MODELLING THE EFFECTS OF OZONE CONCENTRATION
AND PULSE VACCINATION ON SEASONAL INFLUENZA
OUTBREAKS IN GANSU PROVINCE, CHINA

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Abstract. Common air pollutants, such as ozone (O$_3$), sulfur dioxide (SO$_2$) and nitrogen dioxide (NO$_2$), can affect the spread of influenza. We propose a new non-autonomous impulsive differential equation model with the effects of ozone and vaccination in this paper. First, the basic reproduction number of the impulsive system is obtained, and the global asymptotic stability of the disease-free periodic solution is proved. Furthermore, the uniform persistence of the system is demonstrated. Second, the unknown parameters of the ozone dynamics model are obtained by fitting the ozone concentration data by the least square method and Bootstrap. The MCMC algorithm is used to fit influenza data in Gansu Province to identify the most suitable parameter values of the system. The basic reproduction number $R_0$ is estimated to be 1.2486 (95%CI : (1.2470, 1.2501)). Then, a sensitivity analysis is performed on the system parameters. We find that the average annual incidence of seasonal influenza in Gansu Province is 31.3374 per 100,000 people. Influenza cases started to surge in 2016, rising by a factor of one and a half between 2014 and 2016, further increasing in 2019 (54.6909 per 100,000 population). The average incidence rate during the post-upsurge period (2017-2019) is one and a half times more than in the pre-upsurge period (2014-2016). In particular, we find that the peak ozone concentration appears 5–8 months in Gansu Province. A moderate negative correlation is seen between influenza cases and monthly ozone concentration (Pearson correlation coefficient: $r = -0.4427$). Finally, our results show that increasing the vaccination rate and appropriately increasing the ozone concentration can effectively prevent and control the spread of influenza.

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1. Introduction. Seasonal influenza is an acute respiratory infection that is easily transmitted from person to person. During the high season of influenza, the virus spreads around the world. Influenza is a serious public health problem that causes severe illness and death every year around the world [46]. Influenza can cause 3 million to 5 million severe cases worldwide and 290,000 to 650,000 deaths related to respiratory diseases each year. High-risk groups such as pregnant women, infants, the elderly, and patients with chronic diseases have a higher risk of serious illness and death after influenza [31].

Vaccination is one of the most effective ways to prevent seasonal influenza [35, 30]. Vaccination of susceptible people can greatly reduce the spread of influenza, it can also reduce the symptoms of influenza patients and reduce the complications of influenza patients. Infants, the elderly and other people with poor immunity can greatly reduce the occurrence of influenza by giving priority to a vaccination before the occurrence of influenza season [31]. As of 2014, more than 100 countries and regions around the world have formulated seasonal influenza vaccination policies that recommend vaccination of at least one of the risk groups [47]. More than 40% of countries and territories list seasonal influenza vaccination schedules in their National Vaccination Schedules, including North and South America, Europe, and most countries in Africa, Southeast Asia, and the Western Pacific [7, 47].

Mathematical models are widely used in the mechanisms related to the spread and control of infectious diseases [18]. There have been many articles on pulse vaccination [37, 21, 8, 48, 49]. Shulgin et al. (1998) [37] studied pulse vaccination strategies in SIR epidemic models, and the results showed that pulsed vaccination eradicates epidemics under seasonal changes. Jin (2001) [21] studied the SIR pulse immunization model with disease-causing death, and proved the stability of the equilibrium. d’Onofrio (2002) [8] studied the stability of the pulsed vaccination strategy in the SEIR epidemic model and showed that the pulsed vaccination strategy was more efficient than the continuous vaccination strategy. Yang and Xiao (2010) [48] studied a non-autonomous SIR type epidemic model with pulse vaccination in patchy environments, and extended the definition of the basic reproduction number in continuous (autonomous or periodic) systems to hybrid systems. Yang and Xiao (2012) [49] studied the threshold dynamics with an impulse epidemic model, and defined the basic reproduction number and calculation methods for general impulse epidemic models.

Understanding the environmental drivers of influenza transmission will help with early intervention and long-term control strategies for seasonal influenza, which is a serious public health problem [1]. Jing et al. (2020) [22] studied the effects of meteorological factors and unreported cases on influenza. In addition to meteorological factors, it is not clear how common air pollutants, such as ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), nitric oxide (NO), PM₂.₅ and PM₁₀, affect the spread of influenza [25]. The results of Wolcott et al. (1982) [45] showed that the severity of disease in animals exposed to ozone decreased. The results of Jakab and Hmieleski (1988) [20] showed that the severity of disease could be reduced by continuous exposure to ozone of 0.5ppm during the process of mouse influenza virus infection, which proved Wolcott et al.’s conclusion. Tanaka et al. (2009) [40] showed that exposure to a gas with a temperature of 23-29 degrees Celsius, relative humidity of 64%-65%, and an ozone concentration of 10ppm for 210 minutes could inactivate more than 99.99% of influenza A virus particles attached to plastic. When the virus was exposed to 20ppm ozone gas for 150 minutes, the influenza virus inactivation
rate exceeded 99.999%. In contrast, under the same conditions, the virus remained active after 10 hours without ozone gas [40].

Motivated by the above papers [48, 49, 40, 43, 22], we propose a new non-autonomous differential equation model with the effects of ozone and pulsed vaccination in this paper, which includes periodic transmission rate. First, the basic reproduction number of the impulse system is derived, and the global asymptotic stability of the disease-free periodic solution is proved. Further, the consistent persistence of the model is proved. Second, the unknown parameters of the ozone dynamics model are obtained by fitting the ozone concentration data by nonlinear least squares and Bootstrap, and the MCMC algorithm is used to fit influenza data in Gansu Province to identify the optimal parameter values of the non-autonomous differential equation model. We estimate that the basic reproduction number $R_0$ is 1.2486 (95% CI: (1.2470, 1.2501)). At the same time, to determine the key parameters of the model, we carry out a sensitivity analysis of the model parameters.

The organization of this paper is as follows: In Section 2, we propose a new ozone dynamics model with seasonal variation. In Section 3, we propose a new non-autonomous differential equation model with the effects of ozone and pulsed vaccination, which includes periodic transmission rate. We obtain the basic reproduction number $R_0$. The global asymptotic stability of the disease-free periodic solution is demonstrated. The uniform persistence of the model is also proved. In Section 4, we use nonlinear least squares, Bootstrap, and MCMC to estimate the unknown parameters of the ozone dynamics model and non-autonomous differential equation model. In Section 5, we discuss the effects of pulse vaccination, effects of ozone sterilization, and the sensitivity of the main parameters. In Section 6, we give some discussions and conclusions.

2. Dynamic model of ozone. In the near-earth layer, ozone is produced by automobile exhaust, forest fire, volcanic eruption, natural lighting, artificial discharge, and nuclear explosion. But the main source of ozone in the atmosphere is solar ultraviolet radiation. With the decrease of hydrocarbon and NO$_x$ in the air, the concentration of ozone gradually reaches the peak value under the continuous irradiation of ultraviolet or sunlight [51]. This means that ozone concentration is seasonal in the temperate zone. To model the seasonality of ozone concentration, we generalize the AQI model of Tang et al. (2018) [41] and He et al. (2018) [17]. The model is as follows

$$\frac{d\Theta(t)}{dt} = c(t) - b(t)\Theta(t), \quad (1)$$

where $\Theta(t)$ represents the concentration of ozone in the air at time $t$, $c(t)$ represents the input rate of ozone in the air at time $t$, and $c(t)$ can be expressed as

$$c(t) = \begin{cases} 
  c_0 + c_1, & t \in [nT + T_1, nT + T_2], n \in \mathbb{N}, \\
  c_0 + c_1 + c_2, & t \in [nT + T_2, nT + T_3], n \in \mathbb{N}, \\
  c_0 + c_1, & t \in [nT + T_3, nT + T_4], n \in \mathbb{N}, \\
  c_0, & t \in [nT + T_4, (n + 1)T + T_1], n \in \mathbb{N}.
\end{cases}$$

The parameter $c_0$ represents the basic input rate of ozone throughout the year (i.e., industrial emissions such as automobile exhaust). As the temperature rises in the spring and autumn and the solar ultraviolet radiation increases, the ozone concentration gradually increases. Therefore, $c_1$ represents the ozone input rate in the spring and autumn. Summer is the hottest season of the year, the solar ultraviolet
radiation is stronger, and the ozone concentration is the highest. Therefore, $c_1 + c_2$ represents the summer ozone input rate, where $c_2$ represents the increase in ozone input rate in the summer after spring. The function $b(t)$ represents the periodic decomposition rate of ozone affected by meteorological conditions. The periodic function $b(t)$ is expressed as follows:

$$b(t) = b_0 + b_1 \sin(\omega t + \phi_0),$$

where $\omega = \frac{2\pi}{T}$, $b_0$ and $b_1$ represent the decomposition rate coefficients.

The periodic system (1) has a periodic solution which is expressed as follows

$$\Theta(t) = e^{-\int_{T_1}^{T_1+T_2} b(c)dc} \int_{T_1}^{T_1+T_2} c_0 e^{-\int_{T_1}^{\tau} b(\varepsilon)d\varepsilon} d\theta$$

$$+ e^{-\int_{T_3}^{T_1+T_2} b(\varepsilon)d\varepsilon} \int_{T_3}^{T_1+T_2} (c_0 + c_1) e^{-\int_{T_3}^{\tau} b(\varepsilon)d\varepsilon} d\theta$$

$$+ e^{-\int_{T_2}^{T_1+T_2} b(\varepsilon)d\varepsilon} \int_{T_2}^{T_1+T_2} (c_0 + c_1 + c_2) e^{-\int_{T_2}^{\tau} b(\varepsilon)d\varepsilon} d\theta$$

$$+ e^{-\int_{T_4}^{T_1+T_2} b(\varepsilon)d\varepsilon} \int_{T_4}^{T_1+T_2} (c_0 + c_1) e^{-\int_{T_4}^{\tau} b(\varepsilon)d\varepsilon} d\theta$$

$$+ \Theta^*(T_1)e^{-\int_{T_1}^{T_1+T_2} b(\varepsilon)d\varepsilon},$$

where

$$\Theta^*(T_1) = \frac{\left(e^{-\int_{T_1}^{T_1+T_2} b(\varepsilon)d\varepsilon} \int_{T_1}^{T_1+T_2} c_0 e^{-\int_{T_1}^{\tau} b(\varepsilon)d\varepsilon} d\thetaight)}{1 - e^{-\int_{T_1}^{T_1+T_2} b(\varepsilon)d\varepsilon}}.$$

Detailed mathematical analyses of the system (1) can be found in Appendix A.

3. Model derivation. In this section, we propose a new non-autonomous differential equation model with the effects of ozone and pulse vaccination, which includes periodic transmission rates.

