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Optimal control of an influenza model incorporating pharmacological and non-pharmacological interventions

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Abstract

The burden of influenza virus infection poses a challenge due to its significant negative impact on public health. The implementation of intervention measures including vaccination, treatment, and isolation can help alleviate this influence. In this paper, we consider an optimal control problem with both pharmacological and non-pharmacological interventions, which involves widely concerned issues such as the decline of vaccine-based immunity and the emergence of drug resistance. We prove the existence of the optimal control, solve the optimal control problem through applying the Pontryagin's maximum principle, and conduct some numerical experiments to seek out effective prevention and control strategies. We arrive at a conclusion that the best strategy to control the outbreak of influenza is to isolate infected individuals as soon as possible when medical resources are abundant, such as staying at home, avoiding crowded places and so on. Epidemiologically, we find that reducing the waning rate of vaccine-based immunity is also an effective strategy when there is energy available, and may be better than increasing treatment rates.

Keywords: Influenza epidemic model; Optimal control; Vaccination; Antiviral treatment; Isolation

1 Introduction

We divide the total population (denoted by $N(t)$) into four compartments: susceptible $S(t)$, vaccinated $V(t)$, infected $I(t)$ and recovered $R(t)$. Due to the presence of pharmacological intervention, infected individuals $I(t)$ are further divided into four classes, namely, those untreated with drug-sensitive strains ($I_s(t)$), those untreated with drug-resistant strains $I_r(t)$, those treated with drug-sensitive strains $I_{str}(t)$, and those treated with drug-resistant strains $I_{rtr}(t)$. And we describe the evolution of influenza disease based on the following aspects:

(i) *Vaccination:* Before the infection, susceptible individuals with a proportion of ϕ will consider receiving influenza vaccine to resist being infected by the influenza virus. However, the imperfection of vaccines can lead to the loss of vaccine-based immunity at the rate ω, making vaccinated individuals susceptible again.

(ii) *Transmission:* The transmission of influenza virus is due to contact with infected individuals, for example, susceptible individuals may come into contact with infected individuals who shed wild-type (drug-sensitive) and drug-resistant virus at rates β_a $(a = s, str)$ and β_b $(b = r, rtr)$, respectively, resulting in infection. In fact, drug administration may reduce the likelihood of transmitting wild-type viruses, thus assuming $\beta_{str} \leq \beta_s$. Once drug resistance occurs, treatment is almost ineffective, thus assuming that the infection rate is equal when encountering infected individuals with drug-resistant strains, regardless of whether they receive treatment or not, i.e., $\beta_{rtr} = \beta_r$. Because vaccines cannot provide immunity to all vaccinated individuals, they may be infected with influenza virus, but the infection rate is lower than that of unvaccinated individuals (those in compartment S). We use $1 - \sigma$ to represent the proportion of decrease, where σ refers to the effectiveness of the vaccine.

(iii) *Treatment:* Antiviral treatment is administered at rates κ_1 and κ_2 respectively to drug-sensitive and drug-resistant cases to alleviate related symptoms. We assume that drug-resistant viruses can be rarely recognized during a pandemic, resulting in little difference in treatment rates between drug-sensitive and drug-resistant cases, i.e., $\kappa_1 = \kappa_2$. Drug-resistant viruses rapidly emerge at the rate p after the start of treatment, which means that the infected-treated individuals with drug-sensitive strains become infected-treated individuals with drug-resistant strains at this rate.

(iv) *Recovery:* Infected-untreated individuals with drug-sensitive and drug-resistant strains recover at rates ξ_1 and ξ_2, respectively, and they are equal, i.e., $\xi_1 = \xi_2$. Infected-treated individuals with drug-sensitive and drug-resistant strains recover at rates α_1 and α_2, respectively. Receiving treatment may to some extent reduce the infection period and make recovery faster, but we assume this is only applicable to drug-sensitive cases, as the presence of drug resistance makes treatment difficult to work. Therefore, we suppose that infected-treated individuals with drug-resistant strains have the same recovery rate as infected-untreated individuals. These indicate that $\alpha_1 > \alpha_2 = \xi_1 = \xi_2$. Although individuals may develop some immunity after being infected with the influenza virus, it may be lost over time. We assume that the immunity acquired by infection will decrease at the rate γ, causing recovered individuals become susceptible again.

If sufficient and appropriate measures are taken during the course of the epidemic, it becomes possible for diseases to be pushed towards eradication [1, 2]. However, due to the lack of adequate policies and opportune interventions to slow down the process of virus transmission, some diseases eventually develop into endemic ones [3, 4]. Therefore, it is necessary to adopt appropriate proactive strategies to contain the outbreak of epidemic, especially for infectious diseases like influenza that have both vaccines and treatment [5–8]. The optimal control model has been widely used to determine effective strategies to minimize the economic and social impacts of infectious diseases through intervention measures [9, 10]. This can provide solid theoretical support for public health authorities to formulate prevention and control policies.

Naturally, a question arises: what is the optimal strategy to suppress the spread of the influenza (mainly reflected in reducing the number of infected individuals) at minimal cost?

Our contribution is to establish a mathematical model that can be used to characterize the spread of influenza in a single wave by adding control variables to seek the optimal control strategy. The rest of this paper is organized as follows. In Sect. 2, we propose an

influenza epidemic model with controls aimed at minimizing the number of infected individuals and the costs associated with implementing intervention measures. In Sect. 3, we prove the existence of the optimal control. In Sect. 4, we solve the optimal control problem by using Pontryagin's maximum principle. In Sect. 5, we carry out numerical experiments to find the optimal control strategy to contain the outbreak of influenza. And in the last section, Sect. 6, we collect some concluding remarks.

2 Influenza pandemic model with controls

In this section, we invest energy into establishing the control model with both pharmacological and non-pharmacological interventions by introducing control variables. What we are trying to do while minimizing costs is to curb the major outbreak of influenza, which is to reduce the epidemic size and bring the number of infected individuals closer to zero as possible. For this purpose, we design the following control strategies:

(S1) *Reducing the waning rate of vaccine-based immunity:* assume that the waning rate of vaccine-based immunity is decreased by $u_1(t)$. And $(1-u_1(t))\omega$ denotes the reduction in the rate of losing vaccine-based immunity ω by developing the new influenza vaccine, improving vaccination strategies and enhancing individual physical fitness.

(S2) *Improving the treatment rate:* assume that the treatment rate of infected individuals with drug-sensitive strains is increased by $u_2(t)$, and the treatment rate of infected individuals with drug-resistant strains is increased by $u_3(t)$. These can be achieved through reducing the severity level of the disease that requires antiviral therapy, improving the effectiveness and supply of drugs and so on.

