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Theoretical Examination of the Pulse Vaccination Policy in the SIR Epidemic Model

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Abstract—Based on a theory of population dynamics in perturbed environments, it was hypothesized that measles epidemics can be more efficiently controlled by pulse vaccination, i.e., by a vaccination effort that is pulsed over time [1]. Here, we analyze the rationale of the pulse vaccination strategy in the simple SIR epidemic model. We show that repeatedly vaccinating the susceptible population in a series of "pulses," it is possible to eradicate the measles infection from the entire model population. We derive the conditions for epidemic eradication under various constraints and show their dependence on the parameters of the epidemic model. © 2000 Elsevier Science Ltd. All rights reserved.

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1. INTRODUCTION

New guidelines for measles immunization for most areas in the Western world recommend to apply a first vaccination dose to all infants 15 months of age and a second dose at approximately six years. These guidelines are based on the conventional concept of continuous time-constant immunization strategies. However, in such strategies, vaccination affects the amplitude and the period of the epidemics, but it does not antagonize the natural dynamics of the disease. In contrast, a theory of population dynamics in harshly varying environments [2,3] suggests that when the environmental pattern imposed on the population takes the form of discrete episodes of devastation, it is the spacing of these episodes that determines population extinction. Based on this theory, it was hypothesized that measles epidemics can be more efficiently controlled when the natural temporal process of the epidemics is antagonized by another temporal process, i.e., by a vaccination effort that is pulsed in time rather than uniform and continuous. This policy was referred to as *pulse vaccination* and it was shown theoretically that pulse vaccination in which

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children aged one to seven years are immunized once every five years, may suffice for preventing the epidemics [1].

Recently, pulse vaccination has gained in prominence as a result of its reasonably successful application to the control of poliomyelitis and measles throughout Central and South America [4,5]. The strategy has also been examined in the United Kingdom, where children aged five to 16 years were offered a combined measles and rubella (MR) vaccine in November 1994. Coverage of 90% or more was achieved in 133 of 172 district health authorities (77%), and the mean coverage in England and Wales was 92%. As a result of this policy, the number of cases of measles notified to the Office of Population Censuses and Surveys fell significantly. Consequently, it was concluded that pulse vaccination of all children of school age is likely to have a dramatic effect on transmission of measles for several years and prevent a substantial toll of morbidity and mortality. If sufficiently high coverage is achieved, interruption of transmission should occur [6].

However, some serious questions may arise concerning the expected impact of this strategy. On the practical level, it seems essential to determine *a priori* the pulse interval (i.e., time between successive vaccination pulses) required for the efficient implementation of the strategy. Simulations of the pulse model [1] show that for Israel, an interval of about five years between successive vaccination pulses prevents epidemics. A very simplified analysis of the model suggests that this interval is roughly similar to the average age of infection, and evaluation of the average age of infection of unvaccinated population in developed countries as five years [5] support the analysis. Recently however, the pulse vaccination strategy has been explored in a steady-state and dynamic age structured compartmental models, and it has been suggested that changes, due to pulses, in the age distribution of susceptibles, imply uncertainty in defining the optimal pulse interval [7].

Another problem which needs consideration when recommending a vaccination strategy is that chaotic population fluctuations in measles epidemics have been detected in some European and American cities (notably [8–11], etc.). As mathematical models have been able to predict the onset of chaotic epidemics [11–13], it seems important to examine what effect mass pulse vaccination strategies will have on the dynamics of the epidemic.

In this paper, we focus on the problem of epidemic eradication under pulse vaccination policy. By analyzing this strategy in a simple SIR model, we determine the maximal interpulse interval which still ensures eradication of the disease. Elsewhere we examine the influence of the pulse vaccination on the nonlinear and chaotic behavior of the SIR model, with seasonal forcing [14].

2. THE SIR MODEL

In our study, we analyze the dynamics of the SIR model of a population of susceptible (S), infective (I), and recovered (R) individuals, governed by the following system of ordinary differential equations:

$$\frac{dS}{dt} = m - (\beta I + m)S, \qquad \frac{dI}{dt} = \beta IS - (m+g)I, \qquad \frac{dR}{dt} = gI - mR. \tag{1}$$

