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PULSE VACCINATION STRATEGIES IN A METAPOPULATION SIR MODEL

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Abstract. We examine a model for a disease with SIR-type dynamics circulating in a population living on two or more patches between any pair of which migration is allowed. We suppose that a pulse vaccination strategy (PVS) is carried out on each patch. Conditions are derived on each PVS such that the disease will be eradicated on all patches. The PVS on one patch is assumed to be essentially independent of the PVS on the other patches except in so far as they are all performed simultaneously. This independence is of practical value when we bear in mind that the patches may represent regions or countries with autonomous public health authorities, which may make individual decisions about the days appropriate for a vaccination pulse to occur in their own region or country. Simulations corroborate our theoretical results.

1. **Introduction.** Following the global eradication by 1979 of smallpox, the World Health Organisation has set as goals the global eradication of other diseases, including poliomyelitis [30] and Guinea worm disease [4, 14], and the global reduction of, for example, measles [33]. Global eradication of a disease obviously requires eradication from every single region or country in the world. But if, for example, a vaccination program is to be implemented in any particular region, some level of participation or co-ordination will be required by existing health authorities in that region.

Suppose a disease is present in a number of different regions between any pair of which migration may occur. This is a common enough scenario in our world today - economic globalisation and the popularity of international holidays have promoted the development of transport links. Assume that each region has an autonomous public health authority that wishes to eradicate the disease from its region. If one authority were to implement a vaccination program in the region it controls, there would be no guarantee of eradication in that region since new infectives could enter it from the other regions. All of the regions agree, then, after common consultation, to implement vaccination programs. The regions share information on migration rates and on other parameters governing the spread of the disease such as birth rates, death rates, contact rates, and recovery rates. Each region decides to implement a pulse vaccination strategy (PVS), perhaps in consequence of a recommendation by the World Health Organisation that this is a sensible method of control for the disease in contention. (It is certainly true that pulse vaccination strategies have

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attained real-world success in the control of poliomyelitis and measles in Central and South America [26] and of poliomyelitis in India [5].) However, each autonomous public health authority wishes to retain some independence in choosing the exact details of the PVS in its region. After all, the days appropriate for a vaccination pulse in one region may not be appropriate in another - different countries have different customs, national holidays, and election days. The question therefore arises as to whether or not it is possible to eradicate the disease from all regions if the PVS in each region is chosen with some freedom. In this paper we discover, for a particular model, that such eradication is possible, provided each PVS is sufficiently strong.

The model we will study will be for a disease with SIR-type dynamics on $n \geq 2$ regions or "patches", applicable to a disease such as poliomyelitis, influenza, measles, or rubella. Multi-patch disease models are often labelled as metapopulation models in the literature and the populations on the different patches are sometimes called subpopulations [7, 2, 18]. Pulse vaccination strategies in a two-patch SEIR model have been simulated by Earn *et al* [7]. Their simulation shows that the infective populations on the different patches can become synchronised by the influence of the pulse vaccination strategies. The pulse vaccination strategies on the two patches are identical in their simulation. Earn *et al* offer no analytical explanation for their observation but they do comment how Heino *et al* [12] have stressed that synchronicity between subpopulations in ecological models can be an important contributory factor to the extinction of all the subpopulations. Earn *et al* suggest that if pulse vaccination strategies can promote synchronicity on the different patches of a multi-patch epidemiological model, then disease extinction on all the patches may become more likely. We will not explore synchronicity in this paper but remark that such an exploration could yield valuable new results.

Numerical and theoretical studies of pulse vaccination strategies have been appearing regularly since the 1990s. Conditions on pulse vaccination strategies such that disease eradication is guaranteed have been found for many types of model in the last decade [21, 22, 19, 35, 23, 9, 10, 34, 32, 17]. However, the need to design pulse vaccination strategies with care has been emphasised by Choisy *et al* [6], who show by simulation in an SEIR model that increasing the pulse frequency (that is, decreasing the inter-pulse time) can have perverse effects such as increasing the number of infectives by causing resonance in the underlying dynamical system.

This paper has the following format. In section 2 we describe the n-patch SIR model to be investigated. In section 3 we consider the behaviour of the disease in the absence of vaccinations, showing in particular that it may die out naturally or persist indefinitely depending on conditions involving the model parameters. Then in sections 4 and 5 we construct conditions on pulse vaccination strategies on the n patches such that the disease will be eradicated simultaneously on all n patches. In section 6 we comment on how our PVS conditions depend on the model parameters, focusing on migration rates. Simulations are included in section 7 and we end the paper with a discussion in section 8.

2. **The model.**

Assume there are $n \geq 2$ patches on each of which a human population is present. Suppose an infectious disease with SIR-type dynamics is circulating on at least one of the patches. For $1 \leq j \leq n$, let there be $S_j(t)$ susceptibles, $I_j(t)$ infectives, and $R_j(t)$ removeds at time t on patch j. Notice that the population on patch j at time t is $N_j(t) = S_j(t) + I_j(t) + R_j(t)$. Assume, for $1 \leq j \leq n$, that

the population on patch j is mixing homogeneously and that every individual has the same average number of contacts $\beta_j > 0$ per unit time, where β_j is a constant. The assumptions of the last sentence will lead to a standard incidence function on patch j [13].

Suppose all new borns on all patches are susceptible - there is no vertical transmission. Suppose further that the birth rate at time t on patch j is a function of the population on patch j, namely $b_j(N_j(t))$. Let the birth functions satisfy the following biologically sensible requirements:

$$b_j(0) = 0 \quad \text{and} \quad b_j(x) > 0 \text{ for } x > 0 \quad \text{where } 1 \leq j \leq n. \tag{1}$$

There are different ways to model migration [18]. We shall follow an approach used by Arino and van den Driessche [2]. Assume, then, that migration occurs between any pair of patches at the following rates:

- $m^S_{k,j}$ = per capita migration rate of susceptibles from patch k to patch j
- $m^I_{k,j}$ = per capita migration rate of infectives from patch k to patch j
- $m^R_{k,j}$ = per capita migration rate of removeds from patch k to patch j .

These migration rates are all non-negative constants. It is not sensible to think of individuals migrating out of their patch and into it at the same instant, so we set $m^S_{j,j} = m^I_{j,j} = m^R_{j,j} = 0$ for $1 \leq j \leq n$. Natural mortality rates are known to vary significantly from one country to another, so there is no reason to assume that the natural mortality rate is the same on all patches. Similarly the disease mortality and recovery rates may be patch-dependent. Define, then, the following parameters:

- μ^S_j = per capita death rate of susceptibles on patch j
- μ^I_j = per capita death rate of infectives on patch j
- μ^R_j = per capita death rate of removeds on patch j
- γ_j = per capita recovery rate of infectives on patch j

All of these parameters are assumed to be positive constants. Contraction of an infectious disease seldom reduces mortality, so we assume for $1 \leq j \leq n$ that $\mu^I_j \geq \mu^S_j$. Recovery from a disease generally reduces mortality, so we assume for $1 \leq j \leq n$ that $\mu^I_j \geq \mu^R_j$. Assume that recovery confers permanent immunity. By considering the changes in the numbers of susceptibles, infectives, and removeds on patch j $(1 \leq j \leq n)$ in a short time interval $[t, t + dt]$, and letting $dt \to 0$ whilst noticing, for example, that $\lim_{dt\to 0}\left(\frac{S_j(t+dt)-S_j(t)}{dt}\right) = \frac{dS_j(t)}{dt}$, our hypotheses lead to the following model:

$$\frac{dS_j}{dt} = b_j(N_j) - \beta_j\frac{S_jI_j}{N_j} - \mu^S_jS_j + \left(\sum_{k=1}^{n} m^S_{k,j}S_k\right) - \sum_{k=1}^{n} m^S_{j,k}S_j \tag{2}$$

$$\frac{dI_j}{dt} = \beta_j\frac{S_jI_j}{N_j} - (\gamma_j + \mu^I_j)I_j + \left(\sum_{k=1}^{n} m^I_{k,j}I_k\right) - \sum_{k=1}^{n} m^I_{j,k}I_j \tag{3}$$

$$\frac{dR_j}{dt} = \gamma_jI_j - \mu^R_jR_j + \left(\sum_{k=1}^{n} m^R_{k,j}R_k\right) - \sum_{k=1}^{n} m^R_{j,k}R_j \tag{4}$$

for $t > 0$ and for $1 \leq j \leq n$, where we use the shorthand S_j, I_j, R_j, and N_j for $S_j(t)$, $I_j(t)$, $R_j(t)$, and $N_j(t)$ respectively.

Equations (2), (3), and (4) represent a model without vaccinations for the spread of the disease across the n patches. For a sensible model we require initial data.

Therefore assume, for $1 \leq j \leq n$, that

$$S_j(0) \geq 0, \quad I_j(0) \geq 0, \quad R_j(0) \geq 0, \quad S_j(0) + I_j(0) + R_j(0) > 0. \tag{5}$$

We must have $I_j(0) > 0$ for at least one value of j, for otherwise the disease is already absent from all n patches at the initial time $t = 0$.