(S3) *Isolating the infected individuals:* The isolation intervention measures that can be taken for infected individuals usually refer to staying at home, hospitalization, and avoiding crowded places. Let $u_4(t)$ and $u_5(t)$ be the control variables that respectively describe the isolation rates of the infected individuals without and with treatment. The reason we differentiate is that patients receiving treatment are usually more severe, which leads to a lower likelihood of them going out and possibly being hospitalized.

Through adding these variables $u_j(t)$ $(j = 1, 2, 3, 4, 5)$, based on the diagram shown in Fig. 1, we obtain the following influenza model, incorporating the control measures designed above:

$$
\begin{cases}
\dfrac{dS}{dt} = \Lambda - (\beta_s I_s + \beta_{str} I_{str} + \beta_r I_r + \beta_{rtr} I_{rtr})S - \phi S + (1-u_1)\omega V + \gamma R - \mu S, \\
\dfrac{dV}{dt} = \phi S - (1-u_1)\omega V - (1-\sigma)(\beta_s I_s + \beta_{str} I_{str} + \beta_r I_r + \beta_{rtr} I_{rtr})V - \mu V, \\
\dfrac{dI_s}{dt} = (\beta_s I_s + \beta_{str} I_{str})S + (1-\sigma)(\beta_s I_s + \beta_{str} I_{str})V \\
\qquad - (1+u_2)\kappa_1 I_s - \xi_1 I_s - \mu I_s - u_4 I_s, \\
\dfrac{dI_r}{dt} = (\beta_r I_r + \beta_{rtr} I_{rtr})S + (1-\sigma)(\beta_r I_r + \beta_{rtr} I_{rtr})V \\
\qquad - (1+u_3)\kappa_2 I_r - \xi_2 I_r - \mu I_r - u_4 I_r, \\
\dfrac{dI_{str}}{dt} = (1+u_2)\kappa_1 I_s - p I_{str} - \alpha_1 I_{str} - \mu I_{str} - u_5 I_{str}, \\
\dfrac{dI_{rtr}}{dt} = (1+u_3)\kappa_2 I_r + p I_{str} - \alpha_2 I_{rtr} - \mu I_{rtr} - u_5 I_{rtr}, \\
\dfrac{dR}{dt} = \xi_1 I_s + \xi_2 I_r + \alpha_1 I_{str} + \alpha_2 I_{rtr} - \gamma R - \mu R
\end{cases}
\tag{2.1}
$$

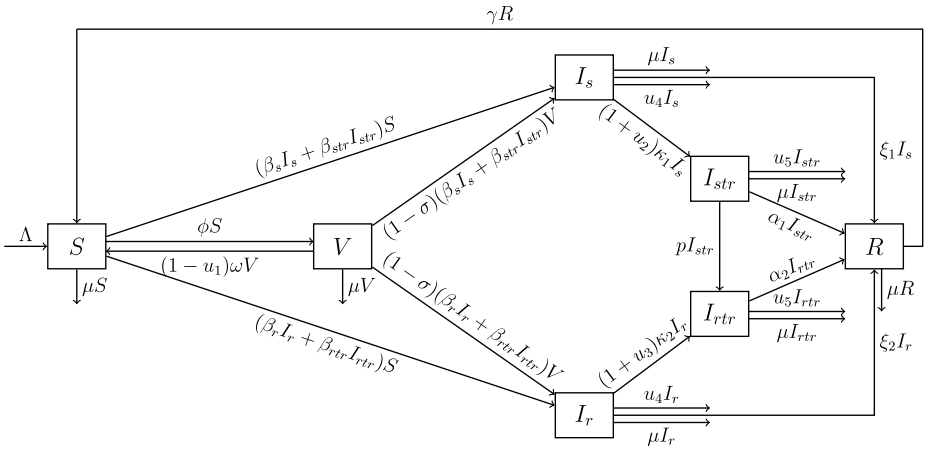

Figure 1 Transfer diagram of the influenza model incorporating intervention measures

with the initial conditions:

$$S(0) > 0,\ V(0) > 0,\ I_s(0) > 0,\ I_r(0) > 0,\ I_{str}(0) > 0,\ I_{rtr}(0) > 0,\ R(0) > 0.$$

Here, Λ and μ represent the recruitment rate of individuals (including birth and migration) and the rate of individuals leaving the population (including death and emigration), respectively.

Note that the feasible region

$$\Gamma = \left\{ (S(t), V(t), I_s(t), I_r(t), I_{str}(t), I_{rtr}(t), R(t)) \in \mathbb{R}_+^7 : N(t) \le \frac{\Lambda}{\mu} \right\} \tag{2.2}$$

is positively invariant for model (2.1), where $N(t) = S(t) + V(t) + I_s(t) + I_r(t) + I_{str}(t) + I_{rtr}(t) + R(t)$. Therefore, it is necessary to limit our dynamic analysis about the model to region Γ.

Our goal is to minimize the number of the infected individuals (including I_s, I_r, I_{str} and I_{rtr}) and the cost due to apply three control strategies. Thus, setting

$$x(t) = [S(t), V(t), I_s(t), I_r(t), I_{str}(t), I_{rtr}(t), R(t)]^{\mathrm{T}},\ \ u(t) = [u_1(t), u_2(t), u_3(t), u_4(t), u_5(t)]^{\mathrm{T}},$$

a control scheme is assumed to be optimal if it minimizes the objective functional:

$$J(u) = \int_0^{t_f} [\mathcal{L}(t, x, u)]\mathrm{d}t, \tag{2.3}$$

where

$$\mathcal{L}(t, x, u) = I_s(t) + I_r(t) + I_{str}(t) + I_{rtr}(t) + \sum_{j=1}^{5} \frac{\zeta_j}{2} u_j^2(t).$$

The first four terms in the objective functional (2.3) represent benefit of $I_s(t)$, $I_r(t)$, $I_{str}(t)$ and $I_{rtr}(t)$ that we hope to reduce. In the quadratic term of (2.3), $\zeta_j (j = 1, 2, 3, 4, 5)$ are positive weight values associated with these controls $u_j(t) (j = 1, 2, 3, 4, 5)$, and the square of

the control variable reflects the severity of the side effect of the adopted measures over the time interval $[0, t_f]$, where t_f is the fixed final time. The optimal control problem is to minimize objective functional (2.3) subject to control model (2.1), that is, to find the optimal control [11] $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ such that

$$J(u^*) = \min_{\mathcal{U}} J(u), \tag{2.4}$$

where $\mathcal{U}$ is the control set defined by

$$\mathcal{U} = \left\{(u_1, u_2, u_3, u_4, u_5) \mid u_i(t) \in L^\infty([0, t_f], \mathbb{R}), 0 \le u_j(t) \le 1, j = 1, 2, 3, 4, 5\right\}.$$

The assumption of the upper bound of control variables $u_j(t)\,(j = 1, 2, 3, 4, 5)$ reflect the reality of the practical limitation of the maximum rate (i.e., 1) that the control strategy may be adopted.

