MODELLING THE EFFECTS OF CONTAMINATED ENVIRONMENTS IN MAINLAND CHINA ON SEASONAL HFMD INFECTIONS AND THE POTENTIAL BENEFIT OF A PULSE VACCINATION STRATEGY

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Abstract. Substantial and increasing outbreaks of EV71-related hand, foot and mouth disease (HFMD) have occurred recently in mainland China with serious consequences for child health. The HFMD pathogens can survive for long periods outside the host in suitable conditions, and hence indirect transmission via free-living pathogens in the environment cannot be ignored. We propose a novel mathematical model of both periodic direct transmission and indirect transmission followed by incorporation of an impulsive vaccination strategy. By applying Floquet theory and the comparison theorem of impulsive differential equations, we obtained a threshold parameter which governs the extinction or the uniform persistence of the disease. The rate, frequency and timing of pulse vaccination were found to affect the basic reproduction number and the number of infected individuals significantly. In particular, frequent vaccination with a high coverage rate leads to declines in the basic reproduction number. Moreover, for a given rate of vaccination or frequency, numerical studies suggested that there was an optimal time (September, just before the start of new school terms) when the basic reproduction number and hence new HFMD infections could be minimised. Frequent high intensity vaccinations at a suitable time (e.g. September) and regular cleaning of the environment are effective measures for controlling HFMD infections.

1. **Introduction.** Hand, Foot and Mouth Disease (HFMD) was first diagnosed in New Zealand in 1957 [12], and has subsequently been reported across the Asia-Pacific region where it is now endemic. Recent outbreaks of HFMD have occurred

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in many areas such as Malaysia [9], Japan [14] and China [30, 40]. HFMD is a contagious viral illness, caused by enteroviruses of the family Picornaviridae, that commonly affects infants and children. The most important common causative pathogens are Coxsackie virus (A16), human enterovirus (EV71) and other enteroviruses including Coxsackie viruses A4, 5, 9, 10, B2 and 5 [25]. Recent outbreaks of HFMD in many areas were caused by EV71 which induced a variety of neurological diseases including aseptic meningitis, encephalitis, and poliomyelitis-like paralysis [19]. Enterovirus 71 (EV71) is a major cause of HFMD in children in China and may even be fatal. It accounts for the majority of cases worldwide [6], and up to 13.8 million cases were reported between 2008 and 2015 [8]. The HFMD data from the Chinese Center for Disease Control and Prevention (CDC) [8] show that outbreaks occur annually in mainland China. Recently, an EV71 vaccine has been successfully developed. Evidence suggests that it consistently elicits immunogenicity and provides protection against mild-to-severe diseases caused by EV71 for at least one year in infants and young children [43]. The vaccine efficacy against EV71-associated HFMD is 97.4% [21].

HFMD spreads primarily among children under five years of age but may also be transmitted among adults [5]. Children are more susceptible to infection than adults because they are less likely to have appropriate antibodies and awareness of self-protection. Susceptible infants are usually infected by close contact with infected individuals. Note that the pathogens of EV71 can survive outside the host for an extended period of time in suitable conditions [2, 10]; in fact, even 75% alcohol cannot eliminate the pathogens. HFMD patients and asymptomatic individuals, releasing the pathogens into the environment, are the major infectious sources, and there is also evidence suggesting that susceptible individuals can be infected by 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 contact in infectious crowds, touching virus-carrying hands, towels, handkerchiefs, toys, bedding, and underclothes, and via the gastrointestinal tract through contaminated water and food [16]. Note that HFMD has become an increasingly complex and serious disease. Therefore, an open research problem and the focus of this study is quantifying the contributions of indirect transmission via free-living viruses in the environment and recessive infected individuals and designing an effective vaccination strategy to control HFMD epidemics.

Mathematical models are widely used to understand and analyse the mechanisms involved in the spread and control of infectious diseases [18]. A number of mathematical models have been formulated to investigate the transmission dynamics and prediction of HFMD infections. Ma et al. [23] formulated a realistic model where infectious individuals were classified into two compartments to investigate the seasonal spread of HFMD in Shandong Province. Yang et al. [38] analysed transmission dynamics with the goal of determining better control strategies through sensitivity analysis. Wang et al. [33, 34] proposed a novel mathematical model to represent both direct and indirect transmission to investigate the effects of a contaminated environment on the transmission dynamics of HFMD. Few models have been proposed to describe the effects of impulsive vaccination on HFMD transmission dynamics.

The main purpose of this study is to extend existing mathematical models by including indirect transmission via free-living viruses in the environment, a periodic transmission rate, and an impulsive vaccination strategy. Our model also considers a

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 analyse the proposed model, and we fit our proposed model to HFMD case data from 2010 to 2015 to estimate unknown parameters. By designing a reasonable vaccination policy, we examine the impact of various vaccination strategies on HFMD infections. The remainder of this paper is organized as follows. In the next section, we establish an HFMD model with impulsive vaccination and demonstrate the existence of a disease-free periodic solution (DFPS). We investigate the threshold dynamics of the system and obtain the extinction or uniform persistence of the disease by applying Floquet theory and the comparison theorem of impulsive differential equations. In Section 3, numerical simulations of the model are implemented and disease control strategies are described. The final section consists of a discussion and our concluding remarks.

2. **Periodic model with pulse vaccination.**

2.1. **Model.** In this section, we propose an impulsive vaccination model with a periodic transmission rate and investigate the dynamical behaviour of the population. The underlying structure of the model is comprised of the following five classes: 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 ($R(t)$) [34]. Let $W(t)$ be the density of pathogens at time t in contaminated environments including door handles, towels, handkerchiefs, toys, utensils, bedding, and underclothes. A susceptible individual is infected at a rate of $\beta_i(t)$ by contacting infected individuals (asymptomatic or symptomatic) or at a rate of $\nu(t)$ by touching contaminated environments; then, the individual 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 a period of T. An individual passing through this latent period will become infectious (with different infectiousness), either asymptomatically or symptomatically, until recovery or death. The model equations are as follows:

$$\begin{cases} \left.\begin{aligned} S'(t) &= \Lambda - \beta_1(t)SI - \beta_2(t)SI_e - \nu(t)SW - \mu S + \eta R,\\ E'(t) &= \beta_1(t)SI + \beta_2(t)SI_e + \nu(t)SW - (\sigma+\mu)E,\\ I'(t) &= \sigma pE - (\gamma_1+\delta_1+\mu)I,\\ I_e(t)' &= \sigma(1-p)E - (\gamma_2+\delta_2+\mu)I_e,\\ R'(t) &= \gamma_1 I + \gamma_2 I_e - (\eta+\mu)R,\\ W'(t) &= \lambda_1 I + \lambda_2 I_e - \zeta W, \end{aligned}\right\} t \neq nT, n \in \mathbb{N}.\\ \left.\begin{aligned} S(nT^+) &= (1-\tau)S(nT),\\ E(nT^+) &= E(nT),\\ I(nT^+) &= I(nT),\\ I_e(nT^+) &= I_e(nT),\\ R(nT^+) &= R(nT) + \tau S(nT),\\ W(nT^+) &= W(nT). \end{aligned}\right\} t = nT, n \in \mathbb{N}. \end{cases} \tag{1}$$

Note that free-living pathogens in the environment, although capable of living for weeks or months, cannot reproduce by themselves [10]. Here, let λ_1 and λ_2 be the rates at which symptomatic and asymptomatic infected individuals shed viruses, respectively. Free-living pathogens are cleared at a rate of ζ due to sterilization and picked up by all individuals at a rate of $\nu(t)$. Here, τ is the fraction of susceptible

TABLE 1. Definitions of the parameters used in the model

Para.	Definition(Units)	Value	References
Λ	Recruitment rate (/month)	1,328,556	[26]
μ	Natural death rate (/month)	1.126×10^{-3}	[26]
p	Proportion of HFMD symptomatic infected individuals	0.025	[34]
η	Rate from recovered to susceptible (/month)	0.115	[34]
$\beta_1(t)$	Periodic transmission rate between $S(t)$ and $I(t)$	$a_1(1+\sin(\frac{2\pi t}{12}+\phi))$	[23]
$\beta_2(t)$	Periodic transmission rate between $S(t)$ and $I_e(t)$	$a_2(1+\sin(\frac{2\pi t}{12}+\phi))$	[23]
$\nu(t)$	Periodic indirect transmission rate	$a_3(1+\sin(\frac{2\pi t}{24}+\phi))$	[34]
$1/\sigma$	Average incubation period (month)	1/6	[23]
γ_1	Recovery rate of the symptomatic infected individuals (/month)	0.1922	[11]
γ_2	Recovery rate of the asymptomatic infected individuals (/month)	0.1922	[11]
δ_1	Disease-related death for symptomatic HFMD individuals (/month)	6.86×10^{-4}	[23]
δ_2	Disease-related death for asymptomatic HFMD individuals (/month)	6.86×10^{-4}	[23]
λ_1	Virus shedding rate from symptomatic infected individuals (/month)	9.38×10^{2}	[34]
λ_2	Virus shedding rate from asymptomatic infected individuals (/month)	7.89×10^{2}	[34]
ζ	Clearance rate of the virus (/month)	27	[34]
a_1	Coefficient of transmission rate between $S(t)$ and $I(t)$ (none)	1.5×5^{-8}	[34]
a_2	Coefficient of transmission rate between $S(t)$ and $I_e(t)$ (none)	2.25×10^{-9}	[34]
a_3	Coefficient of indirect transmission rate (none)	1.8×10^{-11}	[34]
τ	Proportion of susceptible who are vaccinated successfully	varied	–

individuals that are inoculated for the vaccine at $t = nT$. The remaining model parameters are defined in Table 1.

