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Modelling the effects of contaminated environments on HFMD infections in mainland China

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ABSTRACT

Hand-foot-mouth disease (HFMD) has spread widely in mainland China increasing in prevalence in most years with serious consequences for child health. The HFMD virus can survive for a long period outside the host in suitable conditions, and hence contaminated environments may play important roles in HFMD infection. A new mathematical model was proposed and used to investigate the roles that asymptomatic individuals and contaminated environments played in HFMD dynamics. The model includes both direct transmission between susceptible and infected individuals and indirect transmission via free-living infectious unites in the environment. Theoretical analysis shows that the disease goes to extinction if the basic reproduction number is less than unity, whilst otherwise the disease persists. By fitting the proposed model to surveillance data we estimated the basic reproduction number as 1.509. Numerical simulations show that increasing the rate of virus clearance and decreasing transmission rates can delay epidemic outbreaks and weaken the severity of HFMD. Sensitivity analysis indicated that the basic reproduction number is sensitive to the transmission rate induced by asymptomatic infectious individuals and parameters associated with contaminated environments such as the indirect transmission rate, the rate of clearance and the virus shedding rates. This implies that asymptomatic infectious individuals and contaminated environments contribute substantially to new HFMD infections, and so would be targets for effective control measures.

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 (McMinn et al., 2001). Recent outbreaks of HFMD in many areas such as Taiwan (Wang et al., 2002), Japan (Fujimoto et al., 2002), Malaysia (Chua and Kasri, 2011) and China (Zhang et al., 2009) were caused by Enterovirus 71 (EV71) which includes a variety of neurological diseases, including aseptic meningitis, encephalitis, and poliomyelitis-like paralysis (Knipe and Howley, 2007).

HFMD spreads mainly amongst children under five-years old but may also be transmitted among adults (CDC, 2013). 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 pathogen of EV71 can survive for a long period outside the host in suitable conditions (Chung et al., 2001; Bible et al., 2008; Han et al., 2010) and even 75% alcohol cannot eliminate the virus. HFMD patients and asymptomatic recessive individuals, releasing virus to the environment, are the major infectious sources but there is also some evidence that susceptible individuals can be infected via touching free-living pathogens 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, utensils, bedding and underclothes, and via the gastrointestinal tract through contaminated water and food (Hamaguchi et al., 2008).

There are several types of mathematic models that have been used to investigate the transmission dynamics and predict HFMD infections. Chuo and Ting (2008) proposed a simple SIR model to estimate the number of infections. Ma et al. (2013) formulated a

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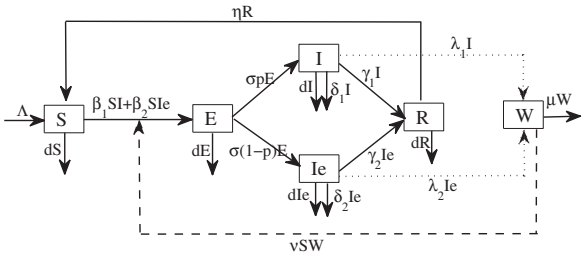

Fig. 1. Flow diagram representing transmission routes and other processes modelled by system (1).

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. Yang et al. (2013) 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 is the subject of this study.

The purpose of this study is to extend the existing mathematical models by including indirect transmission via free living viruses in the environment. 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 was used to analyze the proposed model and concentrate on HFMD case data for 2013. 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 equilibrium and the uniform persistence of the system. In Section 3 we describe simulations of the model and sensitivity analysis with regard to the reproduction number. 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 (Anderson and May, 1981). Our model involves direct transmission between susceptible and infected individuals (including symptomatic and asymptomatic) and indirect transmission to susceptible individuals by contaminated environments. An epidemic model is proposed to reflect some key epidemiological properties of HFMD epidemics and public health interventions such as isolation and hygienic precautions. 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 of the contaminated environments including door handles, towels, handkerchiefs, toys, utensils, bedding, underclothes, etc. at time t. A susceptible individual infected by contacting infected individuals (asymptomatic or symptomatic) or contaminated environments moves to the exposed compartment. 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

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

Note that free-living viruses in the environment, although capable of living for weeks or months, cannot reproduce by themselves without suitable conditions for reproduction. Here, let λ_1 and λ_2 are the rates at which infected individuals (symptomatic or asymptomatic) shed viruses. Free-living viruses are cleared at a rate of μ due to sterilization but are also picked up by all individuals, which induces indirect transmission at a rate of ν. The other parameters are defined in Table 1. Note that for model (1), the parameter ν 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 without considering the term $\nu(S+E+I+I_e+R)W$ in the following study.