A pulse vaccination strategy (PVS) can be introduced onto each patch in accordance with the following definition:

Definition 2.1. On patch j, for $1 \leq j \leq n$, pulses occur every $T_j > 0$ time units, where T_j is constant. The first pulse occurs at time $t_{1,j} > 0$ and, for $i \geq 2$, the i-th pulse occurs at time $t_{i,j} = t_{1,j} + (i-1)T_j$. Each pulse instantaneously transfers a fixed proportion p_j (where $0 < p_j < 1$) of susceptibles in patch j to the removed class in patch j. Thus $S_j(t_{i,j}) = (1-p_j)S_j(t_{i,j}^-)$ and $R_j(t_{i,j}) = R_j(t_{i,j}^-) + p_j S_j(t_{i,j}^-)$ where $t_{i,j}^-$ is the time "momentarily" before time $t_{i,j}$. Between pulses, the system on patch j evolves according to equations (2), (3), and (4), and the system begins with the initial data (5). The birth functions are assumed to satisfy (1). Let $q_j = 1 - p_j$.

The model with pulse vaccination strategies on each patch therefore consists of a series of infinitely many initial value problems (IVPs), with the initial time of the $(i+1)$-th IVP being the time of the first pulse that occurs strictly later than the initial time of the i-th IVP. At the initial time of the i-th IVP, it is possible that pulses occur simultaneously on more than one patch.

For both of the models - without vaccination or with pulse vaccination strategies - it is easy to deduce from standard results that a unique solution exists for $t > 0$. It is also straightforward to deduce from known results (p. 81, [29]) that, given our assumptions on the initial data in (5) and given (1), then $S_j(t) \geq 0$, $I_j(t) \geq 0$, $R_j(t) \geq 0$, and $N_j(t) > 0$ for $t > 0$ for $1 \leq j \leq n$. These properties are collectively known as *positivity*.

3. Natural extinction and endemicity.

If it is known that a particular disease will die out naturally, public health authorites may decide not to implement a vaccination program against it. Of course a disease which is dying out may still claim some victims, but the resources of a public health authority are limited and fatal diseases that are endemic are likely to be of greater priority than diseases that will die out by themselves. Therefore, before constructing successful pulse vaccination strategies in the SIR model defined in the last section, it is sensible to have an understanding of when the disease will die out naturally and when it will persist naturally.

Theorem 3.1. *Consider the model defined by (1), (2), (3), (4), and (5). Suppose for $1 \leq j \leq n$ that $\beta_j < \gamma_j + \mu_j^I$. Then $I_j(t) \to 0$ as $t \to \infty$ for $1 \leq j \leq n$.*

Proof. Add together all n equations defined by (3) for $1 \leq j \leq n$ to obtain:

$$\frac{d}{dt}\left(\sum_{j=1}^{n} I_j(t)\right) = \sum_{j=1}^{n}\left(\beta_j \frac{S_j(t)}{N_j(t)} - \left[\gamma_j + \mu_j^I\right]\right) I_j(t). \tag{6}$$

Let $\theta = \max_{1 \leq j \leq n}\left\{\beta_j - \left(\gamma_j + \mu_j^I\right)\right\}$. Notice that $\theta < 0$ since we know by assumption that $\beta_j < \gamma_j + \mu_j^I$ for $1 \leq j \leq n$. Also, by positivity we know that $\frac{S_j(t)}{N_j(t)} \leq 1$ and $I_j(t) \geq 0$ for $t > 0$ where $1 \leq j \leq n$. Therefore by (6) we can write:

$$\frac{dI(t)}{dt} \leq \theta I(t) \text{ for } t > 0, \tag{7}$$

where $I(t) = \sum_{j=1}^{n} I_j(t)$. Hence (using theorem 1.1, pp. 78-79, [29]) we know that $I(t) \leq I^*(t)$ for $t \geq 0$ where $I^*(0) = I(0) > 0$ and where $\frac{dI^*(t)}{dt} = \theta I^*(t)$ for $t > 0$. Solving for $I^*(t)$ and using positivity of $I_j(t)$, we then have, for $1 \leq j \leq n$:

$$0 \leq I_j(t) \leq I(t) \leq I^*(t) = I(0)e^{\theta t} \text{ for } t > 0. \tag{8}$$

Combining (8) with the fact that $\theta < 0$ immediately yields that $I_j(t) \to 0$ as $t \to \infty$ for $1 \leq j \leq n$, as required. □

Rigorous proofs of endemicity in metapopulation models are, at present, scarce. However, disease persistence for a special case of an SIS model has been established analytically by Jin and Wang [16]. Also, simulations demonstrating endemicity in a two-patch SEIR model for a non-fatal disease have been carried out by Arino *et al* [1]. We shall now demonstrate by simulation that the disease can remain endemic in the model of (2), (3), (4), and (5) when there are two or three patches. Our simulations are not based on real-world data but it is likely that we will use such data in future work.

In figure 1(a) we simulate the model of (2), (3), and (4) when there are $n = 2$ patches and where the parameters are chosen as follows:

$$\begin{array}{lllll} \beta_1 = 12 & \mu_1^S = 1.0 & \mu_1^I = 1.1 & \mu_1^R = 1.0 & \gamma_1 = 0.9 \\ \beta_2 = 15 & \mu_2^S = 1.1 & \mu_2^I = 1.2 & \mu_2^R = 1.1 & \gamma_2 = 1.2. \end{array}$$

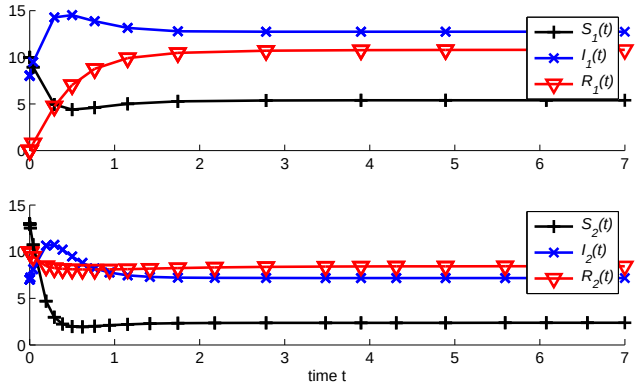
The migration rates are:

$$\begin{array}{lll} m_{1,2}^S = 1.0 & m_{1,2}^I = 0.8 & m_{1,2}^R = 1 \\ m_{2,1}^S = 1.2 & m_{2,1}^I = 1.0 & m_{2,1}^R = 1.2. \end{array}$$

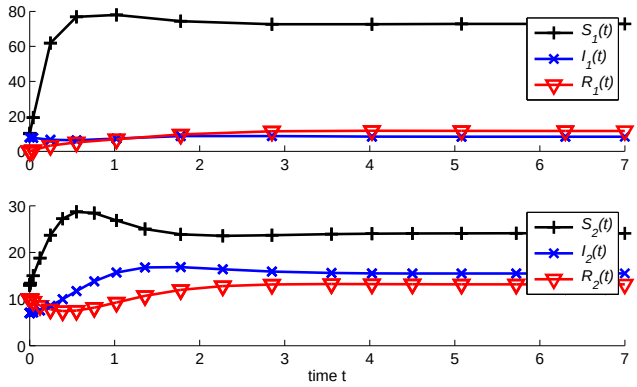
The initial conditions are $(S_1(0), I_1(0), R_1(0)) = (10, 8, 0)$ and $(S_2(0), I_2(0), R_2(0)) = (13, 7, 10)$. The population unit may be thousands of individuals so it is not necessary to worry about stochastic effects from apparently low initial conditions. The birth functions in figure 1(a) are both of the form $b(N) = \lambda_1 N e^{-\lambda_2 N}$: on patch 1 we have $b_1(N_1) = 3N_1 e^{-0.03N_1}$ and on patch 2 we have $b_2(N_2) = 4N_2 e^{-0.09N_2}$. A birth function of the form $b(N) = \lambda_1 N e^{-\lambda_2 N}$ is a Ricker functional form [24, 25], so we shall refer to such a birth function as being of *Ricker type*. Ricker birth functions are commonly used in population models [11, 27, 31]. Notice that if a population N is suitably small, then $b(N) = \lambda_1 N e^{-\lambda_2 N}$ behaves like a linear function, reflecting the idea that a small population may grow quickly because there may be less competition for food or to find a mate.

Figure 1(b) differs from figure 1(a) only in the choice of the contact rates and the birth functions. Thus the contact rates are now $\beta_1 = 1.2$ and $\beta_2 = 6.5$ and the birth functions are as follows: on patch 1 we have $b_1(N_1) = 1.5N_1^2 e^{-0.05N_1}$ and on patch 2 we have $b_2(N_2) = 2N_2^2 e^{-0.1N_2}$. It is not unusual in the literature to see a birth function of the form $b(N) = \alpha_1 N^2 e^{-\alpha_2 N}$ for positive constants α_1, α_2 [27]. In a recent paper, we labelled such a birth function as being of *Allee type* in view of its connection to a phenomenon called the Allee effect in which a population can be small enough as to be unsustainable [31]. The same label will be adopted in this paper.

In figure 2(a) we demonstrate endemicity on three patches when the birth functions on all patches are of Ricker type, namely $b_1(N_1) = 3N_1 e^{-0.03N_1}$, $b_2(N_2) =$



(a) Ricker birth functions



(b) Allee birth functions

FIGURE 1. Natural endemicity on two patches. See section 3 for parameter choices and comments.