The population has a constant size, which is normalized to unity

$$S(t) + I(t) + R(t) = 1. \tag{2}$$

Here, S represents the proportion of individuals susceptible to the disease, who are born at a rate m and die at the same rate, having mean life expectancy $1/m$. Susceptibles become infectious at a rate βI, where I is the proportion of infectious individuals and β is the contact rate. Infectious individuals recover (i.e., acquire lifelong immunity) at a rate g, making the mean infectious period $1/g$. The variable R represents the proportion of recovered individuals. In practice, the equation for $\frac{dR}{dt}$ is not required since $R(t)$ can always be retrieved from (2). A

detailed description of the model and its dynamics may be found in [15,16]. We note for future reference that typical parameters representative of measles dynamics used here are [13]

$$m = 0.02, \qquad \beta = 1800, \qquad g = 100. \tag{3}$$

The dynamical system (1) has two equilibrium points. The "trivial" equilibrium, or "infection-free" equilibrium, corresponds to a state in which there are no infectious individuals and thus complete eradication of the disease

$$S_0^* = 1, \qquad I_0^* = 0. \tag{4}$$

Here, as elsewhere below, the asterisk used in (4) indicates that the attached quantity is to be evaluated at equilibrium.

The "nontrivial" equilibrium point corresponds to "epidemic equilibrium",

$$S_1^* = \frac{m+g}{\beta}, \qquad I_1^* = \frac{m(R_0-1)}{\beta}, \tag{5}$$

where R_0 is defined as the basic reproductive rate of the infectious disease

$$R_0 = \frac{\beta}{m+g} = \frac{1}{S_1^*}.$$

From stability analysis, it is easy to show that if $R_0 > 1$, the "epidemic equilibrium" (S_1^*, I_1^*) is locally stable, while the "infection-free equilibrium" (S_0^*, I_0^*) is unstable. Conversely, if $R_0 < 1$, the "epidemic equilibrium" (S_1^*, I_1^*) is unstable (in fact, I_1^* is negative), while the "infection-free equilibrium" (S_0^*, I_0^*) is locally stable. It has been shown that for both the above cases, local stability of the equilibrium implies global stability in the meaningful domain for S and I (see [16]).

2.1. The Strategy of "Constant Vaccination"

The constant vaccination strategy attempts to vaccinate a designated proportion p of the newborn population. This is conventionally formalized in the SIR model by reducing the effective birth rate (m) of the population, so that (1) becomes

$$\frac{dS}{dt} = (1-p)m - (\beta I + m)S.$$

An examination of the local stability of the model's equilibria reveals that there is a critical vaccination proportion

$$p_c = 1 - \frac{1}{R_0}, \tag{6}$$

which governs the dynamics of the system as follows.

(a) For relatively large vaccination levels, i.e., $p > p_c$, the "infection-free equilibrium" is locally stable with coordinates

$$S_0^{*\prime} = (1-p), \qquad I_0^{*\prime} = 0. \tag{7}$$

The "epidemic equilibrium" point (S_1^*, I_1^*) is unstable.

(b) For relatively weak vaccination, i.e., $p < p_c$, the "epidemic equilibrium" is locally stable and has the coordinates

$$S_1^{*\prime} = S_1^*, \qquad I_1^{*\prime} = I_1^* - \frac{m}{m+g}p. \tag{8}$$

In this case, constant vaccination linearly decreases the equilibrium number of infectious individuals (Figure 1), but the number of susceptibles at equilibrium remains unchanged.

For the standard measles parameters (3) $p_c \approx 95\%$, implying that for constant vaccination to succeed (i.e., for the stabilization of the "infection-free" equilibrium), it would be necessary to immunise at least 95% of all newborn infants. The high coverage required for this vaccination scheme is thus difficult to implement in practice.

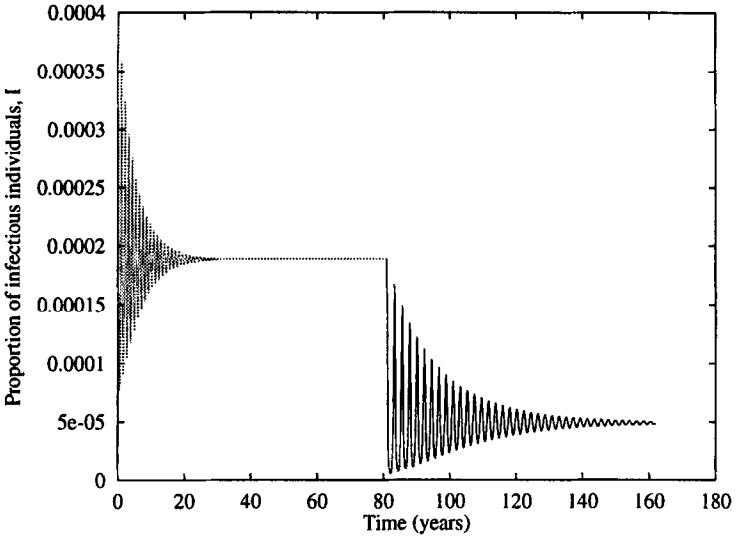


Figure 1. Constant vaccination strategy. Time evolution of the proportion of infectious individuals I before and after the initiation of constant vaccination at $t = 80$. Note that the system relaxes to a new equilibrium point (8) after constant vaccination is applied. Model parameters as given in (3).