Remark 2.1 According the next generation matrix method provided in [12], the basic reproduction number for model (2.1) without control strategies (i.e., $u_j(t) = 0, j = 1, 2, 3, 4, 5$) can be given as follows:

$$\mathcal{R}_0 = \max\{\mathcal{R}_s, \mathcal{R}_r\}, \tag{2.5}$$

where

$$\begin{aligned} \mathcal{R}_s &= \frac{\Lambda\left((1-\sigma)\phi + \omega + \mu\right)\left(\beta_s\alpha_1 + \beta_s\mu + \beta_s p + \beta_{str}\kappa_1\right)}{\mu\left(\mu + \omega + \phi\right)\left(\kappa_1 + \xi_1 + \mu\right)\left(\alpha_1 + \mu + p\right)}, \\ \mathcal{R}_r &= \frac{\Lambda\left((1-\sigma)\phi + \omega + \mu\right)\left(\beta_r\alpha_2 + \beta_r\mu + \beta_{rtr}\kappa_2\right)}{\mu\left(\mu + \omega + \phi\right)\left(\kappa_2 + \xi_2 + \mu\right)\left(\alpha_2 + \mu\right)}, \end{aligned} \tag{2.6}$$

which accounts for the number of secondary cases generated by four groups: infected-untreated individuals with drug-sensitive strains (I_s), infected-untreated individuals with drug-resistant strains (I_r), infected-treated individuals with drug-sensitive strains (I_{str}) and infected-treated individuals with drug-resistant strains (I_{rtr}). Generally, if $\mathcal{R}_0 > 1$, influenza disease will persist, while if $\mathcal{R}_0 < 1$, the influenza disease will go extinct, which can be traced back to sufficient previous work [13–15].

3 Existence of optimal control

In this section, we need to present the results on the existence of optimal control given in [16], as follows, which will guide us to complete this part of the proof.

Lemma 3.1 [16] *Suppose that*

(i) *the set of controls and state variables is non-empty*;
(ii) *the control space $\mathcal{U}$ is closed and convex*;
(iii) *the right side of the control model is bounded by a linear function with the state and control variables*;
(iv) *the integrand in the objective function is convex with respect to the control u*;
(v) *there exists a constant $n > 1$ and positive numbers C_1, C_2 such that*

$$\mathcal{L}(t, x, u) \ge C_1 \mid u \mid^n - C_2.$$

Then there exists $u^*(\cdot) \in \mathcal{U}$ such that $J(u^*(\cdot)) = \min_{\mathcal{U}} J(u(\cdot))$.

Theorem 3.1 *For the control problem with model* (2.1)*, there exists the optimal control* u^* *such that* $J(u^*) = \min_{\mathcal{U}} J(u)$.

Proof What needs to be done now is to verify these conditions about Lemma 3.1 in the following five steps in sequence.

Step 1: The control model (2.1) is uniformly Lipschitz continuous, thereby the set $\mathcal{U}$ and the set of state variables $(S, V, I_s, I_r, I_{str}, I_{rtr}, R)$ to initial values are non-empty.

Step 2: From the definition of $\mathcal{U}$, it can be inferred that the control set $\mathcal{U}$ is allowed to be closed and convex.

Step 3: In fact, the control model (2.1) can be written as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mathcal{A} + \mathcal{B}u,$$

where $\mathcal{A}$ and $\mathcal{B}$ are defined as follows:

$$\mathcal{A} = \begin{pmatrix} \Lambda - (\beta_s I_s + \beta_{str} I_{str} + \beta_r I_r + \beta_{rtr} I_{rtr})S - \phi S + \omega V + \gamma R - \mu S \\ \phi S - \omega V - (1-\sigma)(\beta_s I_s + \beta_{str} I_{str} + \beta_r I_r + \beta_{rtr} I_{rtr})V - \mu V \\ (\beta_s I_s + \beta_{str} I_{str})S + (1-\sigma)(\beta_s I_s + \beta_{str} I_{str})V - \kappa_1 I_s - \xi_1 I_s - \mu I_s \\ (\beta_r I_r + \beta_{rtr} I_{rtr})S + (1-\sigma)(\beta_r I_r + \beta_{rtr} I_{rtr})V - \kappa_2 I_r - \xi_2 I_r - \mu I_r \\ \kappa_1 I_s - p I_{str} - \alpha_1 I_{str} - \mu I_{str} \\ \kappa_2 I_r + p I_{str} - \alpha_2 I_{rtr} - \mu I_{rtr} \\ \xi_1 I_s + \xi_2 I_r + \alpha_1 I_{str} + \alpha_2 I_{rtr} - \gamma R - \mu R \end{pmatrix},$$

$$\mathcal{B} = \begin{pmatrix} -\omega V & 0 & 0 & 0 & 0 \\ \omega V & 0 & 0 & 0 & 0 \\ 0 & -\kappa_1 I_s & 0 & -I_s & 0 \\ 0 & 0 & -\kappa_2 I_r & -I_r & 0 \\ 0 & \kappa_1 I_s & 0 & 0 & -I_{str} \\ 0 & 0 & \kappa_2 I_r & 0 & -I_{rtr} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Therefore, we speculate that condition (iii) in the Lemma 3.1 holds.

Step 4: For all $\theta \in (0,1)$,

$$\begin{aligned} &\mathcal{L}[t, x, \theta u + (1-\theta)v] \\ &= I_s + I_r + I_{str} + I_{rtr} + \frac{\zeta_1}{2}(\theta u_1 + (1-\theta)v_1)^2 + \frac{\zeta_2}{2}(\theta u_2 + (1-\theta)v_2)^2 \\ &\quad + \frac{\zeta_3}{2}(\theta u_3 + (1-\theta)v_3)^2 + \frac{\zeta_4}{2}(\theta u_4 + (1-\theta)v_4)^2 + \frac{\zeta_5}{2}(\theta u_5 + (1-\theta)v_5)^2, \end{aligned}$$

and

$$\begin{aligned} &\theta\mathcal{L}(t, x, u) + (1-\theta)\mathcal{L}(t, x, v) \\ &= I_s + I_r + I_{str} + I_{rtr} + \frac{\zeta_1}{2}(\theta u_1^2 + (1-\theta)v_1^2) + \frac{\zeta_2}{2}(\theta u_2^2 + (1-\theta)v_2^2) \\ &\quad + \frac{\zeta_3}{2}(\theta u_3^2 + (1-\theta)v_3^2) + \frac{\zeta_4}{2}(\theta u_4^2 + (1-\theta)v_4^2) + \frac{\zeta_5}{2}(\theta u_5^2 + (1-\theta)v_5^2), \end{aligned}$$

then

$$\begin{aligned}
&\mathcal{L}[t,x,\theta u+(1-\theta)v]-(\theta\mathcal{L}(t,x,u)+(1-\theta)\mathcal{L}(t,x,v))\\
&=\theta(\theta-1)\left(\frac{\zeta_1}{2}(u_1-v_1)^2+\frac{\zeta_2}{2}(u_2-v_2)^2+\frac{\zeta_3}{2}(u_3-v_3)^2+\frac{\zeta_4}{2}(u_4-v_4)^2+\frac{\zeta_5}{2}(u_5-v_5)^2\right)\\
&\leq 0,
\end{aligned}$$

which yields

$$\mathcal{L}(t,x,\theta u+(1-\theta)v)\leq\theta\mathcal{L}(t,x,u)+(1-\theta)\mathcal{L}(t,x,v).$$

Hence, condition (iv) is proven.

