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## Analysis of a delayed hand–foot–mouth disease epidemic model with pulse vaccination

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In this paper, we have considered a dynamical model of hand–foot–mouth disease (HFMD) with varying total population size, saturation incidence rate and discrete time delay to become infectious. It is assumed that there is a time lag ( $\tau$ ) to account for the fact that an individual infected with virus is not infectious until after some time after exposure. The probability that an individual remains in the latency period (exposed class) at least  $t$  time units before becoming infectious is given by a step function with value 1 for  $0 \leq t < \tau$  and value zero for  $t > \tau$ . The probability that an individual in the latency period has survived is given by  $e^{-\mu t}$ , where  $\mu$  denotes the natural mortality rate in all epidemiological classes. It is reported that the first vaccine to protect children against enterovirus 71, or EV71 has been discovered [Zhu, F. C., Meng, F. Y., Li, J. X., Li, X. L., Mao, A. Y., Tao, H., ..., Shen, X. L. (2013, May 29). Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 381, 2024–2032. doi:10.1016/S0140-6736(13)61049-1]. Pulse vaccination is an effective and important strategy for the elimination of infectious diseases and so we have analyzed this model with pulse vaccination. We have defined two positive numbers  $R_1$  and  $R_2$ . It is proved that there exists an infection-free periodic solution which is globally attractive if  $R_1 < 1$  and the disease is permanent if  $R_2 > 1$ . The important mathematical findings for the dynamical behavior of the HFMD model are also numerically verified using MATLAB. Finally epidemiological implications of our analytical findings are addressed critically.

**Keywords:** hand–foot–mouth disease; pulse vaccination; permanence; extinction; global stability

### 1. Introduction

Infectious diseases have tremendous influence on human life and are usually caused by pathogenic microorganisms, such as bacteria, viruses, parasites, or fungi. The diseases can be spread directly or indirectly. Hand–foot–mouth disease (HFMD) is a contagious (transmitted by bodily contact with an infected individual) disease of early childhood caused by viruses that belong to the enterovirus (EV) genus (group) which includes polioviruses, coxsackieviruses, echoviruses, and EVs. EVs are among the most common human viruses infecting around one billion persons worldwide annually and is divided into 10 species. Most EV infections are asymptomatic (Bracho, González-Candelas, Valero, Córdoba, & Salazar, 2011). The most common viruses causing the spread of HFMD are coxsackievirus A16 (COX A16) and enterovirus 71 (EV71) (Yang, Chen, & Zhang, 2013; Zhu, Hao, Ma, Yu, & Wang, 2011). HFMD may also be caused by other EVs. It is common in children (<10 years of age) but can also occur in adults and most patients with fatal complications are infected by EV71 and coxsackievirus A16 (Bracho et al., 2011). It usually takes 3–7 days for a person to get symptoms of HFMD disease after being exposed to the virus. This is called the incubation period of HFMD. Although

many HFMD-infected people remain asymptomatic, the symptoms of HFMD include sores in or on the mouth and on the hands, feet, and sometimes the buttocks and legs. The sores may be painful. The virus spreads easily through coughing and sneezing. It can also spread through infected stool.

Although HFMD is classically known as a mild disease, outbreaks in Asia have been associated with a high incidence of fatal cardiopulmonary and neurologic complications (Bracho et al., 2011; Wong, Yip, Lau, & Yuen, 2010). It not only causes health problems but also has great social and economical impacts throughout the world. Because of its global spread and the associated morbidity and mortality it inflicts, much attention has been focused on devising methods for controlling the spread of HFMD based on appropriate preventive measures. These measures include quarantine mechanisms (a strict isolation imposed to prevent the spread of the disease) and personal protection against exposure to infected persons (Liu, 2011). In the past, there was no specific treatment for HFMD. On 29 May 2013, it is reported that Chinese scientists have developed the first vaccine to protect children against enterovirus 71, or EV71, that causes the common and sometimes deadly HFMD (Zhu et al., 2013).

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The pulse vaccination strategy (PVS) consists of repeated application of vaccine at discrete time with equal interval in a population in contrast to the traditional constant vaccination (Gakkhar & Negi, 2008; Zhou & Liu, 2003). Compared to the proportional vaccination models, the study of pulse vaccination models is in its infancy (Zhou & Liu, 2003). At each vaccination time a constant fraction of the susceptible population is vaccinated successfully. Since 1993, attempts have been made to develop mathematical theory to control infectious diseases using pulse vaccination (Agur, Cojocaru, Mazor, Anderson, & Danon, 1993; Gakkhar & Negi, 2008). Nokes & Swinton, (1995) discussed the control of childhood viral infections by PVS. Stone, Shulgin, & Agur, (2000) presented a theoretical examination of the PVS in the susceptible-infected-recovered (SIR) epidemic model and d’Onofrio (2002a, 2002b) analyzed the use of pulse vaccination policy to eradicate infectious disease for SIR and susceptible-exposed-infected-recovered (SEIR) epidemic models. Different types of vaccination policies and strategies combining pulse vaccination policy, treatment, pre-outbreak vaccination or isolation have already been introduced by several researchers (Babiuk, Babiuk, & Baca-Estrada, 2002; d’Onofrio, 2005; Gao, Chen, Nieto, & Torres, 2006; Gao, Chen, & Teng, 2007; Gjorrgjieva et al., 2005; Tang, Xiao, & Clancy, 2005; Wei & Chen, 2008).

Mathematical epidemiology is the study of the spread of diseases, in space and time, with the objective to identify factors that are responsible for or contributing to their occurrence. Mathematical models are becoming important tools in analyzing the spread and control of infectious diseases. Epidemic models of ordinary differential equations have been studied by a number of researchers (Anderson & May, 1992; Brauer & Castillo-Chavez, 2001; Cai, Li, Ghosh, & Guo, 2009; Capasso, 1993; Diekmann & Heesterbeek, (2000); Kermack & Mckendrick, 1927; Ma, Song, & Takeuchi, 2004; Mena-Lorca & Hethcote, 1992; Meng, Chen, & Cheng, 2007; Naresh, Tripathi, & Omar, 2006; Thieme, 2003). The basic and important objectives for these models are the existence of the threshold values which distinguish whether the infectious disease will be going to extinct, the local and global stability of the disease-free equilibrium and the endemic equilibrium, the existence of periodic solutions and the persistence of the disease. Stability, persistence and permanence in population biology have been studied by many researchers (Takeuchi, Cui, Rinko, & Saito, 2006a, 2006b). Hence, as a part of population biology, permanence of disease plays an important role in mathematical epidemiology.

Although HFMD is a disease of significant public health importance, the transmission dynamics of the HFMD has not yet received adequate research attention in the mathematical modeling of epidemiology literature. It is noted here that very little attention has been paid to the mathematical modeling and analysis of HFMD to gain insight into

its transmission dynamics at population level. Urashima, Shindo, & Okabe, (2003) and Wang & Sung, (2004) attempted to find the relationship between the outbreaks of HFMD with the weather patterns in Tokyo and Taiwan respectively. Chuo, Tiing, & Labadin, (2008) used a deterministic SIR model to predict the number of infected and the duration of an outbreak of HFMD when it occurs in Sarawak. Then Roy & Halder (2010) proposed a deterministic SEIR model of HFMD and did only numerical simulations. Recently, Liu (2011) and Yang et al. (2013) used the SEIQRS model to take into account of the quarantine measure. Motivated by the above works and the recent development of the first vaccine to children against enterovirus 71, or EV71 (Zhu et al., 2013), in this paper, we are concerned with the effect of pulse vaccination and saturation incidence on the dynamic of a delayed  $SEI_A I_S QRS$  epidemic model of HFMD. Here we have used the Kermack–McKendrick compartmental modeling framework, which entails sub-dividing the entire high-risk human population into mutually exclusive epidemiological compartments (based on disease status), to gain insights into the qualitative features of HFMD in a human population (with the aim of finding effective ways to control its spread). The main feature of this paper is to introduce time delay, saturation incidence rate with valid PVS. We have introduced two threshold values  $R_1$  and  $R_2$  and further obtained that the disease will be going to extinct when  $R_1 < 1$  and the disease will be permanent when  $R_2 > 1$ . The important mathematical findings for the dynamical behavior of the HFMD model are numerically verified using MATLAB and also epidemiological implications of our analytical findings are addressed critically in the Section 5. The aim of the analysis of this model is to trace the parameters of interest for further study, with a view to informing and assisting policy-maker in targeting prevention and treatment resources for maximum effectiveness.