2.2. **Threshold dynamics.** 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 say $u \geq v$ if $u - v \in \mathbb{R}^n_+$, $u > v$ if $u - v \in \mathbb{R}^n_+ \setminus \{0\}$, and $u \gg v$ if $u - v \in \text{Int}(\mathbb{R}^n_+)$. Let $A(t)$ to be a continuous, cooperative, irreducible, and periodic $n \times n$ matrix function with period ω, where $\omega > 0$. 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 [41, 42].

Lemma 2.1. *Let $\theta = \frac{1}{\omega} \ln r(\Phi_{A(.)}(\omega))$. Then there exists a positive $\omega-$periodic function $\rho(t)$ such that $e^{\theta t}\rho(t)$ is a solution to $\dot{x} = A(t)x$.*

The positive invariant set of system (1) is

$$\mathbb{R}^6_+ = \{S, E, I, I_e, R, W \in \mathbb{R}^6 | S \geq 0, E \geq 0, I \geq 0, I_e \geq 0, R \geq 0, W \geq 0\},$$

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

Lemma 2.2. *(See Lemma 2.1 [34]) The solutions of system (1) are uniformly and ultimately bounded, specifically, there exist $M > 0$ and $T > 0$ such that $\big(S(t), E(t), I(t), I_e(t), R(t), W(t)\big) \leq (\frac{\Lambda}{\mu}, \frac{\Lambda}{\mu}, \frac{\Lambda}{\mu}, \frac{\Lambda}{\mu}, \frac{\Lambda}{\mu}, M)$, for $t \geq T$.*

We begin to analyze system (1) by demonstrating the existence of a 'disease-free' solution. Let $E(t) = 0$, $I(t) = 0$, $I_e(t) = 0$, $W(t) = 0$, and $t \geq 0$, consider the following subsystem:

$$\begin{cases} \left.\begin{aligned} S' &= \Lambda - \mu S + \eta R, \\ R' &= -(\eta + \mu)R, \end{aligned}\right\} t \neq nT, n \in \mathbb{N}, \\ \left.\begin{aligned} S(nT^+) &= (1-\tau)S(nT), \\ R(nT^+) &= R(nT) + \tau S(nT), \end{aligned}\right\} t = nT, n \in \mathbb{N}. \end{cases} \tag{2}$$

Clearly, if solutions $S(t)$ and $R(t)$ of (2) in the interval $(nT,(n+1)T]$ are

$$S(t)=\frac{\Lambda}{\mu}-R(nT^+)e^{-(\eta+\mu)(t-nT)}-\big(\frac{\Lambda}{\mu}-S(nT^+)-R(nT^+)\big)e^{-\mu(t-nT)},$$

$$R(t)=R(nT^+)e^{-(\eta+\mu)(t-nT)},$$

then $S((n+1)T)=\frac{\Lambda}{\mu}-R(nT^+)e^{-(\eta+\mu)T}-\big(\frac{\Lambda}{\mu}-S(nT^+)-R(nT^+)\big)e^{-\mu T}$ and $R((n+1)T)=R(nT^+)e^{-(\eta+\mu)T}$. Using the remaining equations of (2), we deduce the stroboscopic map

$$\begin{aligned}S((n+1)T^+)=&(1-\tau)S((n+1)T)\\=&(1-\tau)\Big[\frac{\Lambda}{\mu}-R(nT^+)e^{-(\eta+\mu)T}-\big(\frac{\Lambda}{\mu}-S(nT^+)-R(nT^+)\big)e^{-\mu T}\Big]\\\triangleq&f_s\big(S(nT^+),R(nT^+)\big)\end{aligned}$$

and

$$\begin{aligned}R((n+1)T^+)=&R((n+1)T)+\tau S((n+1)T)\\=&R(nT^+)e^{-(\eta+\mu)T}\\&+\tau\Big[\frac{\Lambda}{\mu}-R(nT^+)e^{-(\eta+\mu)T}-\big(\frac{\Lambda}{\mu}-S(nT^+)-R(nT^+)\big)e^{-\mu T}\Big]\\\triangleq&f_r\big(S(nT^+),R(nT^+)\big)\end{aligned}$$

We obtain the unique fixed points of maps $f_s\big(S(nT^+),R(nT^+)\big)$ and $f_r\big(S(nT^+),R(nT^+)\big)$, which are

$$S^*=\frac{\Lambda}{\mu}\frac{(1-\tau)(1-e^{-(\eta+\mu)T})}{1-(1-\tau)e^{-(\eta+\mu)T}},R^*=\frac{\Lambda}{\mu}\frac{\tau}{1-(1-\tau)e^{-(\eta+\mu)T}}.$$

By checking the Jacobian matrix of $f_s\big(S(nT^+),R(nT^+)\big)$ and $f_r\big(S(nT^+),R(nT^+)\big)$ at the fixed point, we obtain that the characteristic roots of this matrix are $e^{-\mu T}$ and $(1-\tau)e^{-(\eta+\mu)T}$. Since $\|e^{-\mu T}\|<1$ and $\|(1-\tau)e^{-(\eta+\mu)T}\|<1$, the fixed points S^* and R^* are locally stable.

The solutions of (2) on the interval $(nT,(n+1)T]$ initially from the fixed points S^* and R^* follow

$$\begin{aligned}\tilde{S}(t)&=\frac{\Lambda}{\mu}-R^*e^{-(\eta+\mu)(t-nT)}-(\frac{\Lambda}{\mu}-S^*-R^*)e^{-\mu(t-nT)}\\&=\frac{\Lambda}{\mu}\Big[1-\frac{\tau e^{-(\eta+\mu)(t-nT)}}{1-(1-\tau)e^{-(\eta+\mu)T}}\Big],\end{aligned}$$

and

$$\tilde{R}(t)=R^*e^{-(\eta+\mu)(t-nT)}=\frac{\Lambda}{\mu}\frac{\tau e^{-(\eta+\mu)(t-nT)}}{1-(1-\tau)e^{-(\eta+\mu)T}}.$$

Moreover, $\tilde{S}(t)$ and $\tilde{R}(t)$ are periodic in time, thus, $\tilde{S}(t+T)=\tilde{S}(t)$ and $\tilde{R}(t+T)=\tilde{R}(t)$.

From the above discussion, system (1) admits a DFPS (disease-free periodic solution) $E_1(\tilde{S}(t),0,0,0,0,\tilde{R}(t))$ on every impulsive interval $(nT,(n+1)T]$.

The following lemma shows the global asymptotical stability of the periodic solution $(\tilde{S}(t),\tilde{R}(t))$ of system (2).

Lemma 2.3. *System (2) with initial condition* $(S(0), R(0)) \in \{(S, R) : 0 \leq S \leq \Lambda/\mu, 0 \leq R \leq \Lambda/\mu\}$ *has a unique, positive, periodic solution* $\tilde{u}(t) = (\tilde{S}(t), \tilde{R}(t))$, *which is globally asymptotically stable.*

Proof of Lemma 2.3. The global asymptotic stability of the periodic solution $(\tilde{S}(t), \tilde{R}(t))$ of system (2) is obviously equal to the global asymptotic stability of the positive solution (S^*, R^*) of the following difference equation

$$\begin{cases} S((n+1)T^+) = (1-\tau)e^{-\mu T}S(nT^+) + (1-\tau)\big(e^{-\mu T} - e^{-(\eta+\mu)T}\big)R(nT^+) \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad +(1-\tau)\frac{\Lambda}{\mu}(1-e^{-\mu T}), \\ R((n+1)T^+) = \tau e^{-\mu T}S(nT^+) + \Big[(1-\tau)e^{-(\eta+\mu)T} + \tau e^{-\mu T}\Big]R(nT^+) \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad +\tau\frac{\Lambda}{\mu}(1-e^{-\mu T}). \end{cases} \tag{3}$$

The characteristic roots of system (3) are $e^{-\mu T}$ and $(1-\tau)e^{-(\eta+\mu)T}$, and $\|e^{-\mu T}\| < 1$, $\|(1-\tau)e^{-(\eta+\mu)T}\| < 1$, then the positive solution of difference system (3) is globally asymptotically stable. This completes the proof. □

According to the result in [39], we can define the basic reproduction number of system (1). Linearizing system (1) at $E_1(\tilde{S}(t), 0, 0, 0, 0, \tilde{R}(t))$, yields the following four-dimensional equations:

$$\begin{cases} \frac{\mathrm{d}E}{\mathrm{d}t} &= \beta_1(t)\tilde{S}(t)I + \beta_2(t)\tilde{S}(t)I_e + \nu(t)\tilde{S}(t)W - (\sigma+\mu)E, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \sigma pE - (\gamma_1+\delta_1+\mu)I, \\ \frac{\mathrm{d}I_e}{\mathrm{d}t} &= \sigma(1-p)E - (\gamma_2+\delta_2+\mu)I_e, \\ \frac{\mathrm{d}W}{\mathrm{d}t} &= \lambda_1 I + \lambda_2 I_e - \zeta W. \end{cases} \tag{4}$$

Define

$$F(t) = \begin{pmatrix} 0 & \beta_1(t)\tilde{S}(t) & \beta_2(t)\tilde{S}(t) & \nu(t)\tilde{S}(t) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \sigma+\mu & 0 & 0 & 0 \\ -\sigma p & \gamma_1+\delta_1+\mu & 0 & 0 \\ -\sigma(1-p) & 0 & \gamma_2+\delta_2+\mu & 0 \\ 0 & -\lambda_1 & -\lambda_2 & \zeta \end{pmatrix}.$$

Here, $F(t)$ is defined as the Jacobian matrix of the system (1), which considers only new infections, at the DFPS. We define V is defined as the Jacobian matrix of the system (1) in compartments E, I, I_e and W, considering the transfer of individuals at DFPS.

