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Research article

A realistic model for the periodic dynamics of the hand-foot-and-mouth disease

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Abstract: In this paper, an SEIQRS model with a periodic vaccination strategy is studied for the dynamics of the Hand-Foot-and-Mouth Disease (HFMD). This model incorporates a seasonal variation in the disease transmission rate $\beta(t)$. Our model has a unique disease free periodic solution (DFPS). The basic reproductive number R_0 and its lower and upper bounds, R_0^{inf} and R_0^{sup} respectively, are defined. We show that the DFPS is globally asymptotically stable when $R_0^{sup} < 1$ and unstable if $R_0^{inf} > 1$. Computer simulations of our model have been conducted using a novel periodic function of the contact rate. This novel function imitates the seasonality in the observed, multi-peaks pattern, data. Clear and good matching between real data and the obtained simulation results are shown. The obtained simulation results give a good prediction and possible control of the disease dynamics.

Keywords: modelling; simulation; global stability; periodicity; HFMD; R_0
Mathematics Subject Classification: 93A30, 97Mxx

1. Introduction

Hand-foot-and-mouth disease (HFMD) is a disease that mainly affects children younger than five years of age. Symptoms start within three to six days of contact according to the Center for Disease Control and Prevention (CDC), an initial fever and generalized malaise followed by painful sores in the mouth that blister and ulcerate [1].

HFMD causes a major public health problem, especially in Asia. Although most cases of HFMD are mild, there are some severe cases that may develop heart and lung failure and probably leads to death [1–3]. In the last decade, many severe HFMD outbreaks have occurred in East Asia and Southeast Asia. A vaccine for HFMD was approved and applied in China in 2016. However, several HFMD outbreaks occurred recently [4, 5]. This guides the decision makers to focus more on effective prevention and control strategies.

A distinct seasonal pattern in tropical and subtropical regions with more than two peaks may occur

within a year [6–8]. Many research studies have confirmed that climatological changes in humidity and temperature have an important effect on the incidence of HFMD despite the inconsistent results from different studies [9–11]. Another factor that affects the variations in the number of HFMD incidences is the opening and closing of the daycare centers or schools [12, 13].

Many previous efforts have been done to study the dynamics of HFMD. A number of these studies used models without any vaccination. For example, [14] and [15] used an SIR model to analyze the epidemic of HFMD in Taiwan and Malaysia respectively and they found that the disease spread quite rapidly and the number of susceptible persons is the only controllable parameter. Moreover, some studies for the dynamical behaviors of HFMD considered more complicated models including SEIQR models with and without vaccination [16–23]. For example, Zhu [23] used a SEIQR with sinusoidal periodic contact rate, to investigate the spread of seasonal HFMD in Wenzhou and he found that HFMD becomes an endemic disease in Wenzhou. Some other previous studies [17, 18, 24–28] used the sinusoidal function of period one year ($\beta(t) = \beta_0 + \beta sin(\omega t + \phi)$) for simulating the seasonal varying transmission rate. Unfortunately, they failed to simulate the one year multi-peaks pattern which appeared in the reported data of HFMD.

However, our study focuses on analysing and simulating the effect of the above factors and clarify their relations with the observed multi-peaks,(in a one year) pattern. We study an SEIQRS model and consider these factors in the dynamics of HFMD. We try to determine the effect of the periodic transmission and vaccination rates on the spread of HFMD.

In this paper, we formulate an SEIQRS model with seasonal contact rate and periodic vaccination strategy. We find that this model has no disease free equilibrium point. But a disease free periodic solution (DFPS) is possible for this model. The reproduction number R_0 is derived. An upper bound R_0^{sup} and a lower bound R_0^{inf} of the reproduction number R_0 are derived as well. This DFPS is globally asymptotically stable if $R_0^{sup} < 1$ and unstable when $R_0^{inf} > 1$.

In our simulation we use a novel form of periodic contact and vaccination rates with period one year as follows:

$$\beta(t) = \begin{cases} \beta_{10} + \beta_{11} e^{-\beta_{12}(mod(t,52))^2} & 0 < mod(t, 52) \leq 26; \\ \beta_{20} + \beta_{21} e^{-\beta_{22}(mod(t,52)-26)^2} & 26 < mod(t, 52) \leq 52. \end{cases}$$

and

$$r(t) = \begin{cases} \rho_{10} + \rho_{11} e^{-\rho_{12}(mod(t,52))^2} & 0 < mod(t, 52) \leq 26; \\ \rho_{20} + \rho_{21} e^{-\rho_{22}(mod(t,52)-26)^2} & 26 < mod(t, 52) \leq 52. \end{cases}$$

We designed these functions to fit the multi-peaks pattern of the real data. Our new form of periodic functions shows a nicer fitting with the real data, compared with the previous simulation results [23]. These more realistic simulations give a wider insight to the future of the spread of the HFMD. We plot and compare our obtained simulation results with both previous works and real data. On the other hand, our simulation results confirm our analytical results obtained in this paper.

2. The model

In the paper, we shall study a more realistic SEIQRS model with periodic vaccination and loss of immunity. Periodic vaccination gives a more applicable realistic strategy to control the dynamics of the disease.

We assume that the population is mixed uniformly and homogeneously with a constant population size A. The population number A is divided into five groups, $S(t)$, $E(t)$, $I(t)$, $Q(t)$, and $R(t)$ which represent the susceptible, exposed, infected, quarantined, and recovered individuals respectively. Figure 1 illustrates the flowchart of the dynamics of the spread of HFMD. This figure describes the flow of inputs/outputs into each of the five compartments of our model. A proportion of the susceptible individuals who have received the vaccine move to the recovered group, the rest get infected and join the latent period or died for any reason. on the other hand, there is a flux of newborns entering the susceptible class. The latent population in their latency period do not show any symptom. Some of the latent died naturally but after about $3 \sim 7$ days the latent individuals become infectious. A part of the infectious people will be hospitalized for treatment and isolated then they get recovered or died. Another proportion of those infectious moves to the recovery class, while some have died. Finally, some of the recovered lose their immunity and join the susceptibles again, another proportion died.

