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# MODELLING SEASONAL HFMD WITH THE RECESSIVE INFECTION IN SHANDONG, CHINA

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Abstract. Hand, foot and mouth disease (HFMD) is one of the major public-health problems in China. Based on the HFMD data of the Department of Health of Shandong Province, we propose a dynamic model with periodic transmission rates to investigate the seasonal HFMD. After evaluating the basic reproduction number, we analyze the dynamical behaviors of the model and simulate the HFMD data of Shandong Province. By carrying out the sensitivity analysis of some key parameters, we conclude that the recessive subpopulation plays an important role in the spread of HFMD, and only quarantining the infected is not an effective measure in controlling the disease.

1. **Introduction.** Hand, foot and mouth disease (HFMD) is a common infectious disease among infants and children. HFMD is caused by a group of enterovirus which mainly include coxsackievirus A16 (CA16) and enterovirus 71 (EV71) [4]. It is estimated that there are 500,000∼1,800,000 HFMD cases per year in China [21], and a series of recent HFMD outbreaks in China can be found in [9, 10, 22, 26, 27].

In the spread of HFMD, children are more susceptible to be infected than adults, because they are less likely than adults to have antibodies and awareness of self-protection. HFMD spreads mainly among children under five-years old [5], and may

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also occur among adults. A health individual will be infected by contacting with the infectious individuals or touching objects which are touched by the infectious. After a susceptible individual is infected he firstly enters the incubation period of HFMD. The incubation period is about $3 \sim 7$ days. After the incubation period, the infected will show some clinical symptoms, such as have a fever, poor appetite, malaise and sore throat, few people may develop dehydration, febrile seizures, encephalitis, meningitis, cardiomyopathy, etc. However, some infectious individuals especially adults do not show the clinical symptom, and we call them the recessive infection. The recessive infection individuals are also infectious, and they can transmit HFMD virus to the susceptible. After the end of the incubation period an infectious people will recover back to the susceptible in $7 \sim 10$ days.

In general, many infectious diseases fluctuate over time and show seasonal patterns in the incident rate, such as measles, whooping cough, polio, influenza, chickenpox, mumps, etc [1, 6, 11]. Although this phenomenon is familiar with us, the causes and consequences of seasonal patterns in the incident rate are not fully understood. Periodic changing in the birth rate [12] and seasonally changing in the contact rate [7, 16, 17] are often regarded as sources of periodicity. In this paper, based on the characteristics of reported weekly data from the Department of Health of Shandong Province, we consider the periodic transmission attribute to the following three facts: (i) In the winter most children like to stay at home due to the cold weather and while in the summer and fall, people especially children have more frequent outdoor activities. (ii) The warm climate contribute to the reproduction of the virus and the prevalence of the disease in the summer. In fact, it is reported that HFMD cases increase sharply when the average temperature is more than a threshold value of 19°C [20]. (iii) From April to June children usually play and study together at school, while during July and August most schools are closed for summer vacation thus many children play together without supervision. All these reasons cause the disease spread easily and form a seasonal pattern.

Recently, several mathematical models have been developed to study the transmission dynamics of HFMD. For example, Tiing and Labadin [19] studied a simple SIR model to predict the number of infected and the duration of an outbreak in Sarawak Malaysia. Liu [9] constructed a periodic epidemic model to simulate the dynamics of HFMD transmission, and showed that quarantine has a positive impact on controlling the spread of HFMD. In China, with the increasing of the recessive, understanding and exploring the role of the recessive in the spread of HFMD become an important research field. In this paper, taking into account the role of recessive infection, we propose a susceptible, exposed, infected, recessive, quarantined and recovered ($SEII_eQR$) model with periodic transmission rate. We firstly determine the basic reproduction number and analyze the dynamic behaviors of the model, and then carry out numerical simulations and the sensitivity analysis of some key parameters. At last based on the analysis and simulations we discuss some effective strategies in controlling the spread of HFMD in Shandong Province.

The paper is organized as follows. In section 2, we present the model and give the parameters. In section 3, we determine the basic reproduction number $R_0$ and analyze the global asymptotic stability of the disease-free equilibrium and the existence of positive periodic solutions. Simulations of the model and sensitivity analysis are performed in section 4. In section 5, we give a brief discussion. The detailed calculation of the basic reproduction number and the proof of some results are presented in the Appendix.

