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Modeling and optimal control of mutated COVID-19 (Delta strain) with imperfect vaccination

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\textbf{ABSTRACT}

As people around the world work to stop the COVID-19 pandemic, mutated COVID-19 (Delta strain) that are more contagious are emerging in many places. How to develop effective and reasonable plans to prevent the spread of mutated COVID-19 is an important issue. In order to simulate the transmission of mutated COVID-19 (Delta strain) in China with a certain proportion of vaccination, we selected the epidemic situation in Jiangsu Province as a case study. To solve this problem, we develop a novel epidemic model with a vaccinated population. The basic properties of the model are analyzed, and the expression of the basic reproduction number $R_0$ is obtained. We collect data on the Delta strain epidemic in Jiangsu Province, China from July 20, to August 5, 2021. The weighted nonlinear least square estimation method is used to fit the daily asymptomatic infected people, common infected people and severe infected people. The estimated parameter values are obtained, the approximate values of the basic reproduction number are calculated $R_0 \approx 1.378$. Through the global sensitivity analysis, we identify some parameters that have a greater impact on the prevalence of the disease. Finally, according to the evaluation results of parameter influence, we consider three control measures (vaccination, isolation and nucleic acid testing) to control the spread of the disease. The results of the study found that the optimal control measure is to dynamically adjust the three control measures to achieve the lowest number of infections at the lowest cost. The research in this paper can not only enrich theoretical research on the transmission of COVID-19, but also provide reliable control suggestions for countries and regions experiencing mutated COVID-19 epidemics.

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1. Introduction

The outbreak of COVID-19 in 2020 has yet to be fundamentally contained. It puts a long pause button on the lives of people around the globe. It has seriously affected people's health, life and work [1]. To help people out, experts in many countries are working on COVID-19 vaccines. In early 2021, the global epidemic improved thanks to the development of vaccines and the control of vaccination rates by many countries [2].

New strains of COVID-19 with high transmission rates are circulating around the world, such as the Alpha strain in the UK, the Beta strain in South Africa and the Delta strain in India [3]. At a recent WHO regular COVID-19 briefing, Soumya Swaminathan, WHO Chief Scientist, said that this novel Coronavirus variant is on its way to becoming the main circulating novel Coronavirus variant globally due to the significantly increased transmissibility of the Delta variant. It is characterized by rapid transmission, strong infectivity and atypical initial symptoms. The effectiveness of existing COVID-19 vaccines against Delta strain has been reduced, and some vaccinated people can still become infected with Delta strain, but must not become severely infected [4]. When the Chinese mainland was enjoying the victory over the epidemic, the imported Delta strain began a new round of transmission in the Chinese mainland [5].

On July 20, 2021, seven positive samples were found during routine nucleic acid tests at Lukou Airport in Nanjing, all of them from airport cleaning staff [6]. On July 21, four districts in Nanjing were upgraded to medium-risk areas. On July 22, and 23, 12 new cases were confirmed daily, and some areas of Nanjing were elevated to high-risk areas. Since then, six cities in Jiangsu province have confirmed cases of Delta strain.

Many scholars have studied the spread of COVID-19 in various places from different perspectives. One of the important ideas is to study the spread of COVID-19 through mathematical models. To that end, a number of mathematical models have been developed over the past two years to study local infections, estimate peaks

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in the number of people infected, and suggest ways to control the spread of the disease [7-16,28-40].

Sun et al. [7] established a SEIQR mathematical model to analyze the impact of the lockdown measures in Wuhan in 2020 on the spread of COVID-19. Neto et al. [8] built a SEHCR mathematical model, using a multi-objective genetic algorithm to analyze the local COVID-19 prevalence in Sao Paulo, Brazil, and suggested that the best intervention is to limit social distancing. Considering that communities and hospitals are different from other spaces in the process of disease transmission, Zhu et al. [9] proposed a SEIR-HC mathematical model to analyze the dynamic properties of disease transmission in Wuhan. The analysis showed that the base reproduction number for COVID-19 was 7.9, much higher than for many other infectious diseases. Kuwmey et al. [10] developed a SEIR mathematical model, taking into account public behavior and government interventions, and used the genetic algorithms to simulate and analyze COVID-19 data in South Korea in 2020. Olaniji et al. [11] proposed a COVID-19 model with a new incidence, performed parameter estimation and cost-effective analysis on the transmission of COVID-19 in Nigeria, and provided a most cost-effective control scheme.

Optimal control theory, a major branch of modern control theory, is a subject to study and solve the search for optimal solutions from all possible control schemes. Optimal control theory has been applied by many scholars to solve the problem of infectious disease control in recent years [17-20]. Zhang et al. [17] considered a Huanglongbing model with comprehensive intervention means and applied optimal control theory to get the optimal control strategy. The results showed that the coupled control strategy of spraying insecticide and clearing HLB symptom tree was the most cost-effective strategy. Li and Guo [18] considered the influence of media on game addiction and established an online game addiction model with positive and negative media reports. Through the analysis of optimal control theory, the results showed that reasonable control of media coverage can effectively reduce the phenomenon of game addiction. Alzahrani et al. [19] developed a mathematical model of mutated Zika virus, estimated parameters using data from Colombia in 2016, and proposed a set of control measures to eliminate Zika virus from communities. Yildiz and Karaoglu [20] considered the situation of exogenous reinfection of tuberculosis to establish a new dynamic model with treatment at home and treatment at hospital. Through the analysis of optimal control, the control strategy with optimal conversion rate between treatment at home and treatment at hospital was obtained.

There are two important differences between the spread of COVID-19 in 2021 and 2020. The first is that a certain percentage of people in many countries will already be vaccinated in 2021. While these vaccines can’t completely protect people from infection, they can reduce the severity of infection to some extent when fighting COVID-19. The second is that there are many different types of mutations in COVID-19 that make them different in their infectivity and mortality. Much has been written about control measures for COVID-19 as it spreads around the world in 2020. However, noting these differences, there have been few studies on the spread of mutated COVID-19 in populations with a certain proportion of vaccinations.

Inspired by the above literatures, in order to simulate and control the spread of mutated COVID-19 (Delta strain) in a vaccinated population in China, a novel mathematical model with vaccinated populations was developed.

2. The model formulation

2.1. System description

We divided the total population $N(t)$ into seven compartments.

- $S_1(t)$: the group of susceptible people who are not vaccinated;
- $V(t)$: the group that has been vaccinated and has developed antibodies;
- $S_2(t)$: the group that has been vaccinated but whose antibodies decrease over time;
- $A(t)$: the group of asymptomatic infected persons;
- $h_1(t)$: the group of people infected with common symptoms;
- $h_2(t)$: the group of people with severe symptoms;
- $R(t)$: the group that has recovered.

The flow diagram of the model is shown in Fig. 1.
\[ T_1(t) \text{: the confirmed asymptomatic cases; } \\
T_2(t) \text{: the confirmed common cases; } \\
T_3(t) \text{: the confirmed severe cases; } \\
R(t) \text{: the group of people who have been infected with COVID-19 and have recovered.} \]

Thus, the total population is given by:

\[
N(t) = S_1(t) + V(t) + S_2(t) + A(t) + I_1(t) + I_2(t) + T_1(t) + T_2(t) + T_3(t) + R(t).
\] (1)

The population flow among those compartments is shown in Fig. 1. A susceptible person can become infected with COVID-19 when they come into contact with an infected person in A, I_1, or I_2. The intensity of the infection is

\[
\lambda = \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N}
\]

A susceptible person who has not been vaccinated in S_1 may become asymptomatic infected person A, ordinary infected person I_1, or severe infected person I_2. Since the vaccine can prevent the infected person from becoming severe infection I_2 with a 100% probability [4], the susceptible person vaccinated in S_2 may become asymptomatic infection A or ordinary infection I_1.