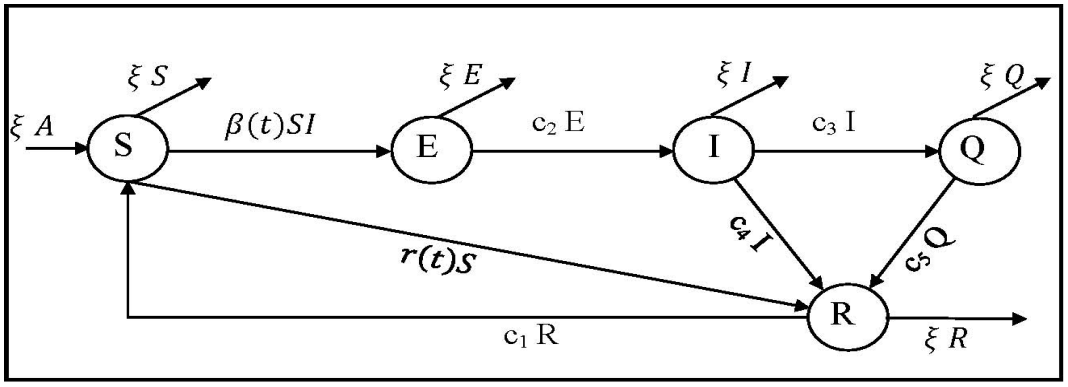

Figure 1. Flowchart of the dynamics of HFMD.

The model parameters are defined and listed as follows :

Parameter	Definition
$\beta(t)$	The annual periodic transmission rate
$r(t)$	The time dependent annual periodic vaccination rate
c_1	The progression rate of the recovered (by losing immunity).
$\frac{1}{c_2}$	The average incubation period
c_3	The quarantine rate
c_4	The infectious recovery rate
c_5	The quarantined recovery rate
ξ	The natural birth and death rate

Note that, $\beta(t)$ and $r(t)$ are time dependent bounded seasonally varied functions with period one year and all parameter values are non negative. Using our assumptions and following [9,18,19] we can write our $SEIQRS$ model as a set of five coupled non-linear ordinary differential equations as follows:

$$\frac{dS(t)}{dt} = \xi A - \beta(t)I(t)S(t) - (\xi + r(t))S(t) + c_1R(t), \tag{2.1}$$

$$\frac{dE(t)}{dt} = \beta(t)I(t)S(t) - (\xi + c_2)\,E(t), \tag{2.2}$$

$$\frac{dI(t)}{dt} = c_2E(t) - (\xi + c_3 + c_4)\,I(t), \tag{2.3}$$

$$\frac{dQ(t)}{dt} = c_3I(t) - (\xi + c_5)\,Q(t), \tag{2.4}$$

and

$$\frac{dR(t)}{dt} = r(t)S(t) + c_4I(t) + c_5Q(t) - (\xi + c_1)\,R(t), \tag{2.5}$$

with

$$S(t) + E(t) + I(t) + Q(t) + R(t) = A.$$

Equations (2.1)–(2.5) represent a nonlinear first order system of differential equations that describes the spread of HFMD disease.

The disease transmission rate $\beta(t)$ and the vaccination rate $r(t)$ are nonconstant, positive, and bounded periodic functions. These periodic functions $\beta(t)$ and $r(t)$ are designed to imitate the seasonal variation in the reported cases for HFMD infectious disease due to climatological changes or opening and closing schools [12, 13].

As we assume that, the vaccination rate $r(t)$ is a nonconstant function therefore, the system (2.1)–(2.5) could not have any equilibrium point. On the other hand, a disease free periodic solution (DFPS) is still possible when $E(t) = I(t) = Q(t) = 0$.

Define the region $D \subseteq R^5$ where,

$$D = \{(S, E, I, Q, R) \in [0, A]^5 : S + E + I + Q + R = A\}.$$

The five dimensional set D, is obviously positively invariant, as the right-hand side of the system (2.1)–(2.5) is differentiable.

3. Disease free periodic solution (DFPS)

In our model, the vaccination rate $r(t)$ is a periodic function, this force the system (2.1)–(2.5) to have no equilibrium point. On the other hand we expect that, there is a disease free periodic solution (DFPS) for the system (2.1)–(2.5) at $(\hat{S}(t), 0, 0, 0, \hat{R}(t))$. Similar to [29–31] this DFPS is given by

$$\begin{aligned} \frac{dS}{dt} &= A\xi - (\xi + r(t))\,S(t) + c_1R(t) \\ &= A(\xi + c_1) - (\xi + r(t) + c_1)S. \end{aligned} \tag{3.1}$$

with the initial condition $S(t_0) \in \mathbb{R}^+$, integrating equation (3.1) we get,

$$S(t) = \frac{\left(S\,(t_0) + A(\xi + c_1)\int_{t_0}^{t} e^{\left((\xi+c_1)(\kappa-t_0)+\int_{t_0}^{\kappa} r(\tau)d\tau\right)}d\kappa\right)}{e^{\left((\xi+c_1)(t-t_0)-\int_{t_0}^{t} r(\tau)d\tau\right)}} \tag{3.2}$$

So,

$$S\,(t_0+(n+1)T) = \frac{\left(S\,(t_0+nT)+A(\xi+c_1)\int_{t_0}^{t_0+T} e^{\left((\xi+c_1)(\kappa-t_0)+\int_{t_0}^{\kappa} r(\tau)d\tau\right)}d\kappa\right)}{e^{\left((\xi+c_1)T+\int_{t_0}^{t_0+T} r(\tau)d\tau\right)}} \tag{3.3}$$

Equation (3.3) represents a recurrence relation between the susceptibles at times $(t_0 + nT; n = 1, 2, ...)$. Now define the mapping G such that

$$G(S_n) = S_{n+1}$$

where $S_n = S(t_0 + nT)$. If $S_{n1} \neq S_{n2}$ we have that,

$$|G(S_{n1}) - G(S_{n2})| \leq |S_{n1} - S_{n2}| \exp(-\xi T).$$

Therefore, the mapping G is a contraction mapping and it has a unique fixed point S^* [32]. Moreover S^*; is depending on t_0; such that,

$$S^*(t_0) = \frac{A(\xi + c_1)\int_{t_0}^{t_0+T} e^{\left((\xi+c_1)(\kappa-t_0)+\int_{t_0}^{\kappa} r(\tau)d\tau\right)}d\kappa}{e^{\left((\xi+c_1)T+\int_{t_0}^{t_0+T} r(\tau)d\tau\right)} - 1}. \tag{3.4}$$

