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M.E. Alexander · S.M. Moghadas · P. Rohani · A.R. Summers

Modelling the effect of a booster vaccination on disease epidemiology

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Abstract. Despite the effectiveness of vaccines in dramatically decreasing the number of new infectious cases and severity of illnesses, imperfect vaccines may not completely prevent infection. This is because the immunity afforded by these vaccines is not complete and may wane with time, leading to resurgence and epidemic outbreaks notwithstanding high levels of primary vaccination. To prevent an endemic spread of disease, and achieve eradication, several countries have introduced booster vaccination programs. The question of whether this strategy could eventually provide the conditions for global eradication is addressed here by developing a seasonally-forced mathematical model. The analysis of the model provides the threshold condition for disease control in terms of four major parameters: coverage of the primary vaccine; efficacy of the vaccine; waning rate; and the rate of booster administration. The results show that if the vaccine provides only temporary immunity, then the infection typically cannot be eradicated by a single vaccination episode. Furthermore, having a booster program does not necessarily guarantee the control of a disease, though the level of epidemicity may be reduced. In addition, these findings strongly suggest that the high coverage of primary vaccination remains crucial to the success of a booster strategy. Simulations using estimated parameters for measles illustrate model predictions.

1. Introduction

Infectious diseases continue to be of substantial concern to health professionals, with a major focus on vaccine administration. Since the pioneering work of Edward Jenner on smallpox [12], the process of protecting individuals from infection by immunization has become routine, with substantial historical success in reducing both mortality and morbidity. In modern times, vaccination has had perhaps the largest impact on the incidence and persistence of childhood infections such as measles and whooping cough [13]. However, decreased immunization coverage together with irregularities in the supply of vaccines, incomplete protection offered

M.E. Alexander, S.M. Moghadas, A.R. Summers: Institute for Biodiagnostics, National Research Council Canada, R3B 1Y6. Winnipeg, Manitoba, Canada.
e-mail: Murray.Alexander@ncr-cnrc.gc.ca

P. Rohani: Institute of Ecology, University of Georgia, Athens, GA, 30602-2202 USA.

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by low-efficacy vaccines, and the loss of vaccine-induced immunity, are known to be major factors in the resurgence and epidemic outbreaks of some infectious diseases [13,17,21,34].

One disease whose mortality and morbidity burden has been dramatically reduced following large-scale vaccination is measles [13]. Newborns are afforded protection to measles through maternal antibodies, which may be effective for up to one year after birth. Vaccination against measles is not recommended until these antibodies have waned. It has been demonstrated that vaccine efficacy is substantially higher in older infants with no maternal antibodies [23,31], hence current policy is to administer the MMR (measles-mumps-rubella) vaccine to infants between their first and second birthdays. While it seems that measles is mostly controlled in the US, Canada and other developed countries, it remains a major killer in the developing world [13,34,46].

Although natural measles infection induces lifelong immunity [3,48], the assumption that the measles vaccine also confers permanent protection has been reconsidered following outbreaks among high school and university students in the US in the 1980s; many of these students had been vaccinated 15–20 years prior to infection [7,16]. Clinical studies have proposed several mechanisms for these outbreaks, the most likely candidates being vaccine failure in some individuals and the subsequent loss of immunity after vaccination [34,35,44]. Mossong et al. [34, 35] estimated the mean duration of vaccine-induced immunity to measles, in the absence of re-exposure, to be 25 years. Additional cases of waning immunity in vaccines that previously were thought to offer lifelong immunity have been reported in many clinical studies (see, for instance, [17,47,50]).

Clearly, the high coverage of the single-dose measles vaccine has played a major role in preventing the spread of measles infection [13]. However, several large measles outbreaks, such as those seen in the US during the 1980s, in Quebec in 1989 and in Ontario in 1991 and 1995 [38,48], have shown the limitations of the single-dose vaccination program. A recent clinical study on measles vaccine efficacy during an epidemic in Poland [22] shows that, despite high vaccination coverage since the 1980s, a measles epidemic with 2255 reported cases occurred between November 1997 and July 1998. In this epidemic, the age-group most affected was 15–19 year-olds who had received one dose of vaccine in their second year of life. This study also reveals that the protection offered by the first-dose vaccine, started in 1975, exceeded 90% and the protection induced by the second dose-vaccine (booster), added in 1991 for children aged 7–9 years, exceeded 99%.

The failure to achieve eradication, even with the high coverage of a single-dose vaccination program, has promoted many countries to introduce a booster [6, 10,13,18,38]. The results of this introduction have been impressive. For instance, a two-dose MMR vaccination program was initiated in Finland in 1982, achieving coverage estimated to be 97–98%, and leading to the elimination of measles, mumps and rubella from Finland [10]. In Canada, upon the recommendation of the National Advisory Committee on Immunization (NACI), a two-dose measles vaccination program was begun in 1992 [38]. A two-dose MMR vaccine, with a coverage exceeding 90% was introduced in Sweden in 1982 [6]. In the US, a two-dose schedule of MMR vaccine has been in effect since 1989 [18]. Based on the

implications of administration of a two-dose vaccine, mostly in developed countries, the WHO recommends this strategy in order to achieve global eradication [13]. Hence, it is necessary to develop a framework that would predict the consequences of the introduction of a booster vaccination program.

