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MODELLING THE EFFECTS OF THE VACCINATION ON SEASONAL INFLUENZA IN GANSU, CHINA*

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Abstract Seasonal influenza is still prevalent and poses a huge health burden, which is the most worth considerable issue that causes economic pressure on the government. Investigating the essential characteristics of seasonal influenza can assist to improve people's vigilance. A new influenza model with vaccination and periodic transmission rate is introduced in this essay. The basic reproduction number R_0 is derived, and formulate that R_0 is an important indicator to measure whether seasonal influenza can spread in the population. Furthermore, the explicit consequences for the implementation of optimal control and the corresponding optimal solutions to alleviate the spread of influenza virus are explored and derived. The best fitting parameters in our model are determined from the seasonal influenza case data reported in Gansu Province via MCMC procedure. The value of R_0 is $1.2266(95\%CI : (1.2230, 1.2302))$ by estimating unknown parameters. The different vigorous control strategies for controlling the transmission of seasonal influenza are also studied and simulated. Finally, the uncertainty and sensitivity of some parameters are shown to determine which critical control strategy is effective. Our numerical results imply that raising the vaccination rate can availably reduce the spread of seasonal influenza in Gansu Province, and vaccination is a more effective method than treatment.

Keywords Influenza, parameter estimation, sensitivity analysis, optimal control, vaccination.

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1. Introduction

The influenza virus which is certain RNA viruses of the Orthomyxoviridae family causes acute respiratory disease that is highly infectious from person to person [9]. Its main clinical manifestations are fever, headache, weakness of the limbs, coughing and so on. When human beings are exposed to influenza virus, influenza virus enters respiratory tract quickly and resides in the human body, which causes people's physical discomfort. In the past 20th century, there have been three major influenza plagues that claimed many lives [19]. The most well-known and deadly of which was the Spanish flu, which had a global average fatality rate of 2.3%∼5%. So far,

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although seasonal influenza will not cause large-scale deaths, influenza viruses still pose a serious threat to human life and health. Especially in places where medical resources are underdeveloped, influenza is particularly serious.

As influenza virus has a high risk to the aged, youngsters, gravidas or other population of impoverished immune systems, it is imperative to find suitable measures to reduce the risk of influenza infection. Vaccination is one of the effective methods to alleviate the influences of seasonal influenza epidemics globally [6]. Recently, a comprehensive investigation of the scientific magazine claimed that the effectiveness of trivalent influenza vaccine for youngsters (ages 6 months to 8 years) was 83% (95% CI: (69%, 91%)) [8]. The other literature claimed that the effectiveness of trivalent inactivated influenza vaccine on healthy grown-ups aged between eighteen to sixty-five years old was 59% (95% CI: (51%, 67%)) and provided remarkable protection against influenza [8, 26, 27]. The above data show that influenza vaccination has a significant effect on reducing the risk of infection.

It is worth mentioning that the mathematical modeling have been played a significant role in formulating the prevention and control strategies [12]. Several recent studies have focused on various models used to forecast and evaluate vaccination strategies [18, 28, 29]. Qiu and Feng [28] showed an autonomous differential equation model with antiviral treatment and vaccination, the threshold condition for the existence of the equilibrium point was given, as well as the stability and uniform persistence of the system were analyzed. Shi et al. [29] proposed and studied and EV71 vaccination model of HFMD(hand-foot-mouth disease) , and concluded that the vaccine was effective in reducing outbreaks of HFMD. Jing et al. [18] proposed a non-autonomous ordinary differential equation model and took into account the impacts of ozone in the air and vaccination on the spread of influenza, and studied the dynamic of proposed mathematical model. Other vaccination models are shown in [11, 14, 20] and references cited therein.

The spread of some viruses has a strong seasonal and diversified spatial characteristic. From the perspective of the above reality, it is shown that the relationship between seasonal periodic outbreaks and epidemic trends can help predict the long-term health risks of diseases. Therefore, many literatures have introduced the periodic transmission rate functions [16, 17, 32, 38]. Zhu et al. [38] showed a mathematical model of SEIQRS to explore the spread of HFMD in Wenzhou region and evaluate the prevention strategies. Wang et al. [32] established a model that regards the particles of pollution in free air as indirect transmission rate and person-to-person contact as direct transmission rate, and concluded that frequent cleaning and sanitation can availably decrease the prevalence of HFMD. Jing et al. [17] proposed a novel mathematical model, as well as considered the impact of meteorological factors and periodic transmission rate on seasonal influenza. Mahmoud et al. [16] formulated a mathematical model of Zika propagation in periodic circumstance, including sexual contact propagation and insect vector propagation, and analyzed the model from the perspective of mathematical dynamics. Other diseases with periodic transmission are also shown in [5, 15, 36].

Since vaccine is only effective against the influenza virus of the year, that is, the validity period of the influenza vaccine is about one year [7, 24], it is assumed that some people will still be infected with the influenza virus after being vaccinated. Motivated by the above, we build up a non-autonomous ordinary differential equation mathematical model, as well as analyze the model by mathematical methods. Moreover, we optimized a variety of mitigation strategies to minimize the final scale

of human infection. Meanwhile, we study the model proposed via adopting the combination of mathematical analysis and certain numerical simulation, focusing on the influenza case information in Gansu Province.

The organize of the paper is as follows: In Section 2, we set up a standard non-autonomous mathematical model for influenza. In Section 3, we make the necessary mathematical investigation of the system. In particular, we obtain the basic reproduction number R_0, which is an important index reflecting the threshold dynamics of the model that we attempt to investigate. In Section 4, we discuss the optimal control issue of influenza virus epidemic by evaluating the optimal control measures and give the control strategy. In Section 5, we employ MCMC algorithm to evaluate the initial value of the vaccinators and several unknown parameters, we also simulate the optimal control measures to alleviate the possibility of influenza transmission. At the same time, we analyze the uncertainty and sensitivity analysis of some parameters. In Section 6, we summarize all sections and put forward prospects for the future.

2. The Model Formulation

2.1. System Description

In this paper, we will extend the classical infectious disease model to achieve our purpose of better studying influenza. The entire population $N(t)$ is composed of six compartments, which are $S(t)$, $V(t)$, $E(t)$, $I_N(t)$, $I_C(t)$, $R(t)$, where $S(t)$ means the size of susceptible individuals, $V(t)$ means the size of vaccinator, $E(t)$ means the size of exposed individuals, $I_N(t)$ refers to individuals who have not been reported by Gansu provincial CDC after being infected with influenza virus, $I_C(t)$ refers to individuals who have been reported by Gansu provincial CDC after being infected with influenza virus, and $R(t)$ indicates the population who have recovered after being infected with influenza viruses. Therefore, we can obtain that the whole population is

$$N(t) = S(t) + V(t) + E(t) + I_C(t) + I_N(t) + R(t).$$

Based on the above assumptions, we can receive the compartment diagram of the system is described as

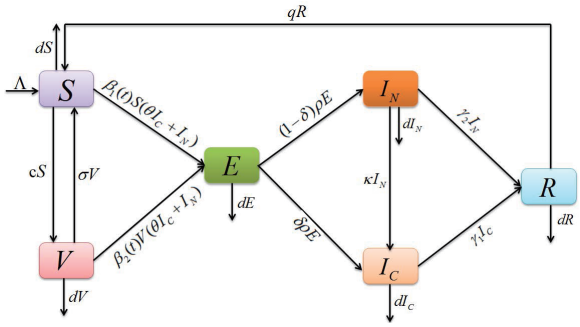


Figure 1. The schematic diagram for the dynamics of influenza system (2.1).

In the proposed model, human infection with influenza virus is divided into two situations, one of which is $\beta_1(t)$ refers to the probability that susceptible groups

will be infected after being exposed to the virus released by an infected person, and the other $\beta_2(t)$ represents the probability that vaccinated population will get sick after being exposed to the virus released by an infected person after the vaccine fails. And the detailed parameter meaning is shown in Table 1.

Table 1. The detailed description of parameters of the influenza system (2.1).

Parameter	Description(Units)
Λ	The average number of people entering the susceptible population ($month^{-1}$)
d	Natural mortality rate ($month^{-1}$)
θ	Modification factor of reported infected individuals (*none*)
δ	Covered rate of infected individuals by CDC in Gansu Province (*none*)
$1/\rho$	The average incubation period (*month*)
q	Progression rate from $R(t)$ to $S(t)$ ($month^{-1}$)
γ_1	Progression rate from $I_N(t)$ to $R(t)$ ($month^{-1}$)
γ_2	Progression rate from $I_C(t)$ to $R(t)$ ($month^{-1}$)
κ	Treatment rate of uncovered infectious ($month^{-1}$)
β_1	The periodic transmission rate between $S(t)$ and infectious (*none*)
β_2	The periodic transmission rate between $V(t)$ and infectious (*none*)
c	Vaccination rate of susceptible individuals ($month^{-1}$)
σ	Vaccination failure rate ($month^{-1}$)

According to the Fig. 1, the following influenza model is established.

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = \Lambda + qR - \beta_1(t)S(\theta I_C + I_N) - cS + \sigma V - dS, \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = cS - \beta_2(t)V(\theta I_C + I_N) - \sigma V - dV, \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = \beta_1(t)S(\theta I_C + I_N) + \beta_2(t)V(\theta I_C + I_N) - \rho E - dE, \\ \dfrac{\mathrm{d}I_N}{\mathrm{d}t} = (1-\delta)\rho E - \gamma_2 I_N - \kappa I_N - dI_N, \\ \dfrac{\mathrm{d}I_C}{\mathrm{d}t} = \delta\rho E - \gamma_1 I_C + \kappa I_N - dI_C, \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} = \gamma_1 I_C + \gamma_2 I_N - qR - dR. \end{cases} \tag{2.1}$$

Next, we will demonstrate whether the solution of the mathematical model is ultimately uniformly bounded, which is illustrated by the following lemma.