Hence, $S^*(t_0 + T) = S^*(t_0)$. So, S^* is a periodic function of t. From (3.4), we have that, $S^*(t_0)$ is continuously differentiable with respect to t_0. On the other hand, we have

$$\begin{aligned}\int_{t_0}^{t} e^{\left((\xi+c_1)(\kappa-t_0)+\int_{t_0}^{\kappa} r(\tau)d\tau\right)}d\kappa &\leqslant \frac{\int_{t_0}^{t} e^{\left((\xi+c_1)(\kappa-t_0)+\int_{t_0}^{\kappa} r(\tau)d\tau\right)}(\xi + c_1 + r(\kappa))d\kappa}{\xi + c_1 + r_{min}} \\ &= \frac{e^{(\xi+c_1)(t-t_0)+\int_{t_0}^{t} r(\tau)d\tau} - 1}{\xi + c_1 + r_{min}},\end{aligned} \tag{3.5}$$

where $r_{min} = \min_{t\in[0,T]} r(t)$. Substituting (3.4) and (3.5) into (3.2), we obtain

$$\begin{aligned}S^*(t) &\leqslant \frac{\frac{A(\xi+c_1)}{\xi+c_1+r_{min}}\left(1 + (e^{(\xi+c_1)(t-t_0)+\int_{t_0}^{t}(r(\tau))d\tau} - 1)\right)}{e^{(\xi+c_1)(t-t_0)+\int_{t_0}^{t} r(\tau)d\tau}} \\ &= \frac{A(\xi + c_1)}{\xi + c_1 + r_{min}} < A\end{aligned}$$

Hence, $\hat{S}(t) = S^*(t), \hat{E}(t) = \hat{I}(t) = \hat{Q}(t) = 0$, and $\hat{R}(t) = R^*(t) = A - S^*(t)$ is a disease-free periodic solution of the system (2.1)–(2.5).

4. The basic reproduction number

The basic reproduction number R_0 is defined as the average number of new cases produced by a single infected individual entered into a pure susceptible population. Now, we can drive a form of

the basic reproduction number R_0 of the system (2.1)–(2.5) using a similar scenario to [33, 34]. By linearizing the system (2.1)–(2.5) around $(\hat{S}(t), 0, 0, 0, \hat{R}(t))$, we find that:

$$\frac{dE(t)}{dt} = \beta(t)I(t)\hat{S}(t) - (\xi + c_2)E(t), \tag{4.1}$$

$$\frac{dI(t)}{dt} = c_2E(t) - (\xi + c_3 + c_4)I(t), \tag{4.2}$$

$$\text{and} \quad \frac{dQ(t)}{dt} = c_3I(t) - (\xi + c_5)Q(t), \tag{4.3}$$

which can be written in the matrix form as:

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

where,

$$x = \begin{pmatrix} E \\ I \\ Q \end{pmatrix}, F(t) = \begin{pmatrix} 0 & \beta(t)\hat{S}(t) & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} c_2 + \xi & 0 & 0 \\ -c_2 & c_3 + c_4 + \xi & 0 \\ 0 & -c_3 & c_5 + \xi \end{pmatrix}$$

Now, let $y(t) = \beta(t)\hat{S}(t)$. Note that $y(t)$ is a nonzero positive periodic function with period T, so $\overline{y(t)} = \frac{1}{T}\int_0^T \beta(\tau)\hat{S}(\tau)d\tau$ is average of $Y(t)$ over the time T. Now, arguing similar to [33], we can obtain the value of the basic reproduction number R_0 as follows:

$$\begin{aligned} R_0 &= \frac{1}{T}\int_0^T \frac{c_2\beta(\tau)\hat{S}(\tau)d\tau}{(\xi + c_2)(\xi + c_3 + c_4)} \\ &= \frac{c_2\overline{y(t)}}{(\xi + c_2)(\xi + c_3 + c_4)} \end{aligned} \tag{4.4}$$

where $\hat{S}(t)$ is a periodic solution of period T and it is the only disease free solution of the system of differential equations (2.1)–(2.5).

Now, we can define R_0^{sup} as an upper bound and R_0^{inf} a lower one for the value R_0 respectively where,

$$R_0^{sup} = \frac{c_2}{(\xi + c_2)(\xi + c_3 + c_4)} \sup_{t\in[0,T]} \int_0^T \frac{(\xi + c_2)\beta(t - \phi)\hat{S}(t - \phi)e^{-(\xi+c_2)\phi}d\phi}{1 - e^{-(\xi+c_2)T}} \tag{4.5}$$

and

$$R_0^{inf} = \frac{c_2}{(\xi + c_2)(\xi + c_3 + c_4)} \inf_{t\in[0,T]} \int_0^T \frac{(\xi + c_2)\beta(t - \phi)\hat{S}(t - \phi)e^{-(\xi+c_2)\phi}d\phi}{1 - e^{-(\xi+c_2)T}} \tag{4.6}$$

5. Stability of the (DFPS)

In this section, we extend the results obtained by [29–31]. We show first that if $R_0^{sup} < 1$ the DFPS $(\hat{S}(t), 0, 0, 0, \hat{R}(t))$ is globally asymptotically stable. In another section we shall prove that the DFPS is unstable when $R_0^{inf} > 1$.

5.1. Stability of the DFPS when $R_0^{sup} < 1$

Now, we show that the DFPS is globally asymptotically stable when $R_0^{sup} < 1$. We use an argument similar to that used in the proof of Theorem 1 [31] with some modifications to fit our SEIQRS model.