The goal of this study is to provide such a framework by developing a mathematical model for the transmission dynamics of some vaccine-preventable infectious diseases, such as measles, mumps, and rubella, in the presence of a booster. Mathematical models have widely been used to investigate the impact of a single-dose vaccination strategy on disease control [27, 28, 32, 33]. These models have discussed the effect of vaccination coverage, vaccine efficacy, and the waning rate of vaccines applied in a single-dose. However, the literature on the consequences of booster vaccination for disease dynamics is rather scant. A few studies of mathematical models with multiple-dose vaccines are available in the literature (see [37] and references therein). For instance, Dietz [9] considered an age-structured model with constant transmission rate to assess the impact of single and two-dose vaccination against rubella. Katzmann and Dietz [24] obtained results for disease eradication in a model with constant transmission rate, passive immunity in children with maternal antibodies, and loss of vaccine induced immunity. Anderson and Grenfell [1] obtained numerical results on the impact of multiple-dose vaccination against rubella. Paulo et al. [37] showed, in a simple age-independent model with constant transmission rate, that the high coverage of the primary vaccination remains crucial even with a booster.

In the model presented here, it is assumed that the primary vaccine induces a partial degree of protection which wanes with time. As motivated by clinical studies, it is also assumed that the booster vaccine induces complete protection conferring permanent immunity to the disease. In a booster vaccination program, two classes of individuals may be considered: (i) the individuals who have received the vaccine and whose immunity has not yet waned (and therefore belong to the primary vaccinated class); (ii) the individuals who never received the vaccine or in whom the immunity induced by primary vaccination has waned (and therefore belong to the fully susceptible class). In practice, it may not be feasible to distinguish between these two classes in a booster program. Therefore, while the second-dose of vaccine may be intended as booster, it may in effect function as primary vaccine to susceptible individuals. On the individual level, due to the uncertainty of having received a primary vaccine, a booster will raise the probability of being covered by at least one dose of vaccine. On the population level, it has the potential of raising vaccination coverage and increasing herd immunity. Hence, it is considered to be an effective control strategy in preventing disease outbreaks [13].

The organization of this paper is as follows. The model is developed in section 2. Using Floquet theory, the threshold condition for disease eradication is determined in section 3 and feasibility of eradication using a booster vaccine is discussed. In section 4, the existence of a unique stable periodic solution under certain conditions, is shown using perturbation theory. Simulation results are also presented to illustrate the model predictions. The paper ends with a discussion section.

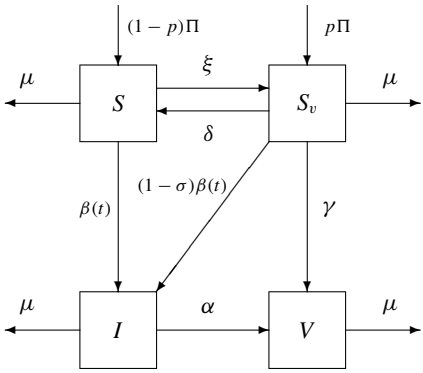

Fig. 1. Transfer diagram of the model.

2. Model derivation

In order to derive the model equations, the total population (N) is divided into four classes: fully susceptible (S), primary vaccinated (S_v), infected (I), and protected individuals (V). Here we shall detail the transitions between these four classes as depicted in Figure 1.

The class S of susceptibles is increased either by birth or immigration at a rate Π. It is decreased by infection following contact with infected individuals at a time-varying rate $\beta(t)$, and diminished by natural death at a rate μ. Furthermore, it is decreased by primary vaccination at a rate ξ, which is administered under a booster program. This term naturally disappears in the absence of booster doses. The model also assumes that the primary vaccination wanes with time, leading to the migration of individuals from S_v to S at a rate δ [34,35,49].

The class S_v of primary vaccinated individuals is generated through administration of the first-dose vaccine to the susceptible class S, either by vaccination of a fraction p of recruited individuals or under a booster program. Since the primary vaccine may not induce complete protection to the infection, the individuals of this class might still become infected, but at a lower rate of infectiousness, $(1-\sigma)\beta(t)I$, than fully susceptible individuals, where σ is the degree of protection induced by primary vaccination. This partial immunity may be due to the presence of maternal antibodies which interfere with vaccine-induced seroconversion [8]. This leads to a response with a lower level of antibody titres and reduces vaccine efficacy [41]. This response could not entirely be attributed to the presence of maternal antibodies (at the time of vaccination), as in addition the vaccine may not be sufficiently immunogenic in inducing adequate antibody response after a single dose [49]. Furthermore, the primary vaccine may wane with time, and thus vaccinated individuals gradually become fully susceptible to the disease again [34,35,49]. The class S_v is decreased by administration of a booster vaccine (as a second dose) at a rate γ and diminished by natural death.

The class I of infected individuals is generated through infection of fully susceptible and/or primary vaccinated individuals. This class is decreased by recovery

from infection at a rate α and diminished by natural death. The model assumes that both recovered and booster vaccinated individuals become permanently immune to the disease. This generates a class V of individuals who have complete protection to the disease.

Since periodically high levels of incidence have been observed for some childhood infections [11,26,42,43], the model considers a time-varying contact rate $\beta(t)$ between susceptible and infected individuals. Models of this type, also known as seasonally-forced, are common in the literature and we recommend [2,25,26] for general references. As popularly used in the literature, we assume that the seasonal forcing is approximated by a sinusoidal function:

$$\beta(t) = \beta_0[1 + \beta_1 \sin(\omega t)], \tag{1}$$

where $\beta_0 \geq 0$ is the baseline transmission parameter, $0 \leq \beta_1 \leq 1$ measures the amplitude of the seasonal variation in transmission, and $\beta(t)$ is a periodic function of period $T = 2\pi/\omega$. There are a few studies [5,11,26] which have taken the contact rate to be governed by some periodic functions such as the school term where $\beta(t) = \beta_0[1 + \beta_1 \text{Term}(t)]$. The function "Term" is assumed to be a periodic function which is $+1$ during school term and -1 during school holidays. However, the results of our model do not depend on particular form of the periodic component of $\beta(t)$.