In this case, system (4) can be rewritten as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = (F(t) - V)x,$$

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

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

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -V(t)y.$$

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

$$\frac{\mathrm{d}Y(t,s)}{\mathrm{d}t} = -V(t)Y(t,s), \forall t \geq s, Y(s,s) = \mathbf{I},$$

where $\mathbf{I}$ is the 4×4 identity matrix. Let C_ω be the ordered Banach space of all $T-$periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, 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; Since $F(t)$ has one discontinuous point $t=nT$ on each interval $[nT,(n+1)T]$, $Y(t,s)F(s)\phi(s)$ has finite discontinuous points in the interval $[a,t]$. Meanwhile, by the boundedness of $F(s)\phi(s)$, the integral $\int_a^t Y(t,s)F(s)\phi(s)ds$ is well-defined.

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

$$(L\phi)(t)=\lim_{a\to-\infty}\int_a^t Y(t,s)F(s)\phi(s)ds,\quad \forall t\in(nT,(n+1)T], n\in\mathbb{N}, \phi\in C_\omega.$$

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

Let $W(t,s,\lambda)$ be the evolution operator of the following linear $T-$periodic system:

$$\frac{\mathrm{d}w}{\mathrm{d}t}=\Big(-V+\frac{F(t)}{\lambda}\Big)w,\quad t\geq s, t\in\mathbb{R},$$

with parameter $\lambda\in(0,\infty)$. Since $F(t)$ is non-negative and $-V$ is cooperative (off-diagonal elements of a matrix are non-negative), $F(t)$ is piecewise continuous and periodic functions. It is easy to verify that (1) satisfies assumptions $H(1)-H(6)$ in [39]. Thus, we have the following result.

Lemma 2.4. *(See Theorem 4.1 [39]). For system (1), the following statements are valid:*

(i) $R_0=1$ if and only if $r(\Phi_{(F-V)(.)}(T))=1$.
(ii) $R_0>1$ if and only if $r(\Phi_{(F-V)(.)}(T))>1$.
(iii) $R_0<1$ if and only if $r(\Phi_{(F-V)(.)}(T))<1$.

Next, we present a threshold parameter that determines the extinction and the uniform persistence of the disease. The following theorem shows that the DFPS of (1) is globally asymptotically stable. To this end, we introduce the following lemma.

Lemma 2.5. *(Comparison theory [20]) Assume $m\in \mathrm{PC}[\mathbb{R}_+,\mathbb{R}]$ with points of discontinuity at $t=nT$ is left continuous at $t=nT, n\in\mathbb{N}$, and*

$$\begin{cases} D_-m(t)\leq g(t,m(t)), & t\neq nT, n\in\mathbb{N},\\ m(nT^+)=\psi_n(m(nT)), & t=nT, n\in\mathbb{N},\end{cases}\tag{5}$$

where $g\in \mathrm{C}[\mathbb{R}_+\times\mathbb{R}_+,\mathbb{R}]$ and $\psi_n(u)$ is non-decreasing in u for each $n\in\mathbb{N}$, let $r(t)$ be the maximal solution of the scalar impulsive differential equation

$$\begin{cases} u'=g(t,m(t)), & t\neq nT, n\in\mathbb{N},\\ u(nT^+)=\psi_n(u(nT)), & t=nT, n\in\mathbb{N},\\ u(t_0^+)=u_0.\end{cases}\tag{6}$$

existing on $[t_0,\infty)$. Then $m(t_0^+)\leq u_0$ implies $m(t)\leq r(t)$.

Remark 1. [20] In Lemma2.5, if inequalities (6) are reversed, we can let $\rho(t)$ be the minimal solution of (7) existing on $[t_0,\infty)$, then $m(t)\geq\rho(t)$.

Assume $\eta=0$, we can obtain the following theorem.

Theorem 2.6. *If $r(\Phi_{(F-V)(.)}(T))<1$, then the DFPS of system (1), $E_1(\tilde{S}(t),0,0,0,0,\tilde{R}(t))$, is globally asymptotically stable; if $r(\Phi_{(F-V)(.)}(T))>1$, then it is unstable.*

Proof of Theorem 2.6. First, we show that the DFPS is locally stable. Linearize system(1) at the periodic solution $E_1(\tilde{S}(t),0,0,0,0,\tilde{R}(t))$. Define $S(t)=s(t)+\tilde{S}(t)$, $E(t)=e(t)$, $I(t)=i(t)$, $I_e(t)=i_e(t)$, $W(t)=w(t)$, $R(t)=r(t)+\tilde{R}(t)$. The linearized equations of system (1) can be written as

$$\begin{cases} Z'=J(t)Z(t), & t\neq nT, n\in\mathbb{N},\\ Z(nT^+)=QZ(nT), & t=nT, n\in\mathbb{N}, \end{cases} \tag{7}$$

where $Z(t)=(s(t),e(t),i(t),i_e(t),w(t),r(t))^T$, $\mathbf{A}=(0,-\beta_1(t)\tilde{S}(t),-\beta_2(t)\tilde{S}(t),-\nu(t)\tilde{S}(t))$, $\mathbf{B}=(0,\gamma_1,\gamma_2,0)$, $\mathbf{E}=diag(1,1,1,1)$,

$$J(t)=\begin{pmatrix} -\mu & \mathbf{A} & \eta\\ 0 & F(t)-V & 0\\ 0 & \mathbf{B} & -(\eta+\mu) \end{pmatrix}, Q=\begin{pmatrix} 1-\tau & \mathbf{0} & 0\\ 0 & \mathbf{E} & 0\\ \tau & \mathbf{0} & 1 \end{pmatrix}.$$

Assume $\zeta=0$ and let $\Phi(t)$ be the fundamental matrix of $Z'=J(t)Z(t)$, then $\Phi(t)=(\phi_{ij}(t))_{1\leq i,j\leq 3}$ and $\phi_{1j},\phi_{2j},\phi_{3j}, j=1,2,3$ are solutions of $Z'=J(t)Z(t)$ with initial values $\phi_{11}=1,\phi_{22}=E,\phi_{33}=1$, and $\phi_{ij}=0, i\neq j, i,j=1,2,3$. Solving the equation $Z'=J(t)Z(t)$ yields $\phi_{11}=e^{-\mu t}$, $\phi_{13}=0$, $\phi_{21}=\mathbf{0}$, $\phi_{23}=\mathbf{0}$, $\phi_{31}=0$, $\phi_{33}=e^{-(\eta+\mu)t}$, $\phi'_{22}=(F(t)-V)\phi_{22}$. It is not necessary to evaluate the exact formulae for ϕ_{12} and ϕ_{32} as they are not required in the following analysis; thus, we denote them with a star. We also denote ϕ_{22} by $\phi_{22}=\Phi_{(F-V)(.)(t)}$. Hence, we obtain

$$\Phi(t)=\begin{pmatrix} e^{-\mu t} & * & 0\\ \mathbf{0} & \Phi_{(F-V)(.)}(t) & \mathbf{0}\\ 0 & * & e^{-(\eta+\mu)t} \end{pmatrix}.$$

Thus, the monodromy matrix of system (8) yields

$$Q\Phi(T)=\begin{pmatrix} (1-\tau)e^{-\mu T} & * & 0\\ \mathbf{0} & \Phi_{(F-V)(.)}(T) & \mathbf{0}\\ \tau e^{-\mu T} & * & e^{-(\eta+\mu)T} \end{pmatrix}.$$

Note that a monodromy matrix, denoted by M, is a nonsingular matrix satisfying $\Phi(t+T)=\Phi(t)M$, where $\Phi(t)$ is the fundamental matrix of ODEs system evaluated at the period of the coefficients of the periodic system $Z'=J(t)Z(t)$, then $\Phi(t+T)$ is also the fundamental matrix of the ODEs system [1].

Thus, Floquet theory and $r(\Phi_{(F-V)(.)}(T))<1$ indicate that the DFPS is locally stable; when $r(\Phi_{(F-V)(.)}(T))>1$ the DFPS is unstable.