Thus, the transfer diagram leads to the following system of ordinary differential equations:

\[
S'_1(t) = \Lambda - S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} - (\mu + \alpha_1) S_1, \\
V'(t) = \alpha_1 S_1 + \alpha_2 S_2 - (\mu + \alpha_3) V, \\
S'_2(t) = \alpha_3 V - S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} - (\mu + \alpha_2) S_2, \\
A'(t) = (1 - \theta_1 - \theta_2) S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + (1 - \theta_3) S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \text{ of (1 - \theta_2)S_1,} \\
I'_1(t) = \theta_2 S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + \theta_3 S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \text{ of (1 - \theta_2)S_1,} \\
I'_2(t) = \theta_2 S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + \theta_3 S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \text{ of (1 - \theta_2)S_1,} \\
T_1(t) = w_1 A - (\mu + w_4) T_1, \\
T'_2(t) = w_2 I_1 - (\mu + w_5) T_2, \\
T'_3(t) = w_3 I_2 - (\mu + d + w_6) T_3, \\
R'(t) = w_4 A + w_2 I_1 + w_3 I_2 - (\mu + \eta) R, \\
\]

where

- \(\Lambda\) is the birth rate;
- \(\mu\) is the natural mortality rate in all classes;
- \(\alpha_1\) denotes the rate of vaccination;
- \(\alpha_2\) denotes the rate of supplemental vaccination;
- \(\alpha_3\) denotes the rate at which antibodies are gradually lost in the body;
- \(\beta_1\) is transmission rate of contact with asymptomatic infected persons;
- \(\beta_2\) is transmission rate of contact with common infected persons;
- \(\beta_3\) is transmission rate of contact with severe infected persons;
- \(\theta_1\) is the proportion of susceptible population \(S_1\) to severe infected persons \(I_2\);
- \(\theta_2\) is the proportion of susceptible population \(S_1\) to common infected persons \(I_1\);
- \(\theta_3\) is the proportion of the population with weakened antibodies \(S_2\) to common infected persons \(I_1\);
- \(w_1\) is the rate of treatment of asymptomatic infected persons A after diagnosis;
- \(w_2\) is the rate of treatment of common infected persons \(I_1\) after diagnosis;
- \(w_3\) is the rate of treatment of severe infected persons \(I_2\) after diagnosis;
- \(w_4\) is the recovery rate of asymptomatic infected persons;
- \(w_5\) is the recovery rate of common infected persons;
- \(w_6\) is the recovery rate of severe infected persons;
- \(d\) is the death rate due to COVID-19 infection.

2.2. Positivity and boundedness of solutions

Since the number of people in each compartment of model (2) is nonnegative and finite, we want to verify here that the solution of model (2) is non-negative and bounded for all \(t > 0\).

System (2) can be put into the matrix form

\[
X' = G(X)
\] (3)

where \(X = (S_1, V, S_2, A, I_1, I_2, T_1, T_2, T_3, R)^T \in \mathbb{R}^{10}\) and \(G(X)\) is given by

\[
G(X) = \\
\begin{pmatrix}
G_1(X) \\
G_2(X) \\
G_3(X) \\
G_4(X) \\
G_5(X) \\
G_6(X) \\
G_7(X) \\
G_8(X) \\
G_9(X) \\
G_{10}(X)
\end{pmatrix}
\]

\[
\begin{pmatrix}
\Lambda - S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} - (\mu + \alpha_1) S_1 \\
\alpha_1 S_1 + \alpha_2 S_2 - (\mu + \alpha_3) V \\
\alpha_3 V - S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} - (\mu + \alpha_2) S_2 \\
(1 - \theta_1 - \theta_2) S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + (1 - \theta_3) S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \\
\theta_2 S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + \theta_3 S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \\
(1 - \theta_1 - \theta_2) S_1 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + (1 - \theta_3) S_2 \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} \\
w_1 A - (\mu + w_4) T_1 \\
w_2 I_1 - (\mu + w_5) T_2 \\
w_3 I_2 - (\mu + d + w_6) T_3 \\
w_4 A + w_2 I_1 + w_3 I_2 - (\mu + \eta) R
\end{pmatrix}
\]

Letting \(\varphi(t) = \frac{\beta_A A + \beta_I I_1 + \beta_2 I_2}{N} + \mu + \alpha_1\), the first equation of model (2) yields

\[
\frac{dS}{dt} = \Lambda - \varphi(t) S.
\]

Since system (2) has non-negative initial values, we use the integrating factor method and the solution is as follows.

\[
S(t) = S(0) \exp \left( - \int_0^t \varphi(u) du \right) \\
+ \exp \left( - \int_0^t \varphi(u) du \right) \int_0^t \Lambda \left[ \int_0^x \varphi(z) dz \right] dx > 0.
\]

Similarly, we can get the rest of the variables to be positive. Because of \(\sum_1^{10} G_i(x) = \Lambda - \mu N - dT_3 \leq \Lambda - \mu N\), we get

\[
\limsup_{t \to \infty} N(t) \leq \frac{\Lambda}{\mu}.
\]

Thus,

\[
\Omega = \{(S_1, V, S_2, A, I_1, I_2, T_1, T_2, T_3, R) \in \mathbb{R}_{+}^{10} | S_1 + V + S_2 + A + I_1 + I_2 + T_1 + T_2 + T_3 \leq \frac{\Lambda}{\mu} \}
\]

is a positive invariant set of system (2).
2.3. The basic reproduction number

By solving system (2), we can get a disease-free equilibrium $E_0$ as follows.

$$E_0 = \left( S_0^0, V_0^0, S_2^0, 0, 0, 0, 0, 0, 0 \right)$$

$$= \left( \frac{\alpha_1 k_2 \Lambda}{k_1 k_2 k_3 - k_1 \alpha_2 \alpha_3}, \frac{\alpha_1 \alpha_3 \Lambda}{k_1 k_2 k_3 - k_1 \alpha_2 \alpha_3}, 0, 0, 0, 0, 0, 0 \right). \quad (4)$$

In the following, the basic reproduction number of system (2) will be obtained by the next generation matrix method [21]. Let $x = (A, I_1, I_2, T_1, T_2, T_3, R, S_1, V, S_2)^T$, then system (2) can be written as

$$\frac{dx}{dt} = \mathcal{F}(x) - \mathcal{V}(x). \quad (5)$$

where

$$\mathcal{F}(x) = \begin{pmatrix}
(1 - \theta_1 - \theta_2) S_1 \frac{\beta_1 A + \beta_2 I_1 + \beta_3 I_2}{N} & (1 - \theta_1) S_2 \frac{\beta_1 A + \beta_2 I_1 + \beta_3 I_2}{N} \\
\theta_1 S_1 \frac{\beta_1 A + \beta_2 I_1 + \beta_3 I_2}{N} & 0 \\
0 & 0 \\
0 & 0 \\
0 & 0 \\
0 & 0 \\
0 & 0
\end{pmatrix}, \quad \mathcal{V}(x) = \begin{pmatrix}
k_2 A \\
k_2 I_1 \\
k_2 T_1 - w_4 A \\
k_2 T_2 - w_5 I_1 \\
k_2 T_3 - w_6 I_2 - w_7 T_3 \\
-\Lambda + S_1 \frac{\beta_1 A + \beta_2 I_1 + \beta_3 I_2}{N} + k_1 S_1 \\
-\alpha_1 S_1 - \alpha_2 S_2 + k_2 V \\
-\alpha_3 V + S_2 \frac{\beta_1 A + \beta_2 I_1 + \beta_3 I_2}{N} + k_3 S_2
\end{pmatrix}. $$

The Jacobian matrices of $\mathcal{F}(x)$ and $\mathcal{V}(x)$ at the disease-free equilibrium $E_0$ are

$$D\mathcal{F}(E_0) = \begin{pmatrix}
F_{3 \times 3} & 0 \\
0 & 0
\end{pmatrix}, \quad D\mathcal{V}(E_0) = \begin{pmatrix}
V_{3 \times 3} & 0 \\
J_1 & J_2
\end{pmatrix}.$$}

where

$$F_{3 \times 3} = \begin{pmatrix}
a_1 & a_2 & a_3 \\
a_4 & a_5 & a_6 \\
0 & 0 & 0
\end{pmatrix}, \quad V_{3 \times 3} = \begin{pmatrix}
k_4 & 0 & 0 \\
k_5 & 0 & 0 \\
k_6 & 0 & 0
\end{pmatrix}.$$}

$$J_1 = \begin{pmatrix}
-W_1 & 0 & 0 \\
0 & -W_2 & 0 \\
0 & 0 & -W_3
\end{pmatrix}, \quad J_2 = \begin{pmatrix}
-k_7 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_8 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & k_9 & 0 & 0 & 0 & 0 & 0 \\
-k_4 & -W_1 & -W_2 & -W_3 & \mu & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k_1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & k_2 & -k_3 & -k_4
\end{pmatrix}.$$}