2. **The HFMD Model.** We classify the population into six compartments according to their states: susceptible, exposed, infected, recessive, quarantined, recovered, which are denoted by $S(t)$, $E(t)$, $I(t)$, $I_e(t)$, $Q(t)$ and $R(t)$, respectively. We denote the total population by $N(t)$, that is $N(t) = S(t)+E(t)+I(t)+I_e(t)+Q(t)+R(t)$. The transition dynamics associated with these subpopulations are illustrated in Figure 1. People who are infected firstly enter the latent period, during which they do not show symptoms and can not infect others. After about $3 \sim 7$ days, these people become the infectious. The infectious people are classified into the infected ($I(t)$) and the recessive ($I_e(t)$), who are different in the transmission rate. Some of the infected people will be hospitalized for treatment, and thus they ($Q(t)$) are isolated from other subpopulations. Because HFMD in Shandong was mainly caused by EV71[27], thus some of the recovered will be reinfected after they lose the immunity.

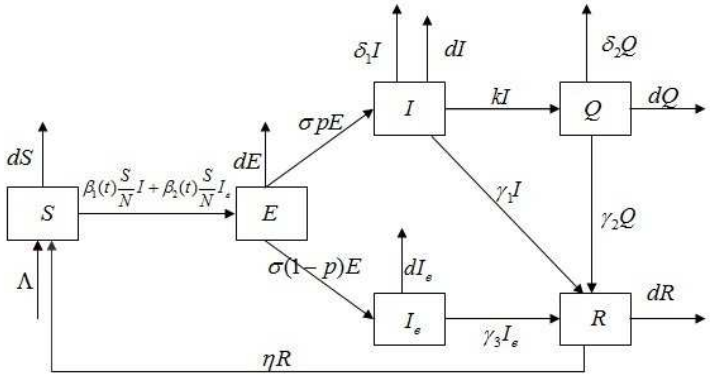


FIGURE 1. Flowchart of HFMD transmission with subpopulations

The standard incidence $\beta(t)SI/N$ is applied in the model because an infectious individual only can contact a finite number of individuals within a unit time among a large population [14]. The transmission rate between $S(t)$ and $I(t)$ is $\beta_1(t)$, and the transmission rate between $S(t)$ and $I_e(t)$ is $\beta_2(t)$. As discussed in the Introduction, many epidemiological models [6, 8, 12, 13, 16, 23, 24, 28] were simulated by using sinusoidal function of period 1 year ($\beta(t) = \beta_0 + \beta\sin(\omega t + \phi)$) for the seasonal varying transmission rate. In this model, we use the periodic functions $\beta_1(t) = a_1 + b_1\sin(\frac{\pi}{26}t + \phi)$ and $\beta_2(t) = a_2 + b_2\sin(\frac{\pi}{26}t + \phi)$ with period $\omega$ (here $\omega = 52$ weeks) as the transmission rates. Here $a_1, b_1, a_2$, $b_2$ and $\phi$ are constant, which can be determined by the least-square fitting in Section 4.

The interpretations and values of parameters are described in Table 1. The source [A] is from Shandong Statistical Yearbook 2010, 2011 and 2012 [18]. From [A] we obtain the values of the annual average birth rate and natural death rate, then we divide them by 52 and derive the weekly birth population $\Lambda$ and natural death rate $d$. The source [B] is the reported data of HFMD in Shandong from April 2009 to October 2011. As similar as the above, we derive the weekly disease-related death $\delta_1, \delta_2$ and the quarantine rate $k$. The average incubation period $1/\sigma$ and the recover

TABLE 1. Descriptions and values of parameters

| Para. | Value | Unit | Interpretation | Source |
|---|---|---|---|---|
| $\Lambda$ | $2.0961 \times 10^4$ | week$^{-1}$ | Birth population | [A] |
| $1/\sigma$ | $4/7$ | week | The average incubation period | [9] |
| $p$ | $2.5 \times 10^{-2}$ | none | The fraction of developing infected cases | Fitting |
| $\delta_1$ | $1.6 \times 10^{-4}$ | week$^{-1}$ | The infected disease-related death rate | [B] |
| $\delta_2$ | $1.6 \times 10^{-4}$ | week$^{-1}$ | The quarantined disease-related death rate | [B] |
| $k$ | $2.85 \times 10^{-2}$ | week$^{-1}$ | The quarantine rate | [B] |
| $\gamma_1$ | 0.8235 | week | The recover rate of the infected | [9] |
| $\gamma_2$ | 0.8235 | week | The recover rate of the quarantined | Assumption |
| $\gamma_3$ | 0.8235 | week | The recover rate of the recessive | Assumption |
| $d$ | $1.37 \times 10^{-4}$ | week$^{-1}$ | Natural death rate | [A] |
| $\eta$ | $1.5 \times 10^{-2}$ | none | The rate from recovered to susceptible | Fitting |

rate of the infected individuals $\gamma_1$ are given by [9]. In this model we also assume that the infected, the quarantined and the recessive have the same recover rate $\gamma_1 = \gamma_2 = \gamma_3$. The values of other parameters can be obtained by the least-square fitting method.