$4N_2e^{-0.09N_2}$, and $b_3(N_3) = 5N_3e^{-0.1N_3}$. Parameters are chosen as follows:

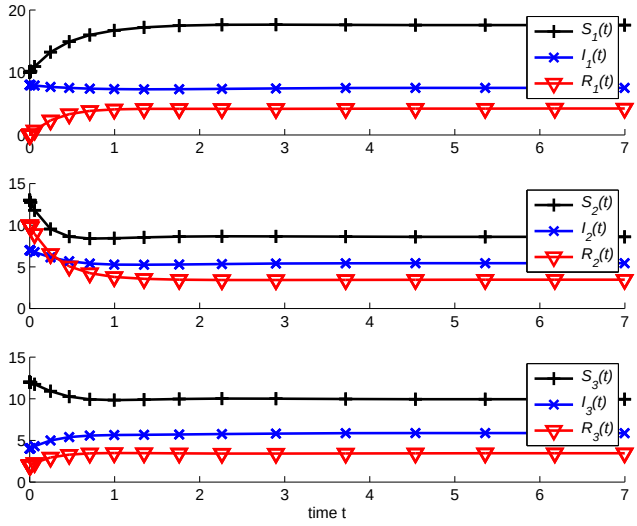
$$\begin{array}{lllll} \beta_1 = 3 & \mu_1^S = 0.8 & \mu_1^I = 1.3 & \mu_1^R = 0.8 & \gamma_1 = 0.5 \\ \beta_2 = 4 & \mu_2^S = 0.9 & \mu_2^I = 1.2 & \mu_2^R = 0.9 & \gamma_2 = 0.6 \\ \beta_3 = 3 & \mu_3^S = 1.0 & \mu_3^I = 1.2 & \mu_3^R = 1.0 & \gamma_3 = 0.5. \end{array}$$

The migration rates are:

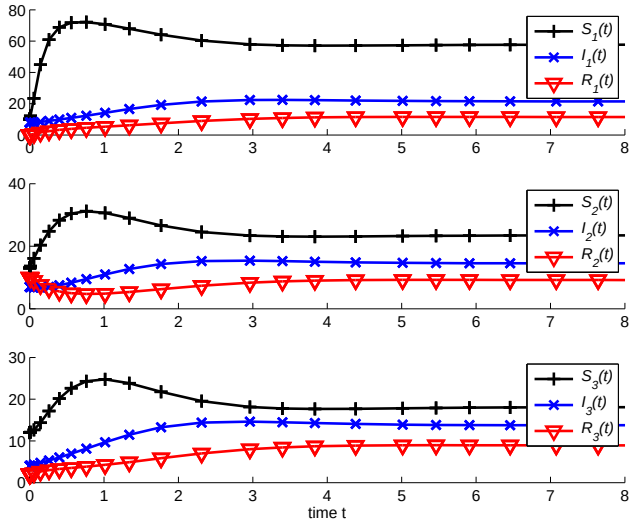
$$\begin{array}{llllll} m_{1,2}^S = 0.7 & m_{1,2}^I = 0.5 & m_{1,2}^R = 0.7 & m_{1,3}^S = 0.7 & m_{1,3}^I = 0.4 & m_{1,3}^R = 0.7 \\ m_{2,1}^S = 0.9 & m_{2,1}^I = 0.6 & m_{2,1}^R = 0.8 & m_{2,3}^S = 1.0 & m_{2,3}^I = 0.8 & m_{2,3}^R = 0.9 \\ m_{3,1}^S = 0.8 & m_{3,1}^I = 0.6 & m_{3,1}^R = 0.8 & m_{3,2}^S = 0.8 & m_{3,2}^I = 0.5 & m_{3,2}^R = 0.8. \end{array}$$

The initial conditions are $(S_1(0), I_1(0), R_1(0)) = (10, 8, 0)$, $(S_2(0), I_2(0), R_2(0)) = (13, 7, 10)$, and $(S_3(0), I_3(0), R_3(0)) = (12, 4, 2)$.

Finally, in figure 2(b) we demonstrate endemicity on three patches when the birth functions on all patches are of Allee type, specifically $b_1(N_1) = 1.5N_1^2e^{-0.05N_1}$,



(a) Ricker birth functions



(b) Allee birth functions

FIGURE 2. Natural endemicity on three patches. See section 3 for parameter choices and comments.

$b_2(N_2) = 2N_2^2 e^{-0.1N_2}$, and $b_3(N_3) = 3N_3^2 e^{-0.2N_3}$. The model parameters and initial conditions are chosen as in figure 2(a).

Figures 1 and 2 show that the disease can remain endemic when the birth functions are of Ricker or Allee types and when there are two or three patches. Certainly,

then, there appear to be grounds for seeking vaccination strategies to eradicate the disease.

4. **Pulse vaccination strategies.** We have seen evidence in the previous section that the disease can remain endemic in the model of (2), (3), (4), and (5). In this section we seek conditions on the pulse vaccination strategies such that the disease will be eradicated on all n patches simultaneously whilst asking if the PVS parameters on every patch can be chosen with some automony along the lines stated in the introduction.

Although many human populations have been growing in recent decades and centuries, this growth is unlikely to continue forever [20]. Also, despite dire predictions by numerous gloomy individuals, there has not been a major global human population crash for many centuries. It seems reasonable to eventually hope for some sort of stability in human populations. The reason we mention these details is because we use the idea that our subpopulations are stable in order to find successful pulse vaccination strategies. We begin with a lemma in which we bound below the populations on every patch.

Lemma 4.1. *Consider the PVS model of definition 2.1. For $1 \leq j \leq n$, define:*

$$D_j = \max\left\{\mu_j^S + \sum_{k=1}^{n} m_{j,k}^S, \quad \mu_j^I + \sum_{k=1}^{n} m_{j,k}^I, \quad \mu_j^R + \sum_{k=1}^{n} m_{j,k}^R\right\}. \tag{9}$$

(A1) If the birth function on patch j is of Ricker type, with $b_j(N_j) = \lambda_{1,j} N_j e^{-\lambda_{2,j} N_j}$, and if $D_j < \lambda_{1,j}$, then $b_j(N_j) = D_j N_j$ has a unique positive solution N_j^* and $N_j(t) > 0.99 N_j^*$ for all t large enough.

(A2) If the birth function on patch j is of Allee type, with $b_j(N_j) = \alpha_{1,j} N_j^2 e^{-\alpha_{2,j} N_j}$, and if $D_j < \frac{\alpha_{1,j}}{e\alpha_{2,j}}$, then $b_j(N_j) = D_j N_j$ has two positive solutions, which we may label $N_{1,j}^*$ and $N_{2,j}^*$, with $N_{1,j}^* < N_{2,j}^*$. If $N_j(0) > N_{1,j}^*$ then $N_j(t) > N_{1,j}^*$ for $t > 0$ and $N_j(t) > 0.99 N_{2,j}^*$ for all t large enough.

Proof. Bearing in mind that $N_j(t) = S_j(t) + I_j(t) + R_j(t)$ and that $N_j(t)$ is not impulsively changed when any vaccination pulse occurs on any patch, we add together (2), (3), and (4) to obtain, for $t > 0$:

$$\begin{aligned}\frac{dN_j}{dt} = b_j(N_j) &+ \left(\sum_{k=1}^{n} m_{k,j}^S S_k\right) + \left(\sum_{k=1}^{n} m_{k,j}^I I_k\right) + \left(\sum_{k=1}^{n} m_{k,j}^R R_k\right) \\ &- \left(\mu_j^S + \sum_{k=1}^{n} m_{j,k}^S\right) S_j - \left(\mu_j^I + \sum_{k=1}^{n} m_{j,k}^I\right) I_j - \left(\mu_j^R + \sum_{k=1}^{n} m_{j,k}^R\right) R_j. \end{aligned} \tag{10}$$

By positivity we have

$$\left(\sum_{k=1}^{n} m_{k,j}^S S_k\right) + \left(\sum_{k=1}^{n} m_{k,j}^I I_k\right) + \left(\sum_{k=1}^{n} m_{k,j}^R R_k\right) \geq 0, \tag{11}$$

and

$$\begin{aligned} &- \left(\mu_j^S + \sum_{k=1}^{n} m_{j,k}^S\right) S_j - \left(\mu_j^I + \sum_{k=1}^{n} m_{j,k}^I\right) I_j - \left(\mu_j^R + \sum_{k=1}^{n} m_{j,k}^R\right) R_j \\ &\geq \quad -D_j S_j - D_j I_j - D_j R_j = -D_j N_j. \end{aligned} \tag{12}$$

Using (10), (11), and (12), we can write, for $t > 0$:

$$\frac{dN_j}{dt} \geq b_j(N_j) - D_j N_j. \tag{13}$$

It follows (using theorem 1.1, pp. 78-79, [29]) that $N_j(t) \geq N_j^*(t)$ for $t \geq 0$ where $N_j^*(0) = N_j(0) > 0$ and where, for $t > 0$, we have $\frac{dN_j^*}{dt} = b_j(N_j^*) - D_j N_j^*$. Results (A1) and (A2) of the lemma now follow trivially. □

Now in real life a birth rate will never be infinite. Also we know by lemma 4.1 that the populations on the different patches can be bounded below for all time large enough. Hence we are in a position to bound above the susceptible, infective, and removed populations on every patch in our next result:

Lemma 4.2. *Consider the PVS model of definition 2.1. For $1 \leq j \leq n$, assume that $N_j(t) \geq L_j$ for $t \geq t_j^*$ where L_j and t_j^* are positive constants (this is a sensible assumption in view of lemma 4.1). Let $L = \min_{1\leq j\leq n}\{L_j\}$ and $\bar{t} = \max_{1\leq j\leq n}\{t_j^*\}$. Suppose that the birth functions are bounded above, that is, suppose, for $1 \leq j \leq n$, that $\max_{N_j\geq 0}\{b_j(N_j)\} \leq M_j$ where M_j is a positive constant. Also let $N(\bar{t}) = \sum_{j=1}^n N_j(\bar{t})$. Then $S_j(t) \leq \frac{M}{d}$ and $I_j(t) \leq \frac{M}{d}$ and $R_j(t) \leq \frac{M}{d}$ for $t > t^*$ where $M = \sum_{j=1}^n M_j$ and $d = \min_{1\leq j\leq n}\{\mu_j^I\}$, and where*

$$t^* = \begin{cases} \bar{t} & \text{if } N(\bar{t}) \leq \frac{M}{d} + L \\ \bar{t} + \frac{1}{d}\ln\left(\frac{N(\bar{t}) - \frac{M}{d}}{L}\right) & \text{if } N(\bar{t}) > \frac{M}{d} + L. \end{cases} \tag{14}$$

Proof. If we add together all $3n$ equations defined by (2), (3), and (4) for $1 \leq j \leq n$, and bear in mind that $S_j(t) + I_j(t) + R_j(t) = N_j(t)$, we obtain, for $t > 0$:

$$\frac{d}{dt}\left(\sum_{j=1}^n N_j(t)\right) = \sum_{j=1}^n \left(b_j(N_j(t)) - \left[\mu_j^S S_j(t) + \mu_j^I I_j(t) + \mu_j^R R_j(t)\right]\right). \tag{15}$$

Equation (15) holds both for the model without vaccinations and for the PVS model. This is because in the PVS model, the model equations are the same between pulses as in the model without vaccinations and each instantaneous pulse on any patch does not alter the total size of the population on that or any other patch.

Let $N(t) = \sum_{j=1}^n N_j(t)$. Then using the definition of d given in the statement of the lemma and the assumptions (in section 2) that, for $1 \leq j \leq n$, then $\mu_j^I \geq \mu_j^S$ and $\mu_j^I \geq \mu_j^R$, we see by (15) that, for $t > 0$:

$$\frac{dN(t)}{dt} \leq \left(\sum_{j=1}^n b_j(N_j(t))\right) - dN(t). \tag{16}$$

Since $N_j(t) > 0$ for all $t > 0$ by positivity, we can use (1), the assumption in the statement of the lemma that $\max_{N_j\geq 0}\{b_j(N_j)\} \leq M_j$ for $1 \leq j \leq n$, and (16) to deduce that:

$$\frac{dN(t)}{dt} \leq M - dN(t), \tag{17}$$

for $t > 0$ where $M = \sum_{j=1}^n M_j$.

Since (17) holds for $t > 0$, it must hold in particular for $t > \bar{t}$ where $\bar{t}$ is defined in the statement of the lemma. But then it follows by theorem 1.1 on pages 78-79 of [29] that $N(t) \leq N^*(t)$ for $t \geq \bar{t}$ where $N^*(\bar{t}) = N(\bar{t}) = \sum_{j=1}^n N_j(\bar{t}) > 0$ (we have

noted that $N_j(t) > 0$ for any $t > 0$ by positivity) and where, for $t > \bar{t}$, we have $\frac{dN^*(t)}{dt} = M - dN^*(t)$. Solving for $N^*(t)$ reveals that:

$$N(t) \leq N^*(t) = \frac{M}{d} + \left(N(\bar{t}) - \frac{M}{d} \right) e^{-d(t-\bar{t})} \text{ for } t \geq \bar{t}. \tag{18}$$

Since $e^{-d(t-\bar{t})} \to 0$ as $t \to \infty$, we can deduce by (18) that, for all t large enough, then

$$N(t) \leq \frac{M}{d} + L, \tag{19}$$

where L is a positive constant defined in the statement of the lemma. In fact (19) can be seen to hold for all $t > t^*$ where t^* is defined in (14).

Consider the j-th patch. By assumption there are at least two patches, so there exists an i-th patch where $i \neq j$. By positivity we know that $0 \leq S_j(t) \leq N_j(t) \leq N(t)$ and that $N_i(t) + N_j(t) \leq N(t)$ for $t \geq 0$ and therefore for $t \geq t^*$. Furthermore we know by assumption that $N_i(t) \geq L_i$ for $t \geq t_i^*$ and that $t^* \geq t_i^*$, so that $N_i(t) \geq L_i$, or equivalently $-N_i(t) \leq -L_i$, for $t \geq t^*$. Combining the observations made so far in this paragraph with the fact that (19) holds for $t > t^*$, we find that:

$$S_j(t) \leq N_j(t) \leq N(t) - N_i(t) \leq \frac{M}{d} + L - L_i \text{ for } t > t^*. \tag{20}$$

But $L - L_i = \min_{1 \leq j \leq n} \{L_j\} - L_i \leq 0$. Hence by (20) we have $S_j(t) \leq \frac{M}{d}$ for $t > t^*$. Similarly we may bound above $I_j(t)$ and $R_j(t)$. □

By lemma 4.1, we know that there will be circumstances under which the population on patch j $(1 \leq j \leq n)$ will remain bounded below. Also we have noted before lemma 4.2 how in real life a birth rate will never be infinite. In particular, however, it is sensible to expect the per capita birth rate on each patch to be finite, that is, to expect $\max_{N_j \geq 0} \left\{ \frac{b_j(N_j)}{N_j} \right\}$ to be finite, and indeed if b_j is either of the two commonly used birth function mentioned in section 3 - Ricker or Allee - then such an expectation holds. Thus we can be sure that the assumptions made in the following theorem are reasonable:

Theorem 4.3. *Consider the PVS model of definition 2.1. As in lemma 4.2, assume, for* $1 \leq j \leq n$, *that* $\max_{N_j \geq 0} \{b_j(N_j)\} \leq M_j$ *where* M_j *is a positive constant, and that* $N_j(t) \geq L_j$ *for* $t \geq t_j^*$ *where* L_j *and* t_j^* *are positive constants. Suppose also, for* $1 \leq j \leq n$, *that* $\max_{N_j \geq 0} \left\{ \frac{b_j(N_j)}{N_j} \right\} \leq K_j$ *for a positive constant* K_j.

Let $M = \sum_{j=1}^n M_j$ *and* $d = \min_{1 \leq j \leq n} \{\mu_j^I\}$. *Also let*

$$A_j = K_j + \left(\sum_{k=1}^n m_{k,j}^S \right) \left(\frac{M}{dL_j} \right) + \mu_j^S + \mu_j^I + \mu_j^R + \sum_{k=1}^n \left(m_{j,k}^S + m_{j,k}^I + m_{j,k}^R \right). \tag{21}$$

Assume, for $1 \leq j \leq n$, *that the PVS on patch* j *satisfies the relationship:*

$$\frac{\left(1 - e^{-A_j T_j}\right) \left[1 + q_j \left(1 - e^{-A_j T_j}\right)\right]}{1 - q_j e^{-A_j T_j}} < \frac{\gamma_j + \mu_j^I}{\beta_j}. \tag{22}$$

Then, for $1 \leq j \leq n$, *we have* $I_j(t) \to 0$ *as* $t \to \infty$.

Proof. First note by the quotient rule for differentiation that:

$$\frac{d}{dt} \left(\frac{S_j}{N_j} \right) = \frac{\frac{dS_j}{dt}}{N_j} - \frac{S_j}{N_j} \left(\frac{\frac{dN_j}{dt}}{N_j} \right) \qquad \text{for } t > 0, \quad t \neq t_{i,j} \text{ where } i \geq 1, \tag{23}$$

where (recall by definition 2.1) $t_{i,j}$ is the time of the i-th pulse on patch j.

By positivity $-\beta_j \frac{S_j(t)I_j(t)}{N_j(t)} \leq 0$ and $N_j(t) > 0$ for $t > 0$, so by (2) we can write:

$$\frac{\frac{dS_j}{dt}}{N_j} \leq \frac{b_j(N_j)}{N_j} + \left(\sum_{k=1}^{n} m_{k,j}^S S_k\right)\left(\frac{1}{N_j}\right) - \left(\mu_j^S + \sum_{k=1}^{n} m_{j,k}^S\right)\left(\frac{S_j}{N_j}\right) \tag{24}$$

for $t > 0$, $t \neq t_{i,j}$ where $i \geq 1$.

By positivity $\sum_{k=1}^{n} m_{k,j}^I I_k \geq 0$ and $\sum_{k=1}^{n} m_{k,j}^R R_k \geq 0$ for $t > 0$. Also $S_j + I_j + R_j = N_j$, so by the positivity of R_j we have $-I_j = -N_j + S_j + R_j \geq -(N_j - S_j)$ for $t > 0$. Similarly $-R_j \geq -(N_j - S_j)$ for $t > 0$. Combining the observations made so far in this paragraph with (10), we find, for $t > 0$, $t \neq t_{i,j}$ where $i \geq 1$, that:

$$\begin{aligned}\frac{dN_j}{dt} \quad \geq \quad & b_j(N_j) + \left(\sum_{k=1}^{n} m_{k,j}^S S_k\right) - \left(\mu_j^S + \sum_{k=1}^{n} m_{j,k}^S\right) S_j \\ & - \left(\mu_j^I + \mu_j^R + \sum_{k=1}^{n} \left(m_{j,k}^I + m_{j,k}^R\right)\right)(N_j - S_j)\,. \end{aligned} \tag{25}$$

Since $N_j > 0$ and $-\frac{S_j}{N_j} \leq 0$ by positivity, we deduce by (25) that

$$\begin{aligned} -\frac{S_j}{N_j}\left(\frac{\frac{dN_j}{dt}}{N_j}\right) \quad \leq \quad & -\left[\frac{b_j(N_j)}{N_j} + \left(\sum_{k=1}^{n} m_{k,j}^S S_k\right)\left(\frac{1}{N_j}\right)\right]\left(\frac{S_j}{N_j}\right) \\ & + P_j\left(\frac{S_j}{N_j}\right)^2 + Q_j\left(1 - \frac{S_j}{N_j}\right)\left(\frac{S_j}{N_j}\right), \end{aligned} \tag{26}$$

where $P_j = \mu_j^S + \sum_{k=1}^{n} m_{j,k}^S$ and $Q_j = \mu_j^I + \mu_j^R + \sum_{k=1}^{n}\left(m_{j,k}^I + m_{j,k}^R\right)$.