It is obvious that any solution of system (1) with non-negative initial values is non-negative (Carvalho and Pinto, 2014). The following lemma shows that the solutions of system (1) are uniformly ultimately bounded.

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

Proof. Consider the population size $N(t)=S(t)+E(t)+I(t)+I_e(t)+R(t)$. It follows from (1) that $N'(t)=\Lambda - dN - \delta_1 I - \delta_2 I_e \le \Lambda - dN$. Then the comparison theorem implies that there exists $t_1>0$ such that $N(t) \le \Lambda/d$, for $t \ge t_1$, then $S(t) \le \Lambda/d$, $E(t) \le \Lambda/d$, $I(t) \le \Lambda/d$, $I_e(t) \le \Lambda/d$, $R(t) \le \Lambda/d$, for $t \ge t_1$.

By the last equation of model (1), we obtain

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

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 sufficiently large $t \ge T$. Then, solutions of system (1) are uniformly ultimately bounded. This completes the proof.□

Following the next generation matrix method developed by Van den Driessche and Watmough (2002), we can calculate the basic reproduction number R_0 as

$$R_0 = \frac{\Lambda\sigma p(\beta_1\mu + \nu\lambda_1)}{d\mu(\sigma+d)(\gamma_1+\delta_1+d)} + \frac{\Lambda\sigma(1-p)(\beta_2\mu+\nu\lambda_2)}{d\mu(\sigma+d)(\gamma_2+\delta_2+d)}$$

Note that R_0 is epidemiologically meaningful. $\frac{\Lambda\sigma p(\beta_1\mu+\nu\lambda_1)}{d\mu(\sigma+d)(\gamma_1+\delta_1+d)}$ is the average number of secondary infected individuals generated by a symptomatic infected individual through direct contact during his or her lifespan and indirect contact through a symptomatic infected individual (contaminated by free-living viruses in the environment shed by the symptomatic infected individual during his or her lifespan). $\frac{\Lambda\sigma(1-p)(\beta_2\mu+\nu\lambda_2)}{d\mu(\sigma+d)(\gamma_2+\delta_2+d)}$ is the average number of secondary infected individuals generated by an asymptomatic infected individual through direct contact during his lifespan and

Table 1
Definitions of the parameters used in the model.

Para.	Definition (Units)	Value	References
Λ	Recruitment rate (/month)	18,025	ChinaNBS (2013)
d	Natural death rate (/month)	1.126×10^{-3}	ChinaNBS (2013)
p	Proportion of HFMD symptomatic infected individuals	0.0044	Fitting
η	The rate from recovered to susceptible (/month)	0.035	Fitting
β_1	The transmission rate between $S(t)$ and $I(t)$ (/person/month)	1.4×10^{-7}	Fitting
β_2	The transmission rate between $S(t)$ and $I_e(t)$ (/person/month)	1.15×10^{-8}	Fitting
ν	The indirect transmission rate (/infectious unit/month)	8.9×10^{-11}	Fitting
$1/\sigma$	The average incubation period (month)	5/30	Ma et al. (2013)
γ_1	The recovery rate of the symptomatic infected individuals (/month)	0.1922	Chuo and Ting (2008)
γ_2	The recovery rate of the asymptomatic infected individuals (/month)	0.1922	Chuo and Ting (2008)
δ_1	Disease-related death for symptomatic HFMD individuals (/month)	6.86×10^{-4}	Ma et al. (2013)
δ_2	Disease-related death for asymptomatic HFMD individuals (/month)	6.86×10^{-4}	Ma et al. (2013)
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

indirect contact through an asymptomatic infected individual (contaminated by free-living viruses in the environment shed by the asymptomatic infected individual during his or her lifespan). So R_0 is the expected number of secondary infectious individuals generated by an infectious individual during his lifespan.