The model is described by the following system of nonautonomous differential equations.

$$\frac{dS}{dt} = \Lambda - \beta_1(t)\frac{S}{N}I - \beta_2(t)\frac{S}{N}I_e + \eta R - dS, \tag{1a}$$

$$\frac{dE}{dt} = \beta_1(t)\frac{S}{N}I + \beta_2(t)\frac{S}{N}I_e - \sigma E - dE, \tag{1b}$$

$$\frac{dI}{dt} = \sigma pE - (\gamma_1 + k + \delta_1)I - dI, \tag{1c}$$

$$\frac{dI_e}{dt} = \sigma(1-p)E - \gamma_3 I_e - dI_e, \tag{1d}$$

$$\frac{dQ}{dt} = kI - (\gamma_2 + \delta_2)Q - dQ, \tag{1e}$$

$$\frac{dR}{dt} = \gamma_1 I + \gamma_2 Q + \gamma_3 I_e - \eta R - dR. \tag{1f}$$

3. **Mathematical analysis.** In this section, we investigate the global stability of disease-free equilibrium and the existence of the positive periodic solution of model (1). It is easy to see that model (1) always has one disease-free equilibrium $P_0 = (\hat{S}, 0, 0, 0, 0, 0)$, where $\hat{S} = \frac{\Lambda}{d}$. By using model (1), we have

$$\frac{dN}{dt} = \Lambda - dN - \delta_1 I - \delta_2 Q \leq \Lambda - dN, \tag{2}$$

therefore

$$X = \left\{(S, E, I, I_e, Q, R) | S, E, I, I_e, Q, R \geq 0, 0 < S + E + I + I_e + Q + R \leq \frac{\Lambda}{d}\right\}$$

is the feasible region for model (1), and we also have

**Theorem 3.1.** *The region $X$ is positively invariant set for model (1).*

It is not difficult to prove Theorem 3.1, thus we put the proof in the Appendix A. We can derive the basic reproduction number of model (1) by the definition of Bacaër and Guernaoui [2], and its calculation is based on Floquet theory introduced in [3] and Wang and Zhao [25]. The details are given in the Appendix B. For

the globally asymptotically stable of the disease-free equilibrium $P_0$, we have the following theorem.

**Theorem 3.2.** *The disease-free equilibrium $P_0$ is globally asymptotically stable when $R_0 < 1$.*

About the proof of Theorem 3.2, we also put it in the Appendix C. The following we consider the existence of the positive periodic solution of model (1). Define

$$X_0 := \{(S, E, I, I_e, Q, R) \in X : E > 0, I > 0, I_e > 0\}$$

and $\partial X_0 = X \setminus X_0$. Denote $u(t, x_0)$ as the unique solution of model (1) with the initial value $x_0 = (S^0, E^0, I^0, I_e^0, Q^0, R^0)$. Let $P : X \to X$ be the Poincaré map associated with model (1), i.e.,

$$P(x_0) = u(\omega, x_0), \ \forall x_0 \in X,$$

where $\omega$ is the period. Applying the fundamental existence-uniqueness theorem[15], we know that $u(t, x_0)$ is the unique solution of model (1) with $u(0, x_0) = x_0$. From Theorem 3.1, we know that $X$ is positively invariant and $P$ is dissipative point. To prove the main result about the existence of positive periodic solution of model (1), we need the following lemma.

**Lemma 3.3.** *When $R_0 > 1$, there exists a $\delta > 0$ such that when*

$$\|(S^0, E^0, I^0, I_e^0, Q^0, R^0) - P_0\| \le \delta$$

*for any $(S^0, E^0, I^0, I_e^0, Q^0, R^0) \in X_0$, we have*

$$\limsup_{m\to\infty} d[P^m(S^0, E^0, I^0, I_e^0, Q^0, R^0), P_0] \ge \delta,$$

*where $P_0 = (\hat{S}, 0, 0, 0, 0, 0)$.*

Because the proof of Lemma 3.3 is similar with the proof of Lemma 2.4 in [28], here we omit it. According to Lemma 3.3, we can get the following theorem about the existence of positive periodic solution of model (1). Similarly, the reader can find the proof in the Appendix D.

**Theorem 3.4.** *Model (1) has at least one positive periodic solution when $R_0 > 1$.*

4. **Simulations and sensitivity analysis.** In this section, by using model (1), we simulate the reported data of HFMD in Shandong, China from April 2009 to October 2011, and carry out the sensitivity analysis based on the parameters.