3.1. Influenza model with effect of ozone and pulse vaccination. The basic structure of the model can be divided into seven compartments: $S(t)$ represents the number of susceptible individuals; $E(t)$ denotes the number of exposed individuals; $I_N(t)$ represents the unreported cases by the CDC in Gansu Province, including asymptomatic infected individuals and some symptomatic infected individuals [22]; $I_C(t)$ represents the reported cases by the CDC in Gansu Province; $R(t)$ represents the number of reflections individuals. The total number of people at time $t$ is expressed as $N(t) = S(t) + E(t) + I_N(t) + I_C(t) + R(t)$. As mentioned in the introduction, the sterilization effect of ozone in the air protects individuals people and reduces the spread of influenza. Therefore, we define the contact transmission rate
between susceptible individuals and infected individuals as $G(t) = (1 - g(\Theta(t)))\beta(t)$ [41, 44], where the saturated function $g(\Theta(t)) = \frac{a_1\Theta(t)}{a_2 + \Theta(t)}$, $\beta(t)$ represents the basic contact transmission rate, which is a positive $T$-periodic function, $a_1(0 < a_1 < 1)$ represents the maximum protection rate due to ozone sterilization, $a_2$ is a saturated constant. To characterize the impact of vaccination, we define $p$ as the fraction of susceptible individuals that are successfully inoculated for the vaccine at $t = nT$. The structural diagram between the compartments is shown in Figure 1.

Figure 1. Flow chart of the influenza system (2).

Base on the above notation and the flowchart, the mathematical model is formulated as follows

$$\begin{align*}
\frac{dS}{dt} &= \Lambda + qR - G(t)S(\theta I_C + I_N) - dS, \\
\frac{dE}{dt} &= G(t)S(\theta I_C + I_N) - \sigma E - dE, \\
\frac{dI_N}{dt} &= (1 - \delta)\sigma E - \gamma_2 I_N - dI_N - \kappa I_N, \\
\frac{dI_C}{dt} &= \delta \sigma E - \gamma_1 I_C - dI_C + \kappa I_N, \\
\frac{dR}{dt} &= \gamma_1 I_C + \gamma_2 I_N - QR - dR, \\
S(nT^+) &= (1 - p)S(nT), \\
E(nT^+) &= E(nT), \\
I_N(nT^+) &= I_N(nT), \\
I_C(nT^+) &= I_C(nT), \\
R(nT^+) &= R(nT) + pS(nT),
\end{align*}$$

where $G(t) = \left(1 - \frac{a_1\Theta(t)}{a_2 + \Theta(t)}\right)\beta(t)$. The parameters of the system (2) are defined in Table 2. Detailed mathematical analyses of the system (2) can be found in Appendix B.

4. A case study. In this section, first, we parameterize the ozone dynamics model (1) through the ozone concentration data from January 2014 to December 2019 in
Table 1. The parameters description of the system (2).

| Parameters | Description (Units) |
|------------|---------------------|
| \( \Lambda \) | The recruitment rate of the susceptible individuals \( \text{(person/month)} \) |
| \( d \) | The natural mortality rate of the population \( \text{(month}^{-1}\text{)} \) |
| \( \theta \) | The modification factor in transmission coefficient of the reported infected individuals \( \text{(none)} \) |
| \( \delta \) | The proportion of infected individuals notified by CDC in Gansu Province \( \text{(none)} \) |
| \( 1/\sigma \) | The mean incubation period of the infected individuals \( \text{(month)} \) |
| \( q \) | The progression rate of the recovered individuals \( \text{(month}^{-1}\text{)} \) |
| \( p \) | The proportion of those vaccinated successfully \( \text{(none)} \) |
| \( \gamma_1 \) | The recovery rate of reported infected individuals \( \text{(month}^{-1}\text{)} \) |
| \( \gamma_2 \) | The recovery rate of unreported infected individuals \( \text{(month}^{-1}\text{)} \) |
| \( \kappa \) | The diagnosis rate of unreported infected individuals \( \text{(month}^{-1}\text{)} \) |
| \( a_1 \) | The maximum protection rate due to ozone sterilization \( \text{(none)} \) |
| \( a_2 \) | Saturated constant \( \text{(none)} \) |
| \( \beta(t) \) | The basic contact transmission rate \( \text{(none)} \) |
| \( T > 0 \) | The vaccination interval \( \text{(month)} \) |

Gansu Province, China, and we obtain the mean value and credible intervals of each parameter. Next, we estimate the unknown parameters of the system (2) using monthly influenza data from January 2014 to December 2019 in Gansu Province, China, and we also obtain the mean value and credible interval of the basic reproduction number \( R_0 \).

4.1. Data sources. The number of influenza cases comes from Gansu Provincial Center for Disease Control and Prevention (CDC) \[10\], as shown in the black histogram in Figure 2(b). The daily ozone concentration data comes from the PM2.5 historical data website: \( \text{https://www.aqistudy.cn/historydata/} \). From this website, we obtain the daily ozone concentration data of 14 the local administrative regions in Gansu Province, which the data of Jiayuguan, Lanzhou, and Jinchuan are from January 1, 2014, to December 31, 2019, and the data of other 11 local administrative regions are from 2015 from January 1, 2019, to December 31, 2019, as shown in Figure C.13 (see Appendix C).

4.2. Ozone data fitting. To fit the daily ozone concentration data of 14 the local administrative regions in Gansu Province, we use the mean value of the daily ozone concentration data of 14 the local administrative regions in Gansu Province to replace the ozone concentration level of Gansu Province, among which the mean value from January 1, 2014, to December 31, 2014, is obtained from the mean value of the data of Jiayuguan, Lanzhou, and Jinchuan, and the mean value from January 2015 to December 31, 2019, is obtained by averaging the data of all 14 the local administrative regions in Gansu, as shown in Figure 2(a).

The nonlinear least square method is used to fit the mean value of daily ozone concentration in Gansu Province from January 1, 2014, to December 31, 2019, we get the unknown parameters of the system (1). Then we use bootstrap to fit the error of the system (1) for 100 times, and we get the mean value and credible intervals of the unknown parameters of the system (1). The mean value, standard
deviation, and credible intervals of parameters are shown in Table 2. The fitting effect is shown in Figure 3.

Table 2. The parameters values of the system (1).

| Parameters | Mean value | Std  | 95% CI             | Reference |
|------------|------------|------|--------------------|-----------|
| \(c_0\)    | 1.4150     | 0.03489 | [1.3466, 1.4833]   | Bootstrap |
| \(c_1\)    | 0.1696     | 0.04515 | [0.08112, 0.2581]  | Bootstrap |
| \(c_2\)    | 0.1172     | 0.03579 | [0.04707, 0.1874]  | Bootstrap |
| \(\phi_0\) | -9.6959    | 0.2251  | [-10.1370, -9.2547]| Bootstrap |
| \(b_0\)    | 0.01733    | 0.001310| [0.01476, 0.01990] | Bootstrap |
| \(b_1\)    | 0.005276   | 0.001394| [0.002545, 0.008007]| Bootstrap |

4.3. Parameter estimation and model fitting. According to the periodic characteristics of influenza in Gansu Province, we define the periodic transmission rate...
between susceptible individuals and infected individuals as follows

$$\beta(t) = \beta_0(1 + \beta_1 \sin(\frac{\pi}{6} t + \phi_1)),$$

where $\pi/6 = 2\pi/12$ (i.e., the period is 12 months), $\beta_0$ and $\beta_1$ indicate coefficient of transmission rate between susceptible individuals and infected individuals, $\phi_1$ indicates the phase of the $T$-periodic function. Since seasonal influenza data is based on months, we redefine the saturated function $g(\bar{\Theta}(t)) = \frac{a_1 \bar{\Theta}(t)}{a_2 + \bar{\Theta}(t)}$, where $\bar{\Theta}(t)$ represents the monthly average ozone concentration.

To simulate the newly infected cases of influenza in Gansu Province, the rationality of the model is verified by the actual number of newly infected cases. In what follows, we use the MCMC method [14, 15] for 50000 iterations with a burn-in of 40000 iterations to fit the system (2). We estimate the unknown parameters and initial conditions for the system (2) ($\hat{\chi} = (\beta_0, \beta_1, \phi_1, a_1, a_2)$), using the monthly number of influenza cases in Gansu Province. Let $C_C(t, \hat{\chi})$ and $C_N(t, \hat{\chi})$ represent the cumulative number of reported and unreported cases, respectively, then, the cumulative infection cases can be expressed as follows

$$\frac{dC_C(t, \hat{\chi})}{dt} = \delta \sigma E + \kappa I_N,$$
$$\frac{dC_N(t, \hat{\chi})}{dt} = (1 - \delta) \sigma E - \kappa I_N.$$  

As for the newly infected cases, it can be expressed as follows

$$P_C(t, \hat{\chi}) = C_C(t) - C_C(t - 1),$$  
$$P_N(t, \hat{\chi}) = C_N(t) - C_N(t - 1),$$

where $P_C$ and $P_N$ represent the number of new cases of reported infected individuals and the number of new cases of unreported infected individuals, respectively, and $t$ is regarded as month in the simulations, then $C_C(0) = P_C(0), C_N(0) = P_N(0)$. We have $\Psi$ independent observations from the data, representing the number of newly infected cases at the $i$th month, where $i = 1, ..., \Psi$. Let $\epsilon$ be the fitting error,
and $\epsilon$ follows the additive independent Gaussian distribution with mean zero and unknown variance $\xi^2$. Thus, the observations $Y$ can be expressed as follows
\[ \bar{Y}_i = P_C(t_i, \hat{\chi}) + \epsilon, \quad \epsilon \sim N(0, \xi^2). \quad (5) \]

Assume that the unknown parameters $\hat{\chi}$ of the system (2) is an independent Gaussian prior specification, therefore, we obtain
\[ \hat{\chi}_j \sim N(\nu_j, \phi_j^2), \quad j = 1, ..., \Psi. \]

We also assume that the inverse of the error variance follows a gamma distribution as prior with the form
\[ L(\xi^{-2}) \sim \Gamma \left( \frac{n_0}{2}, \frac{n_0 S_0^2}{2} \right), \]
where $S_0^2$ and $n_0$ are the prior mean and prior accuracy of variance $\xi^2$, respectively.