Step 5: Note that

$$\begin{aligned}
\mathcal{L}(t,x,u)&=I_s+I_r+I_{str}+I_{rtr}+\frac{\zeta_1}{2}u_1^2+\frac{\zeta_2}{2}u_2^2+\frac{\zeta_3}{2}u_3^2+\frac{\zeta_4}{2}u_4^2+\frac{\zeta_5}{2}u_5^2\\
&\geq\frac{\zeta_1}{2}u_1^2+\frac{\zeta_2}{2}u_2^2+\frac{\zeta_3}{2}u_3^2+\frac{\zeta_4}{2}u_4^2+\frac{\zeta_5}{2}u_5^2\\
&\geq\frac{\zeta_{min}}{2}(u_1^2+u_2^2+u_3^2+u_4^2+u_5^2),
\end{aligned}$$

where $\zeta_{min}=\min\{\zeta_1,\zeta_2,\zeta_3,\zeta_4,\zeta_5\}$. So it follows that if we choose

$$C_1=\frac{\zeta_{min}}{2},n=2,C_2\geq 0,$$

we have

$$\mathcal{L}(t,x,u)\geq C_1\mid u\mid^n-C_2,$$

which means that condition (v) is satisfied. □

4 Characterization of optimal control

In this section, our task is to solve the optimal control problem by using Pontryagin's maximum principle [16]. To this end, the Hamiltonian function with respect to our problem is constructed as follows:

$$\begin{aligned}
\mathcal{H}(t,x,u,q)&=I_s(t)+I_r(t)+I_{str}(t)+I_{rtr}(t)+\frac{\zeta_1}{2}u_1^2+\frac{\zeta_2}{2}u_2^2+\frac{\zeta_3}{2}u_3^2+\frac{\zeta_4}{2}u_4^2+\frac{\zeta_5}{2}u_5^2\\
&\quad+q_1\frac{\mathrm{d}S}{\mathrm{d}t}+q_2\frac{\mathrm{d}V}{\mathrm{d}t}+q_3\frac{\mathrm{d}I_s}{\mathrm{d}t}+q_4\frac{\mathrm{d}I_r}{\mathrm{d}t}+q_5\frac{\mathrm{d}I_{str}}{\mathrm{d}t}+q_6\frac{\mathrm{d}I_{rtr}}{\mathrm{d}t}+q_7\frac{\mathrm{d}R}{\mathrm{d}t},
\end{aligned}\tag{4.1}$$

where q_i $(i=1,2,3,4,5,6,7)$ are the adjoint variables. Then, we obtain the following theorem.

Theorem 4.1 *Given the optimal control u^* and the solutions S^*, V^*, I_s^*, I_r^*, I_{str}^*, I_{rtr}^* and R^* of the corresponding model (2.1), there exist adjoint variables q_i $(i=1,2,3,4,5,6,7)$ that*

satisfy

$$\begin{cases} \dfrac{\mathrm{d}q_1}{\mathrm{d}t} = q_1(\beta_r I_r^* + \beta_s I_s^* + \beta_{rtr} I_{rtr}^* + \beta_{str} I_{str}^* + \mu + \phi) - q_2\phi \\ \qquad -q_3(\beta_s I_s^* + \beta_{str} I_{str}^*) - q_4(\beta_r I_r^* + \beta_{rtr} I_{rtr}^*), \\ \dfrac{\mathrm{d}q_2}{\mathrm{d}t} = -q_1(1-u_1^*)\omega + q_2((1-u_1^*)\omega \\ \qquad +(1-\sigma)(\beta_r I_r^* + \beta_s I_s^* + \beta_{rtr} I_{rtr}^* + \beta_{str} I_{str}^*) + \mu) \\ \qquad -q_3(1-\sigma)(\beta_s I_s^* + \beta_{str} I_{str}^*) - q_4(1-\sigma)(\beta_r I_r^* + \beta_{rtr} I_{rtr}^*), \\ \dfrac{\mathrm{d}q_3}{\mathrm{d}t} = -1 + q_1\beta_s S^* + q_2(1-\sigma)\beta_s V^* \\ \qquad -q_3(\beta_s S^* + (1-\sigma)\beta_s V^* - (1+u_2^*)\kappa_1 - \xi_1 - \mu - u_4^*) \\ \qquad -q_5(1+u_2^*)\kappa_1 - q_7\xi_1, \\ \dfrac{\mathrm{d}q_4}{\mathrm{d}t} = -1 + q_1\beta_r S^* + q_2(1-\sigma)\beta_r V^* \\ \qquad -q_4(\beta_r S^* + (1-\sigma)\beta_r V^* - (1+u_3^*)\kappa_2 - \xi_2 - \mu - u_4^*) \\ \qquad -q_6(1+u_3^*)\kappa_2 - q_7\xi_2, \\ \dfrac{\mathrm{d}q_5}{\mathrm{d}t} = -1 + q_1\beta_{str} S^* + q_2(1-\sigma)\beta_{str} V^* - q_3((1-\sigma)\beta_{str} V^* + \beta_{str} S^*) \\ \qquad +q_5(p+\alpha_1+\mu) - q_6 p - q_7\alpha_1, \\ \dfrac{\mathrm{d}q_6}{\mathrm{d}t} = -1 + q_1\beta_{rtr} S^* + q_2(1-\sigma)\beta_{rtr} V^* - q_4((1-\sigma)\beta_{rtr} V^* + \beta_{rtr} S^*) \\ \qquad +q_6(\alpha_2+\mu+u_5^*) - q_7\alpha_2, \\ \dfrac{\mathrm{d}q_7}{\mathrm{d}t} = -q_1\gamma + q_7(\gamma+\mu), \end{cases} \tag{4.2}$$

with transversality conditions

$$q_i(t_f) = 0, \quad i = 1,2,3,4,5,6,7. \tag{4.3}$$

Furthermore, optimal controls u_j^* $(j = 1,2,3,4,5)$ *are given as*

$$\begin{aligned} u_1^* &= \max\left\{\min\left\{\frac{\omega V^*(q_1-q_2)}{\zeta_1}, 1\right\}, 0\right\}, \\ u_2^* &= \max\left\{\min\left\{\frac{\kappa_1 I_s^*(q_3-q_5)}{\zeta_2}, 1\right\}, 0\right\}, \\ u_3^* &= \max\left\{\min\left\{\frac{\kappa_2 I_r^*(q_4-q_6)}{\zeta_3}, 1\right\}, 0\right\}, \\ u_4^* &= \max\left\{\min\left\{\frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4}, 1\right\}, 0\right\}, \\ u_5^* &= \max\left\{\min\left\{\frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5}, 1\right\}, 0\right\}. \end{aligned} \tag{4.4}$$