Next, we prove the global attractivity of the DFPS. By the first equation of system (1) and the positivity of the solution, we obtain

$$\begin{cases} S'\leq \Lambda-\mu S, & t\neq nT, n\in\mathbb{N},\\ S(nT^+)=(1-\tau)S(nT), & t=nT, n\in\mathbb{N}. \end{cases}$$

Consider the following auxiliary system

$$\begin{cases} x'=\Lambda-\mu x, & t\neq nT, n\in\mathbb{N},\\ x(nT^+)=(1-\tau)x(nT), & t=nT, n\in\mathbb{N}. \end{cases} \tag{8}$$

It is easy to verify that system (8) admits a positive periodic solution

$$\tilde{x}(t)=\frac{\Lambda}{\mu}\Big[1-\frac{\tau e^{-\mu(t-nT)}}{1-(1-\tau)e^{-\mu T}}\Big],$$

which is globally asymptotically stable, i.e., $x(t) \to \tilde{x}(t)$, for $t \to \infty$. By the comparison theorem, we have $S(t) \le x(t)$. Hence, there exists $t_1 > 0$, such that for any $\epsilon > 0$, $S(t) \le \tilde{x}(t) + \epsilon$. Since $\tilde{x}(t) \le \tilde{S}(t)$, it follows that $S(t) \le \tilde{S}(t) + \epsilon$.

By system (1),

$$\begin{cases} E' & \le & \beta_1(t)(\tilde{S}(t)+\epsilon)I + \beta_2(t)(\tilde{S}(t)+\epsilon)I_e + \nu(t)(\tilde{S}(t)+\epsilon)W \\ & & \qquad -(\sigma+\mu)E, \\ I' & = & \sigma pE - (\gamma_1+\delta_1+\mu)I, \qquad t \ge t_1. \\ I_e' & = & \sigma(1-p)E - (\gamma_2+\delta_2+\mu)I_e, \\ W' & = & \lambda_1 I + \lambda_2 I_e - \zeta W. \end{cases}$$

Consider an auxiliary system

$$\begin{cases} u_1' & = & \beta_1(t)(\tilde{S}(t)+\epsilon)u_2 + \beta_2(t)(\tilde{S}(t)+\epsilon)u_3 + \nu(t)(\tilde{S}(t)+\epsilon)u_4 - (\sigma+\mu)u_1, \\ u_2' & = & \sigma p u_1 - (\gamma_1+\delta_1+\mu)u_2, \\ u_3' & = & \sigma(1-p)u_1 - (\gamma_2+\delta_2+\mu)u_3, \\ u_4' & = & \lambda_1 u_2 + \lambda_2 u_3 - \zeta u_4. \end{cases} \tag{9}$$

which is equivalent to

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

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 follows from Lemma2.1. that there exists a positive T-periodic function $\rho(t) = \big(\rho_1(t), \rho_2(t), \rho_3(t), \rho_4(t)\big)$ such that $e^{\mu_1 t}\rho(t)$ is a solution of (9), where $\mu_1 = \frac{1}{T}\ln r(\Phi_{(F-V)(.)+\epsilon M}(T))$. Choose $t_2 > t_1$ and a small number $\alpha > 0$ such that $u(t_2) \le \alpha\rho(0)$. Then we obtain

$$u(t) \le \alpha e^{\mu_1(t-t_2)} v(t-t_2), \quad t \ge t_2.$$

By the standard comparison theorem [28], Theorem B.1, we obtain

$$(E(t), I(t), I_e(t), W(t))^T \le u(t) \le \alpha e^{\mu_1(t-t_2)}\rho(t-t_2), \quad t \ge t_2.$$

Since $r(\Phi_{(F-V)(.)}(T)) < 1$ and $r(\Phi_{(F-V)(.)+\epsilon M}(T))$ are continuous for all small ϵ, we choose a sufficiently small $\epsilon > 0$ such that $r(\Phi_{(F-V)(.)+\epsilon M}(T)) < 1$. Hence, we get $\mu_1 < 0$. It follows that $u(t) \to 0$ as $t \to \infty$. Then we obtain $(E(t), I(t), I_e(t), W(t))^T \to \mathbf{0}$ as $t \to \infty$. By the first and sixth equations of system (1), we get $\lim_{t\to\infty} S(t) = \tilde{S}(t)$ and $\lim_{t\to\infty} R(t) = \tilde{S}(t)$. Thus the DFPS E_1 is globally attractive. This completes the proof. □

Theorem 2.7. *If $r(\Phi_{(F-V)(.)}(T)) > 1$, then there exists a positive constant ξ such that for all initial values $(S^0, E^0, I^0, I_e^0, R^0, W^0) \in \mathbb{R}_+ \times \mathrm{Int}(\mathbb{R}_+^3) \times \mathbb{R}_+ \times \mathrm{Int}(\mathbb{R}_+)$ the solution of system (1) satisfies*

$$\liminf_{t\to\infty} \big(E(t), I(t), I_e(t), W(t)\big) \ge (\xi, \xi, \xi, \xi).$$

Proof of Theorem 2.7. There exist a positive constant m, we first prove the following claim:

$$\limsup_{t\to\infty} E(t) \ge m, \quad \limsup_{t\to\infty} I(t) \ge m, \quad \limsup_{t\to\infty} I_e(t) \ge m, \quad \limsup_{t\to\infty} W(t) \ge m. \tag{10}$$

Without loss of generality, suppose that for any positive constant m, there exists a t_1, such that $W(t) < m$ for all $t \geq t_1$. Then, by the first equation of system (1), we have

$$\begin{aligned} S'(t) &\geq \Lambda - \beta_1(t)SI - \beta_2(t)SI_e - m\nu(t)S - \mu S \\ &> \Lambda - \frac{\Lambda}{\mu}\beta_1(t)S - \frac{\Lambda}{\mu}\beta_2(t)S - m\nu(t)S - \mu S, \quad t \geq t_1. \end{aligned}$$

Consider the following auxiliary system

$$\begin{cases} y' = \Lambda - (\frac{\Lambda}{\mu}\beta_1(t) + \frac{\Lambda}{\mu}\beta_2(t) + m\nu(t) + \mu)y, & t \neq nT, n \in \mathbb{N}, \\ y(nT^+) = (1-\tau)y(nT), & t = nT, n \in \mathbb{N}. \end{cases} \tag{11}$$

Using the same method as above, it follows that (11) admits a positive periodic solution

$$\tilde{y}(t) = \frac{\Lambda}{\mu}\Big[1 - \frac{\tau e^{-(\frac{\Lambda}{\mu}\beta_1(t)+\frac{\Lambda}{\mu}\beta_2(t)+m\nu(t)+\mu)(t-nT)}}{1-(1-\tau)e^{-(\frac{\Lambda}{\mu}\beta_1(t)+\frac{\Lambda}{\mu}\beta_2(t)+m\nu(t)+\mu)T}}\Big],$$

which is globally asymptotically stable, i.e., $y(t) \to \tilde{y}(t)$, for $t \to \infty$. By the comparison theorem, $S(t) \geq y(t)$. Hence, there exists $t_2 > 0$ such that for any $\varepsilon > 0$, $S(t) \geq \tilde{y}(t) - \epsilon$. Since $\tilde{y}(t) \geq \tilde{S}(t)$, $\eta = 0$, so it follows that $S(t) \geq \tilde{S}(t) - \varepsilon$.

By system (1),

$$\begin{cases} E' &\geq \beta_1(t)(\tilde{S}(t)-\varepsilon)I + \beta_2(t)(\tilde{S}(t)-\varepsilon)I_e + \nu(t)(\tilde{S}(t)-\varepsilon)W \\ & \qquad -(\sigma+\mu)E, \\ I' &= \sigma pE - (\gamma_1+\delta_1+\mu)I, \qquad t \geq t_2. \\ I_e' &= \sigma(1-p)E - (\gamma_2+\delta_2+\mu)I_e, \\ W' &= \lambda_1 I + \lambda_2 I_e - \zeta W. \end{cases}$$

Consider an auxiliary system

$$u' = (F(t) - V)u - \varepsilon M(t)u. \tag{12}$$

It follows from Lemma2.1 that there exists a positive T-periodic function $\rho(t) = \big(\rho_1(t), \rho_2(t), \rho_3(t), \rho_4(t)\big)$ such that $e^{\mu_2 t}\rho(t)$ is a solution of (12), where $\mu_2 = \frac{1}{T}\ln r(\Phi_{(F-V)(.)-\varepsilon M}(T))$. Choose $t_3 > t_2$ and a small number $\alpha > 0$ such that $u(t_3) \geq \alpha\rho(0)$. Then we obtain

$$u(t) \geq \alpha e^{\mu_2(t-t_3)}\rho(t-t_3), \quad t \geq t_3.$$

By the standard comparison theorem [28], Theorem B.1, we obtain

$$(E(t), I(t), I_e(t), W(t))^T \geq u(t) \geq \alpha e^{\mu_2(t-t_3)}\rho(t-t_3), \quad t \geq t_3.$$

Since $r(\Phi_{(F-V)(.)}(T)) > 1$ and $r(\Phi_{(F-V)(.)-\varepsilon M}(T))$ is continuous for all small ε, choose a sufficiently small $\varepsilon > 0$, such that $r(\Phi_{(F-V)(.)-\varepsilon M}(T)) > 1$. Hence, we get $\mu_2 > 0$. It follows that $u(t) \to \infty$ as $t \to \infty$. Therefore, we obtain $(E(t), I(t), I_e(t), W(t))^T \to \infty$ as $t \to \infty$, which contradicts the boundedness of $E(t)$, $I(t)$, $I_e(t)$ and $W(t)$. Thus, the claim is proved.