Lemma 1.

$$\limsup_{t\to\infty}(S(t) - \hat{S}(t)) \leq 0.$$

Proof

From Equation (2.1)

$$\begin{aligned} \frac{dS}{dt} &= \xi A - \beta(t)SI - (\xi + r(t))S + c_1 R, \\ &\leq A(\xi + c_1) - (\xi + r(t) + c_1)S. \end{aligned}$$

As $(\hat{S}(t), 0, 0, 0, \hat{R}(t))$ is a solution of the system (2.1)–(2.5) when $E(t) = I(t) = Q(t) = 0$ then arguing similar to [31] we deduce that,

$$\limsup_{t\to\infty}(S(t) - \hat{S}(t)) \leq 0,$$

and the proof of Lemma 1 is completed.

Now we go directly to the first main result which is the global stability of the disease free solution when $R_0^{sup} < 1$. Theorem 1 proves that DFPS is globally asymptotically stable (GAS) when $R_0^{sup} < 1$. Following Theorem 1 in [31], we give proof of the next Theorem.

Theorem 1. *The DFPS, $(\hat{S}, 0, 0, 0, \hat{R})$ is GAS if $R_0^{sup} < 1$,*

Proof

From Equations (2.3) and (2.4) we have

$$\frac{dI(t)}{dt} = c_2 E(t) - (\xi + c_3 + c_4) I(t),$$

and

$$\frac{dQ(t)}{dt} = c_3 I(t) - (\xi + c_5) Q(t),$$

arguing similar to [31] and [35] we can easily find that

$$I^{\infty} \leq \frac{c_2 E^{\infty}}{(\xi + c_3 + c_4)}.$$

and

$$Q^{\infty} \leq \frac{c_3 I^{\infty}}{(\xi + c_5)} \leq \frac{c_3 c_2 E^{\infty}}{(\xi + c_5)(\xi + c_3 + c_4)}.$$

The idea behind this proof is simple as that, from Lemma 1 we have that, given $\epsilon > 0$ there exists t_1 such that $S(t) \leq \hat{S}(t) + \epsilon$, $I(t) \leq I^{\infty} + \epsilon$ and $Q(t) \leq Q^{\infty} + \epsilon$ for all $t \geq t_1$.

Using Eq (2.2), $E(t)$ can be bounded above, then we use this upper bound to show that $E^{\infty} = 0$. Now similar to Theorem 1 [31], suppose that $E^{\infty} > 0$. By integrating Eq (2.2) we have that for $t \geq t_0 > t_1$,

$$E(t) \leq E(t_0)e^{-(\xi+c_2)(t-t_0)} + (I^{\infty} + \epsilon)e^{-(\xi+c_2)t} \int_{t_0}^{t} \beta(\eta)(\hat{S}(\eta) + \epsilon)e^{(\xi+c_2)\eta} d\eta. \tag{5.1}$$

Now, recall that, $y(\eta) = \beta(\eta)\hat{S}(\eta)$. Therefore,

$$e^{-(\xi+c_2)t} \int_{t_0}^{t} y(\eta)e^{(\xi+c_2)\eta} d\eta = \int_{0}^{t-t_0} y(t-u)e^{-(\xi+c_2)u} du \tag{5.2}$$

Suppose that $(k+1)T \geq t - t_0 \geq kT$, then we have,

$$\begin{aligned}
\int_{0}^{t-t_0} y(t-u)e^{-(\xi+c_2)u} du &= \int_{0}^{T} y(t-u)e^{-(\xi+c_2)u} du \Big(1 + e^{-(\xi+c_2)T} + e^{-(\mu+\sigma)2T} + \cdots \\
&\qquad + e^{-(\xi+c_2)(k-1)T}\Big) + \int_{kT}^{t-t_0} y(t-u)e^{-(\xi+c_2)u} du \\
&\leq \int_{0}^{T} y(t-u)e^{-(\xi+c_2)u} du \Big(1 + e^{-(\xi+c_2)T} + e^{-(\xi+c_2)2T} + \cdots \\
&\qquad + e^{-(\xi+c_2)kT}\Big) \\
&< \int_{0}^{T} \frac{y(t-\zeta)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}}
\end{aligned} \tag{5.3}$$

So, for $t \geq t_0$ we find that

$$\begin{aligned}
E(t) &\leq E(t_0)\, e^{-(\xi+c_2)(t-t_0)} + \frac{I^{\infty} + \epsilon}{\xi + c_2} \int_{0}^{T} \frac{(\xi + c_2)\beta(t-\zeta)(\hat{S}(t-\zeta) + \epsilon)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}} \\
&\leq Ae^{-(\xi+c_2)(t-t_0)} + \frac{I^{\infty} + \epsilon}{\xi + c_2} \Bigg(\sup_{t\in[0,T]} \int_{0}^{T} \frac{(\xi + c_2)y(t-\zeta)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}} \\
&\qquad + \epsilon \int_{0}^{T} \frac{(\xi + c_2)\beta(t-\zeta)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}} \Bigg)
\end{aligned} \tag{5.4}$$

Choose $t_2 > t_0$ large enough so that for $t \geq t_2$; $Ae^{-(\xi+c_2)(t-t_0)} < \epsilon$: Then for $t \geq t_2$,

$$E(t) \leq R_0^{sup} E^{\infty} + \epsilon \left(1 + \sup_{t\in[0,T]} \int_{0}^{T} \frac{y(t-\zeta)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}} + \left(\frac{I^{\infty} + \epsilon}{\xi + c_2} \right) \beta_{\max} \right), \tag{5.5}$$

where $\beta_{\max} = sup_{u\in[0,T]}\beta(u)$. Now choose ϵ small enough so that,

$$\epsilon \left(1 + \sup_{t\in[0,T]} \int_{0}^{T} \frac{y(t-\zeta)e^{-(\xi+c_2)\zeta} d\zeta}{1 - e^{-(\xi+c_2)T}} + \left(\frac{I^{\infty} + \epsilon}{\xi + c_2} \right) \beta_{\max} \right) < \psi E^{\infty}, \tag{5.6}$$

where $R_0^{sup} + \psi < 1$ and $\psi > 0$. Hence for $t \geq t_2$, we find that $E(t) \leq \left(R_0^{sup} + \psi \right) E^{\infty}$. Thus, $0 \leq E^{\infty} \leq \left(R_0^{sup} + \psi \right) E^{\infty}$. then , $E^{\infty} = 0$. Hence also $I^{\infty} = 0$ this leads to $Q^{\infty} = 0$ Moreover $E(t) \to 0$, $I(t) \to 0$

and $Q(t) \to 0$ as $t \to \infty$. Finally we go to show that $(S(t) - \hat{S}(t)) \to 0$ and $(R(t) - \hat{R}(t)) \to 0$ as $t \to \infty$. As $\hat{R}(t)$ is a solution of Eq (2.5) when $E(t) = I(t) = Q(t) = 0$, we find that,

$$\frac{d(R - \hat{R})}{dt} = r(t)(S - \hat{S}) + c_4 I + c_5 Q - (\xi + c_1)(R - \hat{R}). \tag{5.7}$$