3. PULSE VACCINATION STRATEGY

Instead of constantly vaccinating an extremely large proportion of all newborn susceptibles, the pulse vaccination scheme proposes to vaccinate a fraction p of the entire susceptible population in a single pulse applied every T years. Pulse vaccination gives life-long immunity to pS susceptibles who as a consequence "recover", as modelled in (1). Immediately following each vaccination pulse, the system (1) evolves from its new initial state without being further affected by the vaccination scheme until the next pulse is applied. In terms of the SIR model, this can be formulated as

$$S(t_n) = (1-p)S\left(t_n^-\right), \qquad t_{n+1} = t_n + T, \tag{9}$$

where T is the period of pulse vaccination, t_n is the time at which we apply the n^{th} pulse, and t_n^- is the time just before applying the n^{th} pulse.

We will show that if the period of pulses T is shorter than a fixed critical value $T_{\max}$ (to be derived below), then the epidemic must eventually die out.

3.1. The Model's Periodic "Infection-Free" Solution

We first show the existence of a periodic solution to the SIR model subject to the pulse vaccination scheme detailed above. The stability of this solution is examined in the section that follows.

It is easy to see that the infected population $I(t)$, which evolves according to (1), has the trivial steady state $I^* = 0$. We initially assume that the infected population I remains unperturbed at this steady state for all time, and then seek the steady-state behaviour (if it exists) of the susceptible population $S(t)$ between two consecutive vaccination pulses occurring at times t_n and $t_{n+1} = t_n + T$.

Since we make the assumption that $I = 0$ for all time, equation (1) for the growth of the susceptible population $S(t)$ simplifies to

$$\frac{dS}{dt} = m(1-S), \tag{10}$$

subject to the pulse vaccination scheme

$$S(t_n) = (1-p)S\left(t_n^-\right), \qquad t_{n+1} = t_n + T. \tag{11}$$

In the time interval $t_n \le t \le t_{n+1}$, equations (10) and (11) have the following solution:

$$S(t) = \begin{cases} Q(t) = 1 + \left(S^\dagger - 1\right) e^{-m(t-t_n)}, & t_n \le t < t_{n+1}, \\ (1-p)Q(t), & t = t_{n+1}. \end{cases} \tag{12}$$

Here, $S^\dagger = S(t_n)$ is the number of susceptibles S immediately after the n^{th} vaccination pulse, and may be viewed as the initial condition for (10) in the time interval $[t_n, t_{n+1})$. The initial condition may change from one pulse interval to another in a manner that is straightforward to calculate. Setting $S_n = S(t_n)$, it is possible to deduce the stroboscopic map F such that

$$S_{n+1} = F(S_n). \tag{13}$$

The map F determines the number of susceptibles, $S(t)$, immediately *after* each pulse vaccination at the discrete times $t = t_n$, and can be obtained from (12) and (13)

$$S_{n+1} = F(S_n) = (1-p)\left(1 + (S_n - 1)e^{-mT}\right). \tag{14}$$

The map F has the unique fixed point

$$S^* = F(S^*) = \frac{(1-p)\left(e^{mT} - 1\right)}{p - 1 + e^{mT}}. \tag{15}$$

It is important to note that if the orbit of the map converges to the fixed point S^*, then the evolution of the susceptible population $S(t)$ converges to a cycle of period T. This is the "infection-free" periodic solution in which the susceptible population S cycles with period T while the infective population is at the equilibrium $I(t) = I^* = 0$.

In order to obtain the complete expression for the "infection-free" periodic solution, it is necessary to deduce the initial condition $S^\dagger$. But, since the map F determines the number of susceptibles $S(t_n)$ immediately *after* each pulse vaccination, it is easy to see that to obtain a periodic solution, we must have $S^\dagger = S^*$.