Since the claim holds, we consider the following two possibilities.

(i) $E(t) \geq m$, $I(t) \geq m$, $I_e(t) \geq m$ and $W(t) \geq m$, for all large t;

(ii) $E(t)$, $I(t)$, $I_e(t)$ and $W(t)$ oscillate about m for all large t.

If (i) holds, then our aim is achieved. Next, consider (ii). Without loss of generality, we only discuss $I(t)$ since $E(t)$, $I(t)$, $I_e(t)$, and $W(t)$ can be proved in the same way. Let $\bar{t}$ and $\underline{t}$ be large enough so that

$$I(\bar{t}) = I(\underline{t}) = m, I(t) < m, \quad t \in (\bar{t}, \underline{t}).$$

Since $I(t)$ is continuous, bounded, and not affected by impulses, it is uniformly continuous. Hence, there exists a constant $\omega > 0$,(ω is independent of the choice of $\underline{t}$) such that $I(t) \geq m/2$ for all $t \in [\underline{t}, \underline{t} + \omega]$.

If $\bar{t} - \underline{t} \leq \omega$, then $I(t) \geq m/2$ for all $t \in [\underline{t}, \bar{t}]$. We can fix $\xi = m/2$, then the claim is obtained.

If $\bar{t} - \underline{t} > \omega$, then $I(t) \geq m/2$ for all $t \in [\underline{t}, \underline{t} + \omega]$.

Next, we prove that $I(t) \geq m/2$ for all $t \in [\underline{t} + \omega, \bar{t}]$. Suppose to the contrary that there exists a constant T_1, such that

$$I(t) \geq m/2, \quad t \in [\underline{t}, \underline{t} + \omega + T_1],$$

and

$$I(t + \omega + T_1) = m/2, \quad I(t) < m/2, \quad 0 < t - (\underline{t} + \omega + T_1) \ll 1.$$

In the same way, we also obtain $E(t) < m/2$, $I_e(t) < m/2$ and $W(t) < m/2$, for $0 < t - (\underline{t} + \omega + T_1) \ll 1$. On the other hand, as previously mentioned, we obtain $S(t) \geq \tilde{S}(t) - \varepsilon, \forall t \in [\underline{t}, \bar{t}]$, and $\underline{t}$, $\bar{t}$ are sufficiently large. By the equation of system (1), we have

$$\begin{cases} E' & \geq & \beta_1(t)(\tilde{S}(t) - \varepsilon)I + \beta_2(t)(\tilde{S}(t) - \varepsilon)I_e + \nu(t)(\tilde{S}(t) - \varepsilon)W - (\sigma + \mu)E, \\ I' & = & \sigma p E - (\gamma_1 + \delta_1 + \mu)I, \\ I_e' & = & \sigma(1 - p)E - (\gamma_2 + \delta_2 + \mu)I_e, \\ W' & = & \lambda_1 I + \lambda_2 I_e - \zeta W. \end{cases}$$

where $0 < t - (\underline{t} + \omega + T_1) \ll 1$. Hence,

$$(E', I', I_e', W')^T \geq (F(t) - V - \varepsilon M(t))(E, I, I_e, W)^T, \quad 0 < t - (\underline{t} + \omega + T_1) \ll 1.$$

By previous arguments, there exists a positive T-periodic function $v(t) = \big(v_1(t), v_2(t), v_3(t), v_4(t)\big)$ such that $e^{\mu_2 t} v(t)$ is a solution of (12), where $\mu_2 = \frac{1}{T} \ln r$ $(\Phi_{(F-V)(.)-\varepsilon M}(T)) > 0$. Choose $\rho > 0$ such that $(E(\underline{t}+\omega+T_1), I(\underline{t}+\omega+T_1), I_e(\underline{t}+\omega+T_1), E(\underline{t}+\omega+T_1)) \geq \rho v(0) > (m/2, m/2, m/2, m/2)$. Since $v(t)$ is a continuous and periodic function, $\rho v(t) \geq (m/2, m/2, m/2, m/2)$ for $0 < t \ll 1$ holds. Then the comparison theorem implies that for $0 < t - (\underline{t} + \omega + T_1) \ll 1$,

$$\begin{aligned} \big(E(t), I(t), I_e(t), W(t)\big) &\geq \rho e^{\mu_2(t - \underline{t} - \omega - T_1)} v(t - \underline{t} - \omega - T_1) \\ &> \rho v(t - \underline{t} - \omega - T_1) \\ &\geq (m/2, m/2, m/2, m/2) \end{aligned}$$

holds. Finally $E(t) > m/2$, $I(t) > m/2$, $I_e(t) > m/2$ and $W(t) > m/2$ for $0 < t - (\underline{t} + \omega + T_1) \ll 1$, which contradicts the assumption. Hence $E(t) \geq m/2$, $I(t) \geq m/2$, $I_e(t) \geq m/2$ and $W(t) \geq m/2$, for any $t \in [\underline{t}, \bar{t}]$, where $m/2 \doteq \xi$ for any $t \in [\underline{t}, \bar{t}]$. Since $\bar{t}$ and $\underline{t}$ are sufficiently large, $\big(E(t), I(t), I_e(t), W(t)\big) \geq (\xi, \xi, \xi, \xi)$ for sufficiently large t. Hence, $\liminf_{t \to \infty} \big(E(t), I(t), I_e(t), W(t)\big) \geq (\xi, \xi, \xi, \xi)$, which completes the proof. □

3. **Numerical results.** In this section, we numerically analyse model (1), concentrating on the effect of pulse vaccination on HFMD infections. Data on symptomatic cases of endemic HFMD in mainland China were obtained from the Chinese CDC [8]. The surveillance system provides monthly real-time statistics for mainland China. From the National Bureau of Statistics of China [26], we obtain the recruitment rate of susceptible individuals (Λ) and the natural death rate (d). We only considered the population of young children under six years of age. Note that the

proportion of children under six years of age is approximately 7.89%; thus, the number of susceptible individuals in 2010 was $S(0) = 105703908$. We obtain the annual human population using annual birth data from the National Bureau of Statistics of China [26]. By dividing the annual population by 12, the human birth population is derived as $\Lambda = 1328556$, specifically. Assume that the symptomatic and asymptomatic individuals have the same recovery rate, which is derived directly in [11]. Transmission coefficient functions are assumed to be $\beta_1(t) = a_1(1 + \sin(\frac{2\pi t}{12} + \phi))$, $\beta_2(t) = a_2(1 + \sin(\frac{2\pi t}{12} + \phi))$ and $\nu(t) = a_3(1 + \sin(\frac{2\pi t}{24} + \phi))$, where $\phi = 2$ is based on an estimate in [23]; and $a_i, i = 1, 2, 3$, are unknown positive constants that will be estimated. The EV71 vaccine consistently elicits immunogenicity and provides protection against mild-to-severe disease caused by EV71 for infants over 1 year old and young children [43]; therefore, the vaccination periodic T is assumed to be 12 months.

Based on known parameters, which are listed in Table1, we plotted the goodness-of-fit to the data from 2010 to 2015 in mainland China, as shown in Fig.1. Using the parameters listed in Table1, we calculated the basic reproduction number to be $R_0 = r(\Phi_{F-V}(24)) = 1.74$, which indicates that HFMD infections will not be eliminated under the current strategies. To examine the effects of pulse vaccination on new symptomatic infections, we assumed that a pulse vaccination strategy was implemented in 2015 and plotted the variation in the monthly number of new symptomatic infections with different rate of coverage of vaccination. Fig.2 (a) shows that the monthly number of new symptomatic infected individuals is significantly reduced once the vaccination strategy is implemented, which means that the vaccination measure can effectively control the number of infected individuals and prevent outbreaks of disease. Fig.2 (b) shows that the monthly number of recovered individuals increases significantly once the vaccination strategy is implemented, and the larger the rate of pulse vaccination τ, the greater the number of recovered individuals; that is, high rates of vaccination lead to an increase in the number of recovered individuals. Hence, the vaccination strategy is beneficial for controlling the spread of disease.

We considered the seasonal transmission rate, where $\beta_1(t) = a_1(1+\sin(\frac{2\pi t}{12}+\phi))$, $\beta_2(t) = a_2(1 + \sin(\frac{2\pi t}{12} + \phi))$ and $\nu(t) = a_3(1 + \sin(\frac{2\pi t}{24} + \phi))$ in model (1). From Fig.3, we find that the seasonal phase-shift parameter ϕ has a significant influence on the monthly average number of symptomatic infected individuals and gives rise to periodic variation. Moreover, we obtain the optimal phase shift such that the number of symptomatic infected individuals reaches a minimum. Fig.4 (a) and (b) show the effects of the pulse vaccination rate τ and seasonal phase shift ϕ on the basic reproduction number R_0 for various vaccination periods. It follows from Fig.4(a) that increasing the phase shift greatly decreases R_0, while enhancing pulse vaccination may or may not reduce R_0, depending on the value of the phase shift. In particular, for relatively low values of the phase shift, the variation with pulse vaccination slightly reduces the basic reproduction number, while for relatively high phase shift values, increasing the rate of pulse vaccination induces periodic variation in R_0. When the vaccination period $T = 24$, it is obvious that no matter what the values of τ and ϕ are, the basic reproduction number R_0 is persistently greater than unity, which means that a less-frequent vaccination strategy cannot effectively control the spread of HFMD.