The likelihood function $L(\bar{Y}|\hat{\chi}, \xi^2)$ for $\Psi$ independent identically distributed observations from Eq. (5) with a Gaussian error model can be expressed as [23]
\[ L(\bar{Y}|\hat{\chi}, \xi^2) = \left( \frac{1}{\sqrt{2\pi \xi^2}} \right)^\Psi \exp \left[ -\frac{SS(\hat{\chi})}{2\xi^2} \right], \]
where $SS(\hat{\chi})$ represents the sum of squares function
\[ SS(\hat{\chi}) = \sum_{i=1}^\Psi \left[ \bar{Y}_i - P_C(t_i, \hat{\chi}) \right]^2. \]

We use the conditional conjugacy property of the Gamma distribution [12, 34, 36, 13, 23], the conditional distribution $L(\xi^{-2}|\bar{Y}, \hat{\chi})$ is also a Gamma distribution with
\[ L(\xi^{-2}|\bar{Y}, \hat{\chi}) = \Gamma \left( \frac{n_0 + \Psi}{2}, \frac{n_0 S_0^2 + SS(\hat{\chi})}{2} \right). \]

This conditional conjugacy property makes it possible to sample and update $\xi^{-2}$ for other parameters within each Metropolis Hastings simulation step. Since we assume independent Gaussian prior specification for parameters $\hat{\chi}$, the prior sum of squares for the given parameters $\hat{\chi}$ can be calculated as follows
\[ SS_{pri}(\hat{\chi}) = \sum_{i=1}^\Psi \left[ \chi_i + \phi_i \right]^2. \]

Then, for a fixed value of variance $\xi^2$, the posterior distribution of parameters $\hat{\chi}$ can be expressed as follows
\[ L(\hat{\chi}|\bar{Y}, \xi^2) \propto \exp \left[ -0.5 \left( \frac{SS(\hat{\chi})}{\xi^2} + SS_{pri}(\hat{\chi}) \right) \right], \]
and the posterior ratio needed in the Metropolis-Hastings acceptance probability can be written as follows
\[ \frac{L(\hat{\chi}^1|\bar{Y}, \xi^2)}{L(\hat{\chi}^2|\bar{Y}, \xi^2)} = \exp \left[ -0.5 \left( \frac{SS(\hat{\chi}^1)}{\xi^2} - \frac{SS(\hat{\chi}^2)}{\xi^2} \right) + 0.5 \left( SS_{pri}(\hat{\chi}^1) - SS_{pri}(\hat{\chi}^2) \right) \right], \]
where $\hat{\chi}^1$ is the value of the current parameter set, $\hat{\chi}^2$ represents the value of generating a new parameter set. The initial value sample of parameters $\hat{\chi}$ are obtained by the Latin Hypercube Sampling technique [28]. Then we find the local
minimum of $SS(\hat{\chi})$ using classical nonlinear least squares technique to obtain the estimated value of the initial value of the parameter set. The minimum value of these estimated $\hat{\chi}$ was used as the initial guess in MCMC simulation. Prior information of unknown parameters are given by $\beta_0 \in (0, 1)$, $\beta_1 \in (0, 1)$, $\phi_1 \in (0, 12)$, $a_1 \in (0, 1)$, $a_2 \in (0, 10)$, and the proposal density is chosen to be a multivariate normal distribution.

Since several parameters and initial values of the system (2) can be obtained according to existing data and experience. Next, all parameters and initial values of the system (2) are estimated in detail:

(i) the recruitment rate of susceptible (i.e. $\Lambda$): According to the relevant data reported by Gansu Provincial Bureau of Statistics [11], the birth rate of Gansu Province at the end of 2013 is 12.16 per thousand. Meanwhile, we obtain a total population of 25821800 at the end of 2013 in Gansu Province [11]. Therefore, we know that the monthly birth population of Gansu Province is about 26166;

(ii) the natural mortality rate of the population (i.e. $d$): According to the National Bureau of Statistics of China [32], we conclude that the monthly natural mortality rate of the population in Gansu Province in 2013 is approximate $d = 1/(73 \times 12)$, where the constant 73 represents the average life expectancy of the population of Gansu Province;

(iii) the recovery rate of reported infected individuals (i.e. $\gamma_1$): We assume that the average recovery time of reported influenza patients is 7 days [9, 27, 5, 22], then the monthly recovery rate is $30/7$;

(iv) the recovery rate of unreported infected individuals (i.e. $\gamma_2$): We assume that the average recovery time of unreported influenza patients is 10 days [9, 27, 22], then the monthly recovery rate is $30/10$;

(v) the mean incubation period (i.e. $1/\sigma$): The incubation period for influenza varies in different books, from a few hours to four days, the most common being three to four days [42, 4]. In this paper, we assume that the average incubation time is 4 days, then monthly the average incubation period $1/\sigma$ can be determined by $4/30$;

(vi) the progression rate of the recovered individuals (i.e. $q$): Influenza confers life-long immunity against the strain with which one has been infected, and loss of

| Parameters | Mean value | Std | 95% CI | Reference |
|------------|------------|-----|--------|-----------|
| $\Lambda$  | 26166      |     |        | [11]      |
| $d$        | $1/(73 \times 12)$ |     |        | [32]      |
| $\gamma_1$ | 30/7       |     |        | [9, 27, 5, 22] |
| $\gamma_2$ | 30/10      |     |        | [9, 27, 22] |
| $\sigma$   | 30/4       |     |        | [42, 4]   |
| $q$        | 30/365     |     |        | [33, 5, 6, 38, 16] |
| $p$        | 2%         |     |        | [47]      |
| $\theta$  | 0.3184     |     |        | [22]      |
| $\delta$  | 0.04211    |     |        | [22]      |
| $\kappa$  | 0.09102    |     |        | [22]      |
| $\beta_0$  | 1.9765 $\times 10^{-7}$ | 2.3187 $\times 10^{-8}$ | [1.7748 $\times 10^{-7}$, 2.6870 $\times 10^{-7}$] | MCMC |
| $\beta_1$  | 0.2386     | 0.02253 | [0.1899, 0.2834] | MCMC |
| $\phi_1$  | 2.5287     | 0.09460 | [2.3211, 2.7052] | MCMC |
| $\phi_2$  | 0.1013     | 0.09390 | [0.0709, 0.1323] | MCMC |
| $\sigma$  | 4.0242     | 3.1987 | [0.2137, 9.9282] | MCMC |

| Initial values | Mean value | Std | 95% CI | Reference |
|----------------|------------|-----|--------|-----------|
| $S(0)$        | 18403500   |     |        | [22]      |
| $E(0)$        | 1484       |     |        | [22]      |
| $I_{C}(0)$    | 1091       |     |        | [16]      |
| $I_{N}(0)$    | 3232       |     |        | [22]      |
| $R(0)$        | 9601       |     |        | [22]      |

Table 3. The parameters and initial values of the system (2).
immunity is an artifact to take into account the process of antigenic drift. Still, barring rare antigenic shifts, it is generally believed that influenza infection in one year provides more or less complete immunity against the current strains for a few years. Thus, we assume that the progression rate of the recovered individuals is $q = 30/365$ [33, 5, 6, 38, 16];

(vii) the proportion of those vaccinated successfully (i.e. $p$): According to the notice of the China Center for Disease Control and prevention (CDC), we know that the annual influenza vaccination time in China is in September and October. Therefore, we assume that the vaccination time for influenza is September. According to the introduction of Yang et al. (2016) [47], the average vaccination rate of seasonal influenza in China from 2004 to 2014 is only 1.5%-2.2%. Hence, we assume that the proportion of successful vaccination is 2%, then $p = 2%$;

(viii) the modification factor in transmission coefficient of the reported infected individuals (i.e. $\theta$), the proportion of infected individuals notified by CDC in Gansu Province (i.e. $\delta$), the diagnosis rate of unreported infected individuals (i.e. $\kappa$): According to the estimation of Jing et al. (2020) [22], we assume that $\theta = 0.3184$, $\delta = 0.04211$, $\kappa = 0.09102$;
(ix) the initial value of the system (2): According to the relevant data reported by the Gansu Provincial Center for Disease Control and Prevention (CDC) [10], we obtain the initial value of $I_C(t)$ as 1091. According to the estimation of Jing et al. (2020) [22], we assume that the initial value of other variables of the system (2) is $S(0) = 18403500$, $E(0) = 1484$, $I_N(0) = 3232$, $R(0) = 9001$.

(x) The other parameters of system (2) are estimated by the MCMC algorithm, as shown in Table 3.

The fitting results of the reported new cases are shown in Figure 4(a), and the fitting results of the unreported new cases are shown in Figure 4(b). Pearson’s correlation between the number of estimated cases and the number of reported cases are shown in Figure 4(c). The posterior distribution and traces of the system (2) unknown parameters values are obtained by MCMC sampling (see Figure D.14 and Figure D.15 in Appendix D).

From the simulation results in Figure 4, we can obtain that there are more unreported new cases than reported new cases. Therefore, infected people who have not received treatment and asymptotically infected individuals should go to the hospital for treatment. According to the parameters in Table 3, we use the theory proposed by Yang and Xiao (2010) [48] to calculate the basic reproduction number of the system (2). $R_0$ is estimated to be $1.2486$ (95%CI : (1.2470, 1.2501)), as shown in Figure 5.

![Figure 5](image_url)

**Figure 5.** The Markov chain of the last 10000 samples of $R_0$. (a) The blue dots indicate the value of $R_0$ within the 95% credible intervals, the red pluses indicate the value of $R_0$ outside the 95% credible intervals, and the black lines indicate the upper and lower credible limits. (b) The frequency distribution of $R_0$. The red curve is the probability density function curve of $R_0$. 
5. Uncertainty and sensitivity analysis. In this section, we mainly study the impact of ozone concentration in the air, vaccination rate, and other parameters on the number of new cases, so that we can explore the optimal control strategies and measures during the influenza epidemic.

5.1. Effect of pulse vaccination. Vaccination is the focus of immunization planning in all countries and regions around the world. Vaccination plays an important role in reducing the epidemic of infectious diseases. According to the parameters and initial values in Table 3, the reported new cases increase with the increase of $p$ when the vaccination rate $p$ is increased, as shown in Figure 6(a). More specifically, the reported cumulative cases in Gansu Province in 2020 be predicted by increasing the vaccination rate $p$ from 2% to 5%, as shown in Figure 6(b).

According to Figure 6(b), when the vaccination rate is $p = 2\%$, the cumulative number of cases reported reach 15925 in 2020. When the vaccination rate is $p = 3\%$, the cumulative number of cases reported reach 5624 in 2020, which is 64.69\% lower than the cumulative number of cases reported when $p = 2\%$. When the vaccination rate is $p = 4\%$, the cumulative number of cases reported reach 1687 in 2020, which is 89.41\% lower than the cumulative number of cases reported when $p = 2\%$. When the vaccination rate is $p = 5\%$, the cumulative number of cases reported reach 468 in 2020, which is 97.06\% lower than the cumulative number of cases reported when $p = 2\%$.