The "infection-free" solution (12) over the n^{th} time-interval $t_n \le t \le t_{n+1} = t_n + T$ may thus be rewritten as

$$\begin{aligned} \tilde{S}(t) &= \begin{cases} 1 + \dfrac{pe^{mT}}{1 - e^{mT} - p} e^{-m(t-t_n)}, & t_n \le t < t_{n+1}, \\ S^*, & t = t_{n+1}, \end{cases} \\ \tilde{I}(t) &= 0. \end{aligned} \tag{16}$$

3.2. Stability of the "Infection-Free" Solution

In order to determine the local stability of the "infection-free" solution (16) found above, it is necessary to linearize the SIR equations (1) about this periodic solution by setting

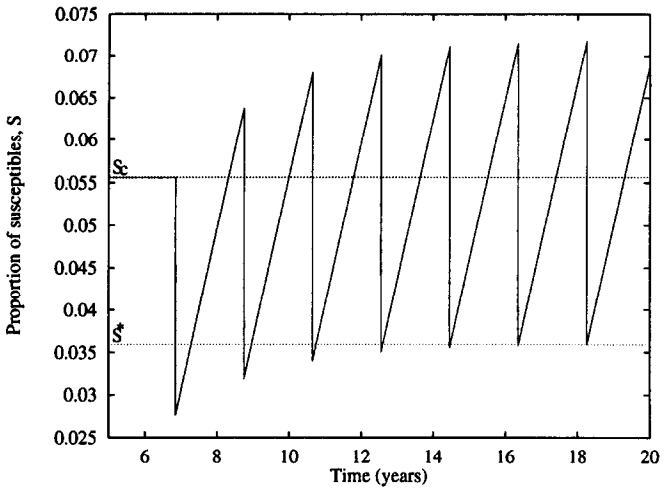
$$S(t) = \tilde{S}(t) + s(t), \qquad I(t) = 0 + i(t), \tag{17}$$

where s and i are small perturbations of susceptibles and infectives, respectively. Equation (1) can then be expanded in a Taylor series, and after neglecting higher-order terms, the linearized equations read

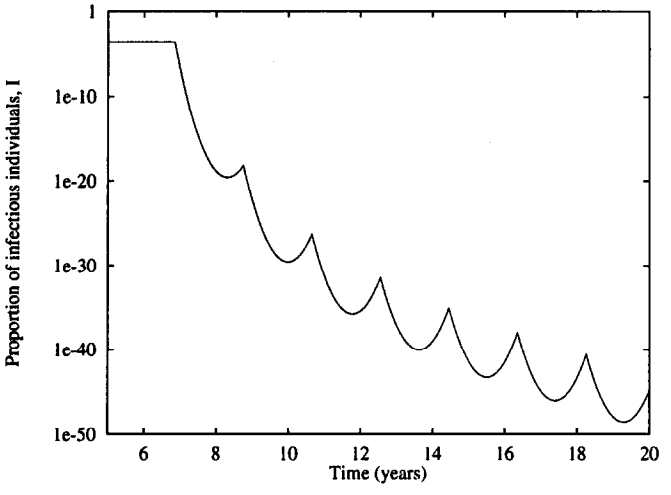
$$\frac{ds}{dt} = -ms - \beta\tilde{S}(t)i, \qquad \frac{di}{dt} = i\left(\beta\tilde{S}(t) - m - g\right), \tag{18}$$

subject to the pulse vaccination scheme

$$s(t_n) = (1-p)s(t_n^-), \qquad t_{n+1} = t_n + T. \tag{19}$$



(a)



(b)

Figure 2. (a) The proportion of susceptibles S when pulse vaccination is applied ($p = 0.5$, and $T = 2$) to the SIR model (1). The susceptibles are attracted to a periodic "infection-free" solution (16). The line at $S_c \approx 0.0556$ marks the "epidemic threshold" (22). (b) Time-series for the corresponding rapidly decreasing infectious population I. Note the logarithmic scale employed. Model parameters as given in (3).

Note that the function $\tilde{S}(t)$ is known explicitly (16) and should be viewed as a periodic coefficient of the variables s and i, respectively. The periodic solution of the full model (1) will be locally stable if the equilibrium $(i^*, s^*) = (0, 0)$ of the above linearized model is locally stable [17].

Examine first the equation for $\frac{di}{dt}$ which is a function of the variable $i(t)$ only. The equation can be readily integrated in the time interval $t_n \leq t \leq t_{n+1} = t_n + T$, i.e., over one pulse interval, yielding

$$i_{n+1} = i_n e^{\int_{t_n}^{t_{n+1}} \left(\beta \tilde{S}(t) - (m+g)\right) dt}, \tag{20}$$

where we have used the notation $i_n = i(t_n)$.

