as above, and for small waning time, $0 < \omega < \omega_m = 457.032$, giving $\mathcal{R}_{vac}(\omega) > 1$, the only stable equilibrium is a large endemic one. This is of course a highly undesirable state in terms of epidemic control. Then increasing ω (*i.e.*, increasing the waning time) past ω_m allows the DFE to become locally stable, and it is found numerically that solutions starting with $I(0)$ below the unstable endemic equilibrium tend to the DFE. Indeed, consider Figure 4(b), which shows the behavior of $I(t)$ as a function of time. This is obtained by running numerical integrations of system (11) using the package `dde23` [23] with $I(t) = c$ for $t \in [-\omega, 0]$, c varying from 0 to 1 by steps of 0.02. The value of the unstable EEP (0.088) is shown as a dashed line, which seems to separate an endemic from the disease free asymptotic state. Increasing ω more is inefficient in terms of disease control, since (see Figure 4(a)) increasing ω beyond 1000 days does not further raise the value of the unstable endemic equilibrium and thus does not allow larger initial values of infectives to tend to the DFE.

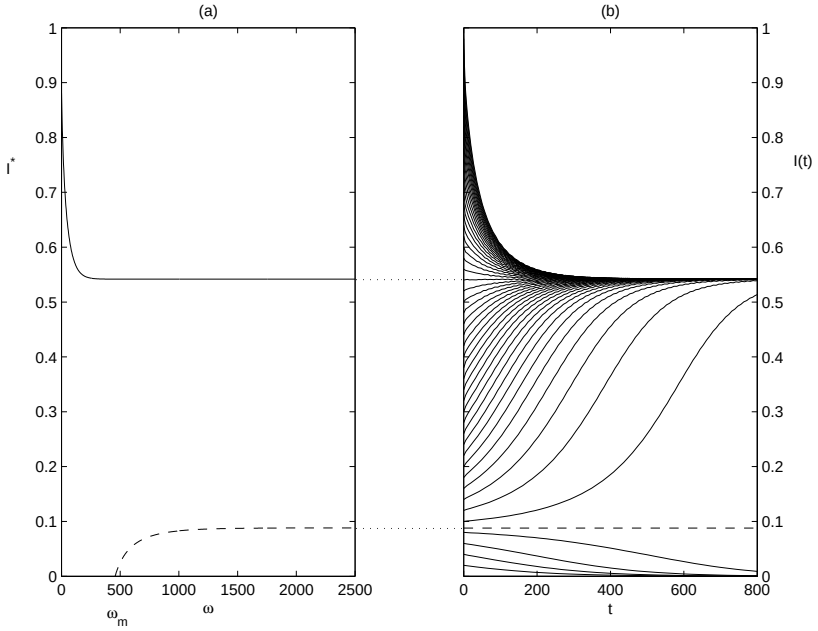

FIGURE 4. (a) Values of I^* as a function of ω by solving $H(I, \mathcal{A}) = 0$ with $a_i = \omega$. (b) Value of $I(t)$ versus time, obtained by numerical integration of system (11) with $\omega = 1767$ and initial data $I(t) = c$, for $t \in [-\omega, 0]$, c varying from 0 to 1 by steps of 0.02. Other parameter values as in the text.

The following table shows, for a given parameter, the (rounded) ranges in which the different types of behaviors are obtained, when all other parameters have the

values given in Section 3 (using $\omega = 1767$). The switch from the two EEPs situation to the single EEP situation is obtained by solving, for the variable under consideration, the equation $\mathcal{R}_{vac} = 1$.

Parameter	DFE only	2 EEPs	1 EEP
σ	$(0, 0.085)$	$(0.085, 0.114)$	$(0.114, 1)$
ϕ	$(0.143, \infty)$	$(0.025, 0.143)$	$[0, 0.025)$
β	$(0, 0.362)$	$(0.362, 0.454)$	$(0.454, \infty)$
γ	$(0.055, \infty)$	$(0.042, 0.055)$	$[0, 0.042)$
ω	impossible	$(457.032, \infty)$	$(0, 457.032)$
α	impossible	[0,1]	impossible

5. **Special cases of the DDE model.**

5.1. **Case $\sigma = 0$ (vaccine totally effective).** Consider the case where the vaccine is totally effective giving complete protection, *i.e.*, that vaccinated individuals can never make the V to I direct transition. In this case, system (11) reduces to

$$\frac{dI(t)}{dt} = \beta(1 - I(t) - V(t))I(t) - (d + \gamma)I(t) \tag{18a}$$

$$\frac{dV(t)}{dt} = \phi(1 - I - V) - \phi(1 - I(t - \omega) - V(t - \omega))e^{-d\omega} - dV(t) + \alpha d(1 - e^{-d\omega}) \tag{18b}$$

Here

$$\mathcal{R}_{vac} = \mathcal{R}_0 \left(1 - \frac{(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})}\right)$$

and we have the following result.

