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Modelling seasonal HFMD infections with the effects of contaminated environments in mainland China

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ABSTRACT

Hand-foot-mouth disease (HFMD) has spread widely in mainland China and exhibited an increasing trend in prevalence in recent years with serious consequences for child health. The HFMD virus can survive for a long period outside the host in suitable conditions, and hence indirect transmission via free-living virus in the environment can not be ignored. We then propose a novel mathematical model to represent both direct transmission and indirect transmission, and also periodic transmission and vaccination rates. We obtain a threshold value, the basic reproduction number which governs whether nor not HFMD infection dies out by applying the persistence theory of periodic systems. Theoretical results indicate that the disease goes to extinction if the basic reproduction number is less than unity and otherwise the disease uniformly persists. By fitting the proposed model to reported data on symptomatic cases of endemic HFMD in mainland China we estimate the basic reproduction number as 1.74. Numerical simulations show that the asymptotic infected individuals and contaminated environments are essential factors substantially contributing to HFMD new infections, and hence they should not be ignored. Sensitivity analysis indicates that the basic reproduction number is sensitive to the transmission rate induced by asymptomatic infectious individuals, vaccination rate and parameters associated with contaminated environments such as the indirect transmission rate and the rate of clearance. Our finding suggests that enhancing vaccination strategy and the frequent cleaning of the environment and enhancing individual sanitation (e.g. regular hand-washing) are effective measures in controlling HFMD infections.

1. Introduction

Hand, foot and mouth disease (HFMD) is a contagious viral illness that commonly affects infants and children. HFMD is caused by enteroviruses of the family Picornaviridae. It is mainly caused by Coxsackie virus (A16), human enterovirus (EV71) or other enteroviruses including Coxsackie viruses A4, 5, 9, 10, B2 and 5 [21]. Recent outbreaks of HFMD in many areas such as Taiwan [25], Japan [11], Malaysia [8] and China [30] were caused by Enterovirus 71 (EV71) which induces a variety of neurological diseases including aseptic meningitis, encephalitis, and poliomyelitis-like paralysis [16]. Enterovirus 71 (EV71) is a major cause of HFMD in children and may be fatal. The HFMD data from the Chinese Center for Disease Control and Prevention (CDC) [4] show that this disease outbreaks every year in mainland China. Recently, the EV71 vaccine [7,18] was successfully developed and shown to

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consistently elicit immunogenicity and provide protection against mild-to-severe disease caused by EV71 for at least 1 year in infants and young children [33]. The vaccine efficacy against EV71-associated HFMD was 97.4% [17].

HFMD spreads mainly amongst children under five-years old but may also be transmitted among adults [4]. Children are more susceptible to infection than adults, because they are less likely to have appropriate antibodies and awareness of self protection than adults. Susceptible infants are usually infected by close contact with infected individuals. Note that the virus of EV71 can survive for a long period outside the host in suitable conditions [3,9,15] and even 75% alcohol can not eliminate the virus. HFMD patients and asymptomatic recessive individuals, releasing virus to the environment, are the major infectious sources, and there is also some evidence that susceptible individuals can be infected via touching free-living viruses in the environment. Hence the transmission routes of EV71 are believed to be multiple, i.e. via the respiratory tract through inhaling infectious droplets by close contacts with infectious crowds, touching virus-carrying hands, towels, handkerchiefs, toys, bedding and underclothes, and via the gastrointestinal tract through contaminated water and food [14].

A number of mathematic models have been formulated to investigate the transmission dynamics and predict HFMD infections. For example [10] proposed a simple SIR model to estimate the number of infections, [19] formulated a more realistic model in which the infectious individuals are classified into two compartments: infected and asymptomatic recessive, to investigate the seasonal spread of HFMD in Shandong Province, [29] analyzed the transmission dynamics with the aim of determining better control strategies through sensitivity analysis. However, the existing mathematical models only considered direct transmission between susceptible and infected individuals. How indirect transmission via free-living viruses in the environment affects HFMD infection remains unclear and hence falls within the scope of this study.

Note that the reported monthly data from China CDC [6] exhibit the periodic pattern of HFMD infection. The seasonal pattern may attribute to the following facts: (i) The warm climate contributes to the reproduction of the virus and the prevalence of the disease in the summer. In fact, it is reported that HFMD cases increase sharply when the average temperature is more than a threshold value of 19°C [24]. (ii) During term time children usually play and study together at kindergarden/school and hence more close contacts are observed [19]. One purpose of this study is to identify the key processes or parameters which influence periodic transmission dynamics.

Our main purpose of this study is to extend the existing mathematical models by including indirect transmission via free living viruses in the environment and periodic transmission rate and vaccination rate. Our model also considers the subgroup of recessive infected individuals to investigate the impact of asymptomatic individuals and contaminated environments on HFMD transmission. A combination of analytical and numerical techniques is used to analyze the proposed model and concentrate on HFMD case data from 2010 to 2014. This paper is organized as follows. In the next section, we establish an HFMD model and investigate the threshold dynamics of the system. In particular, we examine the threshold value, and study the global stability of the disease-free periodic solution and the uniform persistence of the system. In Section 3 we describe simulations of the model and give some disease control strategic. We conclude in the final section with conclusions and discussions.

2. Model

In this paper, we extend the classic transmission model by including indirect transmission via free-living viruses [1,28]. Our model involves direct transmission between susceptible and infected individuals (including symptomatic and asymptomatic) and indirect transmission by touching the contaminated environments. An epidemic model is proposed to reflect some key epidemiological properties of HFMD epidemics and public health interventions such as isolation, hygienic precautions and vaccination. The underlying structure of the model comprises classes of individuals that are susceptible ($S(t)$), exposed but not yet infectious ($E(t)$), infectious but not yet symptomatic (pre-symptomatic) ($I_e(t)$), infectious with symptoms ($I(t)$), and recovered ($R(t)$). Let $W(t)$ be the density of pathogen in the contaminated environments including door handles, towels, handkerchiefs, toys, utensils, bedding, underclothes, etc. at time t. A susceptible individual may be infected by contacting infected individuals (asymptomatic or symptomatic) with rate of $\beta_i(t)$ or touching contaminated environments with rate of $\nu(t)$ and then moves to the exposed compartment. Transmission rates $\beta_i(t)(i = 1, 2)$ and $\nu(t)$ are assumed to be continuous and non-negative periodic functions with period of ω. An individual passing through this latent period will become infectious (with different infectiousness), either asymptomatically or symptomatically, until recovery or death. A flow diagram describing the model is given in Fig. 1 and the model equations are

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta_1(t)SI - \beta_2(t)SI_e - \nu(t)SW - \alpha(t)S - dS + \eta R, \\ \frac{dE}{dt} = \beta_1(t)SI + \beta_2(t)SI_e + \nu(t)SW - (\sigma + d)E, \\ \frac{dI}{dt} = \sigma pE - (\gamma_1 + \delta_1 + d)I, \\ \frac{dI_e}{dt} = \sigma(1 - p)E - (\gamma_2 + \delta_2 + d)I_e, \\ \frac{dR}{dt} = \gamma_1 I + \gamma_2 I_e + \alpha(t)S - (\eta + d)R, \\ \frac{dW}{dt} = \lambda_1 I + \lambda_2 I_e - \mu W - \nu(t)(S + E + I + I_e + R)W. \end{cases} \tag{1}$$

Note that free-living viruses in the environment, although capable of living for weeks or months, cannot reproduce by themselves without suitable conditions. Here, let λ_1 and λ_2 be rates at which symptomatic and asymptomatic infected individuals shed

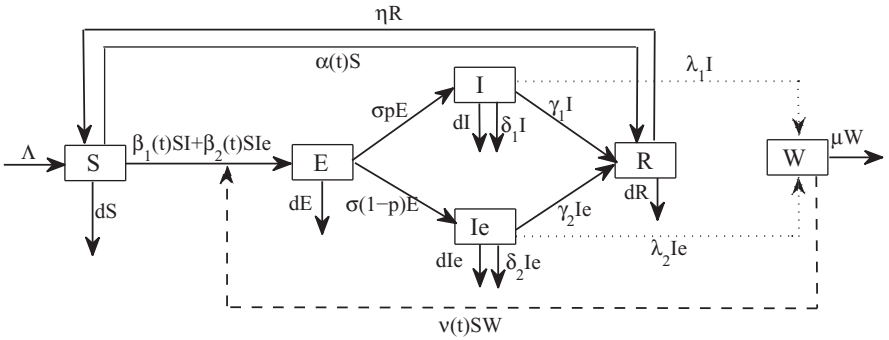

Fig. 1. Flow diagram representing transmission routes and other processes modeled by system (1).