Again by positivity $0 \leq \frac{S_j}{N_j} \leq 1$. But then:

$$P_j\left(\frac{S_j}{N_j}\right)^2 + Q_j\left(1 - \frac{S_j}{N_j}\right)\left(\frac{S_j}{N_j}\right) \leq P_j + Q_j\left(1 - \frac{S_j}{N_j}\right). \tag{27}$$

Using (24), (26), and (27) in (23), we therefore deduce that:

$$\frac{d}{dt}\left(\frac{S_j}{N_j}\right) \leq \left(\frac{b_j(N_j)}{N_j} + \left(\sum_{k=1}^{n} m_{k,j}^S S_k\right)\left(\frac{1}{N_j}\right) + P_j + Q_j\right)\left(1 - \frac{S_j}{N_j}\right) \tag{28}$$

for $t > 0$, $t \neq t_{i,j}$ where $i \geq 1$.

Now we know that $1 - \frac{S_j}{N_j} \geq 0$. Also, by assumption, $\max_{N_j \geq 0}\left\{\frac{b_j(N_j)}{N_j}\right\} \leq K_j$ and, for $t \geq t_j^*$, then $\frac{1}{N_j(t)} \leq \frac{1}{L_j}$. Furthermore, by lemma 4.2, we know that $S_k \leq \frac{M}{d}$ for $1 \leq k \leq n$ for $t > t^*$ where t^* is defined in the statement of lemma 4.2. Note that $t^* \geq t_j^*$ for $1 \leq j \leq n$. By the observations made so far in this paragraph and by (28), we have:

$$\frac{d}{dt}\left(\frac{S_j}{N_j}\right) \leq A_j\left(1 - \frac{S_j}{N_j}\right) \qquad \text{for } t > t^*, \quad t \neq t_{i,j} \text{ where } i \geq 1, \tag{29}$$

where A_j is a positive constant defined in (21).

Let $x_j(t) = \frac{S_j(t)}{N_j(t)}$. We know that pulses occur on patch j at times $t_{i,j}$ as outlined in definition 2.1. Let $t_{u_j,j}$ be the time of the first pulse on patch j to occur strictly

later than t^*. Then we can write, by (29):

$$\frac{dx_j(t)}{dt} \leq A_j\left(1 - x_j(t)\right) \text{ for } t > t_{u_j,j}, t \neq t_{i,j} \text{ where } i > u_j. \tag{30}$$

Then (using theorem 1.1, pp. 78-79, [29]), we can say, for any $i \geq u_j$, that $x_j(t) \leq g_j(t)$ for $t \in [t_{i,j}, t_{i+1,j})$ where $g_j(t_{i,j}) = x_j(t_{i,j})$ and where

$$\frac{dg_j(t)}{dt} = A_j\left(1 - g_j(t)\right) \text{ for } t \in (t_{i,j}, t_{i+1,j}). \tag{31}$$

Solving for $g_j(t)$ reveals that:

$$x_j(t) \leq g_j(t) = 1 + \left(x_j(t_{i,j}) - 1\right) e^{-A_j(t - t_{i,j})} \quad \text{for } t \in [t_{i,j}, t_{i+1,j}), \quad i \geq u_j. \tag{32}$$

But then:

$$x_j(t_{i+1,j}^-) \leq 1 + \left(x_j(t_{i,j}) - 1\right) e^{-A_j T_j} \quad \text{for } i \geq u_j, \tag{33}$$

where (recall by definition 2.1) $t_{i+1,j}^-$ denotes the time "momentarily" before the time $t_{i+1,j}$.

Observe that $x_j(t_{i+1,j}) = q_j x_j(t_{i+1,j}^-)$ since, by definition 2.1, $S_j(t_{i+1,j}) = q_j S_j(t_{i+1,j}^-)$ and $N_j(t_{i+1,j}) = N_j(t_{i+1,j}^-)$. Hence by (33):

$$x_j(t_{i+1,j}) = q_j x_j(t_{i+1,j}^-) \leq q_j\left(1 - e^{-A_j T_j}\right) + q_j e^{-A_j T_j} x_j(t_{i,j}) \quad \text{for } i \geq u_j. \tag{34}$$

Let $z_i = x_j(t_{i,j})$. Then by (34):

$$z_{i+1} \leq E_j + F_j z_i \qquad \text{for } i \geq u_j, \tag{35}$$

where

$$E_j = q_j(1 - e^{-A_j T_j}) > 0 \quad \text{and} \quad F_j = q_j e^{-A_j T_j}. \tag{36}$$

Iterating (35) we quickly find, for $i > u_j$, that:

$$z_i \leq F_j^{i-u_j} z_{u_j} + E_j \sum_{r=0}^{i-u_j-1} F_j^r. \tag{37}$$

Now $0 < F_j = q_j e^{-A_j T_j} < 1$, so the partial sum in (37) will be less than the entire sum, that is, $\sum_{r=0}^{i-u_j-1} F_j^r < \sum_{r=0}^{\infty} F_j^r = \frac{1}{1-F_j}$. Hence:

$$z_i \leq F_j^{i-u_j} z_{u_j} + \frac{E_j}{1 - F_j} \quad \text{for } i > u_j. \tag{38}$$

It is clear by positivity that $\frac{S_j(t_{u_j,j})}{N_j(t_{u_j,j})} \leq 1$. Hence, $z_{u_j} = x_j(t_{u_j,j}) = \frac{S_j(t_{u_j,j})}{N_j(t_{u_j,j})} \leq 1$. Therefore by (38) $x_j(t_{i,j}) = z_i \leq F_j^{i-u_j} + \frac{E_j}{1-F_j}$ for $i > u_j$. But then by (32) we have, for $t \in [t_{i,j}, t_{i+1,j})$ for $i > u_j$, that:

$$\begin{aligned} \frac{S_j(t)}{N_j(t)} = x_j(t) &\leq 1 + \left(F_j^{i-u_j} + \frac{E_j}{1 - F_j} - 1\right) e^{-A_j(t - t_{i,j})} \\ &= 1 - e^{-A_j(t-t_{i,j})} + \left(F_j^{i-u_j} + \frac{E_j}{1 - F_j}\right) e^{-A_j(t-t_{i,j})}. \end{aligned} \tag{39}$$

On the interval $t \in [t_{i,j}, t_{i+1,j})$ (where $i > u_j$) it is clear that $1 - e^{-A_j(t-t_{i,j})}$ is bounded above by $1 - e^{-A_j T_j}$ and that $e^{-A_j(t-t_{i,j})}$ is bounded above by 1. But then, using (39), we can write, for $t \in [t_{i,j}, t_{i+1,j})$, $i > u_j$, that:

$$\frac{S_j(t)}{N_j(t)} \leq 1 - e^{-A_j T_j} + F_j^{i-u_j} + \frac{E_j}{1 - F_j}. \tag{40}$$

Recalling the definitions of E_j and F_j from (36), we may rewrite the right hand side of (40) to obtain:

$$\frac{S_j(t)}{N_j(t)} \leq \frac{\left(1-e^{-A_jT_j}\right)\left[1+q_j\left(1-e^{-A_jT_j}\right)\right]}{1-q_je^{-A_jT_j}} + F_j^{i-u_j}. \tag{41}$$

Now since $0 < F_j = q_je^{-A_jT_j} < 1$, then for any $\epsilon > 0$ we have $F_j^{i-u_j} < \epsilon$ for all i large enough. In particular this is true for

$$\epsilon = \frac{1}{2}\left(\frac{\gamma_j+\mu_j^I}{\beta_j} - \frac{\left(1-e^{-A_jT_j}\right)\left[1+q_j\left(1-e^{-A_jT_j}\right)\right]}{1-q_je^{-A_jT_j}}\right), \tag{42}$$

a quantity which is positive in view of assumption (22). Hence there exists $i_j^* > u_j$ such that, for $i \geq i_j^*$, then $F_j^{i-u_j} < \epsilon$ where ϵ is given by (42). Therefore, by (41), we find, for $t \in [t_{i,j}, t_{i+1,j})$, $i \geq i_j^*$, that:

$$\frac{S_j(t)}{N_j(t)} \leq \frac{1}{2}\left(\frac{\gamma_j+\mu_j^I}{\beta_j} + \frac{\left(1-e^{-A_jT_j}\right)\left[1+q_j\left(1-e^{-A_jT_j}\right)\right]}{1-q_je^{-A_jT_j}}\right). \tag{43}$$