Given $\epsilon_1 > 0$ using Lemma 1, there exists t_3 such that $E(t) + I(t) + Q(t) \leq \epsilon_1$ and $S(t) \leq S(t) + \epsilon_1$ for all $t \geq t_3$. So for $t \geq t_3$

$$\frac{d(R - R)}{dt} \leq (r_{max} + c_4 + c_5)\,\epsilon_1 - (\xi + c_1)(R - \hat{R})$$

where $r_{max} = \sup_{u \in [0,T]} r(u)$. By integrating this inequality, we have that

$$\begin{aligned}(R(t) - \hat{R}(t)) &\leq (R(t_3) - \hat{R}(t_3))e^{-(\xi+c_1)(t-t_3)} + \epsilon_1 \left(\frac{r_{max} + c_4 + c_5}{\xi + c_1}\right)\left(1 - e^{-(\xi+c_1)(t-t_3)}\right) \\ &\leq A e^{-(\xi+c_1)(t-t_3)} + \epsilon_1 \left(\frac{r_{max} + c_4 + c_5}{\xi + c_1}\right)\end{aligned}$$

Now we can show that, given $\epsilon_2 > 0$, there exists t_4 such that $R(t) - \hat{R}(t) \leq \epsilon_2$ for $t \geq t_4$. Therefore, $S(t) = A - R(t) - Q(t) - I(t) - E(t) \geq A - \hat{R}(t) - \epsilon_1 - \epsilon_2$ for $t \geq t_4$. From Lemma 1, we find that $S(t) \to \hat{S}(t)$ as $t \to \infty$. Since $R(t) = A - S(t) - I(t) - Q(t) - E(t)$, then we must have, $R(t) \to A - \hat{S}(t) = \hat{R}(t)$ at $t \to \infty$. This completes the proof of Theorem 1. Thus if $R_0^{sup} < 1$, then DFPS is GAS.

5.2. Instability of the DFPS when $R_0^{inf} > 1$

Here R_0^{inf} is a lower bound for R_0. We use an argument consisting of a mixture of those used in [30], [36], and [37]. So, we can show that if $R_0^{inf} > 1$ the (DFPS) is not stable and the disease will fire up.

The first case when the infection is not present initially, $I(0) = E(0) = Q(0) = 0$ and $S + R = A$, then by Theorem 1, the system (2.1)–(2.5) tends to the DFPS as $t \to \infty$ whatever the value of R_0. The second case is that, all of $E(0) > 0$, $I(0) > 0$, and $Q(0) > 0$ we shall prove that DFPS is unstable by using an argument similar to [30] and [31].

Theorem 2. *If $R_0^{inf} > 1$, then the DFPS is unstable.*

Proof

In this case, we suppose that the DFPS is stable when $R_0^{inf} > 1$ and we get a contradiction with our assumption. So if (S, E, I, Q, R) starts near $(\hat{S}, 0, 0, 0, \hat{R})$ we have that (S, E, I, Q, R) must stay near $(\hat{S}, 0, 0, 0, \hat{R})$ for the time being large. Therefore $(S, E, I, Q, R) \to (\hat{S}, 0, 0, 0, \hat{R})$ as $t \to \infty$. So, given $\varepsilon = (1/2)(1 - (1/R_0^{inf})) > 0$ there exists $t_1 > 0$ such that $|S(t) - \hat{S}| \leq \varepsilon\hat{S}$, $|E(t) - 0| \leq \varepsilon$, $|I(t) - 0| \leq \varepsilon$,$|Q(t) - 0| \leq \varepsilon$ and $|R(t) - \hat{R}| \leq \varepsilon$ for all $t \geq t_1$. Choose $\varepsilon_1 > 0$ such that $(R_0^{inf} + 1)(1 - \varepsilon_1) > 2$.

From Eq (4.6) recall R_0^{inf},

$$R_0^{inf} = \frac{c_2}{(\xi + c_2)(\xi + c_3 + c_4)} \inf_{t \in [0,T]} \int_0^T \frac{(\xi + c_2) y(t - \phi) e^{-(\xi+c_2)\phi} d\phi}{1 - e^{-(\xi+c_2)T}},$$

Therefore, there exists an integer k such that

$$\frac{c_2}{(\xi+c_2)(\xi+c_3+c_4)}\inf_{t\in[0,T]}\int_0^T(\xi+c_2)y(t-\phi)e^{-(\xi+c_2)\phi}d\phi\Big(1+e^{-(\xi+c_2)T}+e^{-(\xi+c_2)2T}+ \cdots+e^{-(\xi+c_2)(k-1)T}\Big)>R_0^{inf}(1-\varepsilon_1). \tag{5.8}$$

Choose $t_2 \geq t_1$ such that, $E(t_2) \geq E(0)e^{-(\xi+c_2)t_2} > 0$, $I(t_2) \geq I(0)e^{-(\xi+c_3+c_4)t_2} > 0$ and $Q(t_2) \geq Q(0)e^{-(\xi+c_5)t_2} > 0$ as $E(0) > 0$, $I(0) > 0$ and $Q(0) > 0$. Now define ε_2 and η as follows:

$$0<\varepsilon_2<\min\left\{\frac{1}{2}I(t_2)e^{-(\xi+c_3+c_4)kT},\frac{(\xi+c_5)}{2c_3}Q(t_2)e^{-(\xi+c_5)kT},\frac{c_2}{2(\xi+c_3+c_4)}E(t_2)e^{-(\xi+c_2)kT}\right\},$$

$$\eta=\inf\left\{\phi\geq 0: I(t_2+\delta)\geq\varepsilon_2, Q(t_2+\delta)\geq\frac{c_3}{(\xi+c_5)}\varepsilon_2 \text{and} E(t_2+\delta)\geq\frac{\xi+c_3+c_4}{c_2}\varepsilon_2, \text{for}\delta\in[0,\phi]\right\}.$$

By continuity $\eta > 0$ and if $\eta < \infty$ then $I(t_2+\eta) = \varepsilon_2$, $Q(t_2+\eta) = (c_3/(\xi+c_5))\varepsilon_2$ or $E(t_2+\eta) = ((\xi+c_3+c_4)/c_2)\varepsilon_2$. This leads to a contradiction.