Table 1
Definitions of the parameters used in the model.

Para.	Definition(Units)	Value	References
Λ	Recruitment rate (/month)	1328556	[22]
d	Natural death rate (/month)	1.126×10^{-3}	[22]
p	Proportion of HFMD symptomatic infected individuals	0.025	Fitting
η	The rate from recovered to susceptible (/month)	0.115	Fitting
$\beta_1(t)$	Periodic transmission rate between $S(t)$ and $I(t)$	$a_1(1+\sin(\frac{2\pi t}{12}+\phi))$	[19]
$\beta_2(t)$	Periodic transmission rate between $S(t)$ and $I_e(t)$	$a_2(1+\sin(\frac{2\pi t}{12}+\phi))$	[19]
$\nu(t)$	Periodic indirect transmission rate	$a_3(1+\sin(\frac{2\pi t}{24}+\phi))$	Assumed
$\alpha(t)$	Periodic vaccination rate	$\alpha(1+\sin(\frac{2\pi t}{12}+\phi))$	Assumed
$1/\sigma$	The average incubation period (month)	1/6	[19]
γ_1	The recovery rate of the symptomatic infected individuals (/month)	0.1922	[10]
γ_2	The recovery rate of the asymptomatic infected individuals (/month)	0.1922	[10]
δ_1	Disease-related death for symptomatic HFMD individuals (/month)	6.86×10^{-4}	[19]
δ_2	Disease-related death for asymptomatic HFMD individuals (/month)	6.85×10^{-4}	[19]
λ_1	The virus shedding rate from symptomatic infected individuals (/month)	9.38×10^{2}	Fitting
λ_2	The virus shedding rate from asymptomatic infected individuals (/month)	7.89×10^{2}	Fitting
μ	The clearance rate of the pathogens (/month)	27	Fitting
a_1	The coefficient of transmission rate between $S(t)$ and $I(t)$ (none)	1.5×5^{-8}	Fitting
a_2	The coefficient of transmission rate between $S(t)$ and $I_e(t)$ (none)	2.25×10^{-9}	Fitting
a_3	The coefficient of indirect transmission rate (none)	1.8×10^{-11}	Fitting
α	The coefficient associated with coverage of vaccination	varied	–

viruses, respectively. Free-living viruses are cleared at a rate of μ due to sterilization, and also picked up by all individuals, which induces indirect transmission at a rate of $\nu(t)$. $\alpha(t)$ is the vaccination rate of all susceptible in the population and is assumed to be a continuous, non-negative periodic function with periodic ω. The other parameters are defined in Table 1. Note that for model (1), the maximum of the $\nu(t)$ is far less than the clearance rate μ, then the loss of viruses due to being taken up by individuals is much less than the loss due to clearance. Hence we can simplify the sixth equation by not considering the term $\nu(t)(S+V+E+I+I_e+R)W$ in the following study.

It is obvious that any solution of system (1) with non-negative initial values is non-negative. The following lemma shows that the solutions of system (1) are uniformly ultimately bounded.

Lemma 2.1. *The solutions of system (1) are uniformly and ultimately bounded, i.e., there exist an $M > 0$ and $T > 0$ such that $(S(t), E(t), I(t), I_e(t), R(t), W(t)) \le (\frac{\Lambda}{d}, \frac{\Lambda}{d}, \frac{\Lambda}{d}, \frac{\Lambda}{d}, \frac{\Lambda}{d}, M)$, for $t \ge T$.*

Proof. It is easy to get that $\mathbb{R}^6_+$ is an invariant set for system (1), that is, any solution initiating from $\mathbb{R}^6_+$ remains into it. Let the population size be $N(t) = S(t) + E(t) + I(t) + I_e(t) + R(t)$. Then from the system (1), we have $N'(t) = \Lambda - dN - \delta_1 I - \delta_2 I_e \le \Lambda - dN$. It follows from the comparison theorem that there exists $t_1 > 0$ such that $N(t) \le \Lambda/d$ for $t \ge t_1$, then which implies $S(t) \le \Lambda/d$, $E(t) \le \Lambda/d$, $I(t) \le \Lambda/d$, $I_e(t) \le \Lambda/d$, $R(t) \le \Lambda/d$ for $t \ge t_1$.

By the last equation of model (1), we can get

$$\frac{dW}{dt} \le (\lambda_1 + \lambda_2)\frac{\Lambda}{d} - \mu W$$

for $t \ge t_1$. This implies that there exists $T > t_1$ such that $W(t) \le \frac{(\lambda_1+\lambda_2)\Lambda}{d\mu} \doteq M$ for $t \ge T$. Then solutions of system (1) are uniformly ultimately bounded. This completes the proof. □

Let $(\mathbb{R}^n, \mathbb{R}^n_+)$ be the standard ordered n-dimensional Euclidean space with a norm $\|.\|$. For $u, v \in \mathbb{R}^n$, we denote $u \ge v$, if $u - v \in \mathbb{R}^n_+$; $u > v$, if $u - v \in \mathbb{R}^n_+ \setminus \{0\}$; and $u \gg v$, if $u - v \in \mathrm{Int}(\mathbb{R}^n_+)$. Consider $A(t)$ to be a continuous, cooperative, irreducible

and periodic $n \times n$ matrix function with period ω, $\omega > 0$. Let $\Phi_{A(.)}(t)$ be the fundamental solution matrix of the linear ordinary differential equation $\dot{x} = A(t)x$. Let $r(\Phi_{A(.)}(\omega))$ be the spectral radius of $\Phi_{A(.)}(\omega)$. By the Perron–Frobenius theorem, $r(\Phi_{A(.)}(\omega))$ is the principal eigenvalue of $\Phi_{A(.)}(\omega)$, in the sense that it is simple and admits an eigenvector $v^* \gg 0$. We introduce a beneficial result for our next arguments from paper [31].

Lemma 2.2. *Let $\theta = \frac{1}{\omega}\ln r(\Phi_{A(.)}(\omega))$. Then there exists a positive, ω−periodic function $v(t)$ such that $e^{\theta t}v(t)$ is a solution of $\dot{x} = A(t)x$.*

It is easy to see that when disease dies out, we can get the following system from model (1).

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - \alpha(t)S - dS + \eta R, \\ \dfrac{dR}{dt} = \alpha(t)S - (\eta + d)R, \end{cases} \tag{2}$$

which is equivalent to

$$\frac{du}{dt} = A(t)u + f(t)$$

where vector $u = (S, R)^T$ and $A(t) = \begin{pmatrix} -(\alpha(t)+d) & \eta \\ \alpha(t) & -(\eta+d) \end{pmatrix}$, $f(t) = (\Lambda, 0)^T$.