5.2. Effect of ozone sterilization. Ozone sterilization effect refers to the oxidation of oxygen atoms that destroys the structure of the microbial membrane to achieve sterilization. According to the announcement of “Ambient Air Quality Standard” issued by the Ministry of Ecology and Environment of the People’s Republic of China (2020) [29], we obtain that the standard for China’s ozone concentration
to reach light pollution is 160ug/m$^3$. Therefore, when the ozone concentration does not reach 160ug/m$^3$, increasing the ozone concentration can kill the influenza virus in the air, as shown in Figure 7.

![Figure 7](image_url)

**Figure 7.** Ozone concentration changes. The black dot represents the actual data, the red curve represents the mean value of 100 simulations, and the yellow area represents more than 160ug/m$^3$ (i.e., ozone light pollution).

![Figure 8](image_url)

**Figure 8.** The dependence of the solution of the number of reported cases $P_C(t)$ as a function of time on the basic input rate of ozone $c_0$. (a) The number of new cases reported changes with the basic input rate of ozone $c_0$. (b) The cumulative cases reported change with the basic input rate of ozone $c_0$ in 2020. The grey area represents the 95% credible intervals.
As can be seen from Figure 8(a), when the ozone concentration increases, the number of new cases of influenza also gradually decreases, which shows that an appropriate increase in ozone concentration can effectively reduce influenza infection. It can be seen from Figure 8(b) that the cumulative number of cases reported is 15925 in 2020 when the basic input rate of ozone is $c_0$. The cumulative number of cases reported is 15107 in 2020 when the basic input rate of ozone is $1.1c_0$, which is 5.13% lower than the cumulative number of cases when the basic input rate of ozone is $c_0$. The cumulative number of cases reported is 14416 in 2020 when the basic input rate of ozone is $1.2c_0$, which is 9.47% lower than the cumulative number of cases when the basic input rate of ozone is $c_0$. Besides, the cumulative number of cases reported is 13881 in 2020 when the basic input rate of ozone is $1.3c_0$, which is 12.83% lower than the cumulative number of cases when the basic input rate of ozone is $c_0$. The cumulative number of cases reported is 13459 in 2020 when the basic input rate of ozone is $1.4c_0$, which is 15.48% lower than the cumulative number of cases when the basic input rate of ozone is $c_0$.

5.3. Sensitivity analysis of parameters. In what follows, we use the Latin Hypercube Sampling (LHS) and the partial rank correlation coefficient (PRCC) [26] to study the global uncertainty and sensitivity of the parameters of the system (2). We select a normal distribution for all input parameters, where the mean and standard deviation are given in Table 3. We use the LHS method to carry out 2000 stratified sampling of the parameters, where the input parameters are $\beta_0$, $a_1$, $a_2$, $\beta(t)$ and $g(\Theta(t))$, the output variables are $P_C$ and $P_N$. A positive (or negative) PRCC value indicates a positive (or negative) correlation between the input parameter and the output variable. The results of the sensitivity analysis of parameters are shown in Figure 9.

![Figure 9](image_url)

**Figure 9.** (a) and (b) The sensitivity of the parameters changes as the dynamics of the system (2) progress. The light gray area represents PRCC values that are not statistically significant ($0 \leq |\text{PRCC}| < 0.2$). The dark gray areas represent PRCC values that are moderate correlation ($0.2 \leq |\text{PRCC}| < 0.4$).

Figure 9(a) and (b) show the sensitivity of the parameters $\beta_0$, $a_1$, $a_2$, $\beta(t)$ and $g(\Theta(t))$ from January 2014 to December 2019. It can be seen from Figure 9(a)
and (b) that the change of parameters over time affects reported new cases $P_C$ and unreported new cases $P_N$. Our results show that there is a strong negative correlation between the maximum protection rate due to ozone sterilization (e.g. $a_1$) and the number of new cases, which means that increasing the parameter $a_1$ can effectively reduce seasonal influenza transmission. The saturated function $g(\Theta(t))$ is also highly negatively correlated with the number of new cases, which means that the sterilization effect of ozone has a significant impact on seasonal influenza. In particular, the basic contact transmission rate $\beta(t)$ and the parameter $\beta_0$ are highly positively correlated with the number of new cases, which means that another way to reduce the spread of seasonal influenza is to reduce the rate of basic contact transmission.

Next, we mainly study the influence of parameters $\theta$, $p$, $\kappa$, and $\beta(t)$ on the basic reproduction number $R_0$, as shown in Figure 10.

![Figure 10](image)

**Figure 10.** Plots of the basic reproduction number $R_0$ in terms of (a) $\theta$ (the modification factor in transmission coefficient of the reported infected individuals), (b) $p$ (the proportion of those vaccinated successfully), (c) $\kappa$ (the diagnosis rate of unreported infected individuals), and (d) $\beta(t)$ (the contact transmission rate between susceptible individuals and infected individuals).

According to Figure 10(a), $R_0$ increases with the increase of parameter $\theta$, which also shows that the treatment effect of the hospital can inhibit the spread of influenza. According to Figure 10(b), it can be seen that $R_0$ decreases with the
increase of parameter $p$, $R_0 < 1$ requires that $p > 25.5\%$, which indicates that increasing vaccination rate is the direct method to prevent the transmission of influenza. According to Figure 10(c), $R_0$ decreased with the increase of parameter $\kappa$, which indicates that the CDC of Gansu Province should enhance the reporting of influenza patients. According to Figure 10(d), $R_0$ increases with the increase of the periodic parameter $\beta(t)$, which indicates that the susceptible population should avoid contact with the infected population. Moreover, if $\Delta$ is less than 0.79 times, then the basic reproduction number $R_0 < 1$, which indicates that the disease is no longer spreading.

6. Conclusion and discussion. In this paper, to study the dynamic effects of ozone concentration in the air and pulse vaccination on influenza, a non-autonomous differential equation model (2) with the effects of ozone and pulsed vaccination is proposed, which includes periodic transmission rate. First, the basic reproduction number of the impulse system is derived, and the global asymptotic stability of the disease-free periodic solution is proved. Further, the consistent persistence of the model is proved. Second, the unknown parameters of the ozone dynamics model are obtained by fitting the ozone concentration data by nonlinear least squares and Bootstrap, and the MCMC algorithm is used to fit influenza data in Gansu Province to identify the optimal parameter values of the non-autonomous differential equation model. At the same time, to determine the key parameters of the model, we carry out a sensitivity analysis of the model parameters.

The study consisted of 49142 influenza cases between January 2014 and December 2019 in Gansu Province. The annualized average incidence was 31.3374 per 100,000 people (shown in Figure 2(d)). Influenza cases started to surge in 2016, rising by a factor of one and a half between 2014 and 2016, further increasing in 2019 (54.6909 per 100,000 population) (shown in Figure 2(d)). The average incidence rate during the post-upsurge period (2017-2019) was one and a half times more than in the pre-upsurge period (2014-2016). In particular, we found that the peak ozone concentration appears 5–8 months in Gansu Province (shown in Figure 2(a)). A moderate negative correlation was seen between influenza cases and monthly ozone concentration (Pearson correlation coefficient: $r = -0.4427$)(shown in Figure 2(c)).

Through the mean value and credible intervals of the parameters in Table 3, we calculate that the basic reproduction number $R_0$ is 1.2486 (95%CI : (1.2470, 1.2501)). According to the sensitivity analysis of parameters to $R_0$, we find that the vaccination rate has a great impact on seasonal influenza in Gansu Province, and when the vaccination rate $p > 25.5\%$, the basic reproduction number is less than 1. $R_0$ increases with the increase of parameter $\theta$, and $R_0$ decreased with the increase of parameter $\kappa$. Therefore, reducing the parameter $\theta$ and increasing the parameter $\kappa$ can effectively reduce the spread of influenza. The PRCCs show that the saturated function $g(\Theta(t))$ and the basic contact transmission rate $\beta(t)$ have a very large impact on new cases ($P_{NC}$, $P_N$). Based on the analysis of the PRCCs, we identify key input variables impacting the seasonal influenza in Gansu Province, and the identification strongly support the call for an integrated strategy of seasonal influenza control, including appropriately increasing ozone concentration and reducing contacts.
Acknowledgments. The authors are very grateful to the anonymous referees for their careful reading, helpful comments and suggestions, which have helped us to improve the presentation of this work significantly.

Appendix A. Mathematical analysis of ozone model. By solving the system (1), we get that the ozone concentration function \( \Theta(t) \) is a piecewise function as follows

\[
\Theta(t) = \begin{cases} 
    e^{\int_{nT+T_1}^{t} e^{b}(c)dz} \int_{nT+T_1}^{t} (c_0 + c_1)e^{-\int_{nT+T_1}^{t} e^{b}(c)dz} d\varrho \\
    + \Theta(nT + T_1)e^{-\int_{nT+T_1}^{t} e^{b}(c)dz}, & t \in [nT + T_1, nT + T_2], n \in \mathbb{N}, \\
    e^{\int_{nT+T_2}^{t} e^{b}(c)dz} \int_{nT+T_2}^{t} (c_0 + c_1)e^{-\int_{nT+T_2}^{t} e^{b}(c)dz} d\varrho \\
    + \Theta(nT + T_2)e^{-\int_{nT+T_2}^{t} e^{b}(c)dz}, & t \in [nT + T_2, nT + T_3], n \in \mathbb{N}, \\
    e^{\int_{nT+T_3}^{t} e^{b}(c)dz} \int_{nT+T_3}^{t} (c_0 + c_1)e^{-\int_{nT+T_3}^{t} e^{b}(c)dz} d\varrho \\
    + \Theta(nT + T_3)e^{-\int_{nT+T_3}^{t} e^{b}(c)dz}, & t \in [nT + T_3, nT + T_4], n \in \mathbb{N}, \\
    e^{\int_{nT+T_4}^{t} e^{b}(c)dz} \int_{nT+T_4}^{t} (c_0 + c_1)e^{-\int_{nT+T_4}^{t} e^{b}(c)dz} d\varrho \\
    + \Theta(nT + T_4)e^{-\int_{nT+T_4}^{t} e^{b}(c)dz}, & t \in [nT + T_4, (n+1)T + T_1], n \in \mathbb{N}.
\end{cases}
\]