Obviously, the number of infectives i_n will always decrease exponentially fast if

$$\int_{t_n}^{t_{n+1}} \left(\beta \tilde{S}(t) - (m+g)\right) dt < 0. \tag{21}$$

Note that in time, as $i(t)$ approaches sufficiently close to zero, it follows from (18) that $s(t)$ must also converge to zero. We make this conclusion more rigorous in a follow-up paper where the stability of the periodic solution is characterized via Flouquet theory [14].

From (21), we see that the "infection-free" solution to the SIR model under pulse vaccination is locally stable if

$$\frac{1}{T}\int_0^T \tilde{S}(t)\,dt < \frac{m+g}{\beta} = S_c, \tag{22}$$

where S_c is sometimes referred to as the "epidemic threshold" [15]. Thus, for local stability, the mean value of the "infection-free" solution $\tilde{S}(t)$ averaged over a single pulse period must be less than the threshold level S_c. We will examine the ramifications of this stability criterion in the section that follows. Our numerical investigations of the system suggest that local stability of the "infection-free" solution implies global stability.

A typical solution of the SIR equation under pulse vaccination is shown in Figure 2. The figure makes clear how the variable $S(t)$ converges to a stable limit cycle that periodically rises above the threshold level S_c. The oscillation is stable since the mean value of $S(t)$ over the interpulse period is less than the threshold level S_c. In contrast, the proportion of infected individuals $I(t)$ rapidly decreases to zero.

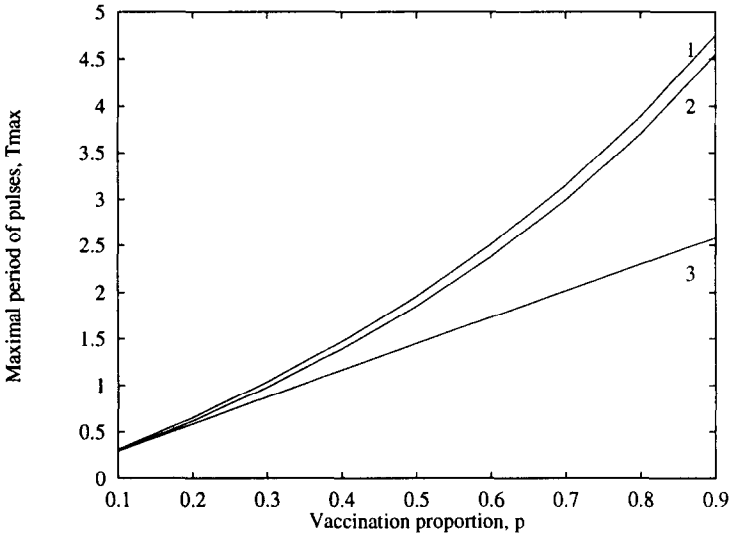


Figure 3. The maximum interpulse interval $T_{\max}$ as a function of vaccination proportion, p. Curve 1: approximation (24); Curve 2: exact result (23); Curve 3: the approximation (25) suggested in [1]. Model parameters as given in (3).

3.3. Calculation of the Maximum Interpulse Interval, $T_{\max}$

The stability condition (22) can be fully specified by substituting the exact expression for $\tilde{S}(t)$ (16), and integrating. One finds that the periodic "infection-free" solution is locally stable if

$$\frac{(p-mT)\left(1-e^{mT}\right)+mpT}{mT\left(p-1+e^{mT}\right)} \leq \frac{m+g}{\beta}. \tag{23}$$

This stability condition makes it possible to obtain an expression for the maximum allowable interpulse period, $T_{\max}$, for which the "infection-free" solution is stable. Clearly, it would be inadvisable in practice to employ an interpulse interval T larger than $T_{\max}$, for there would no longer be a stable "infection-free" solution and this could possibly eventuate in an epidemic outbreak. The maximum allowable value for T occurs when there is equality in (23). (This is a consequence of the left-hand side of (23) being an increasing function of T.) In order to calculate $T_{\max}$, it is helpful to simplify (23) by making use of Taylor expansions, by reasonably assuming

that $T \ll 100$, and that the mean lifetime of an individual is much greater than the duration of disease ($m \ll g$). After neglecting negligible higher-order terms, we finally obtain

$$T_{\max} \simeq \frac{qp}{\beta m} \frac{1}{(1 - p/2 - g/\beta)}. \tag{24}$$

The dependence of the maximal period of the pulses, $T_{\max}$, on vaccination proportion, p, in equation (23), is shown in Figure 3. In contrast to these exact results, we have plotted the predictions for $T_{\max}$ according to the scheme found in [1], where the approximate and conservative estimate is

$$T_{\max} \simeq \frac{1}{m} \ln\left(1 + \frac{p(m+g)}{(\beta - m - g)}\right). \tag{25}$$