Using (43) and (6) and the positivity of $I_j(t)$, we can write,

$$\frac{d}{dt}\left(\sum_{j=1}^n I_j(t)\right) \leq -\sum_{j=1}^n \alpha_j I_j(t) \quad \text{for } t \in [t_{i,j}, t_{i+1,j}), \quad i \geq i_j^*, \tag{44}$$

where $\alpha_j = \left(\frac{\beta_j}{2}\right)\left(\frac{\gamma_j+\mu_j^I}{\beta_j} - \frac{\left(1-e^{-A_jT_j}\right)\left[1+q_j\left(1-e^{-A_jT_j}\right)\right]}{1-q_je^{-A_jT_j}}\right)$. Note that, for $1 \leq j \leq n$, then $\alpha_j > 0$ by (22). It follows that $\alpha > 0$ where $\alpha = \min_{1\leq j\leq n}\{\alpha_j\}$. Therefore by (44) we have:

$$\frac{d}{dt}\left(\sum_{j=1}^n I_j(t)\right) \leq -\alpha\sum_{j=1}^n I_j(t) \quad \text{for } t \in [t_{i,j}, t_{i+1,j}), \quad i \geq i_j^*. \tag{45}$$

Let $I(t) = \sum_{j=1}^n I_j(t)$. Since vaccination pulses do not make the infective population on any patch change impulsively we deduce by (45) that $\frac{dI(t)}{dt} \leq -\alpha I(t)$ for all $t \geq t_{i_j^*,j}$. But then (using theorem 1.1, pp. 78-79, [29]) we know that $I(t) \leq I^*(t)$ for $t \geq t_{i_j^*,j}$ where $I^*(t_{i_j^*,j}) = I(t_{i_j^*,j}) \geq 0$ and where $\frac{dI^*(t)}{dt} = -\alpha I^*(t)$ for $t > t_{i_j^*,j}$. Solving for $I^*(t)$ and using positivity, we then have, for $1 \leq j \leq n$:

$$0 \leq I_j(t) \leq I(t) \leq I^*(t) = I(t_{i_j^*,j})e^{-\alpha(t-t_{i_j^*,j})} \text{ for } t \geq t_{i_j^*,j}. \tag{46}$$

Combining (46) with the knowledge that $\alpha > 0$ immediately yields that $I_j(t) \to 0$ as $t \to \infty$ for $1 \leq j \leq n$, as required. □

5. **Strategy existence.** Now let us comment on how restrictive condition (22) is. If we set $H_j = \frac{\gamma_j+\mu_j^I}{\beta_j} > 0$, then the condition may be written:

$$\frac{\left(1-e^{-A_jT_j}\right)\left(1+q_j-q_je^{-A_jT_j}\right)}{1-q_je^{-A_jT_j}} < H_j. \tag{47}$$

Note first of all that if $0 < q_j < 1$, then (47) clearly holds when $T_j = 0$. Also the left hand side in (47) is a continuous function of T_j for $T_j \geq 0$, so there will exist a range of $T_j > 0$ such that (47) holds. In other words, a PVS can always be found

to satisfy (47), although we have yet to comment on how small T_j might have to be.

Secondly note that if $q_j = 1$, then (47) becomes

$$2 - e^{-A_j T_j} < H_j. \tag{48}$$

Condition (48) holds automatically for $T_j > 0$ if $H_j \geq 2$. Also, if $1 < H_j < 2$ then (48) holds if $0 < T_j < \frac{1}{A_j} \ln\left(\frac{1}{2-H_j}\right)$. Hence if $H_j > 1$ then a PVS exists on patch j which satisfies (47) and for which $q_j = 1$. But if $q_j = 1$, then $p_j = 1 - q_j = 0$, so that the PVS effectively does nothing. Hence when $H_j > 1$ we can say that a PVS is not needed on patch j at all. It follows that if $H_j > 1$ for $1 \leq j \leq n$, then the disease will go extinct on all n patches simultaneously even if there are no vaccinations on any patch. However, this should not surprise us because if $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} > 1$ for $1 \leq j \leq n$ then theorem 3.1 will hold. Hence condition (47) takes into account the possibility that the disease may die out naturally and does not necessarily ask for a PVS to be carried out on patch j.

Now suppose that $H_j \leq 1$. Then (48) cannot hold for any $T_j > 0$, so a non-trivial PVS is needed if condition (47) is to be satisfied. Suppose, then, that $0 < q_j < 1$. Given such a q_j we now find a $T_j^* > 0$ such that condition (47) holds for $0 < T_j < T_j^*$. Let $X_j = e^{-A_j T_j}$ and note that, since $T_j > 0$, we must have $0 < X_j < 1$. If we define $f_{j,1}(X_j) = (1 - X_j)(1 + q_j - q_j X_j)$ and $f_{j,2}(X_j) = H_j(1 - q_j X_j)$, then (47) becomes:

$$f_{j,1}(X_j) = (1 - X_j)(1 + q_j - q_j X_j) < H_j(1 - q_j X_j) = f_{j,2}(X_j). \tag{49}$$

The trivial forms of the functions $f_{j,1}(X_j)$ and $f_{j,2}(X_j)$ make it easy to determine when (49) holds for $0 < X_j < 1$. A simple sketch (see figure 3) reveals that, for $0 < H_j \leq 1$ and $0 < q_j < 1$, then $f_{j,1}(X_j) = f_{j,2}(X_j)$ has two solutions, namely $X_{j,1}$ and $X_{j,2}$ where $0 < X_{j,1} < 1 < X_{j,2}$. Also $f_{j,1}(X_j) < f_{j,2}(X_j)$ for $X_{j,1} < X_j < 1$. Since $f_{j,1}(X_j) = f_{j,2}(X_j)$ is a quadratic equation, we may find $X_{j,1}$ explicitly:

$$X_{j,1} = \frac{(1 + 2q_j - q_j H_j) - \sqrt{\{(1 + 2q_j - q_j H_j)^2 - 4q_j(1 + q_j - H_j)\}}}{2q_j}. \tag{50}$$

The fact that (49) holds for $0 < X_{j,1} < X_j < 1$ may be proven by using the inequalities $0 < q_j < 1$, and $0 < H_j \leq 1$ in (50). We will not include the actual calculations since the results are obvious geometrically.

Since (49) holds for $0 < X_{j,1} < X_j < 1$ when $0 < q_j < 1$ and $0 < H_j \leq 1$, and since $X_j = e^{-A_j T_j}$, we deduce that (47) will hold for any T_j with $0 < T_j < T_j^*$ where

$$T_j^* = \frac{1}{A_j} \ln\left(\frac{1}{X_{j,1}}\right). \tag{51}$$

We may conclude that, when $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} \leq 1$, a PVS of the strength required by theorem 4.3 exists no matter what strength the pulses are, as long as they each do something (so that $0 < q_j < 1$), and the inter-pulse time T_j is less than T_j^* in (51).

In the situation in which $H_j \leq 1$, we can gain further insight into how restrictive condition (47) is by plotting "stability" diagrams. In figure 4 we plot the region in the q_j-T_j parameter space such that (47) holds in two cases, each with a different value of β_j. These regions are called stable regions in the plots. The region in each plot is the set of points (q_j, T_j) where $0 < q_j < 1$ and $0 < T_j < T_j^*$ where T_j^* satisfies (51). Note that T_j^* can be considered a function of q_j.

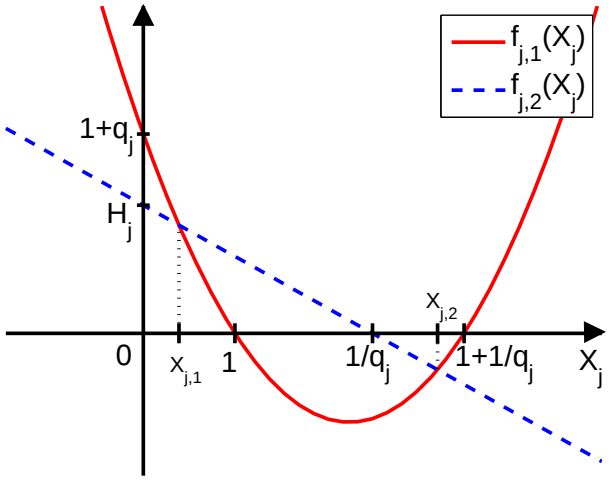


FIGURE 3. Comparison of left and right hand sides of (49) when $0 < H_j \leq 1$ and $0 < q_j < 1$. Here $q_j = 0.4$ and $H_j = 0.9$.

Observe that the stable region shrinks as β_j increases. This is intuitively sensible because, if the contact rate β_j increases, we would expect the disease to spread more easily, so that a stronger vaccination strategy would be needed to bring it under control. Note that a strong PVS will be near the origin, since a PVS is stronger when T_j is smaller and when p_j is larger, making $q_j = 1 - p_j$ smaller. Notice also that successful pulse vaccination strategies may exist which lie outside the stable regions, since we have proven (47) to be sufficient but not necessary for disease eradication.

6. **Comments on model parameters.** It is useful to know in what ways our condition for vaccination strategy success - condition (22) - depends on the model parameters, particularly the migration rates. Now we have already noted in the previous section that when $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} > 1$ then a PVS is not needed on patch j but if $H_j \leq 1$ then a PVS is needed on patch j in order for condition (22) to be satisfied. Hence, by theorem 4.3 at least, the need for a PVS on patch j depends only on the size of $\frac{\gamma_j + \mu_j^I}{\beta_j}$ and not on any migration rates. Of course theorem 4.3 provides conditions *sufficient* for disease eradication from all patches but we have not shown these conditions to be necessary. Future research could involve seeking necessary conditions. In any event, we have uncovered a result that is perhaps a little counter-intuitive - no matter how quickly individuals of any disease class migrate into or out of patch j, a PVS will not be needed on patch j as long as $\frac{\gamma_j + \mu_j^I}{\beta_j} > 1$.