We need to estimate the values of parameters of model (1), most of which can be obtained from the literature or assumed on the basis of common sense. From the Department of Health of Shandong Province, we obtained the data of HFMD. By using the least-square fitting of $I(t)$, we estimated the values of parameters $p, \eta$, and we also obtained $\beta_1(t) = 1 + 0.3\sin(\frac{\pi}{26}t + 2)$ and $\beta_2(t) = 0.878 + 0.3\sin(\frac{\pi}{26}t + 2)$. The values of other parameters are listed in Table 1. We need the initial values to perform the numerical simulations. The number of the initial susceptible population at the end of 2008, $S(0) = 9.3 \times 10^7$, is obtained from the Statistical Information of Shandong Province [18]. The numbers of the initial infected and quarantined population $I(t)$ and $Q(t)$ are obtained from the reported data of HFMD, thus $I(0) = 5.775 \times 10^3$, $Q(0) = 50$. Because the numbers of the initial exposed population $E(0)$, the recessive population $I_e(0)$ and the recovered population $R(0)$ can not be obtained directly, we derive $R(0) = 5\times10^4$ by the parameter $\gamma_1$ and $E(0) = 8.5\times10^4$ and $I_e(0) = 7 \times 10^4$ are estimated by a reasonable assumption.

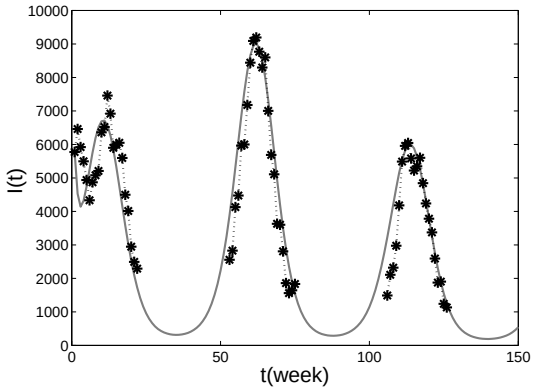


FIGURE 2. The solid curve represents the simulation curve and the stars are the weekly data reported by the Department of Health of Shandong.

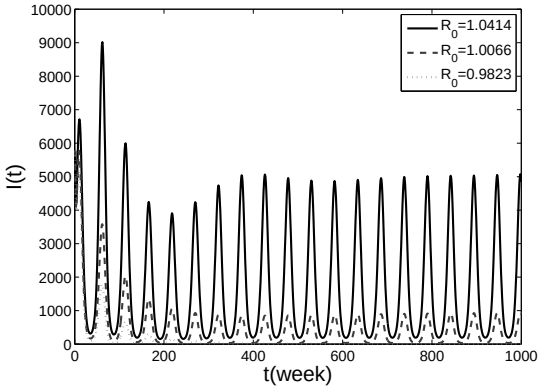


FIGURE 3. Simulations of the infective $I(t)$ with different values $R_0$ in Shandong. Here $(a_1,a_2)$=(1,0.878),(0.95,0.85),(0.93,0.83) and the values of other parameters are same, and $R_0 = 1.0414, 1.0066, 0.9823$, respectively.

The numerical simulation of the model (1) about the number of HFMD infectious cases is shown in Figure 2. It indicates that with these parameter values, there is a good fit between the simulation of the model (1) and the infectious cases in Shandong Province from 2009 to 2011. Moreover, with these parameter values, we can roughly estimate that the basic reproduction number $R_0 \simeq 1.04 > 1$, which show that HFMD in Shandong Province persist under current circumstances. Furthermore we notice $R_0$ is also close to one. This is because that we suppose the whole population of Shandong (almost 100 million people) is homogeneously mixing. If we have try to take for the susceptible population by the children under five-years old and their family (less than 10 million people), the estimate for $R_0$ would be somewhat higher. Moreover, we demonstrate $R_0$ is a threshold, which determine the disease extinct or not. HFMD will persist under the condition $R_0 \simeq 1.01$, where

$a_1 = 0.95, a_2 = 0.85$ in $\beta_1(t)$ and $\beta_2(t)$. If let $a_1 = 0.93$ and $a_2 = 0.83$, we get $R_0 \simeq 0.98$. In this case the disease will extinct (see Figure 3). Next we discover the influence of initial values $S(0), E(0), I_e(0), Q(0)$ and $R(0)$ on the number of infected cases $I(t)$. From Figure 4, we can see that the initial value of $S(t)$ has a greater impact on $I(t)$ while other initial values have little or no impact on $I(t)$.