3. Threshold dynamics

There are two possible biologically realistic equilibria by setting the right hands of equations in model (1) to zero (Liu and Liu, 2014; Nannyonga et al., 2014). One is the disease-free equilibrium $E_0\left(\frac{\Lambda}{d},0,0,0,0,0\right)$ and the other is the unique endemic equilibrium $E_*(S^*,E^*,I^*,I_e^*,R^*,W^*)$ is feasible if $R_0>1$, where

$$S^*=\frac{\Lambda}{R_0 d},\quad I^*=\frac{\Lambda\left(1-\frac{1}{R_0}\right)}{\frac{\Lambda}{R_0 d}(\beta_1+\beta_2 B)+\frac{\Lambda\nu}{R_0 d}(\lambda_1+\lambda_2 B)-\frac{\eta}{\eta+d}(\gamma_1+\gamma_2 B)},$$

$$E^*=\frac{(\gamma_1+\delta_1+d)I^*}{\sigma p},\quad I_e^*=BI^*,\quad R^*=\frac{\gamma_1+\gamma_2 B}{\eta+d}I^*,$$

$$W^*=\frac{\lambda_1+\lambda_2 B}{\mu}I^*,$$

with

$$B=\frac{(1-p)(\gamma_1+\delta_1+d)}{p(\gamma_2+\delta_2+d)}.$$

In the following we examine the local and global stability of the disease-free equilibrium for $R_0<1$ and prove the persistence of the system for $R_0>1$.

Theorem 1. *If $R_0<1$, then the disease-free equilibrium $E_0\left(\frac{\Lambda}{d},0,0,0,0,0\right)$ is locally asymptotically stable; if $R_0>1$, then the disease-free equilibrium E_0 is unstable.*

Proof. On the basis of the Jacobian matrix of the system at E_0, we can obtain the eigenvalues of the characteristic equation for the disease-free equilibrium as $-d$, $-(\eta+d)$, and the roots of

$$\Lambda^4+a_1\Lambda^3+a_2\Lambda^2+a_3\Lambda+a_4=0$$

where

$$a_1=(\gamma_1+\delta_1+d)+(\gamma_2+\delta_2+d)+(\sigma+d)+\mu>0,$$

$$a_2=(\gamma_1+\delta_1+d)(\gamma_2+\delta_2+d)+(\sigma+d)(\gamma_1+\delta_1+d)+(\sigma+d)(\gamma_2+\delta_2+d)+\mu(\gamma_1+\delta_1+d)+\mu(\gamma_2+\delta_2+d)+\mu(\sigma+d)-\frac{\Lambda\sigma}{d}(p\beta_1+(1-p)\beta_2),$$

$$a_3=(\sigma+d)(\gamma_1+\delta_1+d)(\gamma_2+\delta_2+d)+\mu(\sigma+d)(\gamma_1+\delta_1+d)+\mu(\sigma+d)(\gamma_2+\delta_2+d)+\mu(\gamma_1+\delta_1+d)(\gamma_2+\delta_2+d)-\frac{\Lambda\sigma p}{d}(\mu\beta_1+\nu\lambda_1+(\gamma_2+\delta_2+d)\beta_1)-\frac{\Lambda\sigma(1-p)}{d}(\mu\beta_2+\nu\lambda_2+(\gamma_1+\delta_1+d)\beta_2),$$

$$a_4=\mu(\sigma+d)(\gamma_1+\delta_1+d)(\gamma_2+\delta_2+d)(1-R_0).$$

Suppose $R_0<1$. One can get $\frac{\Lambda\sigma p(\mu\beta_1+\nu\lambda_1)}{d\mu(\sigma+d)(\gamma_1+\delta_1+d)}<1$ and $\frac{\Lambda\sigma(1-p)(\mu\beta_2+\nu\lambda_2)}{d\mu(\sigma+d)(\gamma_2+\delta_2+d)}<1$, $\frac{\Lambda\sigma p\beta_1}{d(\sigma+d)(\gamma_1+\delta_1+d)}<1$ and $\frac{\Lambda\sigma(1-p)\beta_2}{d(\sigma+d)(\gamma_2+\delta_2+d)}<1$. It follows that $a_1>0$, $a_2>0$, $a_3>0$, $a_4>0$. Also, we can get

$$\begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix}>0,\quad \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix}>0,\quad \begin{vmatrix} a_1 & a_3 & 0 & 0 \\ 1 & a_2 & a_4 & 0 \\ 0 & a_1 & a_3 & 0 \\ 0 & 1 & a_2 & a_4 \end{vmatrix}>0.$$

According to the Hurwitz criterion, all the roots of the quartic equation are negative. Therefore all the characteristic equation are negative and the disease-free equilibrium of the system, $E_0\left(\frac{\Lambda}{d},0,0,0,0,0\right)$ is locally asymptotically stable. Now suppose $R_0>1$. Then $a_4<0$. So the quartic equation must have at least one positive root. Therefore the disease-free equilibrium of the system is unstable. This completes the proof.□

Theorem 2. *If $R_0<1$, then the disease-free equilibrium $E_0\left(\frac{\Lambda}{d},0,0,0,0,0\right)$ is globally asymptotically stable.*