Now from Eq (2.3) and by the definition of ε_2 we find that,

$$\begin{aligned} I(t_2+\eta) &= I(t_2)e^{-(\xi+c_3+c_4)\eta}+e^{-(\xi+c_3+c_4)(t_2+\eta)}\int_{t_2}^{t_2+\eta}c_2E(\chi)e^{(\xi+c_3+c_4)\chi}d\chi,\\ &\geq I(t_2)e^{-(\xi+c_3+c_4)\eta}+\varepsilon_2\left(1-e^{-(\xi+c_3+c_4)\eta}\right)\\ &> \varepsilon_2, \end{aligned}$$

similarly, from Eq (2.4) we find that,

$$\begin{aligned} Q(t_2+\eta) &= Q(t_2)e^{-(\xi+c_5)\eta}+e^{-(\xi+c_5)(t_2+\eta)}\int_{t_2}^{t_2+\eta}c_3I(\chi)e^{(\xi+c_5)\chi}d\chi,\\ &\geq Q(t_2)e^{-(\xi+c_5)\eta}+\varepsilon_2\left(1-e^{-(\xi+c_5)\eta}\right)\\ &> \frac{c_3}{(\xi+c_5)}\varepsilon_2, \end{aligned}$$

but on the other hand from Eq (2.2) we find that

$$\begin{aligned} E(t_2+\eta) &\geq E(t_2)e^{-(\xi+c_2)\eta}+e^{-(\xi+c_2)(t_2+\eta)}\int_{t_2}^{t_2+\eta}\beta(\chi)S(\chi)I(\chi)e^{(\xi+c_2)\chi}d\chi,\\ &\geq E(t_2)e^{-(\xi+c_2)\eta}+e^{-(\xi+c_2)(t_2+\eta)}\varepsilon_2(1-\varepsilon)\int_{t_2}^{t_2+\eta}y(\chi)e^{(\xi+c_2)\chi}d\chi. \end{aligned} \tag{5.9}$$

Now

$$\begin{aligned} e^{-(\xi+c_2)(t_2+\eta)}\int_{t_2}^{t_2+\eta}y(\chi)e^{(\xi+c_2)\chi}d\chi &= \int_{t_2}^{t_2+\eta}y(\chi)e^{-(\xi+c_2)(t_2+\eta-\chi)}d\chi,\\ &= \int_0^{\eta}y(t_2+\eta-\phi)e^{-(\xi+c_2)\phi}d\phi. \end{aligned}$$

If $\eta \leq kT$ then

$$E(t_2+\eta) \geq E(t_2)e^{-(\xi+c_2)kT} > \frac{(\xi+c_3+c_4)}{c_2}\varepsilon_2.$$

If $\eta \geq kT$ then

$$\begin{aligned}
\int_0^{\eta} y(t_0+\eta-\phi)e^{-(\xi+c_2)\phi}]d\phi &= \int_0^{T} y(t_0+\eta-\phi)e^{-(\xi+c_2)\phi}d\phi\Big(1+e^{-(\xi+c_2)T}+e^{-(\xi+c_2)2T}+\cdots \\
&\quad +e^{-(\xi+c_2)(k-1)T}\Big)+\int_{kT}^{\eta} e^{-(\xi+c_2)\phi}d\phi, \\
&\geq \inf_{t\in[0,T]}\int_0^{T} y(t-\phi)e^{-(\xi+c_2)\phi}d\phi\Big(1+e^{-(\xi+c_2)T}+e^{-(\xi+c_2)2T}+\cdots \\
&\quad +e^{-(\xi+c_2)(k-1)T}\Big), \\
&> \frac{\xi+c_3+c_4}{c_2}R_0^{inf}(1-\epsilon_1), \qquad \text{using Eq (5.8).}
\end{aligned}$$

As $R_0^{inf} > 1$ and $\varepsilon = \frac{(R_0^{inf}-1)}{2R_0^{inf}} > 0$ then using Eq (5.9)

$$\begin{aligned}
E(t_2+\eta) &\geq E(t_2)e^{-(\xi+c_2)\eta}+\varepsilon_2\frac{1}{2}\left(\frac{1}{R_0^{inf}}+1\right)\frac{\xi+c_3+c_4}{c_2}R_0^{inf}(1-\varepsilon_1), \\
&= E(t_2)e^{-(\xi+c_2)\eta}+\frac{(\xi+c_3+c_4)}{2c_2}\varepsilon_2(R_0^{inf}+1)(1-\varepsilon_1), \\
&> \frac{(\xi+c_3+c_4)}{c_2}\varepsilon_2, \quad \text{as } (R_0^{inf}+1)(1-\varepsilon_1) > 2.
\end{aligned}$$

Hence $\eta < \infty$ leads to a contradiction so $\eta = \infty$ and $I(t_2+\delta) \geq \varepsilon_2$, $Q(t_2+\delta) \geq (c_3/(\xi+c_5))\varepsilon_2$ and $E(t_2+\delta) \geq ((\xi+c_3+c_4)/c_2)\varepsilon_2$ for all $\delta \geq 0$. This contradicts the fact that the trajectory tends to the DFPS. Hence the DFPS cannot be stable for $R_0^{inf} > 1$, and the proof is completed.

These results prove that the disease free solution for our SEIQRS model represented by the system (2.1)–(2.5) with a nonconstant periodic transmission and vaccination rates $r(t)$ in $[0,T]$, is globally asymptotically stable if $R_0^{sup} < 1$ and not stable if $R_0^{inf} > 1$. from these results we deduce that,

$$\sup_{t\in[0,T]}\int_0^{T}\frac{y(t-\phi)e^{-(\xi+c_2)\phi}d\phi}{1-e^{-(\xi+c_2)T}} < \frac{\xi+c_3+c_4}{c_2}, \tag{5.10}$$

is the sufficient condition to keep the DFPS globally asymptotically stable.