The basic reproduction number [21], denoted by $R_0$, is given by

$$R_0 = \rho(FV^{-1}) = \frac{\mu}{k_1} \left[ (1 - \theta_3) \alpha_1 \alpha_3 \beta_1 + \beta_1 (1 - \theta_1 - \theta_2) \frac{\mu \alpha_1 \alpha_3}{k_4 (k_2 k_3 - \alpha_2 \alpha_3)} + \frac{\beta_2 \theta_2}{k_5} + \frac{\beta_3 \theta_1}{k_6} + \frac{\alpha_1 \alpha_3 \beta_2 \theta_1}{k_5 (k_2 k_3 - \alpha_2 \alpha_3)} \right].$$

where $\rho(A)$ represents the spectral radius of a matrix $A$. Since $k_2 k_3 - \alpha_2 \alpha_3 = \mu (\alpha_2 + \alpha_3 + \mu)$ is greater than 0, the basic reproduction number $R_0$ is always positive.
2.4. Existence of endemic equilibrium

The Endemic Equilibrium \( E^* = (S_1^*, V^*, S_2^*, A^* \ , I_1^*, I_2^*, T_1^*, T_2^*, R^*) \) of system (2) is determined by equations:
\[
\begin{align*}
\Lambda - S_1 & = 0, \\
\alpha_1 S_1 + \alpha_2 S_2 - k_3 V & = 0, \\
\alpha_3 V - S_2 & = 0, \\
(1 - \theta_1 - \theta_2) S_1 & = 0, \\
(1 - \theta_1 - \theta_2) I_1 + \beta_3 I_2 - k_3 I_1 & = 0, \\
(1 - \theta_1 - \theta_2) I_2 & = 0, \\
w_1 A - k_1 T_1 & = 0, \\
w_2 I_1 & = 0, \\
w_3 I_2 & = 0, \\
w_4 A + w_1 I_1 + w_2 I_2 - k_{10} R & = 0.
\end{align*}
\]

By solving the above equations, we get the following conclusion.
\[
S_1^* = \frac{\Lambda}{k_1 + \lambda_0^*}, \\
V^* = \frac{\alpha_1 \Lambda}{k_2 (k_1 + \lambda_0^*)} (1 + \frac{\alpha_2 \alpha_3}{k_2 k_3 + k_2 \lambda_0^* - \alpha_2 \alpha_3}), \\
S_2^* = \frac{\alpha_1 \alpha_3}{k_2 k_3 + k_2 \lambda_0^* - \alpha_2 \alpha_3} \frac{\Lambda}{k_1 + \lambda_0^*}, \\
A^* = \frac{\lambda_0^*}{k_4} (1 - \theta_1 - \theta_2) + (1 - \theta_3) \frac{\alpha_1 \Lambda}{k_2 (k_1 + \lambda_0^*)} (1 + \frac{\alpha_2 \alpha_3}{k_2 k_3 + k_2 \lambda_0^* - \alpha_2 \alpha_3}), \\
I_1^* = \frac{\lambda_0^*}{k_5} \theta_2 \frac{\Lambda}{k_1 + \lambda_0^*} + \theta_1 \frac{\alpha_1 \Lambda}{k_2 (k_1 + \lambda_0^*)} (1 + \frac{\alpha_2 \alpha_3}{k_2 k_3 + k_2 \lambda_0^* - \alpha_2 \alpha_3}), \\
I_2^* = \frac{\lambda_0^*}{k_6} \theta_1 \frac{\Lambda}{k_1 + \lambda_0^*}, \\
T_1^* = \frac{w_1 A^*}{k_7}, \\
T_2^* = \frac{w_2 I_1^*}{k_8}, \\
T_3^* = \frac{w_3 I_2^*}{k_9}, \\
R^* = \frac{w_4}{\mu} T_1^* + \frac{w_5}{\mu} T_2^* + \frac{w_6}{\mu} T_3^*.
\]

where
\[
\lambda_0^* = \frac{\beta_1 A^* + \beta_2 I_1^* + \beta_3 I_2^*}{N^*}.
\]

Equations in (6) are substituted into Eq. (7), and we get the following relationship.
\[
\xi_1 (\lambda_0^*)^2 + \xi_2 (\lambda_0^*) + \xi_3 = 0.
\]

where
\[
\begin{align*}
\xi_1 & = \frac{\lambda_0^*}{\mu k_2} (1 - \frac{d w_3 \theta_1}{(\mu + w_1) (\mu + w_2 + d)}), \\
\xi_2 & = \frac{\lambda_0^*}{\mu k_2} + \frac{k_2 k_3 - \alpha_2 \alpha_3}{\mu k_2 k_3} (1 - \frac{d w_3 \theta_1}{k_2 k_3} - k_2 \frac{\beta_1 (1 - \theta_1 - \theta_2)}{k_4} + \frac{\beta_2 \theta_2}{k_3} + \frac{\beta_3_3}{k_6}), \\
\xi_3 & = \frac{k_2 (k_1 + \alpha_2 + \alpha_3) (1 - R_0)}. 
\end{align*}
\]

Clearly, \( \xi_1 > 0 \) and \( \xi_3 \) is negative when \( R_0 > 1 \). Thus, the following theorem is established.

Theorem 1. For the model (2), there exists an Disease-Free Equilibrium \( E_0 = (\frac{\Lambda}{k_1}, \frac{\alpha_1 k_1 \Lambda}{k_1 k_2 k_3 - \alpha_1 \alpha_2 \alpha_3}, \frac{\alpha_1 \alpha_2 \Lambda}{k_1 k_2 k_3 - \alpha_1 \alpha_2 \alpha_3}, 0,0,0,0,0,0) \). And the model (2) has:

(i) if \( \xi_2 < 0, \xi_3 > 0 \) or \( (\xi_2)^2 - 4 \xi_1 \xi_3 = 0 \), then model (2) has a unique Endemic Equilibrium.
(ii) if \( \xi_2 < 0, \xi_3 = 0 \) or \( (\xi_2)^2 - 4 \xi_1 \xi_3 > 0 \), then model (2) has two Endemic Equilibrium,
(iii) if \( \xi_2 > 0, \xi_2 < 0 \) and \( (\xi_2)^2 - 4 \xi_1 \xi_3 > 0 \) then model (2) has two Endemic Equilibrium,
(iv) Otherwise no Endemic Equilibrium exists.
3. Stability of disease-free equilibrium

In this section, we will discuss the local and global stability of Disease-Free Equilibrium. For the local stability, we propose the following result.

**Theorem 2.** The Disease-Free Equilibrium $E_0$ is locally asymptotically stable if $R_0 < 1$ and unstable otherwise.

**Proof.** The Jacobian matrix at the Disease-Free Equilibrium $E_0$ is

$$
J(E_0) = \begin{pmatrix}
  a_1 - k_4 & a_2 & a_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
  a_4 & a_5 - k_5 & a_6 & 0 & 0 & 0 & 0 & 0 & 0 \\
  \theta_1 \beta_1 \frac{\mu}{k_1} & \theta_1 \beta_2 \frac{\mu}{k_1} & \theta_1 \beta_3 \frac{\mu}{k_1} - k_6 & 0 & 0 & 0 & 0 & 0 & 0 \\
  w_1 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 & 0 \\
  0 & w_2 & 0 & 0 & -k_8 & 0 & 0 & 0 & 0 \\
  0 & 0 & w_3 & 0 & 0 & -k_9 & 0 & 0 & 0 \\
  0 & 0 & 0 & w_4 & w_5 & w_6 & -\mu & 0 & 0 \\
  -\beta_1 \frac{\mu}{k_1} & -\beta_2 \frac{\mu}{k_1} & -\beta_3 \frac{\mu}{k_1} & 0 & 0 & 0 & -k_{10} & 0 & 0 \\
  \beta_1 \alpha_7 & \beta_2 \alpha_7 & \beta_3 \alpha_7 & 0 & 0 & 0 & 0 & \alpha_1 - k_2 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_3 - k_3 \\
\end{pmatrix}.
$$