To discuss the influence of different vaccination periods on HFMD control, we plotted the variation of monthly average symptomatic infected individuals with

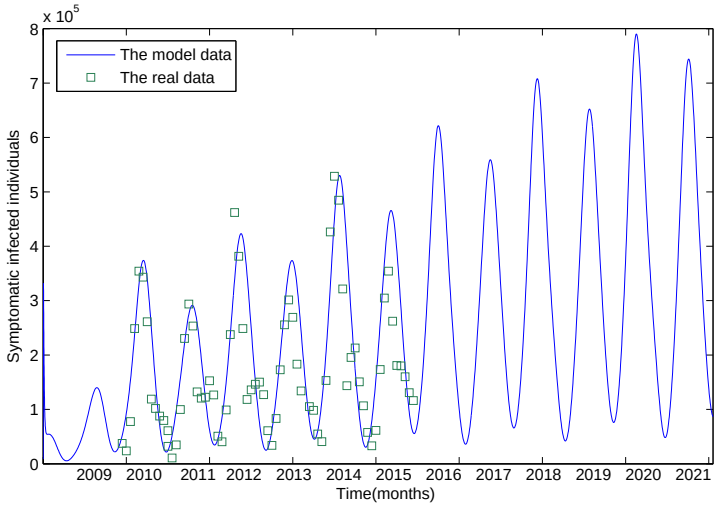

FIGURE 1. Goodness-of-fit to the real data from 2010-2015 in mainland China without pulse vaccination.

different vaccination periods and vaccination rates. Fig.5 (a) shows that when the pulse vaccination rate is $\tau = 0.25$, different vaccination periods do not have a significant influence on the monthly average symptomatic infected individuals. Fig.5 (b) shows that when the pulse vaccination rate is $\tau = 0.75$, the monthly average number of symptomatic infected individuals for $T = 12$ is significantly reduced compared to that for $T = 24$. This suggests that increasing the vaccination rate and shortening the vaccination period can effectively reduce the number of infected individuals and prevent the spread of disease.

In the preceding discussion, HFMD pulse vaccination was assumed to occur at the beginning of each year. Next, we will discuss the influence of different timings of pulse vaccination occurrence on the monthly average number of symptomatic infected individuals. For this purpose, let pulse vaccination occur at times $t = nT + \psi$, where $0 \leq \psi < T$, $n \in \mathbb{N}$. In other words, we study the effect of a phase shift in the pulse vaccinations on disease transmission and control. Fig.6 and Fig.7 show that, when the pulse vaccination period is $T = 12$ and 24 months, the monthly number of symptomatic infected individuals reaches its minimum for phase $\psi = 9$ and 18 months, respectively. This indicates that the optimal timing for vaccination is in September, just before a new term begins. Note that in September, the temperature is suitable for the survival and transmission of EV71. After the new term begins, effective contact among susceptible children are more conducive to the spread of HFMD. Thus, pulse vaccination at this time can effectively control the outbreak of HFMD.

Moreover, we discuss the influence of the pulse vaccination rate τ and timing of pulse vaccination ψ on the basic reproduction number R_0, as shown in Fig.8. It follows from Fig.8 (a) and (b) that for relatively low values of ψ, increasing the rate of pulse vaccination does not significantly affect the basic reproduction number, while for relatively high values of ψ, varying the rate of pulse vaccination induces periodic oscillation in R_0. In particular, there is an optimal combination of the

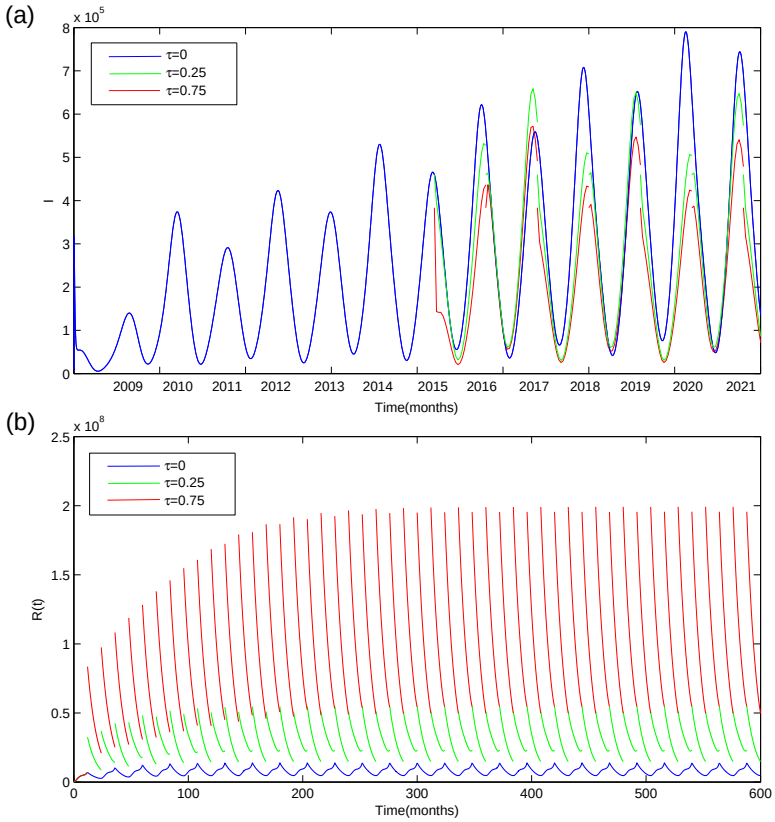

FIGURE 2. The influence of the introduction of pulse vaccination in 2015 on (a) the number of infected individuals and (b) the number of recovered individuals.

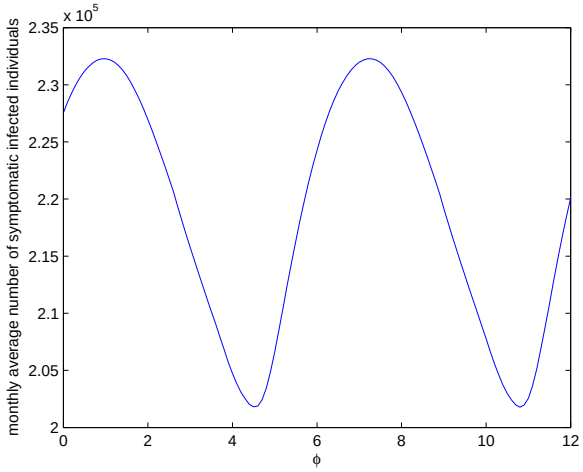

FIGURE 3. The effect of the seasonal phase ϕ on the monthly average number of symptomatic infected individuals.

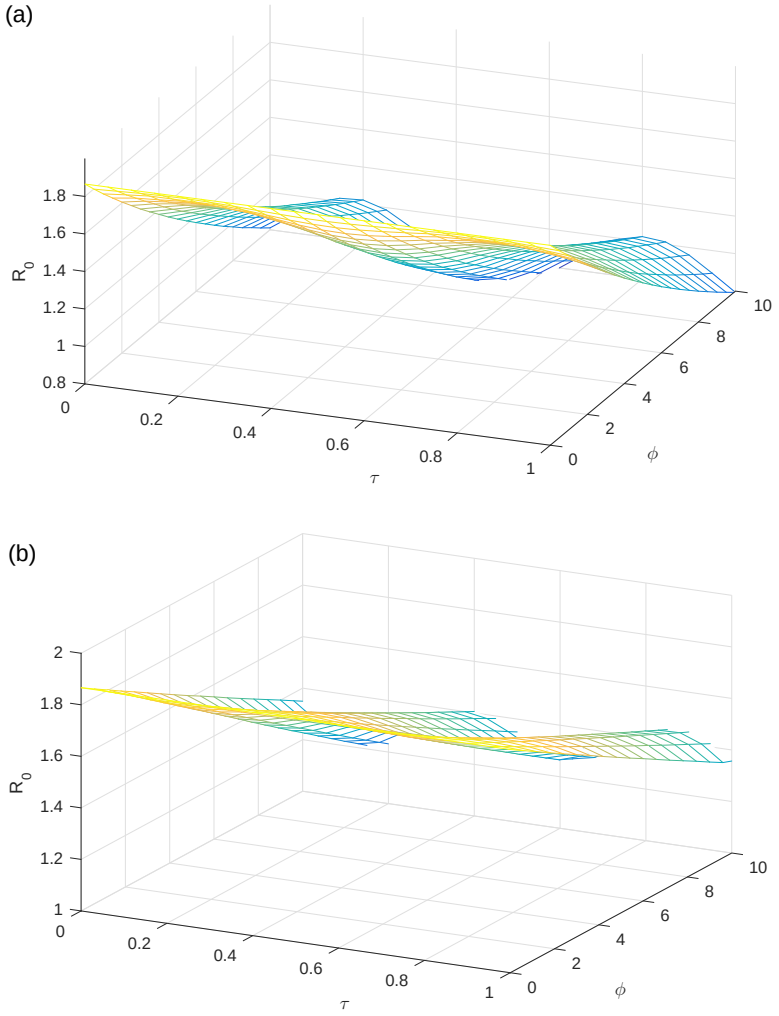

FIGURE 4. The effect of different phase ϕ and proportion of pulse vaccination τ on R_0. The seasonal transmissions are of the forms $\beta_1(t) = a_1(1 + \sin(\frac{2\pi t}{12} + \phi))$, $\beta_2(t) = a_2(1 + \sin(\frac{2\pi t}{12} + \phi))$ and $\nu(t) = a_3(1 + \sin(\frac{2\pi t}{24} + \phi))$, where ϕ is the seasonal phase shift; (a) the pulse vaccination period $T = 12$ months, (b) the pulse vaccination period $T = 24$ months.

rate and timing of the pulse vaccination such that the basic reproduction number reaches a minimum. A comparison of Fig.8 (a) and (b) indicates that when the pulse vaccination period $T = 24$ months is applied, the basic reproduction number is always greater than one; therefore, pulse vaccinations with a period of 24 months are not to be recommended. This result suggests that large outbreaks of HFMD infection could be significantly prevented by annual vaccinations in September, which is also in agreement with the conclusion of Fig.6 and Fig.7.