Even if $\frac{\gamma_j + \mu_j^I}{\beta_j} \leq 1$, so that a PVS is required on patch j, the strength of the required PVS, determined by condition (22) and equation (21), has no dependence on the migration rates of infectives or removeds into patch j. Hence the quarantine

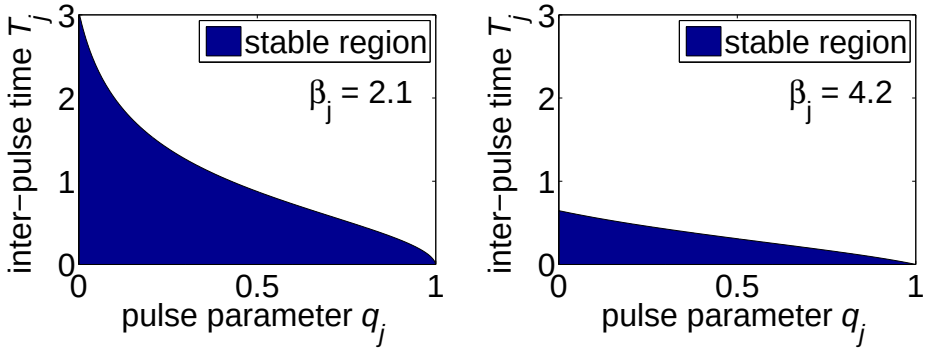


FIGURE 4. Stability diagrams for pulse vaccination strategy on patch j. The stable region depicts where $0 < q_j < 1$ and where condition (47) holds. For further comments see section 5. In both plots, $A_j = 1$, $\gamma_j = 1$, $\mu_j^I = 1$. Left plot: $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} = 0.9524$. Right plot: $H_j = 0.4762$.

of infective individuals entering patch j would make no difference to the strength of the PVS required by theorem 4.3. However, the quarantine of infectives may make a difference to the speed with which the disease is eradicated, an issue we may consider exploring in future work.

So far we have commented on how migration rates do not influence condition (22). Now let us comment on how they *do* influence (22). Assuming that $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} \leq 1$ then we have seen in the last section that a PVS with parameters q_j and T_j will satisfy (22) (or equivalently (47)) if $0 < q_j < 1$ and $0 < T_j < T_j^*$ where T_j^* satisfies (51). For given values of H_j and q_j, the minimum strength of the required PVS will depend on T_j^*, which in turn depends on migration rates by being inversely proportional to A_j, where A_j is given in (21). The constant A_j is proportional to susceptible migration into patch j and to migration of all disease classes out of patch j. No other migration terms appear in A_j.

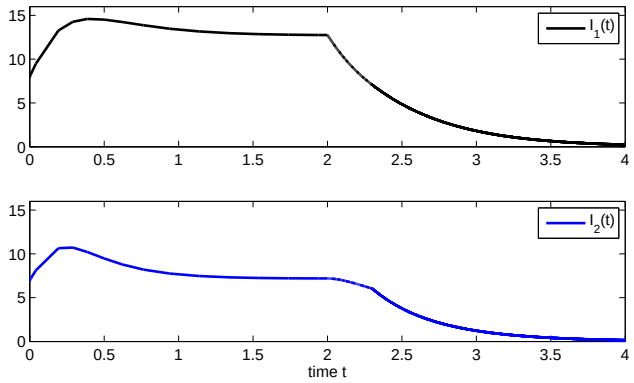
Thus we can say that a stronger PVS is required on patch j (stronger in the sense that the pulse frequency must be higher) if susceptible migration into patch j is higher or if migration of any disease class out of patch j is higher. It is sensible to expect that a stronger PVS will be needed on patch j if susceptible migration into patch j is higher because susceptible migration into patch j provides fuel for the disease on patch j. It is harder to explain the need for a stronger PVS on patch j when migration of any disease class out of patch j is higher. Certainly it is intuitive to expect to need a stronger PVS on patch j if migration of infectives into patch j is higher but we have said that such migration does not feature in the term A_j in (21). Perhaps as individuals migrate out of patch j, the disease may be encouraged to spread on the other patches, which may in turn promote the spread of the disease on patch j as individuals migrate into patch j, with the result that a stronger PVS may be needed on patch j. This is a matter we wish to clarify in future research.

We have noted that if $H_j = \frac{\gamma_j + \mu_j^I}{\beta_j} > 1$ then a PVS is not needed on patch j. It follows that if the disease is particularly deadly, so that μ_j^I is large, then the condition $H_j > 1$ is more likely to hold. In effect, an especially virulent disease can kill more quickly than it infects, causing the disease to kill itself off naturally. Also, if the recovery rate γ_j is large, then the condition $H_j > 1$ is more likely to hold - in other words, if individuals recover more quickly, a PVS is less likely to be needed. Finally, if the contact rate β_j is small, then it is more likely that $H_j > 1$. Thus, a country which does not possess a stockpiled vaccination for the disease can in theory control it by introducing measures to reduce contacts between infectives and susceptibles. Methods of disease control that do not involve vaccinations, including isolation of the sick, voluntary home quarantine, travel restrictions, and the closure of schools and workplaces, have been discussed by a number of authors [15, 8].

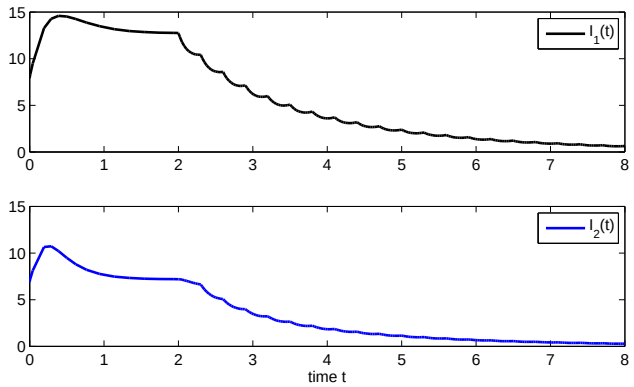
7. **Simulations.** In this section we present simulations in which independent pulse vaccination strategies are carried out when there are two or three patches. In figure 5(a) we plot the number of infectives on two patches by simulating the model of (2), (3), and (4), with the same initial data, model parameters, and Ricker-type birth functions as those used in figure 1(a). In figure 5(a), a PVS with constant pulse strength $p_1 = 0.9$ (so that $q_1 = 1 - p_1 = 0.1$) begins on patch 1 at time $t_{1,1} = 2$, with pulses occurring thereafter every $T_1 = T_1^*$ time units where $T_1^* = 0.0120$ is found by setting $j = 1$ in (51). (The calculation of T_1^* involves the calculation of A_1, which we found by setting $j = 1$ in (21). In order to find A_1, we found L_1 using part (A1) of lemma 4.1.) A PVS with constant pulse strength $p_2 = 0.85$ (so that $q_2 = 1 - p_2 = 0.15$) begins on patch 2 at time $t_{1,2} = 2.2$, with pulses occurring thereafter every $T_2 = T_2^*$ time units where $T_2^* = 0.0075$ is found by setting $j = 2$ in (51). (As in the calculation of T_1^*, we used part (A1) of lemma 4.1 in the calculation of T_2^*.)

If we were to choose T_1 and T_2 to be anything less than the values used in figure 5(a), then theorem 4.3 would guarantee that $I_1(t) \to 0$ and $I_2(t) \to 0$ as $t \to \infty$. As it is, even by choosing T_1 and T_2 as we have, figure 5(a) still apparently shows that $I_1(t) \to 0$ and $I_2(t) \to 0$. But this should not necessarily surprise us. We have not proven that the pulse vaccination strategies of theorem 4.3 are the weakest strategies that succeed in eradication - weakest in terms of frequency of application. Indeed, if we repeat the simulation of figure 5(a), changing only the pulse frequencies, we see by figure 5(b) that disease eradication may still occur when $T_1 = T_2 = 0.3$, that is, when the inter-pulse times are around 30 or 40 times larger than the values required by theorem 4.3. Other simulations (not included) have suggested to us that when T_1 and T_2 are approximately 0.32 then disease eradication does not occur. In future research we will seek to construct the weakest successful independent pulse vaccination strategies.

In figure 6(a) we plot the number of infectives on two patches by simulating the model of (2), (3), and (4), with the same initial data, model parameters, and Allee-type birth functions as those used in figure 1(b). We have seen in section 5 that if $\frac{\gamma_j + \mu_j^I}{\beta_j} > 1$ then vaccinations are not needed on patch j. For the simulation depicted in figure 6(a), this means that no vaccinations are needed on patch 1. However, vaccinations are needed on patch 2. A PVS with constant pulse strength $p_2 = 0.9$ (so that $q_2 = 1 - p_2 = 0.1$) begins on patch 2 at time $t_{1,2} = 3$, with pulses occurring



(a) Inter-pulse times: $T_1 = 0.0120$, $T_2 = 0.0075$.

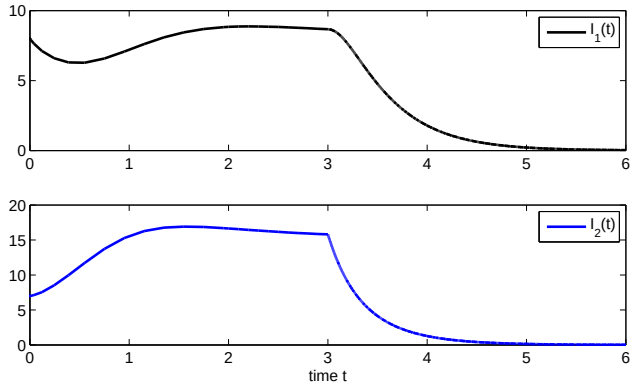


(b) Inter-pulse times: $T_1 = 0.3$, $T_2 = 0.3$.