Thus, we have

\[
\Theta(nT + T_2) = e^{-\int_{nT+T_1}^{T_2} e^{b}(c)dz} \int_{nT+T_1}^{T_2} (c_0 + c_1)e^{-\int_{nT+T_1}^{T_2} e^{b}(c)dz} d\varrho \\
+ \Theta(nT + T_1)e^{-\int_{nT+T_1}^{T_2} e^{b}(c)dz},
\]

\[
\Theta(nT + T_3) = e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} \int_{nT+T_2}^{T_3} (c_0 + c_1)e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} d\varrho \\
+ \Theta(nT + T_2)e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} \\
= e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} \int_{nT+T_2}^{T_3} (c_0 + c_1)e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} d\varrho \\
+ \Theta(nT + T_2)e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} \\
+ \Theta(nT + T_1)e^{-\int_{nT+T_1}^{T_2} e^{b}(c)dz},
\]

\[
\Theta(nT + T_4) = e^{-\int_{nT+T_3}^{T_4} e^{b}(c)dz} \int_{nT+T_3}^{T_4} (c_0 + c_1)e^{-\int_{nT+T_3}^{T_4} e^{b}(c)dz} d\varrho \\
+ \Theta(nT + T_3)e^{-\int_{nT+T_3}^{T_4} e^{b}(c)dz} \\
+ \Theta(nT + T_2)e^{-\int_{nT+T_2}^{T_3} e^{b}(c)dz} \\
+ \Theta(nT + T_1)e^{-\int_{nT+T_1}^{T_2} e^{b}(c)dz},
\]
\[ \Theta(nT + T_4) = e^{-\int_{nT+T_4}^{nT+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_3}^{nT+T_4} (c_0 + c_1) e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta(nT + T_3)e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} \int_{nT+T_3}^{nT+T_4} (c_0 + c_1) e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} d\varrho \\
= e^{-\int_{nT+T_4}^{nT+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_3}^{nT+T_4} (c_0 + c_1) e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{nT+T_4}^{nT+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_3}^{nT+T_4} (c_0 + c_1 + c_2) e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{nT+T_4}^{nT+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_3}^{nT+T_4} (c_0 + c_1) e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta(nT + T_3)e^{-\int_{nT+T_3}^{nT+T_4} b(\varepsilon) d\varepsilon}.
\]

\[ \Theta((n+1)T + T_1) = e^{-\int_{nT+T_4}^{(n+1)T+T_4} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta(nT + T_4)e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
= e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1 + c_2) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta(nT + T_4)e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} \int_{nT+T_4}^{(n+1)T+T_3} (c_0 + c_1) e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta(nT + T_4)e^{-\int_{nT+T_4}^{(n+1)T+T_3} b(\varepsilon) d\varepsilon}.
\]

Since the function \( b(t) \) is a periodic function, we can know that \( \Theta(t) \) is periodic. Therefore, we can know that \( \Theta((n+1)T + T_1) = \Theta(nT + T_1) \). Therefore, the fixed point of the system (1) is \( \Theta^*(T_1) \), and the fixed point \( \Theta^*(T_1) \) is represented as...
follows
\[
\begin{align*}
\Theta^*(T_1) = & \int_{T_4}^{T_4 + T_1} \left( e^{-\int_{T_4}^{T_4 + T_1} b(\varepsilon) d\varepsilon} \int_{T_4}^{T_4 + T_1} c_0 e^{-\int_{T_4}^{T_4 + T_1} b(\varepsilon) d\varepsilon} d\varrho \right. \\
& + e^{-\int_{T_3}^{T_3 + T_1} b(\varepsilon) d\varepsilon} \int_{T_3}^{T_3 + T_1} (c_0 + c_1) e^{-\int_{T_3}^{T_3 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
& + e^{-\int_{T_2}^{T_2 + T_1} b(\varepsilon) d\varepsilon} \int_{T_2}^{T_2 + T_1} (c_0 + c_1 + c_2) e^{-\int_{T_2}^{T_2 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
& + e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon} \int_{T_1}^{T_1 + T_1} (c_0 + c_1) e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
& \left. + \Theta^*(T_1) e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon} \right) \\
& + \Theta^*(T_1) e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon}.
\end{align*}
\]

Then the periodic solution \( \hat{\Theta}(t) \) of the system (1) can be expressed as
\[
\hat{\Theta}(t) = e^{-\int_{T_4}^{T_4 + T_1} b(\varepsilon) d\varepsilon} \int_{T_4}^{T_4 + T_1} c_0 e^{-\int_{T_4}^{T_4 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{T_3}^{T_3 + T_1} b(\varepsilon) d\varepsilon} \int_{T_3}^{T_3 + T_1} (c_0 + c_1) e^{-\int_{T_3}^{T_3 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{T_2}^{T_2 + T_1} b(\varepsilon) d\varepsilon} \int_{T_2}^{T_2 + T_1} (c_0 + c_1 + c_2) e^{-\int_{T_2}^{T_2 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
+ e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon} \int_{T_1}^{T_1 + T_1} (c_0 + c_1) e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon} d\varrho \\
+ \Theta^*(T_1) e^{-\int_{T_1}^{T_1 + T_1} b(\varepsilon) d\varepsilon}.
\]

Appendix B. Mathematical analysis of influenza model.

B.1. Positively invariant set. It is obvious that any solution of the system (2) with non-negative initial values is non-negative. The following lemma shows that the solutions of the system (2) are uniformly ultimately bounded.

**Lemma B.1.** Define
\[
\Omega = \left\{ (S, E, I_N, I_C, R) \in \mathbb{R}_+^5 : 0 \leq S, E, I_N, I_C, R \leq N \leq \frac{\Lambda}{d} \right\}.
\]

*The trajectories of the system (2) are uniformly, ultimately bounded and the set \( \Omega \) is a positive invariant set.*

**Proof.** From the system (2), we can obtain the following system
\[
\frac{dN}{dt} = \Lambda - dN. \tag{B.6}
\]

Through the system (B.6), we can obtain the following inequality
\[
0 \leq N(t) = \frac{\Lambda}{d} + (N(0) - \frac{\Lambda}{d}) e^{-dt} \leq \frac{\Lambda}{d} + N(0) e^{-dt}.
\]

Hence, we obtain \( 0 \leq \lim_{t \to \infty} \sup N(t) \leq \frac{\Lambda}{d} \).

In conclusion, the solutions of the system (2) are uniformly and ultimately bounded. This completes the proof. \( \square \)
B.2. Existence of disease-free periodic solution. In this subsection, we prove the existence of disease-free periodic solutions of the system (2). Let’s assume that \( E(t) = 0, I_N(t) = 0, I_C(t) = 0, t \geq 0 \). We consider the following subsystems

\[
\begin{aligned}
\frac{dS}{dt} &= \Lambda + qR - dS, \\
\frac{dR}{dt} &= -qR - dR,
\end{aligned}
\]

\( t \neq nT, n \in \mathbb{N} \), \( t = nT, n \in \mathbb{N} \).

**(B.7)**

For simplicity, we consider the following equivalent system

\[
\begin{aligned}
\frac{dN}{dt} &= \Lambda - dN, \\
\frac{dR}{dt} &= -qR - dR,
\end{aligned}
\]

\( t \neq nT, n \in \mathbb{N} \),

\[
\begin{aligned}
N(nT^+) &= N(nT), \\
R(nT^+) &= R(nT) + p(N(nT) - R(nT)).
\end{aligned}
\]

\( t = nT, n \in \mathbb{N} \).

**(B.8)**

Through the constant mutation method, the solutions \( N(t) \) and \( R(t) \) of the system (B.8) are obtained on the interval \((nT, (n+1)T]\), that is, \( N(t) \) and \( R(t) \) can be expressed as

\[
\begin{aligned}
N(t) &= \frac{\Lambda}{d} + (N(nT^+) - \frac{\Lambda}{d})e^{-d(t-nT)}, \\
R(t) &= R(nT^+)e^{-(q+d)(t-nT)},
\end{aligned}
\]

then

\[
\begin{aligned}
N((n+1)T) &= \frac{\Lambda}{d} + (N(nT^+) - \frac{\Lambda}{d})e^{-dT}, \\
R((n+1)T) &= R(nT^+)e^{-(q+d)T}.
\end{aligned}
\]

From the last two equations of the system (B.8), the stroboscopic map is derived as

\[
\begin{aligned}
N((n+1)T^+) &= \frac{\Lambda}{d} + (N(nT^+) - \frac{\Lambda}{d})e^{-dT}, \\
R((n+1)T^+) &= (1-p)R(nT^+)e^{-(q+d)T} + p\left(\frac{\Lambda}{d} + (N(nT^+) - \frac{\Lambda}{d})e^{-dT}\right).
\end{aligned}
\]

**(B.9)**

The fixed points \( N^* \) and \( R^* \) can be obtained through the system (B.9), that is, \( N^* \) and \( R^* \) can be expressed as follows

\[
\begin{aligned}
N^* &= \frac{\Lambda}{d}, \\
R^* &= \frac{p\Lambda}{d(1 - (1-p)e^{-(q+d)T})}.
\end{aligned}
\]

The Jacobian matrix of the system (B.9) can be expressed as

\[
\begin{pmatrix}
e^{-dT} & 0 \\
pe^{-dT} & (1-p)e^{-(q+d)T}
\end{pmatrix}.
\]

The eigenvalues of the Jacobian matrix are \( e^{-dT} \) and \( (1-p)e^{-(q+d)T} \). Since the modulus of the eigenvalues is \(||e^{-dT}|| < 1\) and \(||(1-p)e^{-(q+d)T}|| < 1\). Therefore,
The fixed points $N^*$ and $R^*$ are locally stable. Then the solution of the system (B.8) with fixed points $N^*$ and $R^*$ as initial values on the interval $(nT, (n + 1)T]$ is

$$
\hat{N}(t) = \frac{\Lambda}{d}, \quad \hat{R}(t) = R^*e^{-(q + d)(t-nT)} = \frac{p\Lambda e^{-(q + d)(t-nT)}}{d(1 - \frac{p}{1 - p}e^{-(q + d)T})}.
$$

$\hat{S}(t)$ can be expressed as

$$
\hat{S}(t) = \hat{N}(t) - \hat{R}(t) = \frac{\Lambda}{d} \left(1 - \frac{p}{1 - p}e^{-(q + d)T}\right).
$$

Since $\hat{S}(t)$ and $\hat{R}(t)$ are periodic, we know that $\hat{S}(t) = \hat{S}(t + T)$ and $\hat{R}(t) = \hat{R}(t + T)$.

Proof of global asymptotic stability of periodic solution $(\hat{S}(t), \hat{R}(t))$ of the system (B.7) (see paper of Wang et al.(2019) [43]). According to the above discussion, the disease-free periodic solution of the system (2) on each pulse interval $(nT, (n + 1)T]$ is $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$.