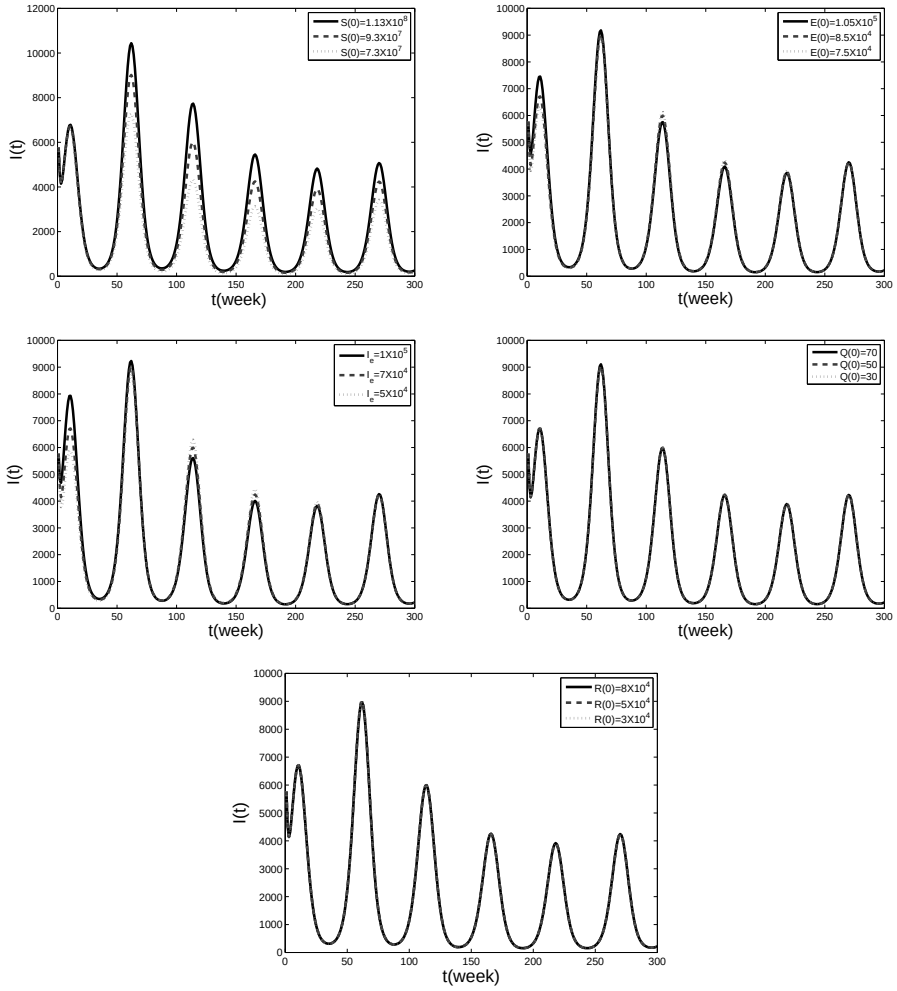


FIGURE 4. Simulations of the infected cases $I(t)$ with different values of $S(0), E(0), I_e(0), Q(0)$ and $R(0)$ in Shandong Province of China. Here $R_0 \simeq 1.04$.

In order to perform sensitivity analysis of parameters $p$ and $k$, we fix all parameters except $p$ and $k$. Figure 5(a) reflects the relation between the basic reproduction number $R_0$ and the parameter $p$. We see that the basic reproduction number $R_0$ increase with the increasing of $p$, and $R_0$ always larger than one even if $p = 0$. From Figure 5(a), we conclude that the parameter $p$ has great influence on $R_0$, and the infected and the recessive subpopulation play the dominant role in the spread of

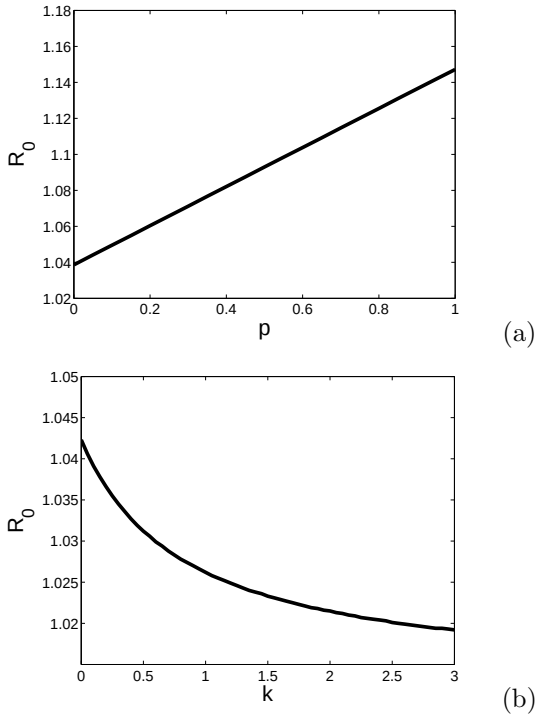


FIGURE 5. The influence of parameters on $R_0$. (a) Versus $p$; (b) versus $k$. Other parameter values in Table 1 do not change.