Lemma 2.3. *System (2) with initial condition $(S(0), R(0)) \in \{(S, R)\colon 0 \le S \le \Lambda/d,\ 0 \le R \le \Lambda/d\}$ has a unique positive ω−periodic solution $\hat{u}(t) = (\hat{S}(t), \hat{R}(t))$, which is globally asymptotically stable.*

Proof. Note that the matrix $A(t)$ has nonnegative off-diagonal entries and it is irreducible. Let $\Psi(t)$ be the fundamental matrix of homogeneous linear periodic system $\frac{du}{dt} = A(t)u$, which satisfies $\frac{d\Psi(t)}{dt} = A(t)\Psi(t)$ and $\Psi(0) = I$. Then the ω-periodic fundamental matrix $\Psi(\omega)$ is a strongly positive operator [12]. By using the $\omega-$ periodic fundamental matrix $\Psi(\omega)$ in the proof of Theorem 1 in [2], the homogeneous linear periodic system $\frac{du}{dt} = A(t)u$ has a positive ω−periodic solution $\bar{u}(t)$, which is globally asymptotically stable with respect to all nonzero solutions.

By using the constant variation formula of nonhomogeneous linear system, we can obtain the solution of system (2),

$$\hat{u}(t) = \Psi(t)\hat{u}_0 + \Psi(t)\int_0^t \Psi^{-1}(s)f(s)ds$$

where $\hat{u}_0 \in \{(S, R) : 0 \le S \le \frac{\Lambda}{d}, 0 \le R \le \frac{\Lambda}{d}\}$. $f(t) = (\Lambda, 0)^T$ is nonnegative constant vector function, it is easy to see that $\hat{u}(t)$ is a ω−periodic solution of system (2), which is globally asymptotically stable.

According to the result from [26], we can define the basic reproduction ratio of system (1). Linearizing system (1) at $E_0(\hat{S}(t), 0, 0, 0, \hat{R}(t), 0)$, we obtain the following four-dimensional equations:

$$\begin{cases} \dfrac{dE}{dt} = \beta_1(t)\hat{S}(t)I + \beta_2(t)\hat{S}(t)I_e + \nu(t)\hat{S}(t)W - (\sigma + d)E, \\ \dfrac{dI}{dt} = \sigma pE - (\gamma_1 + \delta_1 + d)I, \\ \dfrac{dI_e}{dt} = \sigma(1-p)E - (\gamma_2 + \delta_2 + d)I_e, \\ \dfrac{dW}{dt} = \lambda_1 I + \lambda_2 I_e - \mu W. \end{cases} \tag{3}$$

Let

$$F(t) = \begin{pmatrix} 0 & \beta_1(t)\hat{S}(t) & \beta_2(t)\hat{S}(t) & \nu(t)\hat{S}(t) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad V(t) = \begin{pmatrix} \sigma + d & 0 & 0 & 0 \\ -\sigma p & \gamma_1 + \delta_1 + d & 0 & 0 \\ -\sigma(1-p) & 0 & \gamma_2 + \delta_2 + d & 0 \\ 0 & -\lambda_1 & -\lambda_2 & \mu \end{pmatrix}.$$

Then the system (3) can be written as

$$\frac{dx}{dt} = (F(t) - V(t))x,$$

where $x = (E, I, I_e, W)^T$.

Assume that $Y(t, s)$, $t \ge s$, is the evolution operator of the linear periodic system

$$\frac{dy}{dt} = -V(t)y.$$

That is, for each $s \in \mathbb{R}$, the 4×4 matrix $Y(t, s)$, satisfies

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s), \quad \forall t \ge s, \quad Y(s,s) = \mathbf{I}$$

where $\mathbf{I}$ is the 4×4 identity matrix. Let C_ω be the ordered Banach space of all $\omega-$periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. Suppose $\phi(s) \in C_\omega$ is the initial distribution of infectious individuals in this periodic environment; then $F(s)\phi(s)$ is the distribution of new infections produced by the infected individuals who were introduced at time s, and $Y(t,s)F(s)\phi(s)$ represents the distribution of those infected individuals who were newly infected at time s and remain in the infected compartments at time t for $t \geq s$. Hence,

$$\psi(t) := \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced before t.

We define the linear operator $L: C_\omega \to C_\omega$ as follows:

$$(L\phi)(t) = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da, \forall t \in \mathbb{R}, \phi \in C_\omega.$$

Then the basic reproduction ratio of the periodic epidemic model (1) is defined as $R_0 := r(L)$, the spectral radius of L.

Let $W(t,\lambda)$ be the monodromy matrix of the following linear $\omega-$periodic system:

$$\frac{dw}{dt} = \left(-V(t) + \frac{F(t)}{\lambda}\right)w, t \in \mathbb{R},$$

with parameter $\lambda \in (0,\infty)$. Since $F(t)$ is nonnegative and $-V(t)$ is cooperative, it follows that $r(W(\omega,\lambda))$ is continuous and nonincreasing for $\lambda \in (0,\infty)$, and $\lim_{\lambda \to \infty} r(W(\omega,\lambda)) < 1$. It is easy to verify that (1) satisfies assumptions A(1)–A(7) in [26]. Thus, we have the following result. □

Lemma 2.4 (See Theorem 2.1 [26]). *The following statements are valid:*

(i) *If $r(W(\omega,\lambda) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of L, and hence $R_0 > 0$.*
(ii) *If $R_0 > 0$, then $\lambda = R_0$ is the unique solution of $r(W(\omega,\lambda)) = 1$.*
(iii) *$R_0 = 0$ if and only if $r(W(\omega,\lambda)) < 1$ for all $\lambda > 0$.*

Theorem 2.1. *If $r(\Phi_{F-V}(\omega)) < 1$, then the disease-free $\omega-$periodic solution of system (1), i.e., $E_1(\hat{S}(t),0,0,0,\hat{R}(t),0)$ is globally asymptotically stable and if $r(\Phi_{F-V}(\omega)) > 1$, then it is unstable.*

Proof. Firstly, we illustrate the disease-free $\omega-$periodic solution E_1 is locally stable. By Theorem 2.2 in [26], if $R_0 < 1$ then $E_0(\hat{S}(t),0,0,0,\hat{R}(t),0)$ is locally stable; if $R_0 > 1$ then $E_1(\hat{S}(t),0,0,0,\hat{R}(t),0)$ is unstable. Hence, it is sufficient to prove that $E_0(\hat{S}(t),0,0,0,\hat{R}(t),0)$ is globally attractive for $R_0 < 1$.

We now prove the global attractivity of the disease-free $\omega-$periodic solution E_1. By the first equation of system (1) and nonnegativity of the solutions, we get $\frac{dS}{dt} \leq \Lambda - \alpha(t)S - dS + \eta R$. Then $\forall \epsilon > 0$, there exists $T' > 0$ such that $S(t) \leq \hat{S}(t) + \epsilon$ for $t \geq T'$.

Consider an auxiliary system

$$\begin{cases} \dfrac{du_1}{dt} = \beta_1(t)(\hat{S}(t)+\epsilon)u_2 + \beta_2(t)(\hat{S}(t)+\epsilon)u_3 + \nu(t)(\hat{S}(t)+\epsilon)u_4 - (\sigma+d)u_1, \\ \dfrac{du_2}{dt} = \sigma p u_1 - (\gamma_1+\delta_1+d)u_2, \\ \dfrac{du_3}{dt} = \sigma(1-p)u_1 - (\gamma_2+\delta_2+d)u_3, \\ \dfrac{du_4}{dt} = \lambda_1 u_2 + \lambda_2 u_3 - \mu u_4, \end{cases} \tag{4}$$

which is equivalent to

$$u' = (F(t) - V(t))u + \epsilon M(t)u$$

where vector $u = (u_1,u_2,u_3,u_4)^T$ and

$$M(t) = \begin{pmatrix} 0 & \beta_1(t) & \beta_2(t) & \nu(t) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

It follow from Lemma 2.2 that there exists a positive ω-periodic function $v(t) = \left(v_1(t), v_2(t), v_3(t), v_4(t)\right)$ such that $e^{\mu_1 t}v(t)$ is a solution of (4), where $\mu_1 = \frac{1}{\omega}\ln r(\Phi_{F-V+\epsilon M}(\omega))$. Choose $T > T'$ and a small number $\alpha > 0$ such that $u(T) \leq \alpha v(0)$. Then we get $u(t) \leq \alpha v(t-T)e^{\mu_1(t-T)}$ for $t \geq T$. By the standard comparison theorem [23], Theorem B.1, we get $(E(t),I(t),I_e(t),W(t))^T \leq u(t) \leq \alpha v(t-T)e^{\mu_1(t-T)}$ for $t \geq T$.