**B.3. The basic reproduction number for the pulse system.** In this subsection, according to the theory in paper of Yang and Xiao (2010) [48], we define basic reproduction number of the system (2). We linearize the system (2) at the disease-free periodic solution $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$ as follows

$$
\begin{align*}
\frac{dE}{dt} &= G(t)\hat{S}(t)(\theta I_C + I_N) - \sigma E - dE, \\
\frac{dI_N}{dt} &= (1 - \delta)\sigma E - \gamma_2 I_N - dI_N - \kappa I_N, \\
\frac{dI_C}{dt} &= \delta \sigma E - \gamma_1 I_C - dI_C + \kappa I_N.
\end{align*}
$$

(B.10)

Let $x = (E, I_N, I_C)^T$, the system (B.10) can be written as

$$
\frac{dx(t)}{dt} = F(t, x) - V(t, x),
$$

where

$$
F(t, x) = \begin{bmatrix} G(t)\hat{S}(t)(\theta I_C + I_N) \\ 0 \\ 0 \end{bmatrix}, \quad V(t, x) = \begin{bmatrix} (\sigma + d)E \\ -(1 - \delta)\sigma E + (\gamma_2 + d + \kappa)I_N \\ -\delta \sigma E + (\gamma_1 + d)I_C - \kappa I_N \end{bmatrix}.
$$

Then the Jacobian matrix of $F(t, x)$ at the disease-free period solution $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$ is

$$
F(t) = \begin{bmatrix} 0 & G(t)\hat{S}(t) & G(t)\theta \hat{S}(t) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},
$$

(B.11)

the Jacobian matrix of $V(t, x)$ at the disease-free period solution $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$ is

$$
V(t) = \begin{bmatrix} \sigma + d & 0 & 0 \\ -(1 - \delta)\sigma & \gamma_2 + d + \kappa & 0 \\ -\delta \sigma & -\kappa & \gamma_1 + d \end{bmatrix}.
$$

(B.12)

It is very clear that $F(t)$ is non-negative, and $-V(t)$ is cooperative in the sense that the off-diagonal elements of $-V(t)$ are non-negative. It is very clear that the conditions $(H_1)$-$(H_6)$ of the theory proposed by Yang and Xiao (2010) [48] are satisfied.
Let $Y(t, s), t \geq s$, be the evolution operator of the linear $T$-periodic system

$$ \frac{dy}{dt} = -V(t)y. $$

That is, for each $s \in \mathbb{R}$, the $3 \times 3$ matrix $Y(t, s)$ satisfies

$$ \frac{dY(t, s)}{dt} = -V(t)Y(t, s), \ \forall t \geq s, \ Y(s, s) = I, $$

where $I$ is the $3 \times 3$ identity matrix.

According to the paper of Yang and Xiao (2010) [48], let $C_T$ be the ordered Banach space of all $T$-period functions from $\mathbb{R}$ to $\mathbb{R}^3$, where the maximum norm is $\| \cdot \|$ and the positive cone is $C_T^+ := \{ \phi \in C_T : \phi(t) \geq 0, \forall t \in \mathbb{R} \}$. Suppose $\phi(s)$ represents the initial distribution of infected individuals in the periodic environment. Since $F(t)$ has one discontinuous point $t = nT$ on each pulse interval $[nT, (n+1)T]$, then $Y(t, s)F(s)\phi(s)$ has finite discontinuous points on the interval $[a, t]$. According to the boundedness of $F(s)\phi(s)$, the integral $\int_a^t Y(t, s)F(s)\phi(s)ds$ can be defined. Therefore, the linear operator $L : C_T \rightarrow C_T$ can be defined as follows

$$(L\phi)(t) = \lim_{a \to -\infty} \int_a^t Y(t, s)F(s)\phi(s)ds, \ \forall t \in (nT, (n+1)T], n \in \mathbb{N}, \ \phi \in C_T, \ (B.13)$$

where $L$ is called the next-generation infection operator, and the spectral radius of $L$ is defined as the basic reproduction number $R_0$. Therefore, the basic reproduction number $R_0$ of the system (2) can be expressed as follows

$$R_0 := \rho(L). \quad (B.14)$$

In order to calculate the basic reproduction number $R_0$ of the system (2), a linear $T$-period system is introduced as follows

$$\frac{d\omega}{dt} = \left[ -V(t) + \frac{F(t)}{\lambda} \right] \omega, \ t \in \mathbb{R}, \quad (B.15)$$

where parameter $\lambda \in (0, \infty)$. Then, let the evolution operator of the system (B.15) on $\mathbb{R}^3$ be $W(t, s, \lambda), \ t \geq s, \ s \in \mathbb{R}$, where

$$-V(t) + \frac{F(t)}{\lambda} = \begin{bmatrix}
-\sigma + d & \frac{G(t)\delta(t)}{\lambda} & \frac{G(t)\theta(t)\delta(t)}{\lambda} \\
\delta\sigma & -(\gamma_2 + d + \kappa) & 0 \\
\frac{G(t)\theta(t)}{\lambda} & \kappa & -(\gamma_1 + d)
\end{bmatrix}. $$

Lemma B.2. (see Theorem 2.2 in Yang and Xiao (2010) [48]). If the condition $(H_1)$-$ (H_5)$ is established, then the following statements are valid:

1. $R_0 = 1$ if and only if $\rho(\Phi_{F-V}(T)) = 1$.
2. $R_0 > 1$ if and only if $\rho(\Phi_{F-V}(T)) > 1$.
3. $R_0 < 1$ if and only if $\rho(\Phi_{F-V}(T)) < 1$.

B.4. Extinction of the disease. Let $(\mathbb{R}^n, \mathbb{R}^n_+)$ be the standard $n$-dimensional Euclidean space. For $u, v \in \mathbb{R}^n$, if $u - v \in \mathbb{R}^n_+$, then $u \geq v$; if $u - v \in \mathbb{R}^n_+ \setminus \{0\}$, then $u > v$; if $u - v \in \text{Int}(\mathbb{R}^n_+)$, then $u \gg v$.

Let $A(t)$ be a continuous, cooperative and irreducible $n \times n$ matrix function of the $T$-period, and $\Phi_A(t)$ is the fundamental solution matrix of the following system

$$\frac{dx(t)}{dt} = A(t)x(t).$$

Let $\rho(\Phi_A(T))$ be the spectral radius of $\Phi_A(T)$. Thus each element of matrix $\Phi_A(T)$ is positive at $T > 0$ [2, 19]. Through Perron-Frobenius theorem [39], $\rho(\Phi_A(T))$
is the principal eigenvalue of $\Phi_A(T)$ in the sense that it is simple and admits an eigenvector $v^* \gg 0$. Therefore, we have a conclusion as follows

**Lemma B.3.** (see Zhang and Zhao (2007) [50].) Let $p = \frac{1}{T} \ln \rho(\Phi_A(T))$. Then there exists a positive $T$-periodic function $v(t)$ such that $e^{pt}v(t)$ is a solution of $\frac{dv(t)}{dt} = A(t)x(t)$.

In order to prove the global asymptotic stability of the disease-free periodic solution of the system (2), we assume $q = 0$ and we introduce the following theorem.

**Theorem B.4.** When $R_0 < 1$, disease-free periodic solution $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$ of the system (2) is globally asymptotically stable. When $R_0 > 1$, disease-free periodic solution $P_0 = (\hat{S}(t), 0, 0, 0, \hat{R}(t))$ of the system (2) is unstable.

**Proof.** First, we prove the local stability of the disease-free periodic solution $P_0$ of the system (2). Let $S(t) = s(t) + \hat{S}(t)$, $E(t) = e(t)$, $I_N(t) = i_N(t)$, $I_C(t) = i_C(t)$, and $R(t) = r(t) + \hat{R}(t)$. The system (2) can be expanded in a Taylor series, and the higher order terms are omitted, the following linear system can be obtained.

\[
\begin{aligned}
\frac{dZ}{dt} &= J(t)Z(t), \quad t \neq nT, n \in \mathbb{N}, \\
Z(nT^+) &= QZ(nT), \quad t = nT, n \in \mathbb{N},
\end{aligned}
\]

where $Z(t) = (s(t), e(t), i_N(t), i_C(t), r(t))$. The expressions of $J(t)$ and $Q$ are as follows

\[
J(t) = \begin{bmatrix}
-d & 0 & -G(t)\hat{S}(t) & -G(t)\theta\hat{S}(t) & 0 \\
0 & -(\sigma + d) & G(t)\hat{S}(t) & G(t)\theta\hat{S}(t) & 0 \\
0 & (1 - \delta)\sigma & -(\gamma_2 + d + \kappa) & 0 & 0 \\
0 & \delta\sigma & \gamma_2 & -\gamma_1 & -d \\
(1 - p) & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
p & 0 & 0 & 0 & 1
\end{bmatrix},
\]

\[
Q = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}.
\]

To simplify the above formula, $J(t)$ and $Q$ are re-expressed as

\[
J(t) = \begin{bmatrix}
-d & A_{12} & 0 \\
A_{21} & F(t) - V(t) & A_{23} \\
0 & A_{32} & -d
\end{bmatrix}, \quad Q = \begin{bmatrix}
(1 - p) & B_{12} & 0 \\
B_{21} & E & B_{23} \\
p & B_{32} & 1
\end{bmatrix},
\]

where $A_{12} = (0 \quad -G(t)\hat{S} - G(t)\theta\hat{S})$, $A_{21} = B_{21} = B_{12}^T$, $A_{23} = B_{23} = B_{32} = (0 \quad 0 \quad \gamma_2 \quad \gamma_1)^T$, $A_{32} = (0 \quad \gamma_2 \quad \gamma_1)$, $E$ represents the $3 \times 3$ identity matrix, $T$ represents the transposition of the vector.

Let $\Phi(t)$ be the fundamental matrix of the system $\frac{dz}{dt} = J(t)Z(t)$, then $\Phi(t) = (\phi_{ij}(t))_{1 \leq i, j \leq 3}$ and $\phi_{ij}$, $\phi_{2j}$, $\phi_{3j}$, $j = 1, 2, 3$ are solution of system $\frac{dz}{dt} = J(t)Z(t)$ with initial values $\phi_{11} = 1$, $\phi_{22} = E_{3 \times 3}$, $\phi_{33} = 1$ and $\phi_{ij} = 0$, $(i \neq j, i, j = 1, 2, 3)$. Therefore, we can obtain $\phi_{11} = e^{-dt}$, $\phi_{12} = A_{12}\phi_{12}$, $\phi_{13} = 0$, $\phi_{21} = (0 \quad 0 \quad 0)^T$, $\phi_{22} = (F(t) - V(t))\phi_{22}$, $\phi_{23} = (0 \quad 0 \quad 0)^T$, $\phi_{31} = 0$, $\phi_{32} = A_{32}\phi_{32}$, $\phi_{33} = e^{-dt}$.