Proof From Pontryagin's maximum principle [16], we know that if (x^*, u^*) is an optimal control solution of the optimal control problem (2.1), then there exist the adjoint variables vector $q = (q_1, q_2, q_3, q_4, q_5, q_6, q_7)$ satisfying the following inequalities:

$$\frac{\partial \mathcal{H}(t, x^*, u^*, q)}{\partial u} = 0, \tag{4.5}$$

$$\frac{\mathrm{d}q}{\mathrm{d}t} = -\frac{\partial \mathcal{H}(t, x^*, u^*, q)}{\partial x}, \tag{4.6}$$

$$q(t_f) = 0. \tag{4.7}$$

Hence, we can calculate the adjoint equations shown in (4.2) by differentiating the Hamiltonian function (4.1) with respect to the states, that is,

$$\frac{\mathrm{d}q_1}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial S}, \ \frac{\mathrm{d}q_2}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial V}, \ \frac{\mathrm{d}q_3}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial I_s}, \ \frac{\mathrm{d}q_4}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial I_r},$$
$$\frac{\mathrm{d}q_5}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial I_{str}}, \ \frac{\mathrm{d}q_6}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial I_{rtr}}, \ \frac{\mathrm{d}q_7}{\mathrm{d}t} = -\frac{\partial \mathcal{H}}{\partial R}.$$

Since there is no dependence on the states at the final time in the objective functional, the final time boundary conditions (transversality conditions) are zero, i.e., $q_1(t_f) = q_2(t_f) = q_3(t_f) = q_4(t_f) = q_5(t_f) = q_6(t_f) = q_7(t_f) = 0$.

The optimal conditions for the Hamiltonian are given by

$$\frac{\partial \mathcal{H}}{\partial u_1}|_{u_1 = u_1^*(t)} = -q_1 \omega V^* + q_2 \omega V^* + \zeta_1 u_1^*(t) = 0,$$
$$\frac{\partial \mathcal{H}}{\partial u_2}|_{u_2 = u_2^*(t)} = -q_3 \kappa_1 I_s^* + q_5 \kappa_1 I_s^* + \zeta_2 u_2^*(t) = 0,$$
$$\frac{\partial \mathcal{H}}{\partial u_3}|_{u_3 = u_3^*(t)} = -q_4 \kappa_2 I_r^* + q_6 \kappa_2 I_r^* + \zeta_3 u_3^*(t) = 0,$$
$$\frac{\partial \mathcal{H}}{\partial u_4}|_{u_4 = u_4^*(t)} = -q_4 I_r^* - q_3 I_s^* + \zeta_4 u_4^*(t) = 0,$$
$$\frac{\partial \mathcal{H}}{\partial u_5}|_{u_5 = u_5^*(t)} = -q_6 I_{rtr}^* - q_5 I_{str}^* + \zeta_5 u_5^*(t) = 0,$$

which yield that

$$u_1^*(t) = \frac{\omega V^*(q_1 - q_2)}{\zeta_1}, \ u_2^*(t) = \frac{\kappa_1 I_s^*(q_3 - q_5)}{\zeta_2}, \ u_3^*(t) = \frac{\kappa_2 I_r^*(q_4 - q_6)}{\zeta_3},$$
$$u_4^*(t) = \frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4}, \ u_5^*(t) = \frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5}.$$

Considering the property of the control space, we obtain

$$u_1^* = \begin{cases} 0 & \text{if } \dfrac{\omega V^*(q_1 - q_2)}{\zeta_1} \le 0, \\ \dfrac{\omega V^*(q_1 - q_2)}{\zeta_1} & \text{if } 0 < \dfrac{\omega V^*(q_1 - q_2)}{\zeta_1} < 1, \\ 1 & \text{if } \dfrac{\omega V^*(q_1 - q_2)}{\zeta_1} \ge 1, \end{cases}$$

$$u_2^* = \begin{cases} 0 & \text{if } \frac{\kappa_1 I_s^*(q_3 - q_5)}{\zeta_2} \le 0, \\ \frac{\kappa_1 I_s^*(q_3 - q_5)}{\zeta_2} & \text{if } 0 < \frac{\kappa_1 I_s^*(q_3 - q_5)}{\zeta_2} < 1, \\ 1 & \text{if } \frac{\kappa_1 I_s^*(q_3 - q_5)}{\zeta_2} \ge 1, \end{cases}$$

$$u_3^* = \begin{cases} 0 & \text{if } \frac{\kappa_2 I_r^*(q_4 - q_6)}{\zeta_3} \le 0, \\ \frac{\kappa_2 I_r^*(q_4 - q_6)}{\zeta_3} & \text{if } 0 < \frac{\kappa_2 I_r^*(q_4 - q_6)}{\zeta_3} < 1, \\ 1 & \text{if } \frac{\kappa_2 I_r^*(q_4 - q_6)}{\zeta_3} \ge 1, \end{cases}$$

$$u_4^* = \begin{cases} 0 & \text{if } \frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4} \le 0, \\ \frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4} & \text{if } 0 < \frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4} < 1, \\ 1 & \text{if } \frac{q_4 I_r^* + q_3 I_s^*}{\zeta_4} \ge 1, \end{cases}$$

$$u_5^* = \begin{cases} 0 & \text{if } \frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5} \le 0, \\ \frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5} & \text{if } 0 < \frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5} < 1, \\ 1 & \text{if } \frac{q_6 I_{rtr}^* + q_5 I_{str}^*}{\zeta_5} \ge 1. \end{cases}$$

Therefore, the optimal control u^* is characterized as (4.4). □

5 Numerical simulations

In this section, we present several purely illustrative experiments on model (2.1) to find the optimal control strategies that can contain major outbreaks. Our aim is to significantly control the number of infected individuals at an extremely low level, preferably to zero (this situation is considered as the extinction of influenza in this work), with minimal cost under the assumption of abundant medical resources. The specific implementation plan is to study the evolution of the model dynamics with and without control, using the forward-backward sweep method described in [17]. It should be noted that the dynamics of the model are studied in a finite time interval, taking into account the seasonality of the influenza pandemic. Here, infected individuals are only distinguished based on the strain type (i.e. drug-sensitive or drug-resistant strain) of influenza virus they are infected with. Given this, we use the numerical solutions of $I_s + I_{str}$ to measure the number of drug-sensitive cases and $I_r + I_{rtr}$ to measure the number of drug-resistant cases.