Proof. From Theorem 1, we have that E_0 is locally asymptotically stable. Now we prove the global attractivity of the disease-free

equilibrium E_0. By lemma 1, for any $\varepsilon>0$, there exists $t_1>0$, such that $S(t)\le N(t)\le \frac{\Lambda}{d}+\varepsilon$ for $t\ge t_1$. Thus, for $t\ge t_1$, we have

$$\begin{aligned}
\frac{dE}{dt} &\le \beta_1\left(\frac{\Lambda}{d}+\varepsilon\right)I+\beta_2\left(\frac{\Lambda}{d}+\varepsilon\right)I_e+\nu\left(\frac{\Lambda}{d}+\varepsilon\right)W-(\sigma+d)E,\\
\frac{dI}{dt} &= \sigma pE-(\gamma_1+\delta_1+d)I,\\
\frac{dI_e}{dt} &= \sigma(1-p)E-(\gamma_2+\delta_2+d)I_e,\\
\frac{dR}{dt} &= \gamma_1 I+\gamma_2 I_e-(\eta+d)R,\\
\frac{dW}{dt} &= \lambda_1 I+\lambda_2 I_e-\mu W.
\end{aligned}$$

Consider an auxiliary system as follows:

$$u'=M_1(\varepsilon)u, \tag{2}$$

where vector $u=(u_1,u_2,u_3,u_4)^T$, T represents the transpose of the vector and

$$M_1(\varepsilon)=\begin{pmatrix}
-(\sigma+d) & \beta_1\left(\frac{\Lambda}{d}+\varepsilon\right) & \beta_2\left(\frac{\Lambda}{d}+\varepsilon\right) & 0 & \nu\left(\frac{\Lambda}{d}+\varepsilon\right)\\
\sigma p & -(\gamma_1+\delta_1+d) & 0 & 0 & 0\\
\sigma(1-p) & 0 & -(\gamma_2+\delta_2+d) & 0 & 0\\
0 & \gamma_1 & \gamma_2 & -(\eta+d) & 0\\
0 & \lambda_1 & \lambda_2 & 0 & -\mu
\end{pmatrix}$$

Let $s(M_1(\varepsilon))$ be the maximum real part of the eigenvalues of $M_1(\varepsilon)$. Since $M_1(\varepsilon)$ is irreducible and has non-negative off-diagonal elements, $s(M_1(\varepsilon))$ is a simple eigenvalue of $M_1(\varepsilon)$ with a positive eigenvector. From the proof of the stability of the disease-free equilibrium above we have the following two equivalences holding true (Wang and Zhao, 2004):

$$R_0<1\Leftrightarrow s(M_1(0))<0,\quad R_0>1\Leftrightarrow s(M_1(0))>0.$$

Since $s(M_1(\varepsilon))$ is continuous for small ε, there exists an ε small enough such that $s(M_1(\varepsilon))<0$. Thus there is a negative eigenvalue of $M_1(\varepsilon)$ with a positive eigenvector. Let $u(t)=(u_1(t),u_2(t),u_3(t),u_4(t),u_5(t))$ be a solution of system (2), which is strictly decreasing with $u_i(t)\to 0$ as $t\to\infty$, $i=1,2,3,4,5$. Since the system (2) is a quasimonotonic system, applying the comparison principle yields (Smith and Waltman, 1995)

$$\lim_{t\to\infty}E(t)=0,\quad \lim_{t\to\infty}I(t)=0,\ \lim_{t\to\infty}I_e(t)=0,$$
$$\lim_{t\to\infty}R(t)=0,\ \lim_{t\to\infty}W(t)=0.$$

Hence E_0 is globally attractive. Thus it is globally asymptotically stable. This completes the proof.□

Theorem 3. *When $R_0>1$, system (1) is uniformly persistent.*

Proof. In order to prove this result, we need the uniform persistence theorem for infinite dimensional systems from Wang and Zhao (2004) Theorem 2.3. Define

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

Firstly, it is easy to see that both X and X_0 are positively invariant, and, X_0 is relatively closed in X. Lemma 1 implies that the system is point dissipative. Thus the solution of the system admits a global attractor. Define

$$M_\partial=\{(S^0,E^0,I^0,I_e^0,R^0,W^0)\in\partial X_0:(S(t),E(t),I(t),I_e(t),$$
$$R(t),W(t))\in\partial X_0,\forall t\ge 0\}.$$