Since $r(\Phi_{F-V}(\omega)) < 1$ and $r(\Phi_{F-V+\epsilon M}(\omega))$ is continuous for all small ϵ, we can choose $\epsilon > 0$ small enough such that $r(\Phi_{F-V+\epsilon M}(\omega)) < 1$. Hence, we get $\mu_1 < 0$. It follows that $u(t) \to 0$ as $t \to \infty$. Then we get $(E(t), I(t), I_e(t), W(t))^T \to 0$ as

$t \to \infty$. By the first and fifth equation of system (1), we get $\lim_{t\to\infty} S(t) = \hat{S}(t)$ and $\lim_{t\to\infty} R(t) = \hat{R}(t)$. This indicates that the disease-free steady state E_1 is globally attractive.

By the local stability and global attractivity of E_1, we get that the disease-free $\omega-$periodic solution of system (1), E_1, is globally asymptotically stable if $r(\Phi_{F-V}(\omega)) < 1$. This completes the proof. □

Let X be a metric space, f: $X \to X$ be a continuous map, and $X_0 \subset X$ be an open set. Define

$$\partial X_0 := X \setminus X_0, \quad M_\partial := \{x \in \partial X_0 : f^n(x) \in \partial X_0, n \geq 0\}.$$

A_∂ is a maximal compact invariant set of f in ∂X_0. A finite sequence $M_1, \ldots, M_k$ are disjoint, compact and invariant subsets of ∂X_0, and each of them is isolated in ∂X_0. For the convenience of description, we present the following persistence theory in [32].

Lemma 2.5. *Assume that*

(C1) $f(X_0) \subset X_0$ and f has a global attractor A;

(C2) The maximal compact invariant set $A_\partial = A \cap M_\partial$ of f in ∂X_0, possibly empty, admits a Morse decomposition $\{M_1, \ldots, M_k\}$ with the following properties: (a) M_i is isolated in X. (b) $W^s(M_i) \cap X_0 = \varnothing$ for each $i \leq l \leq k$.
Then there exists $\delta > 0$ such that for any compact internally chain transitive set L with $L \nsubseteq M_i$ for all $1 \leq i \leq k$, we have $\in f_{x\in L} d(x, \partial X_0) > \delta$, that is to say f: $X \to X$ is uniformly persistent with respect to $(X_0, \partial X_0)$.

Theorem 2.2. *If $r(\Phi_{M_1(.)}(\omega)) > 1$, then system (1) has at least one positive periodic solution.*

Proof. We fist prove that system (1) is uniformly persistent, i.e., there exists a positive constant ε such that, for all initial values $(S^0, E^0, I^0, I_e^0, R^0, W^0) \in \mathbb{R}^2_+ \times \mathrm{Int}(\mathbb{R}^4_+)$, the solution of system (1) satisfies

$$\liminf_{t\to\infty} (S(t), E(t), I(t), I_e(t), R(t), W(t)) \geq (\varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon).$$

Define $X := \{(S, E, I, I_e, R, W)$: $S \geq 0, E \geq 0, I \geq 0, I_e \geq 0, R \geq 0, W \geq 0\}$, $X_0 := \{(S, E, I, I_e, R, W) \in X$: $E > 0, I > 0, I_e > 0, W > 0\}$, $\partial X_0 = X \setminus X_0$.

Define the Poincaré map $P : \mathbb{R}^6_+ \to \mathbb{R}^6_+$, by satisfying $P(x^0) = u(\omega, x_0)$, $\forall x_0 \in \mathbb{R}^6_+$, where $u(t, x_0)$ is the unique solution of (1) satisfying $u(0, x^0) = x^0$.

Firstly, we show that P is uniformly persistent with respect to $(X_0, \partial X_0)$. It is easy to see from system (1) that X and X_0 are positively invariant. Moreover, ∂X_0 is a relatively closed set in X. It follows from Lemma 2.1 that solutions of (1) are uniformly and ultimately bounded. Thus the semiflow P is point dissipative on $\mathbb{R}^6_+$ and $P : \mathbb{R}^6_+ \to \mathbb{R}^6_+$ is compact. By Theorem 3.4.8 in [13] P admits a global attractor, which attracts every bounded set in $\mathbb{R}^6_+$. Define

$$M_\partial := \{(S^0, E^0, I^0, I_e^0, R^0, W^0) \in \partial X_0 : P^m(S^0, E^0, I^0, I_e^0, R^0, W^0) \in \partial X_0, m \geq 0\}.$$

Next, we claim that $M_\partial = \{(S, 0, 0, 0, R, 0) \in X, S \geq 0, R \geq 0\}$.

Note that $\{(S, 0, 0, 0, R, 0) \in X, S \geq 0, R \geq 0\} \subseteq M_\partial$, we only need to prove that $M_\partial \subseteq \{(S, 0, 0, 0, R, 0) \in X, S \geq 0, R \geq 0\}$

That is for any $\varphi_0 = (S^0, E^0, I^0, I_e^0, R^0, W^0) \in M_\partial$, we suppose that one of E^0, I^0, I_e^0, W^0 is not zero, without loss of generality, we suppose that $E^0 = 0, I^0 = 0, I_e^0 = 0, W^0 > 0$, from the equation we have

$$E(t) = e^{-(\sigma+d)t}\left[E^0 + \int_0^t (\beta_1(s_1)I(s_1) + \beta_2(s_1)I_e(s_1) + \nu(s_1)W(s_1))S(s_1)e^{(\sigma+d)s_1}ds_1\right] > 0, \forall t \geq 0.$$

$$I(t) = e^{-(\gamma_1+\delta_1+d)t}\left[I^0 + \int_0^t \sigma pE(s_1)e^{(\gamma_1+\delta_1+d)s_1}ds_1\right] > 0, \forall t \geq 0.$$

$$I_e(t) = e^{-(\gamma_2+\delta_2+d)t}\left[I_e^0 + \int_0^t \sigma(1-p)E(s_1)e^{(\gamma_2+\delta_2+d)s_1}ds_1\right] > 0, \forall t \geq 0.$$

$$W(t) = e^{-\mu t}\left[W^0 + \int_0^t (\lambda_1 I(s_1) + \lambda_2 I_e(s_1))e^{\mu s_1}ds_1\right] > 0, \forall t \geq 0.$$

For any $\varphi_0 = (S^0, E^0, I^0, I_e^0, R^0, W^0) \notin \{(S, 0, 0, 0, R, 0) \in X : S \geq 0, R \geq 0\}$, we have $(S(t), E(t), I(t), I_e(t), R(t), W(t)) \notin \partial X_0$ for $t > 0$ sufficiently small. Other cases can be proved in the same way. That is to say if $\varphi_0 \notin \{(S, 0, 0, 0, R, 0) \in X$: $S \geq 0, R \geq 0\}$ then $\varphi_0 \notin M_\partial$, which contradicts with $\varphi_0 \notin M_\partial$. So $M_\partial \subseteq \{(S, 0, 0, 0, R, 0) \in X$: $S \geq 0, R \geq 0\}$, therefore $M_\partial = \{(S, 0, 0, 0, R, 0) \in X : S \geq 0, R \geq 0\}$.