Lemma 2.1. *Define*

$$\Phi = \left\{ (S, V, E, I_N, I_C, R) \in R_+^6; 0 \le S, V, E, I_N, I_C, R \le N \le \frac{\Lambda}{d} \right\},$$

the solutions of the system (2.1) *are uniformly, ultimately bounded and the set* Φ *is a positive invariant set.*

Proof. Obviously, we can get the following equation from the system (2.1).

$$\begin{aligned}\frac{\mathrm{d}N(t)}{\mathrm{d}t} &= \Lambda - dS - dV - dE - dI_N - dI_C - dR \\ &= \Lambda - dN.\end{aligned}$$

Through the above formula, the following inequality is obtained:

$$0 \leq N(t) = \frac{\Lambda}{d} + (N(0) - \frac{\Lambda}{d})e^{-dt} \leq \frac{\Lambda}{d} + N(0)e^{-dt},$$

where $N(0)$ denotes the initial value of the entire population, therefore, we obtain $0 \leq \lim\limits_{t\to\infty} \sup N(t) \leq \frac{\Lambda}{d}$. Finally, we can a get positive invariant set which is

$$\Phi = \left\{(S, V, E, I_N, I_C, R) \in R_+^6; 0 \leq S, V, E, I_N, I_C, R \leq N \leq \frac{\Lambda}{d}\right\}.$$

This completes the proof. □

3. Analysis of the model

3.1. The Basic Reproduction Number for the Periodic System

It is well known that basic reproduction number R_0 is a great number of secondary patients by a case in a whole susceptible population, and R_0 will be calculated in this part. According to calculations, the solution of the system (2.1) is $P_0 = (S^0, V^0, 0, 0, 0, 0)$, where $S^0 = \frac{\Lambda(d+\sigma)}{d(d+c+\sigma)}, V^0 = \frac{c\Lambda}{d(d+c+\sigma)}$, and it is a periodic solution. Based on the technical theory of periodic systems generated by Wang and Zhao [33]. Let $x = (S, V, E, I_N, I_C, R)^T$, therefore, the influenza system is written by the following equation

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

where

$$\mathcal{F}(t, x) = \begin{pmatrix} \beta_1(t)S(\theta I_C + I_N) + \beta_1(t)V(\theta I_C + I_N) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

and

$$\mathcal{V}(t,x)=\begin{pmatrix}\rho E+dE\\ -(1-\delta)\rho E+(\gamma_2+d+\kappa)I_N\\ -\delta\rho E+(\gamma_1+d)I_C+\kappa I_N\\ -\gamma_1 I_C-\gamma_2 I_N+qR+dR\\ -\Lambda-qR+\beta_1(t)S(\theta I_C+I_N)+kS+dS\\ -kS+\beta_2(t)V(\theta I_C+I_N)+dV\end{pmatrix}.$$

Obviously, it can be directly obtained that the conditions (A1)-(A5) are satisfied [33]. Next, we can introduce $f(t,x(t))=\mathcal{F}(t,x)-\mathcal{V}(t,x)$, let

$$N(t):=\left(\frac{\partial f_i(t,x^0(t))}{\partial x_j}\right),(5\le i,j\le 6)$$

where $x^0(t)=\left(0,0,0,0,\frac{\Lambda(d+\sigma)}{d(d+c+\sigma)},\frac{c\Lambda}{d(d+c+\sigma)}\right)$ is the solution of the system (2.1).

Supposing that $\Phi_N(t)$ is the monodromy matrix of the linear T-period system $\frac{\mathrm{d}z}{\mathrm{d}t}=N(t)z$, we further get that the spectral radius of $\Phi_N(t)$ is less than unity. Therefore, we verify that the system (2.1) meets the condition (A6) in the mathematical technology theory claimed by Wang and Zhao [33].

The following proves that the condition (A7) is satisfied. Through simple calculations, we obtain

$$\bar{F}(t)=\left(\frac{\partial\mathcal{F}_i}{\partial x_j}\Big|_{P_0}\right)=\begin{pmatrix}0&\beta_1S^0+\beta_2V^0&\beta_2\theta S^0+\beta_2\theta V^0&0\\0&0&0&0\\0&0&0&0\\0&0&0&0\end{pmatrix},1\le i,j\le 4,$$

and

$$\bar{V}(t)=\left(\frac{\partial\mathcal{V}_i}{\partial x_j}\Big|_{P_0}\right)=\begin{pmatrix}\rho+d&0&0&0\\-(1-\delta)\rho&\gamma_2+d+\kappa&0&0\\-\delta\rho&-\kappa&\gamma_1+d&0\\0&-\gamma_2&-\gamma_1&q+d\end{pmatrix},1\le i,j\le 4.$$

From the above matrix, we can directly get that $\bar{F}(t)$ is non-negative, and $-\bar{V}(t)$ is cooperative. That is to say, the $\bar{F}(t)-\bar{V}(t)$ is irreducible for all time t.

Suppose $Y(t,s)(t\ge s)$ be the evolution operator of the linear T-periodic system

$$\frac{\mathrm{d}y}{\mathrm{d}t}=-\bar{V}(t)y. \tag{3.1}$$

For each $s\in R$, let 4×4 matrix $Y(t,s)$ meets

$$\frac{\mathrm{d}Y(t,s)}{\mathrm{d}t}=-\bar{V}(t)Y(t,s),\forall t\ge s,Y(S,S)=I, \tag{3.2}$$

where I is the 4×4 identity matrix. Therefore, the monodromy matrix $\Phi_{-\bar{V}}(T)$ of (3.1) and $Y(t,0)$ have the same meaning. Hence, the condition (A7) can be satisfied.

Next, according to the theory submitted by Wang and Zhao [33], let $\phi(s)$, T-periodic, be the initial distribution of infectious individuals at this periodic circumstance, then $F(s)\phi(s)$ is the rate of new infections generated by infected individuals who are produced at time s, considering $t \geq s$, $Y(t,s)F(s)\phi(s)$ represents the distribution of those newly infected by $\phi(s)$ and remain in the infected compartments at time t, then

$$\int_{-\infty}^{t} Y(t,s)F(s)\phi(s)\mathrm{d}s = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\mathrm{d}a \tag{3.3}$$

gives the distribution of cumulative new infections at time t owning to all infected individuals $\phi(s)$ introduced at time fewer than t.

We define C_T be the ordered Banach space of T-periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, which is involved in the maximum norm $||\cdot||$ and introduce the positive cone $C_T^+ = (\phi \in C_T : \phi(t) \geq 0, \forall t \in R\}$. Therefore, a linear operator $L : C_T \longrightarrow C_T$ is defined as

$$(L\phi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)\mathrm{d}a, \forall t \in R, \phi \in C_T. \tag{3.4}$$

It is known as the next generation infection operator. The spectral radius of L is equal to the basic reproduction number R_0. That is,

$$R_0 := \rho(L). \tag{3.5}$$

Next, to explore the stability of our model (2.1), we attempt to use the following lemma.

Lemma 3.1 (Theorem 2.2, [33]). *The following statements hold:*

(i) $R_0 = 1$ *iff* $\rho(\Phi_{\bar{F}-\bar{V}}(T)) = 1$.

(ii) $R_0 < 1$ *iff* $\rho(\Phi_{\bar{F}-\bar{V}}(T)) < 1$.

(iii) $R_0 > 1$ *iff* $\rho(\Phi_{\bar{F}-\bar{V}}(T)) > 1$.

Therefore, if $R_0 < 1$ the disease-free periodic solution P_0 of system (2.1) is locally asymptotically stable and unstable if $R_0 > 1$. Supposing that $W(t,s,\lambda)$ is a evolution operator of the following linear T-period system

$$\frac{\mathrm{d}\omega}{\mathrm{d}t} = \left(-\bar{V}(t) + \frac{\bar{F}(t)}{\lambda}\right)\omega, \tag{3.6}$$

with parameter $\lambda \in R$, $t \in R_+$. It is straightforward to get that $\Phi_{\bar{F}-\bar{V}}(t) = W(t,0,1)$, therefore, we derive

$$\Phi_{\frac{\bar{F}}{\lambda}-\bar{V}}(t) = W(t,0,\lambda), t \geq 0, \tag{3.7}$$

where

$$-\bar{V}(t) + \frac{\bar{F}(t)}{\lambda} = \begin{pmatrix} -(\rho+d) & \frac{\beta_1(t)S^0+\beta_2(t)V^0}{\lambda} & \frac{\beta_1(t)\theta S^0+\beta_2(t)\theta V^0}{\lambda} & 0 \\ (1-\delta)\rho & -(\gamma_2+d+\kappa) & 0 & 0 \\ \delta\rho & \kappa & -(\gamma_1+d) & 0 \\ 0 & \gamma_2 & \gamma_1 & -(q+d) \end{pmatrix}.$$

In the light of comprehensive mathematical technology theory and means offered by Wang and Zhao in [33], we can clearly know that the basic reproduction number R_0 is the unique solution of $\rho(W(T,0,\lambda))=1$. In subsequent proofs, we will employ it to characterize the basic reproduction number R_0.

3.2. Extinction of the Influzeza

We will make the following preparations for the next proof. Firstly, supposing that $A(t)$ is a continuous, cooperative, irreducible, and assume directly that $\Phi_A(T)$ is the fundamental solution matrix of the system (3.8), the system (3.8) is represented as

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t}=A(t)x(t). \tag{3.8}$$

We can introduce $\rho(\Phi_A(T))$ be the spectral radius of $\Phi_A(T)$. Therefore, this means that every element of Φ_A is positive [4,13]. By Perron-Frobenius theorem [30], $\rho(\Phi_A(T))$ is the principle eigenvalue of Φ_A, which implies that it is simple and has an eigenvector $v^*\gg 0$. Finally, the following conclusions help us to demonstrate the threshold dynamics of system (2.1).

Lemma 3.2 (Lemma 2.1, [35]). *Let $\mu=\frac{1}{T}ln\rho(\Phi_A(T))$, then there exists a positive T-periodic function $V(t)$ such that $e^{pt}v(t)$ is a solution of $\frac{dy}{dt}=A(t)x(t)$.*

Theorem 3.1. *If $R_0<1$, the disease-free periodic solution $P_0(S^0,V^0,0,0,0,0)$ of the system (2.1) is globally asymptotically stable in Φ; if $R_0>1$, then it is unstable.*

Proof. From Lemma 3.1, we know that if $R_0<1$, then P_0 is local asymptotically stable, but if $R_0>1$, then P_0 is unstable. Therefore, it is only necessary to obtain that P_0 is globally attractive when $R_0<1$. From system (2.1) and $V(t)\le N(t)-S(t)$, we can obtain

$$\begin{cases}\dfrac{\mathrm{d}S}{\mathrm{d}t}\le\Lambda+\sigma N-(c+d+\sigma)S,\\[2mm] \dfrac{\mathrm{d}V}{\mathrm{d}t}\le cN-(c+d+\sigma)V.\end{cases} \tag{3.9}$$

Thus, for $\forall\varepsilon>0$, there exists $t_0>0$ such that $S(t)\le S^0+\varepsilon, V(t)\le V^0+\varepsilon$, for $t>t_0$. We can introduce the following comparison system

$$\begin{cases}\dfrac{\mathrm{d}\tilde{E}}{\mathrm{d}t}=\beta_1(t)(S^0+\varepsilon)(\theta\tilde{I}_C+\tilde{I}_N)+\beta_2(t)(V^0+\varepsilon)(\theta\tilde{I}_C+\tilde{I}_N)-\rho\tilde{E}-d\tilde{E},\\[2mm] \dfrac{\mathrm{d}\tilde{I}_N}{\mathrm{d}t}=(1-\delta)\rho\tilde{E}-\gamma_2\tilde{I}_N-d\tilde{I}_N-\kappa\tilde{I}_N,\\[2mm] \dfrac{\mathrm{d}\tilde{I}_C}{\mathrm{d}t}=\delta\rho\tilde{E}-\gamma_1\tilde{I}_C+\kappa\tilde{I}_N-d\tilde{I}_C,\\[2mm] \dfrac{\mathrm{d}\tilde{R}}{\mathrm{d}t}=\gamma_1\tilde{I}_C+\gamma_2\tilde{I}_N-q\tilde{R}-d\tilde{R}.\end{cases} \tag{3.10}$$