Now we prove that

$$M_\partial=\{(S,0,0,0,0,0)\in X:S\ge 0\}.$$

Note that $\{(S,0,0,0,0,0)\in X:S\ge 0\}\subseteq M_\partial$, so we only need to prove that $M_\partial\subseteq\{(S,0,0,0,0,0)\in X:S\ge 0\}$. 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,R^0,W^0 is not zero, without loss of generality, we suppose that $E^0=0,I^0=0,I_e^0=0,R^0=0,W^0>0$, from the equation we have

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

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

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

$$R(t)=e^{-(\eta+d)t}\left[R^0+\int_0^t(\gamma_1 I(s_1)+\gamma_2 I_e(s_1))e^{(\eta+d)s_1}ds_1\right]>0,\quad\forall t\ge 0.$$

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

For any $\varphi_0=(S^0,E^0,I^0,I_e^0,R^0,W^0)\notin\{(S,0,0,0,0,0)\in X:S\ge 0\}$, we have $(S(t),E(t),I(t),I_e(t),R(t),W(t))\notin\partial X_0$, $t>0$ sufficiently small. That is to say $\varphi_0\notin\{(S,0,0,0,0,0)\in X:S\ge 0\}$, then $\varphi_0\notin M_\partial$, which contradicts $\varphi_0\notin M_\partial$. So $M_\partial\subseteq\{(S,0,0,0,0,0)\in X:S\ge 0\}$, therefore $M_\partial=\{(S,0,0,0,0,0)\in X:S\ge 0\}$. Let φ_0 be an initial value, then there is only one equilibrium $E_0(\Lambda/d,0,0,0,0,0)$ in M_∂. So $\cup_{\varphi_0\in M_\partial}=E_0$. Therefore E_0 is a compact and isolated invariant set for φ_0 in M_∂.

We now show that $W^S(E_0)\cap X_0=\emptyset$, where $W^S(E_0)$ denotes the stable manifold of E_0. This can be equivalent to claim that there exists a positive constant δ such that for any solution $\Phi_t(\varphi_0)$, $\varphi_0\in X_0$,

$$\lim_{t\to\infty}\sup\mathbf{d}(\Phi_t(\varphi_0),E_0)\ge\delta.$$

$\mathbf{d}$ is a distant function in X_0. Suppose the claim is not true. Then $\lim_{t\to\infty}\sup\mathbf{d}(\Phi_t(\varphi_0),E_0)<\delta$, for any δ, namely, there exists a positive constant T, such that $\Lambda/d-\xi\le S(t)\le\Lambda/d+\xi$, $0\le E(t)\le\xi$, $0\le I(t)\le\xi$, $0\le I_e(t)\le\xi$, $0\le W(t)\le\xi$, for any $t>T$. While $t>T$, we have,

$$\begin{aligned}
\frac{dE}{dt} &\ge \beta_1\left(\frac{\Lambda}{d}-\xi\right)I+\beta_2\left(\frac{\Lambda}{d}-\xi\right)I_e+\nu\left(\frac{\Lambda}{d}-\xi\right)W-(\sigma+d)E,\\
\frac{dI}{dt} &= \sigma pE-(\gamma_1+\delta_1+d)I,\\
\frac{dI_e}{dt} &= \sigma(1-p)E-(\gamma_2+\delta_2+d)I_e,\\
\frac{dR}{dt} &= \gamma_1 I+\gamma_2 I_e-(\eta+d)R,\\
\frac{dW}{dt} &= \lambda_1 I+\lambda_2 I_e-\mu W.
\end{aligned}$$

Consider an auxiliary system as follows:

$$u' = M_2(\xi)u \tag{3}$$

where vector $u = (u_1, u_2, u_3, u_4, u_5)^T$ and

$$M_2(\xi) = \begin{pmatrix} -(\sigma+d) & \beta_1\left(\frac{\Lambda}{d}-\xi\right) & \beta_2\left(\frac{\Lambda}{d}-\xi\right) & 0 & \nu\left(\frac{\Lambda}{d}-\xi\right) \\ \sigma p & -(\gamma_1+\delta_1+d) & 0 & 0 & 0 \\ \sigma(1-p) & 0 & -(\gamma_2+\delta_2+d) & 0 & 0 \\ 0 & \gamma_1 & \gamma_2 & -(\eta+d) & 0 \\ 0 & \lambda_1 & \lambda_2 & 0 & -\mu \end{pmatrix}$$