To examine the sensitivity of our results to parameter variations, we used Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs) [24,

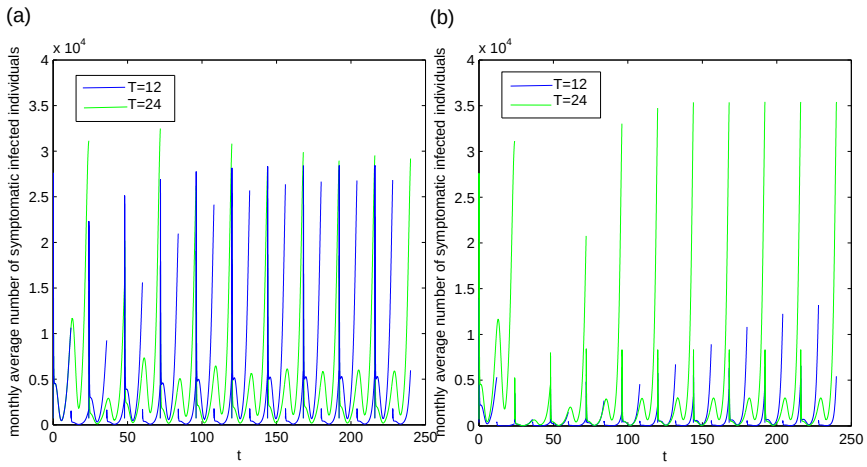

FIGURE 5. The effect of pulse vaccination on the monthly average number of symptomatic infected individuals with a different vaccination period, where $T = 12$ is depicted by a blue line and $T = 24$ is depicted by a green line; (a) proportion of pulse vaccination $\tau = 0.25$, and (b) proportion of pulse vaccination $\tau = 0.75$.

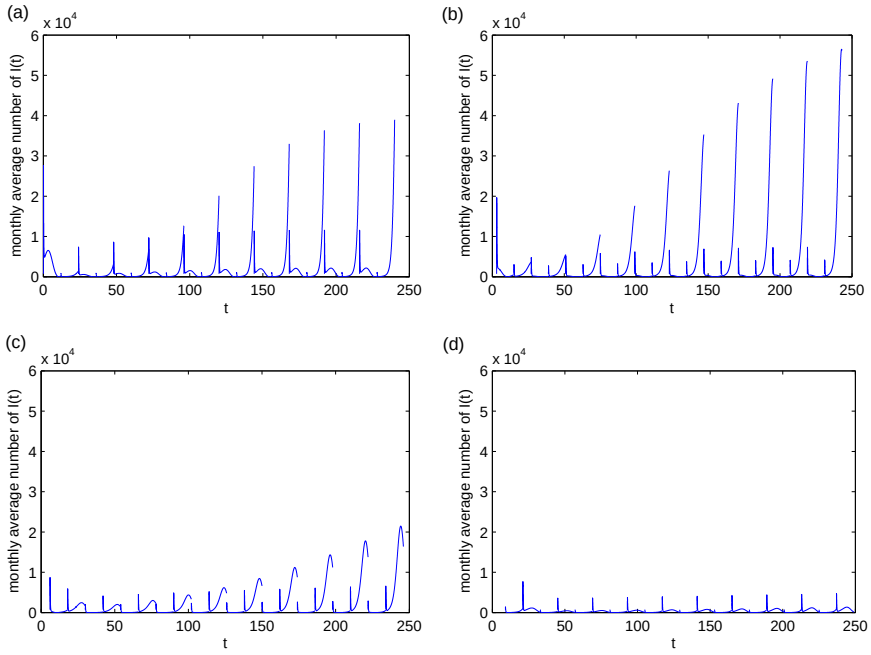

FIGURE 6. The effect of phase differences between pulse vaccinations on the monthly average number of symptomatic infected individuals (pulse vaccinations occur at times $t = nT + \psi$), where the pulse vaccination proportion $\tau = 0.75$, the vaccination period $T = 12$ months. (a) $\psi = 0$, (b) $\psi = 3$, (c) $\psi = 6$, (d) $\psi = 9$.

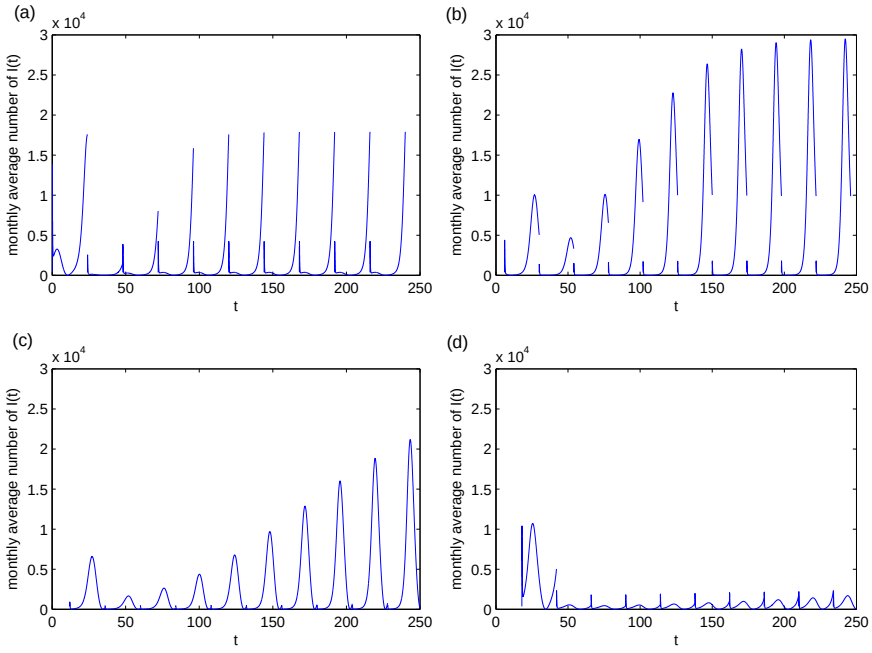

FIGURE 7. The effect of phase differences between pulse vaccinations on the monthly average number of symptomatic infected individuals (pulse vaccinations occur at times $t = nT + \psi$), where the pulse vaccination proportion $\tau = 0.75$, the vaccination period $T = 24$ months. (a) $\psi = 0$, (b) $\psi = 6$, (c) $\psi = 12$, (d) $\psi = 18$.

37] to examine the dependence of the monthly average of $I(t)$ (infectious with symptoms) on uncertain parameters. We carried out 1000 simulations per run. In the absence of available data on the distribution functions, we chose a uniform distribution for the input parameters with ranges listed in Table2 and tested for significant PRCCs for all parameters of the model (1). Fig.9 shows the PRCC values, which illustrates the dependence of the monthly average of $I(t)$ on 13 main 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 [24].

It follows from Fig.9 that the parameters with the greatest impact on the monthly average of $I(t)$ are the direct transmission coefficient of symptomatic and asymptomatic individuals (a_1 and a_2), indirect transmission coefficient (a_3), rate of clearance of the virus (ζ), and rate of pulse vaccination (τ). It is interesting to note that variation in the direct transmission coefficient (a_2), indirect transmission coefficient (a_3), and pulse vaccination rate (τ) have a major influence on the monthly average of $I(t)$. Moreover, Fig.9 suggests that increasing the coverage rate of the pulse vaccination strategy, improving hand hygiene of individuals, and frequently cleaning are effective and feasible strategies for reducing HFMD infections.