We define $x=(\tilde{E},\tilde{I}_N,\tilde{I}_C,\tilde{R})^T$, the system (3.10) can be described by the following system

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t}=(\bar{F}(t)-\bar{V}(t)+\varepsilon M_\varepsilon)x, \tag{3.11}$$

where

$$M_\varepsilon = \begin{pmatrix} 0 & \beta_1(t)+\beta_2(t) & \beta_1(t)\theta+\beta_2(t)\theta & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

According to Lemma 3.2, there is a positive T periodic function $v(t) = (v_1, v_2, v_3, v_4)$ such that $e^{\mu t}v(t)$ is a solution of system (3.10), where $\mu = \frac{1}{T}ln\rho\left(\Phi_{\bar{F}-\bar{V}+\varepsilon M_\varepsilon}(T)\right)$, then we choose $t_1 > t_0$ and a small number α to satisfy the following inequality

$$\tilde{E}(t_1) \le \alpha v_1(0), \tilde{I}_N(t_1) \le \alpha v_2(0), \tilde{I}_C(t_1) \le \alpha v_3(0), \tilde{R}(t_1) \le \alpha v_4(0),$$

so we can get

$$\tilde{E}(t) \le \alpha e^{\mu(t-t_1)}v_1(t-t_1), \tilde{I}_N(t) \le \alpha e^{\mu(t-t_1)}v_2(t-t_1),$$
$$\tilde{I}_C(t) \le \alpha e^{\mu(t-t_1)}v_3(t-t_1), \tilde{R}(t) \le \alpha e^{\mu(t-t_1)}v_4(t-t_1).$$

By the comparison principle, we have

$$E(t) \le \tilde{E}(t) \le \alpha e^{\mu(t-t_1)}v_1(t-t_1), I_N(t) \le \tilde{I}_N(t) \le \alpha e^{\mu(t-t_1)}v_2(t-t_1),$$
$$I_C(t) \le \tilde{I}_C(t) \le \alpha e^{\mu(t-t_1)}v_3(t-t_1), R(t) \le \tilde{R}(t) \le \alpha e^{\mu(t-t_1)}v_4(t-t_1), \forall t > t_1.$$

The Lemma 3.1 means that $\rho(\Phi_{\bar{F}-\bar{V}}(T)) < 1$ is obtained, when $R_0 < 1$. Select sufficiently small number $\varepsilon > 0$ so that $\rho(\Phi_{\bar{F}-\bar{V}-\varepsilon M_\varepsilon(T)}) < 1$, so it's easy to get $\mu < 0$, which implies the following equation is established.

$$\lim_{t\to\infty} E(t) = 0, \lim_{t\to\infty} I_N(t) = 0, \lim_{t\to\infty} I_C(t) = 0, \lim_{t\to\infty} R(t) = 0.$$

According to the theory of asymptotically autonomous system [31], we can obtain $\lim_{t\to\infty} S(t) = S^0$, $\lim_{t\to\infty} V(t) = V^0$. Therefore, when $R_0 < 1$, the disease-free periodic solution P_0 is globally asymptotically stable. This completes the proof. □

3.3. Uniform Persistence of the system

We will continue the mathematical analysis to explore the uniform persistence of the model in this subsection, it will be proved by the theory proposed by Zhao [37]. Firstly, let

$$X := \left\{(S, V, E, I_N, I_C, R)^T : S \ge 0, V \ge 0, E \ge 0, I_N \ge 0, I_C \ge 0, R \ge 0\right\},$$
$$X_0 := \left\{(S, V, E, I_N, I_C, R)^T \subseteq X : S > 0, V > 0, E > 0, I_N > 0, I_C > 0, R > 0\right\},$$
$$\partial X_0 := X \setminus X_0.$$

And $u(t, x_0)$ is defined as the solution of system (2.1), and the system (2.1) is equipped with initial condition x_0, where $x_0 = (S(0), V(0), E(0), I_N(0), I_C(0), R(0))$. From the fundamental existence-uniqueness theorem of the solution [23], we can obtain that $u(t, x_0)$ is unique. Next, we define $f : X \to X$ be the Poincaré map related to system (2.1), so we can get $f(x_0) = u(T, x_0), \forall x_0 \in X$. Obviously, we can obtain $f^m(x_0) = u(mT, x_0)$, then the solution of system (2.1) is uniformly ultimately bounded. In other words, the mapping f is a point dissipative on X.

Lemma 3.3. *If $R_0 > 1$, then there exists a constant $\varepsilon > 0$ such that for any $x_0 \in X_0$ with $\|x_0 - P_0\| < \varepsilon$, we obtain $\lim\limits_{m\to\infty} \sup d\left(f^m(x_0), P_0\right) \geq \varepsilon$, where $d\left(f^m(x_0), P_0\right)$ is distance between $f^m(x_0)$ and P_0.*

Proof. From Lemma 3.1, if $R_0 > 1$, then $\rho(\Phi_{\bar{F}-\bar{V}}(T)) > 1$. So we select a number $\varepsilon > 0$ sufficiently small such that $\rho\left(\Phi_{\bar{F}-\bar{V}+\varepsilon M_\varepsilon}(T)\right) > 1$. Next, we use the contradiction method to prove the result, assuming that

$$\lim_{m\to\infty} \sup d\left[f^m(x_0), P_0\right] \geq \varepsilon.$$

Otherwise, we can obtain

$$\lim_{m\to\infty} \sup d\left[f^m(x_0), P_0\right] < \varepsilon,$$

for any $x_0 \in X_0$. Without losing generality, there exists $m > 0$ such that $d\left[f^m(x_0)\right.$, $\left.P_0\right] < \varepsilon$. From the continuity of the solutions with respect to the initial value condition, when $\|x_0 - P_0\| < \varepsilon$, we can get

$$\|u(\bar{t}, f^m(x_0)) - u(\bar{t}, P_0)\| < \varepsilon^*, m \geq 0, \bar{t} \in [0, T]$$

for $\forall t \geq 0$, we can obtain

$$\|u(t, x_0) - u(t, P_0)\| = \|u(\bar{t}, f^m(x_0)) - u(\bar{t}, P_0)\| < \varepsilon^*,$$

where $t = \bar{t} + mT$, and $m = \left[\frac{t}{T}\right]$, which is the largest integer less than or equal to $\left[\frac{t}{T}\right]$. It follows from Lemma 2.1 that there exists $t_2 > 0$ that $S^0 - \varepsilon^* \leq S(t) \leq S^0 + \varepsilon^*, V^0 - \varepsilon^* \leq V(t) \leq V^0 + \varepsilon^*, 0 \leq E(t) \leq \varepsilon^*, 0 \leq I_N(t) \leq \varepsilon^*, 0 \leq I_C(t) \leq \varepsilon^*, 0 \leq R(t) \leq \varepsilon^*$ for $t > t_2$. Then

$$\frac{\mathrm{d}E}{\mathrm{d}t} \geq \beta_1(t)(S^0 - \varepsilon^*)(\theta I_C + I_N) + \beta_2(t)(V^0 - \varepsilon^*)(\theta I_C + I_N) - \rho E - dE. \quad (3.12)$$

Next, it is similar to the demonstrate of Theorem 3.1, considering the following auxiliary system

$$\begin{cases} \dfrac{\mathrm{d}\hat{E}}{\mathrm{d}t} = \beta_1(t)(S^0 - \varepsilon^*)(\theta\hat{I}_C + \hat{I}_N) + \beta_2(t)(V^0 - \varepsilon^*)(\theta\hat{I}_C + \hat{I}_N) - \rho\hat{E} - d\hat{E}, \\ \dfrac{\mathrm{d}\hat{I}_N}{\mathrm{d}t} = (1-\delta)\rho\hat{E} - \gamma_2\hat{I}_N - d\hat{I}_N - \kappa\hat{I}_N, \\ \dfrac{\mathrm{d}\hat{I}_C}{\mathrm{d}t} = \delta\rho\hat{E} - \gamma_1\hat{I}_C + \kappa\hat{I}_N - d\hat{I}_C, \\ \dfrac{\mathrm{d}\hat{R}}{\mathrm{d}t} = \gamma_1\hat{I}_C + \gamma_2\hat{I}_N - q\hat{R} - d\hat{R}. \end{cases} \quad (3.13)$$

We define $x = (\hat{E}, \hat{I_N}, \hat{I_C}, \hat{R})^T$, the system (3.13) can be described by the following equation

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = (\bar{F}(t) - \bar{V}(t) + \varepsilon M_\varepsilon)x, \quad (3.14)$$

where

$$M_\varepsilon = \begin{pmatrix} 0 & \beta_1(t)+\beta_2(t) & \beta_1(t)\theta+\beta_2(t)\theta & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

According to Lemma 3.2, there is a positive T periodic function $w(t) = (w_1, w_2, w_3, w_4)$ such that $e^{\mu t}w(t)$ is a solution of system (3.13), where $\mu = \frac{1}{T}ln\rho\left(\Phi_{\bar{F}-\bar{V}+\varepsilon M_\varepsilon}(T)\right)$. then we choose $t_3 > t_2$ and a small number $\bar{\alpha}$ to satisfy the following inequality

$$\hat{E}(t_3) \le \bar{\alpha}w_1(0), \hat{I_N}(t_3) \le \bar{\alpha}w_2(0), \hat{I_C}(t_3) \le \bar{\alpha}w_3(0), \hat{R}(t_3) \le \bar{\alpha}w_4(0),$$

so we can get

$$\begin{aligned} &\hat{E}(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_1(t-t_3),\ \hat{I}_N(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_2(t-t_3), \\ &\hat{I}_C(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_3(t-t_3),\ \hat{R}(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_4(t-t_3), \forall t > t_3. \end{aligned}$$

By the comparison principle, we can derive

$$\begin{aligned} &E(t) \le \hat{E}(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_1(t-t_3),\ I_N(t) \le \hat{I}_N(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_2(t-t_3), \\ &I_C(t) \le \hat{I}_C(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_3(t-t_3),\ R(t) \le \hat{R}(t) \le \bar{\alpha}e^{\mu(t-t_3)}w_4(t-t_3), \forall t > t_3. \end{aligned}$$

It implies that the following equation is established. $\lim\limits_{t\to\infty} E(t) = \infty$, $\lim\limits_{t\to\infty} I_N(t) = \infty$, $\lim\limits_{t\to\infty} I_C(t) = \infty$, $\lim\limits_{t\to\infty} R(t) = \infty$. Which is a contradiction. Thence, we have directly completed the proof. □

Theorem 3.2. *If $R_0 > 1$, then there exists $\eta > 0$ such that any solution $(S(t), V(t), E(t), I_N(t), I_C(t), R(t))$ with respect to the initial values $x_0 = (S(0), V(0), E(0), I_N(0), I_C(0), R(0)) \in X_0$ satisfies the following inequality*

$$\lim_{t\to\infty} \inf (E(t), I_N(t), I_C(t), R(t)) \ge (\eta, \eta, \eta, \eta),$$

and has at least one positive periodic solution.