Clearly, E_1 is one fixed point of P in M_∂. If (S, E, I, I_e, R, W) is a solution of system (1) initiating from M_∂, then it follows from system (1) that $S(t) \to \hat{S}(t), E(t) \to 0, I(t) \to 0, I_e(t) \to 0, R(t) \to \hat{R}(t), W(t) \to 0$ as $t \to \infty$.

In the following we shall that if the invariant set E_1 is isolated, then $\{E_1\}$ is an acyclic covering. To do this, it needs to prove any solution of system (1) initiating from M_∂ will remain in M_∂, which can be obtained easily. In the following we will proof the isolated invariance of E_1 .

We now show that $W^s(E_1) \cap X_0 = \phi$. Denote $x^0 = (S^0, E^0, I^0, I_e^0, R^0, W^0) \in X_0$. By the continuity of solutions with respect to the initial values, $\forall \varepsilon > 0$ there exists $\delta_0 > 0$ such that for all $x^0 \in X_0$ with $\|x^0 - E_1\| \leq \delta_0$, we have

$$\|u(t, x^0) - u(t, E_1)\| \leq \varepsilon, \quad \forall t \in [0, \omega].$$

We now claim that

$$\limsup_{m\to\infty} d(P^m(x^0), E_1) \geq \delta_0.$$

Suppose not, then

$$\limsup_{m\to\infty} d(P^m(x^0), E_1) < \delta_0.$$

for some $x^0 \in X_0$. Without loss of generality, we can assume that $d(P^m(x^0), E_1) < \delta_0$, $\forall m > 0$. Then we have

$$\|u(t, P^m(x^0)), u(t, E_1)\| < \varepsilon, \ \forall t \in [0, \omega]$$

For any $t \geq 0$, let $t = m\omega + t'$, where $t' \in [0, \omega]$ and $m = [\frac{t}{\omega}]$ is the greatest integer less than or equal to $\frac{t}{\omega}$. Thus we get

$$\|u(t, x^0) - u(t, E_1)\| = \|u(t', P^m(x^0)) - u(t', E_1)\| < \varepsilon, \ \forall t \geq 0.$$

Let $\big(S(t), E(t), I(t), I_e(t), R(t), W(t)\big) = u(t, x^0)$. It follows that there exists $T' > 0$ such that $\hat{S}(t) - \varepsilon \leq S(t) \leq \hat{S}(t) + \varepsilon$, $0 \leq E(t) \leq \varepsilon$, $0 \leq I(t) \leq \varepsilon$, $0 \leq I_e(t) \leq \varepsilon$, $\hat{R}(t) - \varepsilon \leq R(t) \leq \hat{R}(t) + \varepsilon$, $0 \leq W(t) \leq \varepsilon$ for $t > T'$. Then consider the following auxiliary system

$$\frac{du}{dt} = (F(t) - V(t))u - \varepsilon M(t)u. \tag{5}$$

It follow from Lemma 2.2 that there exists a positive ω-periodic function $p(t) = \big(p_1(t), p_2(t), p_3(t), p_4(t)\big)$ such that $e^{\mu_2 t}p(t)$ is a solution of (5), where $\mu_2 = \frac{1}{\omega}\ln r(\Phi_{F-V-\epsilon M}(\omega))$. Since $r(\Phi_{F-V}(\omega)) > 1$ and $r(\Phi_{F-V-\epsilon M}(\omega))$ is continuous for all small ϵ, we can choose ϵ small enough such that $r(\Phi_{F-V-\epsilon M}(\omega)) > 1$. Choose $T > T'$ and a small number $\alpha > 0$, such that $J(T) \geq p(0)$, where $J(t) = (E(t), I(t), I_e(t), W(t))$. By the standard comparison theorem [23] Theorem B.1 we get

$$J(t) \geq u(t) \geq \alpha e^{\mu_2(t-T)}p(t-T), \ t \geq T.$$

Hence $(E(t), I(t), I_e(t), W(t))^T \to \infty$ as $t \to \infty$. This is a contradiction to $0 \leq E(t) \leq \varepsilon$, $0 \leq I(t) \leq \varepsilon$, $0 \leq I_e(t) \leq \varepsilon$, $0 \leq W(t) \leq \varepsilon$. Thus $W^s(E_1) \cap X_0 = \phi$. Clearly, each orbit in M_∂ converges to E_1, and hence E_1 is acyclic in M_∂.

By Lemma 2.5 P is uniformly persistent with respect to $(X_0, \partial X_0)$. It follow from Theorem 3.1.1 in [32] that the solution of (1) is uniformly persistent.

Furthermore, by Theorem 1.3.6 of [32], P has a fixed point $(S^*(0), E^*(0), I^*(0), I_e^*(0), R^*(0), W^*(0)) \in X_0$. Then we see that $S^*(0) \in \mathbb{R}_+$, $(E^*(0), I^*(0), I_e^*(0), W^*(0)) \in \mathrm{Int}(\mathbb{R}_+^4)$, $R^*(0) \in \mathbb{R}_+$. We further prove that $S^*(0) > 0$ and $R^*(0) > 0$. Supposed not, if $S^*(0) = 0$, then from the first equation of system (1)

$$\frac{dS^*}{dt} \geq \Lambda - \beta_1(t)SI - \beta_2(t)SI_e - \nu(t)SW - \alpha(t)S - dS$$

By the comparison theorem, we have

$$\begin{aligned} S^*(t) &\geq e^{\int_0^t -(d+a(s_1))ds_1}\left[S^*(0) + \int_0^t (\Lambda e^{\int_0^{s_2}(d+a(s_1))ds_1}ds_2\right] \\ &= e^{\int_0^t -(d+a(s_1))ds_1}\int_0^t (\Lambda e^{\int_0^{s_2}(d+a(s_1))ds_1}ds_2, \forall t \geq 0. \end{aligned}$$

where $a(t) = \beta_1(t)I(t) + \beta_2(t)I_e(t) + \nu(t)W(t) + \alpha(t)$. From the inequality we obtain

$$S^*(n\omega) \geq e^{\int_0^{n\omega} -(d+a(s_1))ds_1}\int_0^{n\omega} (\Lambda + \eta R(s_2)e^{\int_0^{s_2}(d+a(s_1))ds_1}ds_2 > 0,$$

but from the periodicity of $S^*(t)$, we have $S^*(0) = S^*(n\omega) = 0$, $n = 1, 2, 3, \ldots$, a contradiction. Thus $S^*(0) > 0$. Similarly, we can prove that $R^*(0) > 0$. Therefore $(S^*(0), E^*(0), I^*(0), I_e^*(0), R^*(0), W^*(0))$ is a positive $\omega-$periodic solution of system (1). Thus we have finished the proof of Theorem 2.2. □

3. Numerical results

In this section we will numerically analyze model (1), concentrating on the effect of the asymptomatic subpopulation, free-living viruses in the contaminated environment and periodic vaccination on HFMD infections. We obtained the data on symptomatic cases of endemic HFMD in mainland China from the Chinese Center for Disease Control and Prevention [6]. The surveillance system provides real-time statistics for mainland China every month. From the National Bureau of Statistics of China [22] we can get the recruitment rate of susceptible individuals (Λ) and the natural death rate (d). We only consider the population of young children under six years old. Note that the proportion of young children under six years old is about 7.89%, thus the number of susceptible individuals in 2010 was calculated as $S(0) = 105703908$. We obtain the annual number of human population using the annual birth data from the National Bureau of Statistics of China [22]. Then we calculate the average and divide it by 12 to derive the human birth population $\Lambda = 1328556$ each month. We assume that the symptomatic and asymptomatic individuals have the same recovery rate, which was derived from [10] directly. Transmission coefficient functions are assumed