HFMD. Figure 5(b) shows that the larger $k$ is, the less $R_0$ is, that is to say, quarantine has a positive impact on controlling the spread of disease. However, even if the quarantine rate $k$ is larger than 3 the basic reproduction number is also larger than one.

5. **Discussion.** The transmission of HFMD has been a growing concern in China. In this paper, by using HFMD data of Shandong Province, we constructed an $SEII_eQR$ model with periodic transmission rates to investigate the spread of seasonal HFMD in Shandong. From the simulations, we concluded that HFMD will persist in Shandong Province under current circumstances. By carrying out the sensitivity analysis of some key parameters, we found that the recessive subpopulation plays an important role in the spread of HFMD while the quarantine subpopulation has a little effect in controlling the disease. Even if the quarantine rate $k$ is larger, the basic reproduction number is still larger than one, that is to say, HFMD still persist even with a larger quarantine rate. Therefore the quarantine is not an effective measure in many measures of controlling HFMD.

According to WHO, there is no an effective vaccine or antiviral treatment specifically for HFMD. However, the risk of infection can be minimized by good hygiene practices, including: (i) washing hands frequently and thoroughly with soap and cleaning dirty surfaces and soiled items; (ii) avoiding close contact with the infective; (iii) not sharing personal items such as spoons, cups and other utensils with

other people. In a word, publicity and education on the risk and prevention of HFMD is necessary and should be strengthened especially in endemic areas.

**Appendix A: Calculation of the basic reproduction number.** We evaluate the basic reproduction number $R_0$ for system (1) following the definition of Bacaër and Guernaoui [2] and the calculation procedure for ODEs based on Floquet theory introduced in [3]. According to Wang and Zhao [25], we have

$$\mathcal{F} = \begin{pmatrix} \beta_1(t)\frac{S}{N}I + \beta_2(t)\frac{S}{N}I_e \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} \sigma E + dE \\ (\gamma_1 + k + \delta_1 + d)I - \sigma p E \\ (\gamma_3 + d)I_e - \sigma(1-p)E \\ (\gamma_2 + \delta_2 + d)Q - kI \\ (\eta + d)R - (\gamma_1 I + \gamma_2 Q + \gamma_3 I_e) \\ \beta_1(t)\frac{S}{N}I + \beta_2(t)\frac{S}{N}I_e + dS - \eta R - \Lambda \end{pmatrix},$$

$$\mathcal{V}^- = \begin{pmatrix} 0 \\ \sigma p E \\ \sigma(1-p)E \\ kI \\ \gamma_1 I + \gamma_2 Q + \gamma_3 I_e \\ \eta R + \Lambda \end{pmatrix}, \quad \mathcal{V}^+ = \begin{pmatrix} \sigma E + dE \\ (\gamma_1 + k + \delta_1 + d)I \\ (\gamma_3 + d)I_e \\ (\gamma_2 + \delta_2 + d)Q \\ (\eta + d)R \\ \beta_1(t)\frac{S}{N}I + \beta_2(t)\frac{S}{N}I_e + dS \end{pmatrix}.$$

So we derive

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

and

$$V(t) = \begin{pmatrix} \sigma + d & 0 & 0 & 0 \\ -\sigma p & \gamma_1 + k + \delta_1 + d & 0 & 0 \\ -\sigma(1-p) & 0 & \gamma_3 + d & 0 \\ 0 & -k & 0 & \gamma_2 + \delta_2 + d \end{pmatrix}.$$

Now we introduce the following linear $\omega$-periodic equation

$$\frac{dw}{dt} = [-V(t) + \frac{F(t)}{z}]w, \ t \in \mathbb{R}_+, \tag{3}$$

with parameter $z \in (0, \infty)$. Let $W(t, s, z), t \geq s, s \in \mathbb{R}$, be the evolution operator of system (3) on $\mathbb{R}^4$. Clearly, $\Phi_{F-V}(t) = W(t, 0, 1), \forall t \geq 0$. To determine the threshold of dynamics, we use Theorems 2.1 and 2.2 in Wang and Zhao [25] which is a generalization of §3.4 in [3]. First of all, we can verify the seven assumptions in the theorems. Then we can obtain that all eigenvalues of the matrix $W(\omega, 0, z)$. Because the $W(\omega, 0, z)$ is more complex, we do not want to show its accurate expression in this paper. Using (ii) in Theorem 2.1 in Wang and Zhao [25], we can calculate the basic reproduction number.