(10)

where

$$
a_1 = (1 - \theta_1 - \theta_2) \beta_1 \frac{\mu}{k_1} + (1 - \theta_3) \beta_1 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_2 = (1 - \theta_1 - \theta_2) \beta_2 \frac{\mu}{k_1} + (1 - \theta_3) \beta_2 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_3 = (1 - \theta_1 - \theta_2) \beta_3 \frac{\mu}{k_1} + (1 - \theta_3) \beta_3 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_4 = \theta_1 \beta_1 \frac{\mu}{k_1} + \theta_2 \beta_1 \frac{\mu}{k_1} + \theta_3 \beta_3 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_5 = \theta_1 \beta_2 \frac{\mu}{k_1} + \theta_2 \beta_2 \frac{\mu}{k_1} + \theta_3 \beta_3 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_6 = \theta_1 \beta_3 \frac{\mu}{k_1} + \theta_2 \beta_3 \frac{\mu}{k_1} + \theta_3 \beta_3 \frac{\mu}{k_1} \frac{\mu \alpha_1 \alpha_3}{k_2 k_3 k_4 - k_1 \alpha_2 \alpha_3},
$$

$$
a_7 = \frac{\mu \alpha_1 \alpha_3}{k_1 (k_2 k_3 - k_1 \alpha_2 \alpha_3)}.
$$

We can easily obtain the characteristic roots of the matrix (10): $\lambda_1 = -k_7$, $\lambda_2 = -k_8$, $\lambda_3 = -k_9$, $\lambda_4 = -\mu$, $\lambda_5 = -k_1$, $\lambda_6$ and $\lambda_7$ are the characteristic roots of $M_1$, $\lambda_8$, $\lambda_9$, and $\lambda_{10}$ are the characteristic roots of $M_2$, where

$$
M_1 = \begin{pmatrix}
  -k_2 & \alpha_2 \\
  \alpha_3 & -k_3
\end{pmatrix},
$$

$$
M_2 = \begin{pmatrix}
  a_1 - k_4 & a_2 & a_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
  a_4 & a_5 - k_5 & a_6 & 0 & 0 & 0 & 0 & 0 & 0 \\
  \theta_1 \beta_1 \frac{\mu}{k_1} & \theta_1 \beta_2 \frac{\mu}{k_1} & \theta_1 \beta_3 \frac{\mu}{k_1} - k_6 & 0 & 0 & 0 & 0 & 0 & 0 \\
  w_1 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 & 0 \\
  0 & w_2 & 0 & 0 & -k_8 & 0 & 0 & 0 & 0 \\
  0 & 0 & w_3 & 0 & 0 & -k_9 & 0 & 0 & 0 \\
  0 & 0 & 0 & w_4 & w_5 & w_6 & -\mu & 0 & 0 \\
  -\beta_1 \frac{\mu}{k_1} & -\beta_2 \frac{\mu}{k_1} & -\beta_3 \frac{\mu}{k_1} & 0 & 0 & 0 & -k_{10} & 0 & 0 \\
  \beta_1 \alpha_7 & \beta_2 \alpha_7 & \beta_3 \alpha_7 & 0 & 0 & 0 & 0 & \alpha_1 - k_2 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_3 - k_3 \\
\end{pmatrix}.
$$

The characteristic equation of $M_1$ is

$$
\lambda^2 + (k_2 + k_3) \lambda + k_2 k_3 - \alpha_2 \alpha_3 = 0.
$$

Because $k_2 + k_3$ and $k_2 k_3 - \alpha_2 \alpha_3$ are positive, the characteristic roots of $M_1$ have negative real parts. The characteristic equation of $M_2$ is

$$
\lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3 = 0,
$$

where

$$
b_1 = k_4 - \beta_1 n_1 + k_5 - \beta_2 n_2 + k_6 - \beta_3 \theta_1 m_1,
$$

$$
b_2 = (k_4 k_5 - k_5 \beta_1 n_1 - k_6 \beta_2 n_2) + (k_4 k_6 - \beta_1 n_1 k_6 - k_5 \beta_3 \theta_1 m_1 k_4) + (k_5 k_6 - \beta_2 n_2 k_6 - \beta_3 \theta_1 m_1 k_5) + 2 \beta_1 \beta_2 n_1 n_2.,
$$

$$
b_3 = k_4 k_5 k_6 (1 - \frac{\beta_3 \theta_1 m_1}{k_4} - \frac{\beta_1 n_1}{k_4} - \frac{\beta_2 n_2}{k_5}) + 2 \beta_1 \beta_2 n_1 n_2 (k_6 - \beta_3 \theta_1 m_1),
$$

$$
n_1 = (1 - \theta_1 - \theta_2) m_1 + (1 - \theta_3) m_2.
$$

$$
n_2 = \theta_2 m_1 + \theta_3 m_2.
$$

$$
m_1 = \frac{\mu}{k_1}.
$$

$$
m_2 = \frac{\mu \alpha_1 \alpha_3}{k_1 (k_2 k_3 - \alpha_2 \alpha_3)}.
$$

And after some simplifying, we can get

$$
b_1 b_2 - b_3 = (k_4 - \beta_1 n_1 + k_5 - \beta_2 n_2) (k_4 k_5 - k_5 \beta_1 n_1 - k_6 \beta_2 n_2 + 2 \beta_1 \beta_2 n_1 n_2)$$

$$+(k_4 k_6 - k_5 \beta_1 n_1 - k_6 \beta_3 \theta_1 m_1) (k_4 - \beta_1 n_1 + k_5 - \beta_2 n_2 + k_6 - \beta_3 \theta_1 m_1)$$

$$+(k_5 k_6 - k_6 \beta_2 n_2 - k_5 \beta_3 \theta_1 m_1) (k_4 - \beta_1 n_1 + k_5 - \beta_2 n_2 + k_6 - \beta_3 \theta_1 m_1)$$

$$+k_5 \beta_1 n_1 \beta_3 \theta_1 m_1 + k_4 \beta_2 n_2 \beta_3 \theta_1 m_1.$$
When $R_0 = \frac{\beta_1 n_1}{k_4} + \frac{\beta_2 n_2}{k_5} + \frac{\beta_3 m_1}{k_6} < 1$, we can conclude that the following inequalities are true.

\[ k_4 > \beta_1 n_1, \quad k_5 > \beta_2 n_2, \quad k_6 > \beta_3 m_1, \]

\[ k_d k_5 > k_4 \beta_1 n_1 + k_4 \beta_2 n_2, \quad k_d k_6 > \beta_1 n_1 k_6 + \beta_3 m_1 k_4, \quad k_d k_6 > \beta_2 n_2 k_6 + \beta_3 m_1 k_5. \]

Thus, we obtain that $b_1 > 0$, $b_3 > 0$ and $b_1 b_2 - b_3 > 0$. By using the Routh-Hurwitz criteria, the Disease-Free Equilibrium $E_0$ of the system (2) is Locally Asymptotically Stable (LAS).

The Global Asymptotic Stability of DFE $E_0$ of the model (2) is proved in the following theorem.

**Theorem 3.** The Disease-Free Equilibrium $E_0$ of model (2) is Globally Asymptotically Stable if $R_0 < 1$ and unstable otherwise.

**Proof.** A continuous differentiable and positive definite Lyapunov function constructed for the COVID-19 model (2) is as follows.

\[ L(t) = x_1 A(t) + x_2 I_1(t) + x_3 I_2(t). \]

where, $x_i$ ($i = 1, 2, 3$) are nonnegative constants to be determined.

The time derivative of $L(t)$ along the solution path of system (2) is given by

\[
\begin{align*}
\frac{dL(t)}{dt} &= x_1[(1 - \theta_1 - \theta_2)S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N} + (1 - \theta_3)S_2 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N} - k_4 A] \\
&+ x_2[\theta_2 S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N} + \theta_3 S_2 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N} - k_5 I_1] \\
&+ x_3[\theta_1 S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N} - k_6 I_2] \\
&\leq x_1[(1 - \theta_1 - \theta_2)S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N^0} + (1 - \theta_3)S_2 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N^0} - k_4 A] \\
&+ x_2[\theta_2 S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N^0} + \theta_3 S_2 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N^0} - k_5 I_1] \\
&+ x_3[\theta_1 S_1 \frac{\beta_{1A} + \beta_{1I_1} + \beta_{1I_2}}{N^0} - k_6 I_2] \\
&= A(x_1(1 - \theta_1 - \theta_2)\beta_{1A} S_1 N^0 + x_1(1 - \theta_3)\beta_{1A} S_2 N^0 - x_1 k_4 + x_2 \theta_1 \beta_{1I_1} S_1 N^0 + x_2 \theta_2 \beta_{1I_1} S_2 N^0) \\
&+ x_2 \theta_1 \beta_{1I_1} S_1 N^0 + I_1[x_1(1 - \theta_1 - \theta_2)\beta_{1I_1} S_1 N^0 + x_1(1 - \theta_3)\beta_{1I_1} S_2 N^0 + x_2 \theta_1 \beta_{1I_2} S_1 N^0] \\
&+ x_2 \theta_2 \beta_{1I_1} S_2 N^0 - x_2 k_5 + x_3 \theta_1 \beta_{1I_2} S_1 N^0 + I_2[x_1(1 - \theta_1 - \theta_2)\beta_{1I_2} S_1 N^0 + x_1(1 - \theta_3)\beta_{1I_2} S_2 N^0] \\
&+ x_2 \theta_2 \beta_{1I_2} S_2 N^0 + x_3 \theta_1 \beta_{1I_2} S_1 N^0 - x_3 k_6].
\end{align*}
\]