Again, from Wang and Zhao (2004) if $R_0 > 1$, then we have $s(M_2(0)) > 0$. Since $s(M_2(\xi))$ is continuous for small ξ, there exists ξ small enough, such that $s(M_2(\xi)) > 0$. Thus there is a positive eigenvalue of $M_2(\xi)$ with a positive eigenvector. Let $u(t) = (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t))$ be a solution of (3), which is strictly increasing $u_i(t) \to \infty$ as $t \to \infty$, $i = 1, 2, 3, 4, 5$. Since the system (3) is a quasi-monotonic system, applying the comparison principle gives

$$\lim_{t\to\infty} E(t) = \infty, \quad \lim_{t\to\infty} I(t) = \infty, \quad \lim_{t\to\infty} I_e(t) = \infty,$$

$$\lim_{t\to\infty} R(t) = \infty, \quad \lim_{t\to\infty} W(t) = \infty.$$

This contradicts with our assumption. Then, E_0 is an isolated invariant set in X and $W^S(E_0) \cap X_0 = \emptyset$. Therefore the system is uniformly persistent if $R_0 > 1$. This completes the proof.□

4. Numerical results and sensitivity analysis

In this part we numerically analyze model (1), concentrating on the effect of the asymptomatic subpopulation and free-living viruses in the contaminated environment 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 (ChinaCDC, 2013). The surveillance system provides real-time statistics for mainland China every month. From the National Bureau of Statistics of China (ChinaNBS, 2013) we can get the recruitment rate of susceptible (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 2013 was calculated as $S(0) = 106833756$. We assume that the symptomatic and asymptomatic individuals have the same recovery rate, which was derived from Chuo and Ting (2008) directly.

By using the Fmincon function in Matlab and least squares method we fit the model and the monthly data on HFMD cases, and then estimate the transmission rates and other parameters associated with contaminated environments, as shown in Table 1. Fig. 2 shows a goodness fit to the real data for 2013. On the basis of our parameter values the basic reproduction number was estimated as 1.509. In particular, if we ignore the influence of asymptomatic infected individuals (i.e., let the direct transmission rate β_2 equal to zero), then the basic reproduction number R_0 becomes 0.8313. Similarly, if we ignore the impact of contaminated environments on the spread of disease (i.e., let the indirect transmission rate ν be zero), then R_0 changes to be 1.2416. This result indicates that direct transmission between susceptible and asymptomatic infected individuals and indirect transmission via free-living stages have substantial influence on the basic reproduction number of model (1). Note that our estimate of the basic reproduction number is greater than that obtained by the previous literature (Yang et al., 2013), who estimated the basic reproduction number as 1.392. This is because our proposed model includes both the indirect transmission via free-living viruses in the environment and asymptomatic infected individuals, which further consolidates the conclusion on the significant contribution of asymptomatic infected individuals and contaminated environments on transmission of HFMD.

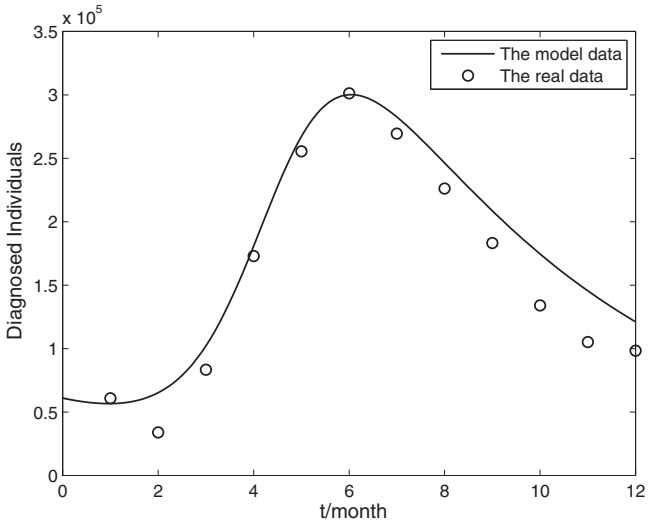

Fig. 2. Goodness fit to the real data for 2013 in mainland China.

To investigate the effect of hygienic precautions such as washing hands, cleaning and disinfecting frequently touched surfaces, common areas and soiled items, we can reduce the transmission coefficients ν and increase the rate of clearance μ. Fig. 3(a), (c) and (d) show the predicted number of symptomatic infected individuals with transmission rates reducing from the baseline values to 75% and 50% of them. Fig. 3(b) shows the effect of increasing the rate of clearance μ on the number of symptomatic infected individuals. It shows that a reduction in transmission rates or an increase in the rate of clearance delay the epidemic outbreak peak and weaken 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 the most effective control strategy. Comparing Fig. 3(a), (c) and (d) indicates that the number of symptomatic infected individuals is not obviously affected by reducing β_1 or ν, but is changed significantly by reducing β_2. This implies that transmission by the asymptomatic infected subpopulation significantly influences HFMD disease and should not be neglected.