According to the insightful work about the influenza dynamics by [18] and [19], the parameter values are adopted as follows:

$$\Lambda = \tfrac{5}{365},\ \mu = \tfrac{1}{80\times 365},\ \beta_s = 6\times 10^{-3},\ \beta_{str} = 4.02\times 10^{-3},\ \beta_r = 1.2\times 10^{-3},$$

$$\beta_{rtr} = 1.2\times 10^{-3},\ \phi = 0.03,\ \omega = 0.003,\ \gamma = 0.011,\ \sigma = 0.85,\ \kappa_1 = 0.7,\ \xi_1 = 0.25,$$

$$\kappa_2 = 0.7,\ \xi_2 = 0.25,\ \alpha_1 = 0.3325,\ \alpha_2 = 0.25,\ p = 0.05,$$

where parameter σ, involved in the reduction proportion of infection rates caused by vaccines, has no unit, while the units of other parameters are day^{-1}. In this case, we ob-

tain

$$\mathcal{R}_0 = 1.283 > 1,$$

indicating a major outbreak of influenza without control strategies.

We consider the optimal control problem developed by control model (2.1) over the time horizon of half a year, that is, $t_f = 183$ days. In particular, we assume that $\zeta_j = 0.8$ ($j = 1, 2, 3, 4, 5$) in the objective functional (2.3). Generally speaking, there are differences in the costs associated with these control strategies, and we ignore them here not only because these cost differences are difficult to accurately measure, but also because of what we plan to do. That is to say, we want to know which of the measures we design is more effective, which requires ensuring that the results are not affected by cost differences or other factors. Based on these considerations, the detailed exploration is as follows.

Strategy 1: Reducing the waning rate of vaccine-based immunity.

As the first scenario, we consider whether drug-sensitive and drug-resistant influenza cases could be effectively eliminated within a certain period of time if efforts could be made to reduce the waning rate of vaccine-based immunity. Figure 2(a) shows the time-dependent optimal control variable u_1 of strategy 1. It is interesting to observe that u_1 to reduce the waning rate of vaccine-based immunity does not need to reach its maximum value at the beginning of the outbreak, as long as it can be achieved within about a month and a half and then last almost the entire control period. Figure 2(b) and Fig. 2(c) show the number of drug-sensitive and drug-resistant cases without control (solid line) and under strategy 1 (dotted line). Unfortunately, we find that this strategy can only slightly cut down the number of infected individuals (including those with drug-sensitive and drug-resistant strains) and cannot suppress the outbreak.

Strategy 2: Improving the treatment rate.

We now shift our attention to the second scenario, which is that we can improve the treatment rate for infected individuals with drug-sensitive and drug-resistant strains. The time-varying optimal control variables u_2 and u_3 of strategy 2 are displayed in Fig. 3(a). This suggests that in the days leading up to the outbreak of the epidemic, medical departments increase treatment rate for drug-sensitive cases as much as possible, but then reduce the treatment rate until the epidemic has passed the rapid growth period. However, during this control period, the effect of improving treatment rate for drug-resistant

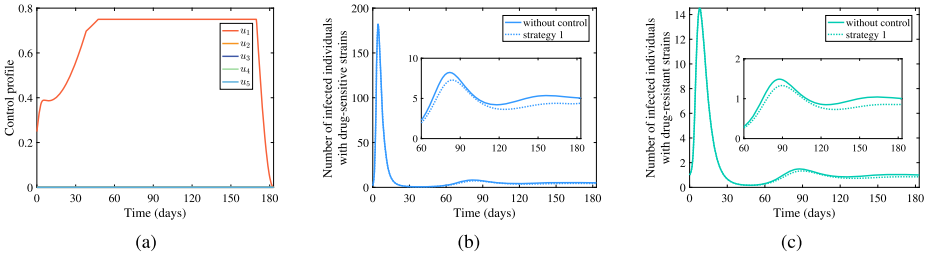

Figure 2 (a) The optimal control variable $u_1(t)$ in the case of reducing the waning rate of vaccine-based immunity (i.e., strategy 1) when weight constants $\zeta_j = 0.8$ ($j = 1, 2, 3, 4, 5$). (b, c) The time-series plots of the number of drug-sensitive cases (b) and drug-resistant cases (c) without (solid line) and with strategy 1 (dotted line)

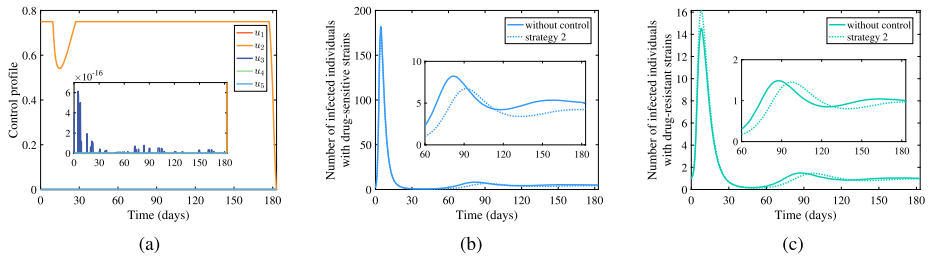

Figure 3 (a) The optimal control variables $u_2(t)$ and $u_3(t)$ in the case of improving the treatment rate (i.e., strategy 2) when weight constants $\zeta_j = 0.8$ ($j = 1, 2, 3, 4, 5$). (b, c) The time-series plots of the number of drug-sensitive cases (b) and drug-resistant cases (c) without (solid line) and with strategy 2 (dotted line)

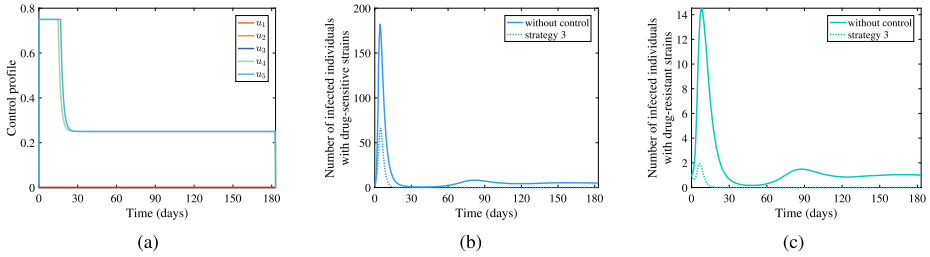

Figure 4 (a) The optimal control variables $u_4(t)$ and $u_5(t)$ in the case of isolating the infected individuals (i.e., strategy 3) when weight constants $\zeta_j = 0.8$ ($j = 1, 2, 3, 4, 5$). (b, c) The time-series plots of the number of drug-sensitive cases (b) and drug-resistant cases (c) without (solid line) and with strategy 3 (dotted line)

cases is actually minimal, which inspires us not to focus on the advancement of this measure. Figure 3(b) and Fig. 3(c) show the numerical and analytical results of the number of drug-sensitive cases and drug-resistant cases. It can be seen that compared to when no control is applied, the implementation of strategy 2 only significantly reduces the number of drug-sensitive cases.