Assuming $x_1 = 1$, we can obtain the expressions of $x_2$ and $x_3$.

\[
x_2 = \frac{k_d k_5 \beta_{1} S_1 (1 - \theta_1 - \theta_2) S^0_1 + (1 - \theta_3) S^0_2}{k_5 k_d - k_6 k_2 S^0_2 - k_5 k_2 S^0_1 - k_5 \theta_1 S^0_2}, x_3 = \frac{k_d k_5 \beta_{1} S_1 (1 - \theta_1 - \theta_2) S^0_1 + (1 - \theta_3) S^0_2}{k_5 k_d - k_6 k_2 S^0_2 - k_5 k_2 S^0_1 - k_5 \theta_1 S^0_2}.
\]

So

\[
\frac{dL(t)}{dt} \leq A \frac{k_d (R_0 - 1)}{1 - \mu \left( \frac{\beta_{1A} S_1 + \theta_2 \beta_{1I_1} S_1 N^0}{\theta_2 \beta_{2I_2} S_2 N^0 + \theta_1 \beta_{1I_1} S_1 N^0 + k_2 \theta_2 \beta_{1I_1} S_2 N^0} \right)}. 
\]

Thus, it is obvious that $\frac{dL(t)}{dt} < 0$ when $R_0 < 1$. By using the LaSalle’s invariant principle, $E_0$ is Globally Asymptotically Stable in the region $\Omega$.

**4. Optimal control**

In this section, we will use the Pontriagin maximum principle in optimal control theory to find the optimal control strategy during the transmission of COVID-19. Our goal is to minimize the cumulative number of infections and the cost associated with the spread of the disease. We consider the following key control measures: increasing vaccination rates, increasing the intensity of daily isolation and nucleic acid testing for all people in the city. The specific control means are described below.

1. $u_1$ represents vaccination measure aimed at preventing and controlling the spread of COVID-19 by increasing the number of people vaccinated. The control measures are mainly implemented through two programmes: one is to increase vaccination in unvaccinated susceptible group $S_1$; The second is to supplement the COVID-19 antibody to $S_2$, a population with weakened antibodies. $r_1$ represents the rate of vaccination in $S_1$ and $S_2$.

2. $u_2$ represents the measure to isolate the virus, which are mainly achieved through isolation of infected persons, disinfection of the environment and increasing the daily wear of masks when going out.

3. $u_3$ stands for nucleic acid test for all people in the city, with the aim of screening out all asymptomatic infected person $A$, common infected person $I_1$ and severe infected person $I_2$, and then treating them separately. $r_2$ represents the probability of successful screening of a nucleic acid test.
We consider the above three control variables into model (2) to determine the optimal control strategy and get the following nonlinear systems.

\[
S_1'(t) = \Lambda - (1 - u_2)S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + \alpha_1 + u_1\tau_1)S_1,
\]

\[
V'(t) = (\alpha_1 + u_1\tau_1)S_1 + \alpha_2S_2 - (\mu + \alpha_3)V + u_1\tau_1S_2,
\]

\[
S_2'(t) = \alpha_3V - (1 - u_2)S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + \alpha_2)S_2 - u_1\tau_1S_2,
\]

\[
A'(t) = (1 - u_2)(1 - \theta_1 - \theta_2)S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} + (1 - u_2)(1 - \theta_3)S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_1 + u_3\tau_2)A,
\]

\[
I_1'(t) = (1 - u_2)\theta_2S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} + (1 - u_2)\theta_3S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_2 + u_3\tau_2)I_1,
\]

\[
I_2'(t) = (1 - u_2)\theta_2S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_3 + u_3\tau_2)I_2.
\]

\[
T_1'(t) = (w_1 + u_3\tau_2)A - (\mu + w_4)T_1.
\]

\[
T_2'(t) = (w_2 + u_3\tau_2)I_1 - (\mu + w_5)T_2.
\]

\[
T_3'(t) = (w_3 + u_3\tau_2)I_2 - (\mu + w_6 + d)T_3.
\]

\[
R'(t) = w_7T_1 + w_8T_2 + w_9T_3 - \mu R.
\]

The effect of control is determined by the following objective function,

\[
J(u_1, u_2, u_5) = \int_0^{t_f} (B_1A + B_2I_1 + B_3I_2 + B_4 \frac{u_1^2}{2} + B_5 \frac{u_2^2}{2} + B_6 \frac{u_3^2}{2}) dt,
\]

where \(B_1, B_2, B_3\) are the weight coefficients of the infected people. The constants \(B_4, B_5, B_6\) are the weight coefficients of the control variables \(u_1, u_2, u_3\). Our main concern is to find optimal controls \((u_1^*, u_2^*, u_3^*)\) such that

\[
J(u_1^*, u_2^*, u_5^*) = \min J(u_1, u_2, u_3), \quad (u_1, u_2, u_3) \in U.
\]

Here, \(u_i(t) \in (0, 1)\), for all \(t \in [0, t_f]\), \(i = 1, 2, 3\). The control set is shown as

\[
U = \{(u_1, u_2, u_3) | u_i(t)\ \text{is Lebesgue measurable on} \ [0, 1], \ (i = 1, 2, 3)\}.
\]

On the basis of the Pontryagin's maximum principle [22], we set up the Hamiltonian function as follows

\[
H = B_1A + B_2I_1 + B_3I_2 + B_4 \frac{u_1^2}{2} + B_5 \frac{u_2^2}{2} + B_6 \frac{u_3^2}{2} + \lambda_1[\Lambda - (1 - u_2)S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + \alpha_1 + u_1\tau_1)S_1]
\]

\[
+ \lambda_2[(\alpha_1 + u_1\tau_1)S_1 + \alpha_2S_2 - (\mu + \alpha_3)V + u_1\tau_1S_2]
\]

\[
+ \lambda_3[\alpha_3V - (1 - u_2)S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + \alpha_2)S_2 - u_1\tau_1S_2]
\]

\[
+ \lambda_4[(1 - u_2)(1 - \theta_1 - \theta_2)S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} + (1 - u_2)(1 - \theta_3)S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_1 + u_3\tau_2)A]
\]

\[
+ \lambda_5[(1 - u_2)\theta_2S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} + (1 - u_2)\theta_3S_2 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_2 + u_3\tau_2)I_1]
\]

\[
+ \lambda_6[(1 - u_2)\theta_2S_1 \frac{\beta_1A + \beta_2I_1 + \beta_3I_2}{N} - (\mu + w_3 + u_3\tau_2)I_2]
\]

\[
+ \lambda_7[(w_1 + u_3\tau_2)A - (\mu + w_4)T_1]
\]

\[
+ \lambda_8[(w_2 + u_3\tau_2)I_1 - (\mu + w_5)T_2]
\]

\[
+ \lambda_9[(w_3 + u_3\tau_2)I_2 - (\mu + w_6 + d)T_3]
\]

\[
+ \lambda_{10}[w_7T_1 + w_8T_2 + w_9T_3 - \mu R],
\]

where \(\lambda_i \ (i = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10)\) are the adjoint variables.
Theorem 4. Given optimal control pairs \((u^*_i, u^*_j, u^*_k)\) and solutions \(S_1(t), V(t), S_2(t), A(t), I_1(t), I_2(t), T_1(t), T_2(t), T_3(t), R(t)\) of the state system (18), there exist adjoint variables \(\lambda_i\), \((i = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10)\), satisfying the following adjoint system:

\[
\begin{align*}
\lambda'_1 &= \lambda_1 (1 - u_2) \frac{\beta_4 + \beta_5}{\beta_3} - (\mu + \alpha_1 + u_1 \tau) - \lambda_2 (\alpha_1 + u_1 \tau) \\
-\lambda'_2 &= \lambda_2 (1 - \theta_2) (1 - \theta_2) \frac{\beta_4 + \beta_5}{\beta_3} - \lambda_5 (1 - u_2) \theta_2 \frac{\beta_4 + \beta_5}{\beta_3} \\
-\lambda'_3 &= \lambda_3 (1 - u_2) \theta_1 \frac{\beta_4 + \beta_5}{\beta_3} - \lambda_5 u_3 \tau_1 + \lambda_3 u_1 \tau_1, \\
\lambda'_4 &= -B_1 + \lambda_1 (1 - u_2) \frac{\beta_4}{\beta_3} S_1 + \lambda_3 (1 - u_2) \frac{\beta_4}{\beta_3} S_2 - \lambda_4 (1 - u_2) (1 - \theta_2) \frac{\beta_4}{\beta_3} S_1 \\
-\lambda'_5 &= -B_2 + \lambda_1 (1 - u_2) \frac{\beta_4}{\beta_3} S_1 + \lambda_3 (1 - u_2) \frac{\beta_4}{\beta_3} S_2 - \lambda_4 (1 - u_2) (1 - \theta_2) \frac{\beta_4}{\beta_3} S_1 \\
+\lambda_5 (1 - u_2) \theta_2 \frac{\beta_4}{\beta_3} S_1 - \lambda_6 (1 - u_2) \theta_3 \frac{\beta_4}{\beta_3} S_1 + \lambda_8 (W_2 + u_3 \tau_2), \\
\lambda'_6 &= -B_3 + \lambda_1 (1 - u_2) \frac{\beta_4}{\beta_3} S_1 + \lambda_3 (1 - u_2) \frac{\beta_4}{\beta_3} S_2 - \lambda_4 (1 - u_2) (1 - \theta_2) \frac{\beta_4}{\beta_3} S_1 \\
-\lambda'_7 &= \lambda_7 (\mu + W_4) - \lambda_10 W_4, \\
\lambda'_8 &= \lambda_8 (\mu + W_5) - \lambda_10 W_5, \\
\lambda'_9 &= \lambda_9 (\mu + W_6 + d) - \lambda_10 W_6, \\
\lambda'_{10} &= \lambda_{10} \mu.
\end{align*}
\]

The terminal condition of adjoint equations is given by

\[
\lambda_i(t_f) = 0, \quad i = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. \tag{15}
\]

And the optimal controls are given by

\[
\begin{align*}
u^*_1 &= \max(0, \min \{ \frac{\lambda_1 - \lambda_2 \tau_1 S_1 + (\lambda_3 - \lambda_2 \tau_1 S_2)}{B_4} \}), \\
u^*_2 &= \max(0, \min \{ \frac{\beta_4 A + \beta_5 I_1 + \beta_6 I_2}{B_5} S_1 \} \{ \frac{-\lambda_1 + \lambda_4 (1 - \theta_2) + \lambda_5 \theta_2 + \lambda_6 \theta_1}{B_6} \}), \\
u^*_3 &= \max(0, \min \{ \tau_2 (\lambda_4 A + \lambda_5 I_1 + \lambda_6 I_2 - \lambda_7 A - \lambda_8 I_1 - \lambda_9 I_2) / B_6 \}).
\end{align*}
\]

Proof. According to the Pontryagin’s Maximum Principle [22], we differentiate the Hamiltonian operator \(H\). The adjoint system can be written as

\[
\begin{align*}
\lambda'_1 &= \frac{\partial H}{\partial S_1}(t), \quad \lambda'_2 = \frac{\partial H}{\partial V}(t), \quad \lambda'_3 = -\frac{\partial H}{\partial S_2}(t), \\
\lambda'_4 &= -\frac{\partial H}{\partial A}(t), \quad \lambda'_5 = -\frac{\partial H}{\partial I_1}(t), \quad \lambda'_6 = -\frac{\partial H}{\partial I_2}(t), \\
\lambda'_7 &= -\frac{\partial H}{\partial T_1}(t), \quad \lambda'_8 = -\frac{\partial H}{\partial T_2}(t), \quad \lambda'_9 = -\frac{\partial H}{\partial T_3}(t), \quad \lambda'_{10} = -\frac{\partial H}{\partial R}(t),
\end{align*}
\]

and \((u^*_1, u^*_2, u^*_3)\) satisfy the condition

\[
\frac{\partial H}{\partial u_i} = 0, \quad (i = 1, 2, 3).
\]

By solving the above equations, the proof is completed. \(\square\)
Table 1
Statistics Population in NHC of Jiangsu Province, China.

| Date      | New cases | Cumulative cases | Confirmed asymptomatic cases | Confirmed common cases | Confirmed severe cases |
|-----------|-----------|------------------|------------------------------|------------------------|-----------------------|
| 2021/07/20 | 7         | 7                | 4                            | 3                      | 0                     |
| 2021/07/21 | 4         | 11               | 6                            | 5                      | 0                     |
| 2021/07/22 | 12        | 23               | 12                           | 10                     | 1                     |
| 2021/07/23 | 12        | 35               | 19                           | 15                     | 1                     |
| 2021/07/24 | 2         | 37               | 20                           | 16                     | 1                     |
| 2021/07/25 | 39        | 76               | 41                           | 33                     | 2                     |
| 2021/07/26 | 31        | 110              | 66                           | 39                     | 2                     |
| 2021/07/27 | 48        | 158              | 81                           | 70                     | 4                     |
| 2021/07/28 | 20        | 178              | 78                           | 90                     | 7                     |
| 2021/07/29 | 18        | 196              | 86                           | 99                     | 8                     |
| 2021/07/30 | 19        | 215              | 93                           | 110                    | 9                     |
| 2021/07/31 | 30        | 245              | 97                           | 137                    | 8                     |
| 2021/08/01 | 40        | 288              | 97                           | 177                    | 8                     |
| 2021/08/02 | 45        | 335              | 116                          | 203                    | 8                     |
| 2021/08/03 | 35        | 373              | 122                          | 234                    | 6                     |
| 2021/08/04 | 40        | 413              | 131                          | 253                    | 12                    |
| 2021/08/05 | 61        | 474              | 135                          | 299                    | 16                    |

Fig. 2. The cumulative cases per day in Jiangsu Province, China from July 20, 2021 to August 8, 2021.

5. Numerical simulation

5.1. Data collection

We obtained relevant case data from the official website of Health Commission of Jiangsu Province, China. The data, including new cases, cumulative cases, asymptomatic cases, common cases and severe cases, are shown in Table 1.

The cumulative cases are shown in Fig. 2. Figure 2 also reflects the spread of mutated COVID-19 (Delta strain) in populations with a certain proportion of vaccination. As can be seen from Fig. 2, the growth rate of the curve is slower than that of [40]. This suggests that the transmission rate of Delta virus in a population in which a fraction of the population has been vaccinated has slowed. Although the mutated strain is more infectious, the intensity of transmission can still be greatly reduced by the vaccine. Vaccination plays a role in controlling the spread of COVID-19 among people.

5.2. Parameter estimation

This section uses COVID-19 model (2) to simulate the data obtained above. Before parameter estimation, some parameter values can be obtained from some existing literatures. For example, according to the data of the seventh national population census released by the National Bureau of Statistics of China in 2020, the average life expectancy of Chinese people is 77 years old [23], so we assume the natural mortality rate $\mu = 1/(77 \times 365)$ per day. It also shows that the total population of Jiangsu province in 2020 is 84,748,016. We assume that $\Lambda/\mu$ is the limit cumulative num-
ber without infection, so $\Lambda = 3015.4$ per day. At the same time, we are pleased to note that there were no deaths due to COVID-19 during this period due to improved health care, adequate medical resources and vaccine protection, so we set the death rate $\delta = 0$.

In order to make full use of the collected data, we choose non-linear weighted least square estimation method for parameter estimation [24]. The main steps of this statistical method are described as follows. The sum of the squares errors (SSE), is expressed mathematically as:

$$SSE = W_1 \sum_{i=1}^{n} (A_i - \tilde{A}_i)^2 + W_2 \sum_{i=1}^{n} (I_i - \tilde{I}_i)^2 + W_3 \sum_{i=1}^{n} (I_2_i - \tilde{I}_2_i)^2,$$

where $(A_i, (I_i), (I_2_i))$ are the reported data, $(\tilde{A}_i, (\tilde{I}_i), (\tilde{I}_2_i))$ are the solution of the model (2) at time $t_i$, $W_1, W_2$ and $W_3$ are the weight coefficients of each reported data sequence, and their values are the reciprocal of the variances of each sequence. The goal is to minimize the following objective function

$$\min SSE \quad \text{subject to system (2).}$$

(16)

We use the fminsearch function in MATLAB to fit the real data, and the fitting results are shown in Fig. 3. It can be seen from the results in Fig. 3 that the fitting results are very close to the real data and the obtained results are reliable. All of the resulting parameter values are shown in Table 2. Combined with the expression of the basic reproduction number in the previous theory, we can get the approximate value of the basic reproduction number is $R_0 \approx 1.378$.

By the biological significance of the basic reproduction number, we know that when $R_0 > 1$, the disease gradually spreads out in the population. The main means of controlling the spread of disease through drug intervention is vaccination. We increased the values of vaccination proportion and supplemental vaccine antibody proportion separately to observe their effects on the number of infections. The results are shown in Fig. 4.