## 2. Model derivation and preliminaries

In the following, we consider a dynamical model of HFMD caused by EVs with discrete time delay and PVS which satisfies the following assumptions:

The underlying high-risk human population is split up into six mutually exclusive classes (compartments), namely, susceptible ( $S$ ), exposed (infected but not yet infectious) ( $E$ ), infective in asymptomatic phase (showing no symptoms of HFMD) ( $I_A$ ), infective in symptomatic phase (showing symptoms of HFMD) ( $I_S$ ), infective in symptomatic phase who follow quarantine (a strict isolation imposed to prevent the spread of the disease) mechanisms and personal protection against infecting others ( $Q$ ) and recovered (infectious people who have cleared (or recovered from) HFMD infection) ( $R$ ).

The susceptible population increases through birth (a constant influx  $\Lambda$  of susceptible is assumed) and from recovered hosts and decreases due to direct contact with

an infectious individual (in  $I_A$  or  $I_S$  compartments), natural death and PVS.

Standard epidemiological models use a bilinear incidence rate  $\beta SI$  based on the law of mass action (Anderson & May, 1979; 1992) and it is reasonable when the mixing of susceptible with infective is considered to be homogeneous. If the population is saturated with infective, there are three types of incidence forms used in epidemiological model: the proportionate mixing incidence  $\beta(SI/N)$  (Anderson & May, 1992; Cooke & van Den Driessche, 1996; Wang, 2002), nonlinear incidence  $\beta S^p I^q$  (Hethcote & van Den Driessche, 1991; Hui & Chen, 2004) and saturation incidence  $\beta(SI/(1 + \sigma S))$  (Anderson & May, 1992; May & Anderson, 1978) or  $\beta(SI^p/(1 + \sigma I^q))$  (Ruan & Wang, 2003). Here incidence rates  $\beta_1(SI_A/(1 + \sigma_1 S))$  and  $\beta_2(SI_S/(1 + \sigma_2 S))$  have been considered.

The infected classes are increased by infection of susceptible. A fraction of the exposed individuals will start to show symptoms of HFMD (and move to the class  $I_S$ ), while the remaining fraction will not (but still remain capable of infecting others and move to the class  $I_A$ ). Also, a fraction of the infective in symptomatic phase takes appropriate preventive measures and move to the quarantined class  $Q$ . It is assumed that there is a time lag to account for the fact that an individual infected with HFMD is not infectious until after some time (typically 3–7 days (Yang et al., 2013)) after exposure. A fraction of the asymptotically infectious individuals eventually show disease symptoms (and move to the class  $I_S$ ) and a fraction recover (and move to the class  $R$ ). The infected classes are decreased through recovery from infection, by disease-related death and by natural death. Motivated by the recent development of the first vaccine to protect children against enterovirus 71, or EV71 (Zhu et al. 2013), we incorporate a PVS in which a fraction  $p$  of the susceptible population is vaccinated successfully at discrete time  $t = T, 2T, 3T, \dots$

Thus, the following dynamical model of HFMD with discrete time delay and PVS is formulated:

$$\begin{aligned} \frac{dS(t)}{dt} &= \Lambda - \beta_1 \frac{S(t)I_A(t)}{1 + \sigma_1 S(t)} - \beta_2 \frac{S(t)I_S(t)}{1 + \sigma_2 S(t)} \\ &\quad - \mu S(t) + \alpha R(t), \quad t \neq nT, \\ \frac{dE(t)}{dt} &= \beta_1 \frac{S(t)I_A(t)}{1 + \sigma_1 S(t)} + \beta_2 \frac{S(t)I_S(t)}{1 + \sigma_2 S(t)} \\ &\quad - \beta_1 e^{-\mu\tau} \frac{S(t-\tau)I_A(t-\tau)}{1 + \sigma_1 S(t-\tau)} \\ &\quad - \beta_2 e^{-\mu\tau} \frac{S(t-\tau)I_S(t-\tau)}{1 + \sigma_2 S(t-\tau)} - \mu E(t), \quad t \neq nT, \\ \frac{dI_A(t)}{dt} &= \rho e^{-\mu\tau} S(t-\tau) \\ &\quad \times \left\{ \frac{\beta_1 I_A(t-\tau)}{1 + \sigma_1 S(t-\tau)} + \frac{\beta_2 I_S(t-\tau)}{1 + \sigma_2 S(t-\tau)} \right\} \\ &\quad - (r_1 + d_1 + \mu)I_A(t), \quad t \neq nT, \end{aligned}$$

$$\begin{aligned} \frac{dI_S(t)}{dt} &= (1 - \rho) e^{-\mu\tau} S(t-\tau) \\ &\quad \times \left\{ \frac{\beta_1 I_A(t-\tau)}{1 + \sigma_1 S(t-\tau)} + \frac{\beta_2 I_S(t-\tau)}{1 + \sigma_2 S(t-\tau)} \right\} \\ &\quad + (1 - k)r_1 I_A(t) - (q + r_2 + d_2 \\ &\quad + \mu)I_S(t), \quad t \neq nT, \\ \frac{dQ(t)}{dt} &= qI_S(t) - (r_3 + d_3 + \mu)Q(t), \quad t \neq nT, \\ \frac{dR(t)}{dt} &= kr_1 I_A(t) + r_2 I_S(t) + r_3 Q(t) \\ &\quad - \mu R(t) - \alpha R(t), \quad t \neq nT, \\ S(t^+) &= (1 - p)S(t), \quad t = nT, \quad n = 1, 2, \dots \\ E(t^+) &= E(t), \quad t = nT, \quad n = 1, 2, \dots \\ I_A(t^+) &= I_A(t), \quad t = nT, \quad n = 1, 2, \dots \\ I_S(t^+) &= I_S(t), \quad t = nT, \quad n = 1, 2, \dots \\ Q(t^+) &= Q(t), \quad t = nT, \quad n = 1, 2, \dots \\ R(t^+) &= R(t) + pS(t), \quad t = nT, \quad n = 1, 2, \dots, \quad (1) \end{aligned}$$

where all coefficients are positive constants. Here  $S(t)$  denotes the number of susceptible,  $E(t)$  denotes the number of exposed,  $I_A(t)$  denotes the number of infective in asymptomatic compartment,  $I_S(t)$  denotes the number of infective in symptomatically infected compartment,  $Q(t)$  denotes the number of symptomatically infective in quarantined compartment and  $R(t)$  denotes the number of recovered individuals. The pulse vaccination does not give life-long immunity, there is an immunity waning for the vaccination with the per capita immunity waning rate  $\alpha$ , and return to the susceptible class. The influx of susceptible comes from two sources: a constant recruitment  $\Lambda$  and from recovered hosts ( $\alpha R$ ). The parameters  $\beta_1, \beta_2, \mu, \rho, d_1, d_2, d_3, r_1, r_2, r_3, \tau, p$  are:

$\beta_1$ : The coefficient of transmission rate from infective in asymptomatic compartment to susceptible humans (and become exposed) and the rate of transmission of infection is of the form:

$$\beta_1 \frac{S(t)I_A(t)}{1 + \sigma_1 S(t)}.$$

$\beta_2$ : The coefficient of transmission rate from infective in symptomatically infected compartment to susceptible humans (and become exposed) and the rate of transmission of infection is of the form:

$$\beta_2 \frac{S(t)I_S(t)}{1 + \sigma_2 S(t)}.$$

$\mu$ : The coefficient of natural death rate of all epidemiological human classes.

$d_1$ : The coefficient of additional disease-related death rate of infective in asymptomatic compartment ( $I_A$ ).

$d_2$ : The coefficient of additional disease-related death rate of infective in symptomatically infected compartment ( $I_S$ ).

$d_3$ : The coefficient of additional disease-related death rate of infective in quarantined compartment ( $Q$ ).

$(1 - \rho)$ : The fraction of the exposed individuals will start to show disease symptoms and move to the class  $I_S$ . The remaining fraction  $\rho$  ( $0 < \rho < 1$ ) will not start to show disease symptoms (but still remain capable of infecting others) and move to the class  $I_A$ .

$(1 - k)r_1$ : The rate at which the asymptotically infectious individuals eventually show disease symptoms (move to the class  $I_S$ ) and recover at the rate  $kr_1$  ( $0 < k < 1$ ) (move to the class  $R$ ).

$r_2$ : The rate at which the infectious individuals showing symptoms of HFMD (in symptomatically infected compartment  $I_S$ ) clear infections and move to the class  $R$ .

$r_3$ : The rate at which symptomatically infected individuals (infective in quarantined compartment  $Q$ ) clear infections and move to the class  $R$ .

$q$ : The quarantine rate.