We use $\phi_{22} = \Phi_{F-V}(t)$ to represent $\phi_{22}$, because the following analysis does not
require the \( \phi_{12} \) and \( \phi_{32} \) specific expression, we use \( * \) to represent \( \phi_{12} \) and \( \phi_{32} \). Then, we can obtain

\[
\Phi(t) = \begin{bmatrix}
e^{-dt} & \phi_{13} \\
\phi_{21} & \Phi_{F-V}(t) & \phi_{23} \\
\phi_{31} & * & \phi_{33}
\end{bmatrix},
\]

Then, the monodromy matrix of the system \((B.16)\) is

\[
Q\Phi(T) = \begin{bmatrix}
(1-p)e^{-dT} & * & 0 \\
0 & 0 & 0 \\
0 & \Phi_{F-V}(T) & 0 \\
e^{-dT} & * & 0
\end{bmatrix}.
\]

According to Floquet theory [24, 3], the sufficient prerequisite for the stability of the disease-free periodic solution is that the modulus of the eigenvalue of matrix \(Q\Phi(T)\) is less than 1. Therefore, when \( \rho(\Phi_{F-V}(T)) < 1 \) (i.e., \( R_0 < 1 \)), the disease-free periodic solution \( P_0 \) is locally stable.

Then, in order to prove the global asymptotic stability of the disease-free periodic solution \( P_0 \), we only need to prove that when \( \rho(\Phi_{F-V}(T)) < 1 \) (i.e., \( R_0 < 1 \)), the system \((2)\) is globally uniformly attractive.

Through the first equation of the system \((2)\), we can obtain

\[
\frac{dS}{dt} \leq \Lambda - dS, \quad t \neq nT, n \in \mathbb{N},
\]

\[
S(nT^+) = (1-p)S(nT), \quad t = nT, n \in \mathbb{N}.
\]

By solving the system \((B.17)\), we have

\[
S(t) \leq \frac{\Lambda}{d} \left( 1 - \frac{pe^{-d(t-nT)}}{1-(1-p)e^{-dT}} \right) = \hat{S}(t).
\]

Therefore, there exists \( \bar{t} > 0 \), such that for \( \forall \epsilon_1 > 0 \), \( S(t) \leq \hat{S}(t) + \epsilon_1 \).

Through the system \((2)\), we have

\[
\begin{align*}
\frac{dE}{dt} & \leq G(t)(\hat{S}(t) + \epsilon_1)(\theta I_C + I_N) - \sigma E - dE, \\
\frac{dI_N}{dt} & = (1-\delta)\sigma E - \gamma_2 I_N - dI_N - \kappa I_N, \quad t \geq \bar{t}, \\
\frac{dI_C}{dt} & = \delta \sigma E - \gamma_1 I_C - dI_C + \kappa I_N,
\end{align*}
\]

We consider the following comparison system

\[
\begin{align*}
\frac{dE}{dt} & = G(t)(\hat{S}(t) + \epsilon_1)(\theta \bar{I}_C + \bar{I}_N) - \sigma E - dE, \\
\frac{dI_N}{dt} & = (1-\delta)\sigma E - \gamma_2 \bar{I}_N - dI_N - \kappa \bar{I}_N, \quad t \geq \bar{t}, \\
\frac{dI_C}{dt} & = \delta \sigma E - \gamma_1 \bar{I}_C - d\bar{I}_C + \kappa \bar{I}_N,
\end{align*}
\]

Let \( x_1 = (E, I_N, I_C)^T \), the system \((B.19)\) is equivalent to the following equation

\[
x_1' = (F(t) - V(t) + \epsilon_1 m_1(t))x_1,
\]
According to Lemma B.3, we know that there is a positive $T$-periodic function $\tilde{v}(T)$ such that $e^{\tilde{p}} \tilde{v}(T)$ is a solution of system (B.19), where $\tilde{v}(t) = (\tilde{v}_1(t), \tilde{v}_2(t), \tilde{v}_3(t))$ and $\tilde{p} = \frac{1}{T} \ln \rho(\Phi_{F-V+\epsilon_1m_1}(T))$. Next, we choose $\bar{t} > \bar{t}$ and all small $\varsigma > 0$ to make the inequality as follows

$$E(\bar{t}) \leq \varsigma \tilde{v}_1(0), \quad \bar{I}_N(\bar{t}) \leq \varsigma \tilde{v}_2(0), \quad \bar{I}_C(\bar{t}) \leq \varsigma \tilde{v}_3(0),$$

then,

$$E(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_1(t - \bar{t}), \quad \bar{I}_N(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_2(t - \bar{t}), \quad \bar{I}_C(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_3(t - \bar{t}), \quad t \geq \bar{t}.$$

According to the standard comparison principle, we can obtain the following inequality

$$E(t) \leq \bar{E}(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_1(t - \bar{t}), \quad \bar{I}_N(t) \leq \bar{I}_N(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_2(t - \bar{t}), \quad \bar{I}_C(t) \leq \bar{I}_C(t) \leq \varsigma e^{\tilde{p}(t-\bar{t})} \tilde{v}_3(t - \bar{t}), \quad t \geq \bar{t}.$$

From Lemma B.2 we know that $R_0 < 1$ if and only if $\rho(\Phi_{F-V}(T)) < 1$. Since $\rho(\Phi_{F-V+\epsilon_1m}(T))$ is continuous for all small $\epsilon_1 > 0$, we can choose small enough $\epsilon_1 > 0$ such that $\rho(\Phi_{F-V+\epsilon_1m}(T)) < 1$. Therefore, we obtain $\tilde{p} < 0$. This means that the following limits are satisfied.

$$\lim_{t \to \infty} E(t) = 0, \quad \lim_{t \to \infty} \bar{I}_N(t) = 0, \quad \lim_{t \to \infty} \bar{I}_C(t) = 0.$$

For the first and fifth equations of the system (2), we can easily prove that $\lim_{t \to \infty} S(t) = \hat{S}(t)$, and $\lim_{t \to \infty} R(t) = \hat{R}(t)$. Hence, when $R_0 < 1$, the disease-free periodic solution $P_0$ of the system (2) is globally asymptotically stable.

We provide some numerical simulations to support the theoretical results of our model. The parameters of the system (2) are fixed as $\beta(t) = 1.55 \times 10^{-7}(1 + 0.2136 \sin(\frac{2\pi t}{3} + 2.5287)), a_1 = 0.1013, a_2 = 4.4024, \delta = 0.04211, \kappa = 0.09102, \theta = 0.3184, \lambda = 26266, d = 1/\sqrt{73 \times 12}, \sigma = 30/4, \gamma_1 = 30/7, \gamma_2 = 30/10, q = 30/365, p = 2/100$. The initial values of the system (2) is $(S(0), E(0), I_N(0), I_C(0), R(0)) = (18403500, 1484, 3232, 1091, 9001)$. We calculate that $R_0 = 0.9891 < 1$. Therefore, the global stability of the disease-free periodic solution $P_0$ of the system (2) can be obtained, as shown in Figure B.11.

**B.5. Uniform persistence of the disease.** In this subsection, we demonstrate the uniform persistence of system (2). First, we introduce the following theorem.

**Theorem B.5.** If $R_0 > 1$, then there is a positive constant $\chi > 0$ such that for all initial value condition $(S(0), E(0), I_N(0), I_C(0), R(0)) \in \mathbb{R}_+ \times \text{Int}(\mathbb{R}_+^5) \times \mathbb{R}_+$ the solution of system (2) satisfies

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

**Proof.** For some positive constant $\nu$, we first prove the following conclusion

$$\lim_{t \to \infty} \sup E(t) \geq \nu, \quad \lim_{t \to \infty} \sup I_N(t) \geq \nu, \quad \lim_{t \to \infty} \sup I_C(t) \geq \nu. \quad (B.20)$$
Assuming that the Eq. (B.20) does not hold, then there exist a $t_1 > 0$ such that $E(t) < \nu$, $I_N(t) < \nu$, $I_C(t) < \nu$. Therefore, without loss of generality, suppose $I_C(t) < \nu$ ($t \geq t_1$). According to the system (2), we have

\[
\begin{align*}
\frac{dS}{dt} &\geq \Lambda - G(t)S(\theta \nu + \frac{\Lambda}{d}) - dS, \\
\frac{dR}{dt} &\geq -dR, \\
S(nT^+) &\equiv (1-p)S(nT), \\
R(nT^+) &\equiv R(nT) + pS(nT).
\end{align*}
\]

Consider the following auxiliary system

\[
\begin{align*}
\frac{dx}{dt} &\equiv \Lambda - G(t)x(\theta \nu + \frac{\Lambda}{d}) - dx, \\
\frac{dy}{dt} &\equiv -dy, \\
x(nT^+) &\equiv (1-p)x(nT), \\
y(nT^+) &\equiv y(nT) + px(nT).
\end{align*}
\] (B.21)

By solving the system (B.21), we can obtain that the system (B.21) has a positive periodic solution as

\[
\hat{x}(t) = e^{-\int_{nT}^{t} [G(\tau_1)(\theta \nu + \frac{\Lambda}{d}) + d] d\tau_1} \left[ \int_{nT}^{t} \Lambda e^{\int_{nT}^{\tau_1} [G(\tau_2)(\theta \nu + \frac{\Lambda}{d}) + d] d\tau_2} d\tau_2 + x^{*} \right].
\]
where $x^* = \frac{(1-p)e^{-\rho(\frac{n+1}{T})}f_{G(G(t))}^{(n+1)T} + \delta d_{m1} d_{m2}}{1 - (1-p)e^{-\rho(\frac{n+1}{T})}f_{G(G(t))}^{(n+1)T} + \delta d_{m1} d_{m2}}$. According to the comparison theorem, we can obtain that $S(t) \geq x(t)$. Hence, there exists $t_2 \geq t_1$ such that for any $\epsilon > 0$, $S(t) \geq \hat{x}(t) - \epsilon$. Since $\hat{x}(t) \geq \hat{S}(t)$, it follows that $S(t) \geq \hat{S}(t) - \epsilon$.