As can be seen from the comparison results in Fig. 4, when we increase $\alpha_1$ and $\alpha_2$, the number of people in all three infected compartments decreases to varying degrees. This result is what we would like to see. By comparing the subplots in Fig. 4, we can see that increasing $\alpha_1$ has better results than increasing $\alpha_2$. But that's just a graphical observation. In order to quantify and evaluate the influence of each parameter on the basic reproduction number $R_0$, we will further perform uncertainty and sensitivity analysis on the model.

### Table 2

| Parameters | Descriptions | Values | Sources |
|------------|--------------|--------|---------|
| $\mu$ | Natural death rate | 1/(77+365) | Estimated |
| $\Lambda$ | Recruitment rate | 3015.4 | Estimated |
| $\alpha_1$ | Rate of vaccination | 0.016699 | Fitted |
| $\alpha_2$ | Rate of supplemental vaccination | 0.006981 | Fitted |
| $\alpha_3$ | The percentage of vaccine antibodies that decline | 0.010396 | Fitted |
| $\beta_1$ | Contact rate of asymptomatic infected people | 0.436923 | Fitted |
| $\beta_2$ | Contact rate of common infected people | 0.768044 | Fitted |
| $\beta_3$ | Contact rate of severe infected people | 0.000131 | Fitted |
| $\theta_1$ | Transmission rate from $S_1$ to $I_1$ | 0.076371 | Fitted |
| $\theta_2$ | Transmission rate from $S_1$ to $I_2$ | 0.008571 | Fitted |
| $\theta_3$ | Transmission rate from $S_2$ to $I_1$ | 0.007979 | Fitted |
| $w_1$ | Rate of being diagnosed in $A_i$ | 0.196831 | Fitted |
| $w_2$ | Rate of being diagnosed in $I_i$ | 0.059082 | Fitted |
| $w_3$ | Rate of being diagnosed in $I_2_i$ | 0.006502 | Fitted |
| $w_4$ | Recovery rate of asymptomatic infected people | 0.715480 | Fitted |
| $w_5$ | Recovery rate of common infected people | 0.000207 | Fitted |
| $w_6$ | Recovery rate of severe infected people | 0.214278 | Fitted |

### 5.3. Uncertainty analysis and global sensitivity analysis

In this section, we discuss the uncertainty and sensitivity analysis of the important threshold parameters, namely, $R_0$, to determine those model parameters that have the greatest impact on disease dynamics. This analysis quantifies the uncertainty in any complex model in math. In particular, sensitivity analysis is used to study the contribution of initial parameters and conditions to model results. In order to achieve this goal, we use a very efficient statistical technique that a combination of latin hypercube sampling (LHS) and partial rank correlation coefficient (PRCC) is used. In the method, we obtain the values of PRCC for each parameter, which can be used to help estimate the level of uncertainty in mathematical models. For a more detailed introduction of this method, please refer to [25].

In order to generate the LHS matrices, we make all parameters subject to uniform distribution. We set up a total of 1000 simulations. After Latin hypercube sampling, we get the LHS matrix of the corresponding basic reproduction number. We removed some sparse outliers less than 0 or greater than 5. The frequency of $R_0$ is shown in Fig. 5. As shown in Fig. 5, we get that the mean, 5th and 95th percentiles being 1.1506, 0.1548 and 3.1995 of the distribution for $R_0$. In the previous section, we estimated $R_0$ to be 1.378, which is close to the mean. The estimate of $R_0$ is indicated by a red dotted line in Fig. 5. We notice that the distribution of $R_0$ is very wide, so its uncertainty is very high. And most of the values of $R_0$ are smaller than the estimated values of $R_0$. Therefore, we want to further analyze which parameters have a greater influence on $R_0$ and consider the control means in reality through the analysis results. PRCC values of all parameters in $R_0$ are shown in Fig. 6 in the form of bar charts, and the corresponding P-values are shown in Table 3.

The PRCC values of all parameters in $R_0$, the significance results of the parameters are given in Table 3. When $p < 0.01$, there is a significant correlation between the input parameters and the out-

### Table 3

| Parameters | PRCC | P-value | Parameters | PRCC | P-value |
|------------|------|---------|------------|------|---------|
| $\mu$ | -0.006183 | 0.846109 | $\theta_1$ | 0.355045 | 0.000000 |
| $\alpha_1$ | -0.422072 | 0.000000 | $\theta_2$ | -0.011950 | 0.707551 |
| $\alpha_2$ | -0.193928 | 0.000000 | $\theta_3$ | -0.014944 | 0.638945 |
| $\alpha_3$ | 0.213412 | 0.000000 | $w_1$ | -0.368768 | 0.000000 |
| $\beta_1$ | 0.276643 | 0.000000 | $w_2$ | -0.340624 | 0.000000 |
| $\beta_2$ | 0.229959 | 0.000000 | $w_3$ | -0.313606 | 0.000000 |
| $\beta_3$ | 0.334942 | 0.000000 | | | |

Sources
put result $R_0$. As can be seen from the results in Fig. 6, $\alpha_3$, $\beta_1$, $\beta_2$, $\beta_3$, and $\theta_1$ have higher positive PRCC values. This suggests that we can reduce $R_0$ by decreasing the value of these parameters. On the other hand, $\alpha_1$, $\alpha_2$, $w_1$, $w_2$ and $w_3$ have large negative PRCC values. This indicates that if we increase the values of these parameters, it will help to reduce the basic reproduction number $R_0$. $\alpha_2$ is the rate at which antibodies disappear in the body, and $\theta_1$ is the percentage of susceptible people who become asymptomatic after becoming infected. These are factors that are not easy to control. The remaining important influence parameters will be divided into three groups for discussion.

1) $\alpha_1$ and $\alpha_2$: represent the rate of vaccination and the rate of supplementary vaccination respectively, which have a very strong influence on $R_0$. Therefore, increasing vaccination to establish an immune barrier as quickly as possible can effectively reduce $R_0$. So we are considering increasing vaccination coverage as an important measure to control the spread of COVID-19.

2) $\beta_1$, $\beta_2$, and $\beta_3$: represent the contact rates of the three infected compartments respectively. We can see from Fig. 6 that their PRCC values are positive, indicating that they are positively correlated with $R_0$. We can consider reducing the exposure rate to reduce the value of $R_0$, so as to achieve the effect of suppressing the spread of COVID-19. In reality, the answer is that all people need to maintain social distancing and reduce the chance of intersecting. Therefore, we consider isolation as the second important measure to control COVID-19.

3) $w_1$, $w_2$ and $w_3$: represent the rates at which people from the three infected compartments were transferred to treatment chambers after being confirmatory by nucleic acid tests. As shown in Fig. 6, they all have large negative PRCC values, which means that we can reduce $R_0$ by increasing their values to achieve the effect of controlling the spread of COVID-19. In practice, the response would be to test everyone in the area for nucleic acid, so as to get as many infected people as possible to treatment and reduce the likelihood of further
transmission. Therefore, we will consider nucleic acid testing for all people as a third important means of control.

5.4. Optimal control

In this subsection, we will perform numerical simulations on the model without control (2) and model with control (9) to illustrate the importance of control means. An efficient forward-backward sweep method is used to solve the system with control. For detailed introduction and application of this method, please refer to references [17–23]. The values of all parameters are shown in Table 2. The time span of the simulation is 30 days. After investigation, it is known that the effective rate of Chinese vaccination to produce antibodies is 65% [4,26]. The usual incubation period for COVID-19 is 14 days, with an average of 7 days [27]. So we choose $\tau_1 = 0.65$, $\tau_2 = 1/7$. After some experimental calculations, these weight parameters are evaluated as $B_1 = B_2 = B_3 = 1$, $B_4 = B_5 = B_6 = 100$. In the objective world, the control effect will be affected by a variety of factors and it is very difficult to achieve the ideal 100% state, so we set the maximum value of the control variable as 0.8. In order to explore the effect of each control means, we set up the following control scheme.

- **Scenario 1:** Single control strategies
  - Strategy A: Vaccination only ($u_1$).
  - Strategy B: Isolation only ($u_2$).
  - Strategy C: Detection only ($u_3$).

- **Scenario 2:** Double control strategies
  - Strategy D: Vaccination ($u_1$) + Isolation ($u_2$).
  - Strategy E: Vaccination ($u_1$) + Detection ($u_3$).
  - Strategy F: Isolation ($u_2$) + Detection ($u_3$).
Fig. 5. Uncertainty analysis of $R_0$.