$\tau$ : The constant latency period from the time of being infected (exposed) to the time of being infectious (capable of infecting others). The probability that an individual remains in the latency period (exposed class) at least  $t$  time units before becoming infectious is given by a step function with value 1 for  $0 \leq t < \tau$  and value zero for  $t > \tau$ . The probability that an individual in the latency period has survived is given by  $e^{-\mu t}$ . The time interval  $[t - \tau, t]$  is typically 3–7 days (Yang et al. 2013).

$p$  ( $0 < p < 1$ ): The fraction of susceptible who are vaccinated successfully at discrete time  $t = T, 2T, 3T, \dots$ , which is called impulsive vaccination rate.

The total high-risk human population size  $N(t) = S(t) + E(t) + I_A(t) + I_S(t) + Q(t) + R(t)$  can be determined by the following differential equation:

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - d_1 I_A(t) - d_2 I_S(t) - d_3 Q(t), \quad (2)$$

which is derived by adding first six equations of system (1). Therefore,

$$\begin{aligned} \Lambda - (\mu + d_1 + d_2 + d_3)N(t) &\leq \frac{dN(t)}{dt} \leq \Lambda - \mu N(t) \\ \Rightarrow \frac{\Lambda}{\mu + d_1 + d_2 + d_3} &\leq \liminf_{t \rightarrow \infty} N(t) \\ &\leq \limsup_{t \rightarrow \infty} N(t) \leq \frac{\Lambda}{\mu}. \end{aligned} \quad (3)$$

Let us simplify the model (1) as follows:

$$\begin{aligned} \frac{dS(t)}{dt} &= \Lambda - \beta_1 \frac{S(t)I_A(t)}{1 + \sigma_1 S(t)} - \beta_2 \frac{S(t)I_S(t)}{1 + \sigma_2 S(t)} \\ &\quad - \mu S(t) + \alpha R(t), \quad t \neq nT, \end{aligned}$$

$$\begin{aligned} \frac{dI_A(t)}{dt} &= \rho e^{-\mu \tau} S(t - \tau) \\ &\quad \times \left\{ \frac{\beta_1 I_A(t - \tau)}{1 + \sigma_1 S(t - \tau)} + \frac{\beta_2 I_S(t - \tau)}{1 + \sigma_2 S(t - \tau)} \right\} \\ &\quad - (r_1 + d_1 + \mu)I_A(t), \quad t \neq nT, \end{aligned}$$

$$\begin{aligned} \frac{dI_S(t)}{dt} &= (1 - \rho) e^{-\mu \tau} S(t - \tau) \\ &\quad \times \left\{ \frac{\beta_1 I_A(t - \tau)}{1 + \sigma_1 S(t - \tau)} + \frac{\beta_2 I_S(t - \tau)}{1 + \sigma_2 S(t - \tau)} \right\} \\ &\quad + (1 - k)r_1 I_A(t) - (q + r_2 + d_2 \\ &\quad + \mu)I_S(t), \quad t \neq nT, \end{aligned}$$

$$\frac{dQ(t)}{dt} = qI_S(t) - (r_3 + d_3 + \mu)Q(t), \quad t \neq nT,$$

$$\begin{aligned} \frac{dR(t)}{dt} &= kr_1 I_A(t) + r_2 I_S(t) + r_3 Q(t) - \mu R(t) \\ &\quad - \alpha R(t), \quad t \neq nT, \end{aligned}$$

$$\begin{aligned} \frac{dN(t)}{dt} &= \Lambda - \mu N(t) - d_1 I_A(t) - d_2 I_S(t) \\ &\quad - d_3 Q(t), \quad t \neq nT, \end{aligned}$$

$$S(t^+) = (1 - p)S(t), \quad t = nT, \quad n = 1, 2, \dots$$

$$I_A(t^+) = I_A(t), \quad t = nT, \quad n = 1, 2, \dots$$

$$I_S(t^+) = I_S(t), \quad t = nT, \quad n = 1, 2, \dots$$

$$Q(t^+) = Q(t), \quad t = nT, \quad n = 1, 2, \dots$$

$$R(t^+) = R(t) + pS(t), \quad t = nT, \quad n = 1, 2, \dots$$

$$N(t^+) = N(t), \quad t = nT, \quad n = 1, 2, \dots, \quad (4)$$

with initial conditions

$$\begin{aligned} S(\vartheta) &= \varphi_1(\vartheta), \quad I_A(\vartheta) = \varphi_2(\vartheta), \quad I_S(\vartheta) = \varphi_3(\vartheta), \\ Q(\vartheta) &= \varphi_4(\vartheta), \quad R(\vartheta) = \varphi_5(\vartheta), \\ N(\vartheta) &= \varphi_6(\vartheta), \quad \text{such that } \varphi_i(\vartheta) \\ &\geq 0 \quad (i = 1, 2, 3, 4, 5, 6), \quad \forall \vartheta \in [-\tau, 0], \end{aligned} \quad (5)$$

where  $\varphi_i(\vartheta) \geq 0$  ( $i = 1, 2, 3, 4, 5, 6$ ) are nonnegative continuous functions on  $\vartheta \in [-\tau, 0]$ . For a biological meaning, we further assume that  $\varphi_i(0) > 0$  ( $i = 1, 2, 3, 4, 5, 6$ ). There exists a unique solution of Equation (4) with initial conditions (5) since the right-hand sides of Equation (4) and the pulse are smooth functions (Bainov & Simeonov, 1993; 1995; Lakshmikantham, Bainov, & Simeonov, 1989).

From biological considerations, we analyze system (4) and (5) in the closed set:

$$\begin{aligned} G = \left\{ (S(t), I_A(t), I_S(t), Q(t), R(t), N(t)) \in \mathbb{R}_+^6 : 0 \leq S \right. \\ \left. + I_A + I_S + Q + R, N \leq \frac{\Lambda}{\mu} \right\}, \end{aligned} \quad (6)$$



where  $\mathbb{R}_+^6$  represents the nonnegative cone of  $\mathbb{R}^6$  including its lower dimensional faces. It can be verified that  $G$  is positively invariant with respect to Equations (4) and (5).

Before starting our main results, we give the following two lemmas which will be essential for study.

LEMMA 2.1 (Song & Chen, 2001) Consider the following equation:

$$\frac{dx(t)}{dt} = ax(t - \tau) - bx(t) - cx^2(t), \quad (7)$$

where  $a, b, c, \tau > 0$ ;  $x(t) > 0$ , for  $-\tau \leq t \leq 0$ . We have

- (I) if  $a > b$ , then  $\lim_{t \rightarrow \infty} x(t) = \frac{a - b}{c}$ ;
- (II) if  $a < b$ , and  $c \geq 0$ , then  $\lim_{t \rightarrow \infty} x(t) = 0$ .

LEMMA 2.2 Consider the following impulsive differential equation:

$$\begin{aligned} \frac{du(t)}{dt} &= a - bu(t), \quad t \neq kT, \\ u(t^+) &= (1 - p)u(t), \quad t = kT, \quad k = 1, 2, \dots \end{aligned} \quad (8)$$

where  $a > 0, b > 0, 0 < p < 1$ . Then there exists a unique positive periodic solution of system (8):

$$\begin{aligned} \tilde{u}_e(t) &= \frac{a}{b} + \left(u^* - \frac{a}{b}\right) e^{-b(t-kT)}, \quad kT < t \leq (k+1)T, \\ \text{where } u^* &= \frac{a(1-p)(1-e^{-bT})}{b\{1-(1-p)e^{-bT}\}}, \end{aligned}$$

and  $\tilde{u}_e(t)$  is globally asymptotically stable.