The transitions between model classes can now be expressed by the following differential equations:

$$\frac{dS}{dt} = (1-p)\Pi - \beta(t)SI - \xi S - \mu S + \delta S_v, \tag{2}$$

$$\frac{dS_v}{dt} = p\Pi + \xi S - (1-\sigma)\beta(t)S_v I - (\mu + \gamma + \delta)S_v, \tag{3}$$

$$\frac{dI}{dt} = \beta(t)SI + (1-\sigma)\beta(t)S_v I - (\mu + \alpha)I, \tag{4}$$

$$\frac{dV}{dt} = \gamma S_v + \alpha I - \mu V, \tag{5}$$

A description of all the model parameters together with their estimated values in published studies is given in Table 1.

3. Disease eradication

In this section, the model is analyzed for its disease-free equilibrium in order to provide the threshold condition for disease control or eradication. Since the class of protected individuals (V) does not appear in equations (2)–(4), the analysis will be restricted to the dynamics of (2)–(4). We also note that the equation for the total population is $dN/dt = \Pi - \mu N$. Thus, $N \to \Pi/\mu$ as $t \to \infty$, and hence $V = \Pi/\mu - S - S_v - I$. This shows that the feasible region

$$\Omega = \{(S, S_v, I, V) : \ S, S_v, I, V \geq 0, \ S + S_v + I + V = \Pi/\mu\},$$

is a positively invariant set for the model. Therefore, we restrict our attention to the dynamics of the model in Ω.

Table 1. Description and estimation of the model parameters.

Parameter	Description	Value	Reference
Π	recruitment rate of individuals	$\gg 1$ people year^{-1}	
p	fraction of recruited individuals who receive vaccine	0–1	
$1/\mu$	mean duration of life expectancy	50 years	[32,42,43]
$1/\delta$	duration of primary vaccine-induced immunity	15–25 years	[34,35]
$1/\alpha$	average infectious period	2 weeks	[32,42,43]
σ	primary vaccine-induced protection	90–99%	[13,22,23]
γ	rate of second-dose of vaccine (booster)	≥ 0	
ξ	rate of primary vaccination under booster administration	≥ 0	
β_0	baseline contact rate	≥ 400 people^{-1} year^{-1}	[42,43]
β_1	fluctuating contact rate amplitude	0–1	[42,43]
ω	seasonal variation frequency	2π year^{-1}	

3.1. Disease-free equilibrium (DFE)

In the absence of infection, the model has a unique disease-free equilibrium $\mathscr{E}_0 = (S^0, S_v^0, 0, V^0)$ where

$$S^0 = \frac{[(1-p)(\mu+\gamma)+\delta]\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta}, \quad S_v^0 = \frac{(\mu p+\xi)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta},$$
$$V^0 = \frac{\gamma(\mu p+\xi)\Pi}{\mu[(\mu+\gamma)(\mu+\xi)+\mu\delta]}.$$

To analyze the stability of the DFE, the model (2)–(4) is linearized around $\mathscr{E}_0$ by setting:

$$S(t) = S^0 + s(t), \quad S_v(t) = S_v^0 + s_v(t), \quad I(t) = i(t).$$

Then, we have:

$$\frac{ds}{dt} = -(\mu+\xi)s - \frac{[(1-p)(\mu+\gamma)+\delta]\beta(t)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta}i + \delta s_v, \tag{6}$$
$$\frac{ds_v}{dt} = \xi s - (\mu+\gamma+\delta)s_v - \frac{(1-\sigma)(\mu p+\xi)\beta(t)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta}i, \tag{7}$$
$$\frac{di}{dt} = \frac{[(1-p)(\mu+\gamma)+\delta+(1-\sigma)(\mu p+\xi)]\beta(t)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta}i - (\mu+\alpha)i. \tag{8}$$

A fundamental matrix of (6)–(8) consists of the solutions $X^j = (s^j(t), s_v^j(t), i^j(t))$, $j = 1, 2, 3$, which satisfy the following initial conditions:

$$X^1(0) = (1,0,0), \quad X^2(0) = (0,1,0), \quad X^3(0) = (0,0,1).$$

It is easy to see that the set of these solutions is given by:

$$X^1 = \begin{pmatrix} \exp[-(\mu+\xi)t] \\ 0 \\ 0 \end{pmatrix}, \quad X^2 = \begin{pmatrix} s^{2*}(t) \\ \exp[-(\mu+\gamma+\delta)t] \\ 0 \end{pmatrix},$$

and

$$X^3 = \begin{pmatrix} s^{3*}(t), \\ s_v^{3*}(t), \\ \exp\left\{\int_0^t \left(\dfrac{[(1-p)(\mu+\gamma)+\delta+(1-\sigma)(\mu p+\xi)]\beta(t)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta} - (\mu+\alpha)\right) d\tau\right\} \end{pmatrix},$$

where $s^{2*}(0) = s^{3*}(0) = s_v^{3*}(0) = 0$. The monodromy matrix is the fundamental matrix $M(t) = [X^1(t), X^2(t), X^3(t)]$ evaluated at the period T. Then, the local stability of $\mathscr{E}_0$ is determined by the modulus of the eigenvalues of $M(T)$. These eigenvalues are $\lambda_1 = \exp[-(\mu+\xi)T]$, $\lambda_2 = \exp[-(\mu+\gamma+\delta)T]$, and

$$\lambda_3 = \exp\left\{\int_0^T \left(\frac{[(1-p)(\mu+\gamma)+\delta+(1-\sigma)(\mu p+\xi)]\beta(t)\Pi}{(\mu+\gamma)(\mu+\xi)+\mu\delta} - (\mu+\alpha)\right) d\tau\right\}.$$