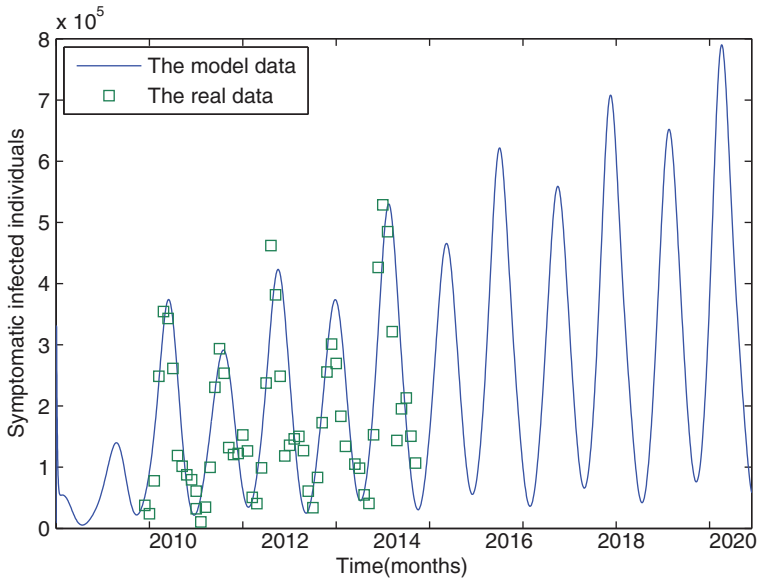

Fig. 2. Goodness fit to the real data for (2010–2014) in mainland China.

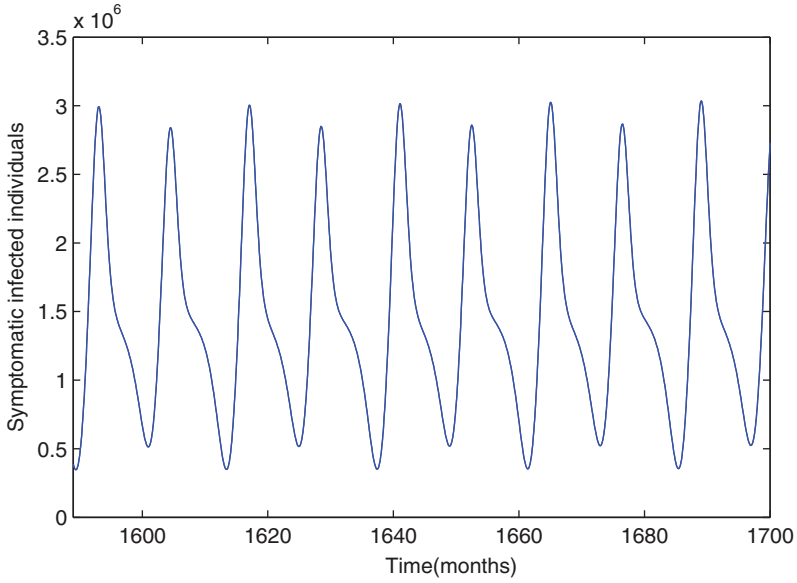

Fig. 3. The graph of the positive periodic solution.

as the following forms, $\beta_1(t) = a_1(1 + \sin(\frac{2\pi t}{12} + \phi))$, $\beta_2(t) = a_2(1 + \sin(\frac{2\pi t}{12} + \phi))$ and $\nu(t) = a_3(1 + \sin(\frac{2\pi t}{24} + \phi))$, where ϕ is chosen to be 2 according to estimation in paper [19], and $a_i, i = 1, 2, 3$ are unknown positive constant and will be estimated. The EV71 vaccine consistently elicited immunogenicity and provided protection against mild-to-severe disease caused by EV71 for at leat 1 year old infants and young children [33], therefore the vaccination rate is assumed as $\alpha(t) = \alpha(1 + \sin(\frac{2\pi t}{12} + \phi))$.

We estimated the transmission coefficients $a_i, i = 1, 2, 3$ and other unknown parameters associated with contaminated environments by fitting our proposed model to the monthly data on HFMD cases from January 2010 to October 2014, and listed in Table 1. Fig. 2 shows a goodness fit to the real data for 2010 to 2014. On the basis of our parameters listed in Table 1, we can calculate the basic reproduction number as $R_0 = r(\Phi_{F-V}(24)) = 1.7424$. It follows from Theorem 2.2 that system (1) admits a positive periodic solution, shown in Fig. 3. To examine the effect of vaccination on new symptomatic infections we assume that vaccination strategy has been implemented since 2015 and plot the variation in the monthly number of new symptomatic infections with different coverage of vaccination. Fig. 4 shows that the monthly number of new symptomatic infected individuals significantly reduce once vaccination strategy is implemented, which means that vaccination measure can effectively prevent the disease outbreak.

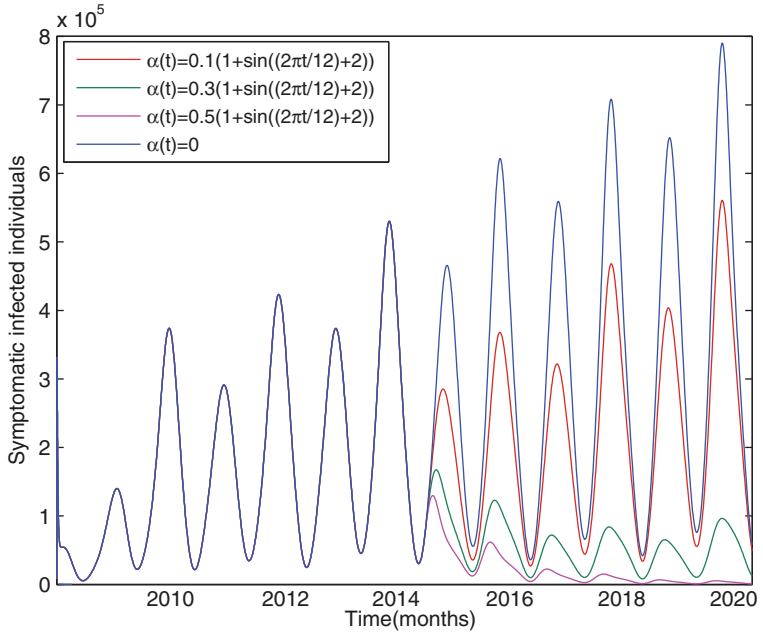

Fig. 4. The influence of vaccine introduction in 2015.

To investigate the influence of asymptomatic subpopulation, environmental contaminant and the effect of hygienic precautions such as washing hands, frequently cleaning and disinfecting touched surfaces, common areas and soiled items, we investigate the variation in number of new symptomatic infections by reducing the transmission rates $\beta_1(t)$, $\beta_2(t)$ and $\nu(t)$ and increasing the rate of clearance μ. Fig. 5(a)–(c) show the predicted number of symptomatic infected individuals with reducing transmission rates from the baseline values to 50% and 30% of them. It shows that a reduction in transmission rates or an increase in the rate of clearance results in decline in the symptomatic infected individuals and then weakens the severity of HFMD disease. This means that hygienic precautions and environmental cleaning, such as hand hygiene of asymptomatic infected infants and other sanitary measures, play important roles in reducing the number of infected individuals and contribute to effective disease control. In particular, it follows from Fig. 5(c) that we can obtain the effect of environment on HFMD infection, that is, contaminated environment greatly contributes the new infections and increases the risk of the spread of disease. Comparing Fig. 5(a)–(c) indicates that the number of symptomatic infected individuals is not obviously influenced by reducing $\beta_1(t)$, but is significantly affected by reducing $\beta_2(t)$ and $\nu(t)$. This implies that direct transmission by the asymptomatic infected individuals or indirect transmission via free-living virus in the contaminated environment significantly influences HFMD infections and should not be neglected.