Through the system (2), we can obtain

\[
\begin{align*}
\frac{dE}{dt} &\geq G(t)(\hat{S}(t) - \epsilon_2)(\delta I_C + I_N) - \sigma E - dE, \\
\frac{dI_N}{dt} & = (1 - \delta)\sigma E - \gamma_2 I_N - dI_N - \kappa I_N, \\
\frac{dI_C}{dt} & = \delta \sigma E - \gamma_1 I_C - dI_C + \kappa I_N,
\end{align*}
\]

Consider the following auxiliary system

\[
\begin{align*}
\frac{d\hat{E}}{dt} & = G(t)(\hat{S}(t) - \epsilon_2)(\delta \hat{I}_C + \hat{I}_N) - \sigma \hat{E} - d\hat{E}, \\
\frac{d\hat{I}_N}{dt} & = (1 - \delta)\sigma \hat{E} - \gamma_2 \hat{I}_N - d\hat{I}_N - \kappa \hat{I}_N, \\
\frac{d\hat{I}_C}{dt} & = \delta \sigma \hat{E} - \gamma_1 \hat{I}_C - d\hat{I}_C + \kappa \hat{I}_N,
\end{align*}
\]

Let $x_2 = (\hat{E}, \hat{I}_N, \hat{I}_C)^T$, the system (B.23) is equivalent to the following equation

\[
x'_2 = (F(t) - V(t) - \epsilon_2 m_2(t))x_2,
\]

where

\[
m_2(t) = \begin{bmatrix} 0 & G(t) & G(t) \theta \\ 0 & 0 & 0 \end{bmatrix}.
\]

According to Lemma B.3, we know that there is a positive $T$-periodic function $\hat{v}(T)$ such that $e^{\hat{v}(T)}$ is a solution of system (B.23), where $\hat{v}(t) = (\hat{v}_1(t), \hat{v}_2(t), \hat{v}_3(t))$ and $\hat{p} = \frac{1}{T} \ln \rho(\Phi_{F-V-\epsilon_2 m_2}(T))$. Next, we choose $t_3 \geq t_2$ and all small $\xi > 0$ to make the inequality as follows

\[
\hat{E}(t_3) \geq \xi \hat{v}_1(0), \quad \hat{I}_N(t_3) \geq \xi \hat{v}_2(0), \quad \hat{I}_C(t_3) \geq \xi \hat{v}_3(0),
\]

then

\[
\hat{E}(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_1(t-t_3), \quad \hat{I}_N(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_2(t-t_3),
\]

\[
\hat{I}_C(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_3(t-t_3), \quad t \geq t_3.
\]

According to the standard comparison principle, we can obtain the following inequality

\[
E(t) \geq \hat{E}(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_1(t-t_3), \quad I_N(t) \geq \hat{I}_N(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_2(t-t_3),
\]

\[
I_C(t) \geq \hat{I}_C(t) \geq \xi e^{\hat{p}(t-t_3)} \hat{v}_3(t-t_3), \quad t \geq t_3.
\]

From Lemma B.2 we know that $R_0 > 1$ if and only if $\rho(\Phi_{F-V-\epsilon_2 m_2}(T)) > 1$. Since $\rho(\Phi_{F-V-\epsilon_2 m_2}(T))$ is continuous for all small $\epsilon_2$, we can choose small enough $\epsilon_2 > 0$.
such that $\rho(\Phi_{F_{\nu}} - \varepsilon_2 m_2(T)) > 1$. Therefore, we obtain $\tilde{p} > 0$. This means that the following limits are satisfied.

$$
\lim_{t \to \infty} E(t) = \infty, \quad \lim_{t \to \infty} I_N(t) = \infty, \quad \lim_{t \to \infty} I_C(t) = \infty,
$$

which contradicts with the boundedness of $E(t)$, $I_N(t)$, and $I_C(t)$. Therefore, the conclusion

$$
\lim_{t \to \infty} \sup_{I_N(t)} \geq \nu, \quad \lim_{t \to \infty} \sup_{I_N(t)} \geq \nu, \quad \lim_{t \to \infty} \sup_{I_C(t)} \geq \nu,
$$

holds.

From the claim, we discuss the following two situations:

(i) $E(t) \geq \nu$, $I_N(t) \geq \nu$, and $I_C(t) \geq \nu$ for all large $t$;

(ii) $E(t)$, $I_N(t)$, and $I_C(t)$ oscillates about $\nu$ for all large $t$.

If (i) holds, then the above conclusion holds. Next, we consider (ii). Since $E(t)$, $I_N(t)$, and $I_C(t)$ have the same conclusion, thus we only discuss $I_N(t)$. First, let $\dot{t}$ and $\dot{i}$ is large enough such that

$$
I_N(\dot{t}) = I_N(\dot{i}) = \nu, \quad I_N(t) < \nu, \quad t \in (\dot{t}, \dot{i}).
$$

Since $I_N(t)$ is continuous and bounded and is not affected by pulses, we know that $I_N(t)$ is uniformly continuous. Therefore, there exists a constant $\varpi$ that does not depend on $\dot{t}$ such that $I_N(t) \geq \nu/2$, $(\forall t \in [\dot{t}, \dot{t} + \varpi])$. When $\dot{i} - \dot{t} \leq \varpi$, then $I_N(t) \geq \nu/2$, $(\forall t \in [\dot{t}, \dot{i}])$, we just need to make $\chi = \nu/2$. When $\dot{i} - \dot{t} > \varpi$, then $I_N(t) \geq \nu/2$, $(\forall t \in [\dot{t}, \dot{t} + \varpi])$.

Next, we prove that $I_N(t) \geq \nu/2$, $(\forall t \in [\dot{t} + \varpi; \dot{i}])$ holds. Suppose not, then there exist a $\varpi_1$ such that

$$
I_N(t) \geq \nu/2, \quad \forall t \in [\dot{t}, \dot{t} + \varpi + \varpi_1],
$$

and

$$
I_N(\dot{t} + \varpi + \varpi_1) = \nu/2, \quad I_N(t) < \nu/2, \quad 0 < t - (\dot{t} + \varpi + \varpi_1) \ll 1.
$$

Similarly, we can also obtain

$$
E(t) < \nu/2, \quad I_C(t) < \nu/2, \quad 0 < t - (\dot{t} + \varpi + \varpi_1) \ll 1.
$$

In addition, from the previous proof, we know that $S(t) \geq \tilde{S}(t) - \varepsilon_2$, $(\forall t \in [\dot{t}, \dot{i}]$.

Through the system (2), we have

$$
\begin{align*}
\frac{dE}{dt} & \geq G(t)(\tilde{S}(t) - \varepsilon_2)(\theta I_C + I_N) - \sigma E - dE, \\
\frac{dI_N}{dt} & = (1 - \delta)\sigma E - \gamma_2 I_N - dI_N - \kappa I_N, \\
\frac{dI_C}{dt} & = \delta \sigma E - \gamma_1 I_C - dI_C + \kappa I_N,
\end{align*}
$$

$0 < t - (\dot{t} + \varpi + \varpi_1) \ll 1. \quad (B.24)$

Let $x_3 = (E, I_N, I_C)^T$, the system (B.24) is equivalent to the following equation

$$
x_3' \geq (F(t) - V(t) - \varepsilon_2 m_2(t))x_3, \quad 0 < t - (\dot{t} + \varpi + \varpi_1) \ll 1.
$$

By previous arguments, we know that there is a positive $T$-periodic function $\tilde{v}(T)$ such that $e^{\tilde{v}(T)}$ is a solution of system (B.23), where $\tilde{v}(t) = (\tilde{v}_1(t), \tilde{v}_2(t), \tilde{v}_3(t))$ and $\tilde{p} = \frac{1}{T} \ln \rho(\Phi_{F_{\nu}} - \varepsilon_2 m_2(T)) > 0$. Next, We can choose a proper $\psi > 0$, such that

$$
E(\dot{t} + \varpi + \varpi_1) \geq \psi \tilde{v}_1(0) \geq \nu/2, \quad I_N(\dot{t} + \varpi + \varpi_1) \geq \psi \tilde{v}_2(0) \geq \nu/2,
$$

$$
I_C(\dot{t} + \varpi + \varpi_1) \geq \psi \tilde{v}_3(0) \geq \nu/2.
$$
Since $\dot{v}(t)$ is a continuous and periodic function, therefore, $\psi\dot{v}(t) \geq \nu/2$ for $0 < t < 1$ holds. According to the standard comparison principle, for $0 < t \leq (\dot{i} + \omega + \omega_1) \ll 1$, we can obtain the following inequality

$$E(t) \geq \psi e^{\dot{v}(t-i-\omega-\omega_1)} \dot{v}_1(t-i-\omega-\omega_1) > \psi \dot{v}_1(t-i-\omega-\omega_1) \geq \nu/2,$$

$$I_N(t) \geq \psi e^{\dot{v}(t-i-\omega-\omega_1)} \dot{v}_2(t-i-\omega-\omega_1) > \psi \dot{v}_2(t-i-\omega-\omega_1) \geq \nu/2,$$

$$I_C(t) \geq \psi e^{\dot{v}(t-i-\omega-\omega_1)} \dot{v}_3(t-i-\omega-\omega_1) > \psi \dot{v}_3(t-i-\omega-\omega_1) \geq \nu/2,$$

which contradicts the assumption $I_N(\dot{i} + \omega + \omega_1) = \nu/2$, $I_N(t) < \nu/2$, $0 < t - (\dot{i} + \omega + \omega_1) \ll 1$. Therefore, $E(t) \geq \nu/2$, $I_N(t) \geq \nu/2$, and $I_C(t) \geq \nu/2$ for any $t \in [\dot{i}, \dot{t}]$ holds. We only need to define $\nu/2 = \chi$, since $\dot{i}$ and $\dot{t}$ are large enough. Hence, we have

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

To verify the uniform persistence of the system (2). The parameters of the system (2) are fixed as $\beta(t) = 1.936 \times 10^{-7}(1 + 0.2386 \sin(\frac{\pi}{150} t + 2.5287))$, $a_1 = 0.1013$, $a_2 = 4.4024$, $\delta = 0.04211$, $\kappa = 0.09102$, $\theta = 0.3184$, $\Lambda = 26266$, $d = 1/(73 \times 12)$, $\sigma = 30/4$, $\gamma_1 = 30/7$, $\gamma_2 = 30/10$, $q = 30/365$, $p = 2/100$. The initial values of the system (2) is $(S(0), E(0), I_N(0), I_C(0), R(0)) = (18403500, 1484, 3232, 1091, 9001)$. We calculate that $R_0 = 1.2354 > 1$. Therefore, we can obtain that the system (2) is uniform persistence, as shown in Figure B.12.
Appendix C. Daily ozone concentration data. Daily ozone concentration data in Jiayuguan (2014-2020), Lanzhou (2014-2020), Jinchuan (2014-2020), Qingyang (2015-2020), Tianshui (2015-2020), Baiyin (2015-2020), Wuwei (2015-2020), Zhangye (2015-2020), Jiuquan (2015-2020), Pingliang (2015-2020), Dingxi (2015-2020), Longnan (2015-2020), Linxia (2015-2020), and Gannan (2015-2020).

Appendix D. Posterior distribution and traces of parameters. The posterior distribution and trace plots of parameter values for the system (2), estimated by Bayesian Markov Chain Monte Carlo (MCMC) methods.
Figure D.14. Posterior distribution of unknown parameters of the system (2).

Figure D.15. Traces of the unknown parameter values as obtained by the MCMC sampling for 100,000 iteration numbers for the system (2). The blue dots indicate the parameter value within the 95\% credible intervals, the red pluses indicate the parameter value outside the 95\% credible intervals, and the black lines indicate the upper and lower credible limits.
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