Since $0 < \lambda_1, \lambda_2 < 1$, the equilibrium $\mathscr{E}_0$ is locally asymptotically stable if $\lambda_3 < 1$. A simple calculation shows that $\lambda_3 < 1$ if and only if

$$\frac{1}{T}\int_0^T \beta(\tau)d\tau < \frac{(\mu+\alpha)[(\mu+\gamma)(\mu+\xi)+\mu\delta]}{[(1-p)(\mu+\gamma)+\delta+(1-\sigma)(\mu p+\xi)]\Pi} \tag{9}$$

Since $\beta(t) = \beta_0[1+\beta_1\sin(\omega t)]$ is a periodic function with the period T, the inequality (9) can be written as $\mathscr{R}_0 < 1$ where

$$\mathscr{R}_0 = \frac{[(1-p)(\mu+\gamma)+\delta+(1-\sigma)(\mu p+\xi)]\beta_0\Pi}{(\mu+\alpha)[(\mu+\gamma)(\mu+\xi)+\mu\delta]}. \tag{10}$$

Consequently, the DFE is locally asymptotically stable if $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$. The threshold quantity $\mathscr{R}_0$ is the basic reproductive number for the model (2)–(5) [2]. This is the number of secondary infectious cases produced by one primary infectious case introduced into the susceptible population of which a fraction p has been vaccinated.

The expression (10) for $\mathscr{R}_0$ can be written as

$$\mathscr{R}_0 = \left(1 - \frac{(\mu p+\xi)(\mu\sigma+\gamma)}{(\mu+\gamma)(\mu+\xi)+\mu\delta}\right) r_0, \tag{11}$$

where $r_0 = \beta_0\Pi/[\mu(\mu+\alpha)]$ is the basic reproductive number for the vaccination-free model with no booster ($p = \gamma = \xi = 0$). The expression (11) for $\mathscr{R}_0$ is used in section 3.3 to discuss the feasibility of disease eradication.

Remark 1. Here, we comment on some erroneous results in the literature [40], related to the determination of $\mathscr{R}_0$ in a seasonally forced SIR model. In [40], $\mathscr{R}_0$ is derived through evaluation of the eigenvalues of a time-dependent Jacobian matrix at disease-free equilibrium which makes $\mathscr{R}_0$ itself time-dependent. However, this approach cannot be applied to non-autonomous dynamical systems. Also, contrary to their results, there can be no endemic equilibrium of the model, and therefore any such stability analysis is invalid. Furthermore, using a Dulac function, the global stability of the disease-free equilibrium is claimed, from which the non-existence of periodic solutions is deduced. This is incorrect, and inconsistent with the results of their simulations, which confirm the existence of periodic solutions for some values of the model parameters.

3.2. Global stability of the DFE

Here, we shall show that the local and global stability of the DFE are equivalent. In fact, we have the following theorem.

Theorem 1. *If $\mathscr{R}_0 < 1$, then the DFE is globally asymptotically stable.*

Proof. Since Ω is a positively invariant region, it is sufficient to establish the global stability of $\mathscr{E}_0$ in Ω. Noting that $S = \Pi/\mu - S_v - I - V$ and $\beta(t) \geq 0$, for all $t \in \mathbf{R}$, it can be seen from (3) that

$$dS_v/dt \leq (\mu + \gamma + \delta + \xi)\Big[\frac{(\mu p + \xi)\Pi}{(\mu + \gamma)(\mu + \xi) + \mu\delta} - S_v\Big].$$

By the Comparison Theorem [29], we see that

$$\lim_{t\to\infty} \sup_{\theta\geq t} S_v(\theta) \leq \frac{(\mu p + \xi)\Pi}{(\mu + \gamma)(\mu + \xi) + \mu\delta}. \tag{12}$$

Thus, for a given $\epsilon > 0$, there is a $t_0 > 0$ such that

$$S_v(t) \leq \frac{(\mu p + \xi)\Pi}{(\mu + \gamma)(\mu + \xi) + \mu\delta} + \epsilon/\delta$$

for $t \geq t_0$. Then, it follows from (2) that

$$\frac{dS}{dt} \leq \epsilon + (\mu + \xi)\Big[\frac{[(1-p)(\mu+\gamma)+\delta]\Pi}{(\mu + \gamma)(\mu + \xi) + \mu\delta} - S\Big], \quad \text{for } t > t_0.$$

Consequently,

$$\lim_{t\to\infty} \sup_{\theta\geq t} S(\theta) \leq \frac{[(1-p)(\mu+\gamma)+\delta]\Pi}{(\mu + \gamma)(\mu + \xi) + \mu\delta}. \tag{13}$$

Using (12) and (13) in (4) for small enough ϵ gives:

$$\frac{dI}{dt} \leq (\mu + \alpha)\left[\left(\frac{\mathscr{R}_0}{\beta_0} + \frac{(2-\sigma)\epsilon}{\mu + \alpha}\right)\beta(t) - 1\right] I, \quad \text{for } t \geq t_1, \tag{14}$$

where $t_1 > t_0$. Integrating this inequality gives:

$$I(t) \le \exp\left\{\int_{t_1}^{t}(\mu+\alpha)\left[\left(\frac{\mathscr{R}_0}{\beta_0}+\frac{(2-\sigma)\epsilon}{\mu+\alpha}\right)\beta(\tau)-1\right]d\tau\right\}, \quad \text{for } t \ge t_1. \tag{15}$$