Proof From the first equation of system (8) we get,

$$\begin{aligned} \frac{d}{dt}(e^{bt}u(t)) &= ae^{bt}. \text{ Integrating between pulses:} \\ &\times \int_{kT}^t d(e^{bt}u(t)) = \int_{kT}^t ae^{bt} dt \\ \Rightarrow u(t) &= \frac{a}{b} + \left[u(kT) - \frac{a}{b}\right] e^{-b(t-kT)}, \\ &kT < t \leq (k+1)T, \end{aligned}$$

where  $u(kT)$  is the initial value at time  $kT$ . Using the second equation of system (8) we have the following stroboscopic map:

$$\begin{aligned} u((k+1)T) &= (1-p) \left[ \frac{a}{b} + \left[u(kT) - \frac{a}{b}\right] e^{-bT} \right] \\ &= f(u(kT)), \end{aligned} \quad (9)$$

$$\text{where } f(u) = (1-p) \left\{ \frac{a}{b} + \left(u - \frac{a}{b}\right) e^{-bT} \right\}.$$

Solving the following equation:

$$\begin{aligned} u &= (1-p) \left\{ \frac{a}{b} + \left(u - \frac{a}{b}\right) e^{-bT} \right\}, \text{ we get,} \\ u^* &= \frac{a(1-p)(1-e^{-bT})}{b\{1-(1-p)e^{-bT}\}}. \end{aligned}$$

Since  $|f'(u)| = (1-p)e^{-bT} < 1$ , as  $0 < p < 1$  and  $b > 0$ , the system (9) has a unique positive equilibrium  $u^* = a(1-p)(1-e^{-bT})/b\{1-(1-p)e^{-bT}\}$  which is globally asymptotically stable. Hence the corresponding periodic solution of system (8)

$$\begin{aligned} \tilde{u}_e(t) &= \frac{a}{b} + \left(u^* - \frac{a}{b}\right) e^{-b(t-kT)}, \quad kT < t \leq (k+1)T, \\ \text{where } u^* &= \frac{a(1-p)(1-e^{-bT})}{b\{1-(1-p)e^{-bT}\}} \end{aligned}$$

is globally asymptotically stable. This completes the proof. ■

### 3. Global stability of the disease-free periodic solution

In this section, we discuss the existence of the disease-free periodic solution of system (4), in which infectious individuals (in  $I_A, I_S, Q$  compartments) are completely absent, that is,  $I_A(t) = 0, \forall t \geq 0, I_S(t) = 0, \forall t \geq 0$  and  $Q(t) = 0, \forall t \geq 0$ . Under this circumstances, system (4) reduces to the following impulsive system without delay:

$$\begin{aligned} \frac{dS(t)}{dt} &= \Lambda - \mu S(t) + \alpha R(t), \quad t \neq nT, \\ \frac{dR(t)}{dt} &= -\mu R(t) - \alpha R(t), \quad t \neq nT, \\ \frac{dN(t)}{dt} &= \Lambda - \mu N(t), \quad t \neq nT, \\ S(t^+) &= (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots \\ R(t^+) &= R(t) + pS(t), \quad t = nT, \quad n = 1, 2, \dots \\ N(t^+) &= N(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \quad (10)$$

From the third and sixth equations of system (10), we have  $\lim_{t \rightarrow \infty} N(t) = \Lambda/\mu$ .

Further, from the second and eighth equations of system (1) it follows that

$$\lim_{t \rightarrow \infty} E(t) = 0 \text{ as } I_A(t) = I_S(t) = Q(t) = 0, \quad \forall t \geq 0.$$

In the following, we shall show that the susceptible population  $S(t)$  and recovered population  $R(t)$  oscillate with period  $T$ , in synchronization with the periodic impulsive vaccination strategy under some condition. Consider the

following limit system of system (10) as per the previous discussions:

$$\begin{aligned} R(t) &= \frac{\Lambda}{\mu} - S(t), \\ \frac{dS(t)}{dt} &= (\mu + \alpha) \left\{ \frac{\Lambda}{\mu} - S(t) \right\}, \quad t \neq nT, \\ S(t^+) &= (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \quad (11)$$

Using Lemma 2.2, the periodic solution of system (11) is given below:

$$\begin{aligned} \tilde{S}_e(t) &= \frac{\Lambda}{\mu} + \left( S^* - \frac{\Lambda}{\mu} \right) e^{-(\mu+\alpha)(t-nT)}, \\ nT < t &\leq (n+1)T, \quad \text{where} \\ S^* &= \frac{\Lambda(1-p)(1 - e^{-(\mu+\alpha)T})}{\mu\{1 - (1-p)e^{-(\mu+\alpha)T}\}} \end{aligned} \quad (12)$$

and  $\tilde{S}_e(t)$  is globally asymptotically stable.

Denote  $R_1 = \frac{\beta e^{-\mu\tau} A}{\{(1 + \sigma A)\theta\}}$ , where  $\beta = \max\{\beta_1, \beta_2\}$ ,

$$\sigma = \min\{\sigma_1, \sigma_2\}, \quad A = \frac{\Lambda(1 - e^{-(\mu+\alpha)T})}{\mu\{1 - (1-p)e^{-(\mu+\alpha)T}\}}$$

$$\begin{aligned} \text{and } \theta &= \min\{kr_1 + d_1 + \mu, r_2 + d_2 \\ &+ \mu, r_3 + d_3 + \mu\} > 0. \end{aligned} \quad (13)$$

**THEOREM 3.1** *If  $R_1 < 1$ , then the disease-free periodic solution  $(\tilde{S}_e(t), 0, 0, 0, \Lambda/\mu - \tilde{S}_e(t), \Lambda/\mu)$  of system (4) with initial conditions (5) is globally asymptotically stable.*

*Proof* Since  $R_1 < 1$ , we can choose  $\epsilon > 0$  small enough such that

$$\frac{\beta e^{-\mu\tau} (A + \epsilon)}{1 + \sigma(A + \epsilon)} < \theta, \quad \text{where } \beta = \max\{\beta_1, \beta_2\},$$

$$\sigma = \min\{\sigma_1, \sigma_2\}, \quad A = \frac{\Lambda(1 - e^{-(\mu+\alpha)T})}{\mu\{1 - (1-p)e^{-(\mu+\alpha)T}\}}$$

$$\text{and } \theta = \min\{kr_1 + d_1 + \mu, r_2 + d_2 + \mu, r_3 + d_3 + \mu\} > 0. \quad (14)$$

From the first and seventh equations of (4), it follows that

$$\begin{aligned} \frac{dS(t)}{dt} &\leq (\mu + \alpha) \left\{ \frac{\Lambda}{\mu} - S(t) \right\}, \quad t \neq nT, \\ S(t^+) &= (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned}$$

So, we consider the following comparison impulsive differential system:

$$\begin{aligned} \frac{dz(t)}{dt} &= (\mu + \alpha) \left\{ \frac{\Lambda}{\mu} - z(t) \right\}, \quad t \neq nT, \\ z(t^+) &= (1-p)z(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \quad (15)$$

By Equations (11) and (12), we know that the periodic solution of system (15),

$$\begin{aligned} \tilde{z}_e(t) &= \tilde{S}_e(t) = \frac{\Lambda}{\mu} + \left( S^* - \frac{\Lambda}{\mu} \right) e^{-(\mu+\alpha)(t-nT)}, \\ nT < t &\leq (n+1)T, \end{aligned} \quad (16)$$

$$\text{where } S^* = \frac{\Lambda(1-p)(1 - e^{-(\mu+\alpha)T})}{\mu\{1 - (1-p)e^{-(\mu+\alpha)T}\}}$$

is globally asymptotically stable. Let  $(S(t), I_A(t), I_S(t), Q(t), R(t), N(t))$  be the solution of system (4) with initial conditions (5) and  $S(0^+) = S_0 > 0$ . If  $z(t)$  be the solution of system (15) with initial value  $z(0^+) = S_0 > 0$ , then by the comparison theorem for impulsive differential equation (Lakshmikantham et al. 1989) there exists an integer  $n_1 > 0$  such that

$$\begin{aligned} S(t) &< z(t) < \tilde{z}_e(t) + \epsilon, \quad nT < t \leq (n+1)T, \quad n > n_1 \\ \Rightarrow S(t) &< \tilde{z}_e(t) + \epsilon \leq \frac{\Lambda(1 - e^{-(\mu+\alpha)T})}{\mu\{1 - (1-p)e^{-(\mu+\alpha)T}\}} \\ &+ \epsilon = \xi \text{ (say)}. \end{aligned} \quad (17)$$

Further, from the second, third and fourth equations of system (4), we have  $\forall t > nT + \tau$  and  $\forall n > n_1$ ,

$$\begin{aligned} \frac{d}{dt} \{I_A(t) + I_S(t) + Q(t)\} &\leq \frac{\beta\xi e^{-\mu\tau}}{1 + \sigma\xi} \{I_A(t - \tau) + I_S(t - \tau) \\ &+ Q(t - \tau)\} - \theta \{I_A(t) + I_S(t) + Q(t)\}. \end{aligned} \quad (18)$$

Consider the following comparison equation:

$$\frac{dy(t)}{dt} = \frac{\beta\xi e^{-\mu\tau}}{1 + \sigma\xi} y(t - \tau) - \theta y(t). \quad (19)$$

From Equation (14), we have

$$\frac{\beta\xi e^{-\mu\tau}}{1 + \sigma\xi} < \theta \Rightarrow \lim_{t \rightarrow \infty} y(t) = 0, \text{ by Lemma 2.1.} \quad (20)$$