In order to investigate effects of environmental clearance and vaccination on the basic reproduction number [34] we plot the variation in R_0 with the rate of clearance (μ) and the coefficient associated with coverage of vaccination (α) in Fig. 6. Fig. 6(a) shows that the larger the rate of clearance μ is, the less the R_0 is, that is to say, Frequently cleaning the environment leads to reduction of new infections and hence is beneficial to controlling the spread of disease. Fig. 6(b) gives that the greater the coverage of vaccination is, the less the R_0 is. The conclusion indicates again that improving clearance of contaminated environment, increasing coverage of vaccination strategy, are effective and feasible strategies in reducing HFMD new infections.

To compare the influence of these three transmission and the clearance of contaminated environment we examine the effects of varying the corresponding parameters a_1, a_2, a_3, α and μ on the basic reproduction number R_0. Let $k(0 \le k < 1)$ be the changing rate of these parameters, then we could increase the level of clearance and vaccinate rate (represented by $(1+k)\mu$ and $(1+k)\alpha$), decrease the direct and indirect transmission coefficients ($(1-k)a_1$, $(1-k)a_2$ and $(1-k)a_3$). Fig. 7(a) shows the variation of the basic reproduction number by varying k, respectively. It follows from Fig. 7(a) that decreasing the direct transmission by the asymptomatic individuals is more effective than vaccination measure, direct transmission by symptomatic individuals and indirect transmission via free-living virus in terms of reducing the reproduction number. Since asymptomatic individuals can not be diagnosed and tracked it is impossible to implement measures related to this group of individuals. Then initiating and enhancing vaccination strategy is essential and feasible in controlling HFMD infection when facing persistence of this disease

To examine the sensitivity of our results to parameter variations, we used Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs) [20] to examine the dependence of R_0 on uncertain parameters. LHS is a statistical sampling method that allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [27]. Note that PRCC, showing which parameters have the largest influence on model outcomes, is calculated using the rank transformed LHS matrix and output matrix [20]. We used 1000 simulations per run. In the absence of available data on the

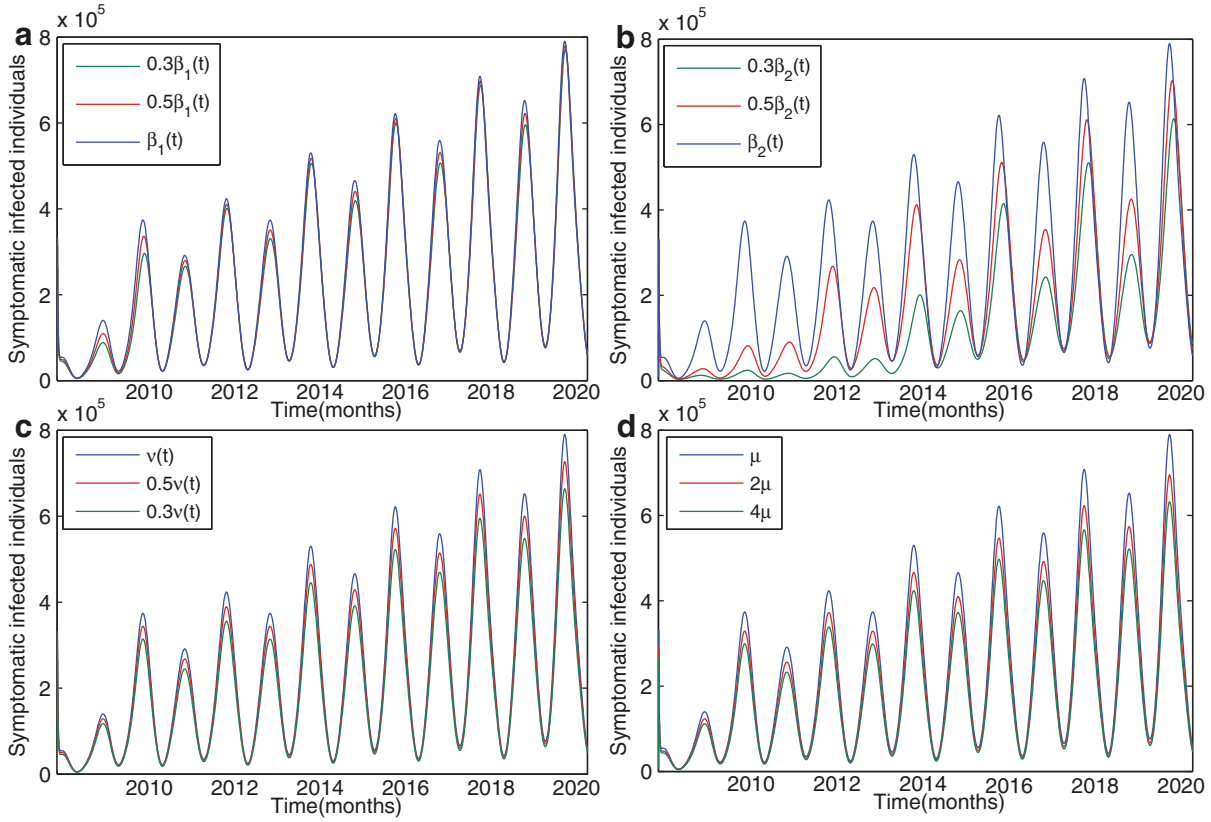

Fig. 5. (a)Simulations of the model for numbers of symptomatic infected individuals as the coefficients of $\beta_1(t)$ is varied by 50% and 30% of its baseline value. (b)Simulations of the model for numbers of symptomatic infected individuals as the coefficients of $\beta_2(t)$ is varied by 50% and 30% of its baseline value. (c)Simulations of the model for numbers of symptomatic infected individuals as the coefficients of $\nu(t)$ is varied by 50% and 30% of its baseline value. (d)Simulations of the model for numbers of symptomatic infected individuals as μ is varied by 200% and 400% of its baseline value. All other parameters are as shown in Table 1.

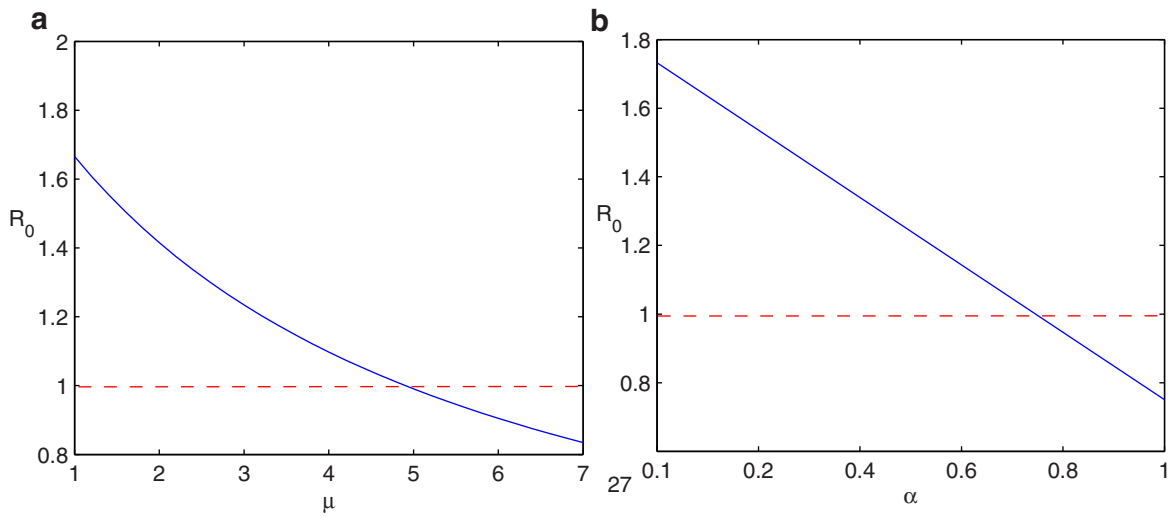

Fig. 6. (a) The graph of the basic reproduction number when μ varies.(b) The graph of the basic reproduction number when α varies. All other parameters are as shown in Table 1.