Suppose n_0 is the smallest positive integer such that $n_0 T > t_1$. Thus,

$$\begin{aligned} L &\equiv \exp\left\{\int_{n_0T}^{\infty}(\mu+\alpha)\left[\left(\frac{\mathscr{R}_0}{\beta_0}+\frac{(2-\sigma)\epsilon}{\mu+\alpha}\right)\beta(\tau)-1\right]d\tau\right\} \\ &= \exp\left\{(\mu+\alpha)\sum_{n_0}^{\infty}\int_{nT}^{(n+1)T}\left[\left(\frac{\mathscr{R}_0}{\beta_0}+\frac{(2-\sigma)\epsilon}{\mu+\alpha}\right)\beta(\tau)-1\right]d\tau\right\} \\ &= \exp\left\{(\mu+\alpha)\sum_{n_0}^{\infty}\int_{0}^{T}\left[\left(\frac{\mathscr{R}_0}{\beta_0}+\frac{(2-\sigma)\epsilon}{\mu+\alpha}\right)\beta(\tau)-1\right]d\tau\right\} \\ &= \exp\left\{T(\mu+\alpha)\left(\mathscr{R}_0-1+\frac{(2-\sigma)\epsilon\beta_0}{\mu+\alpha}\right)\sum_{n_0}^{\infty}1\right\}. \end{aligned}$$

Since $\mathscr{R}_0 < 1$, for $\epsilon > 0$ sufficiently small we have $\mathscr{R}_0 - 1 + (2-\sigma)\epsilon\beta_0/(\mu+\alpha) < 0$, and hence $L = 0$. This implies that

$$0 \le \lim_{t\to\infty} I(t) \le \exp\left\{\int_{t_1}^{n_0T}(\mu+\alpha)\left[\left(\frac{\mathscr{R}_0}{\beta_0}+\frac{(2-\sigma)\epsilon}{\mu+\alpha}\right)\beta(\tau)-1\right]d\tau\right\} L = 0,$$

and consequently, $\lim_{t\to\infty} I(t) = 0$. In order to show that every solution with an initial condition in the positively invariant region Ω approaches $\mathscr{E}_0$, we consider the following two-dimensional system when $I = 0$:

$$\frac{dS}{dt} = (1-p)\Pi - (\mu+\xi)S + \gamma S_v \equiv \mathcal{X}, \tag{16}$$

$$\frac{dS_v}{dt} = p\Pi + \xi S - (\mu+\gamma+\delta)S_v \equiv \mathcal{Y}. \tag{17}$$

Consider the Dulac function $D = 1/S_v$ for $S_v > 0$. Then, it can be seen that:

$$\frac{\partial(D\mathcal{X})}{\partial S} + \frac{\partial(D\mathcal{Y})}{\partial S_v} = -\frac{\mu+\xi}{S_v} - \frac{p\Pi+\xi S}{S_v^2} < 0.$$

Thus, the system (16)–(17) has no limit cycle and hence, the model (2)–(3) has no limit cycle in the SS_v-plane. Since $\lim_{t\to\infty} I(t) = 0$, it follows that $\mathscr{E}_0$ is the ω-limit set of every solution in Ω. Therefore, $\mathscr{E}_0$ is globally asymptotically stable. □

The above theorem shows that reducing $\mathscr{R}_0$ to values less than unity guarantees disease eradication. The results of this section also show that the fluctuating contact rate amplitude (β_1) has no role in changing the basic reproductive number. Indeed, if $\beta_1 = 0$ (which makes the model time-independent), then evaluation of the corresponding Jacobian at $\mathscr{E}_0$ yields the same expression for $\mathscr{R}_0$. However, the dynamics of the seasonally forced model (i.e., $\beta_1 \neq 0$) are very much dependent on small changes in the fluctuating contact rate amplitude β_1, especially when $\mathscr{R}_0 > 1$.

3.3. Feasibility of eradication

The expression (11) represents the overall basic reproductive number $\mathscr{R}_0$ in terms of the reproductive ratio for a population that is wholly susceptible (r_0), with no vaccination. Therefore, it gives a measure of the potential for the infection to spread in the population. It is important to note that a high value of r_0 requires a high coverage level of primary vaccination to prevent the spread of infection, regardless of the type of vaccine being administered [37]. However, it is practically impossible to vaccinate almost all individuals in the susceptible class, in particular, in countries where finances play a major role in the number of people who receive the vaccines. Hence, the next best strategy is to determine the critical number needed to be vaccinated.

In the absence of boosters ($\gamma = \xi = 0$), the minimum primary vaccination level that is required to eliminate the infection is given by:

$$p_0 = \left(1 - \frac{1}{r_0}\right)\left(\frac{\mu + \delta}{\mu\sigma}\right), \tag{18}$$

such that $\mathscr{R}_0 \leq 1$ whenever $p \geq p_0$. This coverage is for a vaccine that confers a protection σ that wanes with a mean duration of $1/\delta$, and reduces to $p_0 = 1 - 1/r_0$ for a perfect vaccine ($\sigma = 1,\ \delta = 0$).