Fig. 6. Global sensitivity analysis of model parameters and PRCC results for $R_0$. 
Scenario 3: Triple control strategies

Strategy C: Vaccination ($u_1$) + Isolation ($u_2$) + Detection ($u_3$).

Fig. 7 (a–c) show the changes in the number of asymptomatic infected people $A(t)$, common infected people $I_1(t)$ and severe infected people $I_2(t)$ in scenario 1. Fig. 7(d–f) reflect the change rule of the control variable $u_1$ in scenario 1. As can be seen from the Fig. 7(d), the control strength of $u_1$ should be maintained at the maximum strength of 0.8 at the beginning for 20 days, and then gradually decrease to 0. In strategy B, the control strength of $u_2$ should be kept at the maximum strength of 0.8 from the beginning, and gradually decreased to 0 until the 22nd day. In strategy C, the control intensity of $u_3$ needs to maintain a maximum intensity of 0.8 for the first 24 days and then gradually decrease to 0.

From Fig. 7(a–c), we can see that the number of infected people under strategy A, strategy B and strategy C are significantly lower than that without control. Moreover, we also found that strategy B had the lowest number of asymptomatic infections, while strategy C had the lowest number of common and severe cases.

These results show that all three control measures have some inhibitory effect on the spread of mutated COVID-19. The best single control measure is strategy C.

Figure 8 (a–c) show the changes in the number of asymptomatic infected people $A(t)$, common infected people $I_1(t)$ and severe infected people $I_2(t)$ in scenario 2. Figure 8 (d–f) reflect the change rule of the control variable $u_1$ in scenario 2. As can be seen from the Fig. 8(d), the control strength of $u_1$ and $u_2$ should be maintained at the maximum strength of 0.8 at the beginning for 2 days and 18 days, then gradually decrease to 0. In strategy E,
the control strength of $u_1$ and $u_3$ should be kept at the maximum strength of 0.8 from the beginning, and gradually decreased to 0 until day 5 and day 12, respectively. In strategy F, the control intensity of $u_2$ and $u_3$ needs to maintain a maximum intensity of 0.8 for the first 12 days and then gradually decrease to 0.

In Fig. 8 (a), we can see that strategy F will have the lowest number of asymptomatic infections. In Fig. 8 (b–c), we can see that the number of cases in both strategy E and strategy F is very small. Therefore, we believe that in scenario 2 of double control measures, strategy F is the most effective double control strategy.

Figure 9 (a–c) show the changes in the number of asymptomatic infected people, common infected people and severe infected people under without control and strategy G. Figure 9(d) shows the changes in the strength of the two control variables under strategy G. The control variables $u_1$, $u_2$ and $u_3$ need to be maintained at the maximum strength of 0.8 at the beginning, which lasts until the 2nd, 9th and 11th day respectively, and then gradually decreases to 0.

As can be seen from Fig. 9(a–c), the number of people in each infected compartment under strategy G decreased significantly compared with that without control. Comparing Fig. 7, 8 and 9, we find that strategy G seems to have the least number of infections, but it is not so clear from the image alone. To compare all control strategies, we need to further calculate the total infectious individuals $T_I = \int_0^T (A + I_1 + I_2)dt$ and the total averted cases $TA = \int_0^T (A + I_1 + I_2 - (\tilde{A} + \tilde{I}_1 + \tilde{I}_2))dt$, where $(A, I_1, I_2)$ denote the infected people of without control, $(\tilde{A}, \tilde{I}_1, \tilde{I}_2)$ denote the infected people of a control strategy. The results of all calculations are shown in Table 4.

As you can see from the IAR data of Table 4, strategy G can prevent more people from becoming infected. This also indicates that strategy G is the optimal control strategy we are looking for. We should implement $u_1$, $u_2$ and $u_3$ at the same time according to the control plan shown in Fig. 9(d), so as to minimize the number of
infections and control the spread of the disease as soon as possible.

In Fig. 9(d), it is shown that the three control measures should change dynamically. The first control, which increased the rate of vaccination, was initially at maximum intensity, rapidly decreasing to a level of 0.2 between day 2 and day 7, and slowly decreasing to 0 over the following 23 days. Because of the level of vaccine production and the number of health workers, it is difficult to rely on vaccination to make a large number of people produce antibodies in a short period of time and stop the spread of COVID-19. Therefore, maintaining maximum vaccination levels is not very effective in preventing the spread of COVID-19. Increased vaccination controls should be viewed as a complementary measure in the event of a sudden outbreak of COVID-19 transmission.

The second control measure (isolation) should be maintained at the maximum control level at the beginning and gradually reduced to zero by the 9th day. This is mainly because, in the case of a sudden outbreak of COVID-19, quarantine measures are effective in stopping the spread of the disease by cutting off the route of transmission in the real world. At the same time, it is worth noting that the effectiveness of this measure depends not only on the control of government departments, but also on the active cooperation of people.

The third control measure (detection), at the beginning, also needs to be maintained at the maximum level of control so that infected people can be quickly transferred to hospitals and isolated for treatment as soon as possible. The control intensity of the test continued until day 11 and then gradually decreased to 0. This measure effectively reduces the source of COVID-19 transmission in the population and plays an important role in the rapid control of COVID-19 transmission from the source.

6. Conclusion

Since the beginning of 2020, COVID-19 has spread rapidly across the globe, posing important challenges to people's health. The spread of the disease has been curbed to some extent by the advent of the COVID-19 vaccine. But the mutated COVID-19 (Delta
strain) is much more contagious, once again creating a pandemic. To study the spread of Delta strain in populations, we developed a new mathematical model of COVID-19 transmission with imperfect vaccination.

The first part of this paper was some theoretical analysis of the model. Firstly, we studied the positivity and boundedness of the solution of the model, and obtained the expression of the basic reproduction number with important biological significance by using the method of the next generation matrix. Then a new status system with control variables was obtained by embedding three controls (vaccination $u_1$, isolation $u_2$ and detection $u_3$). Using the Pontryagin optimal principle, the expression of optimal control was obtained.

The second part of this paper was numerical simulation. First of all, we collected the data of daily infection cases from July 20, to August 5, 2021 on the official website of Jiangsu Provincial Health Commission of China. In order to make full use of these high-quality data, the nonlinear weighted least square estimation method was applied to estimate parameters. The approximate value of the basic reproduction number $R_0 = 1.378$. This result showed a significant decrease in $R_0$ value compared with previous literature, suggesting that vaccination also had a certain inhibitory effect on the transmission of the Delta strain. Through the sensitivity analysis, the effect of each parameter on the system was shown. Finally, we simulated the results of each strategy by using the forward and backward sweep method with the fourth order Runge-Kutta, and obtained the optimal control strategy by analyzing the data of infection averted ratio of each strategy.

Based on the research work done in this paper, some novel contents different from the existing papers are summarized as follows:

- A novel mathematical model of mutated COVID-19 has been developed. In the model, we took into account not only the important differences between vaccinated, antibody weakened and unvaccinated populations, but also the fact that the inactivated vaccine has some effect on the Delta strain, preventing it from becoming severely ill but still potentially infected.
- In parameter estimation, unlike many scholars who only fit the total number of confirmed cases, we used weighted nonlinear least squares estimation method to fit the data of officially reported asymptomatic, mild and severe cases. More detailed fitting results can provide more accurate analysis results and is the basis for effective follow-up work.
- In the control simulation, different from the control measures (isolation and detection) in the previous literature, we consider the control measures to increase the speed of vaccination. Our study found that with the inclusion of vaccination measures, dynamic adjustment of the strength of the three control measures could further reduce the number of infected individuals.

Mutated COVID-19 (the Delta strain), due to its strong infectivity, can produce mass transmission in populations with imperfect vaccination. How to formulate effective control measures has become an important problem. The results of this study suggest how three different control strategies should be dynamically adjusted to minimize the number of infections and cost as much as possible. These findings clearly demonstrate the feasibility of developing an optimal vaccine schedule. The results can provide an important reference for many countries and regions that are experiencing the spread of delta virus to develop vaccine programs.

The fractional derivative can be regarded as the globalization of the integral derivative, which can show more properties that the integral derivative does not have. Many scholars have applied fractional derivative differential equations to study the spread of COVID-19, and many important research results have been obtained [31–36]. If we consider fractional COVID-19 model for parameter estimation, different results with higher fitting degree may be obtained, and the measures taken may be changed. This is an interesting question, and we leave it for later.

Declaration of Competing Interest

There are no conflicts of interest by the authors.

CRediT authorship contribution statement

Tingting Li: Conceptualization, Methodology, Software, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing. Youming Guo: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

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