Proof. To demonstrate that system (2.1) is uniformly persistence with respect to $(X_0, \partial X_0)$, for $\forall x_0 \in X_0$, solving system (2.1), it is obvious that the following inequality can be obtained.

$$\begin{aligned} S(t) =& e^{-\int_0^t [\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau}\left[S(0) + \int_0^t (\Lambda + qR(\tau) + \sigma V(\tau))\right. \\ & \left. e^{\int_0^t [\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau}\mathrm{d}\tau\right], \\ V(t) =& e^{-\int_0^t [\beta_2(\tau)(\theta I_C(\tau)+I_N(\tau))+\sigma+d]\mathrm{d}\tau}\left[V(0) + \int_0^t cS(\tau)\right. \\ & \left. e^{\int_0^t [\beta_2(\tau)(\theta I_C(\tau)+I_N(\tau))+\sigma+d]\mathrm{d}\tau}\mathrm{d}\tau\right], \\ E(t) =& e^{-(\rho+d)t}\left[E(0) + \int_0^t [\beta_1(\tau)S(\tau)(\theta I_C(\tau) + I_N(\tau))\right. \\ & \left. +\beta_2(\tau)V(\tau)(\theta I_C(\tau) + I_N(\tau))]e^{(\rho+d)\tau}\mathrm{d}\tau\right], \end{aligned} \tag{3.15}$$

$$I_N(t) = e^{-(\gamma_2+d+\kappa)t}\left[I_N(0) + \int_0^t (1-\delta)\rho E(\tau)e^{(\gamma_2+d+\kappa)\tau}\mathrm{d}\tau\right],$$
$$I_C(t) = e^{-(\gamma_1+d)t}\left[I_C(0) + \int_0^t (\delta\rho E(\tau) + \kappa I_N(\tau))e^{(\gamma_2+d+\kappa)\tau}\mathrm{d}\tau\right],$$
$$R(t) = e^{-(q+d)t}\left[R(0) + \int_0^t (\gamma_1 I_C(\tau) + \gamma_2 I_N(\tau)e^{(q+d)\tau}\mathrm{d}\tau\right].$$

So X and ∂X_0 is a positive invariant set, and ∂X_0 is relatively closed in X_0. Let

$$M_\partial := \{x_0 \in \partial X_0 : f^m(x_0) \in \partial X_0, \forall M > 0\}.$$

Now, we prove that

$$M_\partial := \left\{(S, V, 0, 0, 0, 0)^T \in \partial X_0 : S \geq 0, V \geq 0\right\} \triangleq M_\partial^{'}.$$

From the definition of the above formula, we can know $M_\partial^{'} \subseteq M_\partial$, all we need to be proved is that $M_\partial \subseteq M_\partial^{'}$. Firstly, we assume that the conclusion is not true, that is, for $x_0 = (S(0), V(0), E(0), I_N(0), I_C(0), R(0))^T \in \partial X_0$, we have $I_N(mT) = I_C(mT) = E(mT) = R(mT) = 0$. If not, there exists an $m_1 \geq 0$ such that $(E(mT), I_N(mT), I_C(mT), R(mT))^T \geq 0$. If by putting initial time $t = 0$ instead of $t = m_1 T$, and it follows from (3.15) that $E(t) > 0, I_N(t) > 0, I_C(t) > 0, R(t) > 0$, for $\forall t > m_1 T$, now we have $f^m(S(0), V(0), E(0), I_N(0), I_C(0), R(0)) \notin \partial X_0$, which is a contradiction, hence, we have $M_\partial \subseteq M_\partial^{'}$.

According to Lemma 3.3, we know that P_0 is a unique fixed point of f in M_∂, further, from the above description, we get that P_0 is an isolated invariant set in X and $W^s(P_0) \bigcap X_0 = \emptyset$, where $W^s(P_0)$ is the stable manifold of P_0, we can infer that P_0 is uniformly persistent with respect to $(X_0, \partial X_0)$, in order to do this, there exists $\eta > 0$ such that any solution $u(t, x_0)$ of the system (2.1) with initial value condition x_0 meets

$$\lim_{t\to\infty} \inf (E(t), I_N(t), I_C(t), R(t)) \geq (\eta, \eta, \eta, \eta).$$

Next, we can testify that $S^*(0) > 0$, $T^*(0) > 0$. Theorem 1.3.6 in [37] means that f has a fixed point $(S^*(0), V^*(0), E^*(0), I_N^*(0), I_C^*(0), R^*(0)) \in X_0$. Therefore, we can get $S^*(0) \geq 0, V^*(0) \geq 0, E^*(0) > 0, I_N^*(0) > 0, I_C^*(0) > 0, R^*(0) > 0$, now, we prove that $S^*(0) > 0$. Suppose not, assuming that $S^*(0) = 0$. From the first formula of the model, we can get

$$\frac{\mathrm{d}S}{\mathrm{d}t} \geq \Lambda - \beta_1(t)S(\theta I_C + I_N) - cS - dS = \Lambda - (\beta_1(t)(\theta I_C + I_N + c + d))S.$$

Through the comparison principle, we can derive

$$\begin{aligned} S(t) \geq & e^{-\int_0^t [\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau_1} \\ & \times \left[S^*(0) + \int_0^t \Lambda e^{\int_0^{\tau_1}[\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau}\mathrm{d}\tau_1\right] \\ = & e^{-\int_0^t [\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau_1}\left[\int_0^t \Lambda e^{\int_0^{\tau_1}[\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau}\mathrm{d}\tau_1\right]. \end{aligned}$$

Consequently, through the above formula, we can receive the following inequality

$$S^*(nT) \geq e^{-\int_0^{nT}[\beta_1(\tau)(\theta I_C(\tau)+I_N(\tau))+c+d]\mathrm{d}\tau_1}$$

$$\times \left[\int_0^{nT} \Lambda e^{\int_0^{\tau_1} [\beta_1(\tau)(\theta I_C(\tau) + I_N(\tau)) + c + d] \mathrm{d}\tau} \mathrm{d}\tau_1 \right].$$

Owning to the periodicity of T, we can get $S^*(0) = S^*(nT) = 0, n = 1, 2, 3, ...$, a contradicts. So we can obtain that $S^*(0) > 0$. Similarly, $V^*(0) > 0$. Hence we have completed the demonstrate of the theorem. □

4. The Optimal Control Problems

We conducted necessary mathematical research and exploration on the proposed mathematical model in the previous section. And we discussed that R_0 is the key threshold parameter to determine whether the influenza virus is epidemic or not. In the next work, we will apply the optimal control to the projected mathematical model. we are going to analyze our model by including four time-dependent control variables, which correspond to four intervention strategies of the system (2.1). Taking into account the real situation of influenza infection in Gansu Province, we introduce $u_1(t), u_2(t), u_3(t), u_4(t)$ related to the four strategies as control parameters to reduce the number of influenza cases. Supposing that one of the control functions $u_1(t)$ indicates that in order to reduce the prevalence of influenza, the susceptible person maintains the necessary social distance from the infected person for their own safety, and the other control function $u_2(t)$ indicates that the vaccinated population intends to avoid contact with the infected person as much as possible for their own safety. For example, wearing a mask, maintaining social distancing, increasing self-protection, etc. The control functions $u_3(t)$ refers to people are more willing to choose vaccination to cut down the probability of infection. The control functions $u_4(t)$ refers to receiving treatment after infection so that the intensity of infection is reduced. Such as taking medical, going to the hospital for treatment, or going to a designated place for influenza vaccination.

Based on the above assumption, the system (2.1) consists of four control measures, which are controlled by:

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = \Lambda + qR - (1 - u_1(t))\beta_1(t)S(\theta I_C + I_N) - (1 + u_3(t))cS + \sigma V - dS, \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = (1 + u_3(t))cS - (1 - u_2(t))\beta_2(t)V(\theta I_C + I_N) - \sigma V - dV, \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = (1 - u_1(t))\beta_1(t)S(\theta I_C + I_N) + (1 - u_2(t))\beta_2(t)V(\theta I_C + I_N) - \rho E - dE, \\ \dfrac{\mathrm{d}I_N}{\mathrm{d}t} = (1 - \delta)\rho E - \gamma_2 I_N - (1 + u_4(t))\kappa I_N - dI_N, \\ \dfrac{\mathrm{d}I_C}{\mathrm{d}t} = \delta\rho E - \gamma_1 I_C + (1 + u_4(t))\kappa I_N - dI_C, \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} = \gamma_1 I_C + \gamma_2 I_N - qR - dR, \end{cases} \tag{4.1}$$

with initial conditions

$$S(0) \geq 0, V(0) \geq 0, E(0) \geq 0, I_N(0) \geq 0, I_C(0) \geq 0, R(0) \geq 0.$$

To figure out the optimal control issue of the system (4.1), our target is to cut down the amount of infected individuals with the least cost in the interval $[0, T]$, where

T refers to control set, and the objective function is defined as

$$J(u_1,u_2,u_3,u_4)=\int_0^T B_1I_N+B_2I_C+\frac{1}{2}\sum_{i=1}^{4}W_iu_i^2(t)dt, \tag{4.2}$$

where B_1, B_2 represent associated adjoints of the I_N and I_C, respectively, W_1, W_2, W_3, and W_4 are associated adjoints of the control function. We introduce the control variables $u(t)=(u_1,u_2,u_3,u_4)$ correspond to the state variables S,V,E,I_N,I_C,R, it is can be measured by

$$\Omega=\{(u_1,u_2,u_3,u_4)|u_i\in L[0,1],0\le u_i\le 1,t\in[0,T],(i=1,2,3,4)\}.$$

The optimal control strategy that minimizes the reported infection individuals and the unreported infection individuals is obtained. Under initial conditions, the system (4.1) has an optimal control pair $U^*=(u_1^*,u_2^*,u_3^*,u_4^*)$ such that the following formula holds.

$$J(U^*)=\min_{\Omega}J(u_1,u_2,u_3,u_4).$$

Next, based on the conclusions of Fleming and Rishel [10], the relevant state and control variables are non-negative and linear function of Ω, the integral of the objective function J associated with u_1,u_2,u_3,u_4 on Ω is convex, consequently, we can get the following conclusion.