The most important implication of this result is that eradication likelihood is determined by the effective period of immunity. Let us consider the optimistic case in which the primary vaccine provides perfect immunity to infection ($\sigma = 1$), but this protection wanes with time ($\delta > 0$). In this scenario, equation (18) means that the critical proportion of the population required to be vaccinated is greater than unity ($p_0 \geq 1$) unless $\mu/(\mu + \delta) > (1 - 1/r_0)$. This means that infection eradication by paediatric vaccination is impossible unless the fraction of a vaccinated individual's life during which they are protected from infection exceeds $(1 - 1/r_0)$. For instance, if $r_0 = 2$, then eradication is only possible if the vaccine protects individuals for more than half their life. Furthermore, when no boosters are administered ($\gamma = \xi = 0$), the expression (11) becomes:

$$\mathscr{R}_0 = \left(1 - \frac{p\mu\sigma}{\mu + \delta}\right) r_0. \tag{19}$$

This shows that a vaccine that offers a complete degree of protection ($\sigma = 1$) with immunity that wanes at the same rate as the average death rate ($\delta = \mu$) is only as good as a vaccine that does not wane ($\delta = 0$), but offers a 50% degree of protection ($\sigma = 1/2$). In this case, the basic reproductive number reduces to $\mathscr{R}_0 = (1 - p/2)r_0$.

In the presence of boosters for an imperfect vaccine, the expression (11) can also be written as:

$$\begin{aligned}\mathscr{R}_0 = {} & \left[1 - \frac{\mu\sigma + \gamma}{\mu + \gamma + \delta}\left(p + \frac{\mu + \gamma + \delta}{(\mu + \gamma)(\mu + \xi) + \mu\delta}\xi\right)\right] r_0 \\ & + \frac{(\mu\sigma + \gamma)(\mu + \gamma)p\xi}{(\mu + \gamma + \delta)[(\mu + \gamma)(\mu + \xi) + \mu\delta]} r_0 \\ > {} & \left[1 - \left(p + \frac{\xi}{\mu}\right)\right] r_0 + \frac{(\mu\sigma + \gamma)(\mu + \gamma)p\xi}{(\mu + \gamma + \delta)[(\mu + \gamma)(\mu + \xi) + \mu\delta]} r_0. \end{aligned} \tag{20}$$

This form of $\mathscr{R}_0$ clearly indicates that if $[1-(p+\xi/\mu)]r_0 > 1$, then $\mathscr{R}_0 > 1$, so that no amount of booster vaccination (as a second-dose) could lead to disease eradication. It also reveals the fact that primary vaccination remains crucial in reducing $\mathscr{R}_0$ to values less than unity, even in the presence of a booster (see [13,37] and references therein). Here, we focus on the effect of the booster vaccination in terms of two major parameters p and r_0.

A recent study [14] has introduced a threshold quantity called the reinfection threshold in transmission induced by partial immunity, above which levels of infection will be high and vaccination programs will fail to protect. Applying this threshold to the model presented here, we considered a range of r_0 below the reinfection threshold, $r_0 < 1/(1-\sigma)$, where the impact of primary vaccination will be significant. This, of course, is sensitive to the assumed parameter values associated with the vaccine administered to susceptible individuals, such as vaccine efficacy and waning rate [32]. As estimated in several studies on measles infection in England and Wales [26,42,43], r_0 is about 17 which would satisfy the reinfection threshold if the vaccine induced protection is higher than 94%. We now introduce a new parameter η as the rate of booster administration, and let $\xi = \lambda\eta$ and $\gamma = (1-\lambda)\eta$ where $0 \le \lambda \le 1$. Let $p_\lambda \equiv p(\eta,\lambda)$ represent the surface on which $\mathscr{R}_0 \equiv 1$. With the value of $r_0 = 17$, Figure 2A illustrates contour plots of p_λ (for feasible ranges of η and λ) using parameter values estimated for measles vaccination [22, 26,34,35,42,43]: $\mu = 0.02$, $\delta = 0.05$, $\sigma = 0.95$, $\alpha = 26$. These values of μ, δ, σ, and α represent, respectively, a life expectancy of 50 years, a mean duration of 20 years for the loss of immunity induced by primary vaccination, a vaccine efficacy of 95%, and a mean duration of 2 weeks for recovery from infection. For each p_λ, there is a critical value η_p (corresponding to a vertical tangent to p_λ in Figure 2B) such that disease control is not feasible if $\eta < \eta_p$. However, for $\eta > \eta_p$, there is a range of λ (bold-line in shaded area in Figure 2B) for which $\mathscr{R}_0 < 1$ and the disease can be eradicated. Decreasing the primary vaccination coverage p_λ makes

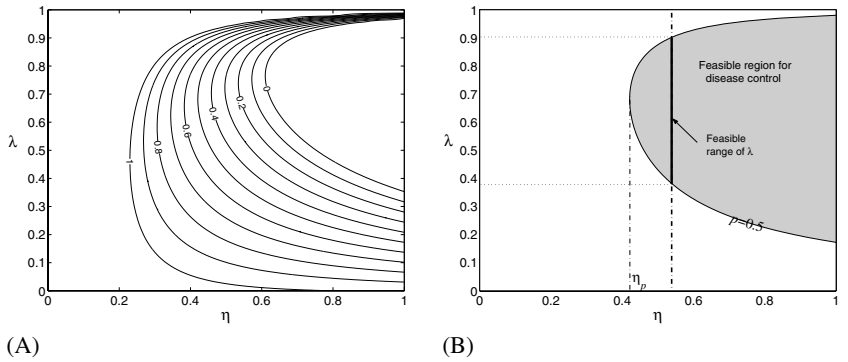

Fig. 2. (A) Contour plots for various values of primary vaccination coverage $p(\eta,\lambda)$ (for feasible ranges of η and λ) for which $\mathscr{R}_0 = 1$. Parameter values are: $\mu = 0.02$, $\delta = 0.05$, $\sigma = 0.95$, $\alpha = 26$ and $r_0 = 17$. (B) Feasible region for disease control ($\eta > \eta_p$) with the same parameter values and $p = 0.5$.