The obtained results, for our SEIQRS model with nonconstant periodic vaccination rate $r(t)$, extend the corresponding results obtained by [30], [31] , [37], and [35]. These results are original for an SEIQRS model with periodicity in the transmission and vaccination rates.

6. Simulation results

Now we look numerically at the behavior of the system (2.1)–(2.5). The software package Mathematica12 is used to solve our system of nonlinear ordinary differential equations (2.1)–(2.5).

Real data about HFMD in Egypt dose not available. So we use data taken from the district of Wenzhou China (Table 1 [23]). We choose Wenzhou China as a subtropical area that is similar to the climate of Egypt. Simulations are performed using parameters from the literature [23]. We compare our simulation results with the reported data of HFMD in Wenzhou from March 2010, to December 2013. Also, we compare our results with the simulation results of [23].

The parameters estimated in [23] are used in our simulation to give a fair comparison with their results. The parameters are set to the following values:

Parameter	value
c_1	0.015.
$\frac{1}{c_2}$	0.571
c_3	0.007177
c_4	0.875
c_5	0.4375
ξ	0.00642

As stated before our novel periodic transmission rate $\beta(t)$ is designed to fit the yearly multi-peaks pattern in the reported data. Recall $\beta(t)$ as follows:

$$\beta(t) = \begin{cases} \beta_{10} + \beta_{11} e^{-\beta_{12}(mod(t,52))^2} & 0 < mod(t,52) \leq 26; \\ \beta_{20} + \beta_{21} e^{-\beta_{22}(mod(t,52)-26)^2} & 26 < mod(t,52) \leq 52; . \end{cases}$$

By using the least-square fitting of the numbers of $I(t)$, we can estimate the values of $\beta_{ij} : i, j = 0, 1, 2$.

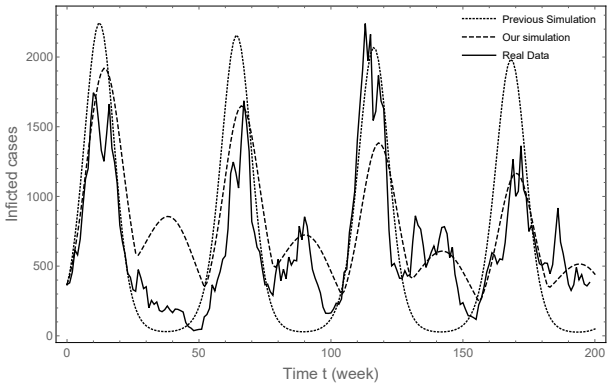

Figure 2. Plots the number of infected $I(t)$, the dotted curve is the previous numerical simulation [23], the dashed curve is the simulation results of our model and the solid one is the reported real data from Wenzhou China during the period from 2010 to 2013 (Table 1 [23]), against time (t) in weeks when $R_0 \leq 1$.

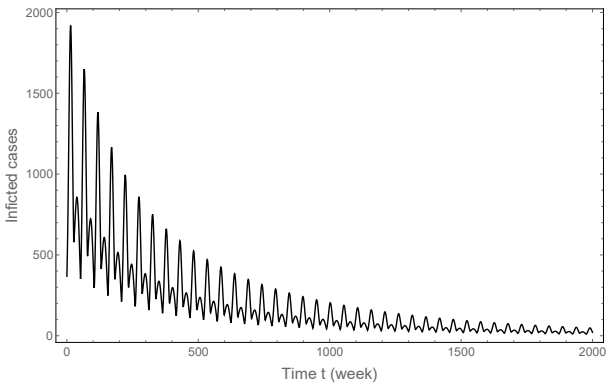

Figure 3. Plots the Infected population $I(t)$ against time (t) in weeks for a long time (2000 weeks) , when R_0 is very close to one in value, for the same parameter set used in Figure (2).

Figure 2 shows that our simulation results are often closer to the real data than the results obtained by [23]. Clear multiple peaks, within a year, are appeared in our simulation which gives a good fitting

to the real data. These results show that our model is more realistic than [23]. In Figure 2 we use the parameters' values of the transmission periodic function which are estimated from the least square fitting of $I(t)$ during the period from 2010 to 2013, as follows: $\beta_{10} = 0.64$, $\beta_{11} = 0.665$, β_{12} =0.0035, $\beta_{20} = 0.63$, $\beta_{21} = 0.445$, $\beta_{22} = 0.0017$.

Figure 3 shows that there is a decrease in the height of the peaks of the number of infected persons $I(t)$ over time. However, this solution has a one year multi-peaks similar to those of the reported real data. Figure 3 predicts that the number of the new HFMD cases will fluctuate around a decreasing level.

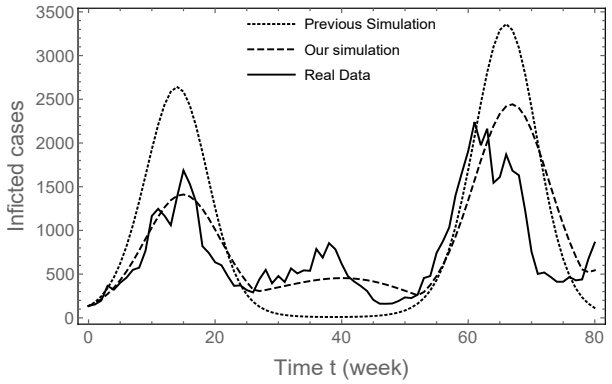

Figure 4. Plots the number of infected $I(t)$, the dotted curve is the previous numerical simulation [23], the dashed curve is the simulation results of our model and the solid one is the reported data from Wenzhou China during the period from 2011 to 2012 (Table 1 [23]), against time (t) in weeks when $R_0 > 1$.