Strategy 3: Isolating the infected individuals.

Our envisioned third scenario is to isolate infected individuals and keep them at a distance from other healthy individuals. The optimal control profiles and the number of drug-sensitive cases and drug-resistant cases under strategy 3 are shown in Fig. 4. The control profiles displayed in Fig. 4(a) provides a justification for the implementation of a policy aiming at immediately ensuring that as many infected individuals (regardless of whether they receive antiviral treatment or not) as possible are in quarantine during the early stages of the epidemic outbreak. As we expect to see, the outbreak of influenza may be effectively contained within about half a month under strategy 3, which is supported by Fig. 4(b) and Fig. 4(c).

Further explorations focus on what the optimal isolation strategy would be and how the influenza dynamics would change if the weight values related to control variables u_4 and u_5 are relatively large. The results obtained will be applicable to situations where the cost and difficulty of implementing isolation measures are relatively high, or where isolation resources are limited, such as facing a variety of sudden major epidemic. Figure 5 and Fig. 6 show the numerical results corresponding to weight constants $\zeta_4 = \zeta_5 = 1000$ or 5000, respectively. We find that compared to the results shown in Fig. 4 with weight constants $\zeta_4 = \zeta_5 = 0.8$, the time it takes to suppress influenza outbreaks is significantly longer in the

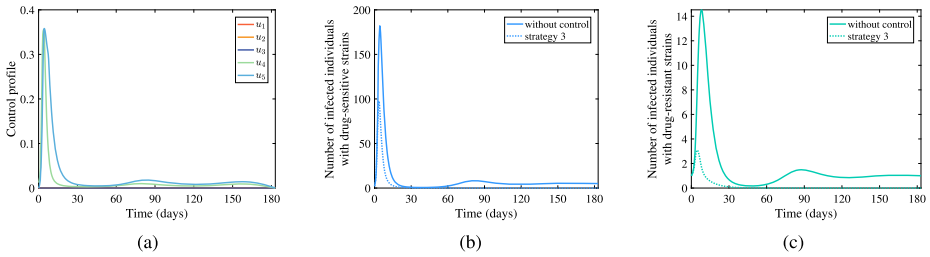

Figure 5 (a) The optimal control variables $u_4(t)$ and $u_5(t)$ in the case of isolating the infected individuals (i.e., strategy 3) when weight constants $\zeta_j = 1000$ ($j = 1, 2, 3, 4, 5$). (b, c) The time-series plots of the number of drug-sensitive cases (b) and drug-resistant cases (c) without (solid line) and with strategy 3 (dotted line)

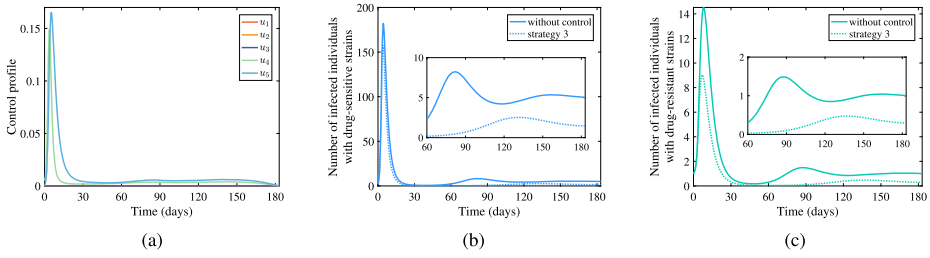

Figure 6 (a) The optimal control variables $u_4(t)$ and $u_5(t)$ in the case of isolating the infected individuals (i.e., strategy 3) when weight constants $\zeta_j = 5000$ ($j = 1, 2, 3, 4, 5$). (b, c) The time-series plots of the number of drug-sensitive cases (b) and drug-resistant cases (c) without (solid line) and with strategy 3 (dotted line)

case of $\zeta_4 = \zeta_5 = 1000$, especially for the extinction of drug-resistant cases, which takes more than a month. When the side effect of implementing isolation measures is particularly significant (such as weight constants $\zeta_4 = \zeta_5 = 5000$), unfortunately, the influenza will continue to spread. Moreover, Fig. 5(a) and Fig. 6(a) tell us a fact that if the side effect of implementing isolation strategies is too significant, they will only be implemented during the rapid development stage of the epidemic.

In reality, the combination of any two measures explored, or even the combination of these three measures, definitely have a better impact on controlling the spread of the epidemic than one of the measures included in the corresponding strategy. Nevertheless, we will not conduct further numerical experiments to illustrate this.

6 Concluding remarks

Viral respiratory epidemics like influenza can lead to serious illness, hospitalization, and even death, especially for the elderly, children, and certain chronic disease patients [20–24]. However, when the pandemic occurs, the imperfect or delayed supply of vaccines, as well as the emergence of the drug resistance that may be caused by the current antiviral treatment, are all obstacles on the road to prevention and control [25–27]. At this point, non-pharmacological interventions such as isolation may bring surprises [28–30]. Therefore, how to alleviate the impact of ongoing influenza transmission by combining pharmacological and non-pharmacological interventions has received great attention. In this paper, we propose an optimal control problem in which three strategies are designed: (i) reducing the waning rate of vaccine-based immunity; (ii) improving the treatment rate; (iii) isolating the infected individuals. Our goal is to minimize the number of infected

individuals with minimal cost as much as possible, preferably approaching zero. Mathematically, we prove the existence of optimal control and obtain the solution to the optimal control problem using Pontryagin's maximum principle. Numerically, we find the optimal control strategy by demonstrating the obtained optimal control and associated optimal state solutions. The main findings are summarized as follows:

(1) *Reducing the waning rate of vaccine-based immunity* (Strategy 1). If efforts are made to effectively reduce the waning rate of vaccine-based immunity, i.e., Strategy 1, the size of infected individuals, including drug-sensitive and drug-resistant cases, may be decreased (see Fig. 2).

(2) *Improving the treatment rate* (Strategy 2). Strategy 2 can only reduce the number of infected individuals with the drug-sensitive strains to a certain extent (see Fig. 3). This serves as a warning that increasing the treatment rate may not necessarily be an extremely effective strategy, and should be carefully considered in conjunction with the actual situation of the epidemic.