4. DISCUSSION

As we can see from Figure 3, condition (23) allows periods of pulses that are, for high vaccination levels p, up to twice as large as those predicted in previous analyses [1]. However, the maximal value of T as obtained via (23), although accurate for the SIR model, may be an overestimate for real community-wide epidemics in human populations. This is due to the inappropriate structure of the SIR equations when the system is close to extinction. In certain cases, during the evolution of the solution of the SIR model under pulse vaccination, the variable I takes unrealistic values, such as $I = 10^{-20}, \ldots, 10^{-40}$ and even less. Considering the normalization used here (2), such a situation becomes senseless when the model is applied to measles epidemics of humans [13,15] where populations are of the order of 10^6 individuals. Clearly, the SIR model fails to take into account the integer structure of populations, where, should the number of infectious individuals become "less than one", the epidemic will die out and will not erupt again until external introduction of the disease later.

It is possible to overcome this unrealistic scenario, by either using a stochastic model based on master equations instead of differential equations or by adding an additional term to the SIR model corresponding to the immigration of infectious individuals [13]. The immigration term prevents $\frac{dI}{dt}$ and I from taking unrealistically small values for lengthy periods of time. Numerical results of this modification and its effect on $T_{\max}$ are shown in Figure 4, and are discussed further in [14].

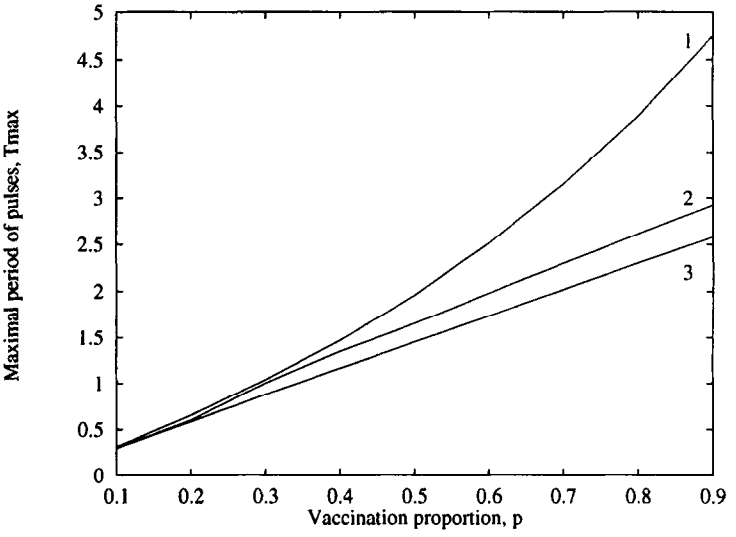


Figure 4. The maximum interpulse interval $T_{\max}$ as a function of vaccination proportion, p. Curve 1: exact result (23) for the SIR model; Curve 2: condition for the model with immigration incorporated according to scheme found in [13,14]; Curve 3: condition (25) suggested in [1]. Model parameters as given in (3).

In this paper, we analyze the rationale of the pulse vaccination strategy [1] in the simple SIR epidemic model. It should be noted that in the theory of dynamical systems, pulse vaccination corresponds to a system of differential equations with impulses. The strict mathematical considerations of pulsed differential equations can be found in the work of Bainov [18]. By a simplified approach, here we deduce the existence and stability of a periodic "infection free" solution to the pulsed SIR model. We show analytically that under planned pulse vaccination, the SIR system may achieve a stable steady state free of infected individuals. This happens when the mean fraction of susceptibles averaged over the interpulse interval is less than a critical value defined by the parameters of the epidemic. We derive the exact conditions for epidemic eradication, under different constraints. This enables us to provide an accurate estimate of the maximal period of pulse vaccination which still ensures an "infection-free" steady state in the SIR model, thereby extending the results of [1]. The nonlinear behaviour of the SIR model under the pulse vaccination policy is comprehensively studied elsewhere [14].

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