4. **Discussion.** A vaccination strategy is used to control or eradicate an infection in a population. HFMD infections appears periodically in mainland China with a

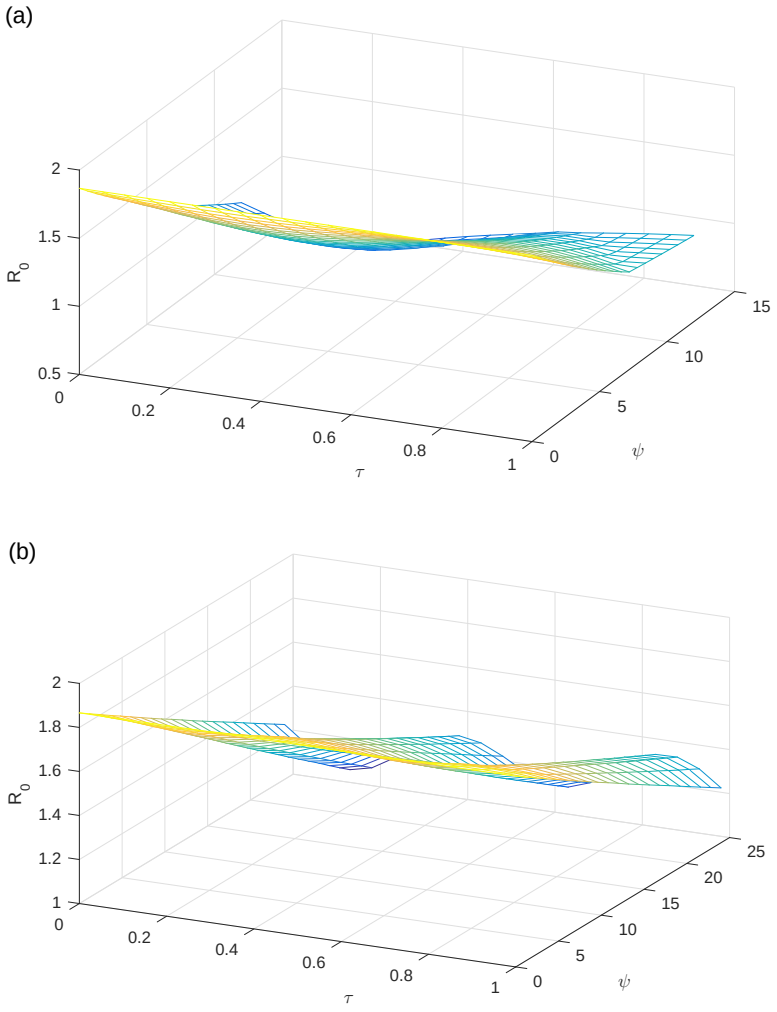

FIGURE 8. The effect of different phases ψ and proportions of pulse vaccinations τ on R_0. Pulse vaccinations occur at times $t = nT + \psi$, where $0 \leq \psi < T$, $n \in \mathbb{N}$. (a) pulse vaccination period $T = 12$ months, (b) pulse vaccination period $T = 24$ months.

relative large oscillation every other year [8]. In this study, we proposed and analysed a HFMD model with periodic transmission rates and impulsive vaccination for seasonal outbreaks. The proposed model extends the existing models by combining effects of contaminated environments, asymptomatic infected subpopulations, and an impulsive vaccination strategy. Models with a periodic transmission rate for HFMD have been previously proposed, but such models mainly considered a direct transmission rate although despite evidence that contaminated environments [2, 10, 17] and recessive (asymptomatic) subpopulations are also important sources for contracting an infection [7, 23]. Hence, in our model, infected individuals were divided into two subgroups (symptomatic and asymptomatic); furthermore, indirect transmission via free-living viruses in the environment were also included. Our proposed model incorporated two routes of transmission: direct transmission between

TABLE 2. PRCC values for monthly average number of I

Parameters	Distribution	PRCC	p-Value
Λ	U(1328000, 1329000)	0.0336	0.1346
η	U(0.1, 0.1)	0.0816	0.0328
p	U(0.022, 0.028)	0.4598	0
a_1	U(0.000000012, 0.000000018)	0.7430	0
a_2	U(0.000000002, 0.0000000025)	0.9579	0
σ	U(5.9, 6.1)	0.0968	0.1147
γ_1	U(0.19, 0.196)	-0.0679	0.0243
γ_2	U(0.19, 0.196)	-0.2475	0.0165
a_3	U(0.000000000015, 0.000000000021)	0.9635	0
λ_1	U(800, 30000)	0.2611	0
λ_2	U(600, 800)	0.5977	0
τ	U(0.1, 1)	-0.7813	0
ζ	U(25, 35)	-0.3812	0.0043

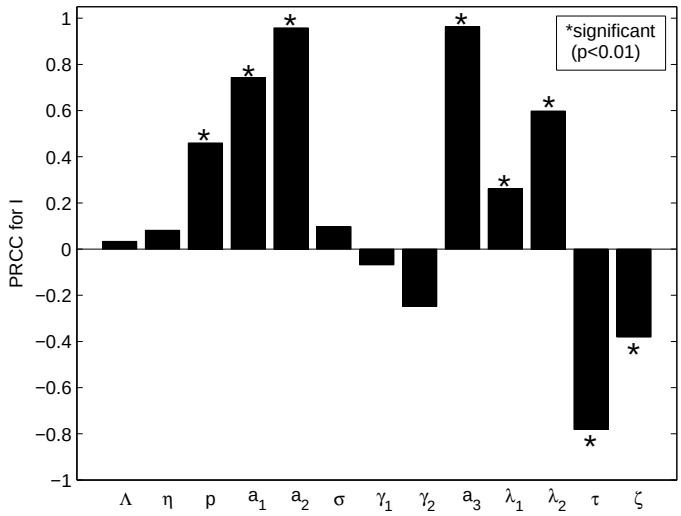

FIGURE 9. PRCCs value for the outcome of the monthly average number I. All the parameters are listed in Table 1.

susceptible and infected (symptomatic or asymptomatic) individuals and indirect transmission via freeliving viruses. Compared with existing models on HFMD infection [23, 38, 33, 34], our proposed model is the first to consider a pulse vaccination strategy. Therefore, with respect to modelling, the main contribution of our proposed model, compared with that of [34], is the inclusion of the pulse vaccination rate. Our main concerns when studying the epidemiology of HFMD are determining what time and to what extent pulse vaccination should be implemented to effectively control HFMD infection and to suggest an optimal pulse vaccination control strategy.

We also theoretically analysed the proposed model. We calculated the periodic solution of an 'infection-free' system (2), then obtained a threshold parameter $r(\Phi_{F-V(.)}(T))$ for system (1), which determines the extinction and the uniform persistence of the disease. The basic reproduction number R_0 was defined by the next infection operator with the relationship $r(\Phi_{F-V(.)}(T)) > 1 \Leftrightarrow R_0 > 1$;

$r(\Phi_{F-V(.)}(T)) < 1 \Leftrightarrow R_0 < 1$ and $r(\Phi_{F-V(.)}(T)) = 1 \Leftrightarrow R_0 = 1$. Our main theoretical results show that when $\eta = 0$, the DFPS for system (1), $E_1(\tilde{S}(t), 0, 0, 0, 0, \tilde{R}(t))$, is globally asymptotically stable if $r(\Phi_{F-V(.)}(T)) < 1$, whilst the disease is persistent for $r(\Phi_{F-V(.)}(T)) > 1$.

We also considered the goodness-of-fit of our proposed model to real data from 2010 to 2015 in mainland China, as shown in Fig.1. We investigated the effect of vaccination rates on HFMD infections and examined the influence of a seasonal phase shift and pulse vaccination rate on the basic reproduction number R_0. We found that frequent vaccination at a high rate leads to a decline in HFMD infection (as shown in Fig.5). Through numerical simulations in Fig.6 and Fig.7, we gained insights into optimizing vaccination strategies. In particular, we found that the best timing for vaccination is in September, just before a new term begins. A sensitivity analysis illustrated that asymptomatic infected individuals and the contaminated environments are essential factors substantially contributing to new HFMD infections; cleaning the environments as well as vaccines are effective measures in reducing HFMD infections. Therefore, the existence of asymptomatic infected individuals and contaminated environments significantly increase the risk of HFMD transmission among children, compared with existing results in the literature [23, 38] where either the asymptomatic compartment or contaminated environment is ignored in the model formulation. Our main results suggest that frequent immunization with a greater coverage rate may significantly reduce HFMD infections. Our findings also suggest that frequent cleaning of the environment and enhanced individual sanitation (e.g., regular hand-washing) are effective measures in controlling HFMD infections; in addition, vaccinating at the optimal time (i.e., September, just before a new term begins) with a greater coverage rate is an effective approach in preventing HFMD outbreaks.

In recent years, HFMD has been increasingly recognized as a public health priority, particularly for children under five years of age. Therefore, it is important to compare the effectiveness of periodic mass (pulse) vaccination versus routine (constant) vaccination. Disease-control authorities should consider certain logistical aspects, which may affect the cost of implementing a particular strategy. Our model considers seasonality and environmental transmission. Note that we use of the mass action incidence $\beta_1(t)SI$ rather than the standard incidence rate, which is more appropriate to describe the contacts of individuals in a community. When we consider the indirect transmission via free-living pathogens in the environment, how to formulate the standard incidence brings great challenges. To keep consistence we use the mass action incidence for direct and indirect transmission. We showed the existence of an optimal pulse vaccination strategy, that is, a well-timed pulse vaccination strategy during the season before the high-transmission season, which is in agreement with the results for the SIR model (susceptible (S), infected (I), and recovered (R)) [27]. More researches need to be conducted on environmental transmission (indirect transmission), pulse vaccination in metapopulations (patch model), and now people pay more attention to this disease, thus media reports may influence the spread of HFMD [31, 37]. This may explain why a relatively large outbreak of HFMD occurs every other year [5], which may be influenced by many environmental factors such as EV71 survival time, average air temperature, humidity, and air pressure. Homogeneous mixing assumptions used in our model may approximate some communities; however, in the whole mainland, transmission dynamics exhibit heterogeneity in the structure of all communities. Considering

the effect of social networks and exploring the occurrence of large outbreaks every other year are interesting topics for future research.

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