Set  $(S(t), I_A(t), I_S(t), Q(t), R(t), N(t))$  be the solution of system (4) with initial conditions (5) and  $I_A(\vartheta) = \varphi_2(\vartheta) \geq 0, I_S(\vartheta) = \varphi_3(\vartheta) \geq 0, Q(\vartheta) = \varphi_4(\vartheta) \geq 0, \forall \vartheta \in [-\tau, 0]$  where  $\varphi_i(0) > 0 (i = 2, 3, 4)$ ,  $y(t)$  be the solution of Equation (19) with initial condition  $y(\vartheta) = \varphi_2(\vartheta) + \varphi_3(\vartheta) + \varphi_4(\vartheta) \geq 0, \forall \vartheta \in [-\tau, 0]$  where  $\varphi_2(0) + \varphi_3(0) + \varphi_4(0) > 0$ . By the comparison theorem of differential equation and the positivity of solution (with  $I_A(t) \geq 0, I_S(t) \geq 0, Q(t) \geq 0$ ), we have

$$\begin{aligned} \lim_{t \rightarrow \infty} \{I_A(t) + I_S(t) + Q(t)\} &= 0 \Rightarrow \lim_{t \rightarrow \infty} I_A(t) = \lim_{t \rightarrow \infty} \\ I_S(t) &= \lim_{t \rightarrow \infty} Q(t) = 0. \end{aligned} \quad (21)$$

Hence for any  $\epsilon_1 > 0$  (sufficiently small), there exists a positive integer  $n_2$ , where  $n_2T > n_1T + \tau$ , such that  $0 <$

$I_A(t), I_S(t), Q(t) < \epsilon_1, \forall t > n_2T$ . Using the sixth equation of system (4), we get

$$\frac{dN(t)}{dt} > \Lambda - \mu N(t) - (d_1 + d_2 + d_3)\epsilon_1, \quad \forall t > n_2T. \tag{22}$$

Now,

$$\begin{aligned} \frac{dz_1(t)}{dt} &= \{\Lambda - (d_1 + d_2 + d_3)\epsilon_1\} - \mu z_1(t) \Rightarrow \lim_{t \rightarrow \infty} z_1(t) \\ &= \frac{\Lambda - (d_1 + d_2 + d_3)\epsilon_1}{\mu}. \end{aligned}$$

So, by the comparison theorem, there exists an integer  $n_3 > n_2$  such that

$$\begin{aligned} N(t) &\geq \frac{\Lambda - (d_1 + d_2 + d_3)\epsilon_1}{\mu} - \epsilon_1, \quad \forall t > n_3T \\ \Rightarrow \lim_{t \rightarrow \infty} N(t) &= \frac{\Lambda}{\mu} \text{ (as } \epsilon_1 > 0 \text{ is arbitrarily small)}. \end{aligned} \tag{23}$$

It follows from Equations (21) and (23) that there exists an integer  $n_4 > n_3$  such that

$$0 < I_A(t), I_S(t), Q(t) < \epsilon_1, \quad N(t) > \frac{\Lambda}{\mu} - \epsilon_1, \quad \forall t > n_4T. \tag{24}$$

Therefore, from the second equation of system (1), we have

$$\frac{dE(t)}{dt} \leq \frac{2\Lambda\beta\epsilon_1}{\mu + \sigma\Lambda} - \mu E(t), \quad \forall t > n_4T. \tag{25}$$

It is clear that there exists an integer  $n_5 > n_4$  such that

$$E(t) < A_1 + \epsilon_1, \quad \forall t > n_5T, \quad \text{where } A_1 = \frac{2\Lambda\beta\epsilon_1}{\mu(\mu + \sigma\Lambda)}. \tag{26}$$

So, from the first and seventh equations of system (4) we get

$$\begin{aligned} \frac{dS(t)}{dt} &\geq \left( \Lambda + \frac{\alpha\Lambda}{\mu} - \alpha A_1 - 5\alpha\epsilon_1 \right) \\ &\quad - (2\beta\epsilon_1 + \mu + \alpha)S(t), \quad t \neq nT, \\ S(t^+) &= (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \tag{27}$$

Let us consider the following comparison impulsive differential system  $\forall t > n_5T$  and  $\forall n > n_5$ :

$$\begin{aligned} \frac{dz_2(t)}{dt} &= \left( \Lambda + \frac{\alpha\Lambda}{\mu} - \alpha A_1 - 5\alpha\epsilon_1 \right) \\ &\quad - (2\beta\epsilon_1 + \mu + \alpha)z_2(t), \quad t \neq nT, \\ z_2(t^+) &= (1-p)z_2(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \tag{28}$$

By Lemma 2.2, we know that the periodic solution of system (28) is

$$\begin{aligned} \tilde{z}_{2e}(t) &= \Phi + (z_2^* - \Phi) e^{-(2\beta\epsilon_1 + \mu + \alpha)(t - nT)}, \\ nT < t &\leq (n+1)T, \end{aligned}$$

$$\text{where } \Phi = \frac{\Lambda + \alpha\Lambda/\mu - \alpha A_1 - 5\alpha\epsilon_1}{2\beta\epsilon_1 + \mu + \alpha} \tag{29}$$

$$\text{and } z_2^* = \Phi \frac{(1-p)(1 - e^{-(2\beta\epsilon_1 + \mu + \alpha)T})}{\{1 - (1-p)e^{-(2\beta\epsilon_1 + \mu + \alpha)T}\}},$$

which is globally asymptotically stable.

By the comparison theorem for impulsive differential equation (Lakshmikantham et al. 1989), there exists an integer  $n_6 > n_5$  such that

$$S(t) > \tilde{z}_{2e}(t) - \epsilon_1, \quad nT < t \leq (n+1)T, \quad n > n_6. \tag{30}$$

Making  $\epsilon_1 \rightarrow 0$ , it follows from Equations (17) and (30) that

$$\begin{aligned} \tilde{S}_e(t) &= \frac{\Lambda}{\mu} \left\{ 1 - \frac{pe^{-(\mu + \alpha)(t - nT)}}{1 - (1-p)e^{-(\mu + \alpha)T}} \right\}, \\ nT < t &\leq (n+1)T, \end{aligned} \tag{31}$$

is globally attractive and so

$$\lim_{t \rightarrow \infty} S(t) = \tilde{S}_e(t). \tag{32}$$

By the positivity of  $E(t)$  and making  $\epsilon_1 \rightarrow 0$ , it follows from Equation (26) that

$$\lim_{t \rightarrow \infty} E(t) = 0. \tag{33}$$

Using Equations (21), (23), (32), (33) and from the restriction  $N(t) = S(t) + E(t) + I_A(t) + I_S(t) + Q(t) + R(t)$ , we have

$$\lim_{t \rightarrow \infty} R(t) = \frac{\Lambda}{\mu} - \tilde{S}_e(t). \tag{34}$$

Therefore, we conclude that if  $R_1 < 1$ , then the disease-free periodic solution  $(\tilde{S}_e(t), 0, 0, 0, \Lambda/\mu - \tilde{S}_e(t), \Lambda/\mu)$  of system (4) with initial conditions (5) is globally asymptotically stable. This completes the proof. ■

#### 4. Permanence

In this section, we wish to discuss the permanence of the system (4), this means that the long-term survival (i.e. will not vanish in time) of all components of the system (4), with initial conditions (5). It demonstrates how the disease will be permanent (i.e. will not vanish in time) under some conditions.



**DEFINITION** The system (4) is said to be permanent, i.e. the long-term survival (will not vanish in time) of all components of the system (4), if there are positive constants  $m_i (i = 1, 2, 3, 4)$  such that:

$$\begin{aligned} \liminf_{t \rightarrow \infty} S(t) &\geq m_1, & \liminf_{t \rightarrow \infty} \{I_A(t) + I_S(t) + Q(t)\} &\geq m_2, \\ \liminf_{t \rightarrow \infty} R(t) &\geq m_3, & \liminf_{t \rightarrow \infty} N(t) &\geq m_4, \end{aligned}$$

hold for any solution  $(S(t), I_A(t), I_S(t), Q(t), R(t), N(t))$  of Equation (4) with initial conditions (5). Here  $m_i (i = 1, 2, 3, 4)$  are independent of Equation (5).