**Appendix B: Proof of Theorem 3.1.**

*Proof.* From model (1), the total population $N(t)$ satisfies the following equation,

$$\frac{dN}{dt} \leq \Lambda - dN.$$

It is clear that $N_1(t) = \frac{\Lambda}{d}$ is a solution of

$$\frac{dN_1}{dt} = \Lambda - dN_1, \tag{4}$$

and for any $N(t_0) \geq 0$, the general solution of (4) is

$$N_1(t) = \frac{1}{d}[\Lambda - (\Lambda - dN_1(t_0))e^{-d(t-t_0)}],$$

that we have $\lim\limits_{t\to\infty} N_1(t) = \frac{\Lambda}{d}$, thus $\lim\limits_{t\to\infty} N(t) \leq \frac{\Lambda}{d}$, which implies that $X$ is positively invariant with respect to system (1). □

## Appendix C: Proof of Theorem 3.2.

*Proof.* If $R_0 < 1$, $P_0$ is locally asymptotically stable by Theorem 2.2 in Wang and Zhao [25]. To show the solution is globally stable, we need show that $P_0$ is globally attractive. Clearly, $S(t) \leq N(t)$, for all $t \geq 0$. Then from system (1), we have

$$\begin{aligned}
\frac{dE}{dt} &\leq \beta_1(t)I + \beta_2(t)I_e - (\sigma + d)E, && \text{(5a)}\\
\frac{dI}{dt} &= \sigma pE - (\gamma_1 + k + \delta_1)I - dI, && \text{(5b)}\\
\frac{dI_e}{dt} &= \sigma(1-p)E - \gamma_3 I_e - dI_e, && \text{(5c)}\\
\frac{dQ}{dt} &= kI - (\gamma_2 + \delta_2)Q - dQ. && \text{(5d)}
\end{aligned}$$

Consider the following comparison system

$$\frac{dh}{dt} = (F(t) - V(t))h(t), \quad h(t) = (E(t), I(t), I_e(t), Q(t))^T. \tag{6}$$

Applying Theorem 2.2 in Wang and Zhao [25], we know that $R_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$. By Lemma 2.1 in Zhang and Zhao [29], it follows that there exists a positive $\omega$-periodic function $\hat{h}(t)$ such that $h(t) = e^{pt}\hat{h}(t)$ is a solution of system (6), where $p = \frac{1}{\omega}\ln\rho(\Phi_{F-V}(\omega))$. We know when $R_0 < 1$, $\rho(\Phi_{F-V}(\omega)) < 1$. Therefore, we have $h(t) \to 0$ as $t \to \infty$, which implies that the zero solution of system (5) is globally asymptotically stable. Applying the comparison principle, we know that for system (1), $E(t) \to 0, I(t) \to 0, I_e(t) \to 0$ and $Q(t) \to 0$ as $t \to \infty$. By the theory of asymptotic autonomous systems, it is also known that $S(t) \to \hat{S}$ as $t \to \infty$. So $P_0$ is globally attractive when $R_0 < 1$. It follows that $P_0$ is globally asymptotically stable when $R_0 < 1$. □

## Appendix D: Proof of Theorem 3.4.

*Proof.* We first prove that $\{P^m\}_{m\geq 0}$ is uniformly persistent with respect to $(X_0, \partial X_0)$. First of all, we explain that $X_0$ and $\partial X_0$ are positively invariant. For any $(S^0, E^0, I^0, I_e^0, Q^0, R^0) \in X_0$, solving the first equation of system (1), we derive that

$$\begin{aligned}
S(t) &= e^{-\int_0^t (d+a(s_1))ds_1}[S^0 + \int_0^t (\Lambda + \eta R(s_2))e^{\int_0^{s_2}(d+a(s_1))ds_1}ds_2]\\
&\geq e^{-\int_0^t (d+a(s_1))ds_1}\int_0^t (\Lambda + \eta R(s_2))e^{\int_0^{s_2}(d+a(s_1))ds_1}ds_2\\
&> 0, \ \forall t > 0, && \text{(7)}
\end{aligned}$$

$$\begin{aligned} E(t) &= e^{-(\sigma+d)t}[E^0 + \int_0^t a(s_1)S(s_1)e^{(\sigma+d)s_1}ds_1] \\ &\geq e^{-(\sigma+d)t}\int_0^t a(s_1)S(s_1)e^{(\sigma+d)s_1}ds_1] \\ &> 0,\ \forall t > 0, \end{aligned} \tag{8}$$

$$\begin{aligned} I(t) &= e^{-(\gamma_1+k+\delta_1+d)t}[I^0 + \int_0^t \sigma p E(s_1)e^{(\gamma_1+k+\delta_1+d)s_1}ds_1] \\ &\geq e^{-(m+\mu)t}\int_0^t \sigma p E(s_1)e^{(\gamma_1+k+\delta_1+d)s_1}ds_1 \\ &> 0,\ \forall t > 0, \end{aligned} \tag{9}$$