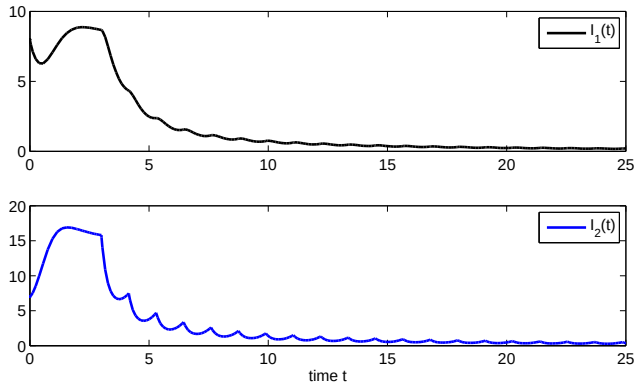
FIGURE 5. Independent pulse vaccination strategies on two patches, when (a) eradication is guaranteed by theorem 4.3 and (b) eradication is determined numerically. The birth function is of Ricker type on both patches. Infective populations depicted. PVS parameters on patch 1: $t_{1,1} = 2$, $p_1 = 0.9$. PVS parameters on patch 2: $t_{1,2} = 2.2$, $p_2 = 0.85$. The inter-pulse times are stated under each subfigure.

thereafter every $T_2 = T_2^*$ time units where $T_2^* = 0.0150$ is found by setting $j = 2$ in (51). (We used part (A2) of lemma 4.1 in the calculation of T_2^*.)

If the PVS on patch 2 has inter-pulse time T_2 smaller than $T_2^* = 0.0150$, then disease eradication is guaranteed for both patches by theorem 4.3. Even with $T_2 = T_2^*$, figure 6(a) suggests disease eradication will occur. In fact, increasing the inter-pulse time T_2 to 1.15 (77 times larger than T_2^*) still suggests the disease will be eradicated, as demonstrated by figure 6(b). Simulations (not included) have suggested to us that when $T_2 = 1.2$ then disease eradication does not occur. It would appear that the restrictions of theorem 4.3 may be quite strong.



(a) No pulses on patch 1. On patch 2 the inter-pulse time is $T_2 = 0.0150$.



(b) No pulses on patch 1. On patch 2 the inter-pulse time is $T_2 = 1.15$.

FIGURE 6. Independent pulse vaccination strategies on two patches, when (a) eradication is guaranteed by theorem 4.3 and (b) eradication is determined numerically. The birth function is of Allee type on both patches. Infective populations depicted. By theorem 4.3, vaccinations are not needed on patch 1 since $\frac{\gamma_1+\mu_1}{\beta_1} I > 1$. PVS parameters on patch 2: $t_{1,2} = 3$, $p_2 = 0.9$. The inter-pulse times are stated under each subfigure.

In figure 7 we plot the number of infectives on three patches, using the same initial data, model parameters, and Ricker-type birth functions as those used in figure 2(a). Pulse vaccination strategies are carried out on each of the patches; the parameters for each PVS are stated in figure 7. The inter-pulse times (T_1, T_2, T_3) were found by the same technique as that used to find the inter-pulse times in figure 5(a). Simulations (not included) have suggested to us that, when $T_1 = T_2 = T_3 = 1.6$ (approximately 50 to 144 times larger than the values for T_1, T_2, T_3 used in figure 7), then disease eradication still occurs. Hence the restrictions of theorem 4.3 may be even stronger for three patches than for two. If this is true, it need not surprise us. Applying theorem 4.3 involves bounding a number of quantities but some of these

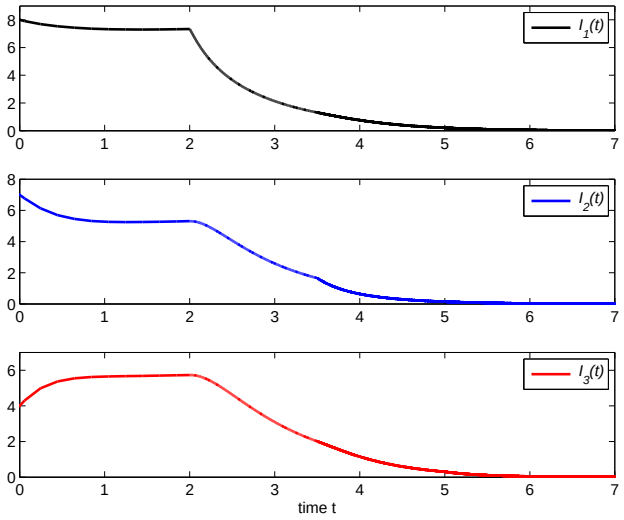


FIGURE 7. Disease eradication on three patches. The birth function is of Ricker type on all patches. Infective populations depicted. PVS parameters on patch 1: $t_{1,1} = 2$, $p_1 = 0.9$, $T_1 = 0.0322$. PVS parameters on patch 2: $t_{1,2} = 3.5$, $p_2 = 0.88$, $T_2 = 0.0111$. PVS parameters on patch 3: $t_{1,3} = 5$, $p_3 = 0.85$, $T_3 = 0.0158$.

bounds may not be extremely tight. Simulating a larger number of patches involves working with a larger number of such bounds, the accumulated effect of which may be to make the conditions of theorem 4.3 more restricted relative to the weakest vaccination strategies that succeed. Repeating the simulation of figure 7 with the inter-pulse times changed to $T_1 = T_2 = T_3 = 1.65$, we have found that eradication does not occur.

Finally, in figure 8 we plot the number of infectives on three patches, using the same initial data, model parameters, and Allee-type birth functions as those used in figure 2(b). Pulse vaccination strategies are carried out on each of the patches - see figure 8 for the PVS parameter values. We calculated the inter-pulse times (T_1, T_2, T_3) by the same technique as that used to find the inter-pulse times in figure 5(a). Simulations (not included) have suggested to us that, when $T_1 = T_2 = T_3 = 1.65$ (approximately 64 to 144 times larger than the values for T_1, T_2, T_3 used in figure 8), then disease eradication still occurs, but eradication does not occur when $T_1 = T_2 = T_3 = 1.7$.

8. **Discussion.** Inter-city, inter-regional, and international travel has increased significantly in the last few decades, promoting the spread of infectious diseases and motivating independent health authorities to co-ordinate their disease-control initiatives. The spread of SARS (Severe Acute Respiratory Syndrome) across aviation routes in 2003 is a well-studied example [28]. Despite co-ordinated control efforts, independent health authorities are likely to retain at least some autonomy in their decisions. In particular, autonomy may be retained in choosing the precise details of a pulse vaccination strategy (PVS).

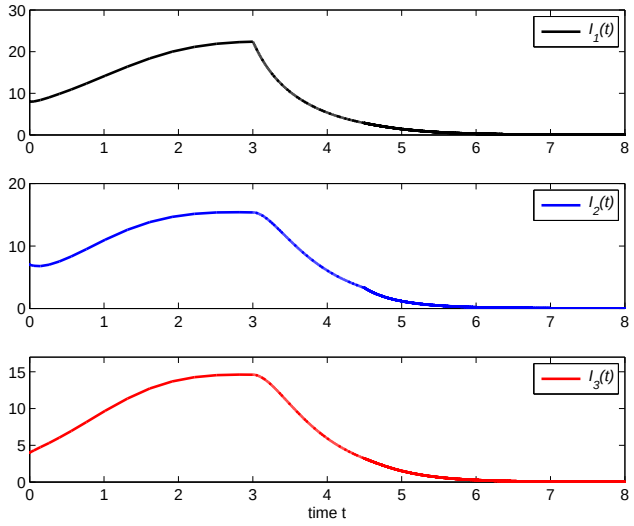


FIGURE 8. Disease eradication on three patches. The birth function is of Allee type on all patches. Infective populations depicted. PVS parameters on patch 1: $t_{1,1} = 3$, $p_1 = 0.9$, $T_1 = 0.0259$. PVS parameters on patch 2: $t_{1,2} = 4.5$, $p_2 = 0.88$, $T_2 = 0.0115$. PVS parameters on patch 3: $t_{1,3} = 6$, $p_3 = 0.85$, $T_3 = 0.0164$.

Such considerations led us to examine an SIR model on $n \geq 2$ patches between any pair of which migration was permitted in either direction. Having seen by simulation that the disease can remain endemic on the different patches, we asked if it could be eradicated on all patches simultaneously if an independent PVS were carried out on each patch. We discovered that, if each PVS were sufficiently strong, then such eradication would occur. We also discovered that a PVS may not be needed on every patch for the disease to be eradicated from every patch. Our analytical results were corroborated by simulations for two-patch and three-patch models but other simulations showed that vaccination strategies weaker than those required by our analytical results can also succeed.

There is often a delay of up two weeks between vaccination and actual protection for some infectious diseases such as influenza and multiple doses are sometimes required for full protection. There can also be an incubation period between contraction of an infection and becoming infectious. Future research could involve incorporating such ideas into our model in an effort to seek greater realism. Other future work could involve rigorously proving for our model that the disease can remain endemic in the absence of vaccinations. Finally it would be of practical value to construct the weakest pulse vaccination strategies that still succeed - weakest in terms of frequency of pulses. A sensible place to begin would be the establishment of local stability conditions of the disease-free steady state using stroboscopic maps, and then seeking to understand if local stability implies global stability.

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