**THEOREM 4.1** If  $R_2 > 1$ , then there exists a positive constant  $m$  such that each positive solution  $(S(t), I_A(t), I_S(t), Q(t), R(t), N(t))$  of the system (4) with initial conditions (5) satisfies  $(I_A(t) + I_S(t) + Q(t)) \geq m$  for sufficiently large time  $t$ , where

$$\begin{aligned} R_2 &= \left( \frac{\beta' e^{-\mu\tau}}{\theta'} - \sigma' \right) \frac{\Lambda(1-p)(1-e^{-\mu T})}{\mu\{1-(1-p)e^{-\mu T}\}}, \\ \beta' &= \min\{\beta_1, \beta_2\}, \\ \sigma' &= \max\{\sigma_1, \sigma_2\}, \\ \theta' &= \max\{kr_1 + d_1 + \mu, r_2 + d_2 + \mu, r_3 + d_3 + \mu\}. \end{aligned} \quad (35)$$

*Proof* From the second, third and fourth equations of system (4), we have

$$\begin{aligned} D'(t) &= \frac{dD(t)}{dt} \geq \beta' e^{-\mu\tau} \frac{S(t-\tau)D(t-\tau)}{1+\sigma'S(t-\tau)} - \theta'D(t) \\ &= D(t) \left\{ \beta' e^{-\mu\tau} \frac{S(t)}{1+\sigma'S(t)} - \theta' \right\} \\ &\quad - \beta' e^{-\mu\tau} \frac{d}{dt} \int_{t-\tau}^t \frac{S(u)D(u)}{1+\sigma'S(u)} du, \end{aligned}$$

$$\text{where } D(t) = I_A(t) + I_S(t) + Q(t). \quad (36)$$

$$\begin{aligned} \text{Define, } V(t) &= D(t) + \beta' e^{-\mu\tau} \int_{t-\tau}^t \frac{S(u)D(u)}{1+\sigma'S(u)} du \\ \Rightarrow V'(t) &= \frac{dV(t)}{dt} \geq D(t) \left\{ \beta' e^{-\mu\tau} \frac{S(t)}{1+\sigma'S(t)} - \theta' \right\}, \\ \text{(using Equation (36))} \\ &= \theta'D(t) \left\{ \frac{\beta' e^{-\mu\tau} S(t)}{\theta'(1+\sigma'S(t))} - 1 \right\}. \end{aligned} \quad (37)$$

$$\text{Define, } D^* = \frac{\mu}{\beta}(R_2 - 1) > 0, \text{ (since } R_2 > 1)$$

$$\Rightarrow D^* \rightarrow 0^+ \text{ as } \epsilon = (R_2 - 1) \rightarrow 0^+ \Rightarrow \frac{\beta' e^{-\mu\tau} \xi'}{\theta'(1+\sigma'\xi')} > 1,$$

$$\begin{aligned} \text{where } \xi' &= \frac{\Lambda(1-p)(1-e^{-(\beta D^* + \mu)T})}{(\beta D^* + \mu)\{1-(1-p)e^{-(\beta D^* + \mu)T}\}} - \epsilon > 0, \\ \beta &= \max\{\beta_1, \beta_2\}, \end{aligned} \quad (38)$$

for a sufficiently small  $\epsilon > 0$ .

If possible, let there exists a  $t_1 > 0$  such that  $D(t) < D^*, \forall t \geq t_1$ . It follows from the first and sixth equations of (4):

$$\begin{aligned} \frac{dS(t)}{dt} &> \Lambda - (\beta D^* + \mu)S(t), \quad \beta = \max\{\beta_1, \beta_2\}, \quad t \neq nT, \\ S(t^+) &= (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \quad (39)$$

Let us consider the following comparison impulsive differential system  $\forall t \geq t_1$ :

$$\begin{aligned} \frac{dz_3(t)}{dt} &= \Lambda - (\beta D^* + \mu)z_3(t), \quad t \neq nT, \\ z_3(t^+) &= (1-p)z_3(t), \quad t = nT, \quad n = 1, 2, \dots \end{aligned} \quad (40)$$

By Lemma 2.2, we know that the periodic solution of system (40) is

$$\begin{aligned} \tilde{z}_{3e}(t) &= \frac{\Lambda}{\beta D^* + \mu} + \left\{ z_3^* - \frac{\Lambda}{\beta D^* + \mu} \right\} e^{-(\beta D^* + \mu)(t-nT)}, \\ nT &< t \leq (n+1)T, \end{aligned}$$

$$\text{where } z_3^* = \frac{\Lambda(1-p)(1-e^{-(\beta D^* + \mu)T})}{(\beta D^* + \mu)\{1-(1-p)e^{-(\beta D^* + \mu)T}\}}, \quad (41)$$

which is globally asymptotically stable.

By the comparison theorem for impulsive differential equation (Lakshmikantham et al. 1989), there exists  $t_2 > t_1 + \tau$  such that the followings hold:

$$S(t) > \tilde{z}_{3e}(t) - \epsilon \Rightarrow S(t) > z_3^* - \epsilon = \xi', \quad \forall t \geq t_2. \quad (42)$$

$$\text{Next, let } D_1 = \min_{t \in [t_2, t_2 + \tau]} D(t) \Rightarrow D(t) \geq D_1, \quad \forall t \geq t_2. \quad (43)$$

Otherwise, there exists a  $T_0 > 0$  such that  $D(t) \geq D_1, \forall t \in [t_2, t_2 + \tau + T_0]$ , where  $D(t_2 + \tau + T_0) = D_1$  and  $D'(t_2 + \tau + T_0) \leq 0$ . However, from Equations (36), (38) and (42), we get

$$D'(t_2 + \tau + T_0) > \theta'D_1 \left\{ \frac{\beta' e^{-\mu\tau} \xi'}{\theta'(1+\sigma'\xi')} - 1 \right\} > 0. \quad (44)$$

So, we have got a contradiction and hence  $D(t) \geq D_1, \forall t \geq t_2$ . As a consequence of Equations (37), (38), (42)

and (43), we get

$$V'(t) > \theta' D_1 \left\{ \frac{\beta' e^{-\mu\tau} \xi'}{\theta'(1 + \sigma' \xi')} - 1 \right\} > 0,$$

$$\forall t \geq t_2 \Rightarrow V(t) \rightarrow \infty \text{ as } t \rightarrow \infty. \tag{45}$$

This is a contradiction because

$$V(t) = D(t) + \beta' e^{-\mu\tau} \int_{t-\tau}^t \frac{S(u)D(u)}{1 + \sigma' S(u)} du$$

$$\leq D(t) + \beta' e^{-\mu\tau} \int_{t-\tau}^t S(u)D(u) du$$

$$\leq \frac{\Lambda}{\mu} + \beta' e^{-\mu\tau} \int_{t-\tau}^t \left(\frac{\Lambda}{\mu}\right)^2 du = \frac{\Lambda}{\mu} \left\{ 1 + \frac{\Lambda\tau\beta' e^{-\mu\tau}}{\mu} \right\}. \tag{46}$$

Therefore, we conclude for any  $t_1 > 0$ , the inequality  $D(t) < D^*$  cannot hold for all  $t \geq t_1$ . Thus we are left to consider the following two cases:

- (i)  $D(t) \geq D^*$  for sufficiently large  $t$ ;
- (ii)  $D(t)$  oscillates about  $D^*$  for sufficiently large  $t$ .

It is clear that if  $D(t) \geq D^*$  for sufficiently large  $t$ , then our desired result is obtained. So, we only need to consider the case (ii). Let

$$m = \min \left\{ \frac{D^*}{2}, D^* e^{-\theta'\tau} \right\},$$

where  $\theta' = \max\{kr_1 + d_1 + \mu, r_2 + d_2 + \mu, r_3 + d_3 + \mu\}$ . (47)

Now, we will show that  $D(t) \geq m$  for sufficiently large  $t$ . Let  $t^* > 0$  and  $t_0 > 0$  satisfy  $D(t^*) = D(t^* + t_0) = D^*$  and  $D(t) < D^*$  for  $t^* < t < t^* + t_0$ , where  $t^*$  is sufficiently large such that  $S(t) > \xi'$  for  $t^* < t < t^* + t_0$ . It is clear that  $D(t)$  is uniformly continuous since the positive solution of Equation (4) is ultimately bounded and  $D(t) = (I_A(t) + I_S(t) + Q(t))$  is not affected by impulsive effects. Hence there exists a constants  $T_1$ , where  $0 < T_1 < \tau$  and  $T_1$  is independent of  $t^*$ , such that  $D(t) > D^*/2$  for  $t^* \leq t \leq t^* + T_1$ . If  $t_0 \leq T_1$ , the required result is obtained. If  $T_1 < t_0 \leq \tau$ , since  $D'(t) > -\theta'D(t)$  and  $D(t^*) = D^*$ , it follows that  $D(t) \geq D^* e^{-\theta't}$  for  $t^* < t < t^* + t_0$ . If  $t_0 > \tau$ ; we have  $D(t) \geq D^* e^{-\theta'\tau}$  for  $t^* < t < t^* + \tau$  and by using the same arguments we can obtain  $D(t) \geq D^* e^{-\theta'\tau}$  for  $t^* + \tau < t < t^* + t_0$  as the interval  $[t^*, t^* + t_0]$  can be chosen arbitrarily. So, we can conclude that  $D(t) \geq m$  for sufficiently large  $t$ . On the basis of the previous discussions, the choice of  $m$  is independent of the positive solution of (4) and hence any positive solution of (4) satisfies  $D(t) \geq m$  for  $t$  large enough. This completes the proof. ■

Table 1. Parameter values for Figure 1.