Theorem 4.1. *Provided there exists optimal control pair U^* of the control system, and $Y^*(t)$ is a solution of the state system (4.1), so that the objective function J is minimized on Ω , In order to verify its correctness, then there are continuous functions $\lambda_i(t)(i=1,2,3,4,5,6)$ which satisfying*

$$\begin{aligned}
\frac{d\lambda_1}{dt}&=(\lambda_1-\lambda_3)(1-u_1(t))\beta_1(t)(\theta I_C+I_N)+(\lambda_1-\lambda_2)(1+u_3(t))c+d\lambda_1,\\
\frac{d\lambda_2}{dt}&=(\lambda_2-\lambda_3)(1-u_2(t))\beta_2(t)(\theta I_C+I_N)+(\lambda_2-\lambda_1)\sigma+d\lambda_2,\\
\frac{d\lambda_3}{dt}&=(\lambda_4-\lambda_5)\delta\rho+(\lambda_3-\lambda_4)\rho+d\lambda_3,\\
\frac{d\lambda_4}{dt}&=-B_1+(\lambda_1-\lambda_3)(1-u_1(t))\beta_1(t)S+(\lambda_2-\lambda_3)(1-u_2(t))\beta_2(t)V\\
&\quad+(\lambda_4-\lambda_5)(1+u_1(t))\kappa+(\lambda_4-\lambda_6)\gamma_2+d\lambda_4,\\
\frac{d\lambda_5}{dt}&=-B_2+(\lambda_1-\lambda_3)(1-u_1(t))\beta_1(t)S\theta+(\lambda_2-\lambda_3)(1-u_2(t))\beta_2(t)V\theta\\
&\quad+(\lambda_5-\lambda_6)\gamma_1+d\lambda_5,\\
\frac{d\lambda_6}{dt}&=(\lambda_6-\lambda_1)q+d\lambda_6,
\end{aligned} \tag{4.3}$$

with the transversality conditions $\lambda_i(T)=0(i=1,2,3,4,5,6)$. Furthermore, the expression of optimal control are

$$\begin{aligned}
u_1^*&=\max\{\min\{1,\ \frac{(\lambda_3-\lambda_1)\beta_1(t)S^*(\theta I_C^*+I_N^*)}{W_1}\},0\},\\
u_2^*&=\max\{\min\{1,\ \frac{(\lambda_3-\lambda_2)\beta_2(t)V^*(\theta I_C^*+I_N^*)}{W_2}\},0\},
\end{aligned} \tag{4.4}$$

$$u_3^* = \max\{\min\{1, \frac{(\lambda_1-\lambda_2)cS^*}{W_3}\}, 0\},$$
$$u_4^* = \max\{\min\{1, \frac{(\lambda_4-\lambda_5)kI_N^*}{W_4}\}, 0\}.$$

Proof. To prove the theorem above, a Hamiltonian function is constructed, and we choose the Pontryagin maximum principle [25] to explore optimal control issue. The Hamiltonian function H is described by

$$\begin{aligned} H =& B_1 I_N(t) + B_2 I_C(t) + \frac{1}{2}W_1 u_1^2(t) + \frac{1}{2}W_2 u_2^2(t) + \frac{1}{2}W_3 u_3^2(t) + \frac{1}{2}W_4 u_4^2(t) \\ &+ \lambda_1[\Lambda + qR - (1-u_1(t))\beta_1(t)S(\theta I_C + I_N) - (1+u_3(t))cS + \sigma V - dS] \\ &+ \lambda_2[(1+u_3(t))cS - (1-u_2(t))\beta_2(t)V(\theta I_C + I_N) - \sigma V - dV] \\ &+ \lambda_3[(1-u_1(t))\beta_1(t)S(\theta I_C + I_N) + (1-u_2(t))\beta_2(t)V(\theta I_C + I_N) - \rho E - dE] \\ &+ \lambda_4[(1-\delta)\rho E - \gamma_2 I_N - dI_N - (1+u_4(t))\kappa I_N] \\ &+ \lambda_5[\delta\rho E - \gamma_1 I_C + (1+u_4(t))\kappa I_N - dI_C] \\ &+ \lambda_6[\gamma_1 I_C + \gamma_2 I_N - qR - dR]. \end{aligned} \tag{4.5}$$

Then, the adjoint equations with transversality satisfy $\lambda_1^{'} = -\frac{\partial H}{\partial S}, \lambda_2^{'} = -\frac{\partial H}{\partial V}, \lambda_3^{'} = -\frac{\partial H}{\partial E}, \lambda_4^{'} = -\frac{\partial H}{\partial I_N}, \lambda_5^{'} = -\frac{\partial H}{\partial I_C}, \lambda_6^{'} = -\frac{\partial H}{\partial R}$, with $\lambda_i(T) = 0 (i = 1, 2, 3, 4, 5, 6)$. Taking the derivative of the above Hamiltonian function with respect to U^* on the control set, we can get that the following equation holds

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= W_1 u_1^*(t) + \beta_1(t)S^*(\theta I_C^* + I_N^*)\lambda_1 - \beta_1(t)S^*(\theta I_C^* + I_N^*)\lambda_3 = 0, \\ \frac{\partial H}{\partial u_2} &= W_2 u_2^*(t) + \beta_2(t)V^*(\theta I_C^* + I_N^*)\lambda_2 - \beta_2(t)S^*(\theta I_C^* + I_N^*)\lambda_3 = 0, \\ \frac{\partial H}{\partial u_3} &= W_3 u_3^*(t) - cS^*\lambda_1 + cS^*\lambda_2 = 0, \\ \frac{\partial H}{\partial u_4} &= W_4 u_4^*(t) - \kappa I_N^*\lambda_4 + \kappa I_N^*\lambda_5 = 0. \end{aligned} \tag{4.6}$$

For system (4.6), we can get

$$\begin{aligned} u_1^* &= \frac{(\lambda_3-\lambda_1)\beta_1(t)S^*(\theta I_C^* + I_N^*)}{W_1}, \quad u_2^* = \frac{(\lambda_3-\lambda_2)\beta_2(t)V^*(\theta I_C^* + I_N^*)}{W_2}, \\ u_3^* &= \frac{(\lambda_1-\lambda_2)cS^*}{W_3}, \qquad u_4^* = \frac{(\lambda_4-\lambda_5)kI_N^*}{W_4}. \end{aligned} \tag{4.7}$$

This completes the proof. □

5. A Case Study

5.1. Data Sources

In this section, we will evaluate some parameters in the system (2.1) through the influenza data of each month from January 2012 to December 2019 obtained from Gansu CDC, which is estimated by MCMC algorithm. We show the monthly number of people infected with influenza from 2012 to 2019 in the form of histogram [2],

as shown in the Fig. 2. Through the Fig. 2, it is revealed that the peak of influenza outbreak is from December last year to January that year. According to the number of patients in this period, we have been informed that relevant departments should take preventive and control measures during this period.

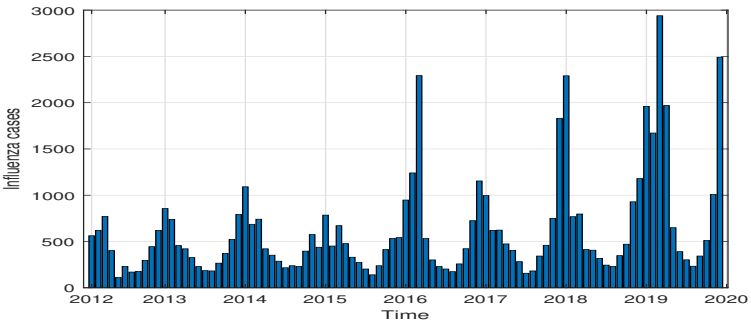


Figure 2. Number of monthly cases of seasonal influenza revealed by Gansu CDC from January 2012 to December 2019.

5.2. Parameter Estimation and Model Fitting

The outbreak of influenza virus presents periodic characteristics. Therefore, from a realistic perspective, the periodic transmission function could be taken into account in system (2.1). The periodic transmission function from the infected to susceptible groups is described as the following function

$$\beta_1(t) = a_1(1 + a_2 \sin(\frac{\pi}{6}t + \phi)),$$

its period is twelve months. a_1 and a_2 mean the transmission coefficients of susceptible individuals and the infected. In addition, the periodic transmission function from the infected to vaccinators is characterized as the following function

$$\beta_2(t) = a_3(1 + a_4 \sin(\frac{\pi}{6}t + \phi)),$$

its period is twelve months. a_3 and a_4 mean the transmission coefficients of the vaccinated and the infected. The ϕ is the phase of the above sinusoidal function.

In order to make better use of the actual number of influenza patients to reflect the practicability of our mathematical model, we take the actual number of people suffering from influenza in Gansu Province as an example for numerical simulation. The unreported cumulative infection cases and reported cumulative infection cases are defined by the following equation, respectively.

$$\frac{\mathrm{d}C_N}{\mathrm{d}t} = (1-\delta)\rho E - \kappa I_N, \frac{\mathrm{d}C_C}{\mathrm{d}t} = \delta\rho E + \kappa I_N. \tag{5.1}$$

Therefore, from equation (5.1), the unreported new infection cases and the reported new infection cases are described by the following equation, respectively.

$$P_N = C_N(t) - C_N(t-1), P_C = C_C(t) - C_C(t-1), \tag{5.2}$$

in addition, the unit of time is month.

Based on the data of Gansu CDC, there are still many people suffer from seasonal influenza each year. Therefore, it is particularly important to characterization the basic reproduction number R_0 and provide theoretical basis for relevant departments and susceptible groups to prevent influenza. In our proposed mathematical model, some parameters and the initial value of vaccinators can be derived from the remaining data by the MCMC algorithm. Next, we will give a detailed description of the parameters:

(1) The average number of people entering the susceptible population per month (i.e., Λ): The data show that the total population at the end of 2011 was 25,641,900, and the birth rate was 12.08 per thousand [1]. Therefore, through simple calculations, we can obtain that the number of births per month is approximately 25,813.

(2) the natural mortality rate (i.e., d): The data show that the mean life expectancy of the population in Gansu Province is 73 [3], therefore, it is about $d = 1/(73 \times 12)$ in 2012.

(3) Progression rate from $R(t)$ to $S(t)$ (i.e., q): Based on Jing's paper, supposing that the progress rate of the recovered individual is 30/365 [18].

(4) Progression rate from $I_N(t)$ to $R(t)$ (i.e., γ_1): Supposing the reported average recovery period of individuals infected with influenza is 7 days [22, 34], so the recovery rate per month is about 30/7.

(5) Progression rate from $I_C(t)$ to $R(t)$ (i.e., γ_2): Supposing the unreported average recovery period of individuals infected with influenza is 10 days [22, 34], so the recovery rate per month is about 30/10.

(6) the average incubation period (i.e., $1/\rho$): We realize that the incubation period influenza ranges from a few hours to four days in different literatures, and the more common is 4 days [21]. Therefore, we presume that the incubation period of influenza is 4 days, and the average monthly incubation period is 4/30.

(7) the vaccination failure rate of susceptible individuals (i.e., σ): Influenza generally has life-long immunity against its infected strains, but because the influenza virus mutates quickly and a vaccine is only effective against the influenza virus of the year, the validity period of the influenza vaccine is generally one year. Therefore, we suppose that the failure rate of influenza vaccination is 1/12 [7, 24].

(8) the coefficient of infected individuals reduced due to a great sum of reported influenza cases (i.e.,θ), the rate of the infected were covered by CDC in Gansu Province (i.e.,δ), the treatment rate of unreported infectious (i.e.,κ): Based on the estimation of Jing [17], we suppose that $\theta = 0.3184$, $\delta = 0.04211$, $\kappa = 0.09102$.

(9) the initial value of the system (2.1):Based on the estimation of Jing [17], we obtain that $S(0) = 18295942$, $E(0) = 579$, $I_C(0) = 562$, $I_N(0) = 1083$, $R(0) = 2706$, the initial value of the vaccinated individuals and other parameters of the system (2.1) will be evaluated via the MCMC algorithm, see the Table 2.