the feasible range of λ shrink, and moreover, the lower limit of the range increases. An important epidemiological consequence of this result is that, for relatively low vaccine coverage p_λ, a booster program may fail to control the disease if it is mostly targeted to primary vaccinated individuals. This situation corresponds to values of λ below the feasible range (dashed-line in white area in Figure 2B), defined by the given η and p_λ. The same conclusion holds when a booster functions, in effect, as mostly primary vaccination (corresponding to values of λ above the feasible range). More importantly, the probability of failure of a booster program increases as primary vaccination coverage p_λ decreases, leading to a more restricted range of λ for disease control. This highlights the significant role that primary coverage plays in ensuring a successful booster program.

Remark 2. There is a debate on the existence of a reinfection threshold in models with partial immunity [4], which was claimed to behave as a bifurcation parameter in the system [14]. However, Gomes et al. [15] emphasize the epidemiological consequences of this threshold, regardless of the terminology used to describe this phenomenon. They point out that above the threshold, vaccination programs will fail to protect; while below the threshold, the disease can be controlled by vaccination, even when the basic reproductive number for the model (with no prior exposure to the disease) is greater than unity.

4. Stable T-periodic solutions

In this section, the existence of T-periodic solutions of the model with $\beta_1 > 0$ will be discussed when $\mathscr{R}_0 > 1$. We note that the model (2)–(5) can be written as

$$\frac{dX}{dt} = F(X) + \beta_1 G(X, t) \tag{21}$$

where $X = (S, S_v, I, V)^T$, $F(X) = (f_1(X), f_2(X), f_3(X), f_4(X))^T$ with

$$\begin{aligned}
f_1 &= (1-p)\Pi - \beta_0 SI - (\mu+\xi)S + \delta S_v \\
f_2 &= p\Pi + \xi S - (1-\sigma)\beta_0 S_v I - (\mu+\gamma+\delta)S_v \\
f_3 &= \beta_0 SI + (1-\sigma)\beta_0 S_v I - (\mu+\alpha)I \\
f_4 &= \gamma S_v + \alpha I - \mu V,
\end{aligned}$$

and

$$G(x,t) = \begin{pmatrix} S \\ (1-\sigma)S_v \\ S + (1-\sigma)S_v \\ 0 \end{pmatrix} I \sin(\omega t).$$

When $\beta_1 = 0$, the model (21) reduces to $dX/dt = F(X)$. Solving $f_2 = f_3 = 0$ for S and S_v (assuming $I \neq 0$), at equilibrium gives:

$$S = \frac{(\mu+\alpha)(\mu+\gamma)}{(\mu\sigma+\gamma)\beta_0} - \frac{(1-\sigma)\Pi}{\mu\sigma+\gamma} + \frac{(1-\sigma)(\mu+\alpha)}{\mu\sigma+\alpha} I. \tag{22}$$

$$S_v = \frac{\mu(\mu+\alpha)}{(\mu\sigma+\gamma)\beta_0}(r_0 - 1) - \frac{\mu+\alpha}{\mu\sigma+\gamma} I. \tag{23}$$

Substituting (22) and (23) into $f_1 = 0$ gives the following equation (at equilibrium) in terms of I:

$$Q(I) = a_2 I^2 + a_1 I + a_0 = 0. \tag{24}$$

where

$$\begin{aligned} a_0 &= (\mu+\alpha)[(\mu+\gamma)(\mu+\xi)+\mu\delta](1-\mathscr{R}_0), \\ a_1 &= \beta_0\{(\mu+\alpha)[(1-\sigma)(\mu+\xi)+\mu+\gamma+\delta]-(1-\sigma)\beta_0\Pi\}, \\ a_2 &= \beta_0^2(1-\sigma)(\mu+\alpha). \end{aligned}$$

Since $\mathscr{R}_0 > 1$, it follows that $a_0 < 0$ and hence (24) has a unique positive root. Thus, the model $dX/dt = F(X)$ has a unique positive endemic equilibrium ($\mathscr{E}^*$) which is located in the feasible region Ω. It is worth noting that if $\mathscr{R}_0 < 1$, then Theorem 1 shows that the model has no positive endemic equilibrium.

Applying the technique used in [33, Theorem A2], it can be shown that $\mathscr{E}^*$ is globally asymptotically stable and it attracts $\Omega \setminus \Omega_0$, where

$$\Omega_0 = \{(S, S_v, I, V) \in \Omega : I = 0\}.$$

Theorem 2. *Suppose $\mathscr{R}_0 > 1$. If $\beta_1 = 0$, then the unique endemic equilibrium $\mathscr{E}^*$ of the model $dX/dt = F(X)$ is globally asymptotically stable and it attracts $\Omega \setminus \Omega_0$.*

Suppose now that the endemic equilibrium $\mathscr{E}^*$ exists ($\mathscr{R}_0 > 1$) and it is hyperbolic. Thus, the eigenvalues of the corresponding Jacobian at $\mathscr{E}^*$ have a strictly negative real part. Then, it follows that there exist positive constants β^*, c^* such that if $0 < \beta_1 < \beta^*$, then a unique stable T-periodic orbit $\phi(t)$ of the model (21) exists with $\|\phi(t) - \mathscr{E}^*\| \leq c^*\beta^*$ for all $t \in \mathbf{R}$ [19]. Therefore, we have the following theorem.