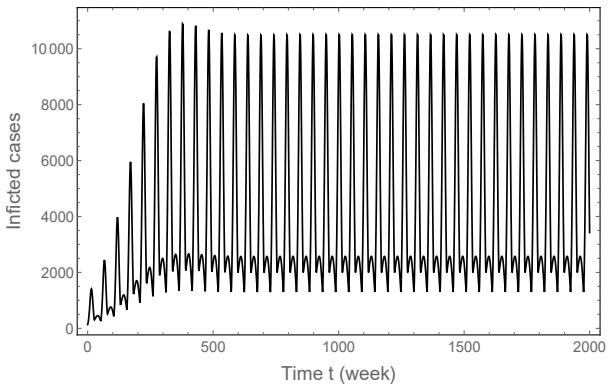

Figure 5. Plots the Infected population $I(t)$ against time (t) in weeks, for 2000 weeks, when $R_0 > 1$ and for the same parameter set used in Figure (4).

Figure 4 plots the number of infected against time in weeks when $R_0 > 1$. This figure shows that our simulation results are always very close to the reported data. Our simulation results give a more precise fitting than the results of [23]. Our model produces a multi-peaks, in one period, solution while the model in [23] has a mono peak carve. In Figure 4 the parameters of the transmission periodic function are given estimated values from the least square fitting of $I(t)$ from 2011 to 2012, as follows: $\beta_{10} = 0.49$, $\beta_{11} = 0.94$, $\beta_{12} = 0.0031$, $\beta_{20} = 0.36$, $\beta_{21} = 0.70$, β_{22} =0.00065.

Figure 5 shows that there is a stable endemic periodic solution of our model, with a period of one year, when the basic reproductive number ($R_0 > 1$). This means that the HFMD will take off and becomes endemic when R_0 is larger enough than one in value.

Now, when we apply the vaccination strategy of the form:

$$r(t) = \begin{cases} \rho_{10} + \rho_{11} e^{-\rho_{12}(mod(t,52))^2} & 0 < mod(t,52) \leq 26; \\ \rho_{20} + \rho_{21} e^{-\rho_{22}(mod(t,52)-26)^2} & 26 < mod(t,52) \leq 52; . \end{cases}$$

Where the parameters of the vaccination function $r(t)$ are given the following values: $\rho_{10} = 0.00098$, $\rho_{11} = 0.00188$, $\rho_{12} = 0.0031$, $\rho_{20} = 0.00072$, $\rho_{21} = 0.0014$, $\rho_{22} = 0.00065$. In this case, we find that the susceptibles and the infected populations tend to the DFPS as shown in Figure 5.

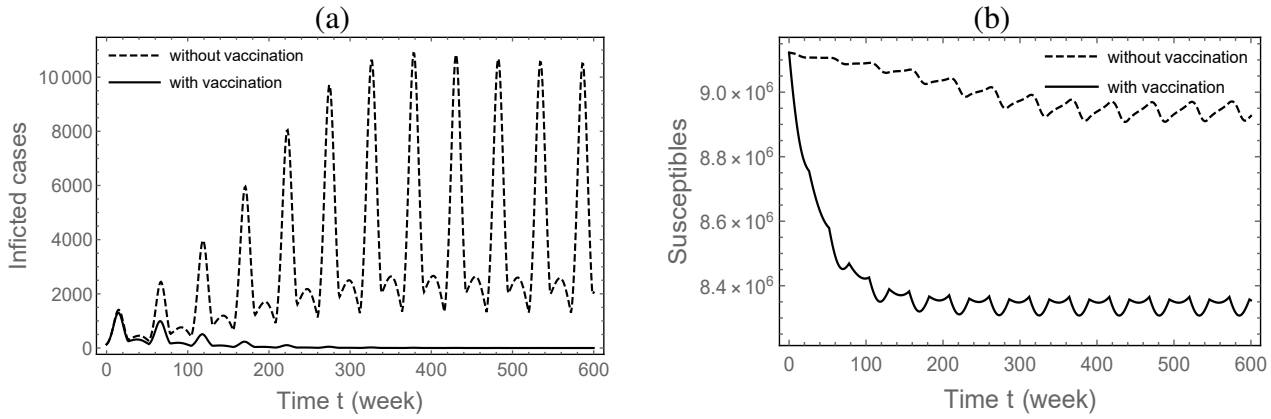

Figure 6. Plots our approximate solution for (a) the infected population I(t) and (b) the susceptibles respectively against the time (t) in weeks, when $R_0 > 1$. The dotted carves are without vaccination while soled ones are with vaccination

Figure 6 (a) shows that in the absence of vaccination the HFMD fire up when $R_0 > 1$. While applying our vaccination strategy forces the disease to die out and (b) show that without vaccination the susceptible population stays high enough to provide a flow of new case which give the disease the chance to persist in the population. On the other hand, applying our vaccination strategy forces the susceptibles to be small enough to fluctuate close to the DFPS and keep R_0 to be less than one.

7. Conclusions

We study an SEIQRS model for the dynamics of HFMD. Our model introducing a seasonality in both the contact and vaccination rates. In section 1 we give a brief introduction to the dynamics of HFMD as a public health problem. In section 2 we formulate our model and define the model parameters. The exitance of the DFPS is proved in section 3 and the formula of the basic reproduction number R_0 is derived in section 4. We define an upper bound of R_0^{sup} and a lower bound R_0^{inf} in this section as well. We use these lower and upper bounds to prove that, the disease free periodic solution DFPS, is globally asymptotically stable when $R_0^{sup} < 1$ and unstable if $R_0^{inf} > 1$. Section 5 contains the stability results. We use our novel form of periodic contact and vaccination rates during all of our simulations in section 6. Previous works used a sinusoidal form of periodic transmission rate which is failed to simulate the yearly multi-peaks pattern in the reported data. We claim that our suggested transmission periodic function forces our model to have a multi-peaks pattern. This result gives our model more realistic behaviours and produces more accurate simulation results. Our simulation results are original for this kind of periodic functions.

Future work

In our study, the population is assumed to be homogeneously mixed and has a constant size. This assumption is unrealistic, so in future work, one can use network epidemic models to simulate the fact that, peoples have different chances to catch the disease [38–40]. Another future work is to study the behaviour of the endemic solution when the reproduction number $R_0 > 1$.

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Conflict of interest

The authors declare that they have no competing interests.

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