Next, we will make a reasonable fitting for the number of people suffering from influenza in our model from January 2012 to December 2019, which is obtained

via the MCMC procedure. In addition, through these actual data, we estimated the unknown parameters in the system (2.1) and the initial values of the vaccinated individuals, the algorithm runs through 15000 iterations until the convergence result is good. By using MCMC algorithm, we get the mean value and the standard deviation of the estimated parameter values. One of the advantages of MCMC algorithm is that it can calculate the 95% CI, so we can get it, see the Table 2. We can see from the parameter value that β_1 is greater than β_2, which indicates that influenza vaccination will protect individuals. Finally, the fitting outcomes are indicated in Fig. 3.

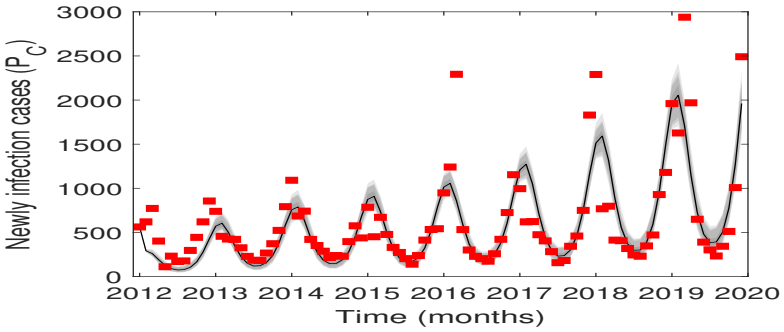


Figure 3. It presents the fitting outcomes of influenza cases, in which the red dot indicates the actual number of infection individuals, the black line indicates the fitted cases, and the gray area from the brightest to the darkest indicates the 50%, 90%, 95%, and 99% posterior limits of the system.

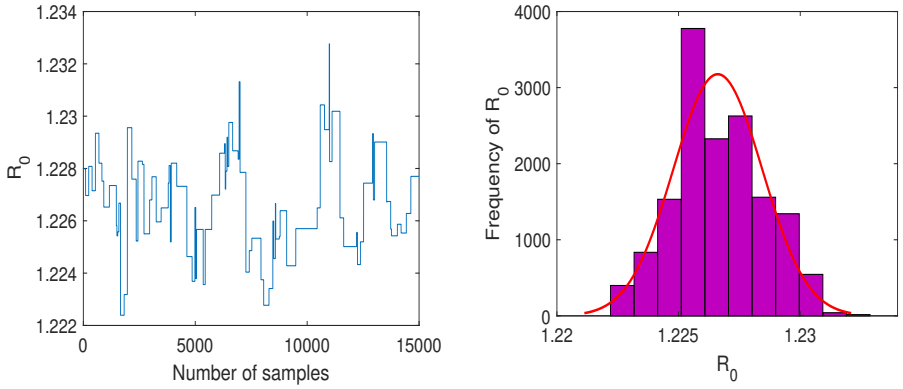


Figure 4. (a) The Markov chain samples of R_0. (b) The distribution of R_0 is derived by the Markov Chain Monte Carlo (MCMC) algorithm. The vermilion line is the probability density function of R_0.

The basic reproduction number R_0 is a very important indicator, which can directly reflect the possibility of influenza outbreak or extinction. We use the last 15000 Markov chain samples to simulate the value of R_0, as shown in Fig. 4(a). According to the parameters in the Table 2 and the calculation method of periodic system, we determine that R_0 is 1.2266 (95% CI:(1.2230, 1.2302)). In addition, it satisfies a normal distribution, as shown in Fig. 4(b) and R_0 is greater than unity,

which also means that influenza cannot be ignored in Gansu Province. This also means that influenza is still an epidemic in Gansu Province, with the possibility of outbreak every year. Considering the seasonal flow of influenza, government departments can remind the public of the danger at the peak of influenza epidemic.

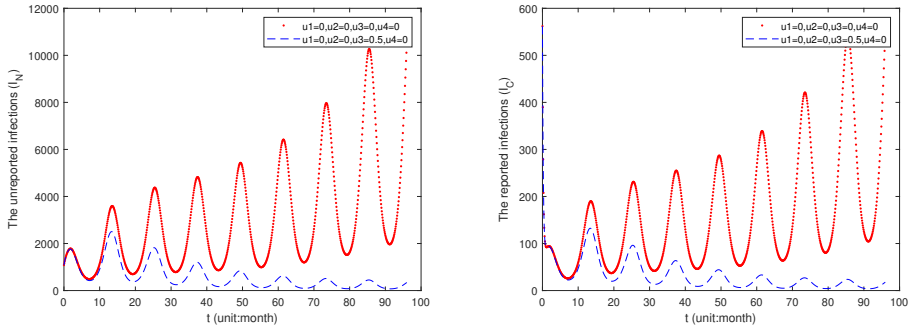
Table 2. The parameters and initial values of the system (2.1).

Parameters	Mean value	Std	95% CI	Reference
Λ	25813	-	-	[1]
d	$1/(73 \times 12)$	-	-	[3]
q	30/365	-	-	Estimate
γ_1	30/7	-	-	[22, 34]
γ_2	30/10	-	-	[22, 34]
$1/\rho$	4/30	-	-	[21]
σ	1/12	-	-	[7, 24]
θ	0.3184	-	-	[17]
δ	0.04211	-	-	[17]
κ	0.09102	-	-	[17]
c	0.025167	0.0014708	[0.0223, 0.0280]	MCMC
a_1	1.8367×10^{-07}	1.9052×10^{-09}	$[0.1799\times10^{-06}, 0.1874\times10^{-06}]$	MCMC
a_2	0.19802	0.017471	[0.1638, 0.2323]	MCMC
a_3	1.3749×10^{-07}	5.1366×10^{-09}	$[0.1274\times10^{-06}, 0.1476\times10^{-06}]$	MCMC
a_4	0.26355	0.051986	[0.1617, 0.3654]	MCMC
ϕ	2.4808	0.055845	[2.3713, 2.5903]	MCMC
$S(0)$	18295942	-	-	[17]
$V(0)$	80607	31271	[14190, 19320]	MCMC
$E(0)$	579	-	-	[17]
$I_N(0)$	1083	-	-	[17]
$I_C(0)$	562	-	-	[17]
$R(0)$	2706	-	-	[17]

5.3. Numerical Simulation of Optimal Control

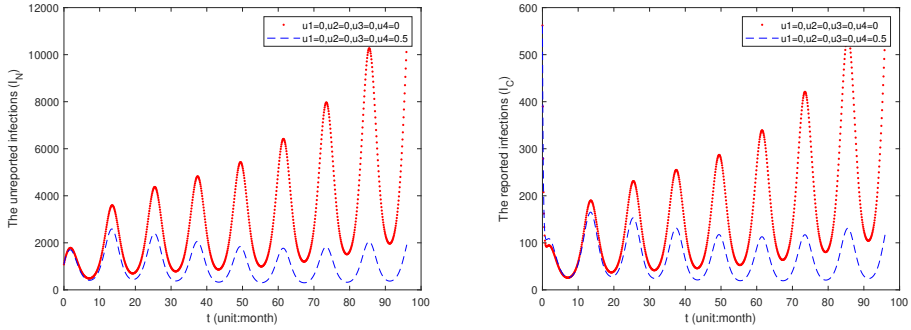
In this section, we will use the fourth-order Runge-Kutta means to numerically simulate the system (2.1) and adjoint system (4.3). Starting with initial guesses for the controls, the forward fourth-order Runge-Kutta means is utilized for calculate the state value, and the backward fourth-order Runge-Kutta means is utilized for calculate the adjoint value. Through the use of optimal conditions to achieve the goal of continuous update of the control variables, this simulation process will be repeated until the convergence effect is good. For numerical simulation, assume that the initial value of the system (2.1) is recorded as $S(0) = 18295942$, $V(0) = 80607$, $E(0) = 579$, $I_N(0) = 1083$, $I_C(0) = 562$, $R(0) = 2706$, the other parameter values are $\beta_1(t) = 1.8367 \times 10^{-7}[1 + 0.19802\sin(\frac{\pi}{6}) + 2.4808]$, $\beta_2(t) = 1.3749 \times 10^{-7}[1 + 0.26355\sin(\frac{\pi}{6}) + 2.4808]$, $\Lambda = 25813$, $d = 1/(73 \times 12)$, $q = 30/365$, $\theta = 0.3184$, $\rho = 30/4$, $\delta = 0.04211$, $\gamma_1 = 30/7$, $\gamma_2 = 30/10$, $\kappa = 0.09102$, $c = 0.025167$, $\sigma = 1/12$, and the control period T is 96 months. We choose the weight constant value of the objective function as $B_1 = 100$, $B_2 = 300$, $W_1 = 400$, $W_2 = 20$, $W_3 = 20$, $W_4 = 200$.

To evaluate different control measures to relieve stress on the public health sector during an influenza epidemic, we will simulate the evolution diagram of the reported infected individuals (I_N) and unreported infected individuals (I_N) over time under different control measures. Fig. 5(a) and Fig. 5(b) describe that when a single control measure u_3 is given, in other words, when the vaccination rate c is increased, the number of people infected with influenza shows a downward trend, which demonstrates that vaccination is a valid means to control influenza outbreaks, but just relying on vaccination cannot completely control influenza. Fig. 6(a) and Fig. 6(b) show that when the single variable u_4 is controlled, the number of people infected will decrease, but the rate of reduction is not as effective as controlling the single variable u_3. This suggests that vaccination is a more effective way than treatment, so people with weak physical fitness can choose to vaccinate. Fig. 7(a) and Fig. 7(b) illustrate that when only considering the two control measures of increasing the number of vaccinations and treatments, the number of people infected with the influenza will drop faster within a period of time, which means that people should receive treatment in time when they are infected with the influenza and take vaccination measures in advance.



(a) (b)

Figure 5. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of one control measure u_3.



(a) (b)

Figure 6. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of one control measure u_4.

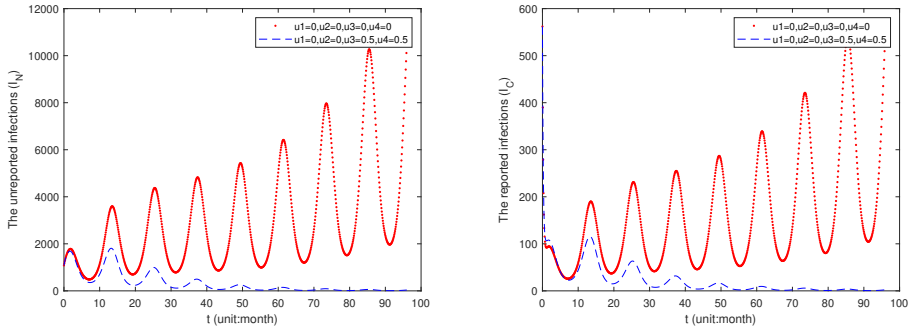


Figure 7. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of two control measures u_3 and u_4.