To examine the sensitivity of our results to parameter variation, we used Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs) (Marino et al., 2008) to examine the dependence of R_0 on uncertain parameters. Note that PRCC, showing which parameters have the largest influence on model outcomes, is calculated using the rank transformed LHS matrix and output matrix (Marino et al., 2008). We used 1000 simulations per run. In the absence of available data on the distribution functions, we chose a uniform distribution for all input parameters with ranges listed in Table 2, and tested for significant PRCCs for all parameters of the model (1).

Fig. 4 shows the PRCC values illustrating the dependence of R_0 on each of the 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. 4 that the parameters with most impact on the basic reproduction are transmission rates (indirect transmission rate ν, the direct transmission rate β_1, β_2),

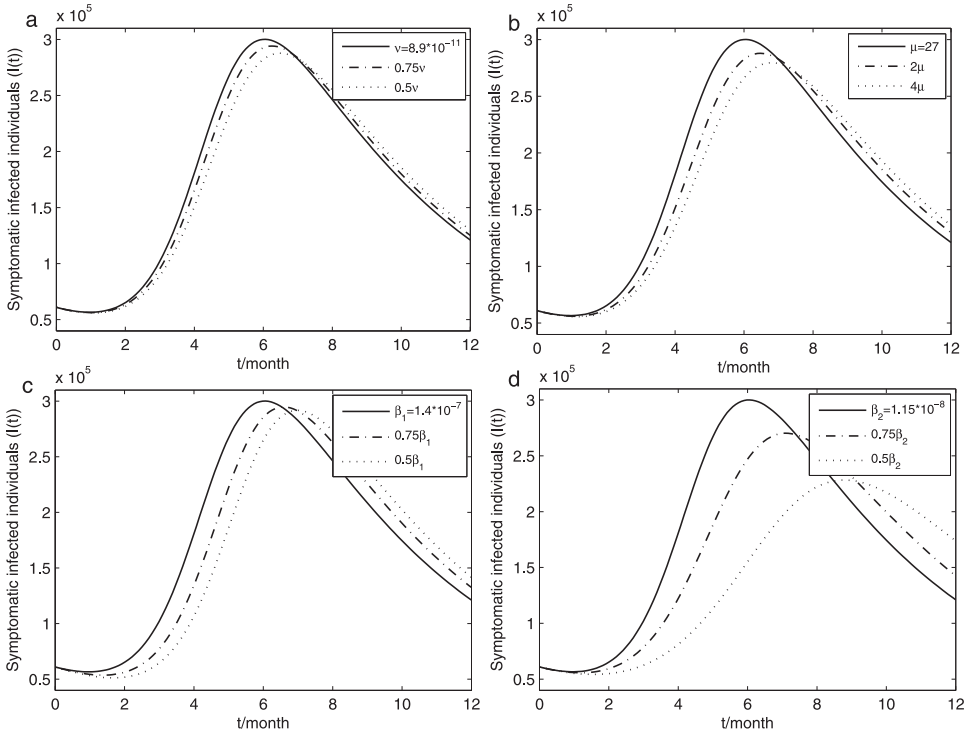

Fig. 3. Simulations of the model for numbers of symptomatic infected individuals as (a) ν is varied by 75% and 50% of its baseline value, (b) μ is varied by 200% and 400% of its baseline value, (c) β_1 is varied by 75% and 50% of its baseline value, (d) β_2 is varied by 75% and 50% of its baseline value. All other parameters are as shown in Table 1.

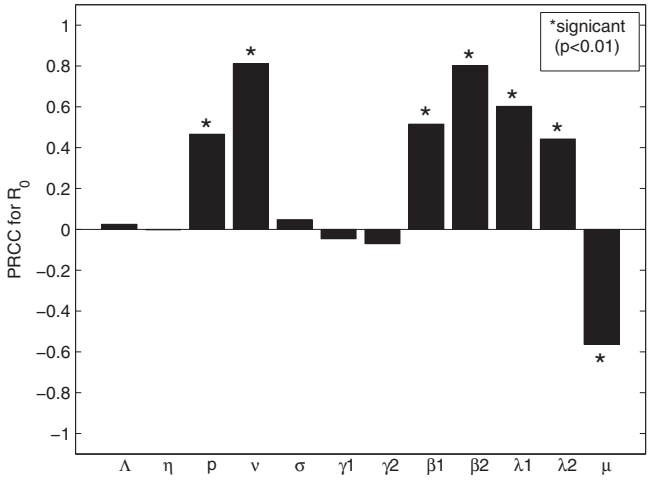

Fig. 4. The values of PRCCs on the outcome of R_0.

the shedding rates (λ_1 and λ_2) and the rate of clearance (μ). It should be noted that variation in the indirect transmission has little effect on the number of symptomatic infected individuals (shown in Fig. 3(a)) but it is highly correlated with new infections (determined by the basic reproduction number).