Theorem 3. *If $\mathscr{R}_0 > 1$, then there exist positive constants β^*, c^* such that the model (21) admits a unique stable T-periodic orbit $\phi(t)$ for $0 < \beta_1 < \beta^*$ with $\|\phi(t) - \mathscr{E}^*\| \leq c^*\beta^*$ for all $t \in \mathbf{R}$.*

In order to illustrate the results of this section when $\mathscr{R}_0 > 1$, numerical experiments were carried out using the parameter values estimated for measles infection [22,25,26,34,35,42,43]. With the notations of the previous section for $\xi = \lambda\eta$ and $\gamma = (1-\lambda)\eta$, Figure 3 shows the profiles of infected individuals for $p = 0.8$ and different values of booster vaccination rate. For $\eta = 0.375 > \eta_p$, Figures 3A–B illustrate the existence of a unique periodic solution (including transient behavior of the model) for $\lambda = 0.1$ and $\lambda = 0.9$, respectively (which lie outside the feasible range of λ for disease control; see dashed-lines in Figure 2B). Similar results were obtained when the model was simulated with $\eta = 0.3 < \eta_p$ and $\lambda = 0.5$ (Figure 3C). However, simulations confirm that increasing η above η_p leads to disease eradication whenever λ lies in the range defined by the given p and η_p (see bold-line in shaded area in Figure 2B). These simulations are consistent with the results of Figure 2, which identify the feasible region for disease control under booster vaccination.

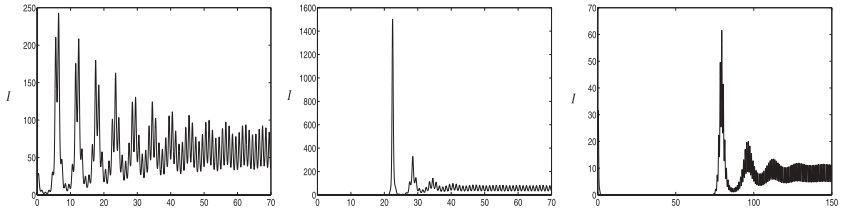

Fig. 3. Profiles of the infected individuals (I) with $\eta = 0.375$ (year)$^{-1}$for (A) $\lambda = 0.1$; and (B) $\lambda = 0.9$. Model parameters are [22,25,26,34,35,42,43]: $\Pi = 10000$ people (year)$^{-1}$, $p = 0.8$, $\mu = 0.02$ (year)$^{-1}$, $\beta_0 = 442/N$ (people year)$^{-1}$, $\beta_1 = 0.1$, $\sigma = 0.95$, $\delta = 0.05$ (year)$^{-1}$, and $\alpha = 26$ (year)$^{-1}$, where the total population $N = 5 \times 10^5$. (C) Profile of infected individuals for $\eta = 0.3 < \eta_p$ and $\lambda = 0.5$ with the same parameter values. In all three cases, λ lies outside its feasible range for disease control.

5. Discussion

Ever since the identification of the basic reproductive number, the focus for public health policy has been to explore the means by which it can be reduced to levels below unity. Such a reduction can be achieved by changing the control parameters associated with an appropriate intervention strategy, such as vaccination. In this paper, we have focused on the impact of vaccination programs on disease epidemiology, by developing a mathematical model that incorporates a booster vaccine and time-varying contact rate. The dynamical analysis of the model, using Floquet theory, led to the determination of the basic reproductive number in the presence of both primary and booster vaccinations. It was shown that if $\mathscr{R}_0 < 1$, then the disease-free equilibrium is globally asymptotically stable which leads to disease eradication. Perturbation theory was also used to show the existence of a unique stable T-periodic solution when $\mathscr{R}_0 > 1$. These results have been numerically illustrated by simulating the model using parameter values estimated for measles infection.

We have studied a seasonally forced epidemic model to evaluate the effect of a booster dose of an imperfect vaccine in reducing $\mathscr{R}_0$. Our findings highlight an important epidemiological implication namely, in relatively high incidence areas where an infected individual can produce at least two new infectious cases, eradication will be impossible with only a single-dose strategy. We have shown that the level of primary vaccination can significantly impact the outcome of booster programs. Having a booster program does not necessarily guarantee successful control of a disease, though may result in reducing the level of epidemicity. The effect of a booster strategy depends greatly on the proportion of individuals who receive the vaccine as a second-dose to boost antibody titres. This poses the problem of estimating the optimal timing of the additional vaccine doses which depends significantly on the levels of primary vaccination achieved [34,44]. While the reported global routine vaccination coverage with the primary dose of measles vaccine among children remained at about 80% between 1990 and 2000, many countries reported vaccination coverage of less than 50% [20,46]. Recent estimates are that a threshold

coverage of greater than 90% is required for being situated in the feasible region of measles control [20,46]. If this criterion is met, then a minimum rate of booster vaccination would be required to ensure elimination of infection. However, these joint criteria impose stringent requirements for any practical public health policy, and in order to achieve global eradication, public health efforts would have to be directed towards maintaining these criteria above their respective thresholds.

The model studied here is based on a constant vaccination strategy with a booster administration. There are several studies on different vaccination policies, including pulse and time-dependent (see [34,39,45] and references therein), which have the consequences of suppressing the complex dynamics of seasonally forced models and reducing chaotic behavior in childhood epidemics. Models of age-structured populations have also been studied in order to determine optimal vaccination strategies, and to explain the re-emergence of some infectious diseases as a result of the waning of vaccine-induced immunity [30,34,36]. The model in this paper can be extended to incorporate age-structured populations, which would then allow for the determination of time-varying vaccination strategies and optimal timing for the administration of booster doses.

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