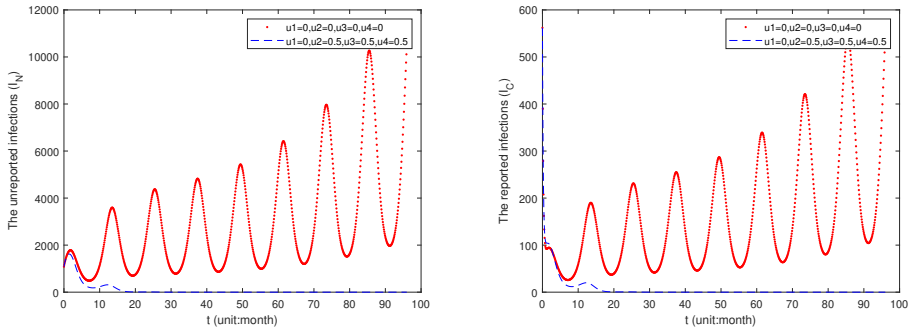


Figure 8. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of three control measures u_2, u_3 and u_4.

To further elaborate as many control measures as possible to cut down the infected groups, we also explored the impact of three control measures: reducing contact rate β_2, increasing vaccination rate c and treatment rate κ on influenza transmission. Fig. 8(a) and Fig. 8(b) reflect the numerical simulation of the three control measures u_2, u_3, u_4. The influenza will be under control in the 18th month. Next, Fig. 9(a) and Fig. 9(b) reflect the intensity of infection mitigation when we consider four control measures, namely, reducing the exposure rate β_1, reducing the exposure rate β_2, and increasing the vaccination rate c and treatment rate κ. Finally, Fig. 10(a) and Fig. 10(b) reflect the optimal control strategy, and we can see that it is better than the above strategies, the influenza will be governed within one and a half months. And the time-varying optimal control parameters u_1, u_2, u_3, u_4, of optimal measures as shown in Fig. 11.

5.4. Sensitivity Analysis

We use some parameters such as vaccination rate c to determine the size of new infections and study sensitivity analysis of our proposed mathematical model in this section. It is well known that vaccination is an effective immunization measure,

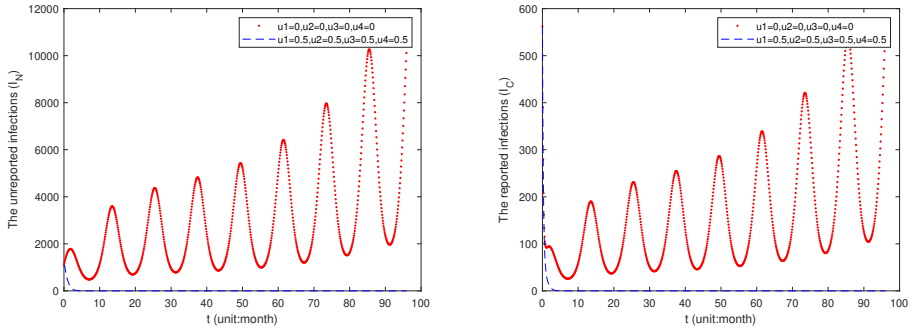


Figure 9. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of four control measures u_1, u_2, u_3 and u_4.

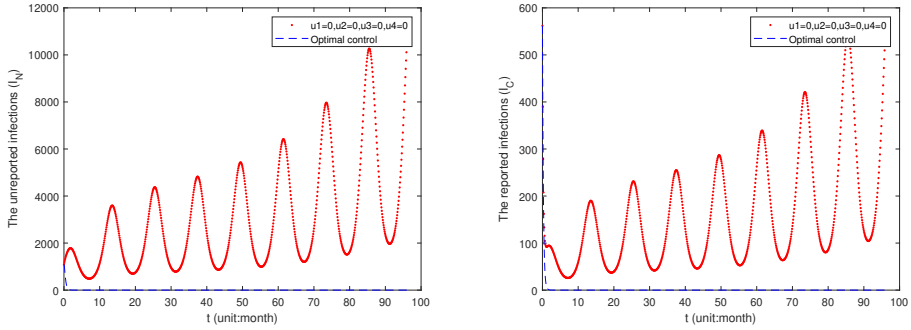


Figure 10. Time varying plots of reported infected individuals and unreported infected individuals under the implementation of the optimal control measures.

so we evaluate the influence of seasonal influenza vaccination rates on influenza outbreaks. In addition, we also assess the impact of human-to-human contact rates on the spread of influenza. From Fig. 12 (a) and Fig. 12 (b), it can be seen that the contact rate $\beta_1(t), \beta_2(t)$ is negatively correlated with the scale of new cases, which reveals that the sick person should pay attention to hygiene and keep social distance with others to reduce the contact rate with susceptible individuals. Fig. 12 (c) means that the vaccination rate c is positively associated with the scale of new cases, vaccination can effectively reduce the proportion of infected individuals to a certain extent.

To test the sensitivity of our results for different parameter changes. In the next part, the uncertainty and sensitivity analysis of parameter values will be studied via applying Latin Hypercube Sampling (LHS) and the Partial Rank Correlation Coefficients (PRCC). LHS is a kind of stratified sampling technique, which is an approximate random sampling method from multivariate parameter distribution. In order to generate an LHS matrix, we performed two thousand stratified samplings on the parameters within a reasonable range. The value of PRCC is calculated

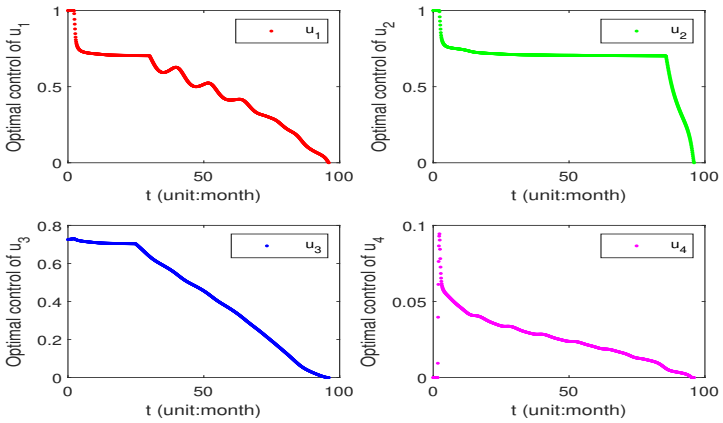
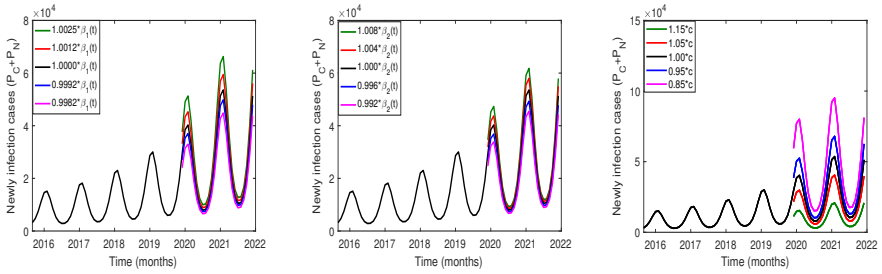
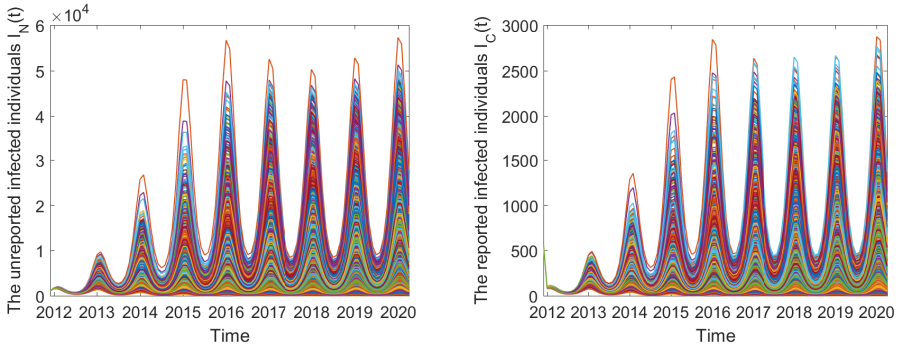


Figure 11. The optimal control variables u_i (i=1, 2, 3, 4) of the optimal control measures.



(a) (b) (c)

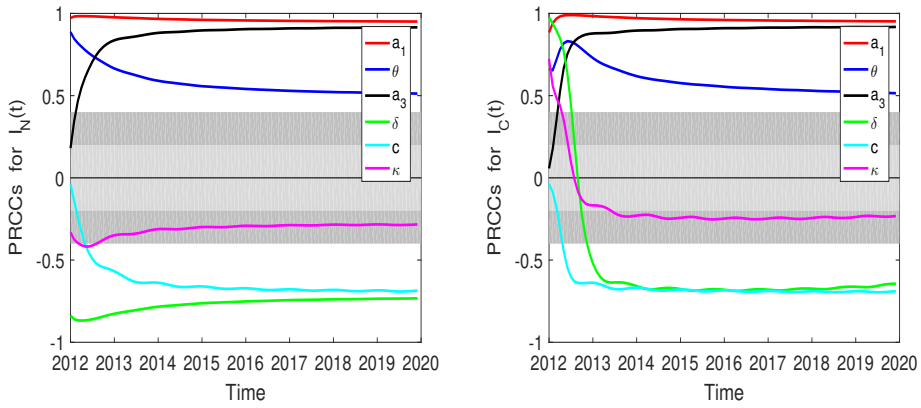
Figure 12. (a) indicates that the change of contact rate function $\beta_1(t)$ has an impact on the size of new cases. (b) indicates that the change of contact rate function $\beta_2(t)$ has an impact on the size of new cases. (c) The impact of vaccination rate c on the size of new cases.



(a) (b)

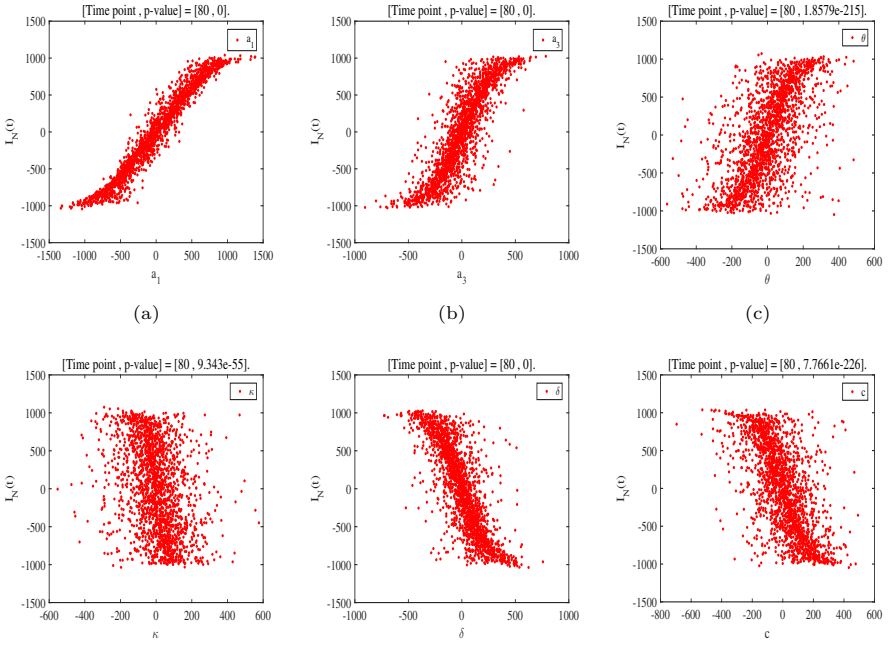
Figure 13. (a) The system (2.1) outputs the results of 2000 runs, the abscissa represents the variable $I_N(t)$, the ordinate represents the time (months). (b)The system (2.1) outputs the results of 2000 runs, the abscissa represents the variable $I_C(t)$, the ordinate represents the time (months)

and plotted based on time, which enables the sensitivity of the parameter to be assessed during the whole time, a positive PRCC value reveals the degree of positive correlation between the two variables, otherwise it is the opposite. These properties will be reflected in our simulation.