THEOREM 5.1. *If $\mathcal{R}_{vac} > 1$, then system (18) admits a unique, locally asymptotically stable EEP.*

Proof. Here (15) is $f(I) = 1 - 1/\mathcal{R}_0 - I$ while (16) is

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega})}{\phi(1 - e^{-d\omega}) + d}$$

Therefore solving (14) yields the explicit value of I^*, namely

$$I^* = \left(1 - \frac{1}{\mathcal{R}_{vac}}\right)(1 - \alpha(1 - e^{-d\omega}))$$

(which is biologically meaningful if $\mathcal{R}_{vac} > 1$), and in turn gives

$$V^* = \frac{\phi(1 - e^{-d\omega})}{d\mathcal{R}_0} + \alpha(1 - e^{-d\omega})$$

Linearization about the EEP yields the characteristic equation

$$\det \begin{bmatrix} \beta(1 - 2I^* - V^*) - (d + \gamma) - z & -\beta I^* \\ -\phi + \phi e^{-z\omega}e^{-d\omega} & -\phi + \phi e^{-z\omega}e^{-d\omega} - d - z \end{bmatrix} = 0$$

Using the EEP, the (1,1) entry is $-\beta I^* - z$. So the characteristic equation becomes

$$z^2 + z[\phi + d + \beta I^*] + d\beta I^* - z\phi e^{-\omega(z+d)} = 0 \tag{19}$$

When $\omega = 0$, this reduces to $(z + d)(z + \beta I^*) = 0$ and the EEP is l.a.s. when the delay is zero.

Suppose $z = iy$, $y > 0$. Then (19) is

$$-y^2 + iy(\phi + d + \beta I^*) + d\beta I^* = iy\phi e^{-d\omega}(\cos \omega y - i \sin \omega y)$$

Taking the absolute value of each side gives

$$(-y^2 + d\beta I^*)^2 + y^2(\phi + d + \beta I^*)^2 = y^2\phi^2 e^{-2d\omega}$$

Now setting $y^2 = Y$ gives

$$Y^2 + Y(\phi^2(1 - e^{-2d\omega}) + d^2 + \beta^2 I^{*2} + 2\phi(d + \beta I^*)) + d^2\beta^2 I^{*2} = 0$$

Since for $\omega \geq 0$ each coefficient is positive, Y cannot be positive and there can be no pure imaginary solution. Also, $z = 0$ is not a solution, as setting $z = 0$ in (19) gives $d\beta I^*$, which is strictly positive. So, by continuity, the EEP is l.a.s. for all $\omega \geq 0$ when it exists, namely for $\mathcal{R}_{vac} > 1$. □

Combining the above result with Theorem 2.2 shows that for a totally effective vaccine, the bifurcation is forward and $\mathcal{R}_{vac}$ behaves as a (local) threshold as in a classical model; see the Introduction. Multigroup models with a totally effective vaccine also have no backward bifurcation [11, 13, 15].

5.2. **No recovery case.** Another interesting special case is the one in which there is no recovery (*i.e.*, $\gamma = 0$), corresponding to vaccination for a disease with no cure. For example, were a vaccine available for HIV/AIDS, this model could roughly fit.

In the DDE model, considering the bifurcation diagram of Figure 5 (in which the direction of the bifurcation is reversed, since as was pointed out in Section 4.1, $\mathcal{R}_{vac}$ is a decreasing function of γ), we can observe that for the parameter values used, there only exists one stable EEP for $\gamma = 0$. Numerical simulations with other parameter values seem to indicate that for $\gamma = 0$ the bifurcation is always forward (as observed in the ODE model of Section 3).

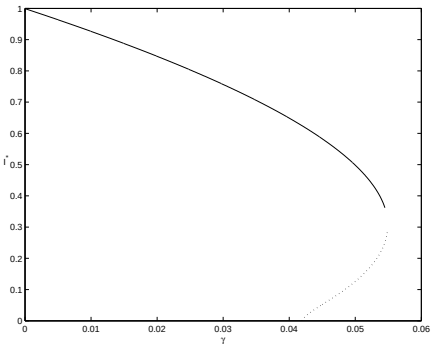

FIGURE 5. Bifurcation diagram of the DDE model, as a function of γ: value of I^* as a function of γ, other parameters as in Section 4.1.

6. **Concluding remarks.** The qualitative behavior of the model appears to be robust with respect to the nature of the general waning function $P(t)$. Our results, based on numerical evidence, show that $P(t)$ for the two cases examined here preserves the phenomenon of multistability. Backward bifurcation can occur for a range of waning periods (both for exponential waning and constant waning time),

for a leaky vaccine (one that does not give total protection), and for a range of susceptible vaccination rates.

Our model and the parameters chosen are relevant to the transmission of pertussis [3]. However, a more detailed model of pertussis should include age structure and more classes, for example, classes corresponding to individuals with infection acquired immunity [12]. Some diseases may need other classes to make the model more realistic; for example, a chronic carrier stage needs to be incorporated in a model for feline calicivirus [17, 22]. However, the backward bifurcation found here should be expected to persist in similar models with more classes.

The presence of backward bifurcation has consequences for epidemic control, since the presence of a hysteresis loop and a separatrix between a stable DFE and a stable EEP means that the endemic state persists for a larger range of $\mathcal{R}_{vac}$ and also that the outcome is initial value dependent. To achieve disease control ($I \to 0$ for all initial values), the value of $\mathcal{R}_{vac}(\phi)$, which depends on the vaccination policy, must be lowered to less than $\mathcal{R}_c(\phi)$. For a given vaccine, the vaccination rate of susceptibles (ϕ) can in principle be controlled. This simple model indicates that it is important that parameter values be accurately estimated before a vaccination strategy is established for a particular disease.

Another interpretation, similar to that of [8, 9], can be given for our model. Consider a population in which there exist two social groups of individuals susceptible to a given pathogen. Thus V represents individuals with different susceptibility to the particular pathogen (due to education, behavioral changes, environmental conditions, biological characteristics, etc.) Then ϕ is a rate of changing behavior, σ is a measure of the difference in susceptibility to infection brought about by this change, and ω is the length of time during which this change of behavior occurs. If the change of behavior decreases the risk of contagion, as assumed in [8, 9] then V individuals are less likely ($\sigma < 1$) to contract the disease, and the possibility of backward bifurcation exists. This should be taken into consideration when designing education and other public health policies.

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