$$\begin{aligned} I_e(t) &= e^{-(\gamma_3+d)t}[I_e^0 + \int_0^t \sigma(1-p)E(s_1)e^{(\gamma_3+d)s_1}ds_1] \\ &\geq e^{-(\gamma_3+d)t}\int_0^t \sigma(1-p)E(s_1)e^{(\gamma_3+d)s_1}ds_1 \\ &> 0,\ \forall t > 0, \end{aligned} \tag{10}$$

$$\begin{aligned} Q(t) &= e^{-(\gamma_2+\delta_2+d)t}[Q^0 + \int_0^t kI(s_1)e^{(\gamma_2+\delta_2+d)s_1}ds_1] \\ &\geq e^{-(\gamma_2+\delta_2+d)t}\int_0^t kI(s_1)e^{(\gamma_2+\delta_2+d)s_1}ds_1 \\ &> 0,\ \forall t > 0, \end{aligned} \tag{11}$$

and

$$\begin{aligned} R(t) &= e^{-(\eta+d)t}[R^0 + \int_0^t (\gamma_1 I(s_1) + \gamma_2 Q(s_1) + \gamma_3 I_e(s_1))e^{(\eta+d)s_1}ds_1] \\ &\geq e^{-(\eta+d)t}\int_0^t (\gamma_1 I(s_1) + \gamma_2 Q(s_1) + \gamma_3 I_e(s_1))e^{(\eta+d)s_1}ds_1 \\ &> 0,\ \forall t > 0. \end{aligned} \tag{12}$$

where $a(t) := \beta_1(t)\frac{I(t)}{N(t)} + \beta_2(t)\frac{I_e(t)}{N(t)}$. So, $X_0$ is positively invariant. Clearly, $\partial X_0$ is relatively closed in X. Set

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

It is easy to show that

$$M_\partial = \{(S, 0, 0, 0, 0, 0) \in X : S \geq 0\}. \tag{13}$$

Note that $\{(S, 0, 0, 0, 0, 0) \in X : S \geq 0\} \subseteq M_\partial$, we only need to prove that $M_\partial \subseteq \{(S, 0, 0, 0, 0, 0) \in X : S \geq 0\}$. That is, for any $(S^0, E^0, I^0, I_e^0, Q^0, R^0) \in \partial X_0$, we have

$$E(m\omega) = I(m\omega) = I_e(m\omega) = 0, \forall m \geq 0.$$

If there exists an $m_1 \geq 0$ such that

$$(E(m_1\omega), I(m_1\omega), I_e(m_1\omega))^T > 0,$$

by replacing the initial time 0 with $m_1\omega$ and following the processes as in (7)-(12). Analogously, we have $(E(t), I(t), I_e(t))^T > 0, \forall t > m_1\omega$. Thus, we have

$$(S(t), E(t), I(t), I_e(t), Q(t), R(t)) \in X_0,\ \forall t > m_1\omega,$$

which contradicts that $(S^0, E^0, I^0, I_e^0, Q^0, R^0) \in \partial X_0$ that requires

$$P^m(S^0, E^0, I^0, I_e^0, Q^0, R^0) \in \partial X_0, \forall m \geq 0.$$

So the equality (13) holds which implies that $P_0$ is the only fixed point of $P$ and acyclic in $\partial X_0$.

Moreover, Lemma 3.3 implies that $P_0 = (\hat{S}, 0, 0, 0, 0, 0)$ is an isolated invariant set in $X$ and $W^S(P_0) \cap X_0 = \emptyset$. By the acyclicity theorem on uniform persistence for maps (Theorem 1.3.1 and Remark 1.3.1 in Zhao [25]), it follows that $P$ is uniformly persistent with respect to $(X_0, \partial X_0)$.

Theorem 1.3.6 in Zhao [25] implies that $P$ has a fixed point

$$(S^*(0), E^*(0), I^*(0), I_e^*(0), Q^*(0), R^*(0)) \in X_0.$$

From the first equation of system (1) we have that

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

The periodicity of $S^*(t)$ implies $S^*(t) > 0$ for all $t > 0$. Following the processes as in inequalities (7)-(12), we have $E^*(t) > 0, I^*(t) > 0, I_e^*(t) > 0, Q^*(t) > 0, R^*(t) > 0$, for all $t \geq 0$. Therefore,

$$(S^*(t), E^*(t), I^*(t), I_e^*(t), Q^*(t), R^*(t))$$

is a positive $\omega-$periodic solution of system (1). □

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