(3) *Isolating the infected individuals* (Strategy 3). We live up to expectations and find an effective strategy to contain the outbreak of influenza, which is to isolate infected individuals (e.g., staying at home), i.e., Strategy 3 (see Fig. 4). However, when encountering sudden major infectious diseases, if the side effect of isolation strategies is too significant, it will evidently increase the difficulty of prevention and control, and even the outbreak of the disease may not be controlled for a certain period of time (see Fig. 5 and Fig. 6). In this case, whether isolation is still necessary will be a question, and the best strategy may be to do nothing.

In the future, the interest may lie in exploring whether reducing the development rate of drug resistance in drug-sensitive cases can ensure that antiviral treatment can definitely be used to control the worsening of influenza outbreaks. Of course, if these works can be further explored based on actual data, it may provide stronger support for government departments to formulate prevention and control strategies.

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Author contributions
XW: Modelling, mathematical analysis, numerical simulation, writing. YC: Modelling, mathematical analysis, writing-reviewing and editing. All authors read and approved the final manuscript.

Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. Prasad, P.V., Steele, M.K., Reed, C., et al.: Multimodeling approach to evaluating the efficacy of layering pharmaceutical and nonpharmaceutical interventions for influenza pandemics. Proc. Natl. Acad. Sci. USA **120**(28), e2300590120 (2023)
2. Ai, M., Wang, W.: Optimal vaccination ages for emerging infectious diseases under limited vaccine supply. J. Math. Biol. **88**(1), 13 (2024)

3. Buonomo, B., Lacitignola, D., Vargas-De-León, C.: Qualitative analysis and optimal control of an epidemic model with vaccination and treatment. Math. Comput. Simul. **100**, 88–102 (2014)
4. Rao, I.J., Brandeau, M.L.: Vaccination for communicable endemic diseases: optimal allocation of initial and booster vaccine doses. J. Math. Biol. **89**(2), 21 (2024)
5. Tchuenche, J.M., Khamis, S.A., Agusto, F.B., Mpeshe, S.C.: Optimal control and sensitivity analysis of an influenza model with treatment and vaccination. Acta Biotheor. **59**, 1–28 (2011)
6. Lee, S., Chowell, G., Castillo-Chávez, C.: Optimal control for pandemic influenza: the role of limited antiviral treatment and isolation. J. Theor. Biol. **265**(2), 136–150 (2010)
7. Bolzoni, L., Della Marca, R., Groppi, M.: On the optimal control of SIR model with Erlang-distributed infectious period: isolation strategies. J. Math. Biol. **83**(4), 36 (2021)
8. Jung, E., Lenhart, S., Feng, Z.: Optimal control of treatments in a two-strain tuberculosis model. Discrete Contin. Dyn. Syst., Ser. B **2**(4), 473–482 (2002)
9. Chen, Y., Zhang, J., Jin, Z.: Optimal control of an influenza model with mixed cross-infection by age group. Math. Comput. Simul. **206**, 410–436 (2023)
10. Lee, S., Golinski, M., Chowell, G.: Modeling optimal age-specific vaccination strategies against pandemic influenza. Bull. Math. Biol. **74**(4), 958–980 (2012)
11. Yong, J., Zhou, X.: Stochastic Controls: Hamiltonian Systems and HJB Equations. Springer, Berlin (1999)
12. Van den Driessche, P., Watmough, J.: Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. **180**(1–2), 29–48 (2002)
13. Cai, Y., Kang, Y., Banerjee, M., Wang, W.: A stochastic SIRS epidemic model with infectious force under intervention strategies. J. Differ. Equ. **259**(12), 7463–7502 (2015)
14. Guan, X., Yang, F., Cai, Y., Wang, W.: Global stability of an influenza A model with vaccination. Appl. Math. Lett. **134**, 108322 (2022)
15. Liu, X., Chen, Y., Li, X., Li, J.: Global stability of latency-age/stage-structured epidemic models with differential infectivity. J. Math. Biol. **86**(5), 80 (2023)
16. Fleming, W.H., Rishel, R.W.: Deterministic and Stochastic Optimal Control. Springer, New York (1975)
17. Lenhart, S., Workman, J.T.: Optimal Control Applied to Biological Models. Chapman and Hall/CRC, Boca Raton (2007)
18. Stilianakis, N.I., Perelson, A.S., Hayden, F.G.: Emergence of drug resistance during an influenza epidemic: insights from a mathematical model. J. Infect. Dis. **177**(4), 863–873 (1998)
19. Xu, Y., Allen, L.J.S., Perelson, A.S.: Stochastic model of an influenza epidemic with drug resistance. J. Theor. Biol. **248**(1), 179–193 (2007)
20. Rambaut, A., Pybus, O.G., Nelson, M.I., et al.: The genomic and epidemiological dynamics of human influenza A virus. Nature **453**(7195), 615–619 (2008)
21. Le Sage, V., Lowen, A.C., Lakdawala, S.S.: Block the spread: barriers to transmission of influenza viruses. Annu. Rev. Virol. **10**(1), 347–370 (2023)
22. He, D., Dushoff, J., Day, T., et al.: Inferring the causes of the three waves of the 1918 influenza pandemic in England and Wales. Proc. R. Soc. Lond. B, Biol. Sci. **280**(1766), 20131345 (2013)
23. Taubenberger, J.K., Morens, D.M.: Influenza: the once and future pandemic. Public Health Rep. **125**(Suppl 3), 15–26 (2010)
24. Han, A.X., de Jong, S.P.J., Russell, C.A.: Co-evolution of immunity and seasonal influenza viruses. Nat. Rev. Microbiol. **21**(12), 805–817 (2023)
25. Alexander, M.E., Bowman, C., Moghadas, S.M., et al.: A vaccination model for transmission dynamics of influenza. SIAM J. Appl. Dyn. Syst. **3**(4), 503–524 (2004)
26. Qiu, Z., Feng, Z.: Transmission dynamics of an influenza model with vaccination and antiviral treatment. Bull. Math. Biol. **72**, 1–33 (2010)
27. Zobayer, A., Ullah, M.S., Ariful Kabir, K.M.: A cyclic behavioral modeling aspect to understand the effects of vaccination and treatment on epidemic transmission dynamics. Sci. Rep. **13**(1), 8356 (2023)
28. Earn, D.J.D., He, D., Loeb, M.B., et al.: Effects of school closure on incidence of pandemic influenza in Alberta, Canada. Ann. Intern. Med. **156**(3), 173–181 (2012)
29. Nuno, M., Feng, Z., Martcheva, M., Castillo-Chavez, C.: Dynamics of two-strain influenza with isolation and partial cross-immunity. SIAM J. Appl. Math. **65**(3), 964–982 (2005)
30. Miranda, M.N.S., Pingarilho, M., Pimentel, V., et al.: A tale of three recent pandemics: influenza, HIV and SARS-CoV-2. Front. Microbiol. **13**, 889643 (2022)

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