Parameter	Values
$\Lambda$	0.1
$\beta_1$	0.09
$\beta_2$	0.1
$\sigma_1$	0.3
$\sigma_2$	0.4
$\mu$	0.01
$\alpha$	0.2
$\rho$	0.4
$r_1$	0.4
$r_2$	0.2
$r_3$	0.3
$d_1$	0.2
$d_2$	0.15
$d_3$	0.05
$k$	0.1
$p$	0.8
$q$	0.1
$\tau$	1
$T$	5

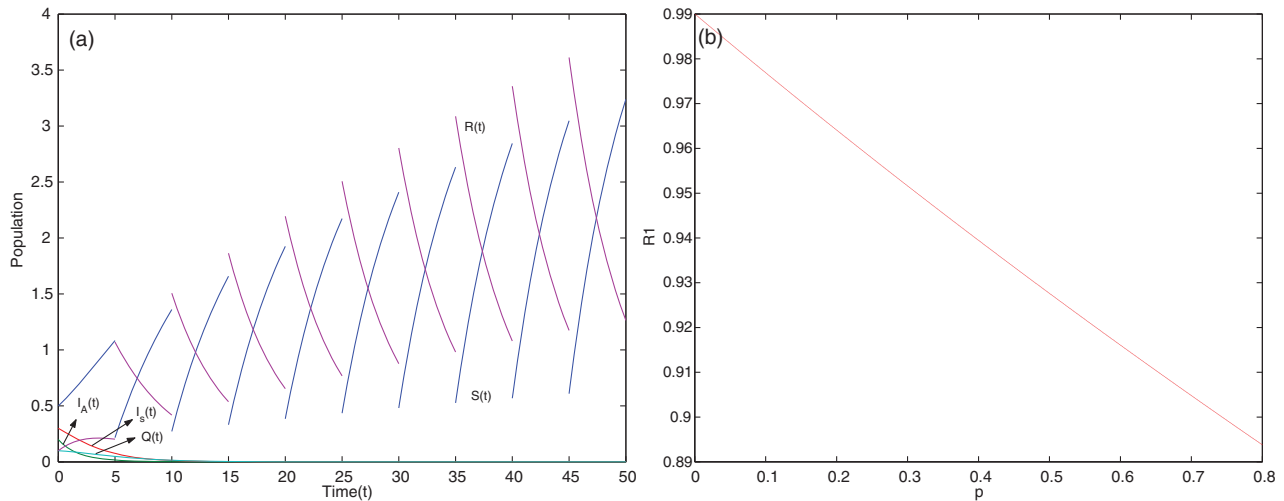


Figure 1. (a) Movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  for  $R_1 = 0.8938 < 1$ , (b) the effects of pulse vaccination ( $p$ ) on the threshold value  $R_1$ , with parameter values given in Table 1.

**THEOREM 4.2** *If  $R_2 > 1$ , then the system (4) with initial conditions (5) is permanent.*

*Proof* Suppose  $(S(t), I_A(t), I_S(t), Q(t), R(t), N(t))$  be any solution of system (4) with initial conditions (5). From the first and sixth equations of system (4), we have

$$\begin{aligned} \frac{dS(t)}{dt} &\geq \Lambda - \beta_1 S(t)I_A(t) - \beta_2 S(t)I_S(t) - \mu S(t) \\ &\geq \Lambda - \left(\frac{\beta\Lambda}{\mu} + \mu\right) S(t), \end{aligned} \quad (48)$$

$$\beta = \max\{\beta_1, \beta_2\} \text{ and } t \neq nT,$$

$$S(t^+) = (1-p)S(t), \quad t = nT, \quad n = 1, 2, \dots$$

Table 2. Parameter values for Figure 2.

Parameter	Values
$\Lambda$	0.1
$\beta_1$	0.8
$\beta_2$	0.9
$\sigma_1$	0.2
$\sigma_2$	0.3
$\mu$	0.01
$\alpha$	0.2
$\rho$	0.4
$r_1$	0.04
$r_2$	0.02
$r_3$	0.03
$d_1$	0.02
$d_2$	0.015
$d_3$	0.005
$k$	0.1
$p$	0.8
$q$	0.1
$\tau$	1
$T$	5

Let us consider the following comparison impulsive differential system:

$$\frac{dz_4(t)}{dt} = \Lambda - \left(\frac{\beta\Lambda}{\mu} + \mu\right) z_4(t), \quad t \neq nT, \quad (49)$$

$$z_4(t^+) = (1-p)z_4(t), \quad t = nT, \quad n = 1, 2, \dots$$

By Lemma 2.2, we know that the periodic solution of system (49) is

$$\begin{aligned} \tilde{z}_{4e}(t) &= \frac{\mu\Lambda}{\beta\Lambda + \mu^2} + \left\{ z_4^* - \frac{\mu\Lambda}{\beta\Lambda + \mu^2} \right\} \\ &\quad \times e^{-(\beta\Lambda/\mu + \mu)(t-nT)}, \\ nT < t &\leq (n+1)T, \end{aligned} \quad (50)$$

$$\text{where } z_4^* = \frac{\mu\Lambda(1-p)(1 - e^{-(\beta\Lambda/\mu + \mu)T})}{(\beta\Lambda + \mu^2)\{1 - (1-p)e^{-(\beta\Lambda/\mu + \mu)T}\}},$$

which is globally asymptotically stable.

By the comparison theorem for impulsive differential equation, there exists sufficiently small  $\epsilon_1 > 0$  such that the following holds:

$$\lim_{t \rightarrow \infty} S(t) \geq \frac{\mu\Lambda(1-p)(1 - e^{-(\beta\Lambda/\mu + \mu)T})}{(\beta\Lambda + \mu^2)\{1 - (1-p)e^{-(\beta\Lambda/\mu + \mu)T}\}} - \epsilon_1 > 0. \quad (51)$$

From the fifth equation of system (4) and using Theorem 4.1, we have

$$\begin{aligned} \frac{dR(t)}{dt} &\geq rm - (\mu + \alpha)R(t) \\ \Rightarrow \lim_{t \rightarrow \infty} R(t) &\geq \frac{rm}{\mu + \alpha} - \epsilon_2 > 0, \text{ where} \quad (52) \\ r &= \min\{kr_1, r_2, r_3\}, \end{aligned}$$

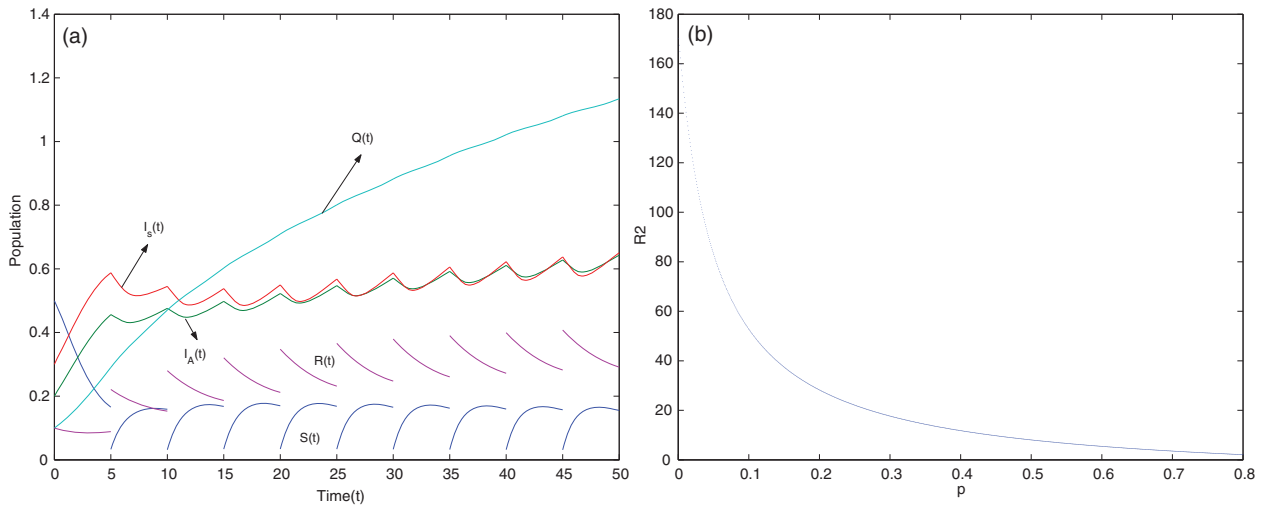


Figure 2. (a) Movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  for  $R_2 = 2.0840 > 1$ , (b) the effects of pulse vaccination ( $p$ ) on the threshold value  $R_2$ , with parameter values given in Table 2.