5. Discussion

Deterministic models for HFMD have been discussed by many researchers, but such models mainly considered the direct transmission rate although there is evidence showing that recessive subpopulation can infect others and so should not be neglected (Ma et al., 2013; Chang et al., 2004). Hence, in our model the infected individuals are divided into two subgroups (symptomatic and asymptomatic). Moreover, enteroviruses have a strong infectivity, the pathogens being capable of surviving for long periods in suitable conditions outside the host (Chung et al., 2001; Bible et al., 2008; Han et al., 2010). So contaminated environments are also important sources from which it is possible for susceptible to become infected. So, we extended an existing model for HFMD by including indirect transmission via free-living viruses

Table 2
PRCC values for R_0

Parameters	Distribution	PRCC	p-Value
Λ	U(18000, 18100)	0.0246	0.0829
η	U(0.003, 0.004)	−0.0025	0.8613
p	U(0.003, 0.005)	0.4654	0
ν	U(0.0000000001, 0.000000000002)	0.8122	0
σ	U(5.9, 6.1)	0.0473	0.08
γ_1	U(0.16, 0.22)	−0.0461	0.0110
γ_2	U(0.16, 0.22)	−0.0704	0.0909
β_1	U(0.0000001, 0.0000004)	0.5150	0
β_2	U(0.00000001, 0.00000003)	0.8016	0
λ_1	U(800, 30000)	0.6019	0
λ_2	U(500, 8500)	0.4419	0
μ	U(20, 29)	−0.5636	0

in the environment. The proposed model incorporates two routes of transmission: direct between susceptible and infected (symptomatic and asymptomatic) individuals and indirect transmission via free-living viruses. Our main concerns in studying the epidemiology of HFMD were how, and to what extent, asymptomatic individuals and contaminated environments influence the disease dynamics.

We analyzed the proposed model theoretically. The basic reproduction number R_0 is defined to determine whether the disease dies out or not. In particular, we proved the disease-free equilibrium is globally asymptotically stable if $R_0 < 1$, whereas the system is uniformly persistent for $R_0 > 1$. This means that the disease will be eradicated when the basic reproduction number is less than unity, whilst otherwise the disease persists in the children. By fitting our proposed model to the case data for 2013 we estimated the basic reproduction number as 1.509, which is greater than that obtained in Ma et al. (2013), in which the influence of contaminated environments is neglected. The discrepancy in the two estimates may be partly attributable to the HFMD virus outside the host, which could be picked up by individuals and transmitted to the susceptible. Similarly, if we ignore the influence of asymptomatic individuals and let the transmission rate β_2 be equal to zero, then the basic reproduction number declines substantially to be less than unity. This means that the asymptomatic subpopulation also plays an important role in the spread of HFMD disease.

Sensitivity analysis indicates that the basic reproduction number is sensitive to the parameters associated with contaminated environments such as the indirect transmission rate ν, the rate of clearance μ and the virus shedding rates (λ_1 and λ_2). This, on the one hand, implies that contaminated environments represent an essential factor substantially contributing to new infections, and should not be ignored. On the other hand, an effective control strategy could also be suggested, that is, the frequent cleaning of the environment and enhancing individual sanitation (e.g. regular hand-washing) would significantly reduce the number of new infections. Further, the basic reproduction number is also sensitive to the direct transmission rate β_2 induced by asymptomatic infected individuals. This indicates that asymptomatic infected individuals could have a strong influence on new infections although they can not be easily spotted.

It should be mentioned that we only fitted our proposed model to the data of 2013 and estimate some unknown parameters. Seasonal infection of this disease has been observed which is not captured by our model. Now people pay more attention to this disease, thus media reports may influence the spread of HFMD (Xiao et al., 2015), which is not considered by us. However, our main purpose is to investigate impact of asymptomatic infected individuals and contaminated environments on disease infection and some control measures are suggested. We will model periodic occurrence of the disease together with contaminated environments and establish sliding mode to control the outbreaks HFMD (Xiao et al., 2012) in future work.

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