(a) (b)

Figure 14. (a) The effect of parameter sensitivity changes over time on unreported infected individuals ($I_N(t)$). (b) The effect of parameter sensitivity changes over time on unreported infected individuals ($I_C(t)$).



(a) (b) (c)

(d) (e) (f)

Figure 15. The p-value of each parameter of $I_N(t)$ at the 80th month.

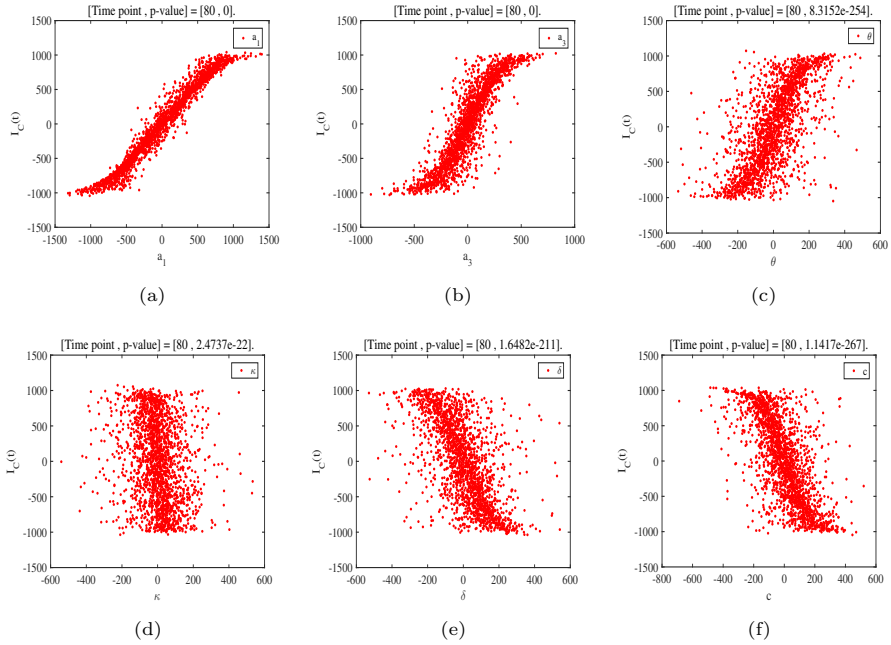
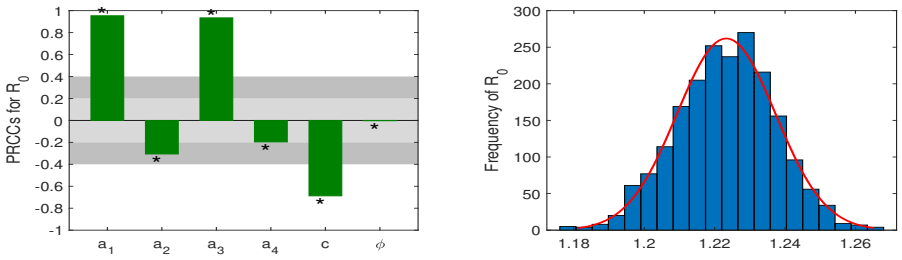


Figure 16. The p-value of each parameter of $I_C(t)$ at the 80th month.

Fig. 13 (a) and Fig. 13 (b) show the 2000 output variables of unreported infected individuals ($I_N(t)$) infected individuals and reported infected individuals ($I_C(t)$) from January 2012 to December 2019, respectively. It is easy to see that the samples of output variables show periodicity. Fig. 14 (a) and Fig. 14 (b) show the impact on infected individuals when several parameter variables change over time. We can see that the parameter values a_1 and a_3 have a strong positive correlation, which indicates that individuals who have been infected with influenza should actively reduce their contact with other people. At the same time, the parameter θ also has a strong positive correlation, indicating that influenza patients should take the initiative to strengthen self-protection measures. The parameters c and δ show a strong negative correlation with infected individuals, which indicates that people with weak physical fitness can be vaccinated to avoid influenza infection. At the same time, the government can enhance the public's awareness of influenza via raising the coverage of seasonal influenza. There is a moderate correlated negatively between parameter κ and infected individuals, which indicates that even in areas with relatively poor medical conditions such as Gansu Province, they should actively receive treatment. Fig. 15 shows the P value of each parameter of $I_N(t)$, specifically expressed as a_1 ($p-value = 0$), a_3 ($p-value = 0$), θ ($p-value = 1.8579\times10^{-215}$), κ ($p-value = 9.343\times10^{-55}$), δ ($p-value = 0$) and c ($p-value = 7.7661\times10^{-226}$). Fig. 16 shows the P value of each parameter of $I_C(t)$, specifically expressed as a_1 ($p-value = 0$), a_3 ($p-value = 0$), θ ($p-value = 8.3152\times10^{-254}$), κ ($p-value = 2.4737\times10^{-22}$), δ ($p-value = 1.6482\times10^{-211}$) and c ($p-value = 1.1417\times10^{-267}$). The results showed that the parameters a_1, a_3, c, θ and δ have great influence on the infected individuals.

Finally, we use the LHS matrix generated from the sensitivity analysis of I_N

and I_C to calculate the 2000 samples of R_0. Note that the parameter value has varying degrees of impact on R_0, so we explore the impact of estimated value on R_0 through PRCC. Figure 17 (a) shows that the parameters that are highly positively correlated with R_0 are the transmission rate coefficient a_1 and the transmission rate coefficient a_3. Therefore, the research results indicate that influenza patients should actively maintain social distancing and wear masks in public. The parameter with high negative correlation with R_0 is the vaccination rate c. It shows that people can go to the vaccination site for vaccination to reduce the possibility of influenza virus infection. Fig. 17 (b) shows the distribution of R_0, we can directly see that R_0 satisfies a normal distribution.



(a) (b)

Figure 17. (a) The PRCCs of the basic reproduction number R_0 in the system (2.1). (b) The 2000 samples of R_0 is derived by the Latin hypercube sampling. (c) The distribution of R_0 is derived by the Latin hypercube sampling.

6. Concluding remarks

In this paper, the main research work is to analyze the impact of vaccination on the spread of influenza virus from the aspects of mathematics and numerical simulation. We concluded that vaccination was one of our priority strategies and it is a critical strategy to alleviate the severity of influenza to a certain extent. Moreover, we have discussed the threshold theory of the system (2.1) by the basic reproduction number R_0: If $R_0 < 1$, the disease-free periodic solution is globally asymptotically stable; while $R_0 > 1$, influenza will always exist and at least has a positive periodic solution, as shown in Fig. 18 and Fig. 19. Further, our study emphasizes that the number of infected people is different under different interventions and gives the optimal solution, we conclude that vaccination is a better method than treatment. Next, we obtained detailed influenza data to fit the model that can reflect the influenza trend in Gansu Province for a long time through the MCMC algorithm. And the unknown parameters of the system (2.1) and the initial values of the vaccinators are revealed by our research results. To find effective control measures, it is worth mentioning that exploring the sensitivity of unknown parameters further confirms our conjecture that the contact rate and vaccination rate control the process of influenza transmission. And further conclude that vaccination is one of the most effective methods to control the spread of influenza.

Since the outbreak of COVID-19 in 2020 makes the data of influenza out of generality, we only take the data from January 2012 to December 2019. And we did not consider the impact of meteorological factors (such as rainfall, air humidity, ozone

concentration in the air, etc.) on the spread of influenza. In the follow-up work, we will explore the impact of COVID-19's Non-pharmacological intervention (such as keeping social distance, wearing masks, limiting population mobility, etc.) on influenza. If possible, we will also consider the impact of meteorological conditions, which will be a very interesting study.

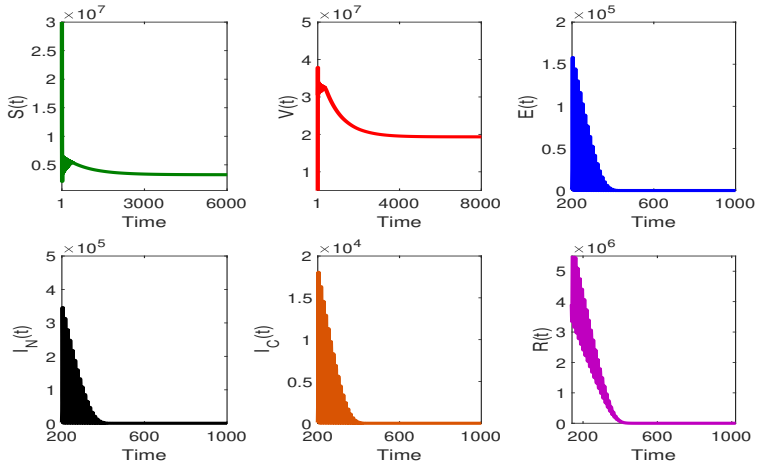


Figure 18. Numerical simulation will be used to verify some theoretical results of the system (2.1). This figure means that when R_0 is less than unity, the influenza will eventually die.

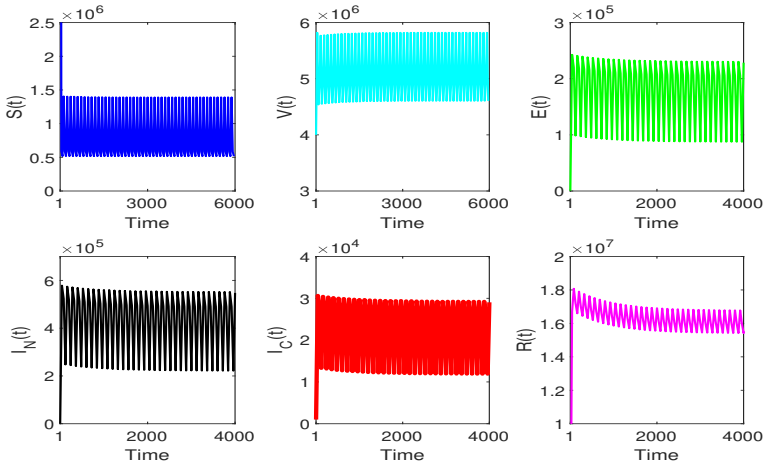


Figure 19. Numerical simulation will be used to verify some theoretical results of the system (2.1). This figure means that when R_0 is greater than unity, the influenza will always exist.

Conflict of interest. The authors declare there is no conflict of interest.

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