for a sufficiently small  $\epsilon_2 > 0$  ( $m$  is given by Equation (47)). Hence system (4) with initial conditions (5) is permanent and this completes the proof. ■

**5. Numerical simulations and biological interpretations**

We first consider the case when  $R_1 = 0.8938 < 1$  using the parameter values given in Table 1. Using these parameter values, the movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  are presented in Figure 1(a). This figure shows that the disease dies out when  $R_1 < 1$ , which supports our analytical result given in Theorem 3.1. Its epidemiological implication is that the infectious population vanishes, i.e. the disease dies out when  $R_1 < 1$  (see Figure 1(a)). In Figure 1(b), the effects of pulse vaccination ( $p$ ) on the threshold value  $R_1$

is presented using the parameter values given in Table 1. It shows that the threshold values  $R_1$  gradually decrease when the pulse vaccination rate ( $p$ ) increases. This implies that the strategy of pulse vaccination is very effective to eradicate the HFMD.

Next, we consider the case when  $R_2 = 2.0840 > 1$  using the parameter values given in Table 2. Using these parameter values, the movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  are presented in Figure 2(a). This figure shows that the disease will be permanent when  $R_2 > 1$ , which supports our analytical result given in Theorem 4.2. In Figure 2(b), the effects of pulse vaccination ( $p$ ) on the threshold value  $R_2$  is presented using the parameter values given in Table 2. It shows that the threshold values  $R_2$  gradually decrease when the pulse vaccination rate ( $p$ ) increases. This also implies that the strategy of pulse vaccination is very effective to eradicate the HFMD.

We also consider the case when  $R_1 = 4.3601 > 1$  and  $R_2 = 0.0679 < 1$  with parameter values given in Table 3. Using these parameter values, the movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  are presented in Figure 3(a). This figure shows that the disease dies out. For  $R_1 = 4.7029 > 1$  and  $R_2 = 0.9205 < 1$  where  $p = 0.2$  and other parameter values are given in Table 3, the movement paths of  $S(t), I_A(t), I_S(t), Q(t)$  and  $R(t)$  are presented in Figure 3(b). This figure shows that the disease is still permanent though the level of disease is very low.

From the figures it is observed that a large pulse vaccination rate will lead to eradication of the HFMD.

*Remark* When  $R_2 \leq 1 \leq R_1$ , the dynamical behavior of the HFMD model (4) and (5) has not been clear.

**6. Conclusions**

Motivated by the recent development of the first vaccine to protect children against enterovirus 71, or EV71 (Zhu

Table 3. Parameter values for Figure 3.

Parameter	Values
$\Lambda$	0.1
$\beta_1$	0.6
$\beta_2$	0.8
$\sigma_1$	0.3
$\sigma_2$	0.35
$\mu$	0.01
$\alpha$	0.2
$\rho$	0.4
$r_1$	0.4
$r_2$	0.2
$r_3$	0.3
$d_1$	0.6
$d_2$	0.4
$d_3$	0.1
$k$	0.1
$p$	0.8
$q$	0.1
$\tau$	1
$T$	5

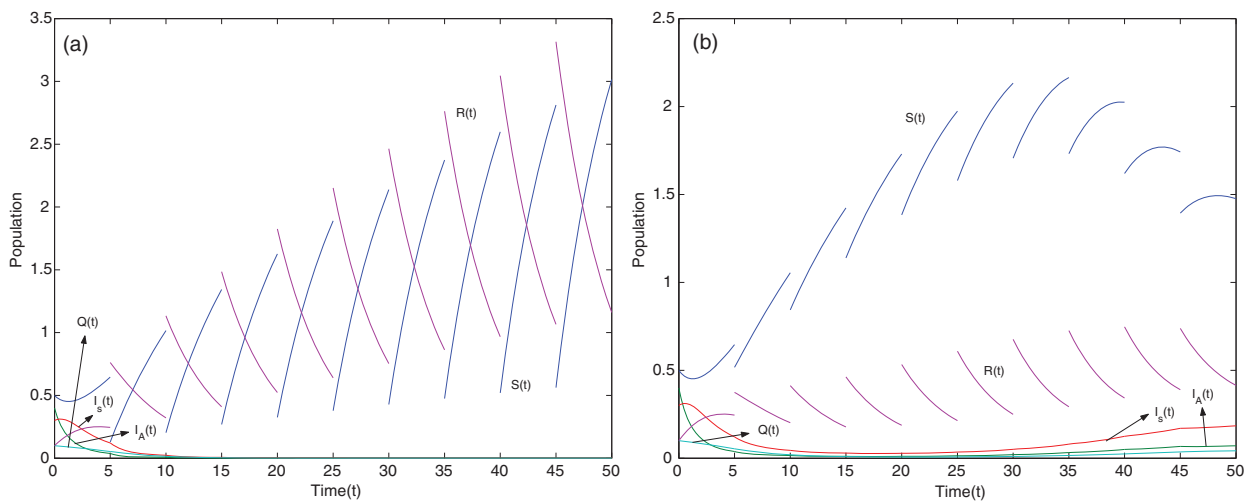


Figure 3. Movement paths of  $S(t), I_C(t), I(t)$  and  $R(t)$  (a) for  $R_1 = 4.3601 > 1$  and  $R_2 = 0.0679 < 1$  with parameter values given in Table 3, (b) for  $R_1 = 4.7029 > 1$  and  $R_2 = 0.9205 < 1$  where  $p = 0.2$  and other parameter values are given in Table 3.

et al., 2013), in this paper we have considered a dynamical model of HFMD with discrete time delay, pulse vaccination strategy and saturation incidence rate. The entire high-risk human population is split up into six mutually exclusive epidemiological compartments (based on disease status), namely, susceptible ( $S$ ), exposed (infected but not yet infectious) ( $E$ ), infective in asymptomatic phase (showing no symptoms of HFMD) ( $I_A$ ), infective in symptomatic phase (showing symptoms of HFMD) ( $I_S$ ), infective in symptomatic phase who follow quarantine (a strict isolation imposed to prevent the spread of the disease) mechanisms and personal protection against infecting others ( $Q$ ) and recovered (infectious people who have cleared (or recovered from) HFMD infection) ( $R$ ). The susceptible population increases through birth (a constant influx  $\Lambda$  of susceptible is assumed) and from recovered hosts and decreases due to direct contact with an infectious individual (in  $I_A$  or  $I_S$  compartments), natural death and PVS. The infected classes are increased by infection of susceptible. A fraction of the exposed individuals will start to show symptoms of HFMD (and move to the class  $I_S$ ), while the remaining fraction will not (but still remain capable of infecting others and move to the class  $I_A$ ). Also, a fraction of the infective in symptomatic phase takes appropriate preventive measures and move to the quarantined class  $Q$ . It is assumed that there is a time lag to account for the fact that an individual infected with HFMD is not infectious until after some time (typically 3–7 days Yang et al. 2013) after exposure. A fraction of the asymptotically infectious individuals eventually show disease symptoms and a fraction recover. The infected classes are decreased through recovery from infection, by disease-related death and by natural death. The most basic and important questions to ask for the systems in the theory of mathematical epidemiology are the persistence, extinctions, the existence of periodic solutions, global stability, etc. Here, we have established some sufficient conditions on the permanence and extinction of the disease by using inequality analytical technique. We have introduced two threshold values  $R_1$  and  $R_2$  and further obtained that the disease will be going to extinct when  $R_1 < 1$  and the disease will be permanent when  $R_2 > 1$ . The important mathematical findings for the dynamical behavior of the HFMD model are also numerically verified using MATLAB. It is observed that a large pulse vaccination rate will lead to eradication of the disease and when  $R_2 \leq 1 \leq R_1$ , the dynamical behavior is not clear. The aim of the analysis of this model is to trace the parameters of interest for further study, with a view to informing and assisting policy-maker in targeting prevention and treatment resources for maximum effectiveness.

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