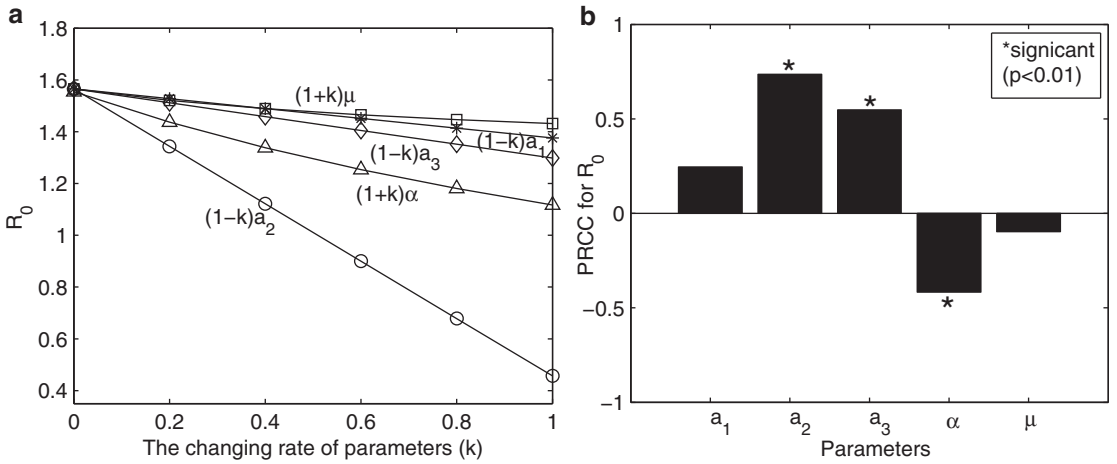

Fig. 7. (a) The basic reproduction number R_0 by varying k (the rate of changing a_1, a_2, a_3, α and μ). (b) The values of PRCCs on the outcome of R_0 while. All other parameters are as shown in Table 1.

Table 2
PRCC values for R_0.

Parameters	Distribution	PRCC	p-Value
a_1	U(0.00000145, 00000255)	0.2460	0.0157
a_2	U(0.000000022, 0.000000043)	0.7357	0
a_3	U(0.00000000175, 0.00000000185)	0.5481	0
α	U(0.1, 1)	−0.4173	0
μ	U(25, 35)	−0.0970	0.3470

distribution functions, we chose a uniform distribution for these four input parameters with ranges listed in Table 2, and tested for significant PRCCs for all parameters of the model (1). Fig. 7(b) shows the PRCC values illustrating the dependence of R_0 on the main four input parameters. We considered absolute values of PRCC > 0.4 as indicating an important correlation between input parameters and output variables, values between 0.2 and 0.4 as moderate correlations, and values between 0 and 0.2 as not significantly different from zero.

It follows from Fig. 7(b) that the parameters with most impact on the basic reproduction number are direct transmission coefficient by asymptomatic individuals (a_2) and indirect transmission coefficient via free-living virus in the contaminated environment (a_3) and the parameter associated with vaccination rate (α). It is interesting to note that variation in the direct transmission coefficient (a_2) greatly influences the basic reproduction number, and hence HFMD new infections, which is in agreement with that shown in Fig. 7(a). This result indicates that asymptomatic individuals, although can not be detected, contribute a lot to the transmission of HFMD compared to symptomatic individuals. Moreover, combining Fig. 7(a) and (b) suggests that increasing cover rate of vaccination strategy, improving hand hygiene of individuals and frequently cleaning are effective and feasible strategies in reducing HFMD new infections.

4. Discussion

In this paper, we have proposed and analyzed a HFMD model with periodic transmission rates and vaccination rate due to seasonal outbreak of HFMD infection [6]. The proposed model extends the existing models by incorporating effects of contaminated environment, asymptomatic infected subpopulation and vaccination strategy. In fact, models with periodic transmission rate for HFMD have been discussed by many researchers, but such models mainly considered the direct transmission rate although there is evidence showing that contaminated environments are also important sources for susceptible getting infection [3,9,15] and recessive subpopulation can infect others [5,19]. Hence, in our model the infected individuals are divided into two subgroups (symptomatic and asymptomatic). And further, indirect transmission via free-living virus in the environment is included in our model. Then, the proposed model incorporates two routes of transmission: direct between susceptible and infected (symptomatic or asymptomatic) individuals and indirect transmission via free-living viruses. Compared to the existing models on HFMD infection [19,29], the proposed model here is the first model in which both direct and indirect transmission routes are considered. Therefore, from the point view of modeling method, the proposed model here mainly extended the existing models by including indirect transmission routes via free-living virus, and it also extended some models by either including periodic transmission rates and vaccination rate compared to the references [33] or including asymptomatic compartment compared to the references [19]. Our main concerns in studying the epidemiology of HFMD were how, and to what extent, asymptomatic

individuals and contaminated environments influence the disease dynamics, and we also want to study the effect of vaccination on the disease control.

We analyzed the proposed model theoretically. We obtained a threshold parameter $r(\Phi_{F-V}(\omega))$ which determines the extinction and the uniform persistence of the disease. Our main theoretical results show that the disease-free periodic solution of system (1), $E_1(\hat{S}(t), 0, 0, 0, \hat{R}(t), 0)$, is globally asymptotically stable if $r(\Phi_{F-V}(\omega)) < 1$, whilst the disease is persistent for $r(\Phi_{F-V}(\omega)) > 1$, and meanwhile there exists a positive periodic solution. This means that the disease will be eradicated when the basic reproduction number is less than unity, otherwise the disease persists in the children.

By fitting our proposed model to the reported data on symptomatic cases of endemic HFMD in mainland China we estimated the basic reproduction number as 1.742, which is greater than the estimate in [19] and [29] where the basic reproduction number were estimated to be 1.0414 and 1.392. The major factors for this difference are those we take into account the direct transmission by symptomatic individuals and indirect transmission via free-living virus in contaminated environments. Numerical results, shown in Figs. 5 and 7(b), imply that the asymptotic infected individuals and contaminated environment are essential factors substantially contributing to HFMD new infections. Therefore, this highlights our conclusion that the existence of asymptotic individuals and contaminated environment significantly increase the risk of HFMD transmission among the children, compared to the results in literature [19,29] that either asymptotic compartment or contaminated environment is ignored in model formulation. Note that asymptomatic individuals, although contribute a lot to the transmission of HFMD compared to symptomatic individuals, can not be tracked and hence feasible measures can only be implemented on tracked individuals and environment. In particular,increasing the cover rate of vaccination (α) and reducing the indirect transmission rate between individuals and environments (a_3) are likely to result in a substantial reduction of new infection. Our finding suggests that enhancing vaccination strategy and the frequent cleaning of the environment and enhancing individual sanitation (e.g. regular hand-washing) are effective measures in controlling HFMD infections.

We find from the real data that the HFMD relatively large outbreak exhibits every other year. Some reasons may generate this phenomenon, such as the EV71 survival time, average air temperature, humidity, vapor pressure, etc. Note that we analyzed the simplified model (1) without considering the term $\nu(t)(S + V + E + I + I_e + R)W$ of the sixth equation since this term causes much trouble in theoretically analyzing, and we may leave this for future work. Homogeneous mixing assumptions used in our model may approximate some communities, however in the whole mainland transmission dynamics exhibits heterogeneity in the structure of the communities. Then considering the effect of social networks and exploring the occurrence of large outbreaks every other year could be interesting issues for future research.

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